New 3,3-disubstituted oxetanes and azetidines: Synthesis, evaluation and new opportunities for drug discovery

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

3,3-Disubstituted oxetanes and azetidines are valuable motifs with attractive physichochemical properties and are potential replacement groups for *gem*-dimethyl, carbonyls and larger heterocycles. The development of robust methods to access such scaffolds is highly desirable. In this thesis, novel 3,3-disubstituted oxetanes and azetidines are prepared through the *in situ* generation of carbocations and radicals. The suitability of these new motifs for drug discovery programmes is also evaluated.

In this regard, 3,3-diaryloxetanes are first assessed as replacement groups for diarylketones and 1,1-diarylalkanes in part 3. These oxetanes are synthesised through a Friedel–Crafts reaction with oxetanols. The comparison of the physicochemical properties between 3,3-diaryloxetanes, benzophenones and 1,1-diarylalkanes shows that these oxetanes are suitable replacements groups for medicinal chemistry application.

The preparation of new 3,3-diarylazetidines and 3-arylsulfanyl-azetidines is then described in part 4. This was achieved through *in situ* generation of azetidinyl carbocations from NCbz-azetidin-3-ols using Ca and Fe catalysts. These carbocations can react with nucleophiles such as (hetero)aromatics and thiols giving new azetidine scaffolds in high yields.

The generation of oxetanyl and azetidinyl carbocations required the alcohol precursors to bear electron-rich aromatics. An alternative Fe-catalysed Friedel–Crafts reaction is then described in part 5, where the use of hexafluoroisopropanol as solvent enables oxetanyl carbocation formation from oxetanols bearing phenyl and electron-poor aromatics. Previously inaccessible 3,3-diaryloxetanes are synthesised as well as one example of 3,3-diarylazetidine and 3-arylsulfanyl-oxetane.

New oxetane and azetidine scaffolds are then prepared through *in situ* generation of radicals in part 6. This was achieved through photoredox-catalysed decarboxylation of oxetane and azetidine carboxylic acid precursors. The radicals are trapped with alkenes to give new 3-aryl-3-alkyl oxetanes and azetidines. A two-step protocol is also described to efficiently access the acid precursors. This involves the preparation of 3-aryl-3-furanyl intermediates through Friedel–Crafts reaction followed by oxidative cleavage of the furan.

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Abbreviations

ADMET	Absorption, distribution, metabolism, excretion and toxicity
AIBN	Azobisisobutyronitrile
aq	Aqueous
Ar	Aryl
Bn	Benzyl
Boc	*tert*-Butyloxycarbonyl
Caco-2	Caucasian colon adenocarcinoma cells
CFL	Compact fluorescent lamp
CLint	Intrinsic clearance
CYP	Cytochrome P enzymes
DBDMH	1,3-Dibromo-5,5-dimethylhydantoin
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-Dichloroethane
DIAD	Diisopropyl azodicarboxylate
DMA	*N*,*N*-Dimethylacetamide
DMAP	4-(Dimethylamino)pyridine
DME	1,2-Dimethoxyethane
DMF	*N*,*N*-Dimethylformamide
DMSO	Dimethyl sulfoxide
DOF	[^{3}H]Dofetilide binding competition to hERG
dppf	1,1'-Bis(diphenylphosphino)ferrocene
EDC	*N*-(3-Dimethylaminopropyl)-*N*′-ethylcarbodiimide
EDG	Electron donating group
EWG	Electron withdrawing group
FDA	Food and Drug Administration
Fsp^3	Fraction of saturated carbon sp^3
FTIR	Fourier transform infrared spectroscopy
GSK	GlaxoSmithKline
hERG	Human Ether-a-Go-Go-Related Gene
HFIP	1,1,1,3,3,3-Hexafluoro-2-propanol

HLM	Human liver microsome
HPLC	High performance liquid chromatography
IC_{50}	Half maximal inhibitory concentration
KHMDS	Potassium bis-(trimethylsilyl)amide
LDL	Low-density lipoprotein
LED	Light-emitting diodes
LSD	Lysergic acid diethylamide
*m*CPBA	3-Chloroperbenzoic acid
MDCK-MDR1	Madin Darby canine kidney cells transfected with the *MDR1* gene.
mp	Melting point
MW	Molecular weight ($g \cdot mol^{-1}$)
NBS	*N*-Bromosuccinimide
NMR	Nuclear magnetic resonance
Papp	Apparent permeability coefficient
PG	Protecting group
PMP	*para*-Methoxyphenyl
ppm	Parts per million
PSA	Polar surface area
PTSA	*para*-Toluenesulfonic acid
RRCK	Ralph Russ canine kidney cell
RSM	Recovered starting material
rt	Room temperature
sat	Saturated
TBAF	Tetrabutylammonium fluoride
TBHP	*tert*-Butyl hydroperoxide
TFA	Trifluoroacetic acid
TFE	2,2,2-Trifluoroethanol
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl

1. Introduction

1.1 Drug Discovery process

1.1.1 Drug Discovery Pipeline and Challenges

A common strategy in drug discovery programs is to screen a library of compounds against a selected target (Figure 1.1). Once a hit has been identified, a long process of "lead" identification followed by "lead" optimisation aims at synthesising multiple analogues to improve the potency, selectivity and drug-likeness. The resulting drug candidate then enters a series of pre-clinical testing and clinical trials before reaching the market. The length of the drug discovery pipeline and the associated high attrition rate of 93-96% in clinical development result in considerable financial costs for the pharmaceutical industry.[1]

Recent studies show that compounds having certain properties in early stages of the process, increases their chances of success through the pipeline and prevents late-stage attrition.[2] A good understanding and control of these properties is key to the success in drug development settings.



Figure 1.1: Drug discovery process.

1.1.2 Desirable Physicochemical Properties for Drug Candidates

1.1.2.1 ADMET Profile

The success of a compound through the drug discovery process does not rely on its potency alone. The absorption, distribution, metabolism, excretion and toxicity (ADMET) profile of the molecule candidate in the body also determines its chance of success (Figure 1.2). For an orally-administrated drug for instance, the candidate has first to be absorbed from the stomach to the blood. This depends on the solubility of the organic molecule in the aqueous medium of the stomach, while being permeable enough to cross the biological membranes to the blood. The compound will then have to be distributed in the body to the biological target in sufficient amount to have the expected effect. The rate with which the candidate is metabolised in the body plays a role on its bioavailability and the dose determination. The metabolism of drugs commonly occurs through hydrolysis, oxidation and reduction by enzymes in the blood or by cytochrome P450 enzymes (CYP450) in the liver. Moreover, the addition of highly polar labile groups through glucuronidation or sulphation for example, helps elimination by renal excretion. Finally the toxicity of a candidate is one of the main cause of attrition in the drug discovery process. Common toxicities to avoid include: cardiovascular hazard with the inhibition of

Human Ether-a-Go-Go-Related Gene (hERG), causing arrhythmia and sudden death, hepatotoxicity with irreversible inhibition of CYP450 for instance, or genetic and mutagenetic toxicities. The control and optimisation of the ADMET profile of a compound is crucial to develop a successful drug.

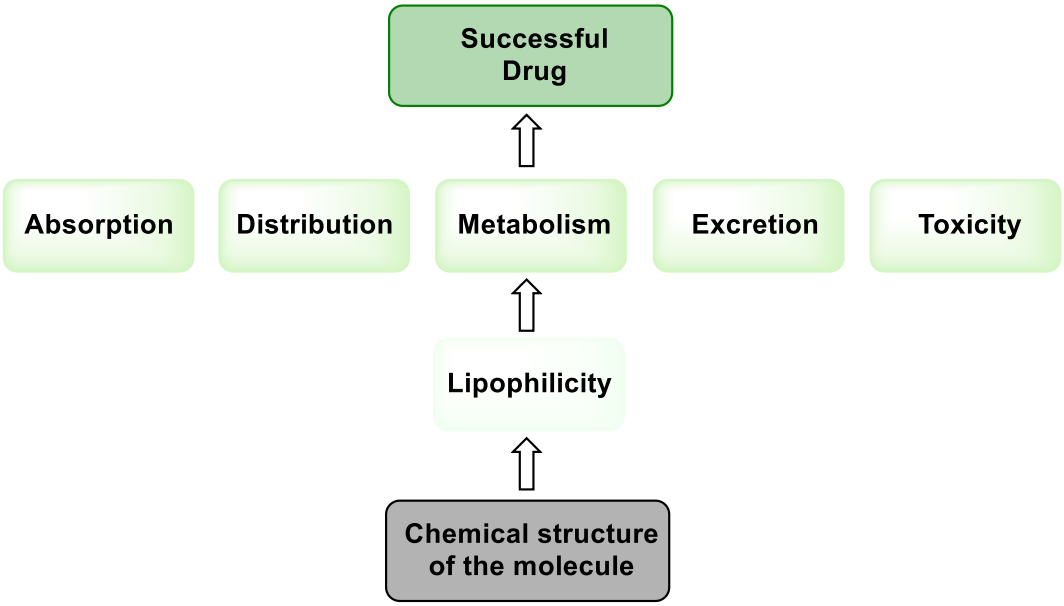


Figure 1.2: The chemical structure of a molecule will govern the physicochemical properties it will have and the quality of the ADMET profile, which has a direct effect on the success of a drug.

Studies in the last ten years have well documented the intrinsic link between ADMET profile and the physicochemical properties of drugs.

1.1.2.2 Desirable Physicochemical Properties

Lipophilicity and ADMET parameters

Lipophilicity and molecular weight (MW), have been shown to be, by far, the most influential properties.[3] The lipophilicity is the octanol/water partition coefficient of a molecule and refers to its ability to dissolve in non-aqueous solvent. This can be calculated (clogP) or experimentally measured on the neutral form of a molecule (logP) or its ionised form (logD).[3] The solubility of a compound is the property most affected by the lipophilicity. Yalkowsky *et al*. proposed a general solubility equation describing the solubility (logS) as a function of lipophilicity and melting point (equation 1).[4] Based on this equation, to achieve a high solubility (> 100 µM), a compound should have a logP < 3.25.[3] In support of this, a study on 44,584 GSK compounds revealed that solubility is increased when logP < 3 and MW < 300.[5]

$$\log Sol_{aq} = 0.5 – \log P – 0.01\ (mp – 25)$$

Equation 1.1: General solubility equation developed by Yalkowsky *et al*[4], describing the solubility as a function of logP and melting point. Melting point expressed in °C.

On the other hand, logP and D are also a mimic of the distribution of a compound between the aqueous phase and the cell membrane.[3] Therefore it also has strong effect on the permeability. In 2009 Waring studied AstraZeneca's Caco-2 data and found that permeability depends on both MW and lipophilicity.[6] The investigation showed that high permeability (Papp > 100 nm/s) is obtained for molecules with MW = 350-400 when logD > 1.7, and when logD > 3.4 for molecules with MW = 450-500.

The link between decreased lipophilicity and reduced clearance/metabolism has also been extensively studied.[7] Within a 47,018 Pfizer compound dataset, Johnson *et al*. observed that low human liver microsomal (HLM) intrinsic clearance < 8.6 mL/min/mg are obtained for compounds with logD < 3.[8] The binding site of CYP enzymes being generally lipophilic explains their greater affinity for lipophilic compounds and the increased clearance for those molecules by the liver.[9] Importantly, low logP and logD was also found detrimental, with higher renal clearance for compounds with logD ~ 0 due to low reabsorption through kidney tubules.[7,10]

Finally, high logP and logD have been proven to increase risk of toxicity in the body.[3] Leeson and Springthrope analysed a 2,133 drug dataset and found that poor binding-specificity is increased for compounds having a logP > 3.[2] Problematic hERG inhibition (IC50 < 10 μM) and CYP enzyme inhibition are examples of promiscuity leading to cardiac and hepatic complications, which increases with higher logP and logD.[5,11]

Overall, these studies show the effect of lipophilicity and MW on ADMET parameters, with general detrimental effects with higher logP and logD.[2] As a result, control of the lipophilicity is key to the success of a molecule as drug.

<u>Shape, Complexity and ADMET parameters</u>

More recently, studies have highlighted the link between the shape and complexity of a molecule with its ADMET parameters. For example, increasing the number of aromatic rings in a molecule lowers the aqueous solubility, and increases lipophilicity with higher risk of failures in the drug discovery process.[12] Polar surface area (PSA) that arises from oxygen and nitrogen atoms, was also found to influence ADMET parameters.[13] Reducing the PSA, rotatable bonds, H-bond donors and acceptors was shown to increase permeability.[13] In 2009, an important correlation between the complexity of a molecule as potential drug candidate and its success through the development was published.[14] In this study, Lovering *et al.* used the fraction of saturated carbon atoms (Fsp^3) = (number of sp^3 hybridised carbons / total carbon

counts) in a molecule to describe its complexity.[15] Based on a data set of 1,202 compounds, it was shown that solubility increases with Fsp^3.[14] On another data set of 4,432 molecules, the average Fsp^3 was found to go down as the melting point increases.[14] Overall, compounds with greater saturation are more likely to succeed in the drug discovery process. Indeed, incorporation of saturation allows the preparation of more 3-dimensional compounds which could increase receptor/ligand interactions, the potency and the selectivity of the molecule for a target.[14]

Based on all studies and observations described so far, guidelines of properties requirement to increase clinical success have been described (Figure 1.3).

Guidelines of physicochemical properties

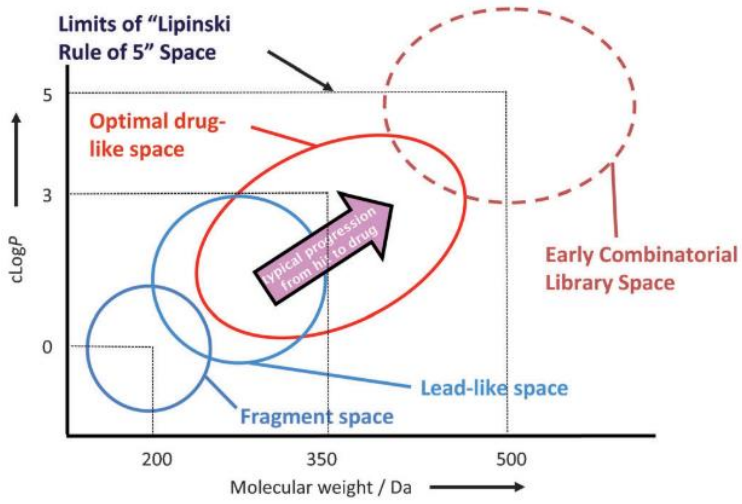


Figure 1.3: Figure from Churcher and co-workers, *Angew. Chem. Int. Ed.* **2012**, *51*, 1114–1122. Guidelines of physicochemical properties the candidate should have through the process to increase its chance of success. The figure shows the evolution of these guidelines as the molecule progress.

Lipinski's "rule of 5" first predicted that poor absorption and permeability is more likely for drug candidates in later stage when: logP > 5, MW > 500, > 5 H bond donors, > 10 H bond acceptors.[16]

In 2003, Jhoti defined a "rule of 3" where fragments screened in the early stage of the process, have higher chance to succeed with: logP < 3, MW < 300, H-bond donor < 3 and PSA < 60.[17] However, further studies in the following decade led to a revised guideline by Rees and Murray, highlighting the need for fragments with: 0 < logP < 2, 140 < MW < 230, with more 3-dimensional shape and greater Fsp^3.[18] The lead optimisation of the hit obtained during the fragment screen, aims at improving the potency at the drug target. This often involves increasing MW, complexity and the size of the molecule.[19] Therefore the guidelines for desirable physicochemical properties evolve and change as the process advances. Optimum

ADMET parameters are predicted to be obtained for lead molecules with: 0 < logP < 3, 200 < MW < 350, increased 3-dimensionality and limiting the number of aromatics to three.[19]

Figure 1.3 summarises guidelines on these properties as molecules progress in the drug discovery programme. LogP and MW tend to increase over the process but should remain between 0 < logP < 4 and MW < 400 to optimise the ADMET profile. These increase the chance of success and prevent late stage attrition. These key physicochemical properties directly depend on the structure of the candidate, and thus the decision on the design by medicinal chemists is crucial.

Although medicinal chemistry, as a discipline, has made significant progress in understanding those properties and adapted their design, synthetic chemistry has not progressed accordingly to allow such design.

1.1.3 Organic Synthetic Chemistry as Limiting Factor

The impact of organic synthetic chemistry in drug discovery programmes is shown in orange in Figure 1.4. The first role of synthetic chemistry is to produce libraries of fragments made in maximum four steps from commercially available materials,[18] and designed to have desirable properties shown in green. Once the hit is obtained, optimisation of the potency and properties are investigated *via* synthesis of hundreds to thousands of analogues with lead-like properties and obeying the rule of 5. The time restrictions limit the scope investigation, thus robust and predictable chemistry is needed. Once a single molecule is chosen as clinical candidate, its structure and properties will not be modified further. Efficient synthesis to produce the compound on multi-kg scale is required, with safe reactions for chemists and the environment, while being robust and cost efficient.

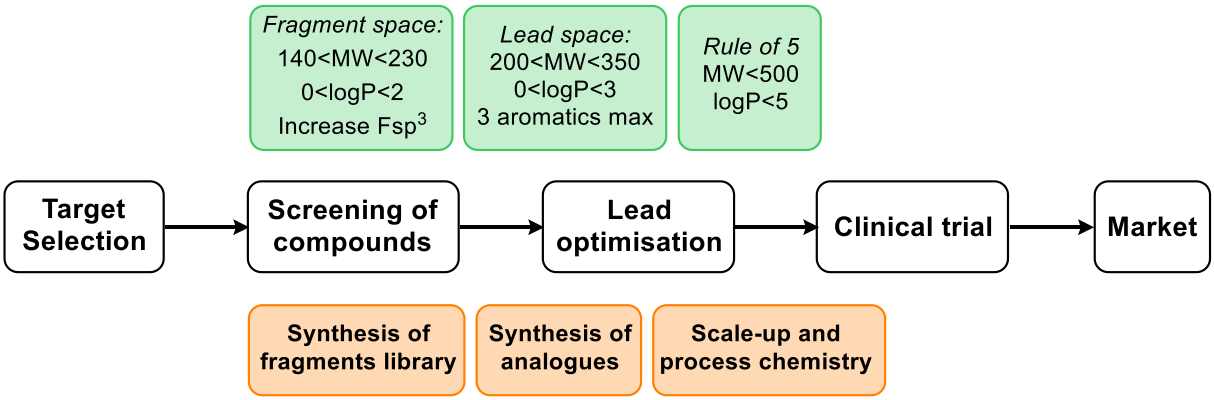


Figure 1.4: Drug discovery process with: the ideal physicochemical properties compounds should have to increase chance of success (in green); and the role of synthetic chemistry across the process (in orange).

The current synthetic methods available do not promote the synthesis of compounds with desirable properties, especially at early stages of the process. This limits the design that medicinal chemists can envisage. An analysis of the chemical reactions used by medicinal chemists in 2014 shows that amide-bond formation, Suzuki-Miyaura cross–coupling and S_NAr are the most frequent reactions in drug discovery.[20] These reactions promote compounds with an increased degree of aromatic and sp^2 character, instead of compounds with higher Fsp^3 and desirable properties.

Another challenge for organic synthetic chemists is to develop robust and scalable reactions, along with tolerance for polar functional groups including nitrogen atoms.[21] These limit the synthesis and modifications of highly desirable motifs, including aliphatic oxygen and nitrogen heterocycles.[21]

1.2 Oxetanes and Azetidines as Desirable Motifs

1.2.1 Importance of Nitrogen and Oxygen Heterocycles

Saturated nitrogen and oxygen heterocycles are polar structures with high Fsp^3 character and desirable physicochemical properties. Their 3-D complementarity can confer high-affinity binding interactions with biological targets.[21] In 2014, a study showed that 59% of small-molecule drugs approved by US FDA contained nitrogen heterocycles.[22] Oxygen-heterocycles were the second most common type of heterocycle in FDA approved pharmaceuticals in 2017.[23] These studies revealed that five and six-membered rings are by far the most prevalent among all *N*- and *O*-heterocycles, in approved drugs.

Although β-lactams are the third most prevalent rings in drugs containing saturated *N*-heterocycles, four-membered nitrogen and oxygen rings are underrepresented. For example,

oxetanes represent only 1% of approved drugs containing an oxygenated heterocycle,[22,23] despite attracting considerable attention in recent years.

1.2.2 Attractive Features of Oxetanes and Azetidines

1.2.2.1 Oxetanes and Azetidines in Bioactive compounds

Oxetane and azetidine rings are found in very few natural products (excluding β-lactams) with interesting and diverse biological activities (Figure 1.5).[24,25,26,27,28] For example, Taxol is an antimitotic agent and the most famous bioactive molecule containing an oxetane ring. The oxetane is crucial to the reactivity as it orients the adjacent acetyl group to the hydrophobic binding pocket.[29] Oxetanocin A and oxetin possess anti-HIV and antibacterial activities respectively.[30,31] Only rare examples of natural products containing azetidines can be found, including mugineic acid, a phytosiderophore, and the penaresidin family which show ATPase activation in actomycin.[32,33]

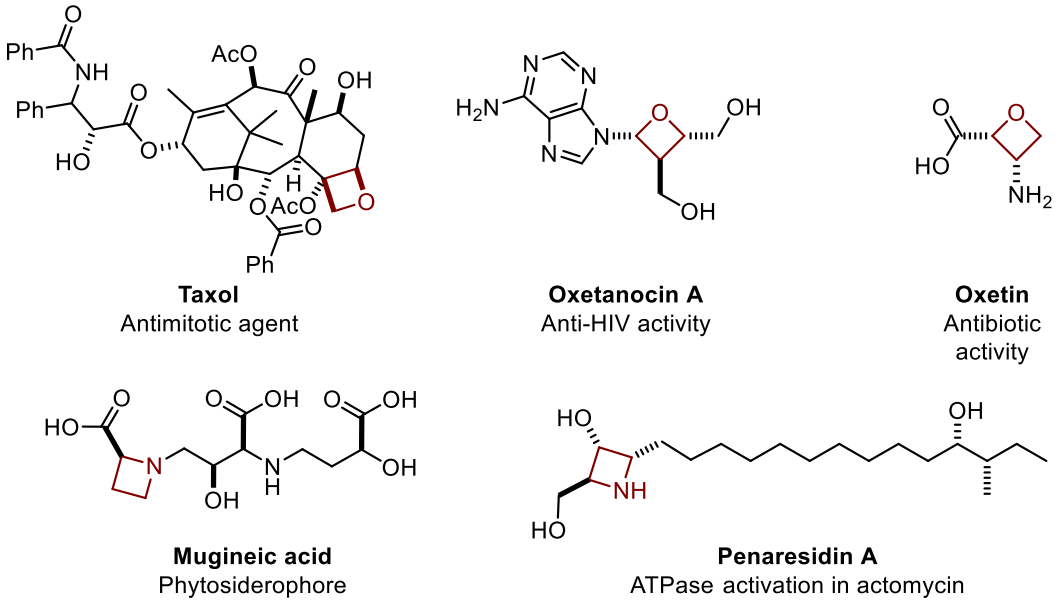


Figure 1.5: Natural products containing oxetane and azetidine rings.

Recent pharmaceuticals also display an azetidine ring such as Azelnipidine, Delafloxacin and Siponimod, albeit with less frequency than 5- and 6-membered *N*-heterocycles (Figure 1.6). In contrast, oxetanes are scarcely found in pharmaceuticals aside from Taxol. Although oxetanes and azetidines are underrepresented in pharmaceuticals, they are attracting increased attention due to their interesting features for drug discovery.

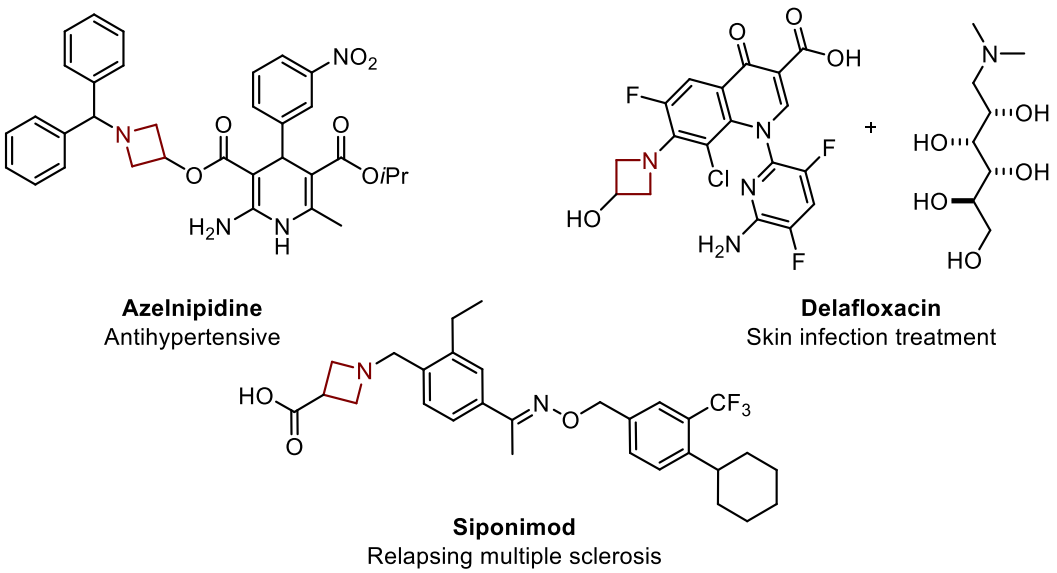


Figure 1.6: Recent pharmaceuticals containing azetidine rings.

1.2.2.2 Physicochemical Properties

Physical properties of oxetanes and azetidines

Oxetanes and azetidines are four-membered cyclic ethers and amines with high strain character of 106 kJ·mol^{-1} and 104.6 kJ·mol^{-1} respectively compared to five and six membered rings (THF: 25 kJ·mol^{-1}, pyrrolidine: 20.9 kJ·mol^{-1}, THP and piperidine: ~0 kJ·mol^{-1}).[34] The presence of oxygen and nitrogen atoms in the cycles and the minimisation of the strain, generate a small puckering angle. This varies from 10° to 20° depending on substitution, and reduces planarity while increasing 3-dimensionality.[35] This influences the bond lengths and angles within each rings as shown in Table 1.1. In unsubstituted oxetane and azetidine, the carbon–oxygen bond length is 1.46 Å and the carbon–nitrogen bond length is 1.48 Å.[35b,36] Both rings have similar carbon–heteroatom bond length, with a slight difference in their bond angles. In the oxetane ring, the C–O–C bond angle of 90.2° is slightly smaller than the C–N–C bond angle of 92°in azetidine.[35b,36] The strain and the steric in the oxetane exposes the lone pairs of electrons and increases its H-bond acceptor and Lewis base character.[35b] Similarly, the steric in the azetidine ring places the lone pair of electrons in pseudo-axial position and increases the nitrogen inversion barrier (~41.8 kJ·mol^{-1} at rt)[37] compared to amines (~20 kJ·mol^{-1} at rt)[38] and piperidine (25.1 kJ·mol^{-1} at rt)[39]. It also enhances its H-bond acceptor and donor character. Finally, azetidine can act as a secondary amine base with a pKaH of 11.29 (H_2O).[35d] Although unsubstituted azetidine has a higher s character due to the particular hybridization of small hindered ring, the pKaH is surprisingly similar to pyrrolidine (11.31)[35d] and piperidine (11.28)[35d]. Combined together, these particular structural features modulate and give the advantageous properties oxetanes and azetidines can offer to medicinal chemists.

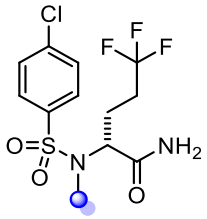
		Oxetanes (X = O)	Azetidines (X = N)
Bond length	C–C	1.53 Å	1.56 Å
	C–X	1.46 Å	1.48 Å
Bond angle	C–C–C	84.8°	87°
	X–C–C	92°	86°
	C–X–C	90.2°	92°

Table 1.1: Bond length and angle in an unsubstituted oxetane and azetidine.

Oxetanes as replacement groups

These last fifteen years, oxetanes have emerged in drug discovery programmes and started to be used by medicinal chemists to fine-tune physicochemical properties.

In 2011, Stepan *et al*. studied the effects of cycloalkanes and different oxygen heterocycles on the physicochemical properties of *N*-arylsulfonamide based γ-secretase inhibitors (Table 1.2).[40] The cycloalkanes series suffered from high lipophilicity (elogD) and subsequent metabolic instability. Replacing the cyclic chain with 2-substituted THP and THF lowered the elogD without reducing clearance. In particular, incorporating 2-substituted oxetane improved the ADMET profile of the molecule, lowering elogD to 2.60. In addition the clearance was decreased nearly 5-fold compared to 2-substituted THP and THF while enhancing the permeability. The 3-substituted *O*-heterocyclic series presented improved properties compared to the 2-substituted compounds, with drastic reduction of the clearance. In both series, replacing 5- and 6-membered THF and THP with an oxetane led to greater microsomal stability and lower lipophilicity, while preserving activity, suggesting oxetanes as suitable surrogates for cyclic ethers and cycloalkanes.



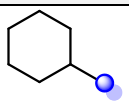
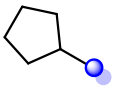
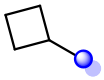
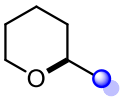
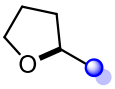
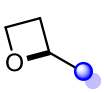
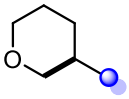
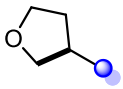
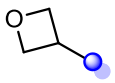
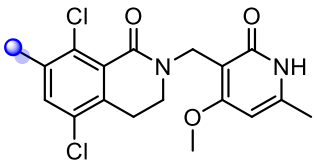
Compound series		eLogD	CLint (mL/min/mg)	RRCK Papp[41] (10^{-6} cm/s)
Cycloalkanes		5.6	176	4.42
		5.15	229	6.01
		4.67	207	11.1
2-substituted		4.30	>300	15.4
		3.50	210	1.37
		2.60	63.8	28.7
3-substituted		3.70	136	18.4
		2.80	69.8	20.5
		2.50	28.6	25.4

Table 1.2: Effect of *O*-heterocycles and cycloalkanes on lipophilicity (elogD), intrinsic clearance (CLint) and permeability (RRCK Papp) in series of *N*-arylsulfonamide-based γ-secretase inhibitors.[40]

A recent study used this strategy to optimise Zeste homolog 2 (EZH2) inhibitors, where replacing 3-substituted THF with an oxetane reduced the clearance four-fold as well as lowering logD and improving solubility (table 1.3).[42]



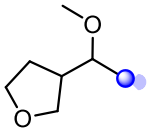
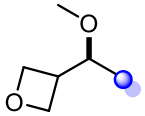
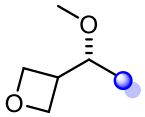
Compound	HLM (μL/min/mg)	logD	Sol (μM)
	66.9	2.5	439
	39	1.9	538
	17	1.6	543

Table 1.3: Optimisation of physicochemical properties in Zeste homolog 2 (EZH2) inhibitors.[42]

In a comparison of a series of CK2 kinase inhibitors containing 3-aminooxetane, cyclopropane or cyclobutane rings, Dowling showed the unique advantage that oxetanes offer over other rings, improving both lipophilicity and microsomal stability while lowering hERG inhibition (Table 1.4).[43]

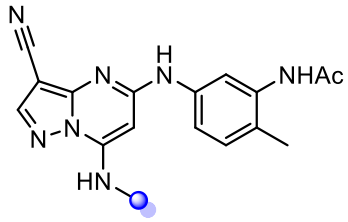
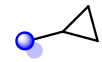
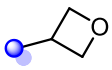
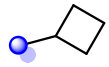
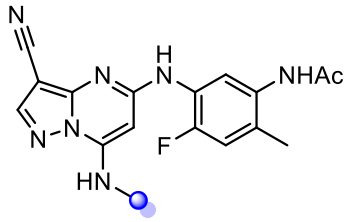
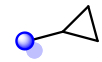
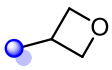
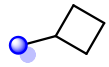
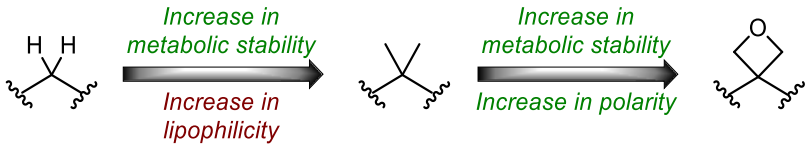
Compound		LogD	CLint (μL/min/mg)
		2.4	15
		1.6	17
		3	48
		2.3	38
		1.5	6
		3	30

Table 1.4: Comparison of series of 3-aminooxetanes, cyclopropane and cyclobutane in CK2 kinase inhibitors.[43]

Overall, the work carried out by Stepan, Edwards and Dowling highlight the potential of oxetanes as replacement groups, also called isosteres, for cycloalkanes and other ether rings.

Since 2006, Carreira published influential works on the potential of 3,3-disubstituted oxetanes as isosteres which had an important impact on medicinal chemistry.[44] *gem*-Dimethyl groups are commonly used in medicinal chemistry to block metabolically labile methylene positions.[3] However, this often results in undesirable increase in lipophilicity which can adversely affect the ADMET profile. Carreira proposed 3,3-disubstituted oxetane as a polar replacement group for *gem*-dimethyl as they have similar molecular volume and spatial arrangement.[45] When incorporating oxetanyl moieties into *N*,*N*-dimethyl-4(*p*-*tert*-butylphenyl)butylamines (Table 1.5), lower logD, logP and drastic enhancement of solubility were obtained compared to methylene and *gem*-dimethyl-containing compounds. In addition, the basicity of the amine could be modulated by the oxetane ring. When placed in α-position of amines, the pKaH was lowered by three units, reducing the solubility compared to other oxetane analogues as a higher proportion of neutral amine is present at pH 9.9.



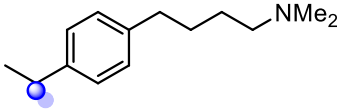
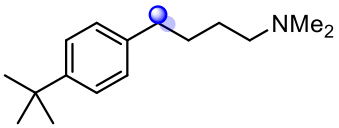
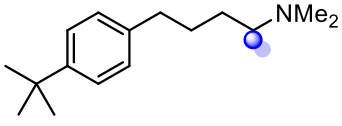
Compound		logD (logP)	Sol (μM)[a]	CLint (μL/min/mg)	pKaH
		2.5 (5.0)	<4	16	9.9
		0.8 (3.3)	18,000	0	9.9
		1.8 (4.3)	250	37	9.9
		/[b]	24	13	9.8
		1.7 (3.9)	980	0	9.6
		/	/	20	10.4
		3.3 (3.6)	210	13	7.3

Table 1.5: Physicochemical properties of *N*,*N*-dimethyl-4(*p*-*t*ert-butylphenyl)butylamine analogues containing oxetanes, *gem*-dimethyl or methylene.[45] [a] Solubility (μmol/L) of the neutral base in 50 mM phosphate buffer at pH 9.9 and 22.5 °C. [b] Not determined because of insufficient UV absorption.

3,3-Disubstituted oxetanes were also proposed as carbonyl isosteres, having similar dipole and H-bond properties.[46] Carbonyl groups are vulnerable to enzymatic attack within the body as well as α-deprotonation and epimerisation. Incorporation of an oxetane could prevent these issues, while preserving desirable physicochemical properties.[46] Perhaps the most powerful example to illustrate this, is the study on the physicochemical properties of thalidomide and its oxetane analogue (Table 1.6).[47] The *R*-isomer of thalidomide is an anti-emetic which can epimerise within the body into the *S*-isomer which is a teratogen. Replacing the labile carbonyl with an oxetane resulted in nearly threefold increase in solubility, reduced lipophilicity while preserving excellent microsomal stability. Most importantly, the incorporation of the oxetane fixed the configuration of the α-centre preventing further racemisation in human blood plasma (Table 1.6).



Exposed to enzymatic attack
Vulnerable to epimerisation

Blockage of enzymatically exposed site
Stable towards epimerisation

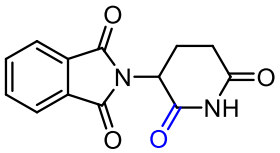
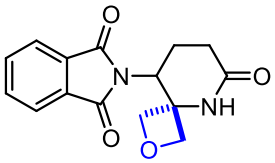
	LogD	Sol (µg/mL)	CLint (µL/min/mg)
	0.24	29	6
	0.00	78	5

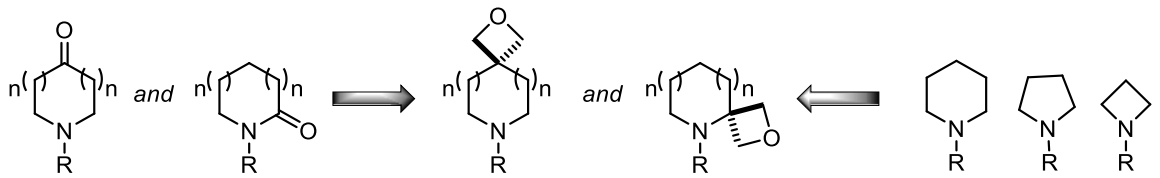
Table 1.6: 3,3-Disubstituted oxetanes as surrogates for carbonyl groups. Comparison of logD, solubility and clearance between thalidomide and its oxetane analogue.[47]

A series of works have since been published further investigating substituted oxetane as a carbonyl replacement. Shipman and Carreira suggested 3,3-aminooxetane as new peptidomimetic resistant to enzymatic bond cleavage.[48] During the course of the research reported in this thesis, other oxetane motifs were investigated as replacement group. Ballatore and Brunden studied the effect of incorporating oxetan-3-ols in place of carboxylic acids in a phenylpropionic acid model.[49] Oxetan-3-ols were found to have higher lipophilicity and permeability compared to carboxylic acid with a drastic increase of pKa. Bull and co-workers recently proposed 3,3-diaryloxetanes (see section 3), 3-sulfanyl-oxetanes (see section 4.2)

and 3-aryloxetan-3-ethers, as potential replacement for enzymatically exposed diarylketones, thioesters and esters.[50,51,52]

Spirocycles have more recently attracted attention as their inherent three-dimensionality can improve interaction between ligand and binding site.[53] In 2008, Carreira and co-workers published pioneering work on spirocyclic oxetane motifs, investigating their use and properties for medicinal chemistry.[46a] They proposed *N*-heterocycle-oxetane spirocyclic motifs as replacement groups for *N*-heterocycles, and heterocyclic ketones (Table 1.7). They compared the lipophilicity, solubility, clearance in human and pKaH of spirocyclic oxetanes with the corresponding azetidines, pyrrolidines and piperidines being unsubstituted or bearing a ketone or *gem*-dimethyl group at the 2-, 3- or 4- positions (table 1.7). Interestingly, introducing oxetanes into cyclic amines reduced the pKaH significantly compared to the parent heterocycles and *gem*-dimethyl analogues. This is emphasised when the oxetane is placed in α-position to the nitrogen atom, which is consistent with the study on *N*,*N*-dimethyl-4(*p*-*tert*-butylphenyl)butylamine analogues (table 1.5).[45] This trend in basicity leads to a higher proportion of neutral species at pH 7.4, explaining the increase in logD as the oxetane unit is closer to the nitrogen. However the logP of the oxetanes on all the 2-, 3- and 4-substituted series were lower than the parents heterocycles and *gem*-dimethyl analogues. Similarly, oxetane compounds were more soluble than *gem*-dimethyl, azetidine and pyrrolidine parent cycles, but intriguingly less than piperidine. Generally, the logP, solubility and pKaH of oxetanes were between that of *gem*-dimethyl and ketone analogues. Looking then at the oxidative metabolic oxidation (CLint, Table 1.7), all 3- and 4-substituted ketonamines were surprisingly quickly degraded. Replacing the ketone with an oxetane moiety in these series increased their stability towards oxidation. Curiously, this trend was not found in the 2-substituted series where the oxetanes were more exposed to metabolism than ketones and *gem*-dimethyl, although clearance remained low (<31 µL/min/mg).

Overall, all oxetane spirocycles investigated in this study presented low logD and low degradation by metabolic oxidation and high solubility.[46a] Their physicochemical properties were found to sit between those from *gem*-dimethyl and ketones analogues. It was highlighted that when *N*-heterocycles present issues in their properties, the incorporation of spirocyclic oxetanes can improve the physicochemical features.



Exposed to enzymatic attack
Vulnerable to epimerisation

Stable to metabolism and epimerisation
High 3-dimentionality

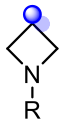
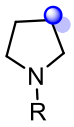
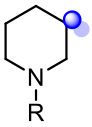
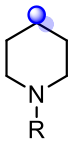
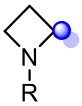
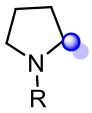
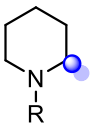
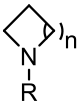
	Structure	Substitution	logD[a] (logP)	Sol (μM)[b]	CLint (μL/min/mg)	pKaH
3- and 4-substituted		*gem*-dimethyl	0.8 (3.1)	1,300	0	9.6
		oxetane	0.5 (1.2)	100,000	3	8.0
		carbonyl[c]	/	/	/	/
		*gem*-dimethyl	1.4 (3.7)	170	10	9.7
		oxetane	0.7 (1.5)	3,000	2	8.1
		carbonyl	-0.1 (-0.1)	19,000	100	6.1
		*gem*-dimethyl	2.3 (4.3)	53	31	9.4
		oxetane	1.7 (2.3)	7,700	16	7.9
		carbonyl	0.1 (0.5)	9,000	120	7.6
		*gem*-dimethyl	2.3 (4.4)	890	23	9.5
		oxetane	1.0 (2.0)	5,400	6	8.3
		carbonyl	1.2 (1.6)	17,000	120	7.5
2-substituted		*gem*-dimethyl	0.1 (2.8)	1,700	7	10.1
		oxetane	1.3 (1.3)	6,000	21	6.2
		carbonyl	1.1 (1.1)	10,000	5	-
		*gem*-dimethyl	0.9 (3.5)	180	0	10.0
		oxetane	1.9 (1.9)	8,500	31	6.3
		carbonyl	1.2 (1.2)	6,800	5	-
		*gem*-dimethyl	1.1 (3.9)	120	0	10.2
		oxetane	2.2 (2.4)	2,900	19	7.0
		carbonyl	1.6 (1.6)	27,000	8	-
Parent cycles		x = 1	-0.1 (2.1)	2,100	0	9.5
		x = 2	0.2 (2.5)	2,800	6	9.7
		x = 3	0.9 (3.1)	12,000	8	9.6

Table 1.7: Measured physicochemical properties of oxetane-spirocycle, *gem*-dimethyl, ketone and unsubstituted *N*-heterocycles. [46a] [a] Logarithm of the *n*-octanol/water distribution coefficient at pH 7.4. [b] Solubility of the neutral base in 50 mM phosphate buffer at pH 9.9 and 22.5 °C. [c] Not measured due to instability. R = piperonyl.

Azetidines as replacement groups

Interestingly, another comparison can be made from the data collected by Carreira on these spirocyclic series, focusing on the effect of the ring size of the *N*-heterocycles.

Although the pKaH does not seem to be affected by the ring size, both logP and logD decreases from piperidine to azetidine ring in all series (Table 1.7).[46a] This trend seems to correlate with the intrinsic clearance, with azetidine compounds being overall more stable towards microsomal degradation. Similarly, the 3-substituted azetidines were more soluble than 3- and 4-substituted pyrrolidines and piperidines. However this trend is reversed for the parent heterocycles and seems to be substituent-dependant when 2-substituted. Based on this study, azetidines could be used as surrogates for pyrrolidines and piperidines to potentially improve physicochemical properties when incorporated. This strategy was applied in the optimisation of LpxC inhibitors,[54] $\alpha_4\beta_2$-nicotinic acetylcholine receptor agonist,[55] and estrogen receptor degraders,[56] where the introduction of the azetidine ring respectively improved solubility, receptor-ligand interactions and robustness towards oxidative metabolism compared to other *N*-heterocycles (Figure 1.7).

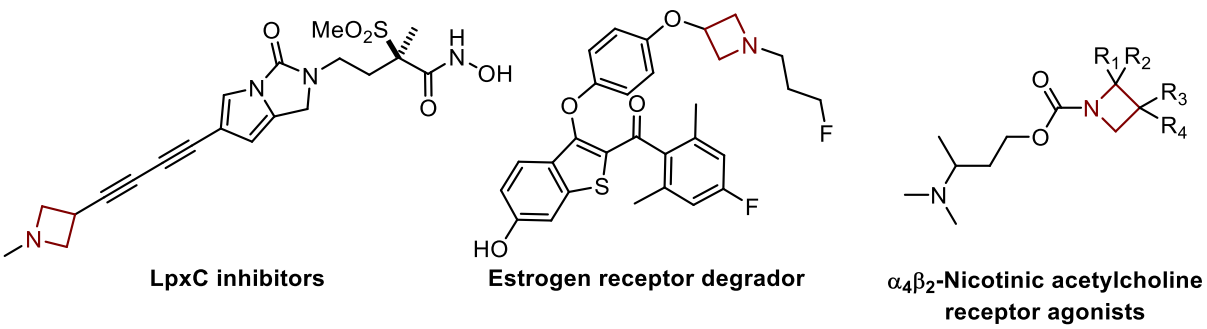


Figure 1.7: Example of biologically active molecules that had their potency and physicochemical properties optimised when incorporating azetidines in place of other *N*-heterocycles.

Carreira later proposed azetidine-spiro[3,3]heptane analogues as replacement groups for piperazines, piperidines, morpholines and thiomorpholines and compared their properties (Table 1.8).[57] Generally, amines in spirocycles were more basic than 6-membered ring, which correlates with their lower logD at pH 7.4 and higher solubility at pH 9.9. The metabolic stability was found to be structure-dependant. The clearance was decreased when piperazines are replaced with azetidine spirocycles, while it was not affected in the piperidine and morpholine series and dependant of the degree of oxidation of the sulfur atom for thiomorpholines. Overall, replacing six membered *N*-monocycles with corresponding azetidine-spiro[3,3]heptane analogues may improve the physicochemical properties, illustrating the advantage azetidines can offer.



A B

Series	Structure		logD[a] (logP)	Sol (µM)[b]	CLint (µL/min/mg)	pKaH
	Y	A or B				
Piperazine	NTs	A	3.4 (3.4)	13	310	6.0
		B	2.5 (2.8)	23	25	7.4
	NMe	A	0.5 (1.1)	>59,800	18	7.9
		B	-0.5 (1.6)	26,800	12	9.5
	NAc	A	0.9 (1.0)	>14,900	13	6.4
		B	0.0 (0.5)	>10,600	6	7.7
	NBn	A	2.8 (3.2)	/	26	7.6
		B	1.6 (2.7)	/	6	8.4
	NBoc	A	3.1 (3.1)	287	32	6.7
		B	2.2 (2.8)	2,620	2	7.8
	NAr	A	>3.7 (>3.8)	12	184	6.9
		B	>3.0 (>3.0)	12	29	8.1
Thiomorpholines	S	A	2.2 (2.4)	1,740	28	7.3
		B	1.6 (2.3)	4,560	18	8.1
	SO_2	A	0.1 (0.1)	1,440	7	4.0
		B	0.5 (0.6)	4,930	21	6.7
	SO	A	0.5 (0.5)	>33,000	0	5.5
		B	0.1 (0.3)	>32,000	9	7.2
Piperidine	CH_2	A	0.9 (3.1)	2,060	8	9.6
		B	1.0 (3.2)	3,280	9	9.6
Morpholine	O	A	1.5 (1.6)	36,300	9	7.0
	O	B	0.5 (1.1)	100,000	3	8.0

Table 1.8: Physicochemical properties of 6-membered N-cycles and azetidine-spiro[3,3]heptane analogues.[57] [a] Logarithm of the *n*-octanol/water distribution coefficient at pH 7.4. [b] Solubility of the neutral base in 50 mM phosphate buffer at pH 9.9 and 22.5 °C. Ar=3,5-difluorophenyl. R=piperonyl.

Recently, Grygorenko proposed 3-((hetero)-cyclobutyl)azetidines as “stretched” analogues of piperidines, piperazines and morpholines, being attractive for their 3-dimensionality, their larger size and increased conformational flexibility (Figure 1.8).[58]

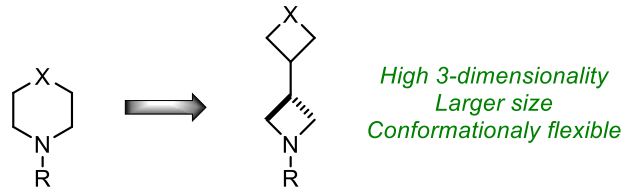


Figure 1.8: Grygorenko’s 3-((hetero)-cyclobutyl)azetidines as “stretched” analogues of piperidines, piperazines and morpholines.[58]

Finally, Nichols *et al.* studied the binding orientation of diethylamine moiety of LSD and found 2,4-dialkylazetidine analogues with similar activity as LSD.[59] They suggested that 2,4-dialkylazetidines can be suitable replacements for a variety of *N*,*N*-dialkylamines constraining the conformation which may preserve the activity while reducing side effects.[59]

In conclusion, all the compounds containing oxetane and azetidine rings described in this part present attractive physicochemical properties, including low lipophilicity, resistance to HLM oxidation and high solubility. In addition, introduction of oxetane and azetidine rings into molecules generally results in enhanced properties. In particular, an increased interest from medicinal chemistry is given to 3,3-disubstituted oxetanes and azetidines for their utility as replacement groups for a variety of functionalities (Figure 1.9). The development and study of further 3,3-disubstituted oxetanes and azetidines is highly desirable and can open new opportunities for drug discovery. However, their incorporation and use in drug discovery programmes is currently undermined by being difficult motifs to make and due to lack of synthetic methodologies.

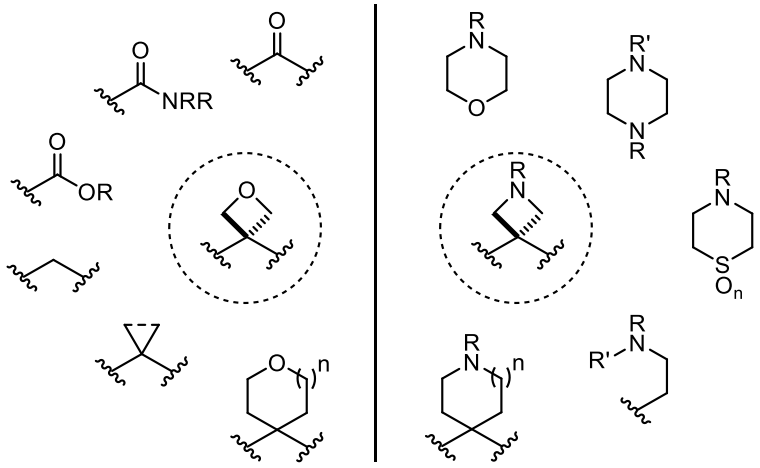


Figure 1.9: Summary of 3,3-disubstituted oxetanes and azetidines as replacement groups.

1.3 Current Syntheses of Oxetanes and Azetidines and Limitations

The common synthetic approaches towards oxetanes and azetidines are presented in Figure 1.10.

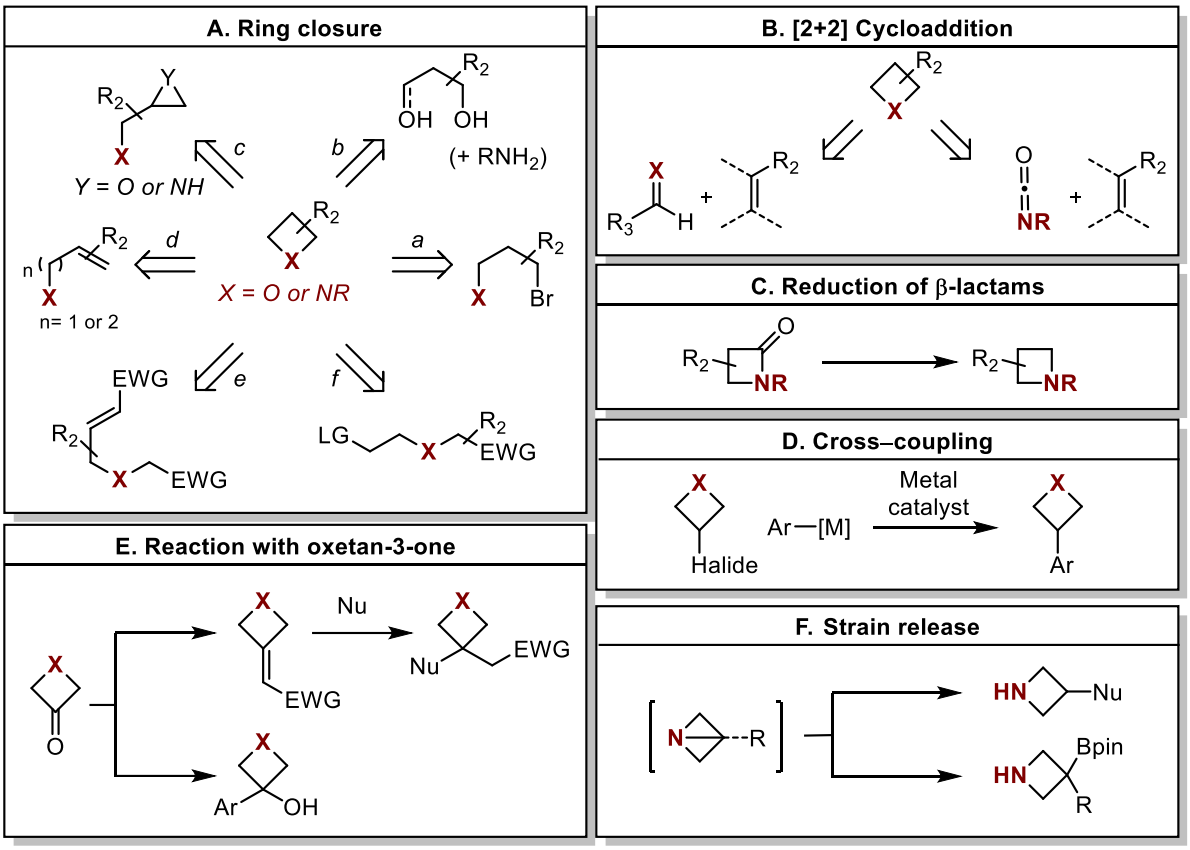
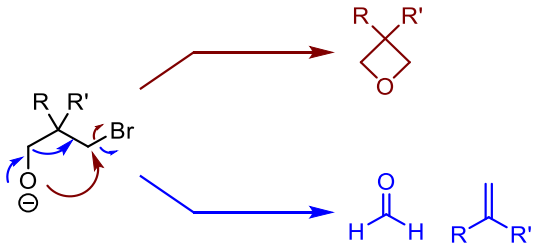


Figure 1.10: Common synthetic strategies towards oxetanes and azetidines.

Ring closure strategies are by far still the most employed methods to synthesise these rings, either by C–O/C–N (route *a* to *d*, Figure 1.10.A) or C–C bond formation (route *e* and *f*, Figure 1.10.A).[24,26]

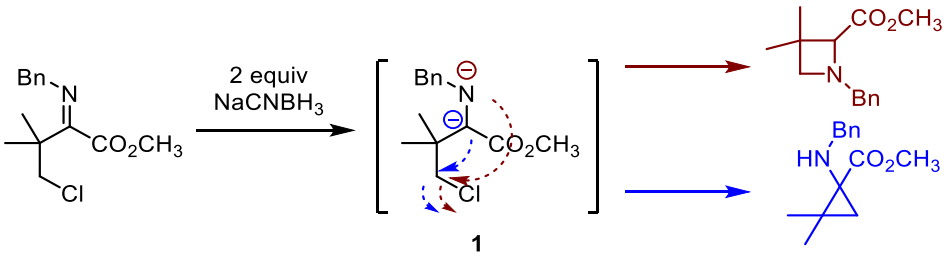
C–O or C–N bond formation: Nucleophilic substitution (S_N2) of halides by either oxygen or nitrogen atom is the most common reaction type of ring closure reaction (route *a*). The Williamson etherification has been widely used for the preparation of oxetanes *via* base-mediated nucleophilic substitution between an alcohol and an aliphatic carbon centre bearing usually a bromide.[26] However, worked carried out by Searles in 1953 and 1999 revealed the drawback of this strategy, with γ-bromoalkoxide species being susceptible to undergo Grob fragmentation into aldehyde and alkene (Table 1.9).[60] In these studies, the degree of fragmentation is shown to be dependent on the base and solvent used, but also on the substitution pattern with significant degradation observed when 3-substituted.



R, R'	Yield oxetane (%)	Yield aldehyde (%)
Me, Me	12	60
Et, Et	27	54
Et, *i*Pr	14	50
Et, H	23	19
Ph, H	0	26

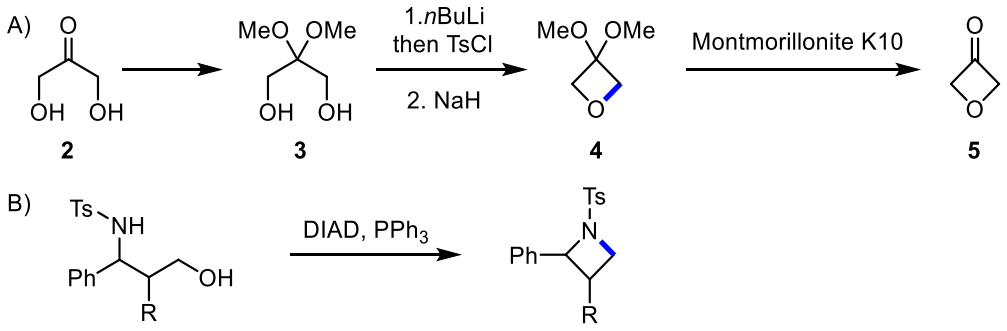
Table 1.9: Effect of substitution on the reactivity of γ-bromoalkoxide. Red pathway: successful Williamson etherification. Blue pathway: Grob fragmentation.

Similarly, De Kimpe showed that γ-chloroalkylamine **1** under basic conditions can result either in the attack of the amine into C–Cl bond giving azetidine (red path), or cyclopropane formation *via* α-H deprotonation followed by C–Cl cleavage (blue path, Scheme 1.1).[61]



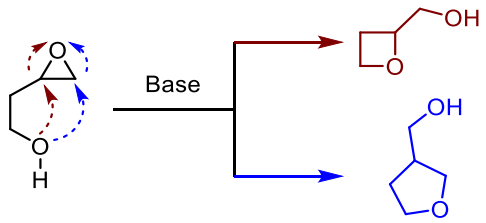
Scheme 1.1: Azetidine formation (red pathway) *vs* cyclopropane formation (blue pathway).

The use of an oxygenated leaving group was also later used (route *b*, Figure 1.10.A).[26] For example, Carreira developed in 2006 a four step synthesis to oxetan-3-one **5** starting from diol **2** (Scheme 1.2 A).[45] After transforming one of the alcohols into an OTs leaving group, base-mediated cyclisation led to 3,3-dimethoxyoxetane **4**. This strategy was also used in the synthesis of azetidines, by cyclisation *via* Mitsunobu reaction (Scheme 1.2 B).[62] Although this strategy allows the incorporation of substituents at the 3-position of the rings, the method can suffer from competitive intermolecular polymerisation and elimination of the acidic proton in the β–position to the leaving group.



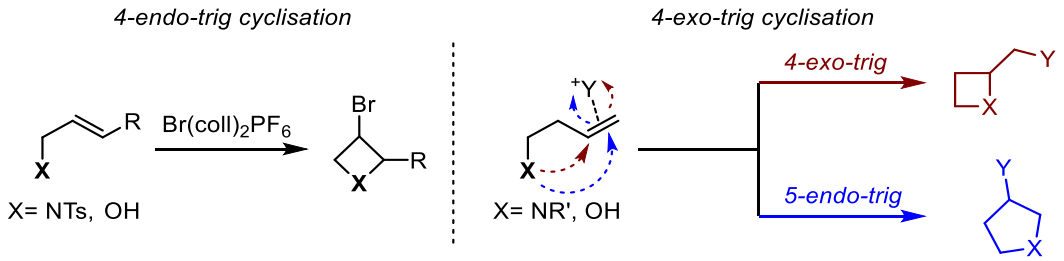
Scheme 1.2: Example of syntheses employing intramolecular nucleophilic substitution with oxygenated-leaving group.

Another cyclisation method going through C–O or C–N bond formation includes intramolecular opening of epoxides or aziridine rings (route *c*, Figure 1.10.A), which has been used by Bonnet-Delpon and De Kimpe in the synthesis of 3-hydroxy and 3-aminoazetidines respectively,[63] and in the synthesis of oxetanocin analogues.[64] In this latter study, the authors reported the formation of either the oxetane or THF ring due to competing epoxide-opening paths (Scheme 1.3).



Scheme 1.3: Representation of the competitive intramolecular epoxide-opening reactions leading to oxetane or THF rings.

Oxetanes and azetidines can also be accessed by intramolecular addition of amines or alcohols to alkenes (route *d*, Figure 1.10 A).[26] For example, Rousseau showed that activation of allylic and homoallylic amides, amine and alcohols with electrophilic bromide sources allows highly unfavourable 4-*endo*-trig cyclisation to occur (left, Scheme 1.4).[65] However, the method is limited to the formation of 3-bromo-substituted oxetanes and azetidines in moderate yields, with no example with 3,3-disubstitution pattern. 4-*Exo*-trig cyclisation is more common although it has been little used towards oxetanes and azetidines. In this case, the alkene moiety is placed one carbon further away from the heteroatom. Magnus and Outurquin have used this strategy for the synthesis of oxetanes and azetidines respectively, but observed regioselectivity issues with competitive 5-*endo*-trig cyclisation leading to THF and pyrrolidine rings (right, Scheme 1.4).[66,67]



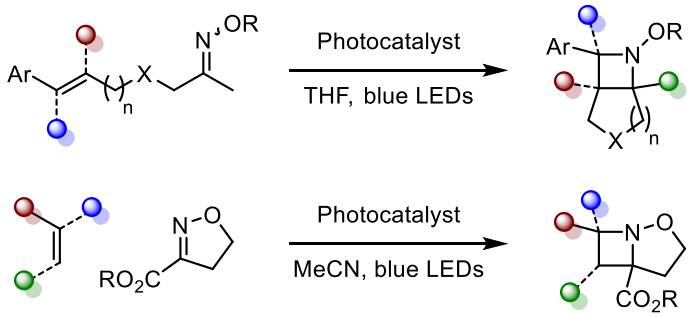
Scheme 1.4: Strategies for the 4-*endo*-trig or 4-*exo*-trig cyclisation of amines or alcohols with alkenes.

C–C bond formation: Finally ring closure can also occur *via* nucleophilic substitution or intramolecular Michael addition with the carbon in α to the heteroatom (route *e* and *f*, Figure 1.10 A).[26] Route *f* in particular allowed the formation of interesting motifs such as: 2-carboxylic acid azetidines,[68] 2-CN azetidines,[69] and more recently 2-(arylsulfonyl)-oxetanes and 2,2-disubstituted oxetanes and azetidines by the Bull group.[70] These C–C bond formation strategies are particularly efficient for the synthesis of 2- and 2,2-substituted oxetanes and azetidines but are not suitable for the incorporation of 3,3-disubstitution, as the steric hindrance prevents the nucleophilic substitution.

Overall, cyclization strategies have allowed the synthesis of a wide range of oxetanes and azetidines but suffer from side reactions leading to low yield and undesirable side-product formation. These often involve the preparation of complex starting materials requiring several step syntheses, reducing their attractiveness. Although some methods allow efficient synthesis of 2-substituted oxetanes and azetidines, the 3,3-disubstitution pattern is usually inaccessible by ring closure due to the inherent steric hindrance involved.

[2+2] Cycloaddition is the second most well-known strategy to access *O*- and *N*-four membered rings (Figure 1.10 B). The light-induced Paternò-Büchi reaction between carbonyls and olefins towards oxetanes has been extensively discussed in a series of recent reviews.[71,72] Certain substitution patterns on the oxetane have only been accessed using this reaction such as 3,3-diaryl substituted oxetanes by Xu and Inoue.[73] In comparison, only a few examples of azetidines have been reported using a concerted [2+2] cycloaddition strategy.[24] The aza-Paternò-Büchi reaction is particularly inefficient due to: the decreased photoreactivity of imine precursors, lack of reactivity towards alkenes and poor regioselectivity.[24,25] However, the Schindler group recently developed visible-light mediated photocatalysed intra- and intermolecular aza-Paternò-Büchi reactions between oximes and alkenes (Scheme 1.5).[74] These methods give access to highly complex azetidine scaffolds under mild conditions and short reaction times. The intermolecular procedure is particularly attractive as the products are obtained from readily accessible starting materials. Although the reactions represent highly efficient methods to synthesise interesting azetidines, some limitations remain. Only highly substituted azetidines can be accessed, with only a few examples bearing a substituent on the

3-position for the intermolecular reaction, and only 2 examples were 3,3-disubstituted over the two methodologies. In addition, only cyclic oximes were successful for the intermolecular reaction and simple azetidine rings cannot be prepared.



Scheme 1.5: Visible-light mediated photocatalysed intra- and intermolecular aza-Paternò-Büchi reactions developed by the Schindler group.[74]

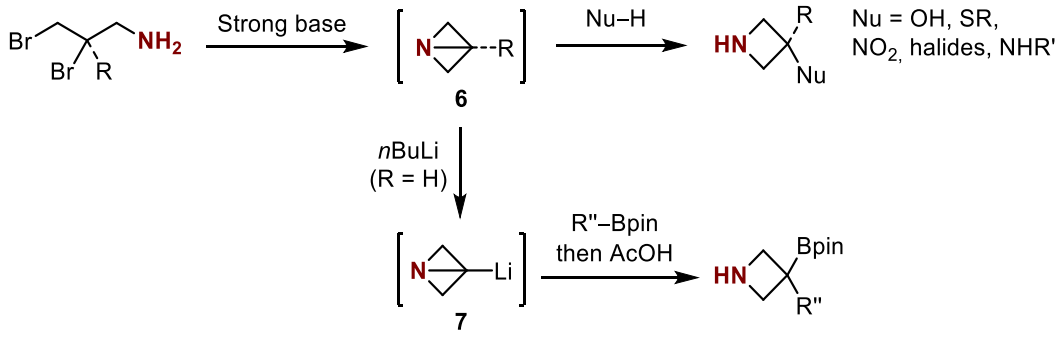
Instead, formal [2+2] cycloadditions are usually applied to the synthesis of β-lactams. Subsequent reduction leads to azetidine rings, which is a much more frequently employed strategy (Figure 1.10.B and C).[24] In this case, the cycloaddition occurs between activated species including: ketene and imine,[75] or isocyanates and olefins,[24] which explains the easier formation of a β-lactam compared to an azetidine ring. However, the use of strong reducing agents can lead to ring opening and limit the functional group tolerance. In addition, the method usually does not allow incorporation of 3,3-disubstituents while requiring high degree of other substitution to overcome regio, site and stereoselectivity issues. These limit the applicability of the method to access simple 3,3-disubstituted oxetanes and azetidines.[24,72]

Cross-coupling reaction: As oxetanes and azetidines attracted attention for their physicochemical properties, more building blocks have become commercially available, including 3-halo azetidines and oxetanes. These were used to prepare a variety of 3-aryloxetanes and azetidines *via* cross–coupling reactions catalysed by nickel, palladium, iron or cobalt catalysis (Figure 1.10 D).[76] This is a powerful strategy to rapidly access libraries of 3-aryloxetanes and azetidines from a single commercial starting material. However, this strategy is not viable for the synthesis of 3-aryl-3-substituted oxetanes and azetidines as cross–coupling reactions between sp^2 and tertiary sp^3 centres remain a well-known challenge.

Reaction with oxetan-3-one: After the improved synthesis of oxetan-3-one **5** by Carreira in 2006, this compound was commercialised and proved to be an important versatile building block for the preparation of 3,3-disubstituted oxetanes (Figure 1.10 E).[45] Addition of organolithium or Grignard reagents led to the synthesis of 3-substituted oxetan-3-ols in very high yields with high diversity in aromatic and alkyl groups that can be incorporated.[45,77] The 3-aryl-oxetan-3-ol products were themselves reactive towards a range of transformations to

displace the alcohol functionality with hydride and chloride,[45] as well as fluoride.[78] Oxetan-3-one **5** can also undergo a Wittig reaction to form oxetane Michael acceptors which can then react with a variety of nucleophile to form 3-substituted-3-alkyloxetanes.[46b] This powerful strategy allows fast generation of diversified 3,3-disubstituted oxetane products from one alkene starting material, and was later applied to the synthesis of spirocyclic azetidines.[79] The functionalisation of oxetan-3-one **5** and oxetane Michael acceptors are currently the only synthetic approaches towards 3,3-disubstituted oxetanes and mainly access 3-substituted-3-alkyl oxetanes.

Strain release strategy: The strain release strategy of azabicyclo[1.1.0]butanes has gained attention recently (Figure 1.10 F). In 1969, Funke reported the first synthesis of various 1-azabicyclo[1.1.0]butane **6** *via* base-mediated ring closure. Reaction of intermediate **6** with HCl and thiophenol gave 3-chloro and 3-sulfanyl azetidine products through cleavage of the central C–N bond and release of the strain (Scheme 1.6).[80]



Scheme 1.6: Synthesis of azetidines *via* strain-release strategies.

Thirty years later the strain release functionalisation of 1-azabicyclo[1.1.0]butane **6** caught the attention of organic chemists who started to exploit this methodology more extensively. From 1993, a series of work on the nucleophilic addition to **6** was published, incorporating alcohols, halides and other thiols groups,[81] as well as nitro group,[82] alkane chains,[83] and more recently amines.[84] Although this is a very attractive divergent method to access different products from a single intermediate, this procedure seemed mainly adapted to 3-monosubstituted azetidines, with only a couple of examples of 3,3-disubstituted azetidines reported by Marchand *et al*.[83] This is mainly due to the challenging synthesis of the starting material, which requires further synthetic steps to incorporate a substituent in the 3–position. In 2019, Aggarwal reported the first and only strain release strategy towards 3,3-disubstituted azetidines (Scheme 1.6).[85] This work reported an unprecedent lithiation of **6** with *n*BuLi to give **7**, which can react with boronic acids to give 1-azabicyclo[1.1.0]butyl boronate complexes. These can in turn undergo 1,2-migration with cleavage of the central C–N bond affording 3-substituted-3-Bpin azetidines. This

method allows incorporation of substituent in the 3 position during the reaction, instead of having it pre-installed.

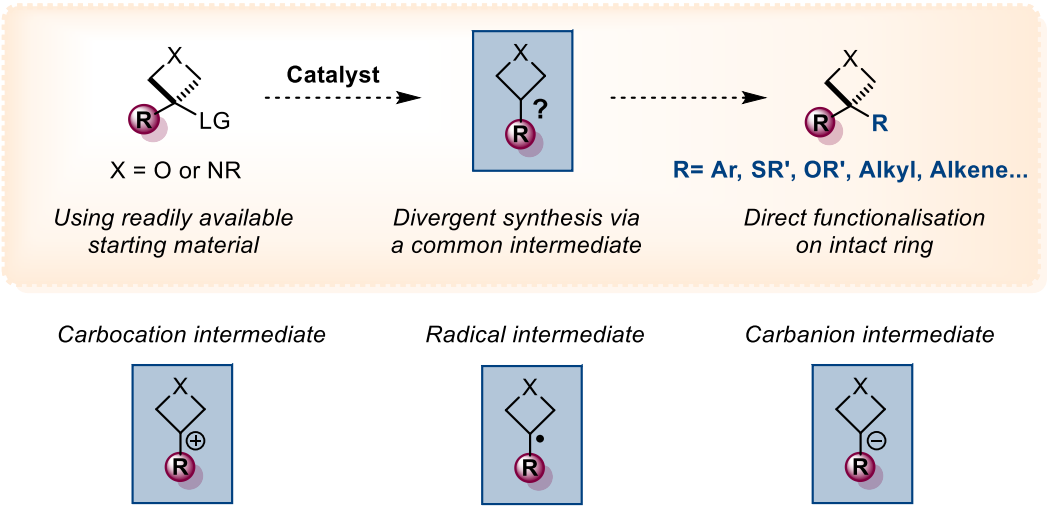
Conclusion: There remains a significant need for the development and study of new 3,3-disubstituted oxetanes and azetidines for medicinal chemistry. Their incorporation and use in drug discovery programmes is limited by the lack of efficient synthetic methodologies. The inherent strained ring, the presence of the heteroatom and the steric bulk generated at the 3-position by two substituents, make their synthesis difficult. However, the recent functionalisation of oxetane Michael acceptors and strain release approaches have provided new 3-substituted-3-alkyl oxetanes and azetidines, and 3-substituted-3-Bpin azetidines respectively, from commercial or synthetically accessible starting materials. These methods are currently the only general ways to access 3,3-disubstituted oxetanes and azetidines, albeit with a restricted substitution pattern. Therefore, the development of new divergent methods to easily and quickly access new 3,3-disubstituted oxetanes and azetidines, with novel substitution patterns, is highly desirable in drug discovery.

2. Project Aims

The research in this thesis aims to develop new 3,3-disubstituted oxetanes and azetidines for drug discovery and is divided in two mains goals:

1) Development of new synthetic methods towards novel 3,3-disubstituted oxetanes and azetidines:

The first goal was to develop divergent methods that would rapidly and easily afford a variety of novel 3,3-disubstituted oxetanes and azetidines. This was envisaged through direct functionalisation on the intact ring of a common reactive intermediate, generated *in situ* (Scheme 1.7). This intermediate will have to be formed from commercially available or readily accessible starting materials, preferentially catalytically to allow mild conditions. This intermediate could be a carbocation, a carbanion or a radical species, and their reactivity with different partners (such as aromatics, thiols, and alkenes) will be investigated to achieve new and currently inaccessible substitution pattern on oxetanes and azetidines. This strategy poses interesting questions on a) the feasibility to form, and b) the behaviour and reactivity of such intermediates, in these strained rings in the presence of oxygen and nitrogen heteroatoms.



Scheme 1.7: Direct functionalisation on the intact azetidine and oxetane rings of an intermediate.

2) Evaluation of the new oxetane and azetidine products for drug discovery:

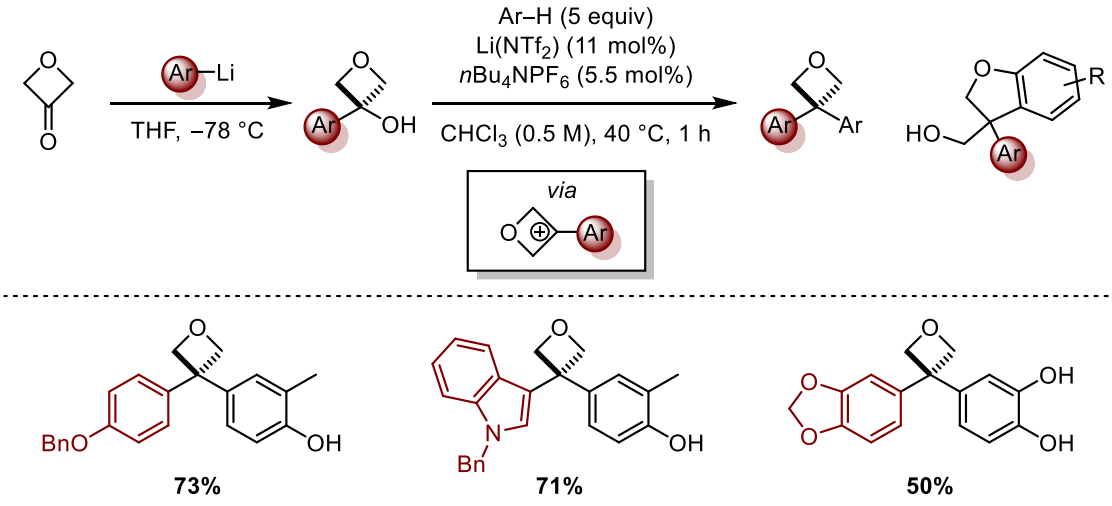
Once the new 3,3-disubstituted oxetanes and azetidines were formed, their physicochemical properties and ADMET profile would be investigated to evaluate their suitability for incorporation in drug discovery programmes.

Prior investigation within the Bull group focused on the formation of oxetanyl carbocation species, which led to the first methodology to synthesise 3,3-diaryloxetanes (section 3.1)[50], and 3-sulfanyl-oxetanes (section 4.2)[51]. The next chapter will present the evaluation of 3,3-diaryloxetanes for medicinal chemistry, which is the starting point of this investigation.

3. Evaluating 3,3-Diaryloxetanes as New Bioisosteres

3.1 Synthesis of 3,3-Diaryloxetanes *via* Oxetanyl Carbocation

Catalytic functionalisation of π-activated alcohols has emerged as a powerful and green method for alkylation. Carbocation species are formed from readily accessible alcohol starting materials, in an S_N1 reaction, and generating water as the only by-product.[86,87] In 2016, the Bull group in collaboration with Pfizer adopted this strategy to form oxetanyl carbocations *in situ* from π-activated 3-aryl-oxetan-3-ols.[50,88] In this study, a screen of catalysts identified $Li(NTf_2)$, together with nBu$_4$NPF$_6$, as the optimum catalyst to promote the carbocation formation while overcoming: 1) the strain of the ring, 2) competitive ring opening followed by polymerisation, 3) the electron-withdrawing and Lewis-basic effects of the oxygen atom of the oxetane ring. Friedel–Crafts reactions on these carbocations with phenols and electron-rich arenes gave 3,3-diaryloxetanes which is the first method to access these new motifs (Scheme 3.1). In addition, competitive 2,3-dihydrobenzofuran products are also formed in this transformation, which are easily separable from 3,3-diaryloxetanes. This occurs when the Friedel–Crafts reaction takes place at the *ortho* position of phenols followed by ring opening of the oxetane with the phenolic OH.



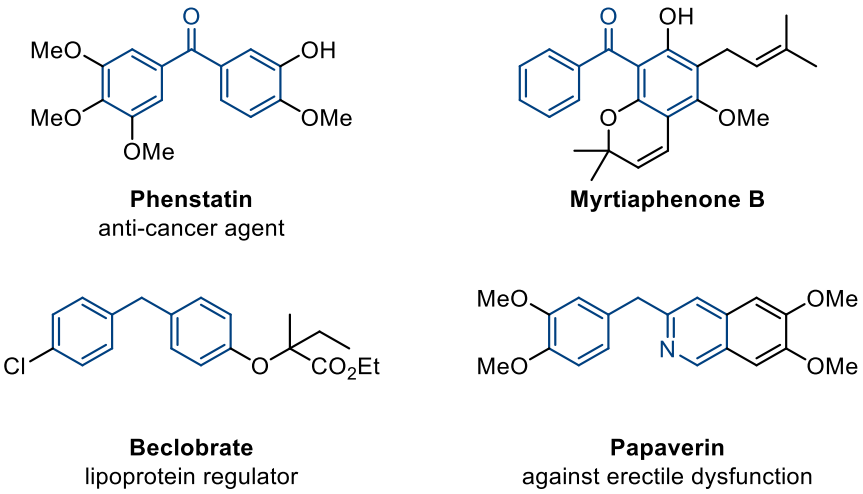
Scheme 3.1: Bull group synthesis of 3,3-diaryloxetanes *via* oxetanyl carbocation intermediate.

The Bull group and Pfizer were particularly interested in these oxetane motifs as potential isosteres for benzophenones and other diarylmethane groups, and this is the starting point of this thesis.

3.2 3,3-Diaryloxetanes as Proposed New Isosteres

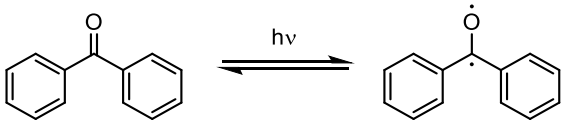
3.2.1 Importance of Diaryl-Ketones and Diarylmethanes in Bioactive Compounds

Benzophenones (or diarylketones) and 1,1-diarylmethanes are prevalent motifs in natural products and pharmaceuticals displaying diverse biological activities (Scheme 3.2).[89]



Scheme 3.2: Examples of natural products and pharmaceuticals containing benzophenones and 1,1-diarylmethanes.

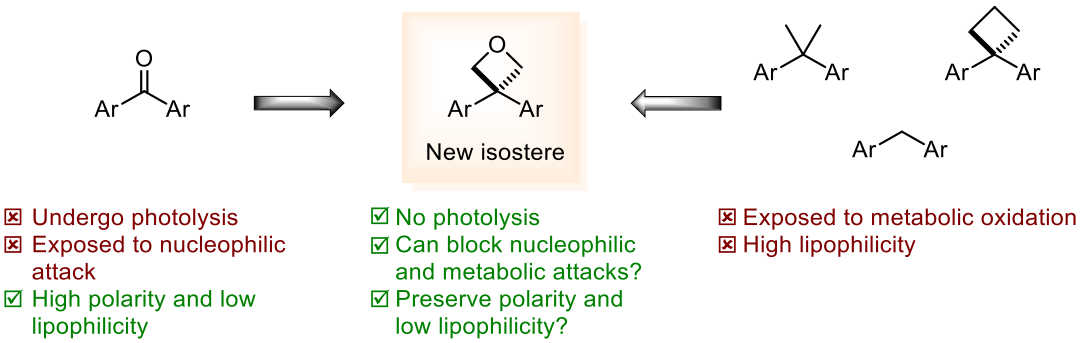
Benzophenones have attracted attention for their ability to undergo photolysis giving a di-radical species (Scheme 3.3), which was first used in 1974 to form photo-induced cross-link to the α-carbon of glycine.[90,91] Benzophenones have been shown to be more suitable than other arylketones for biological application such as protein labelling as their photolysis occurs under milder conditions (λ > 320 nm) limiting biological damage.[90] Although benzophenones are useful tools for photo-induced cross linking, their facile photolysis can generate side reactions and make them easily metabolised within the body. In addition, the electrophilic ketone is exposed to biological nucleophilic attack which limits their use in medicinal chemistry. On the other hand, diarylmethanes can suffer from metabolic oxidation due to their acidic benzylic position.[3] Therefore, the development of suitable isosteres for benzophenones and diarylmethanes, that would preserve desirable physicochemical properties while preventing nucleophilic and metabolic attacks, is highly desirable.



Scheme 3.3: Photolysis of benzophenone.

3.2.2 Hypothesis: 3,3-Diaryloxetanes as Replacement Groups

In collaboration with Pfizer, the Bull group proposed 3,3-diaryloxetanes as new isosteres for diarylketones and diarylmethanes (Scheme 3.4). The term isosteres refer to atoms or groups of atoms that possess similar molecular shape, volume, electronics and physicochemical properties.[92] The use of isosteres in medicinal chemistry is a tactical approach to replace a problematic functionality with another to enhance physicochemical properties, reduce metabolism and eliminate toxicity.[92] The introduction of 3,3-diaryloxetanes in place of benzophenones and diarylmethanes could block photolysis reaction as well as nucleophilic and metabolic attacks to occur. In addition, these new oxetane motifs present high Fsp^3 character and are polar groups, which could improve physicochemical properties. Furthermore, *gem*-dimethyl groups are commonly used to replace methylene moiety albeit with detrimental increase in lipophilicity.[3] Therefore, in this study 3,3-diaryloxetanes could be potential replacement groups for 1,1-diaryl-*gem*-dimethyl and 1,1-diarylalkanes more generally (Scheme 3.4), as the polar oxetane moiety could improve the lipophilicity of such molecules. In order to prove our hypothesis and establish 3,3-diaryloxetanes as suitable isosteres, a matched molecular pair analysis (MMPA) was carried out.



Scheme 3.4: 3,3-Diaryloxetanes as proposed isosteres for diarylketones and diarylalkanes.

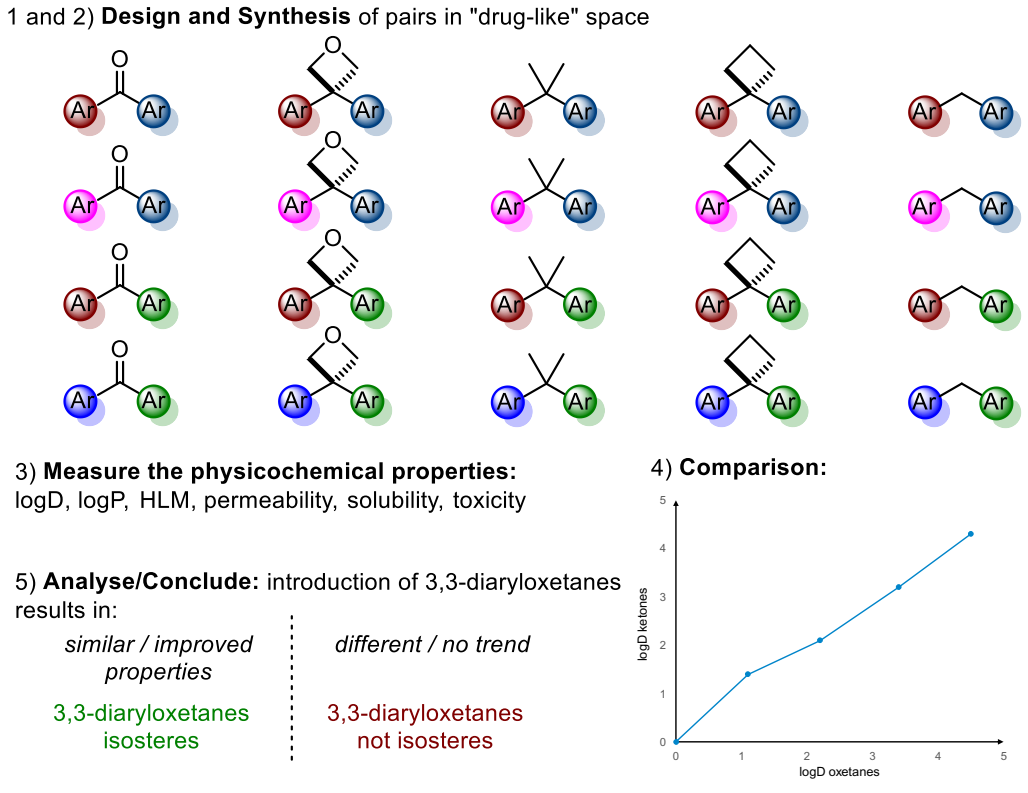
3.2.3 Method: Matched Molecular Pair Analysis

The method of MMPA is used to establish isosterism and consists of: a) comparing an initial compound and the new compound as "matched pair" linked by a single structural modification, b) looking at the effects of this structural change on physicochemical properties.[93] The new and the initial structures will be considered isosteres if the initial compound and the new compound have similar or enhanced physicochemical properties. A minimum of four matched pairs is necessary.[93]

This chapter aims to (Scheme 3.5):

1) Design pairs of diarylketones and 3,3-diaryloxetanes on one hand, and 1,1-diarylalkanes and 3,3-diaryloxetanes on the other hand. The diarylketone and diarylalkane motifs correspond to the initial structures, while the incorporation of 3,3-diaryloxetane motifs is the single structural change. These pairs will be designed to have "drug-like" properties, with MW < 500, and logP < 5 for instance (see section 1.1.2.2).
2) Synthesis of the pairs
3) Measure the physicochemical properties of each compound, including lipophilicity, solubility, permeability, metabolic stability, and toxicity.
4) Compare the effect of replacing the initial motifs with 3,3-diaryloxetanes on these physicochemical properties.
5) Analyse the results: two types of conclusion could be made based on whether introduction of 3,3-diaryloxetanes results in:
    - similar and/or improved properties. (Then 3,3-diaryloxetanes are suitable isosteres).
    - adverse effect on properties or without clear trend. (Then 3,3-diaryloxetanes cannot be considered as isosteres).

Additionally, 3,3-diaryloxetanes are new motifs and their physicochemical properties and ADMET profile are unknown. This MMPA will allow the collection of these data and evaluate the potential of these new motifs for drug discovery on their own right.



Scheme 3.5: Planned MMPA for evaluating 3,3-diaryloxetanes as isosteres.

3.3 Synthesis of Matched Molecular Pairs

3.3.1 Design of the Pairs

Pfizer designed more than 150 compounds with “drug-like” properties, having MW < 500 and 0.5 < clogP < 5. Sixteen compounds were selected, forming 6 pairs of diarylketones and 3,3-diaryloxetanes, 3 pairs of 1,1-diarylalkanes and 3,3-diaryloxetanes respectively, as well as additional examples of 3,3-diaryloxetanes (Figure 3.1). The pairs differ by a single structural change on the central carbon defined by a blue or black circle in figure 3.1, which can be an oxetane (a), ketone (b), methylene (c), *gem*-dimethyl (d) or cyclobutane (e). The physicochemical properties for these compounds were calculated by Pfizer (see Appendix, Table 10.1). The MW of these compounds are between 297 and 423, while the lipophilicity was predicted to sit between 1.44 and 4.92 with an average of clogP = 4.12 and clogD = 3.03. Only *gem*-dimethyl **12d** and cyclobutane **12e** were predicted to have a lipophilicity higher than 5. Based on calculated HLM (cHLM), these compounds are not predicted to be sensitive to metabolic oxidation, although their cHLM remained elevated. On the other hand, the calculated passive permeability (cRRCK) seemed to strongly vary from one compound to the other. Pleasingly, the PSA for these molecules was found to be below 55, which fits into the “rule of 3” defined by Jhoti.[17]

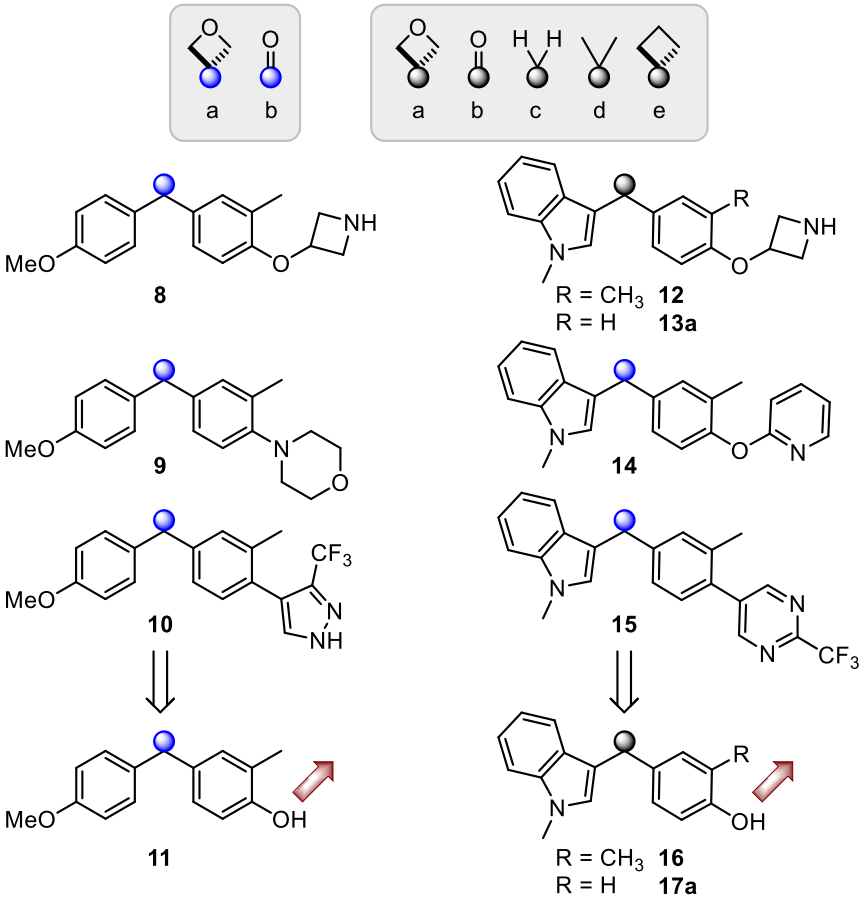


Figure 3.1: Designed pairs.

These compounds were also chosen based on the feasibility of their synthesis, which was envisaged by derivatisation of three main phenol cores: **11**, **16** and **17a** (Figure 3.1). Although phenols are usually not incorporated into drug discovery programmes due to their potential toxicity, these phenol building blocks represent themselves additional pairs for the study.

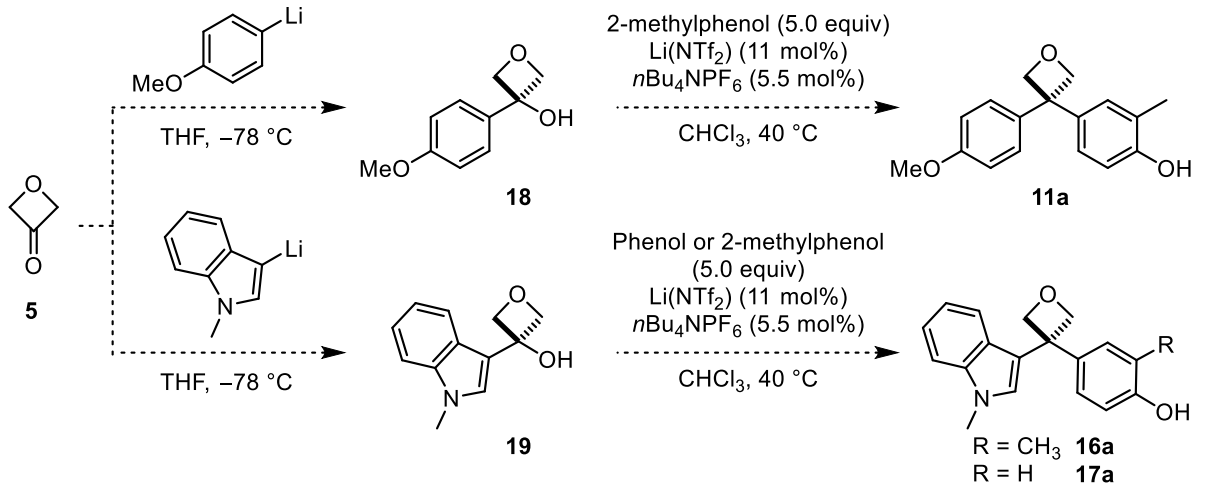
In total, 24 compounds were to be synthesised forming: 8 pairs of diarylketones and 3,3-diaryloxetanes; 6 pairs of 1,1-diarylalkanes and 3,3-diaryloxetanes; as well as two additional examples of 3,3-diaryloxetanes (**13a** and **17a**). A variety of functionalities such as phenols, aromatics and heteroaromatics, with electron-rich or electron-poor groups were incorporated.

3.3.2 Synthesis of 3,3-Diaryloxetane and Diarylketone Pairs

The synthetic work in some part of this section was carried out in collaboration with MRes student Yujie Ding,[94] as indicated.

*3.3.2.1 Synthesis of Phenolic Oxetane Building Blocks **11a**, **16a** and **17a***

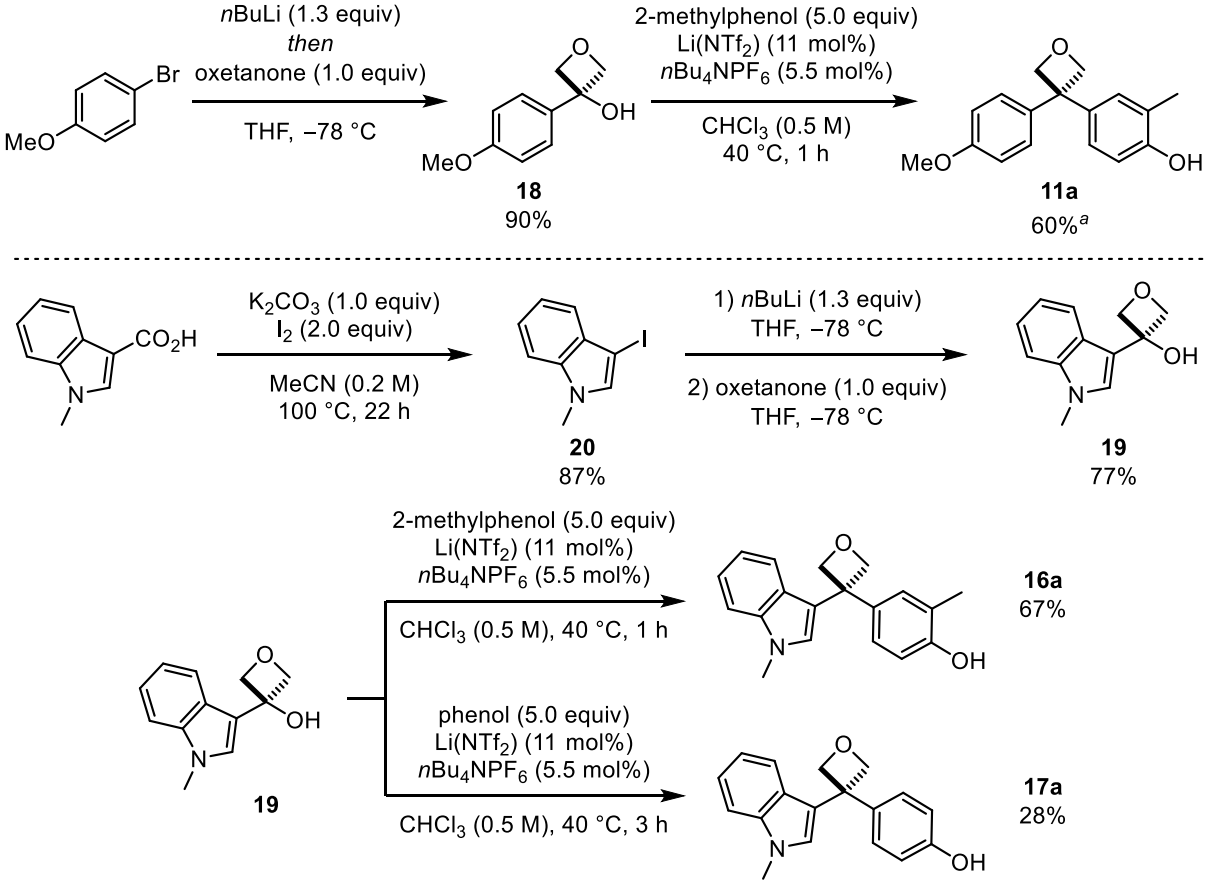
The synthesis of 3,3-diaryloxetane building blocks **11a**, **16a** and **17a** was envisaged using the lithium-catalysed Friedel–Crafts reaction developed by the Bull group,[50] using 2-methylphenol or phenol as nucleophiles with either 3-methoxyphenyl-oxetan-3-ol **18** or 3-methylindolyl-oxetan-3-ol **19** (Scheme 3.6).



Scheme 3.6: Proposed route to oxetane building blocks **11a**, **16a** and **17a**.

The synthesis of oxetanol **18** has been previously described.[50] 4-Methoxyphenyllithium was pre-formed, adding *n*BuLi to 4-bromoanisole, and then reacted with commercial oxetan-3-one **5** to give oxetanol **18** in 90% yield (Scheme 3.7). Friedel–Crafts alkylation of 2-methylphenol with oxetanol **18** afforded oxetane **11a** in 60% yield. On the other hand, the synthesis of methylindole oxetanol **19** was more challenging. 3-Halo-methylindoles are not commercially available and had first to be made. Bromination of methylindole using DBDMH,[95] or HBr and DMSO,[96] gave 3-bromo-1-methylindole in low yield or as a mixture with dibrominated indole.

In addition, 3-bromo-1-methylindole was found rather unstable, which made its synthesis and use tedious. During the course of this work, Larrosa described the synthesis of 3-iodo-1-methylindole **20** using a metal-free decarboxylative iodination of arenes.[97] Using this method, **20** was obtained in 87% yield in nearly 2.7 g. Addition of *n*BuLi followed by oxetanone **5** afforded oxetanol **19** in 77% yield. Friedel–Crafts reaction of **19** with 2-methylphenol gave oxetane **16a** in 67% yield, and 28% of **17a** could be obtained using phenol, due to side products formation.

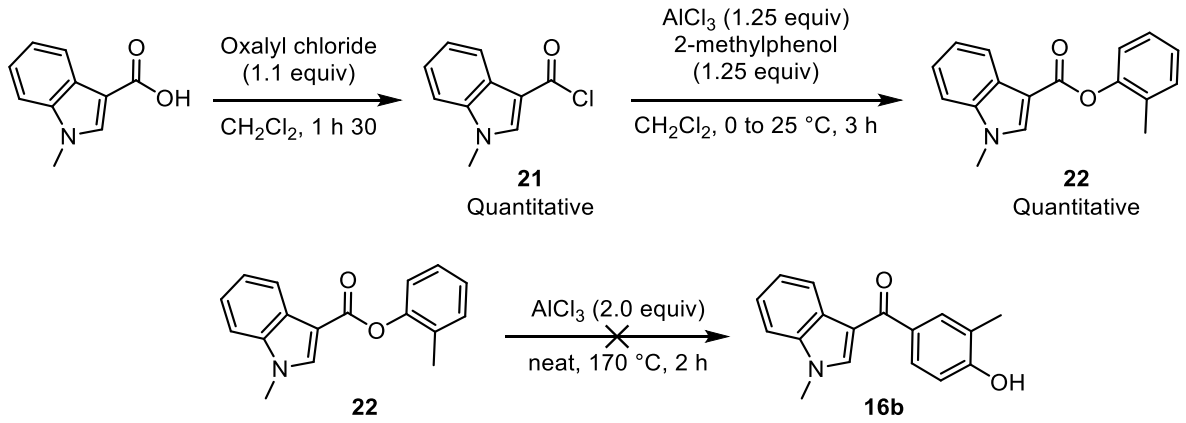


Scheme 3.7: Synthesis of oxetane building blocks **11a**, **16a** and **17a**. [a] Synthesised by Yujie Ding.

*3.3.2.2 Synthesis of Phenolic Ketone Building Blocks **11b** and **16b***

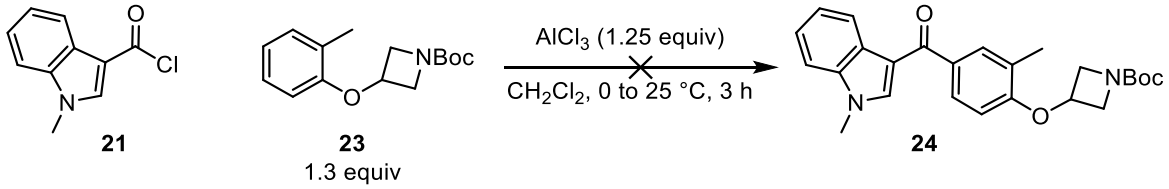
Synthesis of indole-containing ketone **16b**

Synthesis of indole containing ketone **16b** was envisaged by Friedel–Crafts acylation of 2-methylphenol (Scheme 3.8). Acyl chloride **21** was made from the commercial carboxylic acid using oxalyl chloride. Reaction of **21** with 2-methylphenol in presence of $AlCl_3$ in CH_2Cl_2 at 0 °C gave ester **22** in quantitative yield instead of the desired ketone **16b**. A Fries rearrangement was attempted to convert ester **22** into the desired **16b**, however this mainly led to degradation (Scheme 3.8).



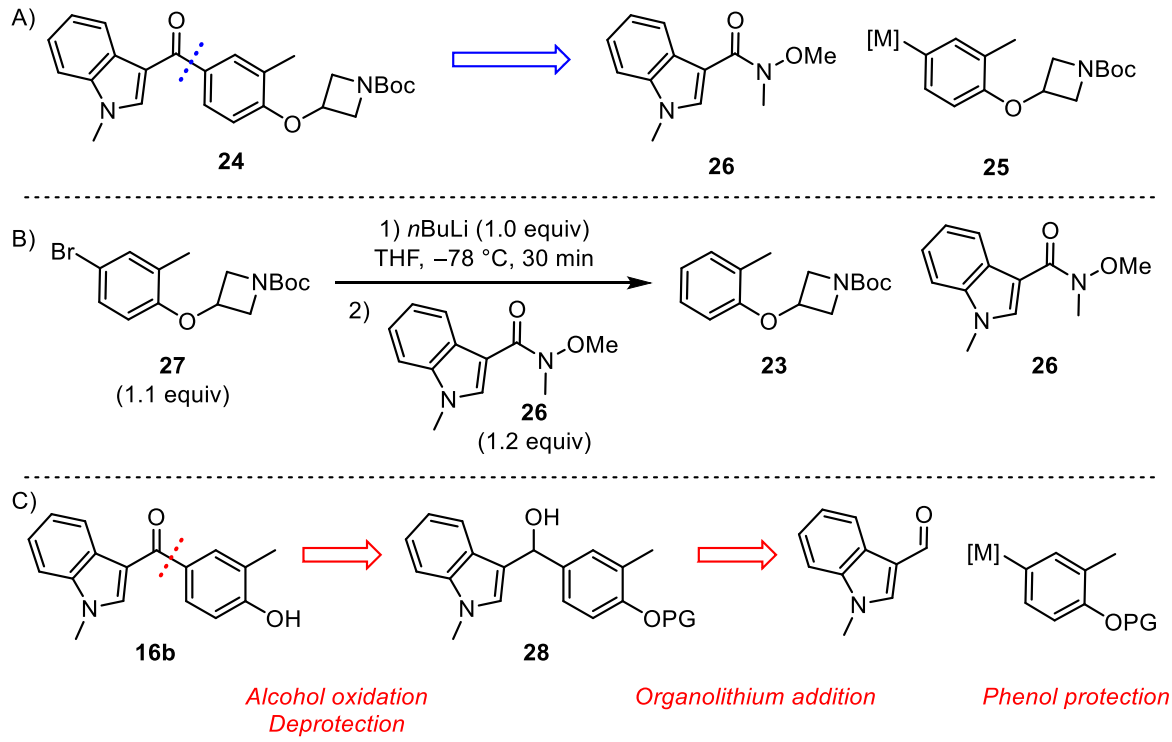
Scheme 3.8: Attempted synthesis of ketone **16b** by Friedel–Crafts acylation and Fries rearrangement.

2-Methylphenol was instead masked with a Boc-protected azetidine moiety by nucleophilic substitution, giving arene **23**. This was subjected to the Friedel–Crafts acylation but did not form ketone **24** (Scheme 3.9). The Boc protecting group was unstable in presence of $AlCl_3$ and the azetidine ring degraded under the reaction conditions.



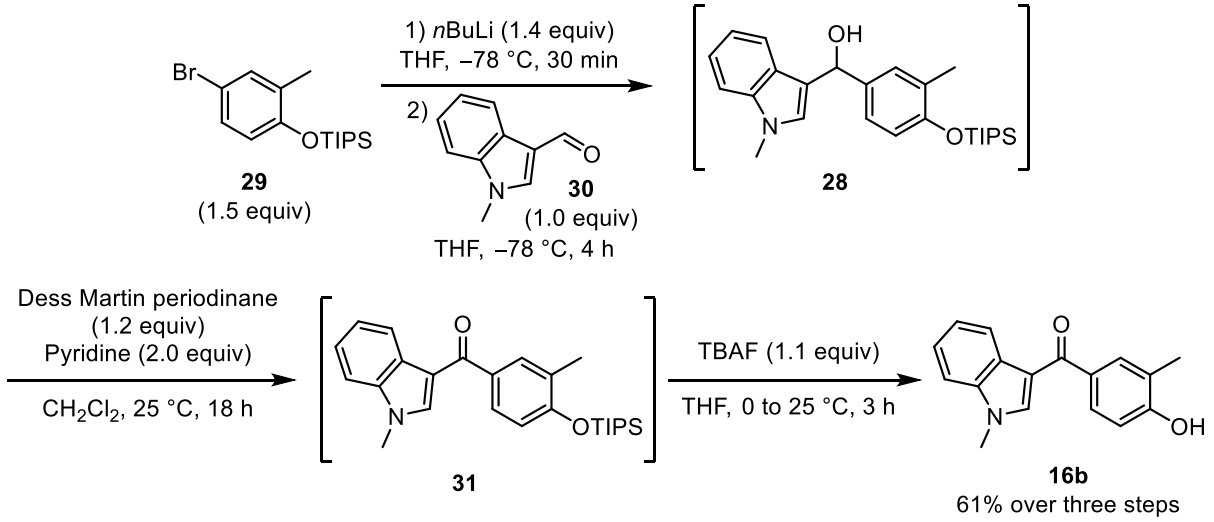
Scheme 3.9: Attempted synthesis of ketone **24** by Friedel–Crafts reaction of acyl chloride **21** and arene **23**.

Therefore the direct synthesis of ketone **12b** from intermediate **24** was undertaken by addition of organometallic **25** to Weinreb amide **26** (Scheme 3.10, A). Amide **26** was easily accessed from the commercial carboxylic acid, while the azetidine ring was installed by nucleophilic substitution with 2-methyl-4-bromophenol to give bromo-aryl **27** (Scheme 3.10, B). Addition of *n*BuLi to bromoaryl **27** followed by amide **26**, was expected to give the desired ketone **24**. Surprisingly, amide **26** was recovered after reaction while arene **23** was obtained. This indicated that bromide **27** underwent lithium-bromide exchange but did not react with amide **26** due to its lack of electrophilicity in presence of highly electron-donating indole group. Other strategies involving addition of organolithium to Weinreb amides were envisaged, but these are often difficult to control and multiple addition could lead to alcohol products. The formation and oxidation of an alcohol intermediate **28** was instead considered, as this would involve a four step synthesis from inexpensive starting materials and straightforward transformations (Scheme 3.10, C).



Scheme 3.10: Synthesis of **12b** and **16b** by addition of organometallic to either Weinred amide (A and B) or to aldehyde followed by oxidation (C).

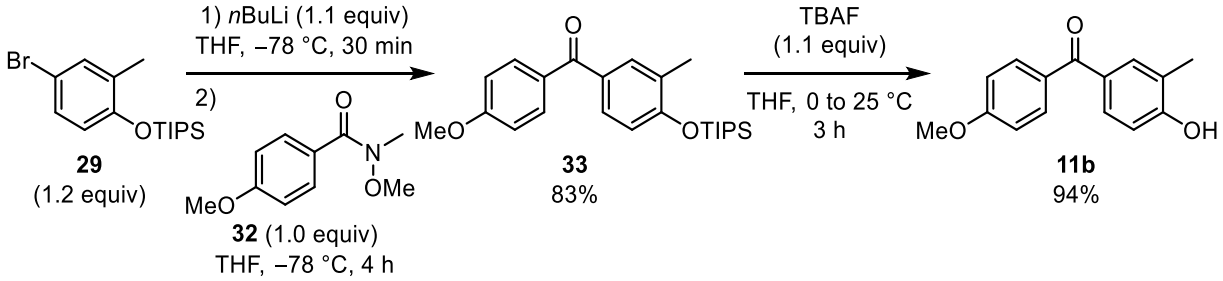
TIPS-protected bromo phenoxy **29** was easily made under standard conditions (Scheme 3.11). While lithium-bromide exchange with *n*BuLi occurred smoothly, the reaction of the corresponding organolithium with commercial 1-methylindole-3-carboxaldehyde **30** was slow at –78 °C. Similarly to Weinreb amide **26**, aldehyde **30** is electron rich and required longer reaction time to reach completion. In addition, alcohol **28** was found to be highly unstable on silica and under air over time, and had to be used quickly after work up. The oxidation of **28** was also challenging and standard conditions employing MnO_2 were inefficient. Switching to Dess-Martin periodinane as oxidant initially produced trace amounts of ketone **31** with low recovery of the starting material **28**. The Dess-Martin periodinane reagent releases two equivalents of acetic acid during the oxidation process, which could degrade alcohol **28**. Addition of two equivalents of pyridine as a base prevented loss of alcohol **28** and ketone **31** was afforded successfully. TIPS protected ketone **31** could not be purified and an impurity formed under the oxidation step remained. However, subjection of the mixture to TBAF deprotection produced building block **16b** cleanly in 61% yield over three steps.



Scheme 3.11: Synthesis of building block **16b** by alcohol formation followed by oxidation.

Synthesis of *para*-methoxyphenyl-containing ketone **11b:**

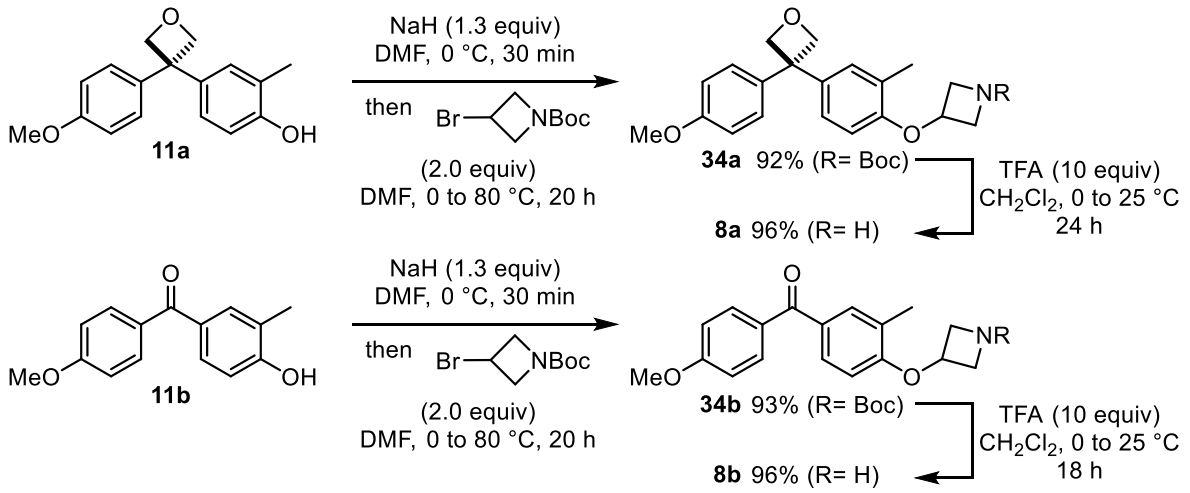
para-Methoxyphenyl (PMP) ketone **11b** being less electron-rich than **16b**, was synthesised in excellent yield by simple addition of an organolithium to Weinreb amide **32** followed by deprotection (Scheme 3.12).



Scheme 3.12: Synthesis of ketone building block **11b**.

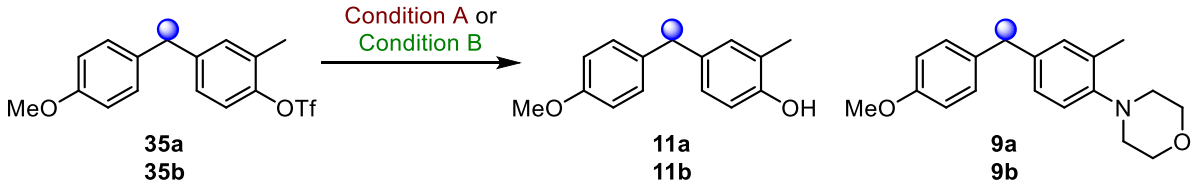
*3.3.2.3 Derivatisation of para-Methoxyphenyl Building Blocks **11***

With oxetane and ketone building blocks **11a** and **11b** available, pairs **8–10** (a and b) were prepared taking advantage of the phenol function. Alkylation of phenols **11a** and **11b** occurred smoothly in presence of NaH and Boc-protected 3-bromoazetidine, giving Boc-protected oxetane **34a** and ketone **34b** in 92% and 93% yield respectively (Scheme 3.13). Interestingly, Boc deprotection under strong acidic conditions using TFA resulted in **8a** and **8b** both in 96% yield, indicating the high stability of 3,3-diaryloxetanes under both strong basic and acidic conditions.



Scheme 3.13: Synthesis of pair **8** (a and b).

Triflation of phenols **11a** and **11b** occurred in high yield (Scheme 3.14). These were then used in a cross–coupling reaction with morpholine. In 2000, Buchwald developed conditions to install a morpholine group (condition A, Table 3.1) using a combination of $Pd(OAc)_2$ and JohnPhos as ligand in THF at 80 °C.[98]



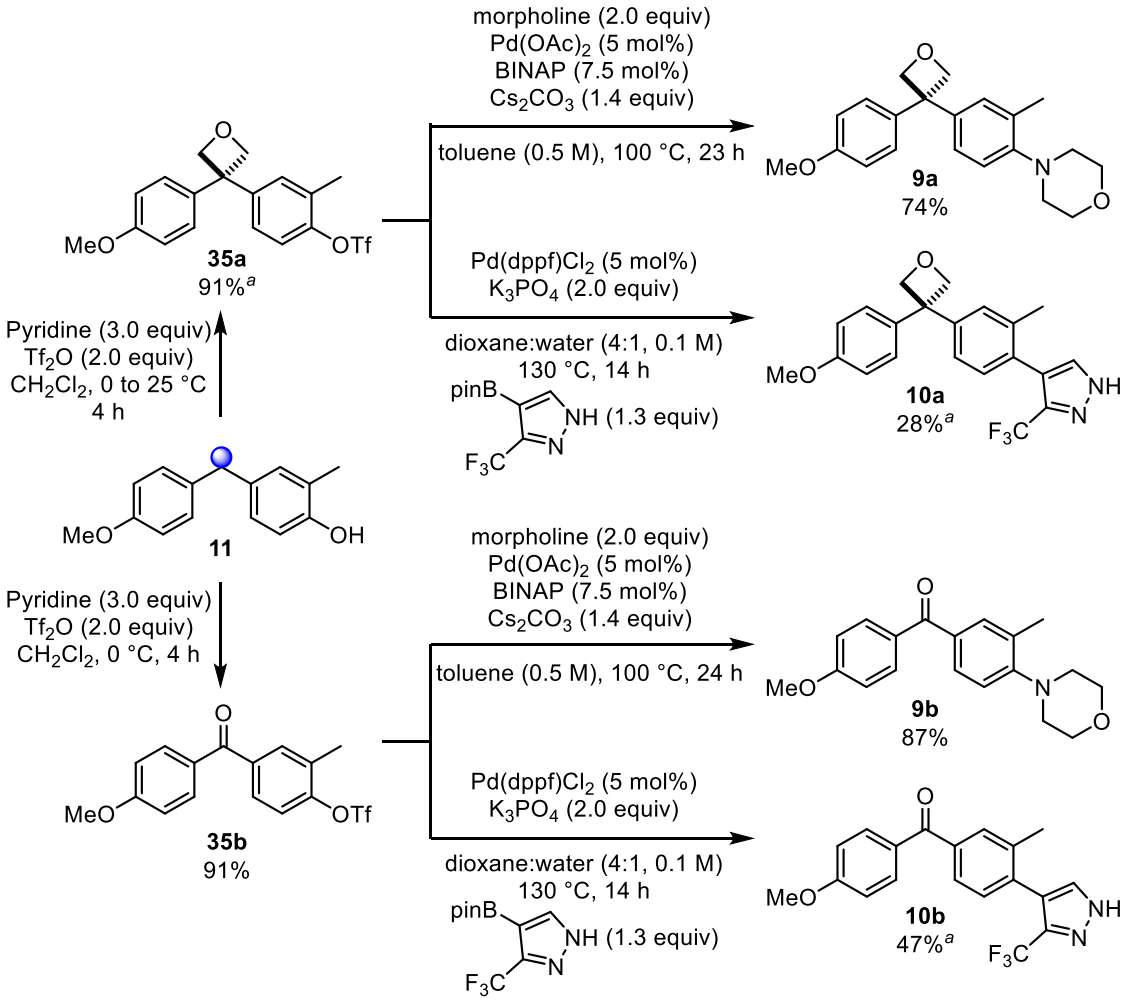
Triflate		Condition	Ratio 35/11/9[a]	Yield 9 (%)[b]
	**35a**	A	66/17/17	5
	**35b**	A	32/55/13	10
	**35a**	B	19/0/81	81 (74)[c]
	**35b**	B	0/0/100	100 (87)

Table 3.1: Optimisation for the synthesis of morpholines **9a** and **9b**, using triflates **35a** or **35b** as limiting reagent. Conditions A: morpholine (1.4 equiv), $Pd(OAc)_2$ (1 mol%), JohnPhos (2 mol%), K_3PO_4 (1.4 equiv), THF (0.5 M), 80 °C.[98] Condition B: morpholine (2.0 equiv), $Pd(OAc)_2$ (5 mol%), BINAP (7.5 mol%), Cs_2CO_3 (1.4 equiv), toluene (0.5 M), 100 °C.[99] Ratio determined by ^1H NMR spectroscopy. [b] Yield determined by ^1H NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard. [c] Yields in bracket correspond to isolated yields.

Applying conditions A on triflate **35a** and **35b** gave only 10% and 5% yield of desired products **9a** and **9b** (entry 1 and 2, Table 3.1). In addition, triflates **35** and phenols **11** were also

recovered in: 66/17/17 ratio (triflate **35a**/phenol **11a**/product **9a**) for oxetane and 32/55/13 (triflate **35b**/phenol **11b**/product **9b**) for ketone. In 1997, Buchwald also observed the formation of phenol derivatives when using NaO*t*Bu as a base in the reaction.[99] NaO*t*Bu was suspected to act as nucleophile attacking the triflate group leading to phenol side products. This competitive reaction may occur because of slower reductive elimination due to: a) steric group in *ortho* position hindering the triflate, or b) when an electron-withdrawing group is present on the *para* position. This is the case with triflate **35a** and **35b**, hindered by the methyl group in *ortho* position. The Buchwald group used a bidentate ligand BINAP to accelerate the rate of the reductive elimination compared to the side reaction.[99] Under these conditions (condition B, entry 3 and 4, Table 3.1), the coupling of oxetane and ketone triflates **35** with morpholine were successful and products **9a** and **9b** were obtained in 74% and 87% isolated yield, with no further side products (Scheme 3.14).

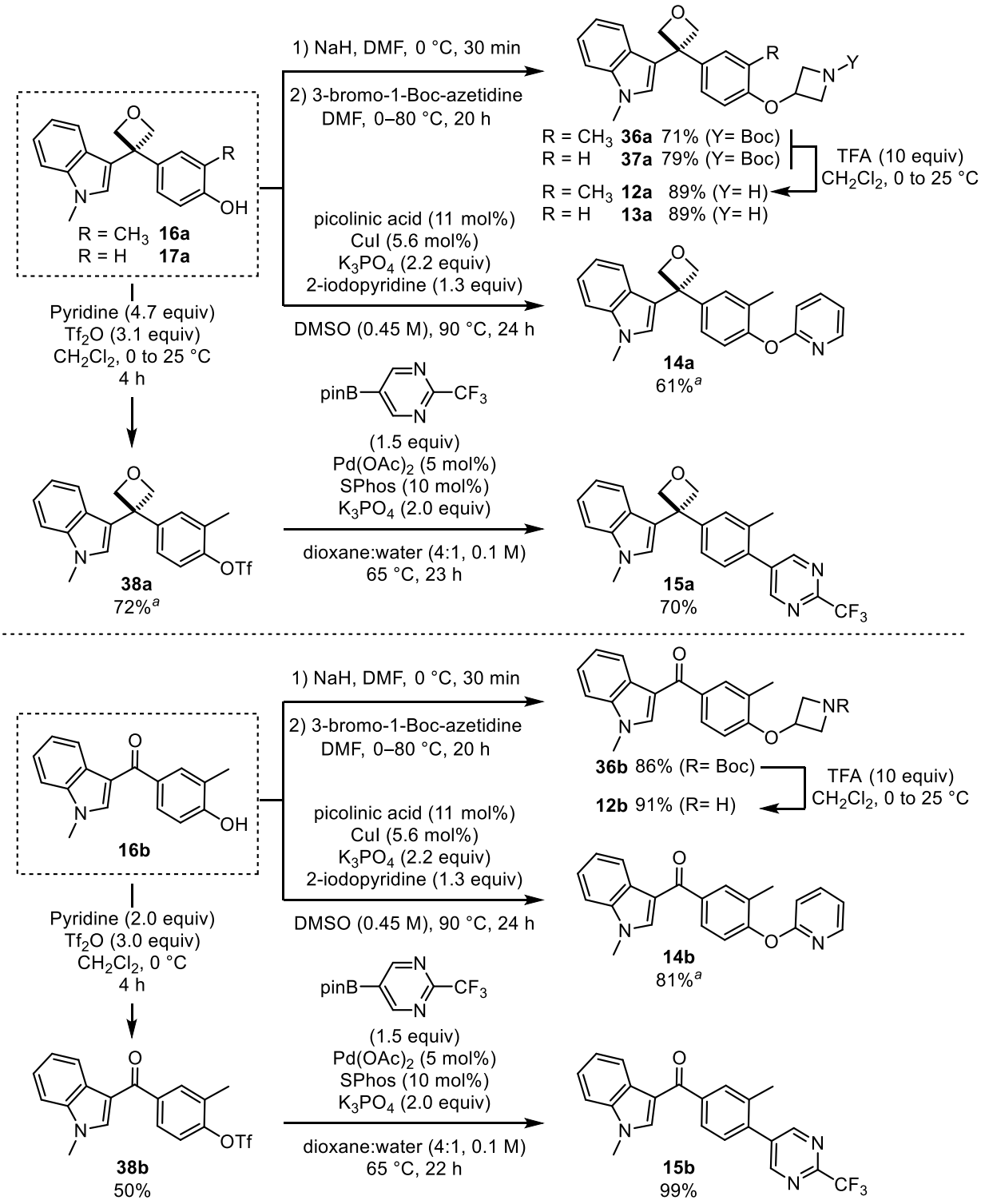
Finally, the pair **10** was synthesised by Yujie Ding who installed a pyrazole using a Suzuki–Miyaura cross–coupling reaction, giving **10a** and **10b** in 28% and 47% yield respectively (Scheme 3.14).[94]



Scheme 3.14: Synthesis of **9–10** (a and b).[a] Synthesised by Yujie Ding.

3.3.2.4 *Derivatisation of 1-Methylindole Building Blocks **16** and **17**.*

Pairs **12**–**15** were also synthesised by derivatisation of the phenol functionality from building blocks **16a/b** and **17a** (Scheme 3.15).



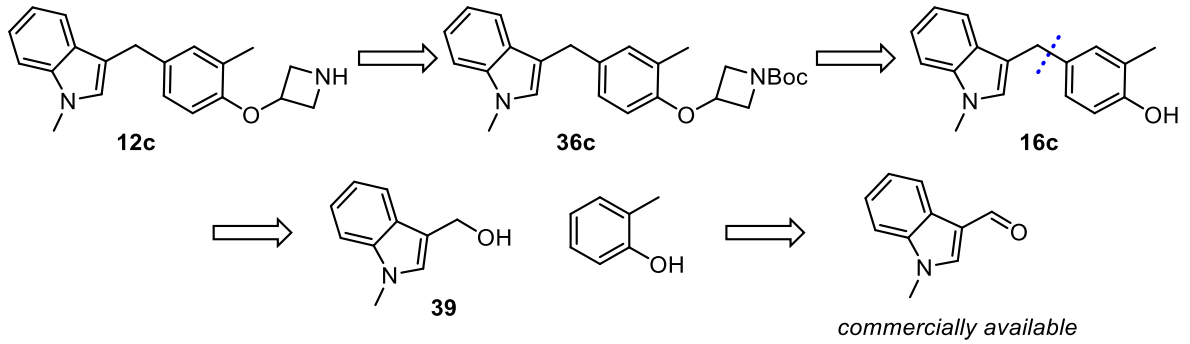
Scheme 3.15: Synthesis of **12–15** (a and b). [a] Synthesised by Yujie Ding.

Azetidines **12a/b** and **13a** were all made in excellent yields from *O*-alkylation of the corresponding phenols (**16a/b**, or **17a**) followed by TFA-mediated Boc-deprotection. Yujie Ding synthesised oxetane **14a** and ketone **14b** in 61% and 81% yield using a copper–catalysed Ullman cross–coupling reaction between the corresponding phenols and 2-iodopyridine.[100] Phenols **16a** and **16b** were triflated (**38**) and used in Suzuki–Miyaura cross–coupling to achieve pyrimidines **15a** and **15b** in 70% and 99% yield.

3.3.3 Synthesis of 1,1-Diarylalkane Pairs

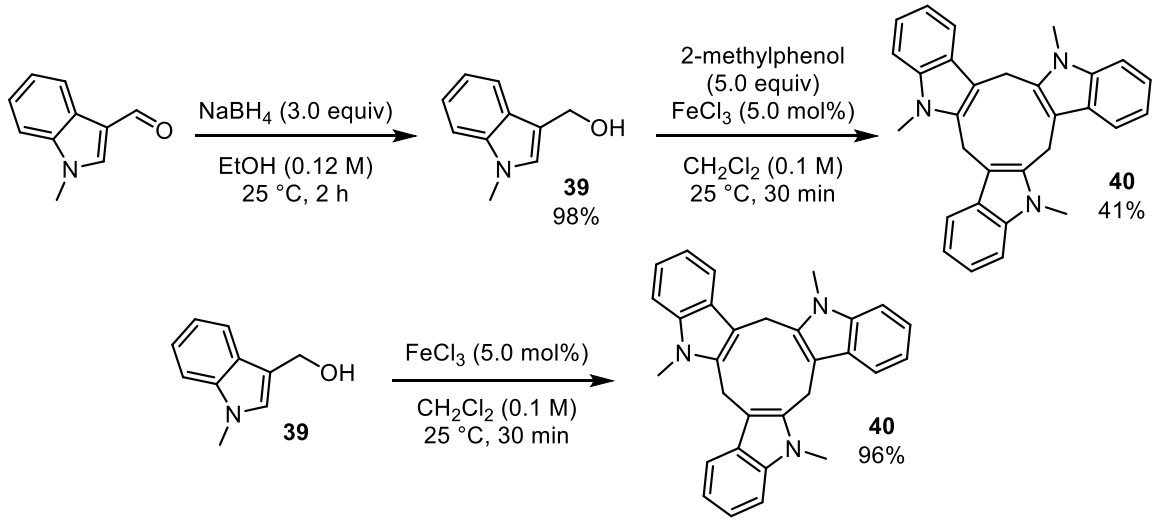
*3.3.3.1 Synthesis of Diarylmethanes **16c** and **12c***

Retrosynthetically, diarylmethanes **12c** can be made similarly to **12a** and **12b** from phenol **16c** after *O*-alkylation and deprotection steps (Scheme 3.16). This phenol intermediate could be accessed from indole-3-methanol **39** and 2-methylphenol using a Friedel–Crafts reaction, and alcohol **39** could be made from reduction of the corresponding commercial aldehyde.



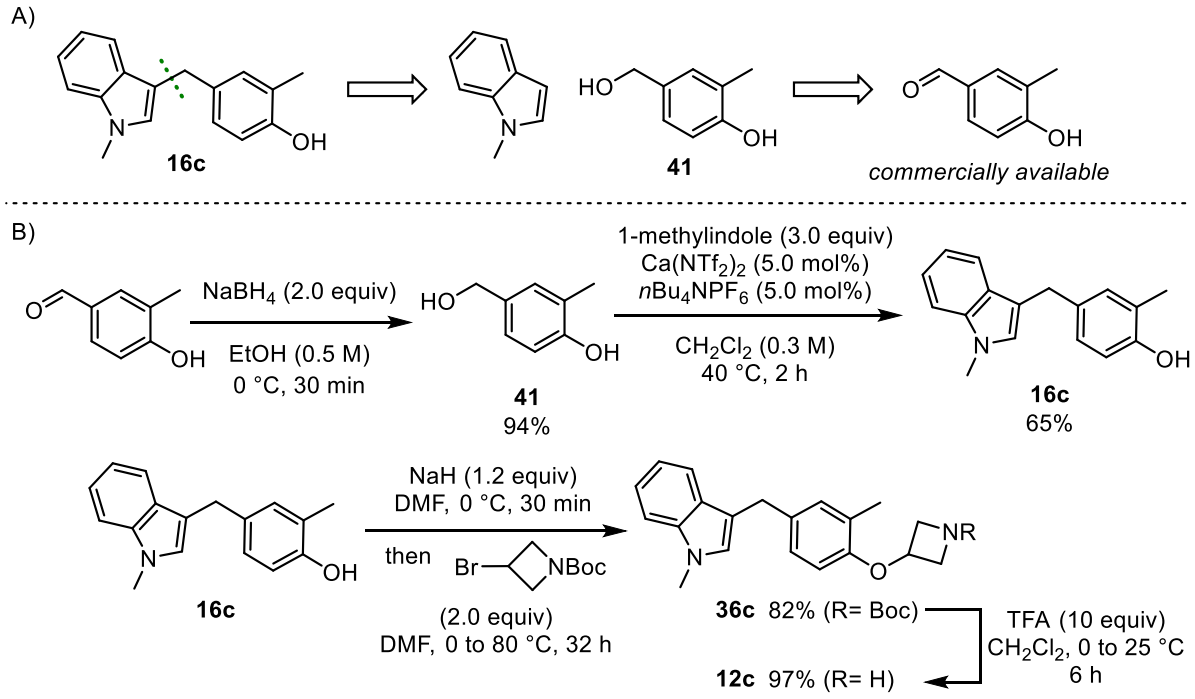
Scheme 3.16: Retrosynthesis of **12c**.

However the forward synthesis was not successful. Alcohol **39** was obtained in 98% yield from commercial aldehyde after reduction with $NaBH_4$, and was highly unstable (Scheme 3.17). Subjecting **39** to $FeCl_3$-catalysed Friedel–Crafts reaction with 2-methylphenol as nucleophile gave indolocyclotriveratrylene **40** in 41% yield. This is the result of trimerization of alcohol **39** under acidic condition, which was previously described by Santoso *et al*. using PTSA as catalyst.[101] Subjecting alcohol **39** to the same $FeCl_3$-catalysed conditions without nucleophile gave 96% yield of **40** without requiring purification.



Scheme 3.17: Attempt towards the synthesis of **16c**, subjecting alcohols **39** to Friedel–Crafts reaction.

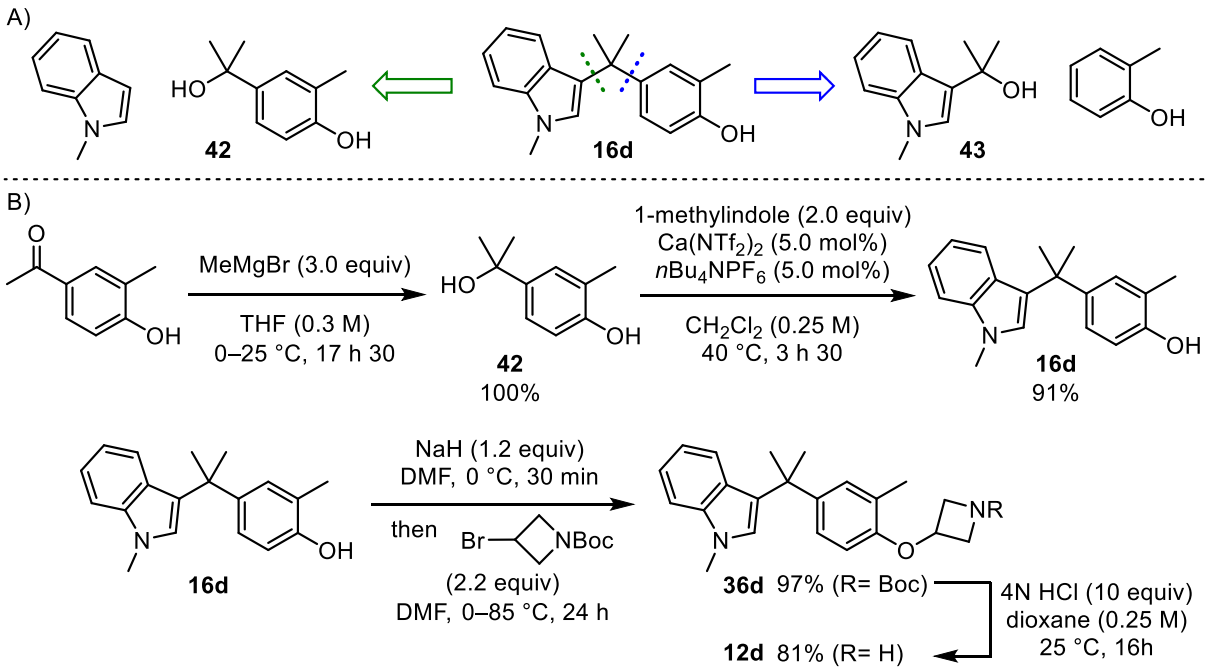
The retrosynthesis of intermediate **16c** was then revised, and **16c** can be instead disconnected between the benzylic carbon and the indole ring to start with alcohol **41** (Scheme 3.18, A). Alcohol **41** was easily accessed from reduction of commercial aldehyde (Scheme 3.18, B). Friedel–Crafts alkylation of aromatics with benzylic alcohols has been previously reported using $FeCl_3$,[102] $Ca(NTf_2)_2$[103] and $Li(NTf_2)$[50], and these three catalyst systems were tested for the reaction of alcohol **41** with 3 equivalents of 1-methylindole in CH_2Cl_2. $Ca(NTf_2)_2$ with nBu$_4$NPF$_6$ as an additive was the only catalyst that gave a clean reaction and product **16c** was obtained in 65% yield (Scheme 3.18, B). Alkylation of phenol **16c** with 3-bromo-Boc azetidine followed by deprotection afforded diarylmethane **12c** in 49% over four steps.



Scheme 3.18: Synthesis of **16c** and **12c**.

3.3.3.2 *Synthesis of gem-Dimethyl Compounds **16d** and **12d***

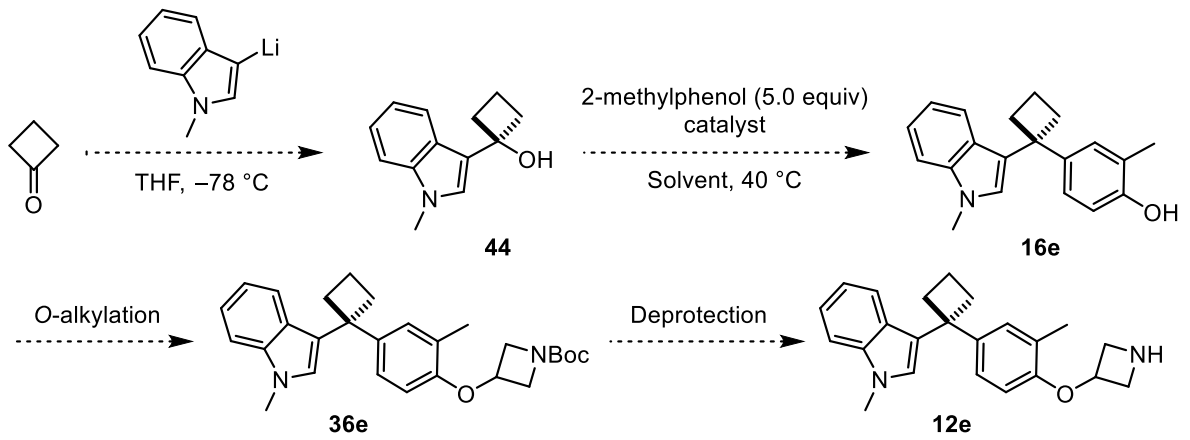
Synthesis of *gem*-dimethyl **12d** was very similar to **12c** and also involved *O*-alkylation and deprotection from the corresponding phenol intermediate **16d**. Although phenol **16d** can be made from two different alcohols **42** and **43** (Scheme 3.19, A), the ketone precursor for alcohol **42** was much less expensive and Grignard addition afforded alcohol **42** in quantitative yield (Scheme 3.19, B). Friedel–Crafts reaction with 1-methylindole using conditions developed by Niggemann, produced 91% of phenol **16d**,[103] which was then *O*-alkylated to obtain azetidine **36d** in 97% yield. Surprisingly, subjecting Boc-protected **36d** to TFA conditions previously used, resulted in complete degradation of the starting material, showing the high instability of this compound under acidic conditions. Instead, the use of HCl in dioxane, afforded **12d** in 81% yield, and in 72% overall yield.



Scheme 3.19: Synthesis of **16d** and **12d**.

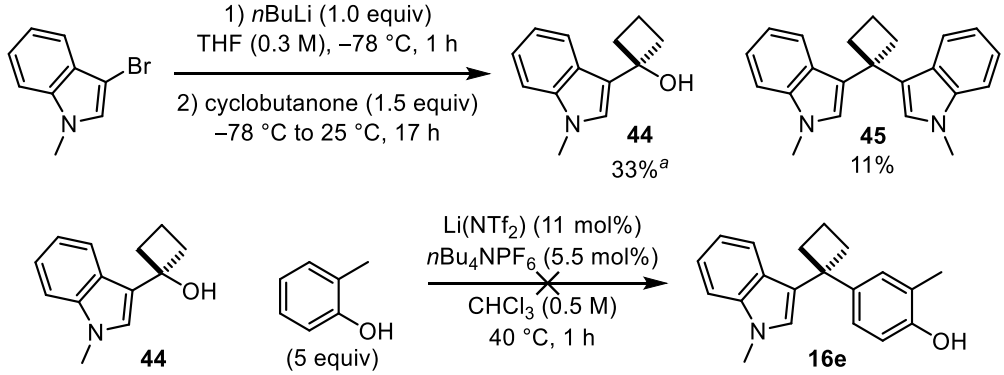
3.3.3.3 *Synthesis of Diarylcyclobutanes **16e** and **12e***

1,1-Diarylcyclobutanes were suspected to have similar reactivity as 3,3-diaryloxetanes and therefore the same synthetic strategy was applied towards **12e** *via* phenol **16e**, employing alcohol **44** (Scheme 3.20).



Scheme 3.20: Proposed synthetic route to **12e**.

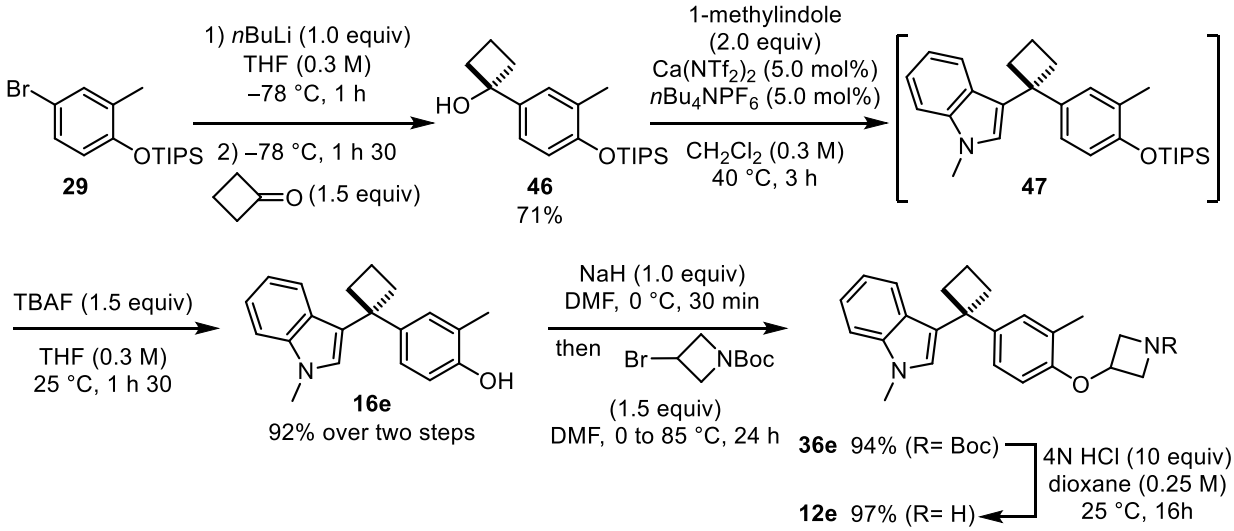
Synthesis of alcohol **44** from 3-bromo-1-methylindole, *n*BuLi and cyclobutanone appeared to proceed smoothly based on ^{1}H NMR spectroscopy of the crude product. However, the purification of this product through silica column chromatography resulted in only 33% of impure alcohol **44** along with 11% of dimer **45** which was not present in the crude reaction mixture (Scheme 3.21). Dimer **45** was likely formed from Friedel–Crafts alkylation of 1-methylindole (dehalogenation product from the quench of indole organolithium) and alcohol **44** with silica acting as an acid catalyst. When subjecting alcohol **44** to the lithium-catalysed Friedel–Crafts reaction previously used, no desired product **16e** was obtained and none of the alcohol **44** was recovered, attesting of the high instability of this alcohol. Thus, the synthetic approach was revised.



Scheme 3.21: Attempt towards the synthesis of **16e** from alcohol **44**. [a] Could not be isolated as a pure compound.

Instead, the synthesis of phenol **16e** was investigated starting with TIPS protected cyclobutanol **46**, which was made in 71% yield (Scheme 3.22). Both lithium[50] and calcium[103] conditions were tested for the Friedel–Crafts reaction of **46** with 1-methylindole, but only calcium triflimide gave a clean reaction. In addition, product **47** was too non polar to be purified by column chromatography and was instead taken to the next step without further purification. TIPS deprotection using TBAF successfully produced phenol **16e** in 92% yield over two steps.

Introduction of the azetidine ring by nucleophilic substitution was also high yielding. Aware of the instability of indole cyclobutanol **44** under acidic conditions, Boc protected cyclobutane **36e** was expected to react and degrade similarly as *gem*-dimethyl **36d** in presence of TFA. To prevent any loss, HCl was used to deprotect the azetidine and **12e** was obtained in 97% yield and 60% yield over five steps.



Scheme 3.22: Synthesis of **16e** and **12e** from alcohol **46**.

3.3.4 Chemical Stability of the Pairs

Comparing the reactivity of indole-containing alcohols **19**, **39** and **44** already gave an indication on the chemical stability of these diarylmotifs (Table 3.2). Oxetanols usually cause concern because of their instability towards acids. However, oxetanol **19** was remarkably stable in the presence of silica gel, on the bench over time, but also under acid-catalysed Friedel–Crafts conditions. In comparison, benzylic alcohol **39** rapidly degraded under air, over time and trimerised into **40** under acidic conditions. Finally, cyclobutanol **44** was slightly more stable than benzylic alcohol **39**, but also easily degraded in the presence of acids including silica gel.

Pleasingly, all oxetanes synthesised were stable to various chemical transformations, such as addition of organolithium reagents and under strong basic and acidic conditions. However, the possible concern about pH stability required a definitive answer to convince medicinal chemists that 3,3-diaryloxetanes can be incorporate in drug discovery programmes. With all the pairs in hand, their physicochemical properties and ADMET profile were then investigated first testing their pH stability.

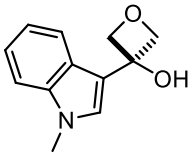
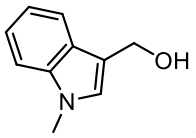
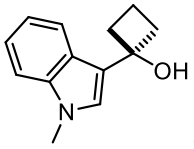
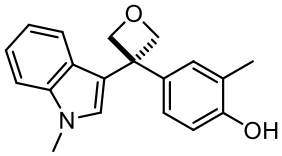
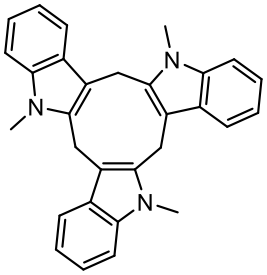
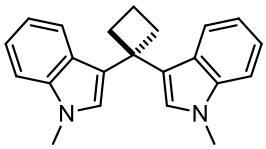
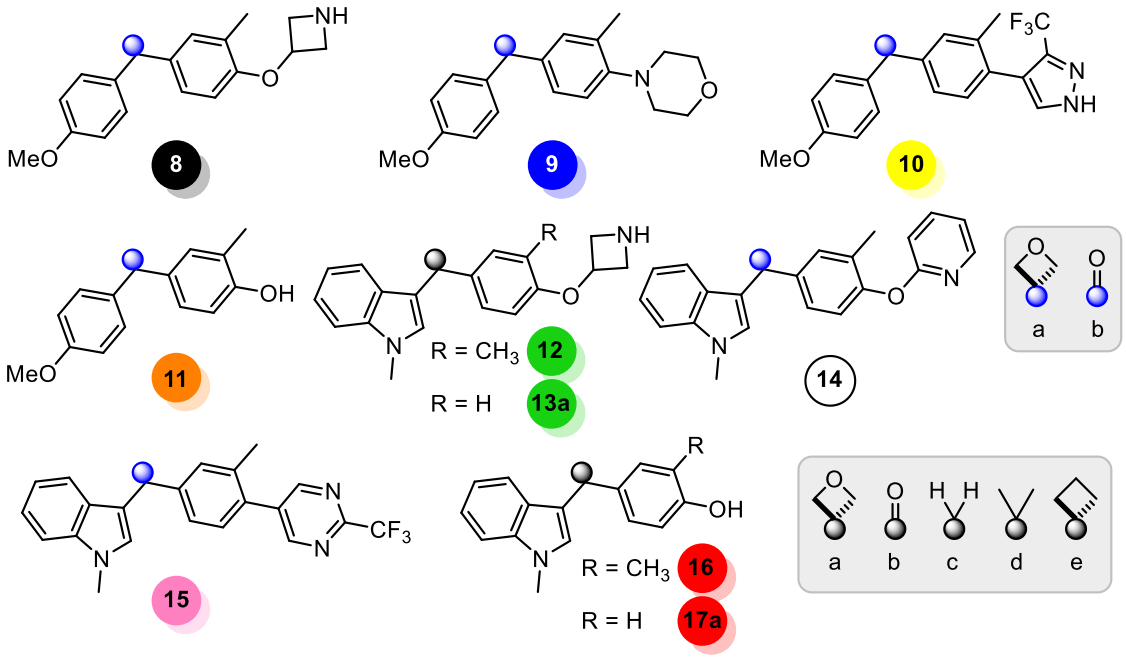
	 **19**	 **39**	 **44**
Stable under silica gel column chromatography	☑	n.a[a]	☒
Bench stable	☑	☒	☑
Stable over time (>overnight)	☑	☒	☑
Product obtained under acidic conditions, in presence or absence of nucleophile	 **16a** High yield	 **40**	 **45**

Table 3.2: Comparison of the stability of alcohols **19**, **39** and **44** under various conditions. [a] Alcohol **39** not purified by silica gel column chromatography.

3.4 Matched Molecular Pairs: Analysis of Physicochemical Properties

All physicochemical properties and ADMET profiles were measured at Pfizer, and all the data can be found in the Appendix (Table 10.2). Only the compounds for which data could be collected will be discussed. Numbers have been attributed for each compound and a colour code has been attributed to the pairs and will be used throughout this section:



3.4.1 pH Stability

Comparison between 3,3-diaryloxetanes and diarylketones

The pH stability for pairs **9** to **17** could be obtained. The stability was tested in pH 1.2, 7.4 and 10 and percentages of remaining compound after 1 h, 4 h and 24 h are presented in Table 3.3. Each pair is represented by a colour and each line of the table corresponds to one compound.

Pleasingly, most 3,3-diaryloxetanes were found stable in basic to acidic pH over time, and only **16a** (red pair) showed sign of degradation in acidic and basic conditions. It is worth noting that the paired ketone **16b** was similarly degraded in pH 1.2 after 24 h as well as in pH 7.4. This suggests that the instability of this red pair is due to the structure and not to the presence of oxetane or ketone itself. Overall, diarylketones and 3,3-diaryloxetanes display similar stability in various pH. Interestingly, removing the methyl group in *ortho* position from **16a** seemed to improve the stability, with 77% of **17a** remaining after 24 h at pH 1.2 compared to 29% for **16a**. However, this was the opposite for compounds **12a** and **13a**, suggesting that the stability of these pairs also depends on the aryl groups.

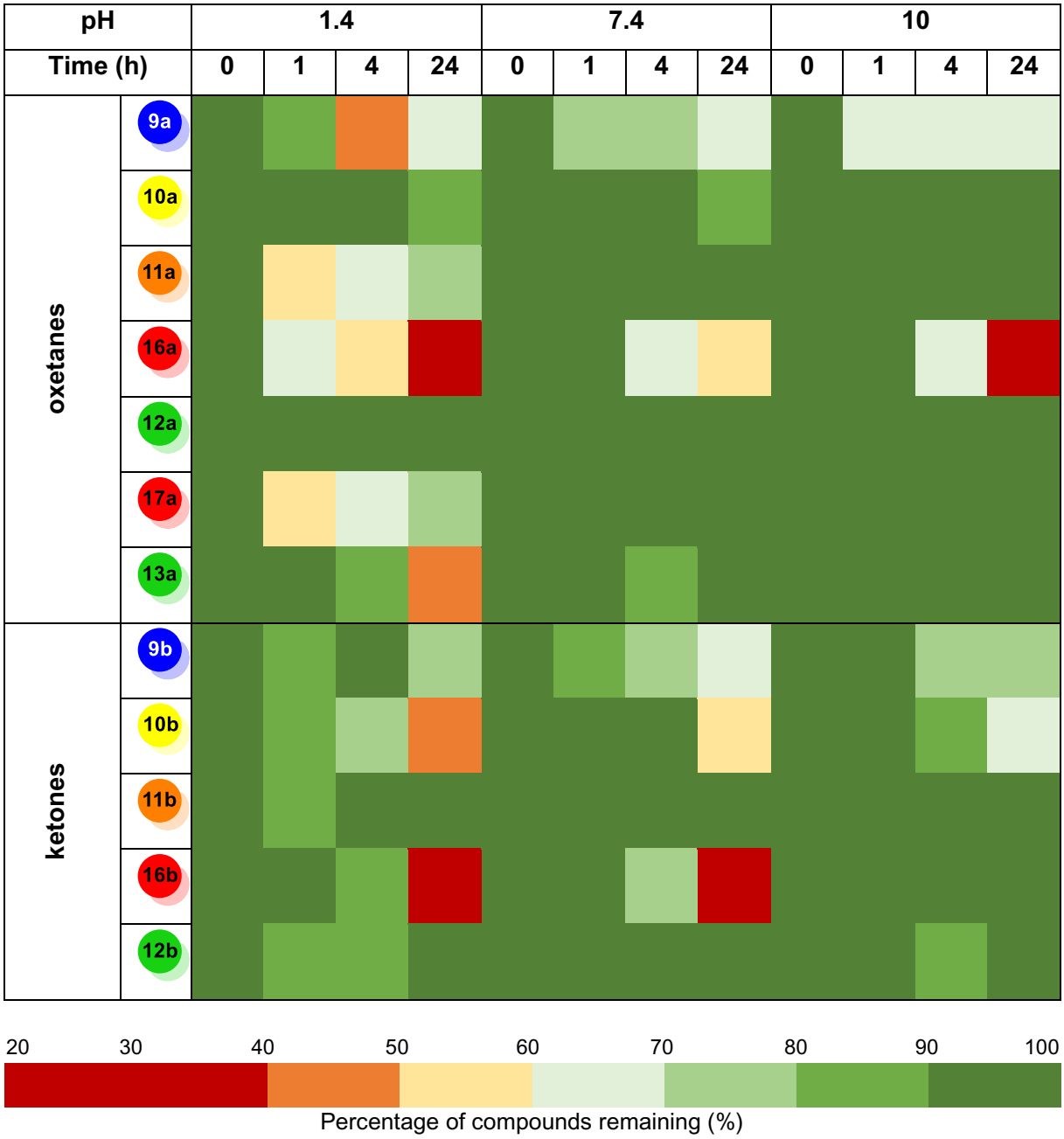


Table 3.3: pH stability of the pairs of 3,3-diaryloxetanes and diarylketones. The table represents the percentage of compound remaining at pH and time indicated.

Comparison between 3,3-diaryloxetanes, diarylketones and 1,1-diarylalkanes

Similarly, the pH stability of the series **12 (a–e)** and **16 (a–e)** were tested and the results are presented in Table 3.4. Overall all compounds in the phenolic series **16** were unstable independently of the linkers, which is in agreement with the previous observation on oxetane **16a** and ketone **16b**. In comparison, compounds in the azetidines serie **12** were all stable in acidic to basic conditions over time, apart from *gem*-dimethyl **12d** with 50% remaining after 1 h at pH 1.2. This correlates with degradation observed during the Boc-deprotection of **36d** to

synthesise **12d** with TFA (section 3.3.3), whereas the corresponding oxetane **36a**, ketone **36b** and methylene **36c** were stable.

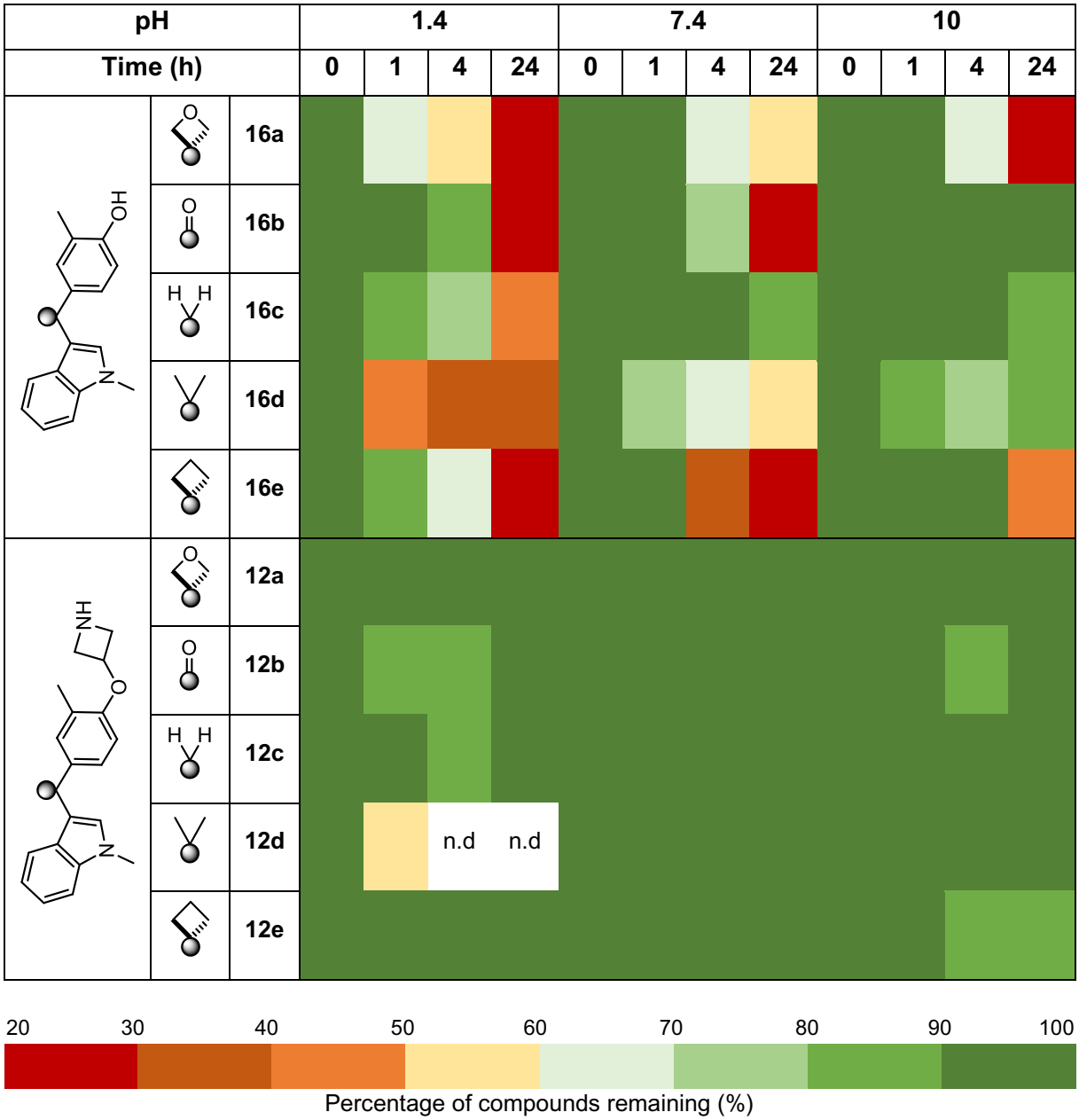


Table 3.4: pH stability of the pairs of 3,3-diaryloxetanes, diarylketones and 1,1-diarylalkanes. The table represents the percentage of compound remaining at pH and time indicated.

3.4.2 Lipophilicity Comparison

Comparison between oxetane and ketone pairs

elogD is an automated reversed phase-HPLC method developed by Lombardo *et al*. used for logD (pH 7.4) measurements.[104] sflogD is the measurement of logD (pH 7.4) based on a shake-flask method.[105] The elogD and sflogD of the pairs of 3,3-diaryloxetanes and diarylketones were measured at pH 7.4 and are shown in Figure 3.2 and Table 3.5.

The elogD for the 3,3-diaryloxetanes sit between 1.70 and 5.10 and between 1.00 and 4.62 for sflogD, with an average of 3.37 and 2.89 respectively. These correspond to ideal lipophilicity for “drug-like” molecules (Table 3.5). Interestingly, the initial predicted lipophilicity (clogP) for these oxetanes was 3.14, which sits between the value obtained for measured sflogD and elogD. The comparison of elogD and sflogD between 3,3-diaryloxetanes and diarylketones are shown on Figure 3.2, where each coloured spot corresponds to one pair.

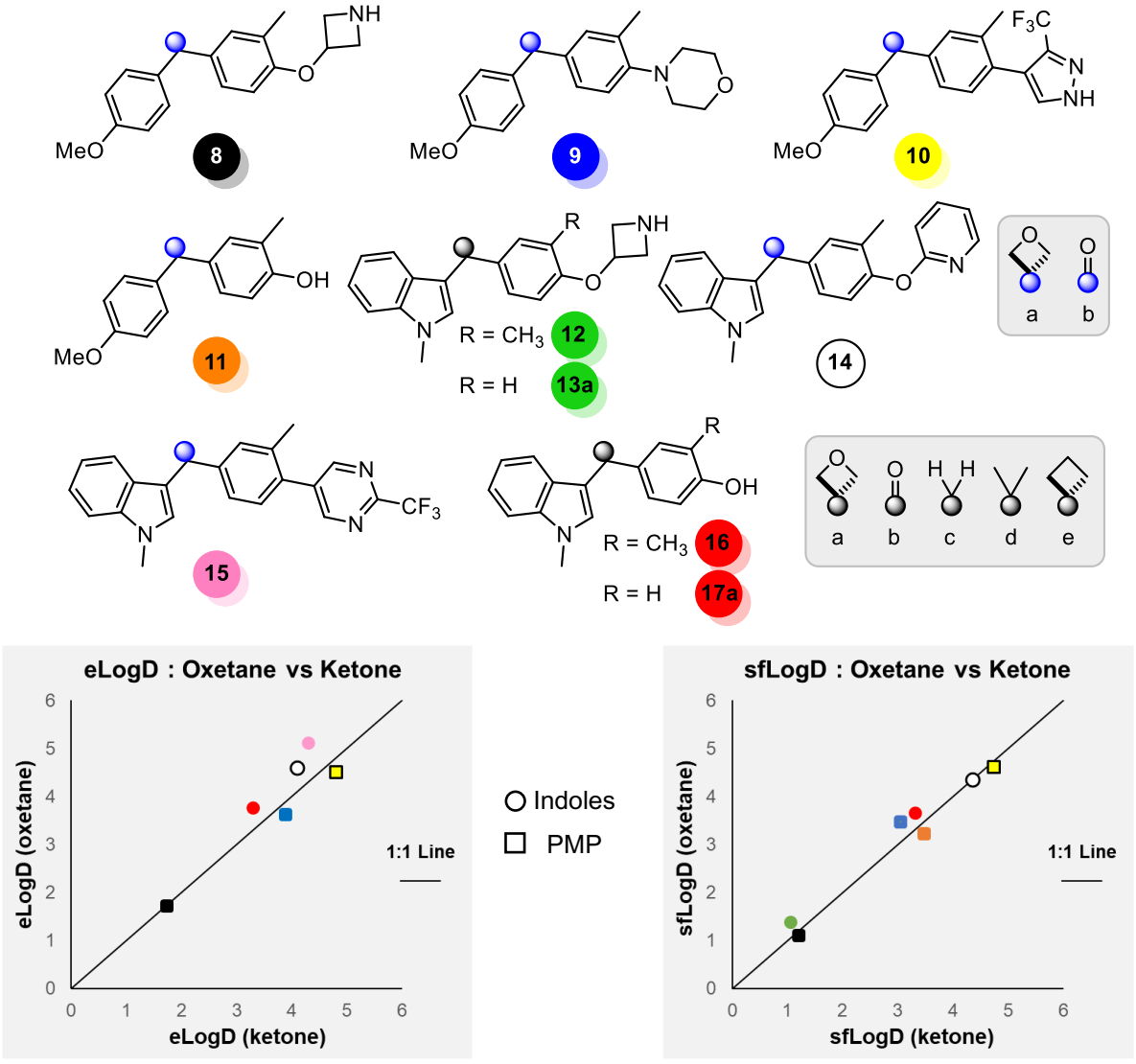


Figure 3.2: Comparison of elogD (left) and sflogD (right) of 3,3-diaryloxetanes *vs* diarylketones.

On both graphs, all the pairs are distributed along the 1:1 line, indicating that 3,3-diaryloxetanes and diarylketones have similar lipophilicity. In addition, the mean of ΔelogD (ketone–oxetane) and mean of ΔsflogD (ketone–oxetane) in Table 3.5, show that replacing the ketone with the oxetane overall generates a small rise of 0.19 units in elogD and 0.07 units in sflogD. These suggest that 3,3-diaryloxetanes are scarcely more lipophilic, and replacing diarylketones with 3,3-diaryloxetanes generally conserves low and similar lipophilicity.

Pairs	elogD			sflogD			clogD		
	 b	 a	ΔelogD[a]	 b	 a	ΔsflogD[a]	 b	 a	ΔclogD
16	3.30	3.76	–0.46	3.33	3.64	–0.31	n.d	n.d	n.d
12	n.d	2.10	n.d	1.07	1.37	–0.30	2.12	2.13	–0.01
11	n.d	n.d	n.d	3.49	3.22	0.27	n.d	n.d	n.d
8	1.74	1.71	0.03	1.21	1.10	0.11	1.44	1.76	–0.32
9	3.90	3.61	0.29	3.06	3.46	–0.40	3.46	3.40	0.06
10	4.80	4.50	0.30	4.74	4.62	0.12	4.26	4.52	–0.26
14	4.10	4.60	–0.50	4.36	4.36	0	3.99	4.13	–0.14
15	4.31	5.10	–0.79	n.d	n.d	n.d	3.78	4.19	–0.41
17a	-	3.29	-	-	3.26	-	-	n.d	-
13a	-	1.70	-	-	1.00	-	-	1.89	-
	Mean **ΔelogD[a]=**		–0.19	Mean **ΔsflogD[a]=**		–0.07	Mean **ΔclogD[a]=**		–1.08

Table 3.5: elogD and sflogD of the pairs of 3,3-diaryloxetanes and diarylketones. [a] elogD, sflogD and clogD (ketone–oxetane). Data collected by Pfizer.

Comparison between oxetane and other linker pairs

In contrast, the difference in elogD and sflogD between 3,3-diaryloxetanes and diarylalkanes is more pronounced than with diarylketones (Table 3.6).

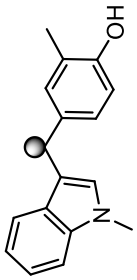
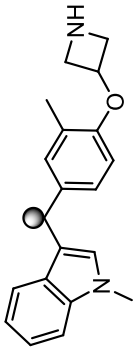
		N°	elogD	ΔelogD[a]	sflogD	ΔsflogD[a]	clogD	ΔclogD[a]
		**16a**	3.76	-	3.64	-		
		**16b**	3.30	–0.46	3.33	–0.31		
		**16c**	4.82	1.06	2.74	–0.90		
		**16d**	5.12	1.36	3.77	0.13		
		**16e**	5.40	1.64	4.40	0.76		
		**12a**	2.10	-	1.37	-	2.13	-
		**12b**	n.d	n.d	1.07	–0.30	2.12	–0.01
		**12c**	3.10	1.00	2.13	0.76	2.26	0.13
		**12d**	2.90	0.80	2.59	1.22	2.27	0.14
		**12e**	3.20	1.10	2.81	1.44	2.87	0.74
			Mean **ΔelogD[a]**	0.81	Mean **ΔsflogD[a]**	0.35	Mean **ΔclogD[a]**	1.00

Table 3.6: elogD and sflogD of the pairs of 3,3-diaryloxetanes and linkers. [a]ΔelogD, ΔsflogD and ΔclogD (linkers–oxetane). Data collected by Pfizer.

Replacing the linkers with the oxetane overall lowered the lipophilicity of the compounds by 0.81 units in elogD and 0.35 units in sflogD. 3,3-Diaryloxetanes were found especially much less lipophilic than diaryl-methanes, *gem*-dimethyl and cyclobutanes, which can be explained by the introduction of a polar oxygen atom. It is worth noting that the comparison of clogD between 3,3-diaryloxetanes and diarylalkanes predicted a significant advantageous effect of introducing the oxetane motif on the lipophilicity (Mean ΔclogD= 1.00), which was revised downwards experimentally (sflogD).

Overall, replacing diaryl-methanes, *gem*-dimethyl and cyclobutanes with 3,3-diaryloxetanes is a suitable strategy to decrease the lipophilicity in these motifs.

3.4.3 Metabolic Stability (HLM)

Comparison between oxetane and ketone pairs

The clearance by HLM of 3,3-diaryloxetanes and diarylketones are shown in Table 3.7. Pleasingly, the oxetanes do not seem to be metabolically labile, with clearance between 7.0–80 µL/min/mg and 22.2 µL/min/mg on average. Removing the *ortho*-methyl group does not affect the clearance with compounds **16a** and **17a**, **12a** and **13a** being similarly metabolised. Interestingly, 3,3-diaryloxetanes and diarylketones are similarly robust to metabolic oxidation, with only a small rise of 1.80 µL/min/mg (Mean ΔHLM Cl, Table 3.7) when the ketone is replaced with the oxetane moiety.

	Compound		HLM Cl[a]	ΔHLM Cl[a,b]	cHLM Cl
		**16b**	18.0	–4.90	
		**16a**	22.9		
		**17a** (R = H)	22.4	-	
		**12b**	7.0	0	34.0
		**12a**	7.0		30.1
		**13a** (R = H)	7.0	-	13.8
		**11b**	77.4	–2.60	
		**11a**	80.0		
		**8b**	7.50	0	43.1
		**8a**	7.50		50.1
		**15b**	7.00	–1.48	24.0
		**15a**	8.48		32.9
Mean:		**$\Delta Cl_{(HLM)}$ [a,b]**		–1.80	

Table 3.7: Clearance by human liver microsomes for the pairs of 3,3-diaryloxetanes and diarylketones. [a] Clearance by human liver microsomes in µL/min/mg. [b] Ketone–oxetane. Data collected by Pfizer.

Comparison between oxetane and other linker pairs

The clearance for the diarylalkanes are shown in Table 3.8 and were overall metabolically stable. Interestingly, compounds in the phenolic series **16** were more degraded than the azetidines **12**. Replacing the linkers **16b–e** with 3,3-diaryloxetane **16a** resulted in similar clearance with a slight increase of 2.23 µL/min/mg (Mean ∆HLM Cl). In contrast, introducing the oxetane moiety in the azetidine series **12** conserved low clearance. The difference between the two series indicates that the clearance of these compounds might be structure-dependant rather than linker-dependant. Therefore the clearance could be driven by the lipophilicity independently to the linkers on the central carbon, and further analyses on this relationship were then carried out.

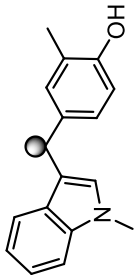
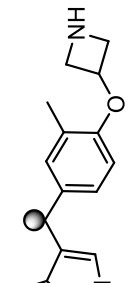
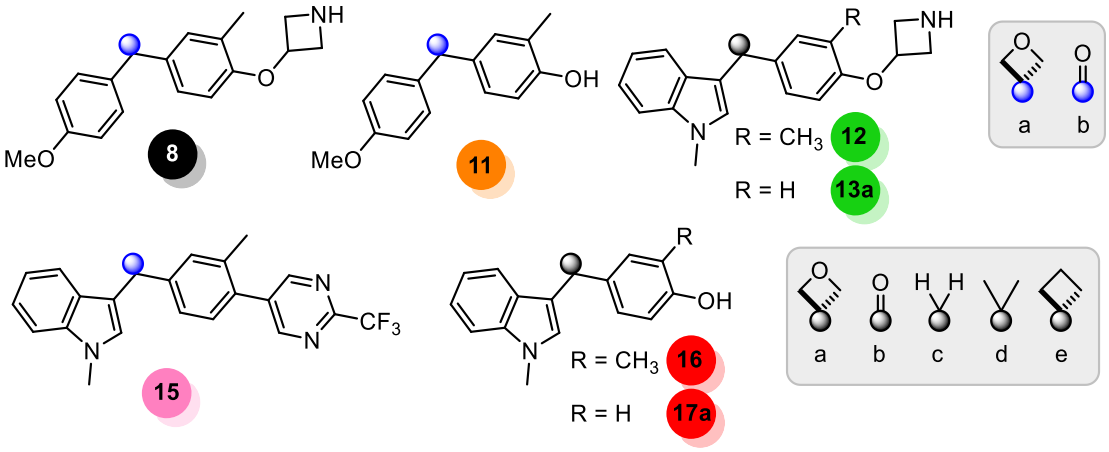
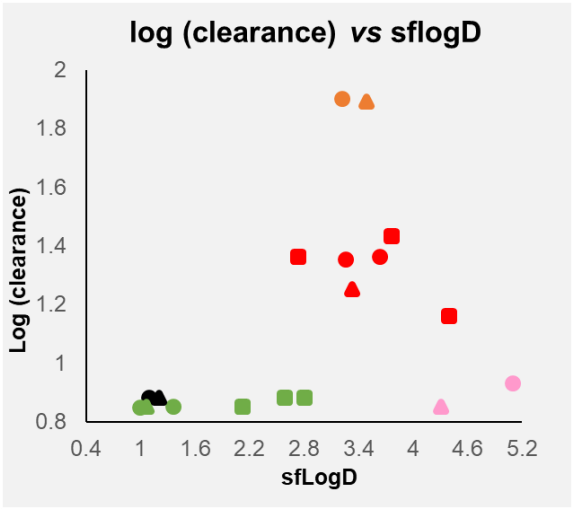
		N°	HLM Cl[a]	∆HLM Cl[a,b]	log HLM Cl	cHLM Cl
		**16a**	22.9	-	1.36	
		**16b**	18.0	–4.9	1.25	
		**16c**	23.0	0.10	1.36	
		**16d**	27.2	4.30	1.43	
		**16e**	14.5	–8.40	1.16	
			Mean ∆Cl$_{(HLM)}$ [a,b]	–2.23		
		**12a**	7.00	-	0.86	30.1
		**12b**	7.00	0	0.85	34.0
		**12c**	7.00	0	0.85	37.7
		**12d**	7.50	0.50	0.88	41.1
		**12e**	7.50	0.50	0.88	42.3
			Mean ∆Cl$_{(HLM)}$ [a,b]	0.25		

Table 3.8: Clearance by human liver microsomes (HLM) for the pairs of 3,3-diaryloxetanes, diarylketones and diarylalkanes. [a] Clearance by human liver microsomes in µL/min/mg. [b] Linker–oxetane. Data collected by Pfizer.

Study of the correlation between clearance and lipophilicity

In order to understand if the clearance of the compounds studied is driven by the lipophilicity, the log(HLM Cl) *vs* the sflogD was compared (Figure 3.3). Each colour corresponds to a pair, circles are oxetanes, squares are other linkers and triangles are ketones. Overall all the points are scattered without clear trend, although the clearance seems to increase for compound with sflogD>3. However, there is a distinct difference between the phenols series (orange **11**, and red **16** and **17**), with the others non-phenolic (black **8**, green **12** and **13,** and pink **15**). All phenol-containing compounds were more metabolically exposed than the others series independently to their lipophilicity, suggesting that the clearance is strictly structure-dependant.





○ oxetanes △ ketones □ other linkers

Figure 3.3: Comparison of log(clearance) *vs* sflogD.

In conclusion, 3,3-diaryloxetanes are generally not susceptible to metabolic oxidation. Although the clearance for the compounds studied seemed to be structure-dependant, 3,3-diaryloxetanes, diarylketones and diarylalkanes were similarly metabolically robust. This suggests that 3,3-diaryloxetanes would be suitable isosteres for these linkers.

3.4.4 Passive Permeability Comparison (RRCK)

Passive permeability assay were carried out using low-efflux MDCKII cells developed by Troutman, also called Ralph Russ Canine Kidney cell (RRCK) (Table 3.9).[41] The permeability for the 3,3-diaryloxetanes was found between 4.80–24.4 × 10^{-6} cm/s with an average of 12.4 × 10^{-6} cm/s. Similar results were obtained for the diarylketones, with an average permeability of 13.4 × 10^{-6} cm/s. In addition, among the six pairs of 3,3-diaryloxetanes and diarylketones, introducing the oxetane resulted in similar or improved permeability in four of them.

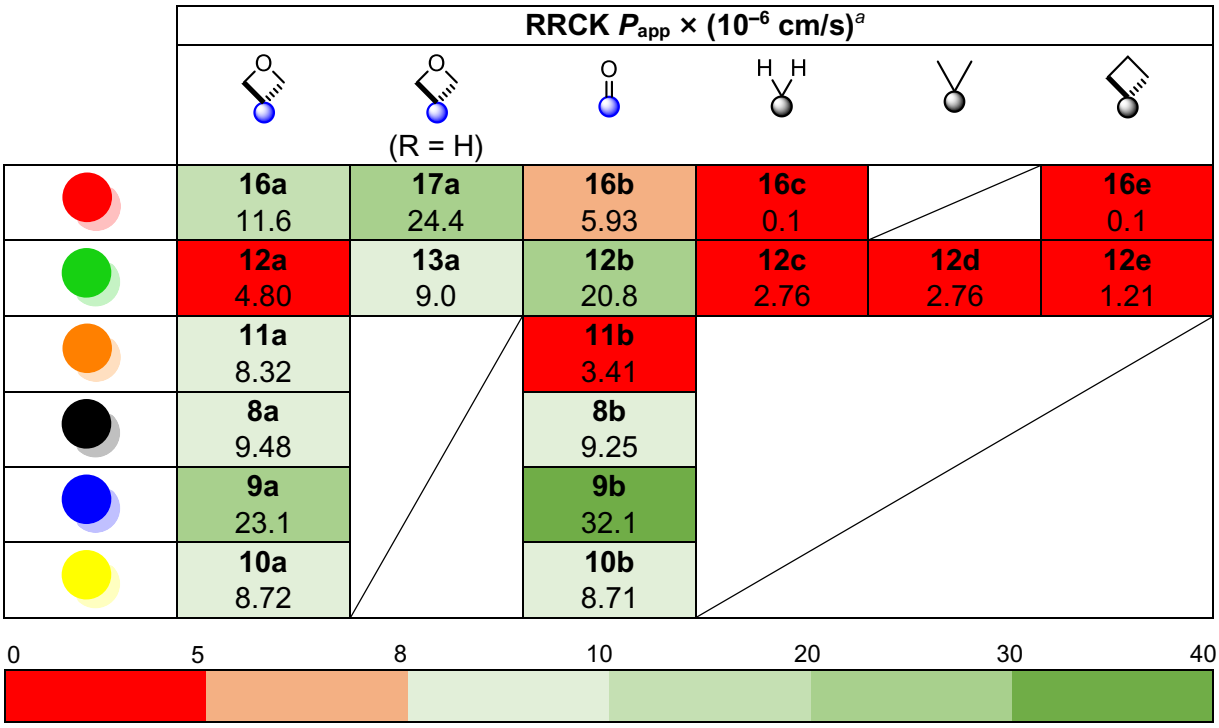


Table 3.9: Permeability comparison between 3,3-diaryloxetanes, diarylketones and diarylalkanes (10^{-6} cm/s). Data collected by Pfizer. [a] Papp (Apical to Basal).

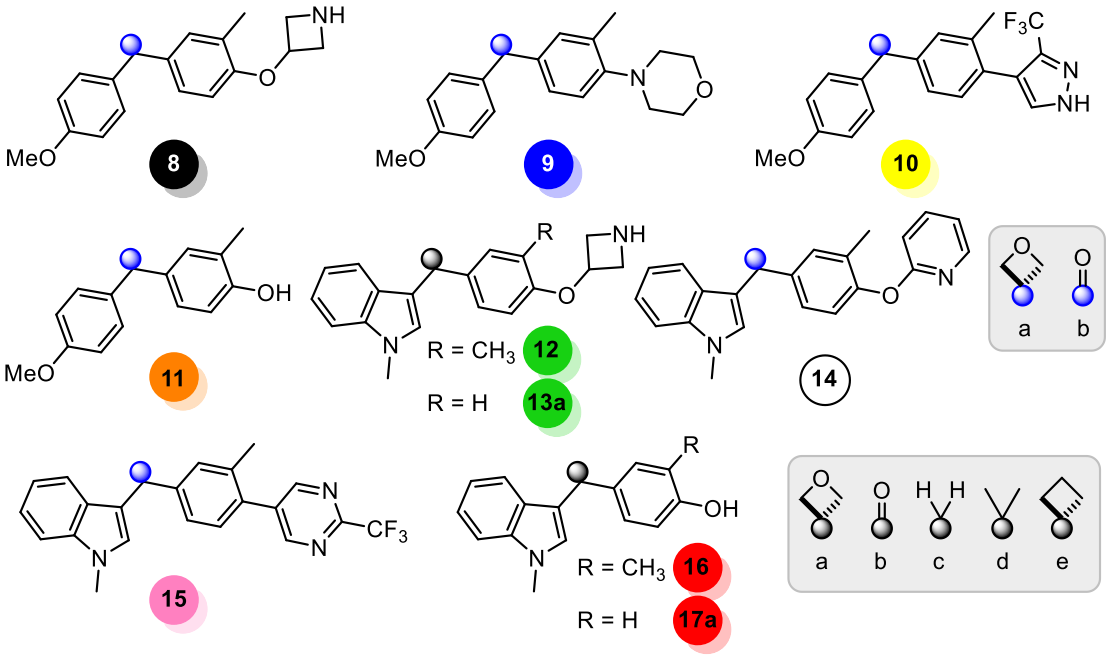
Importantly, 3,3-diaryloxetanes had improved permeability compared to diarylalkanes. Oxetane **16a** was 100 times more permeable than diarylalkanes **16c** and **16e**, while methylene **12c** and *gem*-dimethyl **12d** had their permeability risen by nearly two fold when replaced with 3,3-diaryloxetane **12a**. This effect was even more pronounced for cyclobutane **12e** which is four times less permeable than oxetane **12a**.

These preliminary results suggest that 3,3-diaryloxetanes can replace diarylketones and diarylalkanes without affecting negatively the permeability. More pairs would be required to confirm this trend.

3.4.5 Solubility

Comparison between oxetane and ketone pairs

The solubility of the 3,3-diaryloxetanes and diarylketones in aqueous solution at different pH are represented in Table 10.3 (Appendix), Table 3.10 and Figure 3.4.



pH \ Pair	16	12	11	8	9	10	14
Ketones (b) 3							
Ketones (b) 6.5	n.d	n.d	n.d		n.d	n.d	n.d
Ketones (b) 7.4							
Ketones (b) 10							
Oxetanes (a) 3							
Oxetanes (a) 6.5		n.d	n.d			n.d	n.d
Oxetanes (a) 7.4							
Oxetanes (a) 10							

0 20 100 200 300 400 500 600 (μM)

Table 3.10: Comparison of solubility (μM) between pairs of 3,3-diaryloxetanes and diarylketones in different pH.

The solubility of the 3,3-diaryloxetanes strongly varies between 0.10 to 600 µM. No clear trend was observed comparing the solubility between 3,3-diaryloxetanes and diarylketones (Table 3.10). In the orange pair **11**, the solubility was improved when replacing the ketone with the oxetane. The phenolic O-H of **11b** was expected to be more acidic due to the presence of the ketone. Therefore it was expected that ketone **11b** would be more soluble at lower pH than oxetane **11a**, which is not the case. This was the opposite for phenols **16** (red pair), where the solubility decreased when moving to the oxetane. Five pairs (blue **9**, green **12**, black **8**, yellow **10** and white **14** pairs) demonstrated very similar solubility between the two linkers. These results suggest that the solubility is strictly governed by the aromatic groups and not by the presence of the central ketone or oxetane. The log(solubility) was then calculated and the solubility between oxetanes and ketones in different pH was compared (Figure 3.4). The data suggests that the effect of replacing diarylketones with 3,3-diaryloxetanes on the solubility might also be pH-dependant, with an improved solubility in acidic pH and decreased solubility in neutral and basic conditions moving from ketones to oxetanes.

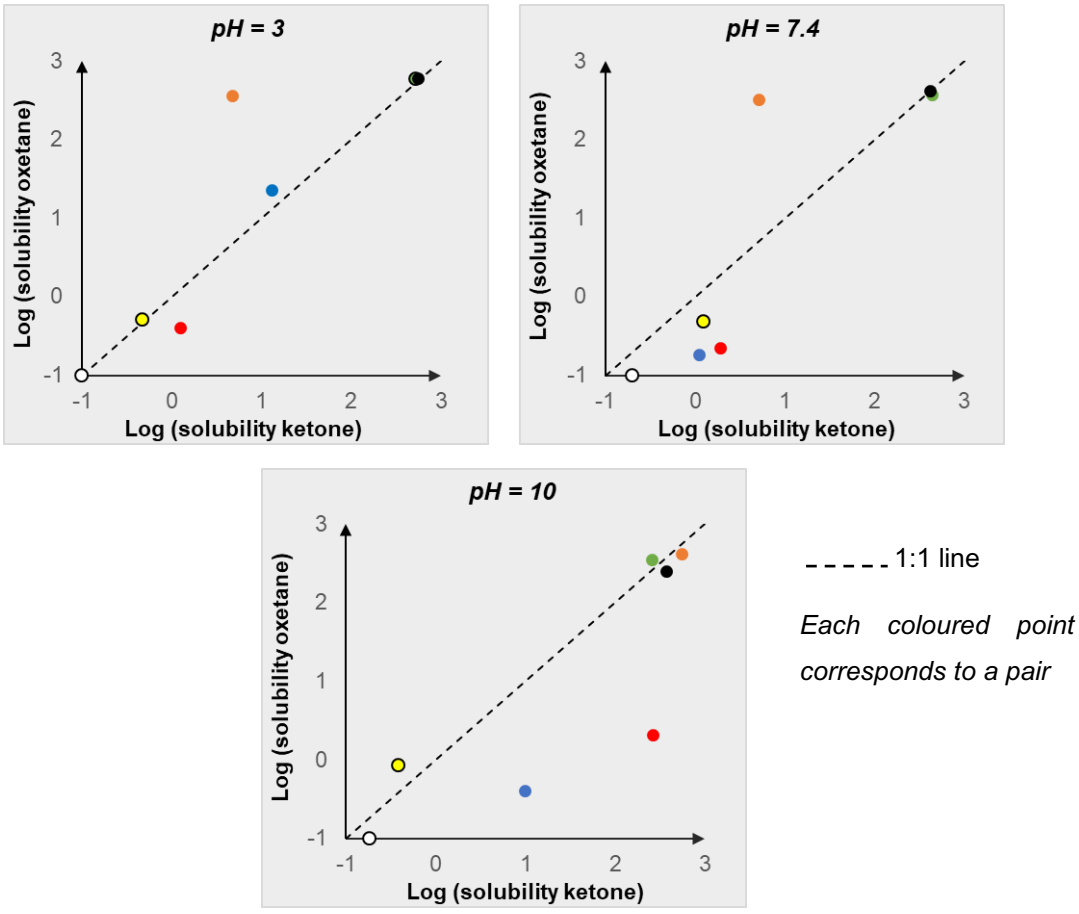
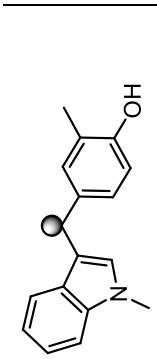
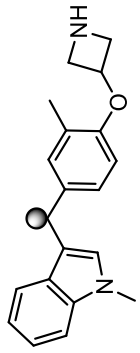


Figure 3.4: Comparison of log(solubility) between oxetanes *vs* ketones in different pH. The comparison was not carried out at pH=6.5 due to the lack of data.

Comparison between oxetane and other linkers pairs

A similar comparison was conducted between 3,3-diaryloxetanes and other linkers (Table 3.11). A sharp difference in solubility was observed between the two series: while most azetidines **12 a–e** were soluble, all phenols **16 a–e** were particularly insoluble. In addition, replacement of diarylalkanes with 3,3-diaryloxetanes does not guarantee conservation or improvement of the solubility. Therefore, the data confirms the dependence of the solubility to the aromatic groups that was previously observed, rather than being linker-dependant.

	N°	Solubility (µM)			
		pH = 3.0	pH = 6.5	pH = 7.4	pH = 10
	**16a**	0.40	8.30	0.22	2.06
	16b	1.27	n.d	1.91	262.9
	16c	16.7	167.4	12.2	11.1
	16d	0.10	45.9	0.10	0.10
	16e	0.97	n.d	3.89	0.58
	**12a**	600	n.d	372.2	343.9
	12b	518.2	n.d	435.3	258.2
	12c	600	n.d	164.9	32.2
	12d	600	n.d	257.1	9.21
	12e	511.6	n.d	22.4	2.53

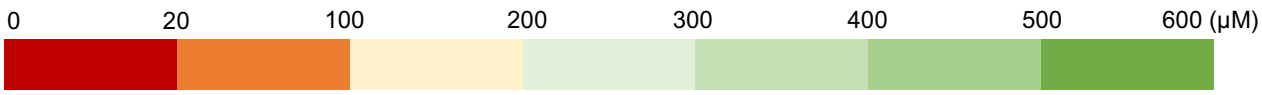


Table 3.11: Comparison of solubility (µM) between 3,3-diaryloxetanes, diarylketones, and diarylalkanes in different pH. Data collected by Pfizer

Influence of π–stacking and lipophilicity on solubility

The solubility of 3,3-diaryloxetanes, diarylketones and diarylalkanes was previously shown to be governed by the aromatic groups. Yalkowsky's equation,[4] demonstrated that the solubility decreases with both the lipophilicity and the melting point of a molecule. Therefore the

relationship between the solubility, lipophilicity and melting points (mp) of these diarylmotifs was investigated (Figure 3.5). Comparing the sflogD *vs* the log(solubility) of these molecules in three different pH (Figure 3.5, left column), showed a slight trend where the solubility increases as the lipophilicity decreases. The comparison between log(mp) and log(solubility) gave a similar trend although less pronounced, where higher solubility is obtained for compounds with lower mp (Figure 3.5, right column). Therefore the π-stacking of these diaryl-motifs seems to affect their solubility in aqueous medium.

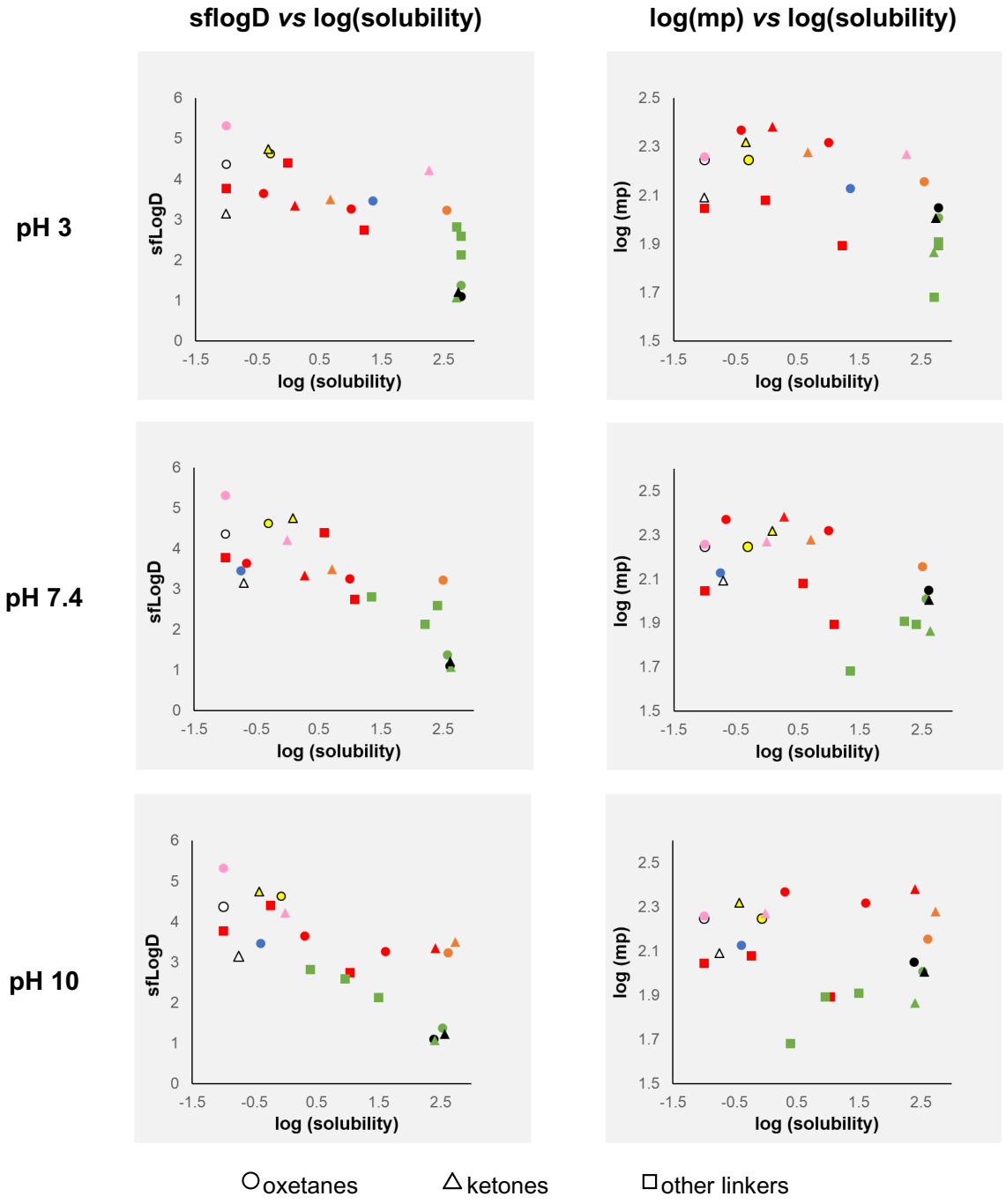


Figure 3.5: Left column: comparison of sflogD *vs* log(solubility) in different pH. Right column: comparison of log (mp) *vs* log(solubility) in different pH. Melting points measured in °C. Each colour corresponds to a pair.

3.4.6 hERG inhibition

hERG inhibition is an important cause of attrition in drug discovery. The risk of toxicity associated to the use of 3,3-diaryloxetanes needed to be assessed prior incorporation to medicinal chemistry programmes. The binding of the diaryl compounds to hERG was measured (Table 3.12). Pleasingly, nine out of ten 3,3-diaryloxetanes had a DOF(IC50)>10 μM, demonstrating that they are relatively safe to use. Oxetanes **12a** and **13a** did not display hERG inhibition compared to linkers **12b**–**12e** (green pair). In addition, in six pairs out of eight, the replacement of diarylketones with 3,3-diaryloxetanes resulted in similar or higher IC50, confirming the low risk of toxicity associated with the introduction of these oxetanes. Overall, replacing linkers **b** to **e** with 3,3-diaryloxetanes can be a tactic to avoid cardiac toxicity in some cases.

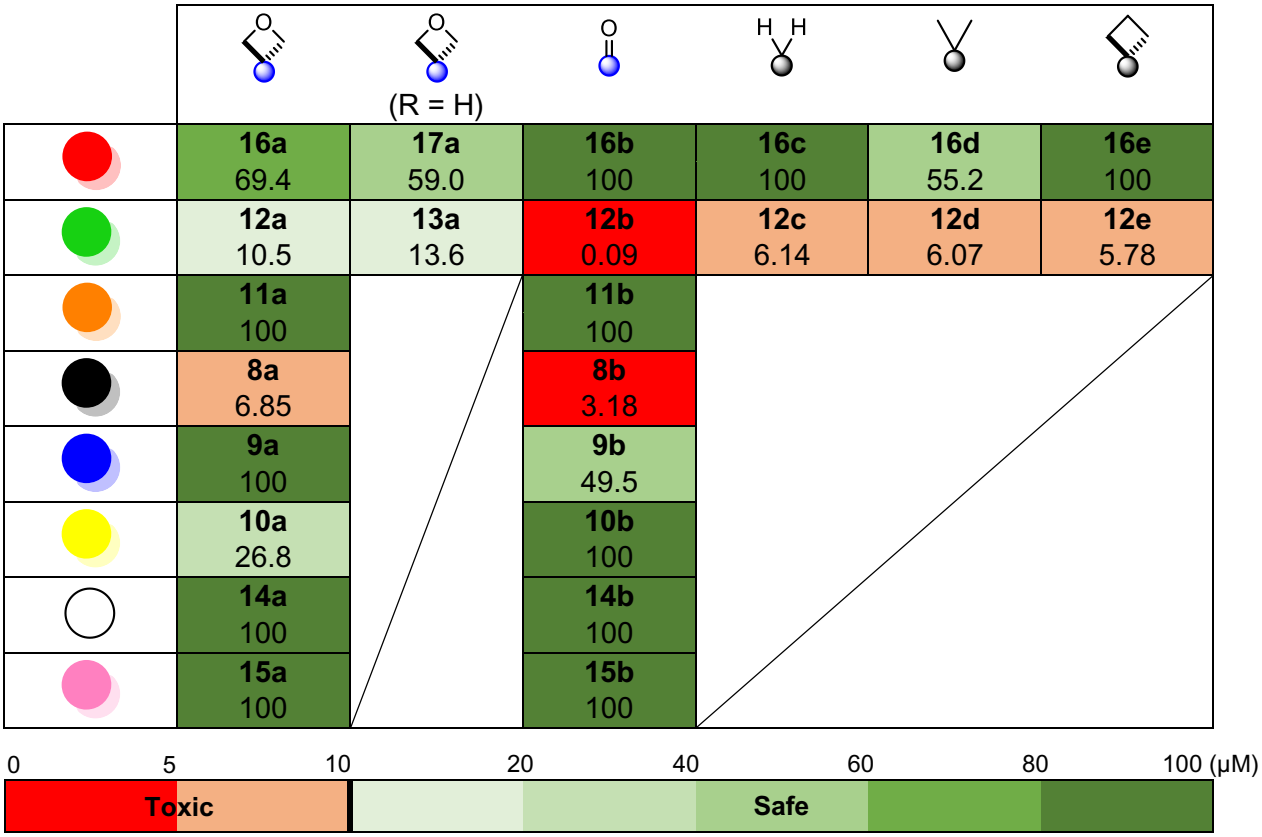


Table 3.12: Toxicity comparison between 3,3-diaryloxetanes, diarylketones and diarylalkanes. This table compares the inhibition (IC50) of [^{3}H] dofetilide-binding to hERG (DOF) by 3,3-diaryloxetanes, diarylketones, and diarylalkanes. If less than 10 μM of a compound is required to inhibit 50% of [^{3}H] dofetilide binding, the compound is considered toxic as it binds hERG. Data collected by Pfizer.

3.4.7 Conclusion

In order to evaluate 3,3-diaryloxetanes as new motifs for drug discovery and as new isosteres for diarylketones and 1,1-diarylalkanes, a matched molecular pair analysis of their physicochemical properties was performed. A total of 24 compounds were designed to have desirable “drug-like” properties, respecting the “rule of 5”. Diarylketones were produced in high yields by addition of organolithium to Weinreb amide or oxidation of alcohols. 3,3-Diaryloxetanes were synthesised applying the lithium-catalysed Friedel–Crafts reaction previously developed by the Bull group, demonstrating the applicability of the method in a drug discovery setting.[50] Diarylmethane, *gem*-dimethyl and cyclobutane compounds were also accessed through Friedel–Crafts reactions. Importantly, the oxetanes displayed high chemical stability under a variety of reaction conditions compared to the corresponding diarylmethanes, *gem*-dimethyls and cyclobutanes. In total, the compounds formed 8 pairs of diarylketones and 3,3-diaryloxetanes; 6 pairs of 1,1-diarylalkanes and 3,3-diaryloxetanes; as well as two additional examples of oxetanes. The lipophilicity, solubility, permeability, clearance and toxicity of these molecules were measured and compared pairwise (Table 3.13 and 3.14).

Overall, 3,3-diaryloxetanes displayed desirable properties, with high pH stability, low lipophilicity and metabolic degradation, as well as acceptable cell permeability (Table 3.13). In addition, these oxetanes are relatively safe to incorporate into molecules and represent suitable motifs for drug discovery programmes (Table 3.13).

Physicochemical properties	**ADMET profile for the collection of 3,3-diaryloxetanes**
PSA	30.9–47.1 Å
pH stability	Stable under acidic and basic conditions over time
lipophilicity	elogD ~ 3.37 slogD ~ 2.89
HLM clearance	7.0–80 μL/min/mg
permeability	4.80–24.4 × 10^{-6} cm/s
solubility	0.1–600 μM
toxicity	>10 μM, safe

Table 3.13: ADMET profile for 3,3-diaryloxetanes designed in “drug-like” space.

In order to establish 3,3-diaryloxetanes as isosteres for diarylketones and diarylalkanes, the replacement of these motifs with the oxetanes should result in similar or improved physicochemical properties. The comparison of these properties and changes are summarised in Table 3.14. Replacing diarylketones with 3,3-diaryloxetanes, resulted in: 1) similarly pH stability and safety, 2) similar low lipophilicity, and 3) same or improved permeability. The replacement of diarylmethanes, *gem*-dimethyl and cyclobutanes with 3,3-diaryloxetanes improved importantly the lipophilicity while similar or better pH stability was observed. In addition, introduction of 3,3-diaryloxetanes may solve cardiac toxicity associated with diarylalkanes and diarylketones in some cases. On the other hand, more pairs would be required to fully understand the effect of replacing these diarylalkanes with these oxetane motifs on the clearance and permeability. Finally, the solubility of all these diaryl compounds is dependent on the lipophilicity and melting points and not on the central linkers.

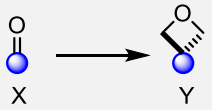
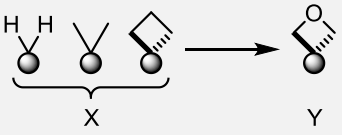
Physicochemical properties	**Effect of replacing X with Y on:**	
		
lipophilicity	=	↘
HLM clearance	=	structure dependant more pairs required
permeability	= or ↗	↗
solubility	Lipophilicity and mp dependant	Lipophilicity and mp dependant
toxicity	= or ↘	= or ↘

Table 3.14: Summary of the effect of replacing diarylketones and diarylalkanes with 3,3-diaryloxetanes on physicochemical properties. ↗ = increase. ↘ = decrease.

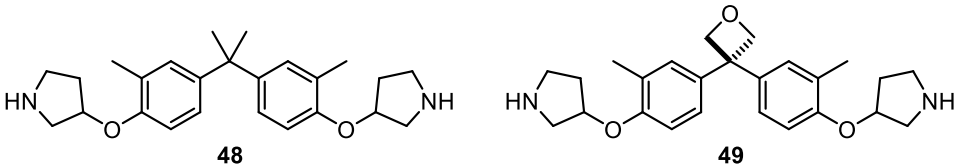
Overall, the replacement of diarylketones and 1,1-diarylalkanes with 3,3-diaryloxetanes results in similar or improved physicochemical properties, suggesting that 3,3-diaryloxetanes would be suitable isosteres for these functional groups. In addition, these oxetanes present attractive properties and ADMET profile and could be incorporated in medicinal chemistry programmes.

3.5 ADMET Study on Oxetane-Containing-Drug Analogues

3.5.1 Selection of the Drugs and Bioactive Molecules

To further study the effect of incorporating 3,3-diaryloxetanes on physicochemical properties of a molecule, the replacement of diarylketones, diaryl-methanes and *gem*-dimethyls in drugs or biologically active compounds with diaryloxetanes was examined. This would demonstrate the robustness and applicability of the Friedel–Crafts reaction previously developed within the Bull group,[50] applying the conditions to more complex and challenging structures. Moreover, this study would allow to further assess 3,3-diaryloxetanes as isosteres for benzophenones and 1,1-diarylalkanes. The biological activity of the parent molecules and the new 3,3-diaryloxetane analogues could also be compared to evaluate 3,3-diaryloxetanes as potential bioisosteres.

Three drugs were selected based on their synthetic feasibility *via* lithium-catalysed Friedel–Crafts reaction. In particular, the need of electron-donating groups on both pre-installed 3-aryloxetan-3-ols and aromatic nucleophiles was considered. A patent from 2007 displayed a sodium channel modulator **48** containing a *gem*-dimethyl.[106] The synthesis of 3,3-diaryloxetane **49** as analogue would be facilitated by the presence of the two symmetrical masked phenoxy groups (Figure 3.6).



48
Sodium channel modulator

49

Figure 3.6: Selected bioactive active molecule containing a *gem*-dimethyl **48** and proposed 3,3-diaryloxetane analogue **49**.

In 1998, a structure-activity relationship on natural antineoplastic agents combretastatin A-1, A-2 and A-4, led to the development of phenstatin **50** and methylated phenstatin **51** (Figure 3.7).[107] The two benzophenones showed respectively higher and similar tubulin polymerisation inhibition and cytotoxicity activity than combretastatin A-1, A-2 and A-4. Interestingly, diarylmethane analogue **52** was also previously shown to have antineoplastic activity,[108] linking the common diaryl-core in **50**, **51** and **52** to the anti-cancer activity of these molecules. Therefore 3,3-diaryloxetanes analogues **53** and **54**, with similar aromatic core, are interesting in their own right with potentially similar biological activities. In addition, they could also have improved physicochemical properties compared to benzophenones **50** and **51** and diarylmethane **52**. The synthesis of **53** and **54** was also anticipated to be feasible *via* Friedel–Crafts reactions as both aromatic rings are highly electron-rich.

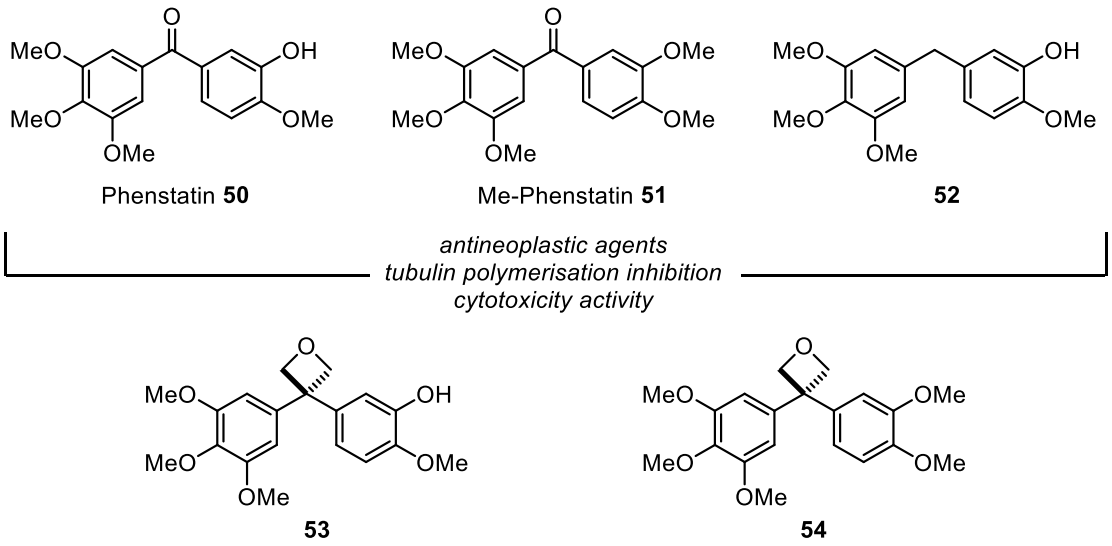


Figure 3.7: Selected bioactive benzophenones **50** and **51**, and diarylmethane **52**, and proposed 3,3-diaryloxetane analogues **53** and **54**.

Diarylmethane **55**, called sobetirome, displays multiple biological activities (Figure 3.8).[109] Sobetirome **55** preferentially binds to thyroid hormone receptor TRβ1 over TRα (responsible for thyrotoxic effect on heart, muscles and bones). It significantly reduces LDL cholesterol and serum triglycerides involved in cardiovascular diseases and dyslepidemia, and could be used to treat related obesity.[109] Sobetirome **55** is highly active while causing minor harmful side effects due to its selectivity for TRβ1 in the liver. Although the compound reached phase Ib in human clinical trials, it was withdrawn due to a similar but not identical molecule, eprotirome, that generated unexpected cartilage defects in dogs after long-term exposure.[109] However, sobetirome **55** did not show sign of thyrotoxic effect or adverse side effects so far, and is still under investigation for the treatment of orphan disease X-linked adrenoleukodystrophy.[109] Interestingly, other selective thyroid hormone analogues have been developed where the central CH_2 was replaced with a methyl or ketone (**56** and **57**, Figure 3.8).[110] 3,3-Diaryloxetane analogue **58** would be an interesting new option for medicinal chemists and could improve the physicochemical properties of these compounds. Oxetane **58** would be synthetically challenging, as the Friedel–Crafts reaction developed by the Bull group has never been tested on such hindered system.[50,88]

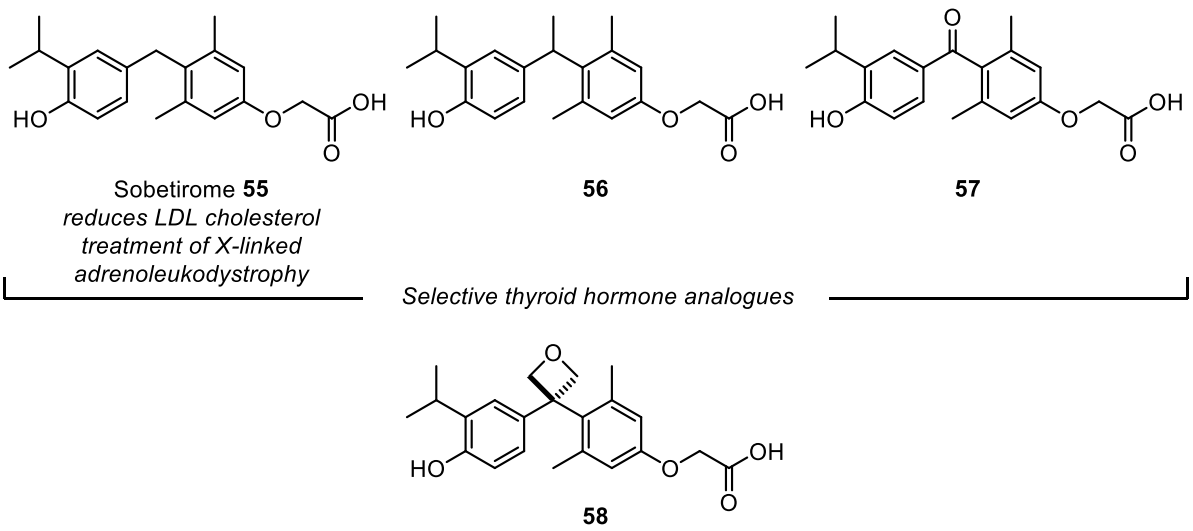


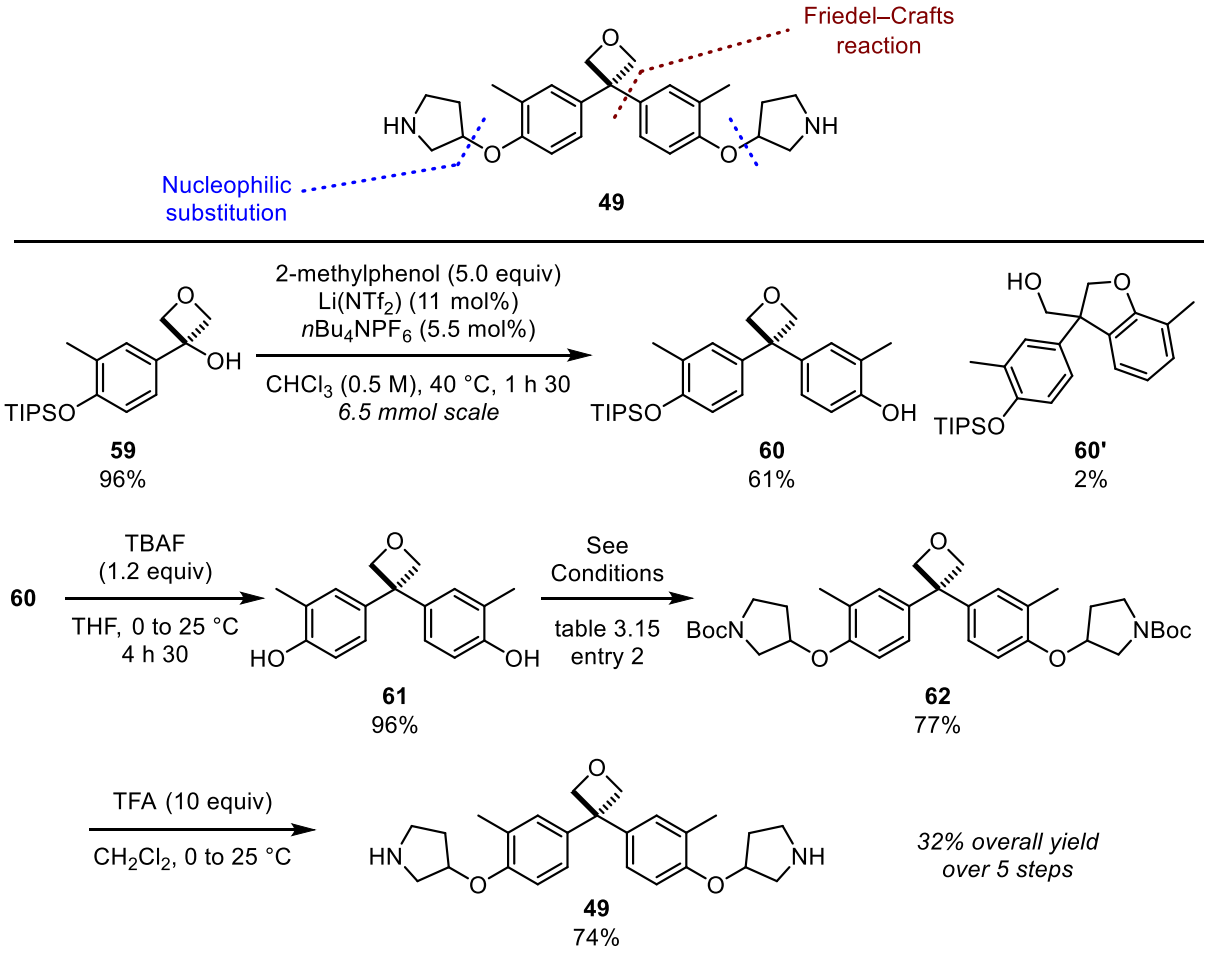
Figure 3.8: Sobetirome **55** and its analogues **56** and **57**, and proposed 3,3-diaryloxetane analogue **58**.

With the selection of the four drugs or bioactive molecules *gem*-dimethyl **48**, phenstatin **50** and methylated analogue **51**, and sobetirome **55**, the synthesis of 3,3-diaryloxetane analogues **49**, **53**, **54** and **58** was investigated.

3.5.2 Synthesis of 3,3-Diaryloxetanes Analogues **49**, **53**, **54** and **58**.

*3.5.2.1 Synthesis of 3,3-Diaryloxetane **49***

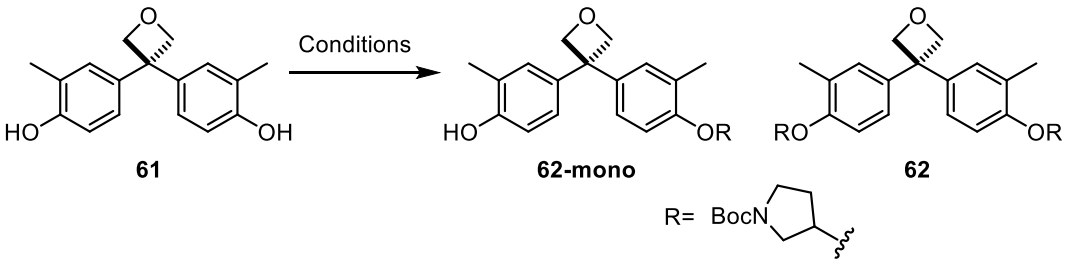
The synthesis of oxetane **49** involved two main disconnections: the incorporation of two pyrrolidine rings through nucleophilic substitution from a di-phenol intermediate, and a Friedel–Crafts reaction to build the 3,3-diaryloxetane core accessible from an oxetanol (Scheme 3.23, top). Oxetanol **59** was made in 96% yield from aryl bromide **29**, *n*BuLi and oxetanone **5**. Subjecting oxetanol **59** to the lithium-catalysed Friedel–Crafts alkylation of 2-methylphenol gave 61% of diaryloxetane **60**, along with trace amounts of dihydrobenzofuran **60'** (Scheme 3.23). The reaction was carried out on 6.5 mmol scale and 1.7 g of oxetane **60** was obtained. Removal of the TIPS protecting group with TBAF, afforded 96% of di-phenol intermediate **61**.



Scheme 3.23: Synthesis of 3,3-diaryloxetane **49**.

The introduction of the two Boc-protected pyrrolidines was attempted substituting 3-bromo-pyrrolidine with di-phenols **61** (entry 1, Table 3.15). Despite the excess amount of reagents and a long reaction time of 53 h, only 5% of the desired product **62** was obtained, while mono-substituted phenol **62-mono** was the major product. A Mitsunobu reaction was employed instead, using 3-hydroxypyrrolidine, which gave **62** in 77% yield when an excess of reagents and longer reaction time were applied (entry 2). Finally, Boc-deprotection using TFA yielded 74% of **49** in 32% over 5 steps.

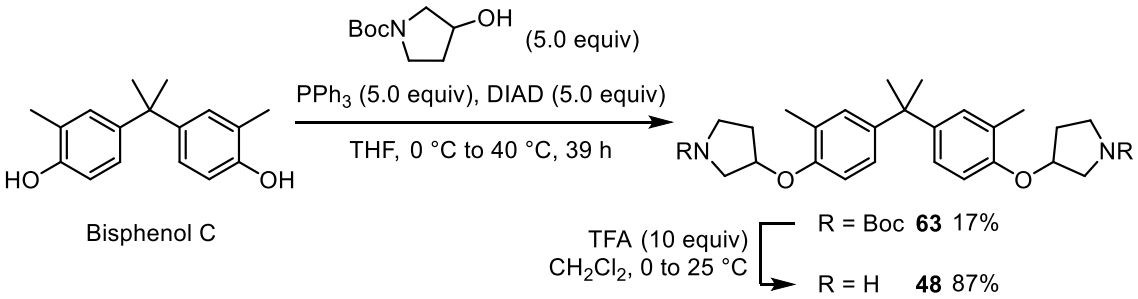
The bioactive *gem*-dimethyl **48** was not commercially available and needed to be synthesised in order to measure the physicochemical properties of this molecule and compare them with those for **49**. Product **48** can be made from commercially available bisphenol C (Scheme 3.24).



Entry	Conditions	Yield 62-mono (%)	Yield 62 (%)
1	BocN–Br (3.5 equiv) K_2CO_3 (4.0 equiv) DMF, 80 °C, 53 h	32	5
2	BocN–OH (6.0 equiv) PPh_3 (6.0 equiv), DIAD (6.0 equiv) THF, 0 to 80 °C, 48 h	0	77

Table 3.15: Synthetic investigation towards oxetane **62**.

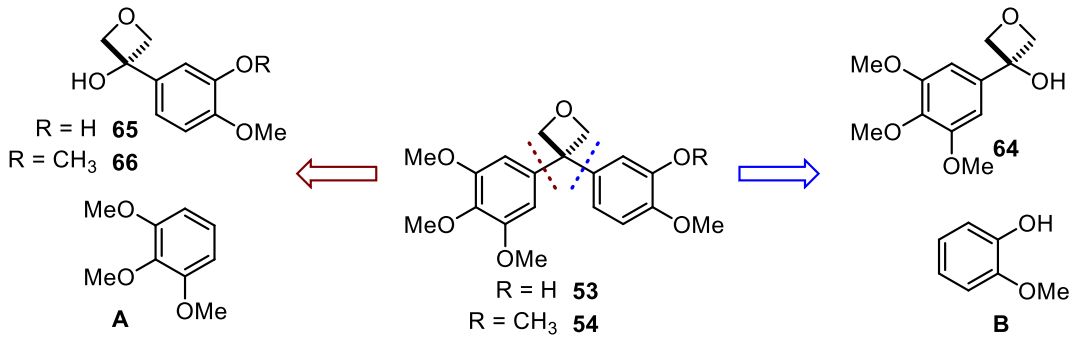
A Mitsunobu reaction between bisphenol C and 3-hydroxy-pyrrolidine gave only 17% of Boc-protected **63** despite increasing the amount of reagents, the temperature to 40 °C, and the reaction time. Removal of the Boc protecting group, afforded *gem*-dimethyl **48** in 87% yield.



Scheme 3.24: Synthesis of *gem*-dimethyl **48**.

*3.5.2.2 Synthesis of 3,3-Diaryloxetanes **53** and **54**.*

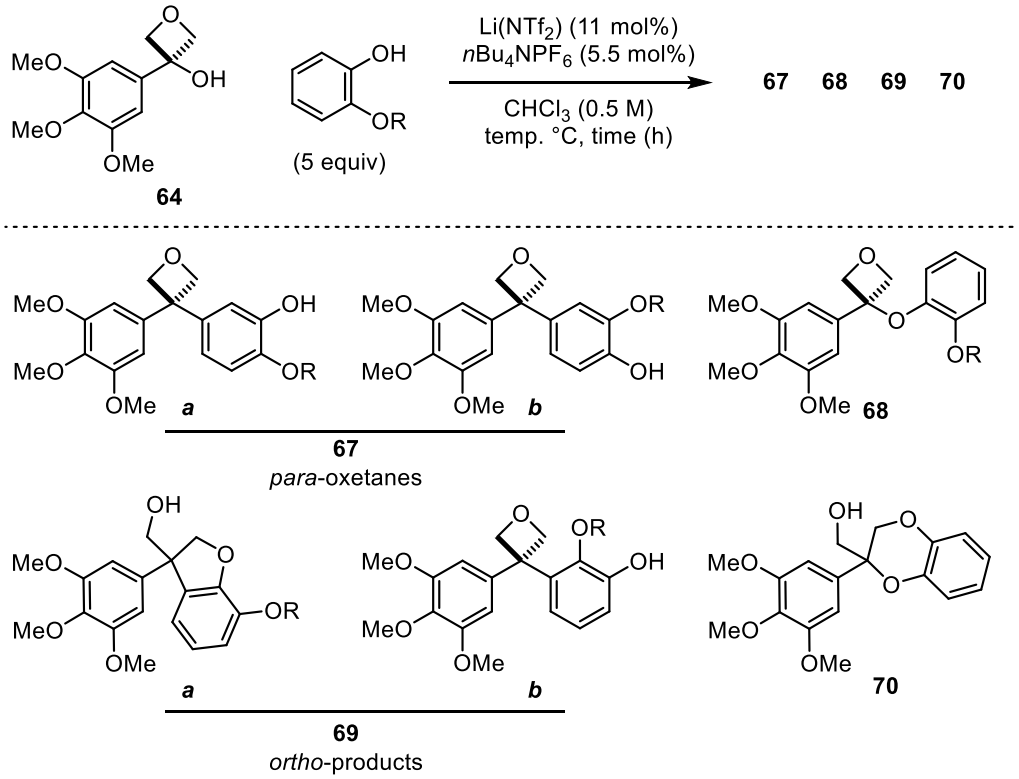
Oxetanes **53** and **54** can be made *via* two different Friedel–Crafts reactions, disconnecting either after the trimethoxybenzene ring (red disconnection) or before the right hand side aromatic (blue disconnection, Scheme 3.25). However, previous work in the Bull group found both trimethoxybenzene **A** and 2-methoxyphenol **B** were unsuccessful as nucleophiles for the lithium-catalysed Friedel–Crafts reaction.[88]



Scheme 3.25: Initial retrosynthesis for oxetanes **53** and **54**.

The Friedel–Crafts alkylation of alternative nucleophiles with oxetanol **64** was first investigated (Table 3.16). It was hypothesised that 2-methoxyphenol **B** was inefficient due to catalyst coordination between the two oxygen atoms. Replacing the methyl group with a protecting group could prevent this, while offering additional synthetic options. Indeed, the subsequent methylation could be achieved selectively on the desired hydroxyl group by protection-deprotection strategy.

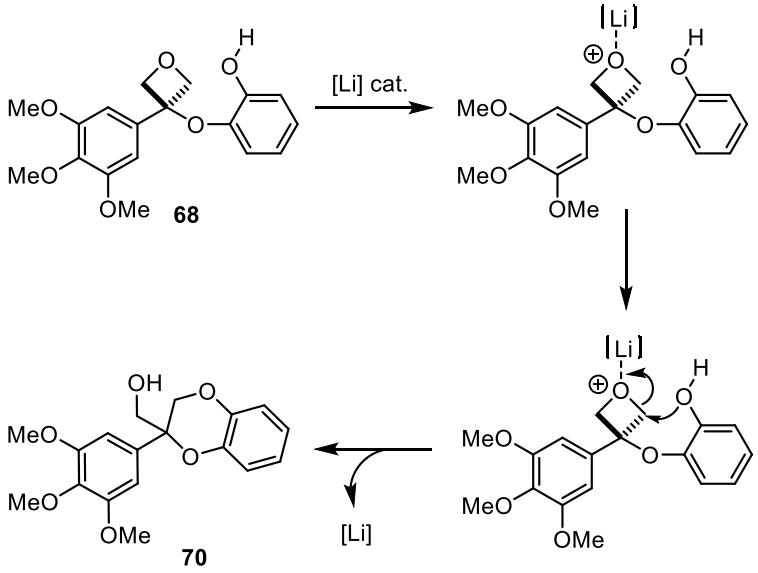
Five products were expected to be formed with 2-protected hydroxy-phenol (Table 3.16): two possible *para*-oxetanes **67** (a and b) where the reaction occurred in *para* position of the free or protected phenol, one oxetane ether **68** intermediate which has been shown to form reversibly during the reaction,[52] and two products resulting from reaction on the *ortho* position of the free phenol (dihydrobenzofuran **69a**) or the protected phenol (oxetane **69b**). However, no reactivity was observed when subjecting oxetanol **64** with TIPS protected phenol to the Friedel–Crafts conditions, even at longer reaction time or higher temperature, and starting material was mostly recovered (entry 1 and 2). Benzyl protected phenol as nucleophile resulted in a similar outcome (entry 3). Although heating the reaction to 60 °C afforded 9% of a complex mixture of oxetane **67** (a and b, entry 4), the reaction could not be improved further. The reaction was then run with unprotected 1,2-dihydroxybenzene as the nucleophile (entry 5). Surprisingly, this was the only nucleophile that promoted the reaction efficiently, giving 20% of the desired product **67**, with starting material recovered and a small amount of ether **68**. In addition, 32% of what was thought to be dihydrobenzofuran **69a** was obtained. However, after careful analysis, the compounds was actually dioxane **70**, which has never been observed before in this reaction. This was formed from ether **68**, where the *ortho*-hydroxyl group on the aromatic can ring open the oxetane to form a dioxane ring (Scheme 3.26). Completion of the reaction was achieved when the temperature was raised to 50 °C, though dioxane **70** was formed as the major product (entry 6). Increasing the temperature further to 60 °C gave nearly a 50:50 ratio between **67** and **70**, with 42% of oxetane **67** formed (entry 7).



Entry	R =	Temp. (°C)	Time (h)	Yield *para*-oxetane 67(%)[a,b]	Yield 70 (%)[a,b]
1	TIPS	40	20	0	0
2	TIPS	60	20	0	0
3	Bn	40	20	0	0
4	Bn	60	20	9	0
5	H	40	4	20	32
6	H	50	4	36	64
7	H	60	5	42	37

Table 3.16: Friedel–Crafts alkylation of various nucleophiles with oxetanol **64**. [a] Yield calculated by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard. [b] 0.20 mmol scale.

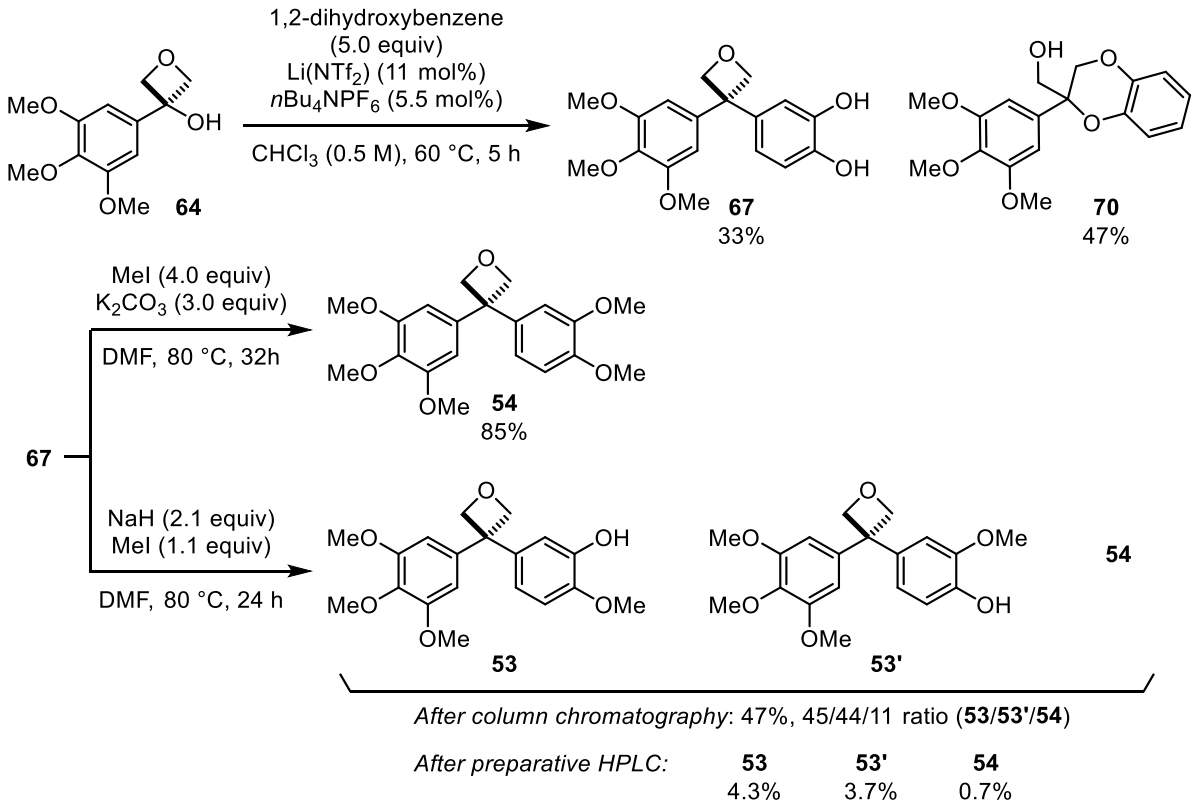
1,2-Dihydroxybenzene was surprisingly reactive while being able to coordinate the catalyst similarly to the other protected phenol. This suggests that the lack of reactivity of the other nucleophiles was not simply due to catalyst coordination.



Scheme 3.26: Formation of dioxane **70** from oxetane ether **68**.

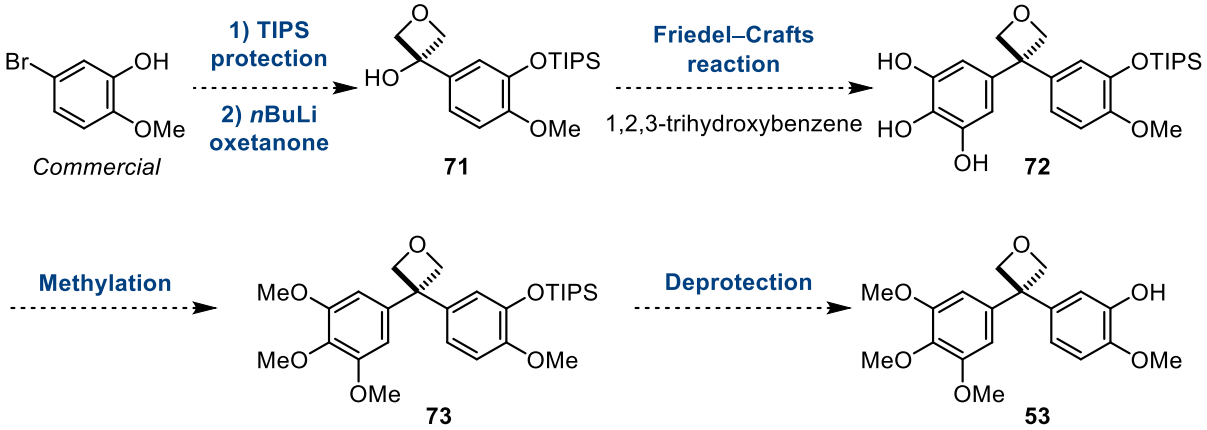
Scaling the Friedel–Crafts reaction (entry 7, Table 3.16) to 5 mmol afforded 3,3-diaryloxetane **67** in 33% yield with 47% of dioxane **70** which were separated by column chromatography (Scheme 3.27). Di-methylation of oxetane **67** to **54** was high yielding using excess MeI in the presence of K_2CO_3 in DMF (Scheme 3.27). In contrast, selective mono-methylation of **67** to **53** was more challenging. Using 2.1 equivalents of NaH followed by addition of 1.1 equivalents of MeI gave a 60:40 mixture of **53** and **53'**. Reducing the amount of NaH used to 1.1 equivalents did not improve the ratio and resulted in a mixture of 35:28:37 ratio (**53**/**53'**/**54**). The reaction was scaled up using the first conditions giving 47% of a 45:44:11 mixture of **53**/**53'**/**54**. Unfortunately, these could not be separated by column chromatography and preparative HPLC purification led to dramatic drop in yield, affording **53** in 4.3%, **53'** in 3.7% and traces amount of **54** (0.7%).[a]

[a] Separation performed by Pfizer.



Scheme 3.27: Synthesis of 3,3-diaryloxetanes **53** and **54**.

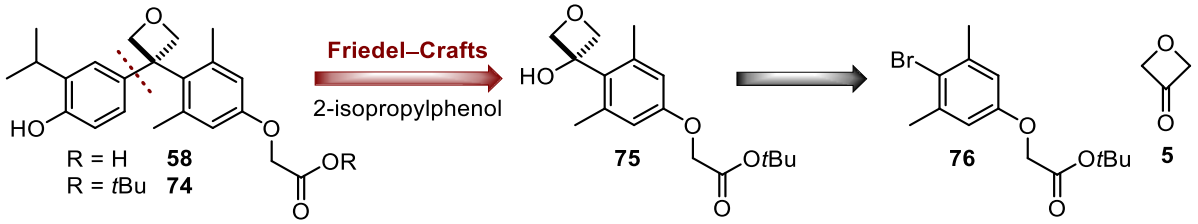
An alternative route could be adopted to achieve **53** selectively and in higher yield (Scheme 3.28). Protected oxetanol **71** can easily be made in two steps from commercial 5-bromo-2-methoxyphenol and oxetanone. Although 1,2,3-trimethoxybenzene is incompatible as a nucleophile in the lithium-catalysed Friedel–Crafts reaction, 1,2,3-trihydroxybenzene should react similarly as 1,2-dihydrobenzene to give oxetane **72** along with potential dihydrobenzofuran and dioxane side products. The methylation of all hydroxyl groups, followed by phenol deprotection would afford **53**.



Scheme 3.28: Alternative route to oxetane **53** from oxetanol **71**.

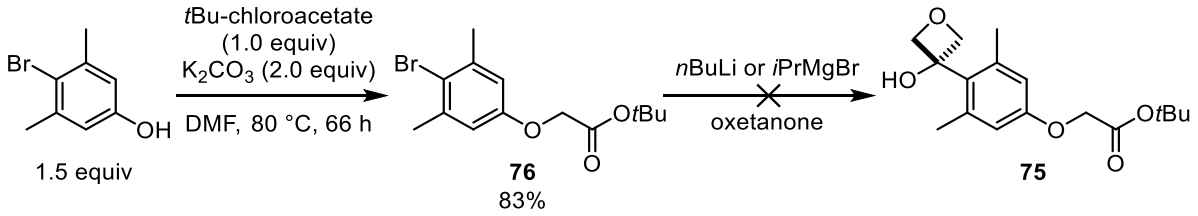
3.5.2.3 *Synthesis of 3,3-Diaryloxetane **58**.*

Oxetane **74**, with a protected acid, can be disconnected into 2-isopropylphenol and oxetanol **75** (Scheme 3.29), which in turn could be prepared from bromo-aryl **76** and oxetan-3-one **5**.



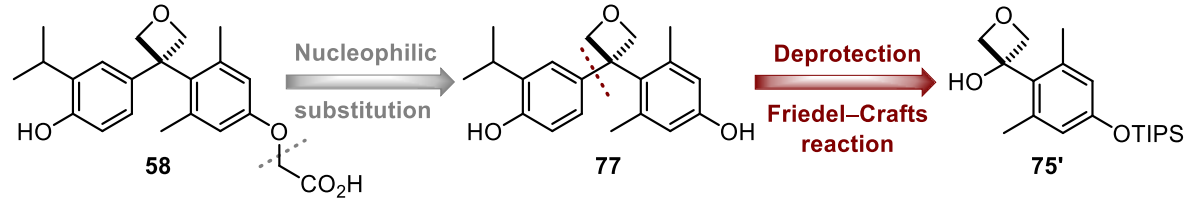
Scheme 3.29: Retrosynthesis of oxetane **58**.

*t*Bu-ester-protected arylbromide **76** was successfully prepared in 83% yield using standard nucleophilic substitution conditions (Scheme 3.30). The *t*Bu protecting group was selected as it is easy to remove under acidic conditions and as 3,3-diaryloxetanes proved to be stable in acidic solution (see part 3.4.1). However, oxetanol **75** could not be obtained from **76**, as *n*BuLi and Grignard reagents added onto the ester group instead of doing lithium-halide exchange due to the two hindering methyls, and the synthetic strategy had to be revised.



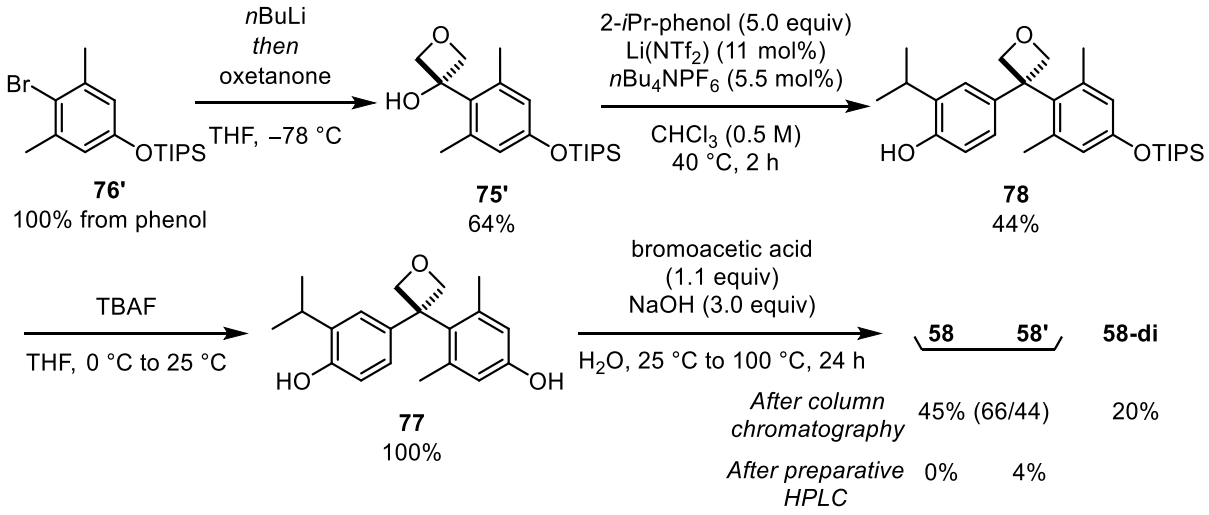
Scheme 3.30: Synthesis of oxetanol **75**.

The synthesis of oxetane **58** was then attempted in three steps from oxetanol **75'** (Scheme 3.31).



Scheme 3.31: Revised retrosynthesis of oxetane **58**.

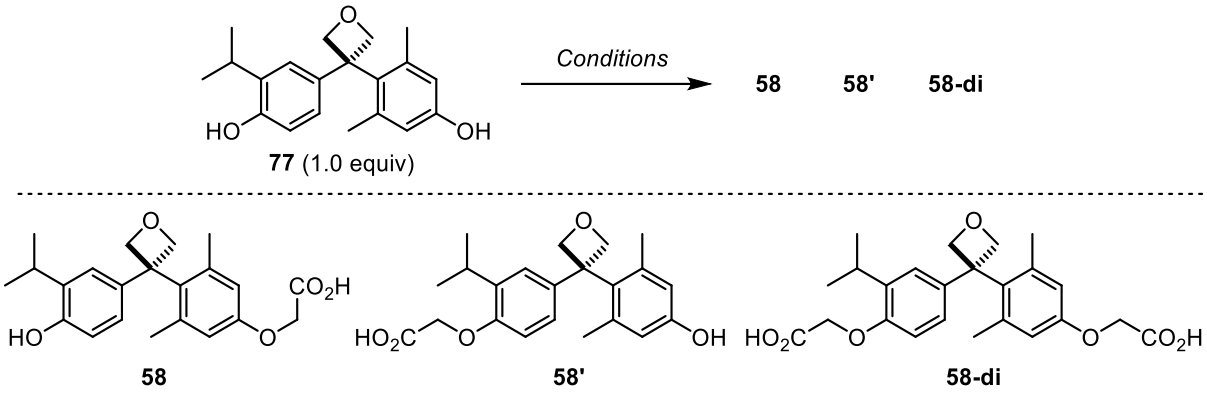
Oxetanol **75'** was made in 64% yield from TIPS protected aryl bromide **76'** (Scheme 3.32). Despite the steric hindrance on oxetanol **75'**, this reacted well under the Friedel–Crafts conditions giving protected oxetane **78** in 44% yield. TIPS deprotection afforded phenol **77** quantitatively. Unfortunately, incorporation of the alkyl chain was not selective despite the bulky *i*Pr group on one phenol ring. Several conditions were investigated and are shown in Table 3.17.



Scheme 3.32: Attempt to synthesise oxetane **58** from oxetanol **75'**.

Using 3 equivalents of NaOH as a base, with a 1:1 ratio of bromoacetic acid and phenol **77**, gave 48% of an inseparable 62/38 mixture of oxetane **58** and **58'**, along with 12% of di-alkylated product **58-di** (entry 1, Table 3.17). The use of a different base such as NaH in THF did not improve the selectivity nor the yield (entry 2). Reaction of oxetane **77** with protected *t*Bu-chloroacetate was investigated instead of the free carboxylic acid in order to improve the yield of the reaction, but also the selectivity as the *tert*-butyl group might sterically clash with the *i*Pr of the phenol ring (entry 3). The free carboxylic acid would then be available after simple deprotection. However, lower yield of **74** and **74'** were obtained with worse ratio compared to entry 1, and more of the di-alkylated product **74-di** was formed. Therefore the conditions developed in entry 1 were used for scaling the reaction, which gave 42% of **58** and **58'** (66/44 ratio), and 20% of di-acid **58-di** (scheme 3.32). Preparative HPLC was required in order to separate both mono acids,[b] which led to drastic loss of product with only 4% of **58'** isolated and none of the desired **58** recovered.

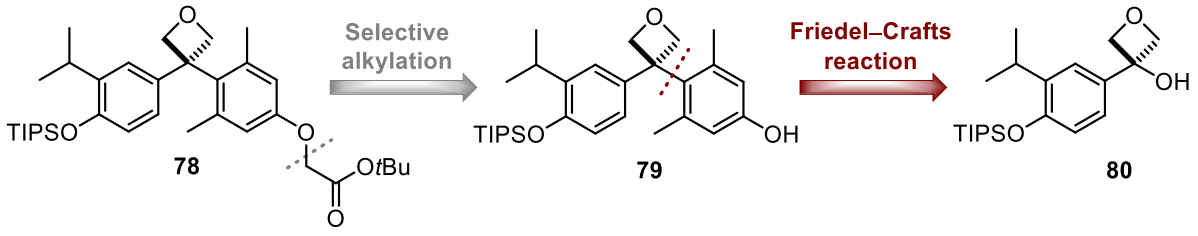
[b] Separation performed by Pfizer.



Entry	Conditions[a]			Results[b]			
	Base and reagent (equiv)	Solvent	Temp. (°C)	Yield 58+58' (%)	Ratio 58/58'	Yield 58-di (%)	Yield 77 (%)
1	NaOH (3.0 equiv) Bromo acetic acid (1.0 equiv)	H_2O	25 to 100	48	62/38	12	32
2	NaH (3.0 equiv) Bromo acetic acid (1.0 equiv)	THF	0 to 80	15	50:50	31	51
3[c]	K_2CO_3 (1.2 equiv) *t*Bu-chloroacetate (1.0 equiv)	DMF	80	31 (**74+74'**)	56:44 (**74**:**74'**)	32 (**74-di**)	12

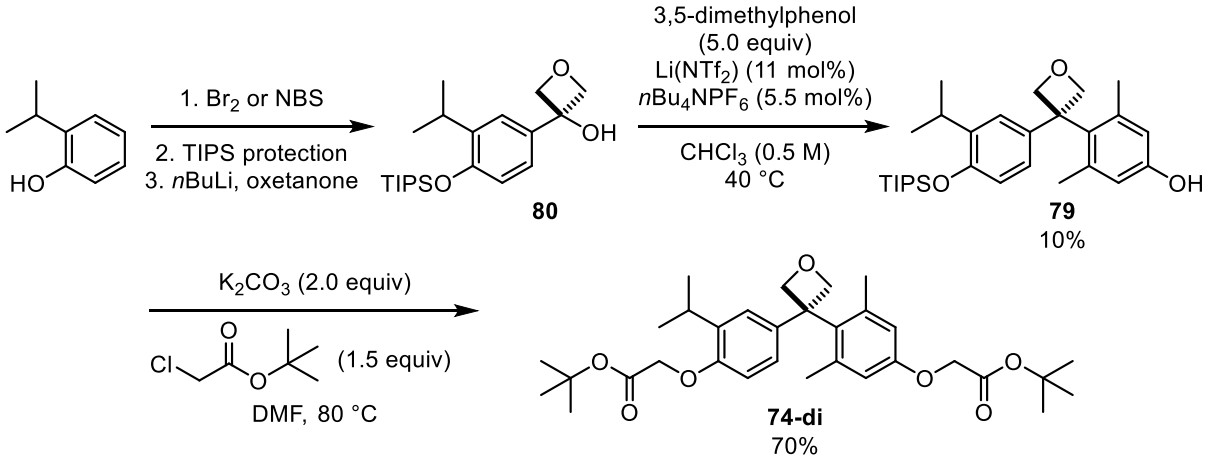
Table 3.17: Conditions screening for the synthesis of **58** from oxetane **77**. [a] Reaction on 0.10 mmol scale. [b] Isolated yield. [c] Reaction on 0.05 mmol scale.

An alternative Friedel–Crafts reaction was then investigated, introducing a phenol protecting group early in the synthesis to achieve selective alkylation of the 3,5-dimethylphenol group (Scheme 3.33). The Friedel–Crafts reaction between oxetanol **80** and 3,5-dimethylphenol poses interesting question about the tolerance of the Friedel–Crafts reaction towards steric hindrance on the nucleophile. Indeed, the *para* position on 3,5-dimethylphenol will be highly congested which might favour dihydrobenzofuran formation through reaction on the least-hindered *ortho* position.



Scheme 3.33: Third strategy towards oxetane **58** from acid-protected **78**.

Friedel–Crafts alkylation of 3,5-dimethylphenol with oxetanol **80**[c], gave 10% of oxetane **79** despite steric hindrance on the nucleophile (Scheme 3.34). Substitution of *t*Bu-chloroacetate with phenol **79** under mild basic conditions led to unexpected TIPS deprotection and only **74-di** was formed in 70% yield. TIPS protecting groups are usually highly stable in presence of bases but not under strong acidic conditions. The *t*Bu-chloroacetate reagent might have decomposed over time producing HCl and leading to deprotection. Purification of *t*Bu-chloroacetate might solve this issue. Alternatively, other *t*Bu-halide-acetate could be used as well, or acid-stable benzyl protecting group could be employed instead. These routes will be investigated in the future.



Scheme 3.34: Synthesis of oxetane **58** was attempted from oxetanol **80**, protecting one phenol to selectively alkylate the other.

3.5.3 Conclusion

The preparation of four 3,3-diaryloxetane-containing drug analogues has been attempted in this section, with three successfully achieved to date. Their synthesises showed the utility of the Friedel–Crafts reaction, previously developed by the Bull group,[50] in a drug discovery context. In addition, the robustness of the reaction towards steric hindrance on the oxetanol has been further demonstrated. The physicochemical properties and ADMET parameters of the oxetane analogues and the parents molecules are currently being measured by Pfizer. This will allow further assessment of 3,3-diaryloxetanes as isosteres for benzophenones and 1,1-diarylalkanes in actual drugs, drug candidates or biologically active molecules. The biological activity of the active parent molecules and the new 3,3-diaryloxetane analogues will also be studied and compared, to understand the effect of this replacement on the biological activity and establish 3,3-diaryloxetanes as bioisosteres. With the promising results obtained on 3,3-diaryloxetanes, we then turned our attention towards the aza–analogues: 3,3-diarylazetidines.

[c] Synthesised by Juan Rojas.

4. Catalytic Generation and Reaction of Azetidinyl Carbocations

The investigations discussed in this section have been published in *Org. Lett.*[111] and *J. Org. Chem.*[112] These works were carried out in collaboration with Dr Camille Denis[113] and Anna Lazaridou[114] respectively.

4.1 3,3-Diarylazetidines

4.1.1 3,3-Diarylazetidines in Bioactive Molecules

3,3-Diarylazetidines represent an interesting alternative linking group for diarylmethanes and diarylalkanes offering an additional diversification point on the nitrogen atom and increased Fsp^3 character (Figure 4.1). In addition, use of 3,3-diarylazetidines leads to conformational constraints, potentially increasing interaction with a desired biological target, making diarylazetidines valuable replacement groups for diarylamines.

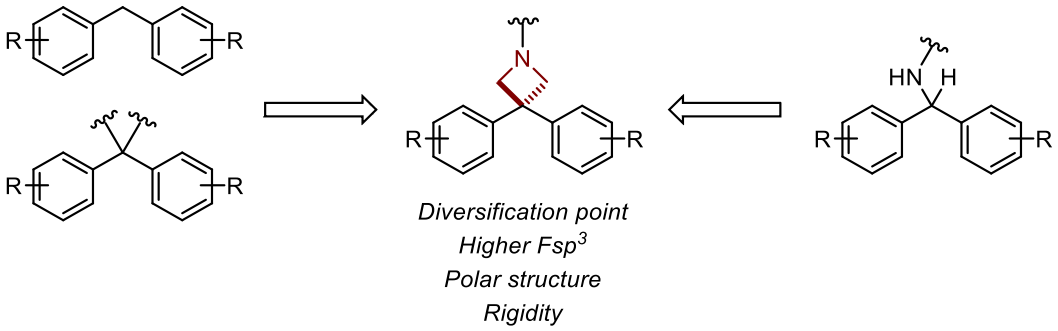


Figure 4.1: 3,3-Diarylazetidines as potential isosteres for diarylmethanes, diarylalkanes and diarylamines.

Prior to this work, only few examples of molecules containing a 3,3-diarylazetidine motif were known in the literature, with biological activities such as: kinase and cyclohexane-based prolylcarboxypeptidase (PrCP) inhibition, or β2 adrenergic receptor agonist (Figure 4.2).[115]

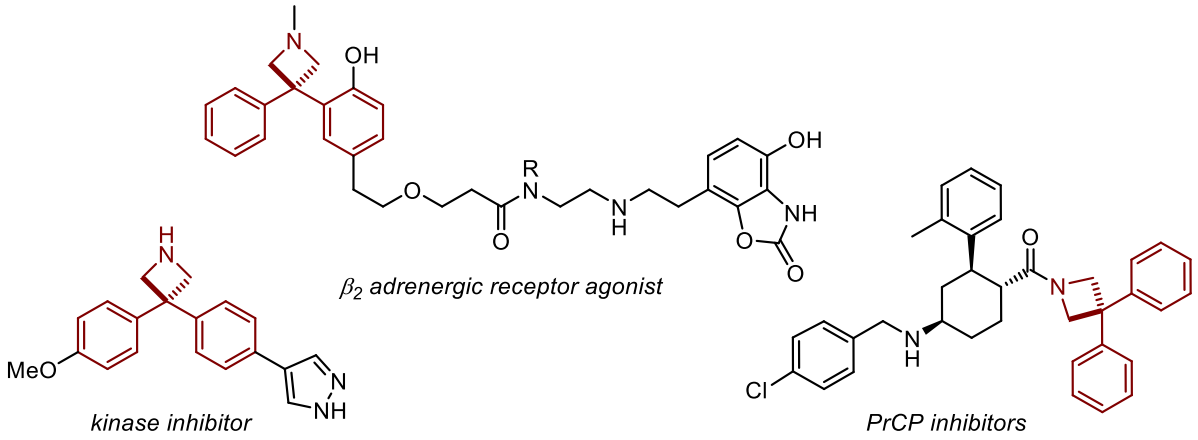
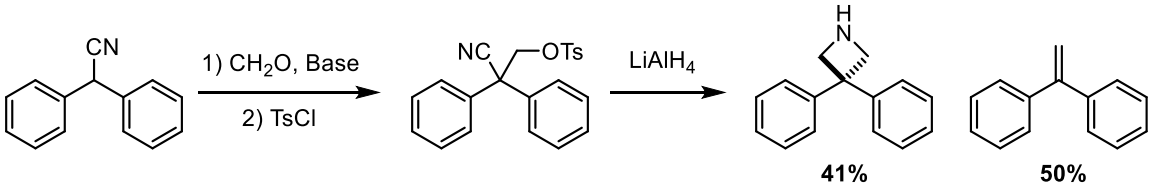


Figure 4.2: Examples of bioactive molecules containing a 3,3-diarylazetidine.

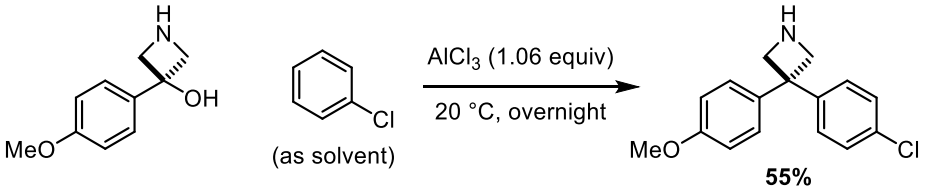
4.1.2 Synthetic Approaches to 3,3-Diarylazetidines

A limited number of synthetic methods were available to access this motif at the start of this work. In 1994, Fröhlich reported one example of a 3,3-diarylazetidine made in three steps from a nitrile intermediate, *via* a $LiAlH_4$-mediated ring-closure strategy (A, Scheme 4.1).[116] During the last ring closing step, the authors observed 50% of the 1,1-diarylalkene as the major product alongside a 41% yield of the desired diarylazetidine. This was formed through competitive elimination promoted by the highly π–conjugated system. The competitive elimination makes the method inefficient for accessing 3,3-diarylazetidines more widely. More recently, two patents reported the first synthesis of two 3,3-diarylazetidines in moderate yield *via* Friedel–Crafts reaction with 3-arylazetidin-3-ols using stoichiometric or excess amount of $AlCl_3$ and TfOH to promote the reaction. These methods showed the possibility of generating azetidinyl carbocation species in strained ring system from easily accessible azetidinol starting materials, generating water as the only by-product (B and C, Scheme 4.1).[115a,b] However, the use of strong Lewis and Brønsted acids limits the functional group tolerance of these methods. Moreover, large excesses of aromatic nucleophile, long reaction times and toxic solvent further decrease the attractiveness of these methodologies. Therefore, a general method to broadly access 3,3-diarylazetidines was required with mild conditions that would allow incorporation of a variety of functional groups in high yields.

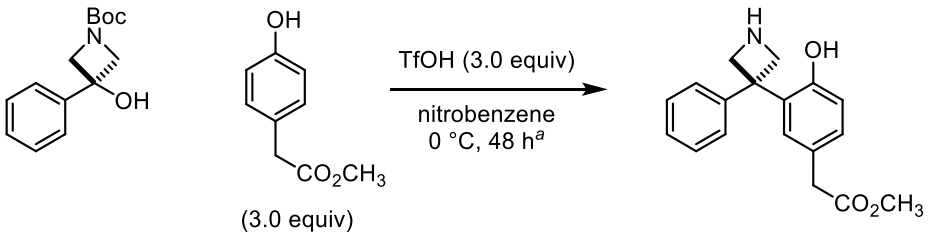
A) Fröhlich, J. *et al*. *Heterocycles* **1994**, 37, 1879.



B) Woodhead, S. J. *et al*. WO2006136830A1, **2006**.

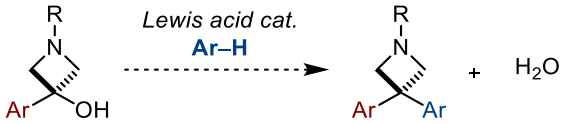


C) Donald, D. K. *et al*. WO2011048409A1, **2011**.



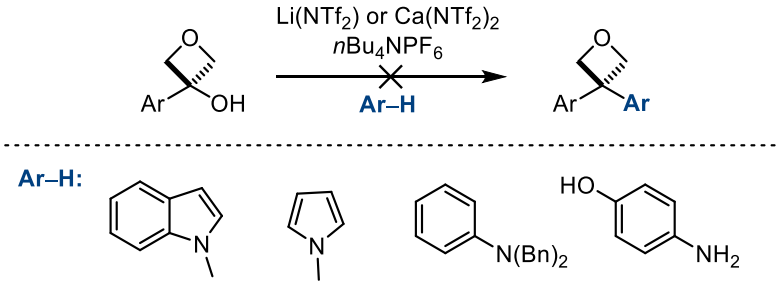
Scheme 4.1: Previous synthetic methods towards 3,3-diarylazetidines.[a] Yield not reported.

Inspired by these works and the previous Friedel–Crafts methodology towards 3,3-diaryloxetanes developed by the Bull group,[50] the synthesis of 3,3-diarylazetidines was envisaged *via* a catalytic Friedel–Crafts reaction (Scheme 4.2). The use of a mild Lewis acid was particularly interesting to catalyse this reaction as it was hoped this would lead to higher functional group tolerance.



Scheme 4.2: Proposed Lewis acid-catalysed Friedel–Crafts reaction of 3-arylazetidin-3-ols with arenes towards 3,3-diarylazetidines.

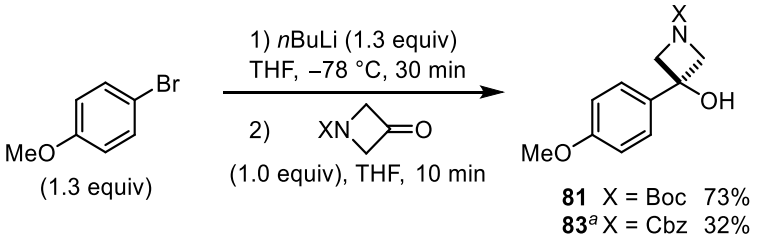
However, concerns were raised at the start of this investigation. The prior work on 3,3-diaryloxetanes showed that nitrogen-containing nucleophiles, such as 1-methylindole and (un)protected anilines, were unsuccessful under the lithium-catalysed Friedel–Crafts conditions, with only oxetanol starting material returned (Scheme 4.3).[88] It was hypothesised that the lack of reactivity of the anilines may be due to the coordination of the lithium catalyst to the nitrogen atom. Therefore, the formation of an azetidinyl carbocation mediated by a mild Lewis acid catalyst represents a substantial challenge. The nitrogen atom of the azetidine ring or the atoms of the protecting group on the nitrogen have the potential to strongly coordinate the catalyst preventing the reaction occurring.



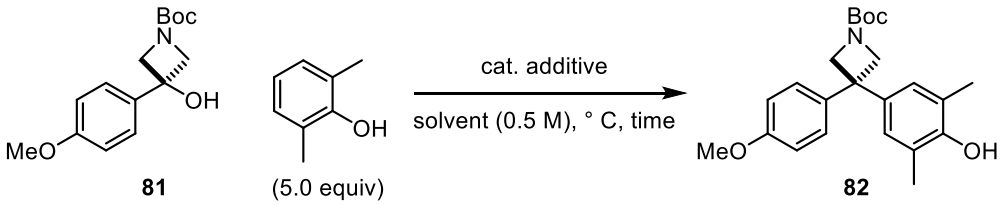
Scheme 4.3: Unsuccessful nitrogen-containing nucleophiles under lithium-catalysed Friedel–Crafts reaction towards 3,3-diaryloxetanes.

4.1.3 Initial Screening with Boc-Protected Azetidin-3-ols

Boc-protected azetidinol **81** was chosen for initial screening as the electron-rich character of the pre-installed aromatic group would stabilise and aid the carbocation formation.[113] It was synthesised by adding 1-Boc-azetidin-3-one to the corresponding preformed organolithium (Scheme 4.4). 2,6-Dimethylphenol was selected as the initial nucleophile as *O*-alkylation is prevented and so only the *para*-substituted product is obtained. Camille Denis first investigated the conditions previously developed for 3,3-diaryloxetanes, using Li(NTf_2) as catalyst with an ammonium additive. They were inefficient in promoting the Friedel–Crafts reaction with azetidinol **81** recovered (entry 1, Table 4.1). Ca(NTf_2)$_2$ and $FeCl_3$ were also chosen for screening as they were previously successful Lewis acid for oxetanols and other π-activated alcohols,[50,86,103] and are inexpensive catalysts and abundant metals.[117] Niggemann's calcium catalyst[103] was investigated first. Using 5 mol% afforded the desired 3,3-diarylazetidine **82** in 2% yield, along with 6% of a side product, possibly the *O*-alkylated product, and 90% of returned starting material (entry 2). The good overall recovery of material indicated that the azetidinol and the product were not degrading under the reaction conditions. Leaving the reaction for 24 h only led to a small increase in yield of 3,3-diarylazetidine **82** to 11% (entry 3), with no side product observed. This suggests that the formation of *O*-alkylation product is reversible and can be converted into product **82**. Running the reaction for a further 24 h or increasing the temperature to 60 °C did not improve the outcome (entry 4 and 5). When chloroform was replaced with CH_2Cl_2, a slight improvement was observed, but this could not be increased further despite longer reaction time (entry 6). Using stoichiometric amount of $FeCl_3$ or increasing Ca(NTf_2)$_2$ loading only resulted in slightly higher yield of 36% and 21% (entries 8 and 9).



Scheme 4.4: Synthesis of azetidinols **81** and **83**. [a] Synthesised by Camille Denis.



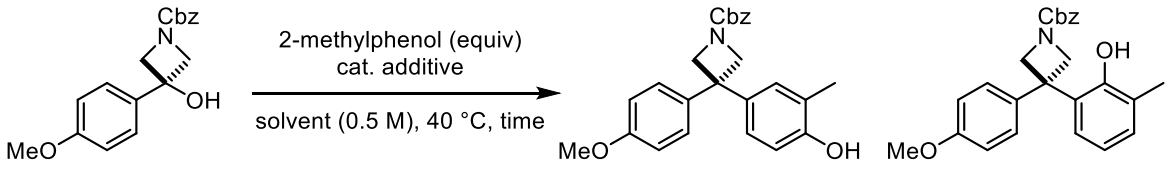
Entry	Catalyst/ additive (mol%)	Time (h)	Temp. (°C)	Solvent	Yield (%)[a]		
					82	Side product	RSM 81
1	$Li(NTf_2)/nBu_4NPF_6$ (11/5.5)	2	40	$CHCl_3$	0	0	100
2	$Ca(NTf_2)_2/nBu_4NPF_6$ (5/5)	2	40	$CHCl_3$	2	6	90
3	$Ca(NTf_2)_2/nBu_4NPF_6$ (5/5)	24	40	$CHCl_3$	11	0	80
4	$Ca(NTf_2)_2/nBu_4NPF_6$ (5/5)	48	40	$CHCl_3$	8	6	74
5	$Ca(NTf_2)_2/nBu_4NPF_6$ (5/5)	2	60	$CHCl_3$	6	0	78
6	$Ca(NTf_2)_2/nBu_4NPF_6$ (5/5)	2	40	CH_2Cl_2	10	0	78
7	$Ca(NTf_2)_2/nBu_4NPF_6$ (5/5)	14.5	40	CH_2Cl_2	18	0	73
8	$FeCl_3$/- (100)	2	40	CH_2Cl_2	36	0	49
9	$Ca(NTf_2)_2/nBu_4NPF_6$ (20/20)	2	40	CH_2Cl_2	21	0	52

Table 4.1: Optimisation of the Friedel–Crafts alkylation of 2,6-dimethylphenol with Boc-protected azetidinol **81**, carried out by Camille Denis.[a] Yield calculated by ^1H NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard.

None of the parameters tested in table 4.1 seemed to improve the reaction profile despite Camille's efforts, showing the reduced reactivity of azetidine compared to oxetane.[113] At this point, the coordination of the catalyst to the nitrogen atom of the azetidine or to the atoms of the Boc-protecting group was thought to be the reason for the poor reactivity. The effect of the protecting group on the reaction was then investigated and Cbz-protected azetidinol **83** was initially prepared by Camille Denis in 32% yield under standard conditions adding 1-Cbz-azetidin-3-one to a preformed organolithium species (Scheme 4.4).[113]

4.1.4 Optimisation with Cbz-Protected Azetidinol **83**

2-Methylphenol was selected as the nucleophile in order to study the regioselectivity of the reaction. Surprisingly, subjecting Cbz-protected azetidinol **83** to the lithium-catalysed Friedel–Crafts conditions led to a dramatic increase in reactivity compared to Boc-protected azetidinol **81**, with 3,3-diarylazetidine **84** obtained in 45% yield (entry 1, Table 4.2). This unexpected difference in reactivity will be studied in greater detail later in this chapter (section 4.1.8). Pleasingly, the reaction was selective for the *para*-substituted product **84** with only 1% of *ortho*-substituted azetidine **84'** observed, and both were easily separated by flash column chromatography. It is worth noting that the hydroxyl group of *ortho*-substituted **84'** did not undergo ring opening of the azetidine as was the case with the oxetane derivatives, and *ortho*-phenol substituted azetidine can be obtained. $FeCl_3$ and $Ca(NTf_2)_2$ were far more effective catalysts than $Li(NTf_2)$ (entries 2 and 3), with $Ca(NTf_2)_2$ being the most successful catalyst giving 3,3-diarylazetidine **84** in 92% yield (entry 3). In agreement with Niggemann's and Leonori's works, the nBu$_4$NPF$_6$ additive was crucial to the reactivity due to anion metathesis leading to a stronger Lewis acid, $Ca(NTf_2)(PF_6)$ (entry 4).[118] In addition, the reaction time was also important and no product was formed after only 1 h (entry 5). Pleasingly, the equivalents of nucleophile could be reduced to three without adversely affecting the yield (entry 6). The replacement of CH_2Cl_2 with more environmental friendly and less harmful solvents was then investigated. The reaction in coordinating solvents such as EtOAc and THF was unsuccessful, while heptane and toluene were suitable for the reaction giving high yields of **84** (entries 7 to 10). Although toluene gave a slightly higher yield of 96% (entry 10) compared to 92% in CH_2Cl_2 (entry 3), the latter showed better substrate solubility and so these conditions were chosen to study the scope of the reaction.



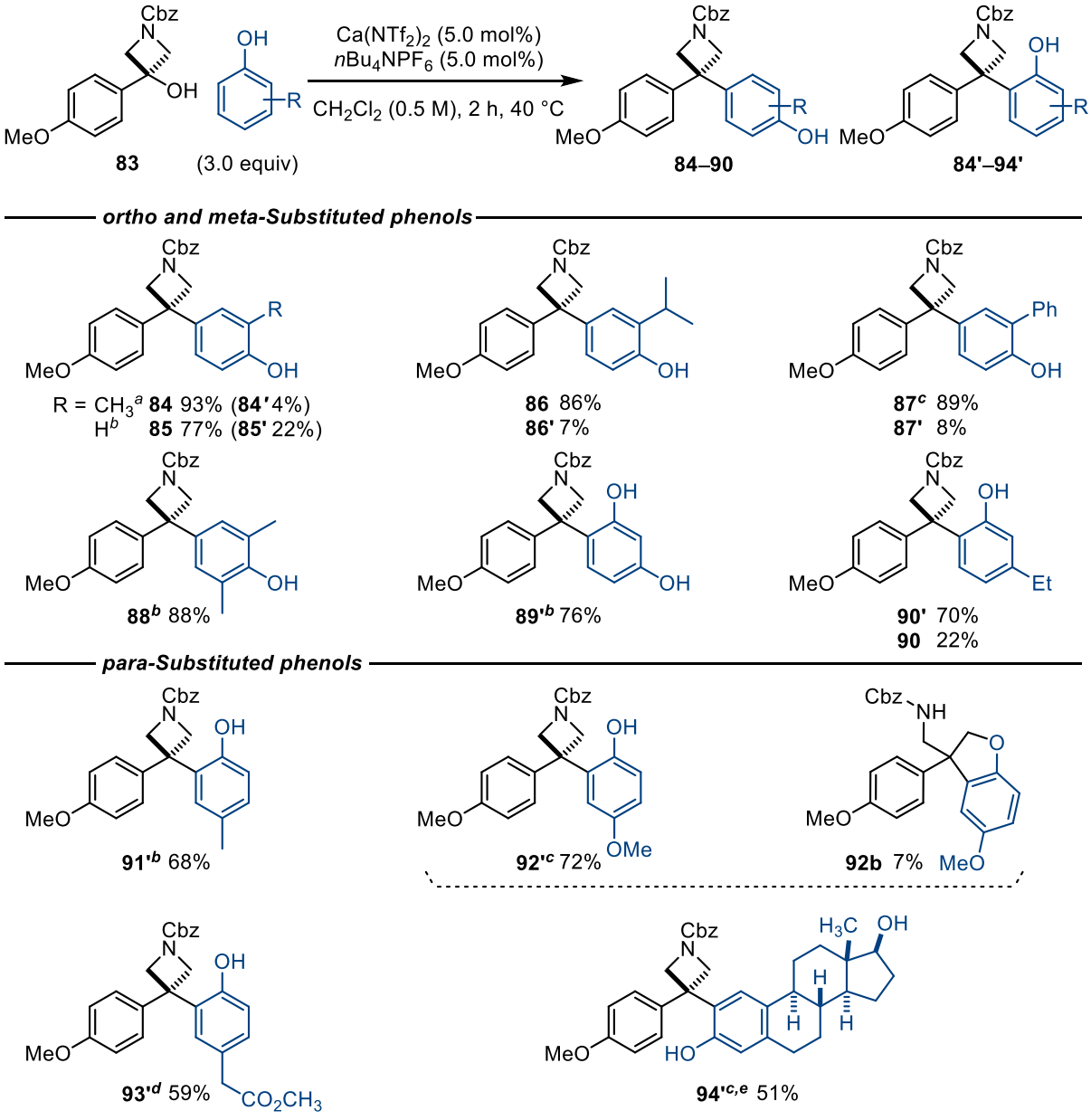
83 (1.0 equiv) **84** **84'**

Entry	Catalyst/ additive (mol%)	Time (h)	Equiv. nucleophile	Solvent	Yield (%)[b]		
					84	84'	RSM 83
1[a]	$Li(NTf_2)/nBu_4NPF_6$ (11/5.5)	2	5	CH_2Cl_2	45	1	23
2	$FeCl_3$/- (5)	2	5	CH_2Cl_2	75	4	0
3[a]	$Ca(NTf_2)_2/nBu_4NPF_6$ (5/5)	2	5	CH_2Cl_2	92	6	0
4	$Ca(NTf_2)_2$/- (5)	2	5	CH_2Cl_2	0	0	100
5[a]	$Ca(NTf_2)_2/nBu_4NPF_6$ (5/5)	1	5	CH_2Cl_2	0	0	100
6	$Ca(NTf_2)_2/nBu_4NPF_6$ (5/5)	2	3	CH_2Cl_2	94	5	0
7[a]	$Ca(NTf_2)_2/nBu_4NPF_6$ (5/5)	2	3	EtOAc	0	0	100
8[a]	$Ca(NTf_2)_2/nBu_4NPF_6$ (5/5)	2	3	THF	4	3	80
9[a]	$Ca(NTf_2)_2/nBu_4NPF_6$ (5/5)	2	3	heptane	91	4	0
10	$Ca(NTf_2)_2/nBu_4NPF_6$ (5/5)	2	3	toluene	96	3	0

Table 4.2: Optimisation of the Friedel–Crafts alkylation of 2-methylphenol with Cbz-protected azetidinol **83**. Reaction conditions: azetidinol **83** (0.25 mmol), solvent (0.5 mL). [a] Experiment carried out by Camille Denis. [b] Yield calculated by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as the internal standard.

4.1.5 Scope of Nucleophiles for the Synthesis of 3,3-Diarylazetidines

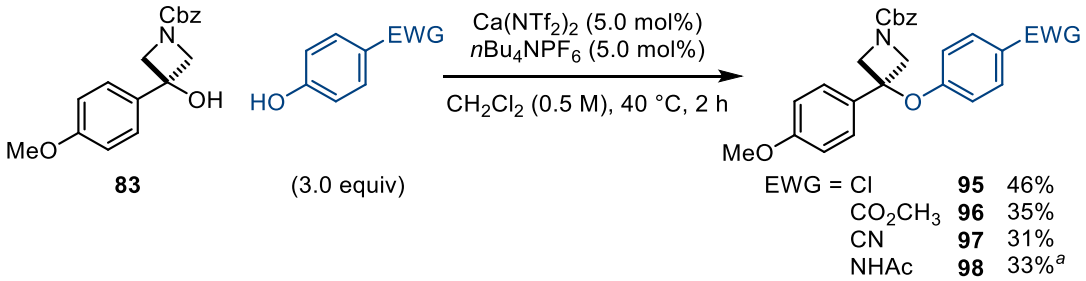
Pleasingly, the reaction between azetidinol **83** and 2-methylphenol could be scaled up to 4 mmol to provide 1 g of 3,3-diarylazetidine **84** in 93% yield and 4% of azetidine **84'** (Scheme 4.5). Using phenol as the nucleophile reduced the regioselectivity with 22% of *ortho* addition product **85'** formed and 77% of **85** resulting from the reaction at *para* position. *ortho*-Substituted phenols were generally high yielding with excellent regioselectivity and isopropyl, phenyl or dimethyl groups could be incorporated in 86–89% yields (**86**, **87** and **88**, Scheme 4.5).



Scheme 4.5: Friedel–Crafts alkylation of phenols with azetidinol **83**. General reaction conditions: azetidinol **83** (0.50 mmol), nucleophile (1.50 mmol), $Ca(NTf_2)_2$ (5.0 mol%), nBu_4NPF_6 (5.0 mol%), CH_2Cl_2 (1.0 mL), 40 °C, 2 h. [a] 4.00 mmol scale. [b] Synthesised by Camille Denis. [c] 4 h. [d] 24 h. [e] 0.25 mmol scale.

In the previous work from the Bull group, the synthesis of 3,3-diaryloxetanes with phenolic OH groups in the *ortho* position were inaccessible due to the competitive ring opening by the adjacent hydroxyl group.[50,88] For this reason, *meta*-substituted phenols were low yielding due to poor regioselectivity leading to formation of dihydrobenzofurans.[50,88] In comparison, the azetidine is stable towards ring opening under the reaction conditions, and *meta*-substituted phenols gave product in high yield. For instance, the *ortho*-addition product **89'** could be synthesised in 76% yield using 1,3-dihydroxybenzene as the nucleophile. Interestingly, 3-ethylphenol reacted on the least hindered position giving *ortho*-substituted azetidine **90'** as major product instead of the expected *para*-substituted **90**. Further *ortho*-addition products, such as 3,3-diarylazetidine **91'**, can be prepared in good yield when using *para*-substituted phenols with electron donating groups. A longer reaction time was required for the reaction to proceed when employing *para*-methoxyphenol as the nucleophile. With an extended reaction time of 4 h, azetidine **92'** was isolated in a 72% yield. Surprisingly, this nucleophile was the only phenol tested that led to opening of the azetidine ring and formation of dihydrobenzofuran **92b** in 7% yield. The highly electron-donating *para*-methoxy group increasing the nucleophilicity of the phenol may explain this observation. Although coordinating ester groups seemed to slow the reaction down, they were still tolerated when the reaction was left for 24 h allowing the synthesis of azetidine **93'** in a respectable yield. Importantly, highly functionalised phenols were successful nucleophiles. For example, β-estradiol reacted on the least hindered *ortho*-position, giving azetidine **94'** in 51% yield, showing the possibility to apply this methodology to late-stage functionalisation.

In contrast, phenols bearing less electron-rich or electron withdrawing group such as Cl, ester, or cyanide at the *para* position, did not give 3,3-diarylazetidines (Scheme 4.6). Instead *O*-alkylation occurred exclusively giving ethers **95** to **97** in 31% to 46% yields. Paracetamol produced azetidine ether **98** in 33% yield and required higher temperature and longer reaction time to overcome catalyst coordination. These products are interesting on their own right, as previous examples of 3-arylazetidin-3-ethers have been reported with interesting biological activities. For example ethers of this type have been reported to have activity as ligands for monoamine transporters and modulators of melanocortin receptors.[119]

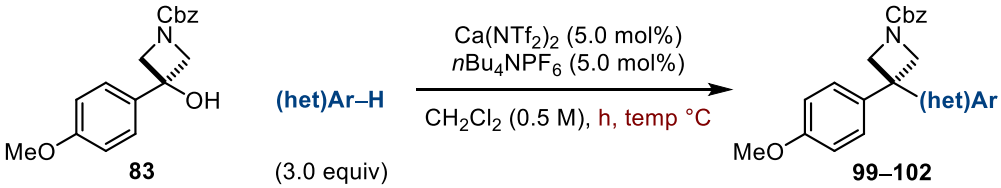


Scheme 4.6: Reaction between azetidinol **83** and phenols, bearing an *para*-EWG group, produced unexpected azetidine ethers. [a] 60 °C, 28 h.

These results are consistent with previous observations from the Bull group on the formation of oxetane ethers during the lithium-catalysed Friedel–Crafts alkylation of phenols.[52] In this study, oxetane ethers were identified as off-cycle products formed from *O*-alkylation of *para*-substituted phenols, which was quickly reversible for most substituents but not when the *para*-substituent was a nitrile.[52] Interestingly, the yield of Cl-azetidine ether **95** remained constant when the reaction was left for longer time, which was not the case for Cl-oxetane ether which was converted into Friedel–Crafts product after 20 h.[52] This suggests that the formation of azetidine ether may not be reversible in the case of phenols substituted with a *para*-EWG, and this method could therefore be used for the synthesis of such azetidine products.

Non-phenolic aromatics and heteroaromatics were then assessed as nucleophiles (Table 4.3). 1,3-Dimethoxybenzene was less reactive than 1,3-dihydroxybenzene, giving 3,3-diarylazetidine **99** in 54% yield (entry 1, Table 4.3). The reaction with heteroaromatics generally required longer time and higher temperatures to proceed, likely due to catalyst coordination. Nitrogen heteroaromatics are prevalent in medicinal chemistry and both indole and pyrrole rings were successfully incorporated into 3,3-diarylazetidines **100** and **101** under the developed calcium-catalysed Friedel–Crafts conditions (entries 2 to 4). Azetidine indole **100** was initially obtained in 22% yield in CH_2Cl_2 at 60 °C (entry 2) but could be optimised to 45% when the temperature was increased to 80 °C in toluene (entry 3). Interestingly, the 2– and 3–positions of 1-methylpyrrole reacted with the azetidinyl carbocation, affording pyrrole **101a** in 33% yield as major product and azetidine **101b** in 12% yield. The two isomers were successfully separated through column chromatography (entry 4). 2-Methylfuran and 2-methylthiophene rings were also compatible nucleophiles with 80% and 60% yields of **102** and **103** obtained respectively (entries 5 and 6). Other nucleophiles such as thioanisole, pyridine and 1-methylpyrazole were tested under the reaction conditions. Unfortunately, no product was observed with only starting material returned.

The difference in reactivity of non-phenolic and heteroaromatic nucleophiles between oxetanes and azetidines in Friedel–Crafts reactions is quite fascinating. 1,3-Dimethoxybenzene was poorly reactive with oxetanol under lithium-catalysed Friedel–Crafts reaction giving only 17% of 3,3-diaryloxetane,[50,88] whereas 54% of azetidine **99** was obtained with the same nucleophile. Most importantly, 1-methylindole, 1-methylpyrrole and 2-methylthiophene were unsuccessful nucleophiles for the synthesis of 3,3-diaryloxetanes. This difference in reactivity might originate from a difference in carbocation intermediate stabilisation.



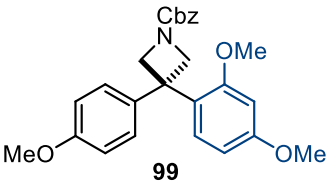
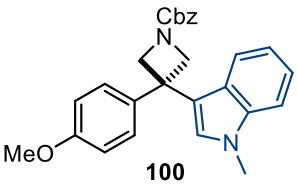
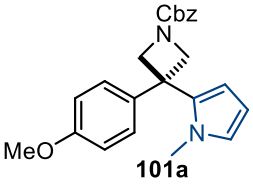
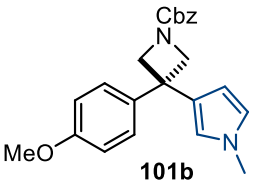
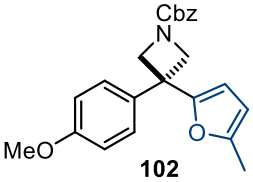
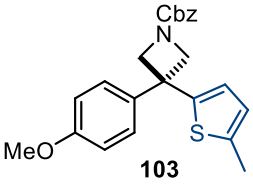
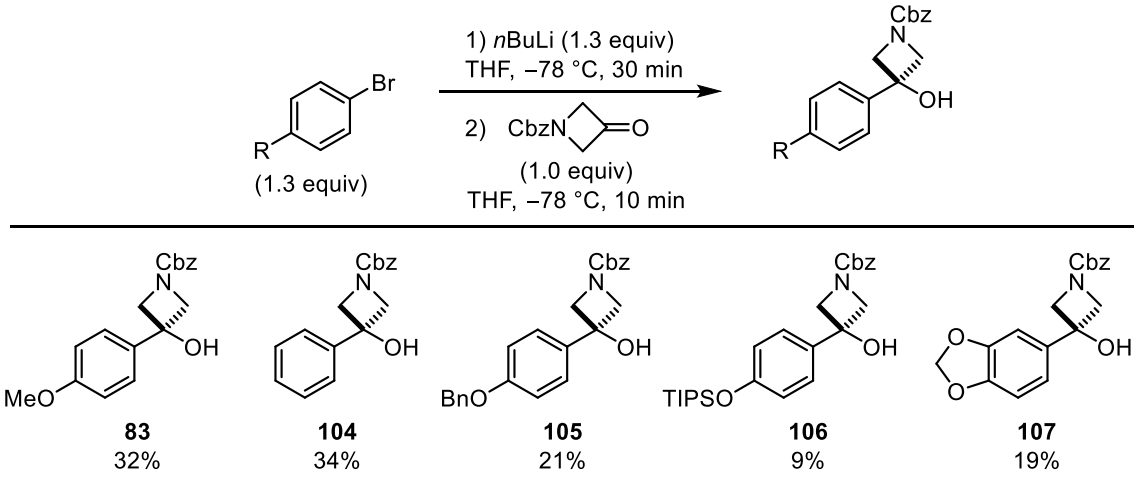
Entry	Nucleophile	Time (h)	Temp. (° C)	Product	Yield (%)[a]
1	1,3-dimethoxybenzene	2	40	 **99**	54
2	1-methylindole	24	60	 **100**	22
3[b]		24	80		45
4	1-methylpyrrole	24	60	 **101a**	33
				 **101b**	12
5	2-methylfuran	24	40	 **102**	80
6	2-methylthiophene	24	60	 **103**	60

Table 4.3: Friedel–Crafts alkylation of various aromatic and heteroaromatic nucleophiles with azetidinol **83**. General reaction conditions: azetidinol **83** (0.50 mmol), nucleophile (1.50 mmol), $Ca(NTf_2)_2$ (5.0 mol%), nBu$_4$NPF$_6$ (5.0 mol%), solvent (1.0 mL). [a] Isolated yields. [b] Toluene as solvent.

The effect of the preinstalled aromatic on the carbocation formation was then explored through preparation and reaction of alternative azetidinols.

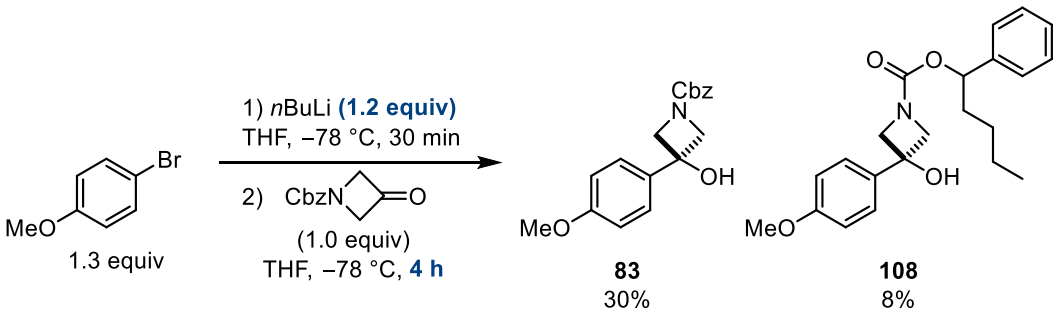
4.1.6 Preparation of Cbz-Protected Azetidin-3-ols

A collection of Cbz-protected azetidinols were prepared by Camille Denis adding 1-Cbz-azetidin-3-one to the corresponding preformed organolithium (Scheme 4.7).[113] Azetidinols **83**, **104**–**107** were prepared in 9% to 34% yields with the rest of the mass balance accounted for by starting material as well as multiple side products which complicated purification.



Scheme 4.7: Synthesis of azetidinols **83**, **104**–**107** by Camille Denis, by addition of 1-Cbz-azetidin-3-one to the corresponding preformed organolithium.

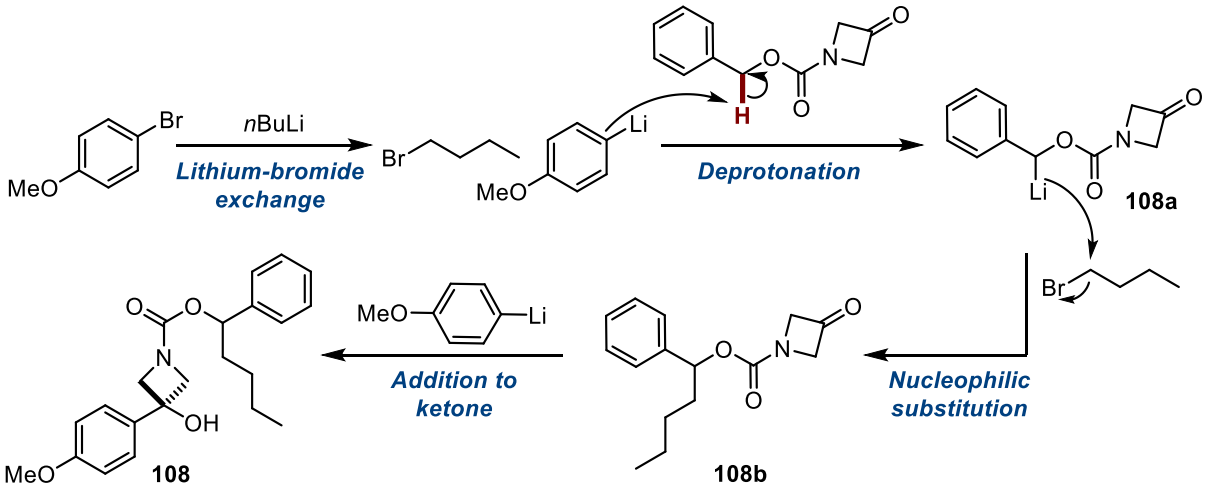
Despite the use of excess aryl bromide relative to *n*BuLi to prevent competitive addition to the azetidinone, and a longer reaction time of 4 h, a similar yield was obtained for azetidinol **83** (Scheme 4.8). Interestingly, side product **108** could be isolated from the mixture. Understanding the formation of such product could help improving the reaction.



Scheme 4.8: Modified conditions for the synthesis of azetidinol **83**.

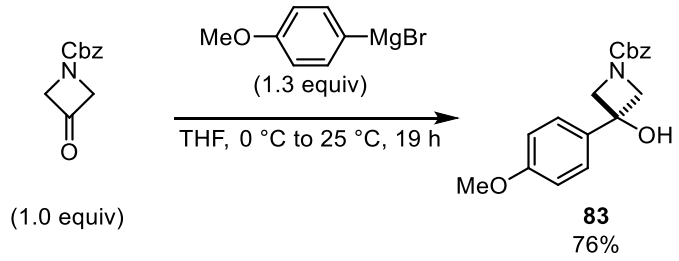
The deprotonation of the acidic benzylic position on 1-Cbz-azetidin-3-one by preformed (4-methoxyphenyl)lithium is thought to be the main side reaction occurring (Scheme 4.9). The resulting organolithium **108a** can undergo nucleophilic substitution on 1-bromobutane, produced from the initial lithium-bromide exchange reaction, affording butyl **108b**. Addition of the organolithium onto ketone **108b** provides the observed side product **108**. The use of a less

basic organometallic species such as the corresponding Grignard reagents could prevent deprotonation of the benzylic proton and improve the yield of desired azetidinol.



Scheme 4.9: Proposed mechanism for the formation of side product **108**.

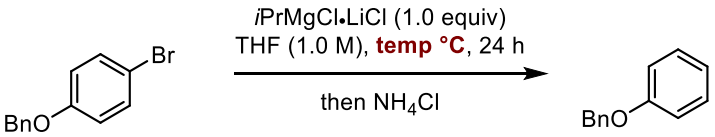
Addition of commercial 4-methoxyphenylmagnesium bromide to azetidinone in THF, afforded azetidinol **83** in 76% yield, compared to a 32% yield obtained with organolithium species. This reaction was successfully scaled up to 38 mmol (Scheme 4.10). The reaction only gave the desired azetidinol with no side product observed.



Scheme 4.10: Synthesis of azetidinol **83** by addition of 4-methoxyphenylmagnesium bromide to azetidinone.

Synthesis of further azetidinols required the preparation of Grignard reagents. Halogen-metal exchange is one of the easiest and most convenient method for the preparation of organolithiums. In contrast, this method is less effective for the formation of Grignard reagents, as the halogen-magnesium exchange is slower especially for electron-rich aromatic halides.[120] In 2004, Knochel developed *i*PrMgCl·LiCl, also known as Turbo Grignard which is now commercialised, as an excellent reagent for preparation of electron-rich aromatic Grignard reagents.[120] The study showed effective bromide–magnesium exchange to form 4-methoxyphenylmagnesium chloride in THF at 25 °C, though it required 68 h to reach completion. The bromide–magnesium exchange between 4-benzyloxybromobenzene and Turbo Grignard was investigated, varying the temperature in order to shorten the reaction time

(Table 4.4). Performing the reaction at 25 °C for 24 h, followed by an acid quench, gave less than 10% yield of benzyl phenyl ether. Heating the reaction to 50 °C did increase the conversion but gave only 65% yield of dehalogenated product after 24 h, illustrating the difficulty of the exchange.

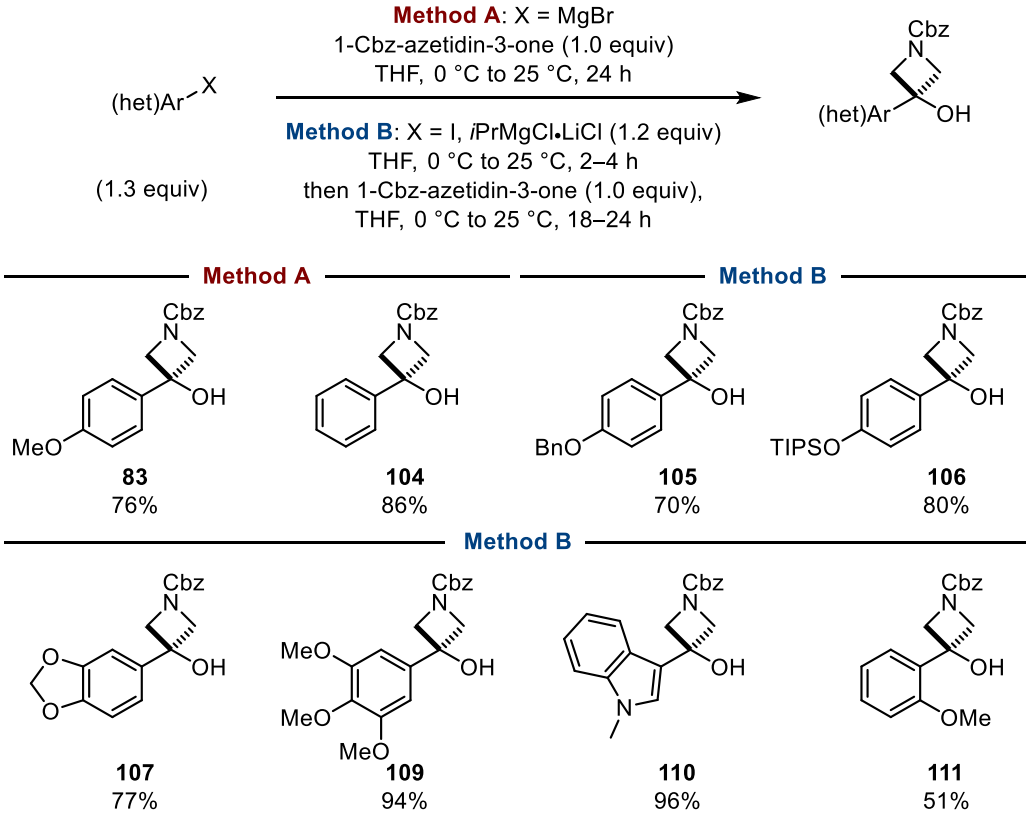


Entry	Temperature (° C)	Yield benzyl phenyl ether (%)[a]
1	25	<10
2	50	65

Table 4.4: Bromide–magnesium exchange between 4-benzyloxybromobenzene and Turbo Grignard at different temperatures. [a] Yield calculated by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as the internal standard.

Iodine–magnesium exchange has been previously reported for the synthesis of amino-substituted aromatic Grignard reagents using simple *i*PrMgCl.[121] However, these conditions were inefficient for the iodine–magnesium exchange with 4-iodobenzyloxybenzene and azetidinol **105** was not obtained. Later, Knochel used Turbo Grignard for iodide–magnesium exchange in the preparation of cyclic alkenylmagnesium reagents.[122] The use of Turbo Grignard with 4-iodobenzyloxybenzene, successfully promoted iodine–magnesium exchange after 2 h at 25 °C, and subsequent addition of azetidinone afforded azetidinol **105** in 70% yield, without deprotonation of the benzylic positions (Scheme 4.11). Further 1-Cbz-azetidin-3-ols could be prepared *via* the two different methods whether the Grignard was commercially available (method A) or was made *in situ* using Turbo Grignard and an aryl iodide (method B, Scheme 4.11). Phenyl azetidinol **104** was made from commercial phenylmagnesium bromide in 86% yield while TIPS-protected azetidinol **106** was prepared in 80% yield. Benzodioxole **107**, trimethoxybenzene **109** and 1-methylindole **110** were all synthesised in high yields up to 96%. Finally, product **111** was obtained in lower yield due to steric hindrance generated by the *ortho*-substituent. This yield may be improved by heating up the reaction after the addition of azetidinone.

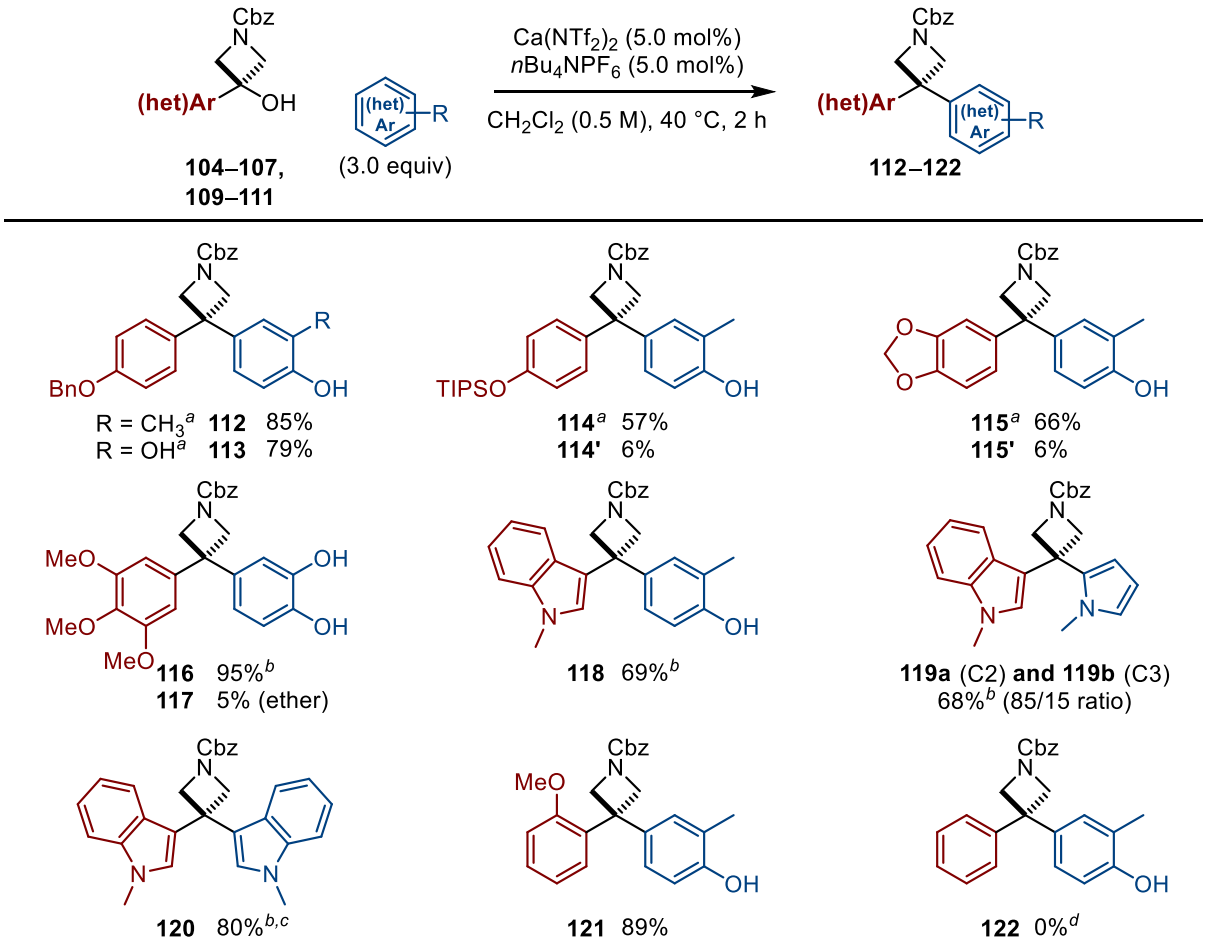
The effect of the preinstalled aromatic component on the Friedel–Crafts reaction was then investigated with the collection of azetidinols in hand.



Scheme 4.11: Preparation of 1-Cbz-azetidin-3-ols using Grignard reagents.

4.1.7 Scope of 1-Cbz-Azetidin-3-ols

Bn and TIPS-protecting groups were compatible with the reaction conditions, and azetidinols **105** and **106** gave 3,3-diarylazetidines **112** to **114** in 57% to 85% yields, along with small amounts of *ortho*-addition products (Scheme 4.12). The ability to incorporate these protecting groups offers useful synthetic options, as they open options for further derivatisation following deprotection. Catechol proved to be a suitable nucleophile with azetidinol **105** giving **113** in high yield. A preinstalled benzodioxole aromatic group was also stable and azetidine **115** was obtained in 66% yield by Camille Denis. Interestingly, trimethoxyazetidinols **109** needed longer reaction time to react with catechol likely due to catalyst coordination to the multiple oxygen atoms, and yielded 95% of 3,3-diarylazetidine **116**, as well as 5% of azetidine ether **117**. In comparison, the synthesis of 3,3-diaryloxetane **67** (section 3.5.2.2) also required longer reaction time and higher temperature, but was produced in only 33% yield. In addition, 47% of benzodioxane **70** was formed from *O*-alkylation followed by ring opening of the oxetane by the adjacent phenolic OH. In the case of the azetidine, *O*-alkylation did occur leading to azetidine ether **117** but seemed to be reversible due to the stability of the azetidine towards ring opening, and 3,3-diarylazetidines **116** was obtained in high yield.

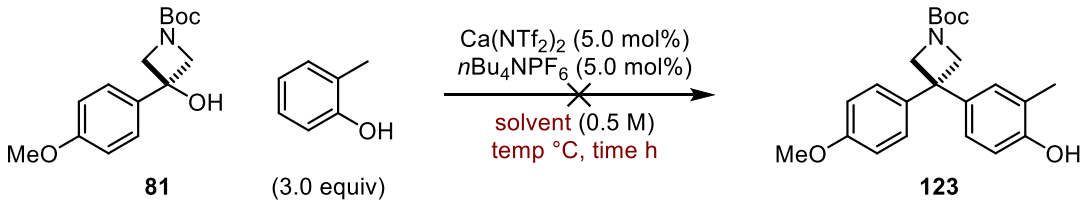


Scheme 4.12: Friedel–Crafts alkylation of aromatic nucleophiles with various azetidinols. General reaction conditions: azetidinol (0.50 mmol), nucleophile (1.50 mmol), $Ca(NTf_2)_2$ (5.0 mol%), nBu$_4$NPF$_6$ (5.0 mol%), CH_2Cl_2 (1.0 mL), 40 °C, 2 h. [a] Synthesised by Camille Denis. [b] 24 h. [c] 60 °C. [d] toluene as solvent, 80 °C, 24 h.

Pleasingly, indole-containing azetidinol **110** was a very successful precursor when the reaction was run for 24 h. Using 2-methylphenol as the nucleophile gave indole **118** in 69% yield as the only product. Importantly, two nitrogen-heteroaromatics can be easily introduced into 3,3-diarylazetidines, without adverse catalyst coordination. Reacting indole-azetidinol **110** with either pyrrole or 1-methylindole afforded 3,3-diarylazetidines **119** and **120** in 68% and 80% yields. The tolerance of the reaction towards steric hindrance was then investigated and *ortho*-substituted azetidinol **111** was subjected to the Friedel–Crafts conditions with 2-methylphenol. The capacity to stabilise, form and react the carbocation intermediate did not seem to be affected by *ortho*-substitution and 89% of 3,3-diarylazetidine **121** was obtained. In addition, the congestion around the carbocation intermediate led to the formation of *para*-product **121** selectively. Finally, it was confirmed that electron-rich pre-installed aromatic on azetidinol is a requirement to stabilise and form the azetidinyl carbocation as phenyl-azetidinol **104** was unreactive and did not give any 3,3-diarylazetidine **122** even at 80 °C and after a 24 h reaction.

4.1.8 Investigating the Role of the Cbz-Protecting Group

The difference in reactivity between Boc-protected and Cbz-protected azetidinols **81** and **83** was further examined. Resubjecting azetidinol **81** to the optimised reaction conditions with 2-methylphenol, confirmed the early results obtained, with starting material returned unreacted (entry 1, Table 4.5). Heating the reaction to 80 °C in toluene for 24 h gave a similar outcome with no product **123** observed (entry 2).

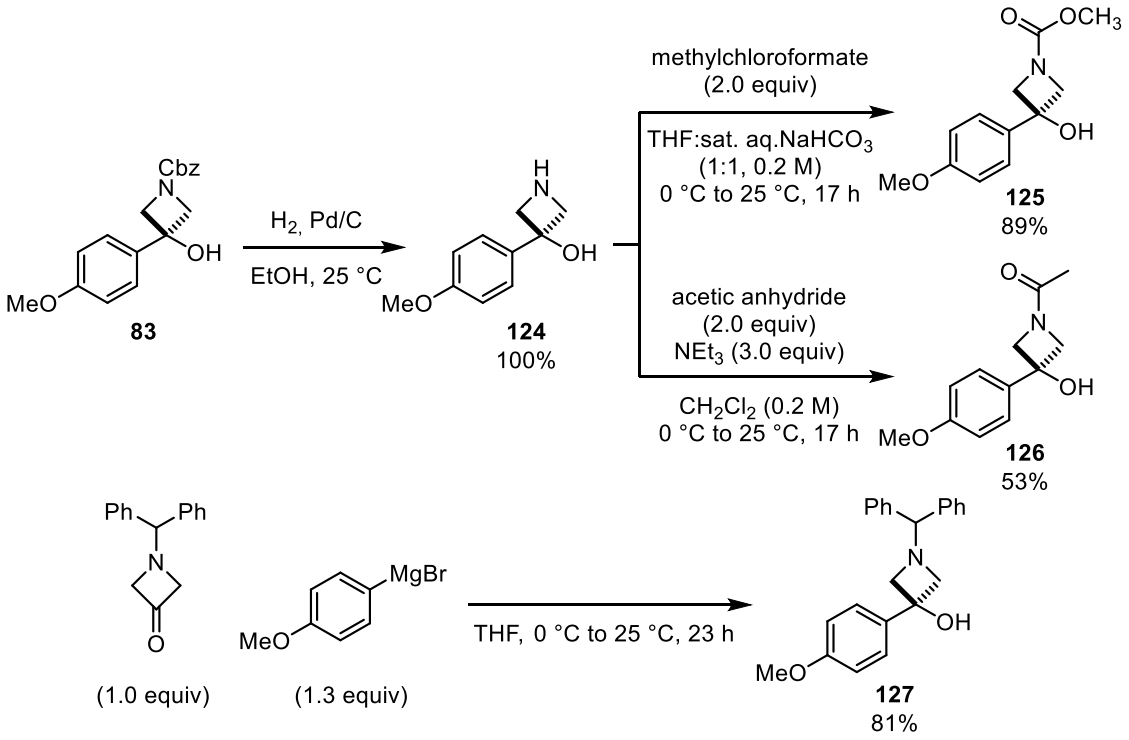


Entry	Solvent	Temperature (° C)	Time (h)	Yield 123 (%)
1	CH_2Cl_2	40	2	0
2	toluene	80	24	0

Table 4.5: Friedel–Crafts alkylation of 2-methylphenol with Boc-protected azetidinol **81** under different conditions.

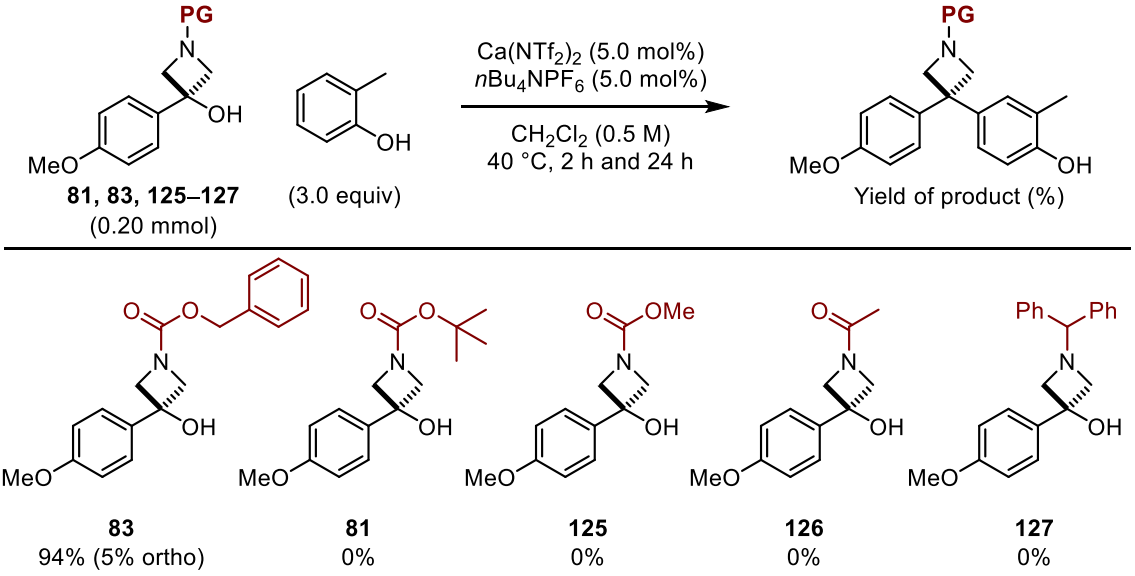
The lack of reactivity of Boc-protected azetidinol **81** can be attributed to the steric hindrance the *t*Bu group generates. In order to test this hypothesis, employment of a less bulky carbamate protecting group such as methyl carbamate was investigated. In addition, the requirement of a carbamate protecting group for the reactivity was evaluated by subjecting alternative protected azetidinols to the reaction conditions, including amide or simple alkyl substituted azetidinols.

Deprotection of Cbz-azetidinol **83** under hydrogenation conditions gave free azetidinol **124** quantitatively, from which methyl carbamate **125** and amide **126** were prepared in 89% and 53% yields respectively (Scheme 4.13). Benzhydryl-protected azetidinol **127** was made in 81% yield by adding 4-methoxyphenylmagnesium bromide to commercial 1-(diphenylmethyl)azetidin-3-one. With the new azetidinols in hand, their reactivity was then tested under the standard reaction conditions.



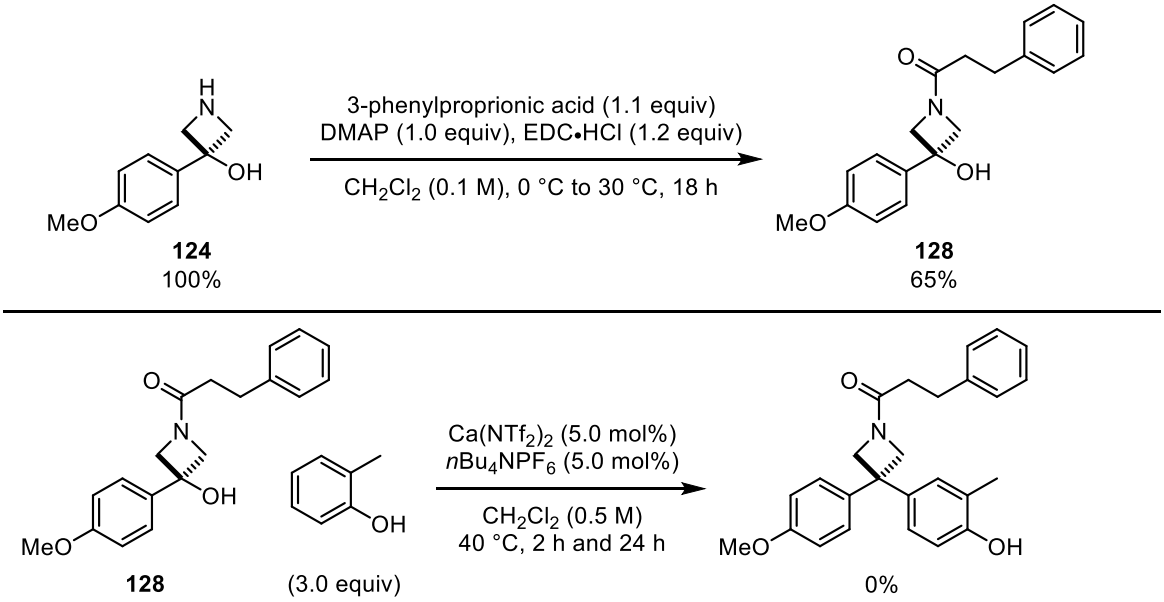
Scheme 4.13: Synthesis of alternative protected-azetidinols.

Azetidinols **125**, **126** and **127** were subjected to the calcium-catalysed Friedel–Crafts reaction with 2-methylphenol in CH_2Cl_2 at 40 °C (Scheme 4.14). After 2 h, all azetidinols **125**–**127** were recovered unreacted and leaving the reaction for 24 h did not change the outcome. Methylcarbamate **125** being as unreactive as Boc-azetidinol **81** shows that steric hindrance is not the reason for the lack of reactivity of this substrate, and shows the enhancing effect of the phenyl group of Cbz. Changing the electronic nature of the protecting group by incorporating an amide or alkyl group also led to no reaction, likely due to catalyst coordination for the latter.



Scheme 4.14: Effect of the protecting group of the azetidinol on the Friedel–Crafts alkylation of 2-methylphenol.

To better understand whether the carbamate of the Cbz group is also important for the reactivity, the corresponding amide **128** was prepared from amine **124** *via* amide bond formation (Scheme 4.15). Interestingly, subjecting amide **128** to the Friedel–Crafts conditions did not give any desired 3,3-diarylazetidine and the azetidinol was recovered unreacted, suggesting that the carbamate group is also crucial to the reactivity.



Scheme 4.15: Synthesis of amide **128** and reactivity in Friedel–Crafts reaction.

Although the reason for the enhanced reactivity of Cbz-azetidinols **83** remains unclear, it is proposed that the phenyl group might aid the stabilisation of the carbocation intermediate through π–cation interaction (Figure 4.3). The delocalisation of electrons from the carbamate oxygen atom to the carbonyl would make the nitrogen atom of the carbamate Cbz group less strongly sp^2 hybridised compared to amides, perhaps slightly sp^3, and would therefore be less planar. This might reduce the strain of the azetidine ring and enable azetidinyl carbocation formation. In addition, it might also direct the phenyl group towards the carbocation, allowing π–cation interaction, which explains the pivotal role of both carbamate and phenyl functional groups of Cbz.

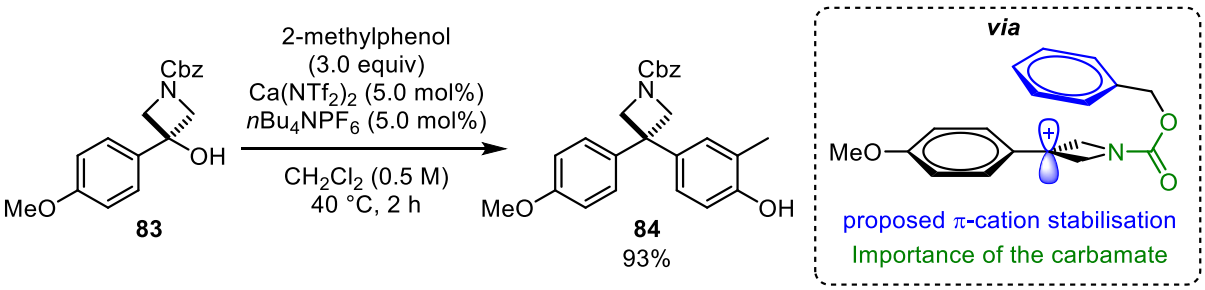
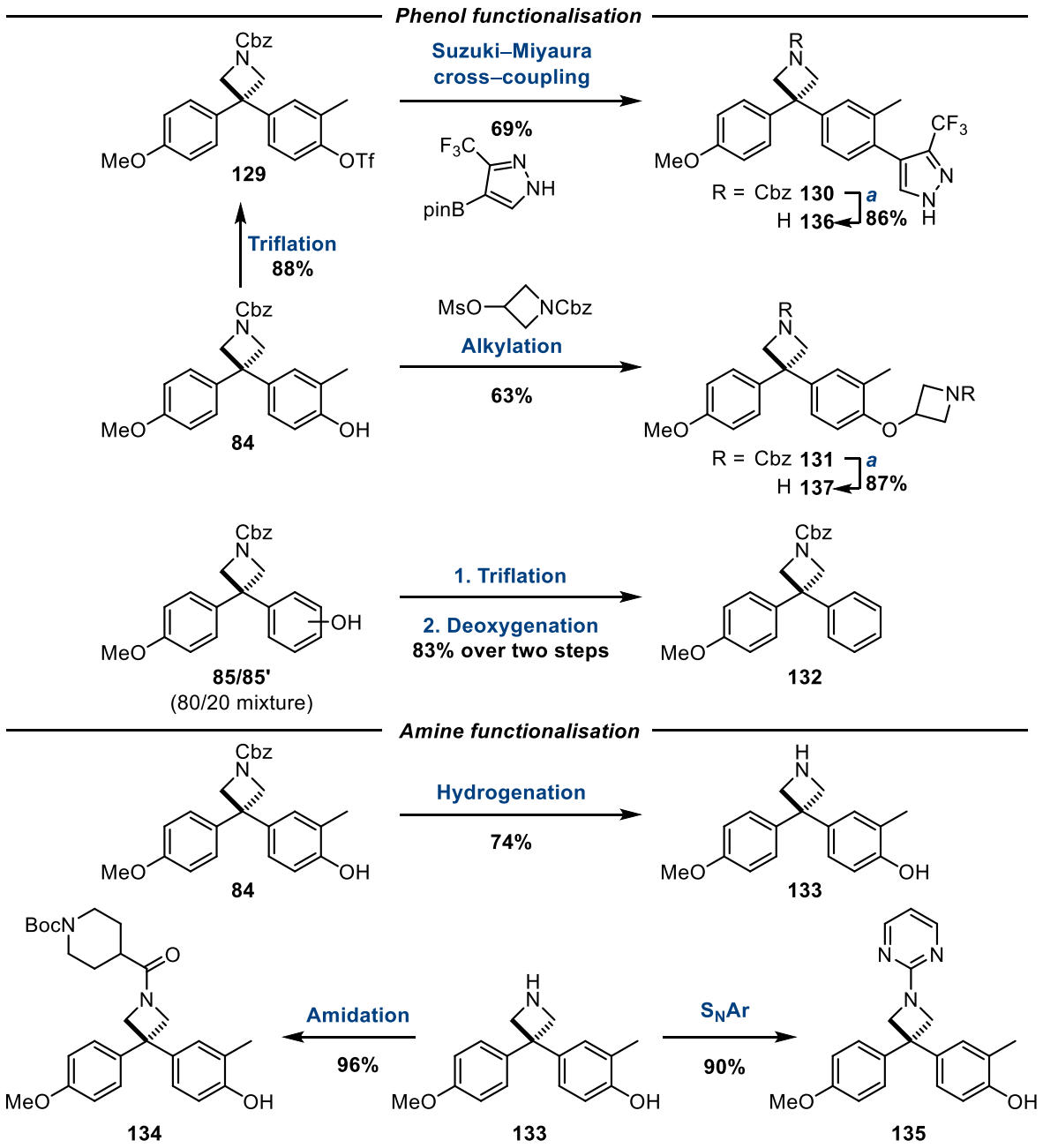


Figure 4.3: Importance of the phenyl and carbamate groups for the formation and reactivity of azetidinyl carbocation intermediate.

4.1.9 Derivatisation of 3,3-Diarylazetidines

The calcium-catalysed Friedel–Crafts reaction developed in this chapter enabled the synthesis of new 3,3-diarylazetidines containing functional groups that could not be introduced with previous methods, such as heteroaromatics, various phenols and Cbz protecting groups. These groups are useful synthetic handles allowing further elaboration to access a wide range of medicinally relevant 3,3-diarylazetidines.

The phenol function of azetidine **84** could be converted to triflate **129** in 88% yield and used in Suzuki–Miyaura cross–coupling to introduce a pyrazole moiety giving azetidine **130** in 69% yield (Scheme 4.16). Phenol **84** could also be easily alkylated with a second azetidine ring to afford 63% of 3,3-diarylazetidine **131**. Although phenyl could not be installed into 3,3-diarylazetidine *via* the developed calcium-catalysed Friedel–Crafts reaction, it was easily and rapidly accessed from the corresponding phenol. Triflation of a mixture of phenols **85** and **85'**, followed by deoxygenation using Pd-catalysed conditions developed by Ortar,[123] gave phenyl **132** as single product in 83% yield over two steps. Importantly, the Cbz protecting group was removed using standard hydrogenation conditions on 1.5 mmol scale, affording free azetidine **133** in 74% yield. This was further functionalised by introducing a piperidine ring through amide bond formation, using standard EDC coupling agent, to give product **134** in high yield. Moreover, a pyrimidine ring could also be introduced in 90% yield through an S_NAr reaction. Interestingly, both reactions occurred selectively on the nitrogen in presence of an unprotected phenol group. The Cbz protecting group could also be removed later after derivatisation of the phenol moiety. Hydrogenation of pyrazole **130** afforded free-azetidine **136** in good yield, and is similar to a compound reported in the patent literature,[115a] while both Cbz groups could be deprotected from **131** in one step giving **137** in similar yield.



Scheme 4.16: Derivatisation of 3,3-diarylazetidines. Triflation conditions: Tf_2O (2.0 equiv), NEt_3 (3.0 equiv), CH_2Cl_2 (0.5 M), 0 to 25 °C, 2 h. Suzuki–Miyaura cross–coupling conditions: pyrazole Bpin (1.3 equiv), $Pd(PPh_3)_4$ (8.0 mol%), K_2CO_3 (2.0 equiv), DME:H_2O (8:2, 0.1 M), 100 °C, 25 h. Alkylation conditions: mesylate (1.1 equiv), K_2CO_3 (2.5 equiv), DMF (0.2 M), 90 °C, 19 h. Deoxygenation conditions: NEt_3 (3.0 equiv), formic acid (2.0 equiv), $Pd(OAc)_2$ (5.0 mol%), dppf (5.0 mol%), DMF (0.1 M), 60 °C, 2 h. Hydrogenation conditions: H_2, Pd/C (10% w/w), EtOH (0.2 M), 25 °C, 21 h. Amidation conditions: DMAP (3.0 equiv), EDC·HCl (1.2 equiv), boc-Inp-OH (1.0 equiv), CH_2Cl_2 (0.2 M), 0 to 25 °C, 19 h. S_NAr conditions: 2-chloropyrimidine (1.2 equiv), KF (2.0 equiv), H_2O:MeCN (3:1, 0.25 M), 100 °C, 2 h. [a] See hydrogenation conditions.

4.1.10 Conclusion

The generation of an azetidinyl carbocation intermediate was successfully achieved from readily prepared 3-arylazetidin-3-ols using an inexpensive and abundant calcium catalyst. These carbocations reacted through a Friedel–Crafts alkylation reaction to synthesise >25 examples of new 3,3-diarylazetidines (Figure 4.4). The reaction was in most cases complete after 2 h in CH_2Cl_2 at 40 °C, and could be scaled up to 1 g. Importantly, the chlorinated solvent could be replaced with less harmful and more environmental friendly solvents such as toluene, without adversely affecting the yields. A variety of electron-rich phenols, non-phenolic arenes as well as nitrogen heteroaromatics of high importance for medicinal chemistry could be incorporated. In addition, highly elaborated phenols, such as β-estradiol, were introduced, demonstrating the possibility to apply this methodology to late-stage functionalisation. Moreover, high regioselectivity in favour of *para*-substituted 3,3-diarylazetidines was observed when using phenols as nucleophiles, and both *para* and *ortho* products were easily separated by flash column chromatography.

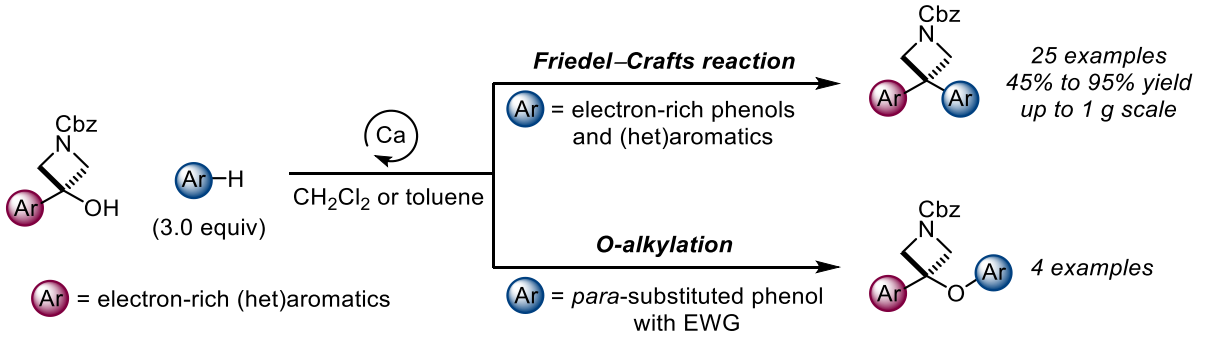


Figure 4.4: Friedel–Crafts alkylation of phenols and (het)aromatics with Cbz-azetidinols gives 3,3-diarylazetidines, and divergent *O*-alkylation of electron-poor *para*-substituted phenols leads to 3-arylazetidin-3-ethers.

The previous methodology on the synthesis of 3,3-diaryloxetanes from the Bull group, showed that nitrogen heteroaromatics and anilines were not viable nucleophiles. This might be due to strong catalyst coordination to nitrogen atoms or poor reactivity. Surprisingly, the tertiary hydroxyl groups of azetidinols could be activated without adverse coordination to the nitrogen of the azetidine ring, and nitrogen heteroaromatics were reactive in this methodology. In addition, the azetidine ring was more stable than oxetane towards ring opening by adjacent phenolic OH, and *para*-substituted phenols bearing EDG were suitable nucleophiles. Interestingly, new 3-arylazetidin-3-ethers were selectively obtained when electron poor *para*-substituted phenols were used, which also represent attractive motifs for medicinal chemistry. Moreover, high yields of 3,3-diarylazetidines were obtained with non-phenolic aromatics and *ortho*-substitution on the pre-installed aromatic was also tolerated, showing the enhanced reactivity of azetidines compared to oxetanes.

The Cbz protecting group on azetidinols was stable under the reaction conditions and was crucial to the reactivity. Subjecting other protected azetidinols to the reaction conditions showed that both phenyl and carbamate groups of the Cbz had pivotal roles. Stabilisation of the azetidinyl carbocation *via* π–cation interaction with phenyl could explain the enhanced reactivity of Cbz azetidinols. In addition, the electronic of the Cbz carbamate function might reduce planarity and strain in the azetidine ring while directing the phenyl group towards the carbocation, aiding the formation and the stabilisation of this intermediate.

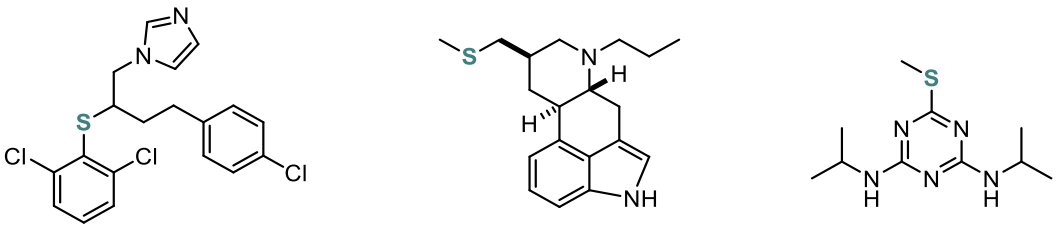
Importantly, the Cbz protecting group could be easily removed from 3,3-diarylazetidines under standard conditions, and medicinally relevant motifs were introduced through functionalisation of the nitrogen atoms or the phenol OH group.

The reactivity of these azetidinyl carbocations with others type of nucleophiles was then investigated, to access new chemical space and novel 3-aryl-3-substituted azetidines. The use of thiols as nucleophiles was particularly interesting to access 3-arylsulfanyl azetidines. Research in this area will be covered in the next section.

4.2 3-Aryl-3-Sulfanylazetidines

4.2.1 Azetidine Sulfides as Interesting Motifs for Medicinal Chemistry

Organosulfur compounds are prevalent in pharmaceuticals and agrochemicals and display a wide range of biological activities.[124,125] Of the US FDA-approved sulfur-containing drugs from 2016, 31 contained a thioether, and 15 of these examples had a Csp^3–S–Csp^2 substitution pattern (Figure 4.5).[124] Thioethers are also particularly important as synthetic intermediates to sulfoxides, sulfones and sulfoximines.



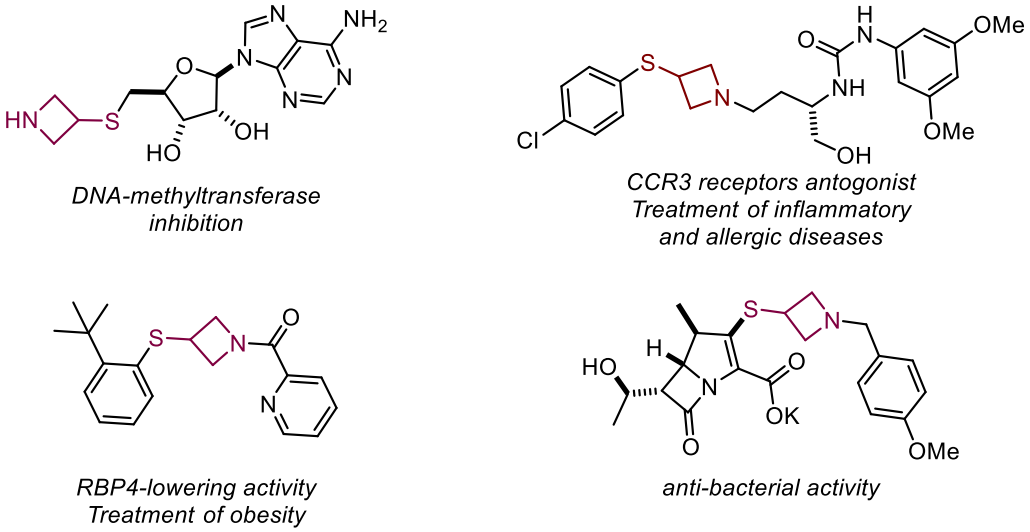
Butoconazole
antifungal

Pergolide
dopamine receptor antagonists
Treatment of Parkinson's disease

Prometryn
herbicide

Figure 4.5: Examples of drugs and agrochemicals containing a thioether.

Examples of azetidine-3-thioethers can be found in bioactive molecules in the literature, mostly monosubstituted, with a range of biological activities, such as DNA methyltransferase inhibition,[126a] CCR3 receptors antagonist activity,[126b] RBP4-lowering activity,[126c] and anti-bacterial activity[126d] (Figure 4.6). In contrast, 3-substituted-3-thioether azetidines remain underexplored.



DNA-methyltransferase inhibition

CCR3 receptors antogonist
Treatment of inflammatory and allergic diseases

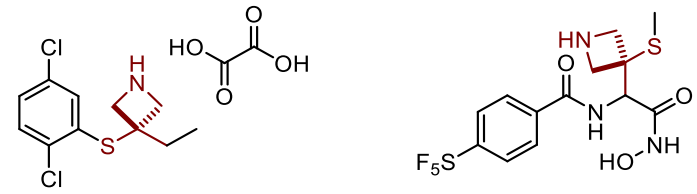
RBP4-lowering activity
Treatment of obesity

anti-bacterial activity

Figure 4.6: Examples of bioactive molecules containing azetidine-3-thioethers.

In 1969, Funke reported the first example of a 3-methyl-3-thioether azetidine made *via* a strain release strategy.[80] 3-Alkyl-3-thioether azetidines have particularly attracted the attention of medicinal chemists since, with recent works reporting compounds containing this motif as nitric

oxide synthase inhibitors and antibacterial agents (Figure 4.7).[127] The synthesis of such motifs have been achieved *via* a strain release strategy,[80,128] and mainly through the addition of thiols to Michael acceptors.[127,129]



nitric oxide synthase inhibition *antibacterial activity*

Figure 4.7: Examples of bioactive molecules containing 3-substituted-3-thioether azetidines.

Surprisingly, only one 3-aryl-3-sulfanyl azetidine had been reported in the literature at the outset of the work presented in this section (Figure 4.8).[127a] This was synthesised through nucleophilic substitution on a protected azetidinol with the corresponding thiol, followed by removal of the nitrogen protecting group. No yield was reported and the synthesis required pre-installation of a mesylate group on the azetidinol.

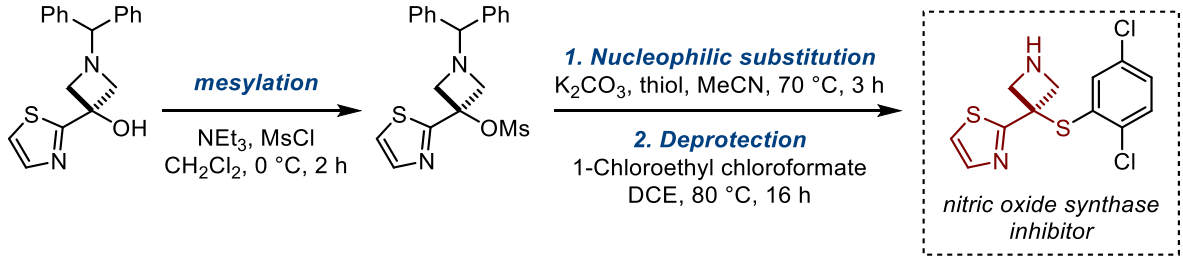


Figure 4.8: Synthesis of a bioactive compound containing a 3-aryl-3-sulfanyl azetidine.[127a]

The development of a general method to access a diverse range of 3-aryl-3-sulfanyl azetidine would provide new achiral and Fsp^3 rich motifs for medicinal chemistry, with defined exit vectors through the nitrogen and sulfur atoms, or through the pre-installed aromatic and thioether groups.

4.2.2 Approach for the Synthesis of 3-Aryl-3-Sulfanylazetidines

The direct *S*-alkylation of easily accessible azetidinols represents an attractive method for the synthesis of such azetidines, as it would generate water as the only by-product and would not require pre-installation of a mesylate activating group (Figure 4.9).

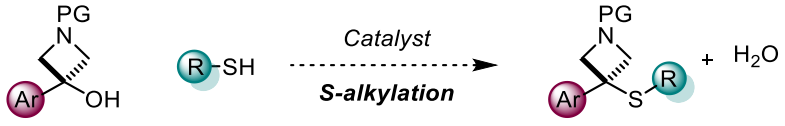


Figure 4.9: Planned synthesis towards 3-aryl-3-sulfanyl azetidines.

Few examples of thioetherification of π–activated alcohols have been reported in the literature. This transformation often requires high catalyst loading or use of expensive metal catalysts, and most methods were carried out in chlorinated solvents.[86,130,131] The Bull group recently published a thiol-alkylation with oxetanols, through the formation of an oxetanyl carbocation intermediate under mild and inexpensive lithium catalysed conditions (Figure 4.10).[51,88] Careful monitoring of the reaction was necessary to prevent ring opening of the oxetane by the excess thiol present in the reaction mixture. Through this method, 3-aryl-3-sulfanyl oxetanes were synthesised and represent potential bioisosteres for thioesters. Encouraged by this work the synthesis of 3-aryl-3-sulfanyl azetidines was envisaged through a similar strategy. The formation of azetidinyl carbocations was achieved in the previous section using a mild and inexpensive calcium catalyst, and it was thought that the reaction of these carbocations with thiols could give access to 3-arylazetidine sulfides. However, the previous work from the Bull group showed that thiols containing protected amines or nitrogen heteroatoms did not proceed in the reaction, likely due to catalyst coordination to the nitrogen atoms. Thus the presence of the azetidine nitrogen atom could similarly prevent the reaction occurring.

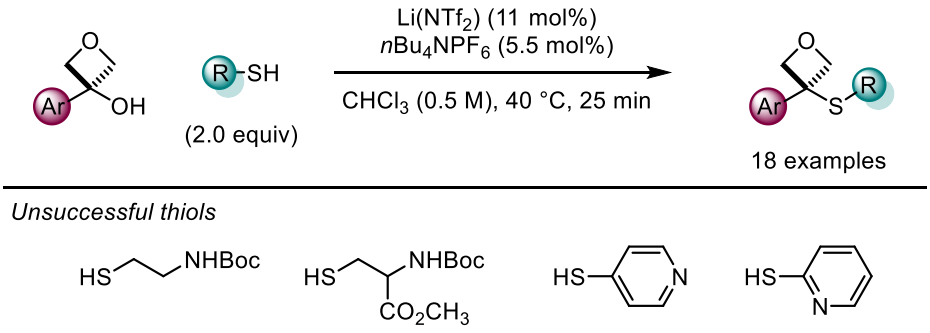
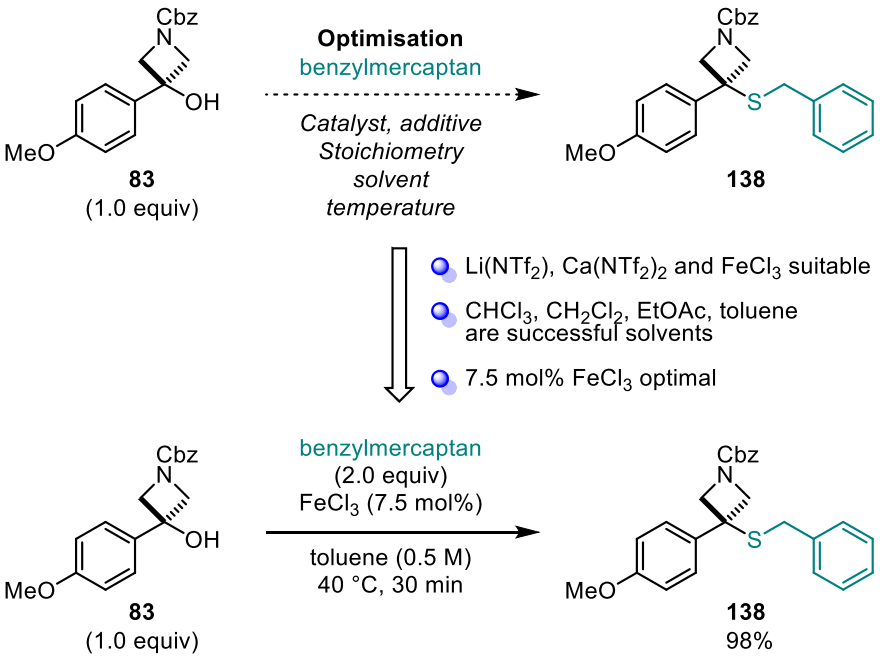


Figure 4.10: Previous synthesis of 3-arylsulfanyl oxetanes *via* lithium-catalysed thioetherification of oxetanol.

4.2.3 Optimisation

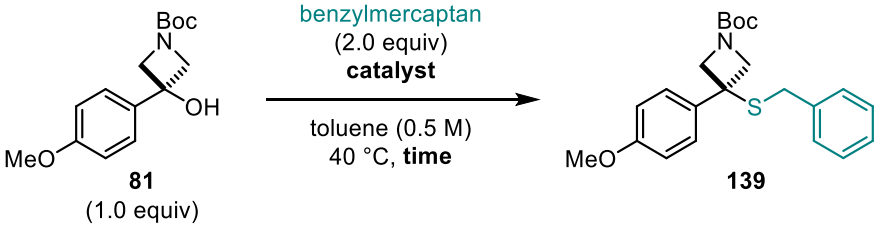
Anna Lazaridou investigated various catalysts and additives, as well as the stoichiometry, solvents and temperature for the reaction of azetidinol **83** with benzylmercaptan (Scheme 4.17).[114] The reaction was first run using the conditions developed for the synthesis of 3-arylsulfanyl oxetanes, using $Li(NTf_2)$/nBu_4NPF_6 as the catalyst in chloroform. This gave product **138** in 88% yield after only 30 min.



Scheme 4.17: Optimisation of the thioetherification of azetidinol **83** with benzylmercaptan. Optimisation conducted by Anna Lazaridou.

The reaction proved to be tolerant to various conditions and sulfanyl azetidine **138** was obtained in high yield with $Ca(NTf_2)_2/n$Bu$_4$NPF$_6$, or $FeCl_3$ as catalysts. $FeCl_3$ is the least expensive of the two and was therefore selected for further investigation. The reaction was run in different solvents including coordinating type solvents such as EtOAc, and non-chlorinated solvents such as toluene, with high product yields reported in all cases. Anna Lazaridou found that two equivalents of thiol was optimum, but could be decreased to 1.5 equivalents with a slight reduction in yield. Interestingly, the reaction seems to proceed even at 25 °C albeit in low yield. The use of 7.5 mol% of $FeCl_3$ with 2 equivalents of thiols at 40 °C in toluene were found to be the optimum conditions for this transformation.

Similarly to the Friedel–Crafts alkylation reaction with carbon based nucleophiles, the Cbz protecting group was crucial to the reactivity for this transformation. Boc-protected azetidinol **81** was unreactive under the reaction conditions, even after longer reaction times (entries 1 and 2, Table 4.6). Using $Ca(NTf_2)_2/n$Bu$_4$NPF$_6$ as catalyst did give 11% of desired sulfanyl azetidine **139**, but this could not be improved further.[114]



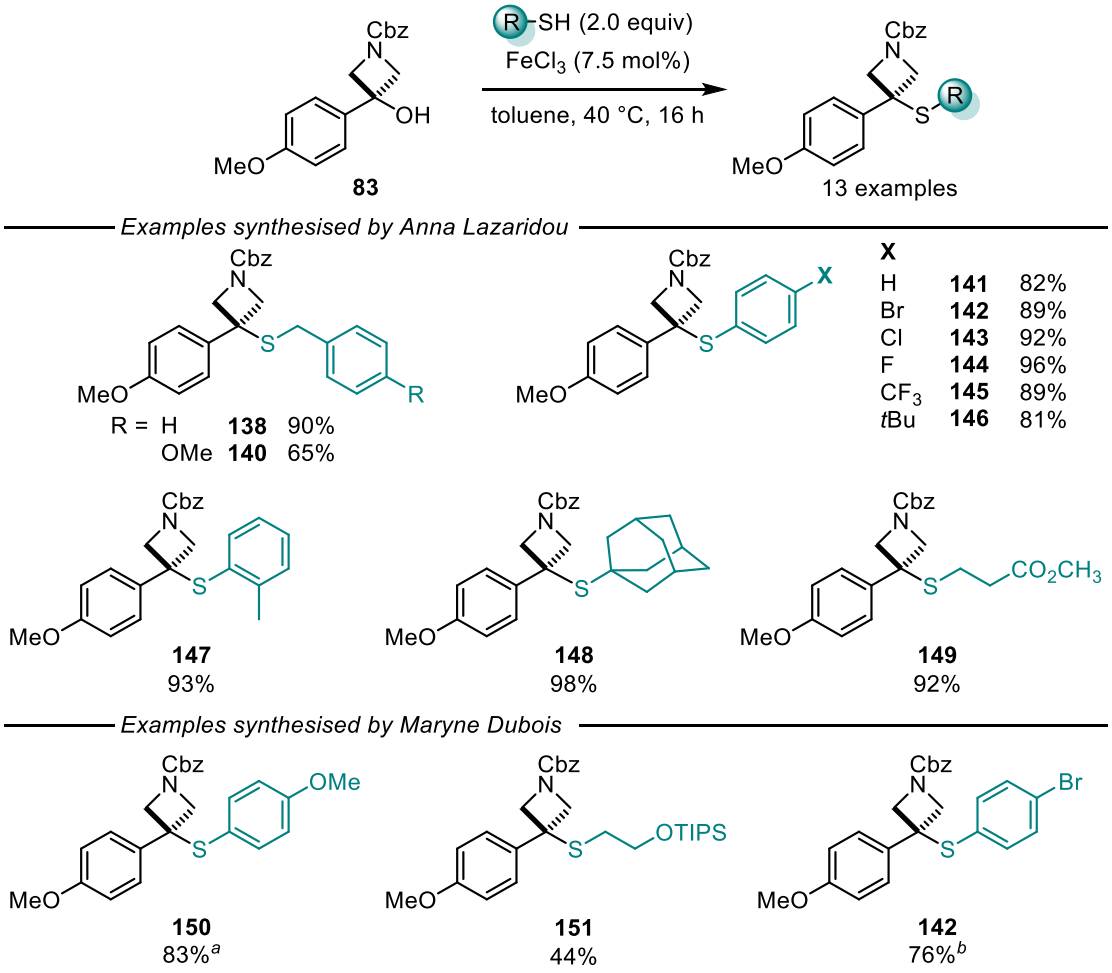
Entry	Catalyst	Loading (mol%)	time	Yield 139 (%)
1	$FeCl_3$	7.5	30 min	0
2	$FeCl_3$	7.5	15 h	0
3[a]	$Ca(NTf_2)_2/nBu_4NPF_6$	5/5	2 h	11
4[a]	$Ca(NTf_2)_2/nBu_4NPF_6$	5/5	15 h	14

Table 4.6: Attempts towards the thioetherification of azetidinol **81** with benzylmercaptan. [a] Carried out by Anna Lazaridou.

4.2.4 Scope of Azetidine Sulfides

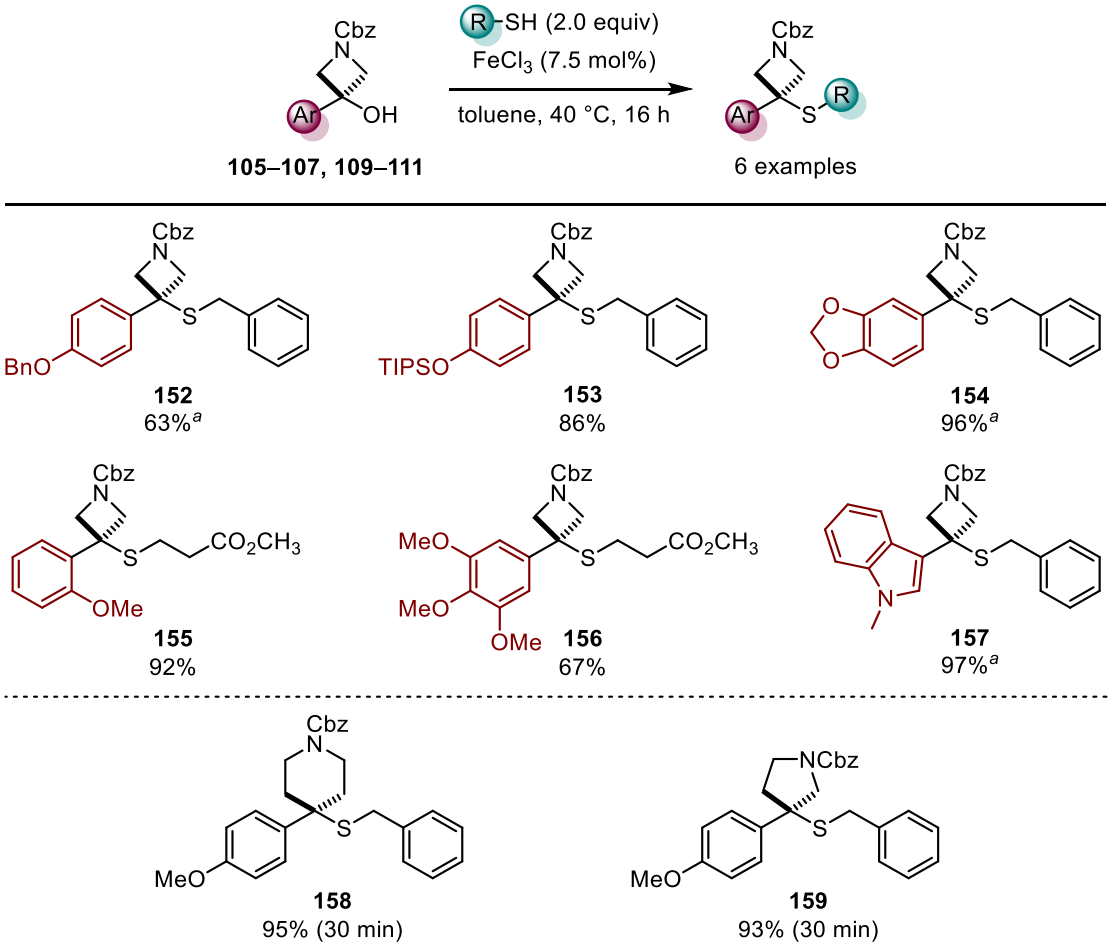
The scope of thiols suitable for the thioetherification of azetidinol **83** was studied and found to be extensive (Scheme 4.18).[114] At the start of this investigation, it was found that most thiols required longer reaction times than benzylmercaptan to reach completion. Contrary to the reaction with oxetanol, ring opening was not observed in this case.[51] Benzylic thiols, thiophenols and alkyl thiols were all successful nucleophiles in this reaction. Sulfides with both *para*-EWGs and EDGs such as Br-substituted **142**, CF_3-substituted **145**, or *t*Bu-substituted **146**, were all made in high yields between 81% and 96%. *ortho*-Substitution and steric bulk were also well tolerated under the reaction conditions with azetidines **147** and **148** obtained in 93% and 98% yields.

Thiophenols bearing highly EDGs, such as OMe, were more challenging and required a higher reaction temperature to give sulfanyl azetidine **150** in 83% yield. TIPS-protected ethane thiol gave only 44% of azetidine **151** with the rest of the mass balance accounted for by returned starting material. Pleasingly, the reaction with 4-bromothiophenol could be scaled to 1 g with only a slightly reduced yield of 76%.



Scheme 4.18: Scope of thiols for the thioetherification of azetidinol **83**. [a] 80 °C. [b] 1 g scale.

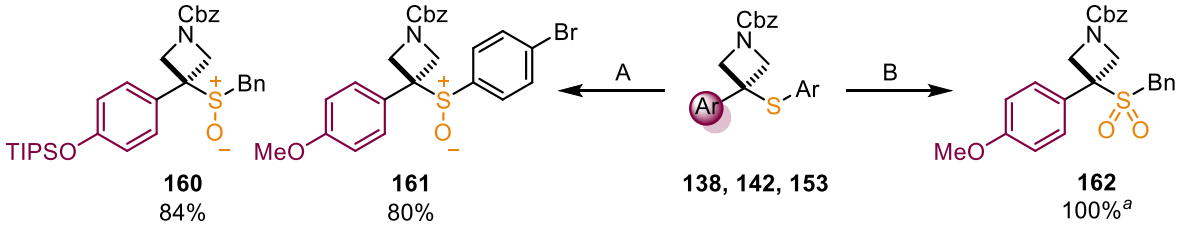
Bn and TIPS protecting groups on the pre-installed aromatics of azetidinols **105** and **106** were compatible with the reaction conditions, giving Bn and TIPS sulfanyl azetidine **152** and **153** in 63% and 86% yields respectively (Scheme 4.19). Benzodioxole could also be incorporated into sulfanylazetidine **154** in 96% yield using azetidinol **107**. The reaction proceeded well in presence of an *ortho*-substituent on azetidinol **111** with methyl 3-mercaptopropionate, giving **155** in high yield. The reaction between trimethoxybenzene azetidinol **109** and methyl-3-mercaptoproprionate was also successful leading to the formation of product **156** in 67% yield. In addition, 3-arylsulfanyl azetidine containing nitrogen-heteroaromatics could be synthesised using this method, with indole **157** made in 97% yield. Similarly to the Friedel–Crafts reaction (section 4.1.7), phenylazetidinol **104** did not give any azetidine sulfide product, even at 80 °C. Finally, the method was extended to the synthesis of 4-aryl-4-sulfanylpiperidines and 3-aryl-3-sulfanylpyrrolidines, with **158** and **159** synthesised in 95% and 93% yields respectively.



Scheme 4.19: Thioetherification of various azetidinols and alcohols. [a] Synthesised by Anna Lazaridou.

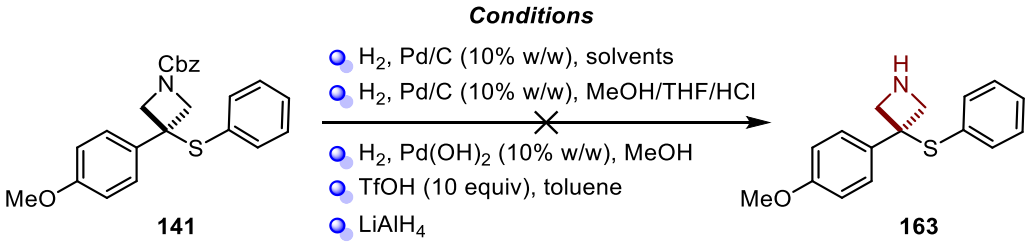
4.1.10 Derivatisation of 3-Aryl-3-Sulfanylazetidines

The new 3-aryl-3-sulfanyl azetidine products could be further derivatised to access a range of medicinally relevant functional groups. For example, the thioether motif could be oxidised to either sulfoxides, with **160** and **161** obtained in 84% and 80% yields, or to sulfones with **162** synthesised in quantitative yield. Selectivity was achieved by controlling the amount of *m*CPBA used and the temperature (Scheme 4.20). These products also represent interesting motifs for medicinal chemistry.



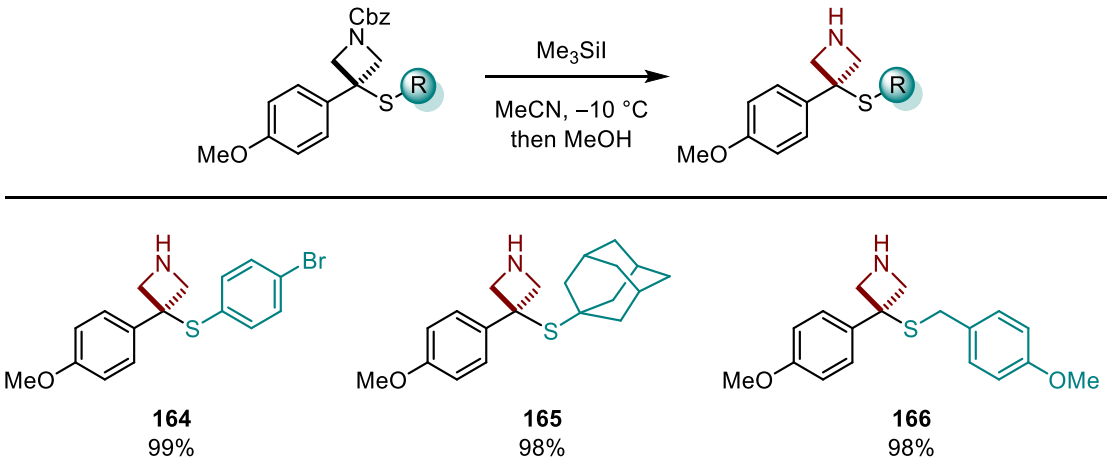
Scheme 4.20: Oxidation of 3-aryl-3-sulfanyl azetidine towards sulfoxide **160** and **161**, and sulfone **162**. [a] Synthesised by Anna Lazaridou. Conditions A: *m*CPBA (1.05 equiv), CH_2Cl_2, 0 °C. Conditions B: *m*CPBA (3.00 equiv), CH_2Cl_2, 25 °C.

The nitrogen atom of the azetidine ring was an important vector for further elaboration in 3-dimension that could be exploited. Initial attempts by Anna Lazaridou to remove the Cbz protecting group from azetidine **141**, using standard hydrogenation conditions with Pd/C and H_2, were unsuccessful with only starting material returned (Scheme 4.21).[114] Different solvents were tested, including MeOH, EtOH and THF, as well as addition of HCl, but no reaction was observed. Using $Pd(OH)_2$ as catalyst did not promote the reaction either, and the lack of reactivity was attributed to catalyst poisoning by the sulfur atom. Brønsted acid and strong reducing agents were also investigated leading to no reaction or complete degradation of the starting material.



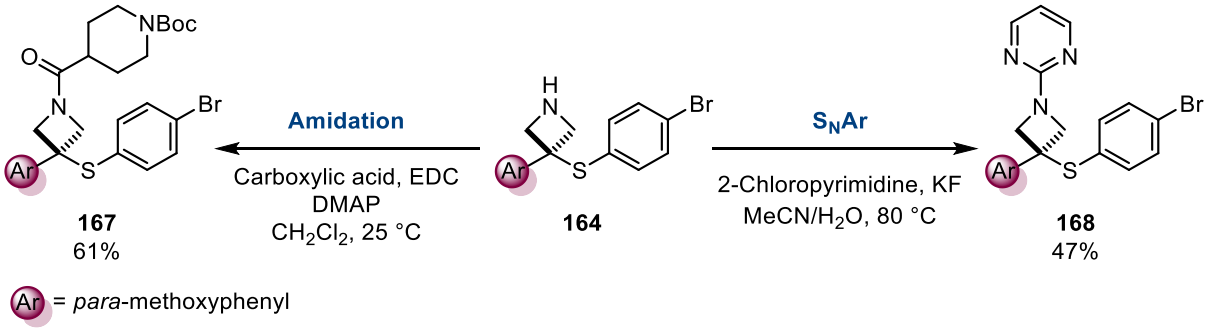
Scheme 4.21: Attempts by Anna Lazaridou to remove the Cbz protecting group from azetidine **141**.

In 1978, Jung showed that treatment of alkyl carbamates with trimethylsilyl iodide followed by addition of MeOH gave free amines in high yield.[132] Using these conditions on Cbz-azetidine **142** in MeCN at –10 °C gave free azetidine **164** in 99% yield on 1.0 mmol scale with no ring opening or adverse effect on the thioether bond (Scheme 4.22). The reaction was selective for the Cbz benzylic position, and bulky alkyl group and electron-rich benzylic position were tolerated affording amines **165** and **166** in nearly quantitative yields. These amines are useful building blocks which can be further functionalised.



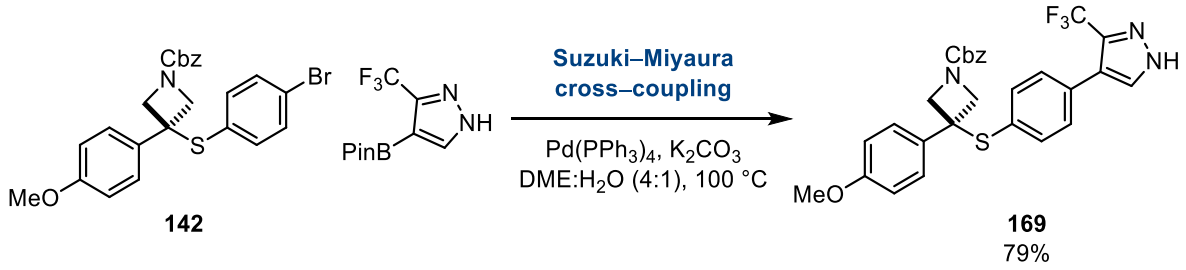
Scheme 4.22: Cbz-deprotection of 3-aryl-3-sulfanyl azetidines using Me_3Si and MeOH.

Amine **164** was derivatised through amide bond formation to give piperidine **167** in 61% yield using EDC coupling reagent. A pyrimidine ring could also be introduced with an S_NAr reaction affording azetidine **168** in 47% yield (Scheme 4.23).



Scheme 4.23: Derivatisation of amine **164**.

Finally, 3-aryl-3-sulfanylazetidines could be further decorated by taking advantage of functional groups present on the sulfide moiety. For example, bromide **142** reacted in Pd–catalysed Suzuki–Miyaura cross–coupling to give pyrazole **169** in 79% yield (Scheme 4.24).



Scheme 4.24: Derivatisation of azetidine **142** through a Suzuki–Miyaura cross–coupling reaction.

4.1.11 Conclusion

In this section, it was shown that the azetidinyl carbocation intermediate can also be generated from azetidinols using $FeCl_3$ as catalyst, and undergo *S*-alkylation with a wide variety of thiols to produce 23 new examples of 3-aryl-3-sulfanyl azetidines (Scheme 4.25). The reaction could be scaled up to 1 g and could be run in toluene or EtOAc without a detrimental effect on yield. This represents a rare example of an *S*-alkylation reaction with π–activated alcohols in a non-chlorinated solvent.[131] As previously observed in the synthesis of 3,3-diarylazetidines, the Cbz protecting group on azetidinols was crucial to the reactivity. Importantly, the Cbz protecting group could not be removed using traditional methods, but was easily and selectively deprotected over other electron-rich benzylic positions using Me_3SiI and MeOH at low temperature. These gave access to unprotected azetidine sulfides which are attractive motifs for medicinal chemistry and important synthetic intermediate. The azetidine nitrogen, sulfur atom, as well as bromide on the sulfide moiety, could be further functionalised through amide bond formation, S_NAr, oxidations and cross–coupling reactions to produce new medicinally

relevant molecules. Finally, this method could be extended to piperidine and pyrrolidine rings, with the synthesis of two 4-aryl-4-sulfanyl piperidine and 3-aryl-3-sulfanyl pyrrolidine examples in high yields (Figure 4.25).

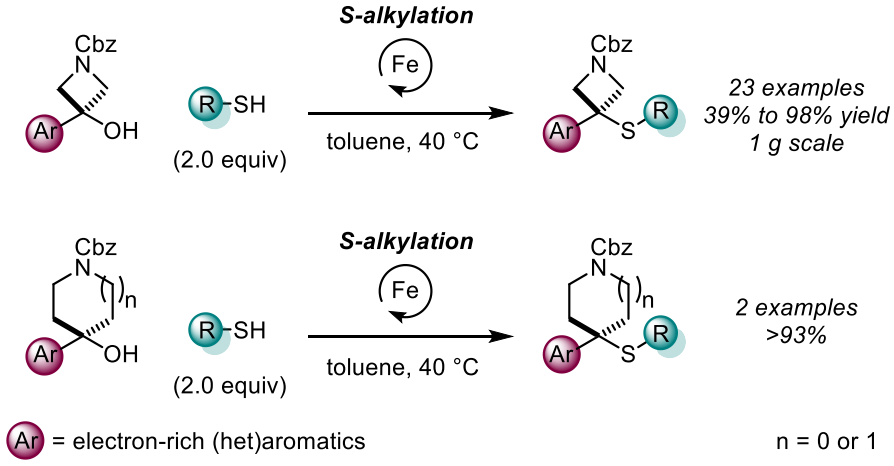


Figure 4.25: Synthesis of aryl-sulfanyl azetidines, piperidines and pyrrolidines by Fe-catalysed thiol alkylation with alcohol precursors.

4.3 Limitations and Challenges of the Methods

In this chapter, 3-arylazetidinyl carbocations were successfully formed from readily accessible Cbz-azetidin-3-ols using inexpensive, abundant and mild calcium and iron Lewis acid catalysts (Figure 4.26). These carbocations were reacted *via* Friedel–Crafts reaction to prepare 3,3-diarylazetidines or 3-arylazetidin-3-ethers, or *via* thiol alkylation to form 3-aryl-3-sulfanylazetidines in high yields. Both reactions could be scaled to 1 g and could be run in non-chlorinated solvents. The product azetidines could be derivatised to drug-like compounds through the azetidine nitrogen, the aromatic groups or sulfur atom, demonstrating the stability of the new motifs and their potential for incorporation in drug discovery programs. Importantly, the NCbz group was crucial to reactivity by stabilising the azetidinyl carbocation intermediate.

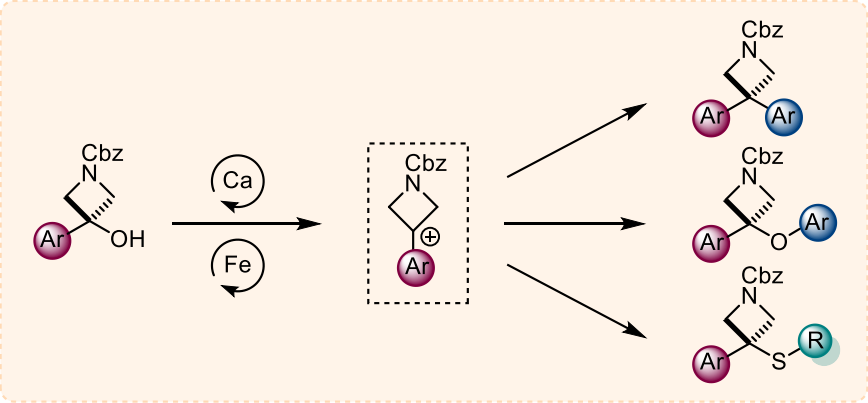
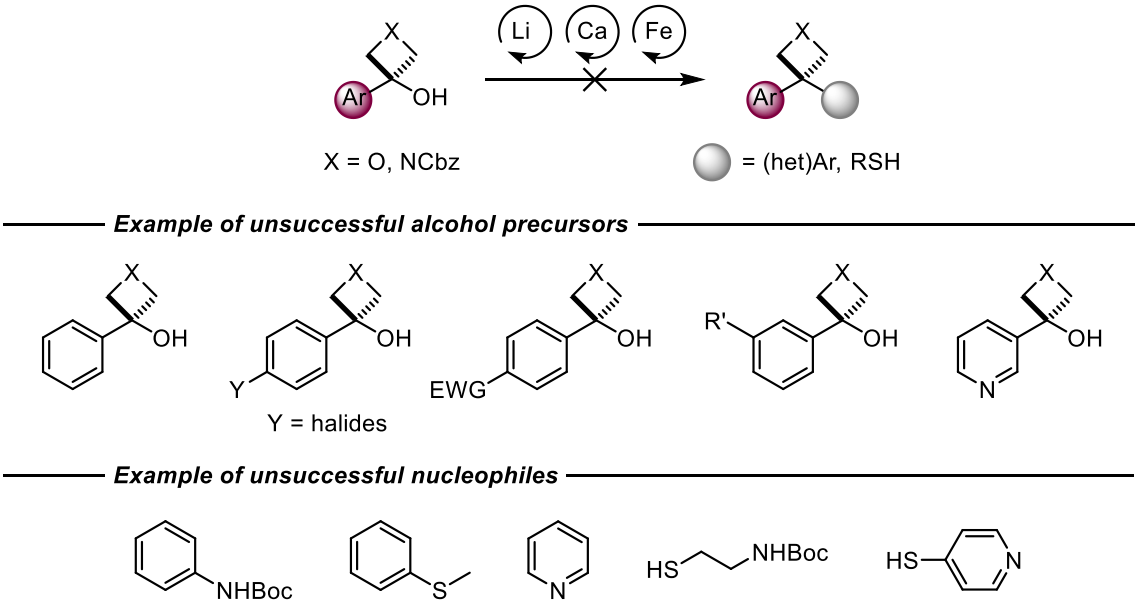


Figure 4.26: Synthesis of 3-aryl-3-substituted azetidines *via* catalytic generation of a carbocation from Cbz-azetidinols.

Despite the efficiency of these methods and the advantages they offer, important limitations remain, which are in common with the previous methods developed within the Bull group towards 3,3-diaryloxetanes and 3-arylsulfanyl oxetanes (Scheme 4.25).[50,51,88] The stabilisation of the azetidinyl and oxetanyl carbocation intermediates requires highly electron-rich pre-installed aromatics on the alcohol precursors. This prevents incorporation of simple phenyl ring, aromatics bearing halides or EWG as well as pyridines. In addition, *meta*-substitution on 3-arylazetidinols and oxetanols were insufficient to stabilise the corresponding carbocations. Many nucleophiles presenting a free or protected amine group, such as anilines or cysteamines, lacked reactivity most likely due to Lewis acid catalyst coordination to the nitrogen atom. Pyridines are prevalent in drug discovery programmes, but pyridine-containing nucleophiles were unsuccessful and could not be introduced for similar reasons.



Scheme 4.25: Unsuccessful alcohols precursors and nucleophiles in Friedel–Crafts reactions and *S*-alkylation towards 3,3-diarylazetidines and oxetanes, and 3-aryl-3-sulfanyl azetidines and oxetanes.

These limitations restrict the incorporation of these motifs into drug discovery programmes. Alternative methods were needed to solve these issues and efforts towards this goal will be discussed in the next chapter.

5. Friedel–Crafts Reaction with Deactivated Oxetanols and Arenes.

5.1 HFIP as Alternative Solvent for Carbocation Stabilisation

Polyfluorinated alcohols, especially TFE and HFIP, have recently emerged as new versatile solvents in organic chemistry.[133,134] In 2006, Berkessel *et al*. showed that aggregation of HFIP as dimers or timers enhanced the hydrogen bond donor (HBD) ability of this solvent, while increasing its Brønsted acidity (pKa = 9.3).[135] The author also showed that the hydrogen bond donation is dependent on the conformation along the C–O bonds in HFIP monomers. These remarkable strong HBD properties have been shown to increase the rate of epoxidation of olefins by activation of hydrogen peroxide,[136] and to promote other reactions such as cycloadditions with imines and metal-catalysed C–H activation.[133,134] Moreover, HFIP is suitable for industrial application being easily recovered by distillation due to its low boiling point,[137] which reduces the solvent waste and counterbalances initial cost (£87/kg[d]).

In 2012, Nájera developed a metal-free substitution of allylic alcohols with amines and carbamates, reporting the first alcohol activation by TFE and HFIP.[138] Later, Hall and Moran independently developed Friedel–Crafts conditions for the preparation of diarylmethanes from highly electronically deactivated benzylic alcohols, catalysed by boronic acid and TfOH respectively and enabled by HFIP (a and b, Figure 5.1).[139,140]

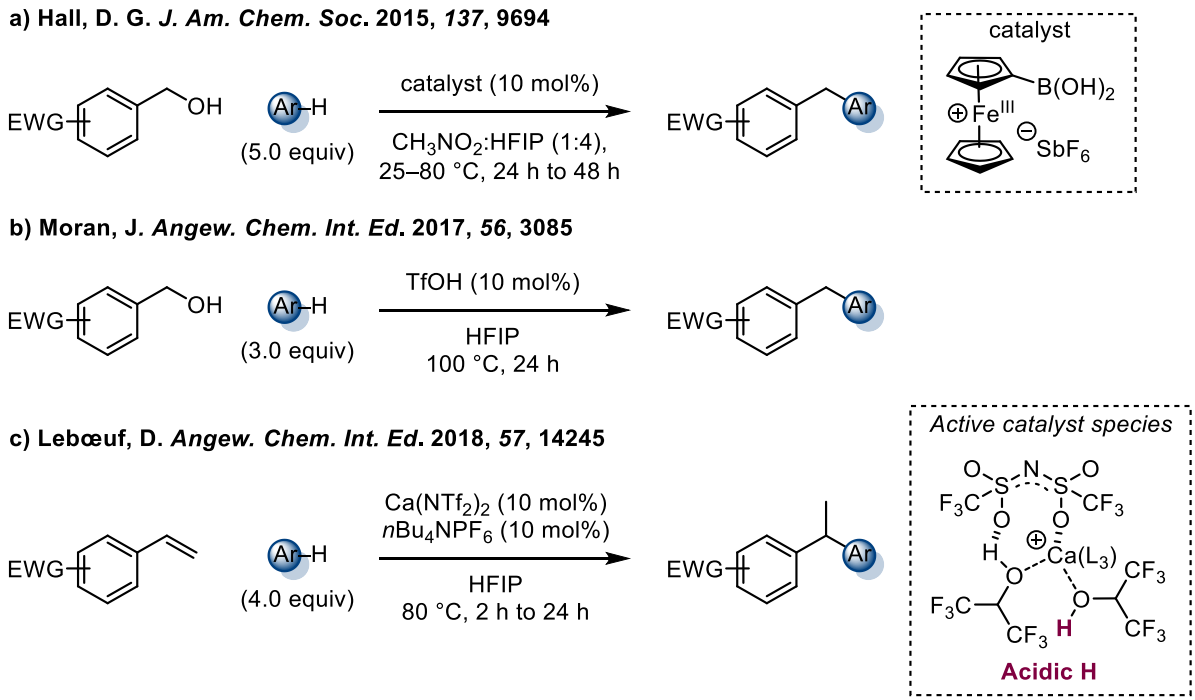


Figure 5.1: Previous Friedel–Crafts reactions and hydroarylation with deactivated benzylic alcohols and styrene, enabled by HFIP. L_3 = HFIP and two H_2O molecules

[d] Supplier: Fluorochem, price on the 5th April 2020 in UK.

In both studies, HFIP was integral to the reactivity. Hall suggested that the carbocation intermediate could be stabilised through solvation by molecules of HFIP, due to their particularly high dielectric constant (ε = 15.7).[139,133] In addition, Moran proposed that aggregates of HFIP and Brønsted acids form active catalytic species that enable ionisation of benzylic alcohols.[140] This was recently supported by DFT computations on the hydroarylation of deactivated styrenes in HFIP catalysed by $Ca(NTf_2)_2$ (c, Figure 5.1).[141] In this study, the calculation showed that a $[Ca(NTf_2)_2+(HFIP)_n]^+$ complex was the active catalytic species (Figure 5.1). The coordination of HFIP to the calcium ion was shown to increase the acidity of the solvent O–H enabling protonation of the styrene.

Encouraged by these works, it was thought that HFIP could stabilise the oxetanyl and azetidinyl carbocation intermediates which could promote Friedel–Crafts reactions with less electron-rich 3-aryl-3-oxetanols and azetidinols. This may enable the incorporation of phenyl, pyridines and electron-poor arenes bearing halides for instance, so far inaccessible, either on the preinstalled aromatics of the alcohol precursors or on the nucleophile (Figure 5.2).

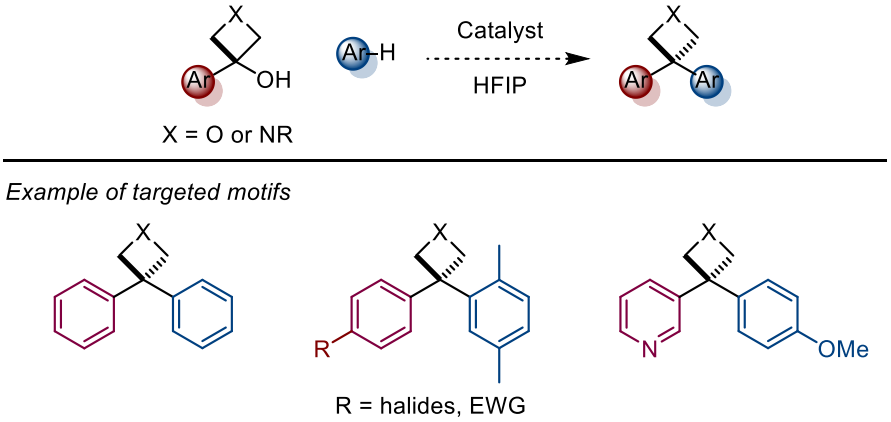


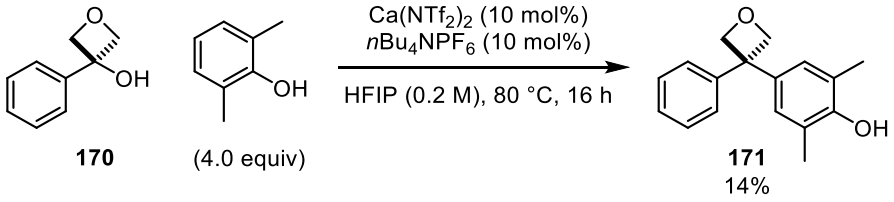
Figure 5.2: Proposed new Friedel–Crafts reaction with inactivated oxetanols and azetidinols, mediated by HFIP.

However, concerns were raised on the stability of the oxetane ring in presence of HFIP. The ability of this solvent to make strong hydrogen bond with ethers,[135] and the increased acidity of the solvent's O–H in presence of catalyst, could lead to ring opening and degradation through polymerisation.[140,141] Aware of these challenges, investigation with 3-phenyloxetan-3-ol was first undertaken.

5.2 Optimisation and Synthesis of New 3,3-Diaryloxetanes

5.2.1 Optimisation Using Phenol Nucleophiles

The conditions developed by Leboeuf discussed above seemed most appropriate to start the investigation with, as the $Ca(NTf_2)_2$ catalyst used in their study was successful in the previous Friedel–Crafts reaction towards 3,3-diaryloxetanes.[141,50] Electron-rich 2,6-dimethylphenol was chosen as the initial nucleophile to prevent *O*-alkylation and dihydrobenzofuran formation. 3-Phenyloxetan-3-ol **170**[e] was subjected to the reaction conditions employing 4 equivalents of nucleophile, with a combination of $Ca(NTf_2)_2$/nBu$_4$NPF$_6$ in HFIP at 80 °C (Scheme 5.1). Pleasingly, 14% of 3,3-diaryloxetane **171** was obtained. Although this result was promising, the starting material degraded under the conditions which made the improvement of this reaction challenging.

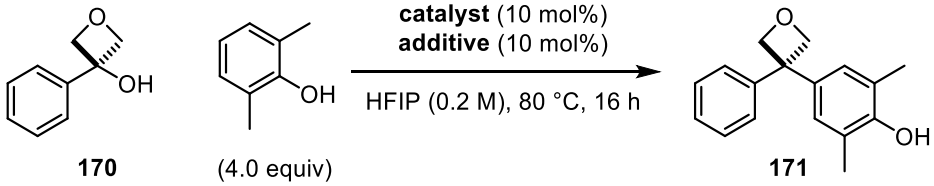


Scheme 5.1: Initial hit obtained subjecting oxetanol **170** to the HFIP-mediated Friedel–Crafts alkylation of 2,6-dimethylphenol.

Various Lewis and Brønsted acids were then tested in order to modulate the acidity and improve mass recovery (Table 5.1). Using lithium triflimide doubled the yield of oxetane **171** compared to calcium triflimide, albeit with similar loss of material (entry 2). Surprisingly, employing $FeCl_3$ resulted in a sharp increase in yield with 53% of **171** obtained and 25% of starting material recovered (entry 3). The combination of LiCl and HFIP was reported by Zhu to catalyse the Friedel–Crafts alkylation of phenol with ethylglycoxylate,[142] however this catalyst was found unreactive in our reaction (entry 4). Brønsted acids such as TFA, triflic acid and Tf_2NH were also investigated (entry 5 to 7), but none promoted efficiently the reaction leading to recovered starting material or degradation. McCubbin reported in 2010 a Friedel–Crafts alkylation with benzylic alcohol catalysed by $F_5C_6B(OH)_2$.[143] Subjecting this catalyst to our reaction conditions resulted only in starting material returned (entry 8). Finally, HFIP on its own was unable to promote the reaction and oxetanol **170** was fully recovered (entry 9).

$FeCl_3$ was the only catalyst that promoted the reaction without dramatic loss of starting material. In addition, this Lewis acid is an attractive catalyst being inexpensive and an earth-abundant metal and the reaction was further investigated with iron catalysts.

[e] Synthesised by Pfizer

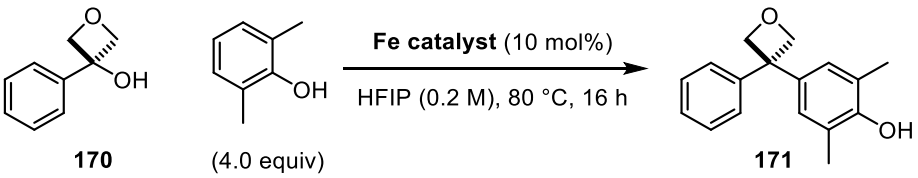


170 (4.0 equiv) **171**

Entry	catalyst/additive	Yield 171 (%)[a]	Yield 170 (%)[a]	Total (%)[a]
1	$Ca(NTf_2)_2/nBu_4NPF_6$	17	0	17
2[b]	$Li(NTf_2)/nBu_4NPF_6$	38	0	38
3	$FeCl_3$/-	53	25	78
4	LiCl/-	0	100	100
5	TFA	5	91	96
6	TfOH	21	0	21
7[c]	Tf_2NH	1	5	6
8	$F_5C_6B(OH)_2$	0	100	100
9	-	0	100	100

Table 5.1: Initial catalyst screen for the Friedel–Crafts alkylation of 2,6-dimethylphenol with oxetanol **170**. General conditions: oxetanol (0.20 mmol), 2,6-dimethylphenol (0.80 mmol), catalyst (10 mol%), HFIP (1.0 mL), 80 °C, under argon. [a] Yields calculated by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as the internal standard. [b] $Li(NTf_2)$ (11 mol%) and nBu_4NPF_6 (5.5 mol%) used. [c] 20 mol% of catalyst used.

All iron catalysts were chosen for being relatively easy to handle and inexpensive (Table 5.2). The addition of an ammonium additive, commonly used with lithium and calcium triflimide, seemed to be detrimental to the reaction in combination with $FeCl_3$ (entry 2), while $Fe(acac)_3$ did not give any product (entry 3). Interestingly, $FeCl_2$ was unreactive compared to $FeCl_3$ (entry 4), but $Fe(OTf)_2$ gave 20% of product **171** showing the importance of the counter ion. With the optimum $FeCl_3$ catalyst in hand, the effect of the catalyst loading on the reaction was examined (Table 5.3).



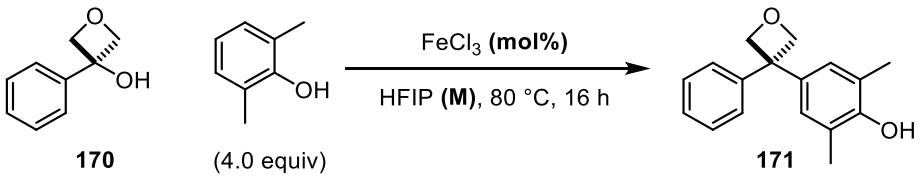
170 (4.0 equiv) **171**

Entry	Catalyst	Yield 171 (%)[a]	Yield 170 (%)[a]	Total (%)[a]
1[b]	$FeCl_3$	53	25	78
2	$FeCl_3$/nBu$_4$NPF$_6$	4	64	68
3	$Fe(acac)_3$	0	100	100
4	$FeCl_2$	0	98	98
5	$Fe(OTf)_2$	20	0	20

Table 5.2: Iron catalysts screen for the Friedel–Crafts alkylation of 2,6-dimethylphenol with oxetanol **170**. [a] Yields calculated by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as the internal standard. [b] Previous best conditions.

Surprisingly, doubling the catalyst loading to 20 mol% resulted in lower yield and more degradation (entry 2, Table 5.3). In comparison, halving the loading to 5 mol% afforded a better overall mass recovery, but with lower yield of product obtained (entry 3). Increasing the concentration to 0.4 M did not improve the yield but increased the mass recovery (entry 4). In contrast, dilution to 0.1 M strongly affected the reaction with 73% of **171** obtained and no oxetanol returned (entry 5), which represented the best outcome so far.

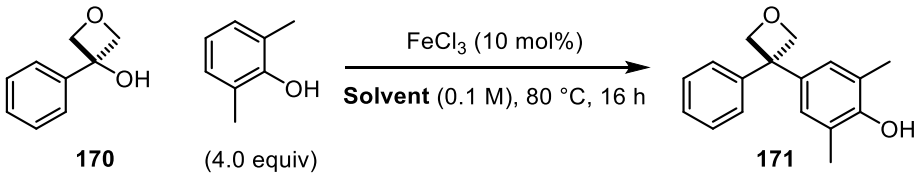
Alternative solvents were tested for this reaction (Table 5.4). TFE was not as efficient as HFIP to promote the reaction, with lower yield obtained (entry 2). Different combinations of solvent with HFIP were then tested. Mixtures of HFIP and $MeNO_2$ have been extensively used as solvents for the catalytic substitution of π–activated alcohols,[86,139] and gave 38% of product **171** when used in the reaction (entry 3). Toluene, EtOAc and acetonitrile as co-solvents all resulted in lower yield or no reaction, and HFIP was found to be the optimum medium for this reaction.



170 (4.0 equiv) **171**

Entry	Catalyst loading (mol%)	Concentration (M)	Yield 171 (%)[a]	Yield 170 (%)[a]	Total (%)[a]
1[b]	10	0.2	53	25	78
2	20	0.2	43	0	43
3	5	0.2	41	53	94
4	10	0.4	20	74	94
5	10	0.1	73	0	73

Table 5.3: Effect of the catalyst loading and concentration on the Friedel–Crafts alkylation of 2,6-dimethylphenol with oxetanol **170**. [a] Yields calculated by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as the internal standard. [b] Previous best conditions.

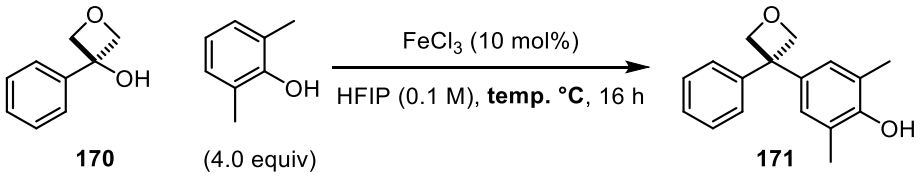


170 (4.0 equiv) **171**

Entry	Solvents (ratio 1:1)	Yield 171 (%)[a]	Yield 170 (%)[a]	Total (%)[a]
1[b]	HFIP	73	0	73
2	TFE	13	73	86
3	$MeNO_2$/HFIP	38	44	82
4	toluene/HFIP	20	75	95
5	EtOAc/HFIP	7	74	81
6	MeCN/HFIP	0	100	100

Table 5.4: Solvents screen for the Friedel–Crafts alkylation of 2,6-dimethylphenol with oxetanol **170**. [a] Yields calculated by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as the internal standard. [b] Previous best conditions.

The high temperature of 80 °C seemed to be important to the reaction, as running the reaction at 40 °C or 60 °C lowered the yield and the mass recovery (Table 5.5).

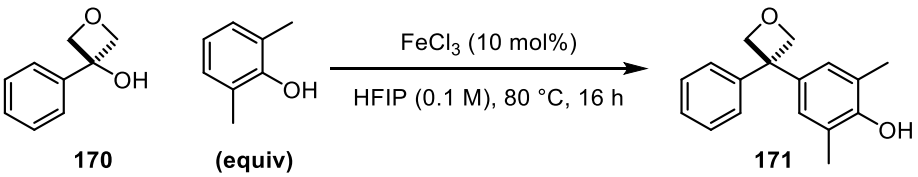


Entry	temp. °C	Yield 171 (%)[a]	Yield 170 (%)[a]	Total (%)[a]
1[b]	80	73	0	73
2	40	53	0	53
3	60	52	0	52

Table 5.5: Effect of the temperature on the Friedel–Crafts alkylation of 2,6-dimethylphenol with oxetanol **170**. [a] Yields calculated by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as the internal standard. [b] Previous best conditions.

The equivalents of nucleophile was found to be the most influential parameter on the reaction (Table 5.6). Indeed, halving the equivalents of the nucleophile to 2 improved the yield to 88% (entry 2). This was surprising as a larger amount of nucleophile is usually required to reach high yield in Friedel–Crafts reactions.[86] Reducing the equivalents further to 1.7 resulted in even higher yield of 94% (entry 3). Using 1.5 equivalents resulted in a similar outcome with 8% of oxetanol **170** returned (entry 4). Fewer equivalents of nucleophile led to a loss of 10% yield, due to non-completion of the reaction (entry 5). Overall, reduction of the equivalents of nucleophile led to an important rise in yield but also to better mass recovery, which points out the detrimental effect of the phenol nucleophile on the reaction.

Employing 1.7 equivalents of nucleophile, in 0.1 M HFIP at 80 °C was optimal to reach high yield with minimum loss of material. Importantly, running the reaction without precaution to exclude water or oxygen had little effect on the outcome producing **171** in 83% and demonstrating the robustness of the methodology (entry 6). With the optimised conditions in hand, the reaction scope was studied by varying the nucleophile.



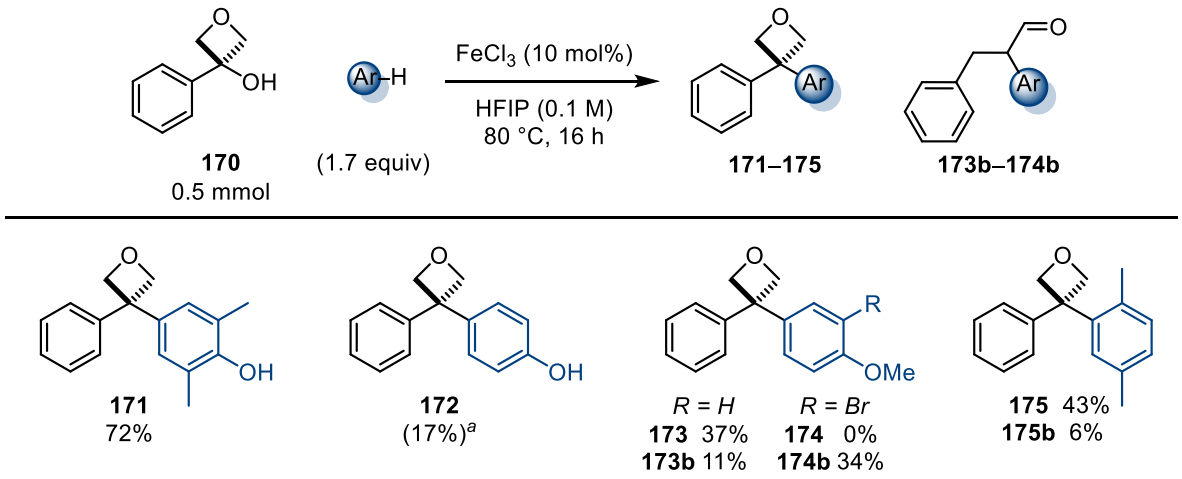
Entry	Equivalents	Yield 171 (%)[a]	Yield 170 (%)[a]	Total (%[a])
1[b]	4	73	0	73
2	2	88	0	88
3	1.7	94	0	94
4	1.5	91	8	99
5	1.2	80	20	100
6[c]	1.7	83	10	93

Table 5.6: Effect of the temperature on the Friedel–Crafts alkylation of 2,6-dimethylphenol with oxetanol **170**. [a] Yields calculated by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as the internal standard. [b] Previous best conditions. [c] No action taken to avoid water and oxygen.

5.2.2 Difference Between Oxygen-Containing and Non-Oxygen-Containing Nucleophiles

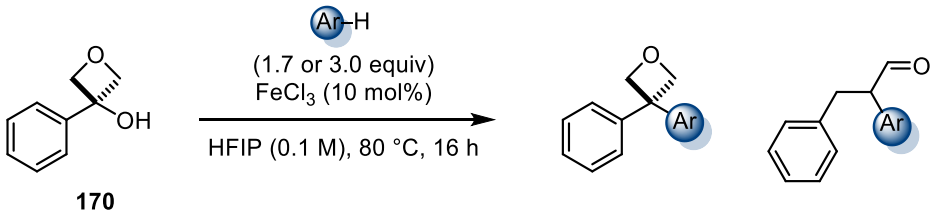
Scaling the reaction to 0.5 mmol of oxetanol **170** using 2,6-dimethylphenol gave **171** in 72% isolated yield (Scheme 5.2). Using phenol itself resulted in a complex mixture with only 17% of the product **172** (^{1}H NMR), as well as dihydrobenzofuran and other unidentified products with no starting material recovered. The desired product could not be isolated, and unhindered phenols seem unsuitable nucleophiles for this transformation. Masking the phenolic OH with a methyl group limited side product formation: anisole as the nucleophile produced 37% of oxetane **173**. Pleasingly, the reaction was selective for the *para*-substituted product **173** and no reaction occurred at the *ortho* position. In contrast 2-bromoanisole did not give any desired product most likely due to the electron-withdrawing effect of the bromine atom. The non-activated nucleophile *para*-xylene was successful giving 3,3-diaryloxetane **175** in 43% yield. Only phenols were efficient in the previous Friedel–Crafts reaction towards 3,3-diaryloxetanes, showing the complementarity of this new method.

Curiously, new side products were isolated for the reaction with the last three nucleophiles. Aldehydes **173b**, **174b** and **175b** were purified in 11%, 34% and 6% yields respectively using anisole, 2-bromoanisole and *para*-xylene as nucleophiles. Studies to understand the origin of these aldehyde products will be discussed later (section 5.3).



Scheme 5.2: Initial scope of nucleophiles for the Friedel–Crafts reaction with oxetanol **170**. [a] Yield calculated by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as the internal standard.

In addition, an interesting difference in mass recovery was observed when using anisole and *para*-xylene, with no oxetanol recovered with the former. Increasing the equivalents of anisole to 3.0 increased the yield of aldehyde **173b** to 33% and resulted in a similar yield of oxetane **173** (entry 2, Table 5.7). On the other hand, the use of three equivalents of *para*-xylene improved the yield of oxetane **175** to 63% with no aldehyde formed (entry 4). These results taken with observations from table 5.6 suggest that nucleophiles containing oxygen atoms have a deleterious effect on the reaction leading to more degradation of oxetanols or promoting aldehyde formation. In contrast, reaction with *para*-xylene was improved when more nucleophile was employed, indicating that the reaction could be further improved, and attempts were next made to optimise the reaction.

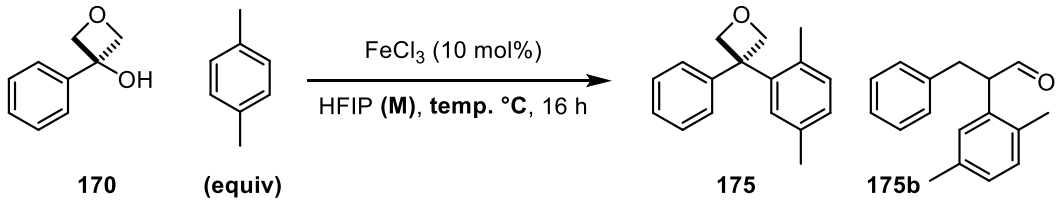


Entry	Nucleophile	Equivalents	Yield oxetane (%)[a]	Yield aldehyde (%)[a]
1[b]	anisole	1.7	37	11
2	anisole	3.0	38	33
3[b]	*para*-xylene	1.7	43	6
4	*para*-xylene	3.0	63	0

Table 5.7: Effect of the equivalents of nucleophiles on the Friedel–Crafts reaction of anisole or *para*-xylene with oxetanol **170**. [a] Yields calculated by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as the internal standard. [b] Isolated yields.

5.2.3 Optimisation Using a Non-Oxygenated Nucleophile

When the equivalents of *para*-xylene were increased to 4.0, 74% of oxetane **175** was obtained with 6% of aldehyde **175b** (entry 3, Table 5.8). Increasing the amount of nucleophile further to 5.0 gave an optimum yield of 81% (entry 4). However using *para*-xylene in large excess as co-solvent adversely affected the reaction, halving the yield (entry 5). Five equivalents seemed to be the optimum limit to ensure good outcome without loss of material. Lowering the temperature to 60 °C still produced oxetane **175** although with a loss of 20% in yield (entry 6). On the other hand, heating the reaction to 100 °C led to similar yields (entry 7). Finally, concentrating the reaction to 0.3 M (entry 8) only led to a reduced yield of **175** compared to 0.1 M in entry 1.

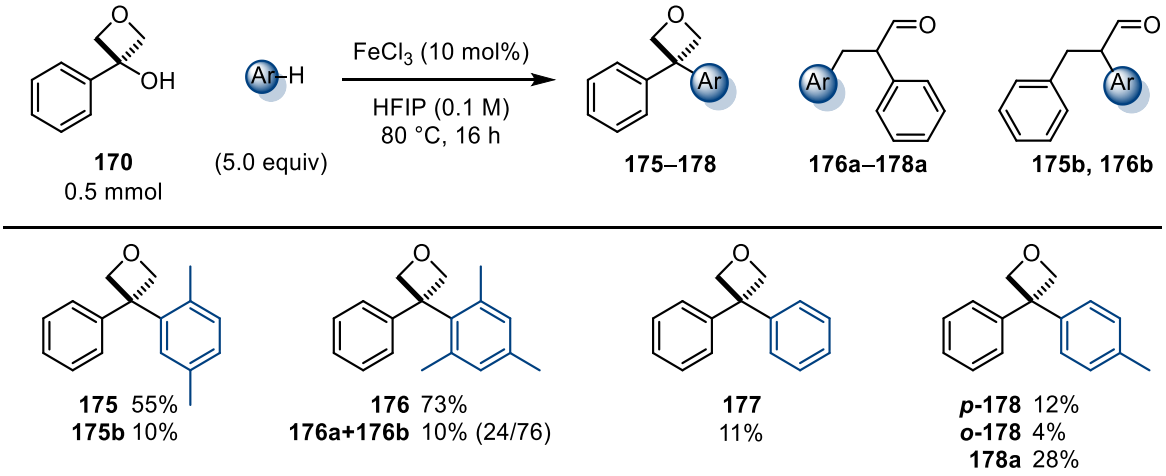


170 **(equiv)** **175** **175b**

Entry	Equiv.	Concn. (M)	Temp. (° C)	Yield 175 (%)[a]	Yield 175b (%)[a]
1[b,c]	1.7	0.1	80	43	6
2[c]	3.0	0.1	80	63	0
3	4.0	0.1	80	74	6
4	5.0	0.1	80	81	5
5[d]	32.4	0.1	80	44	2
6	5.0	0.1	60	61	16
7	5.0	0.1	100	79	3
8	1.7	0.3	80	30	4

Table 5.8: Optimisation of the Friedel–Crafts alkylation of *para*-xylene with oxetanol **170**. [a] Yields calculated by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as the internal standard. [b] Isolated yields. [c] Results previously obtained in table 5.7. [d] HFIP:*para*-xylene = 3:1 as the solvent.

The reaction was scaled to 0.5 mmol which resulted in a lower yield of 55% of **175**, showing the sensitivity of the methodology to the scale (Scheme 5.3). The scope of non-oxygenated nucleophiles was further examined. Mesitylene was high yielding compared to *para*-xylene producing oxetane **176** in 73% yield. Surprisingly, 10% of a mixture of aldehydes **176a** and **176b** was also obtained. Benzene is usually not reactive in catalytic Friedel–Crafts reactions being not electron-rich enough. Indeed, it was only moderately successful under our reaction conditions and 3,3-diaryloxetane **177** was obtained in only 11% yield. Similarly, toluene gave moderate yield, with 28% of aldehyde **178a**, 12% of *para*-substituted oxetane ***p*-178** and 4% of the *ortho* isomer ***o*-178**, which were all separated by simple flash column chromatography.

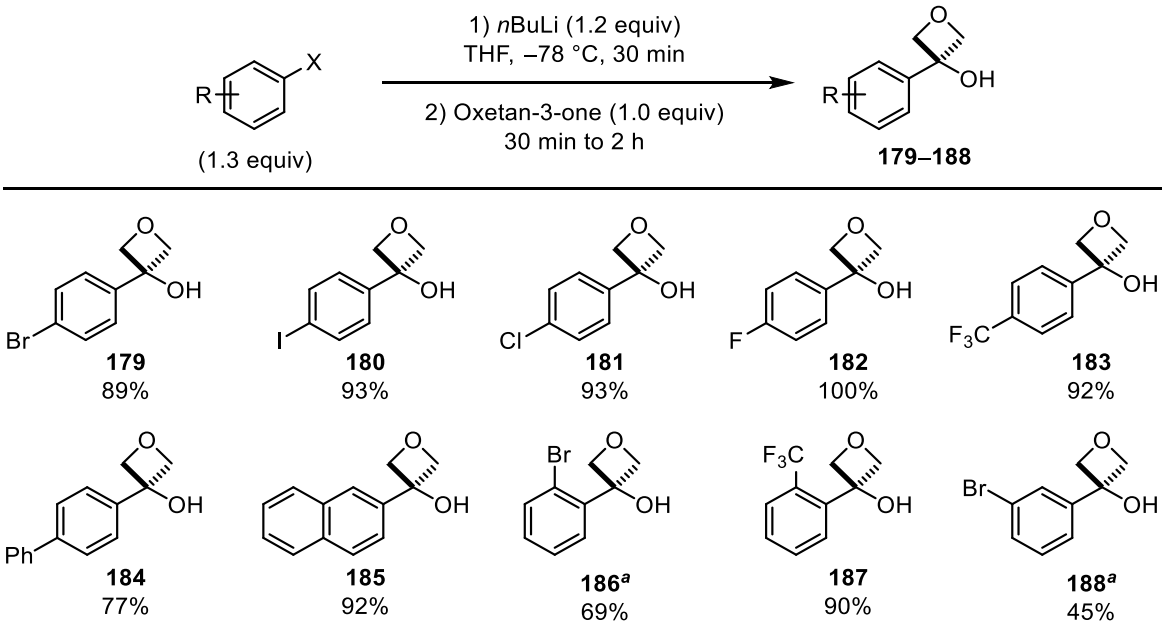


Scheme 5.3: Scope of non-oxygenated nucleophiles for the Friedel–Crafts reaction with oxetanol **170**. General conditions: oxetanol (0.5 mmol), nucleophile (2.5 mmol), $FeCl_3$ (0.05 mmol), HFIP (5.0 mL).

With the two sets of optimised conditions in hand, the scope of oxetanols was investigated.

5.2.4 Scope of Oxetan-3-ols and Effects of the Substituent

A collection of 3-aryloxetan-3-ols, bearing halides, OMe[f], Me or Ph groups in *para*, *ortho* or *meta* positions were prepared in high yields by addition of aryllithium or Grignard reagents to oxetan-3-one (Scheme 5.4). *ortho*-Methoxyphenyl oxetanol **189** was previously synthesised by Rosie Croft[88] while *meta*-methoxy, *meta*-CF_3 and *para*-methyl substituted oxetanols **190**, **191** and **192** were kindly provided by Pfizer.

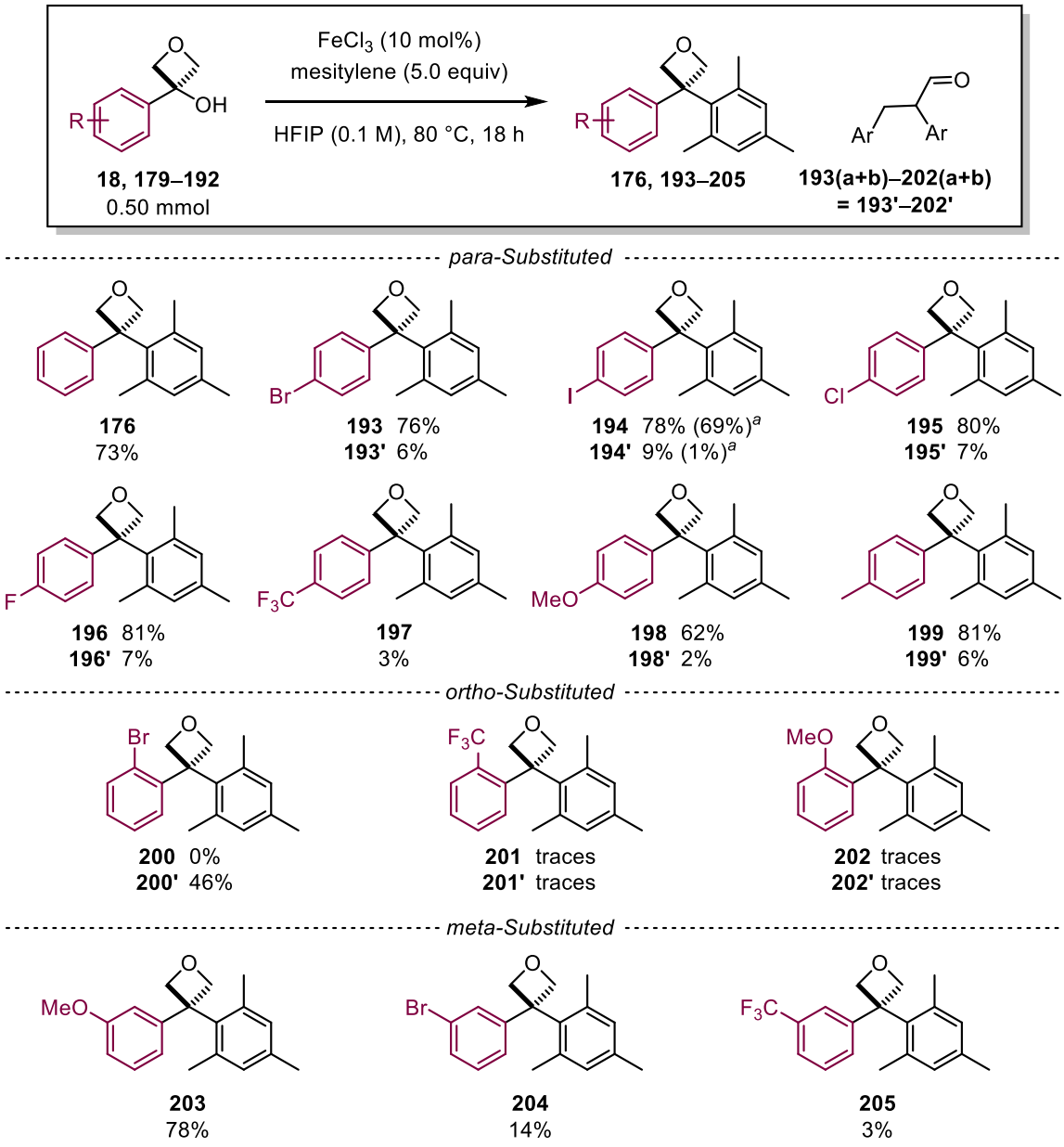


Scheme 5.4: Preparation of 3-aryloxetan-3-ols. [a] *i*PrMgCl·LiCl was used instead of *n*BuLi.

5.2.4.1 Scope of oxetanols with mesitylene as nucleophile

The scope of 3-aryloxetan-3-ols was first studied with mesitylene as nucleophile which previously gave the highest yield (Scheme 5.5). Pleasingly, oxetanols **179**–**182** bearing halide in the *para* position were all suitable substrates, affording 3,3-diaryloxetanes **193** to **196** in 76% to 81% yields, with less than 10% yield of aldehydes (see details on aldehydes distribution in Table 5.9). Synthesis of halide-containing 3,3-diaryloxetanes was difficult and low yielding with the previous methodology.[50] The bromine, iodine and chloride functionalities of the new 3,3-diaryloxetanes represent useful synthetic handles for further derivatisation. The reaction of oxetanol **180** with mesitylene could be scaled up to 4.0 mmol producing 1 g of oxetane **194** in 69% yield, demonstrating the scalability of the reaction albeit with a 10% decrease in yield compared to 0.5 mmol scale. The reactivity of oxetanol **183** was dramatically lowered due to the presence of electron-withdrawing CF_3 group, being unable to stabilise the oxetanyl carbocation intermediate. Nevertheless, 3% of product **197** was still obtained which is the first example of 3,3-diaryloxetane containing a CF_3 group.

[f] Previously synthesised in section 3.3.2.1

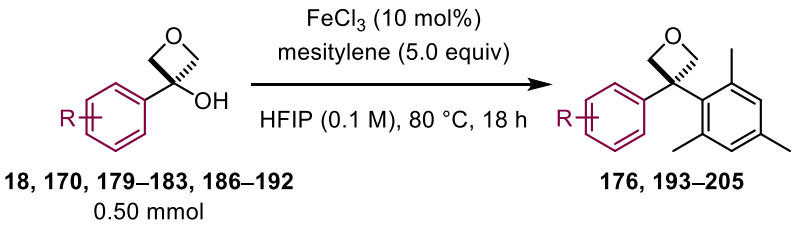


Scheme 5.5: Friedel–Crafts alkylation of mesitylene with oxetanols. General conditions: oxetanol (0.50 mmol), nucleophile (2.5 mmol), $FeCl_3$ (0.05 mmol), HFIP (5.0 mL). [a] 1 g scale. The ratio of the two aldehyde types will be presented in table 5.9.

Electron-rich oxetanols were expected to give high yield of product due to better stabilisation of the carbocation intermediate. Unexpectedly, *para*-methoxy oxetanol **18** gave lower yield and oxetane **198** was obtained in 62% yield, whereas Me-substituted oxetanol **192** afforded oxetane **199** in 81% yield. *ortho*-Substituted oxetanols **186**, **187** and **189** were incompatible precursors in this reaction with no 3,3-diaryloxetanes formed, likely due to steric hindrance. Interestingly, bromo-substituted aldehyde **200'** was formed in 46% instead of the desired product with oxetanol **186**. In comparison, *meta*-substitution was well tolerated, with 78% and 14% of methoxy **203** and bromide **204** obtained respectively. Interestingly, *meta*-CF_3

substituted oxetanol **191** gave 3% of the desired oxetane **205** demonstrating the possibility to form an oxetanyl carbocation intermediate on such electron-poor system.

Overall, higher yields were obtained when the substituent on the oxetanol was placed in the *para* position, likely due to better stabilisation of the carbocation through more donating mesomeric and inductive effects compared to *meta* position. The relationship between the electronic nature of the substituent and the yield of 3,3-diaryloxetane was examined in Figure 5.3, using electrophilic substituent constants σ_p^+ and σ_m^+ calculated by Okamoto and Brown (Table 10.4, appendix).[144]



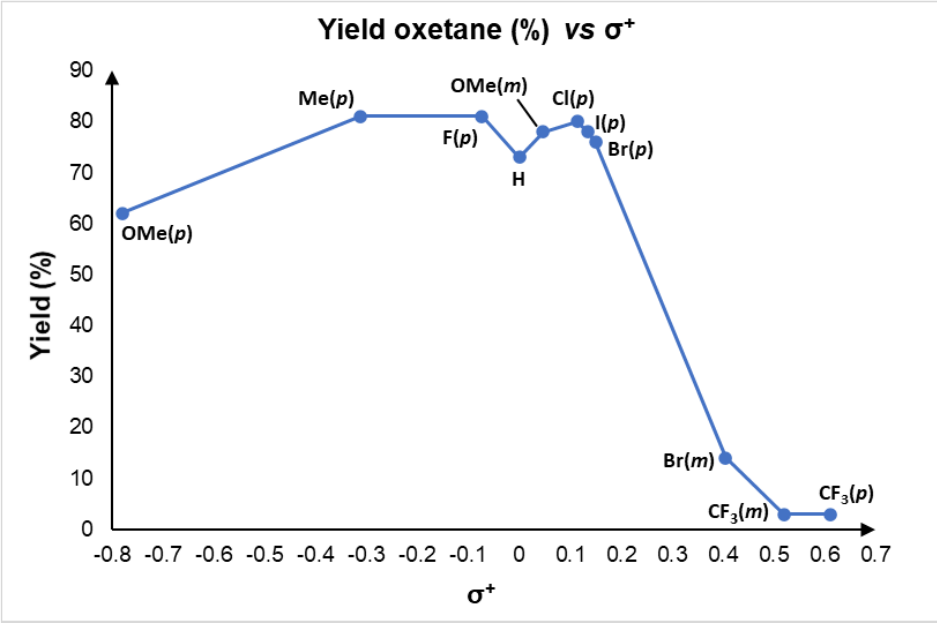
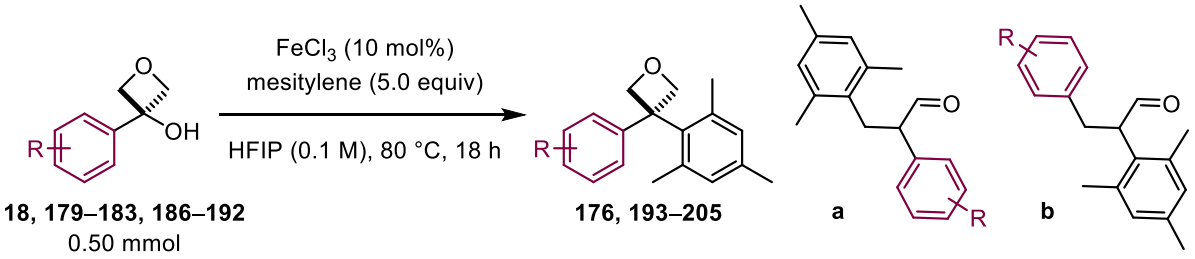


Figure 5.3: Graph representing the yield of 3,3-diaryloxetane *vs* σ^+ of the corresponding substituent on oxetanol, for the reaction with mesitylene as the nucleophile.

A preliminary correlation was found between the yield of oxetane products and the electronic nature of the oxetanols' substituent with higher yields obtained for groups with $-0.31 < \sigma^+ < 0.15$. Interestingly, the most electron-donating substituent *para*-OMe ($-0.31 < \sigma^+$) led to lower yield. The carbocation, being more stable, could be present in the reaction for longer and react in non-productive pathways. Oxetanols with substituents having $\sigma^+ > 0.15$ were unproductive or afforded very low yield due to the poor stabilisation of the carbocation intermediate. Although this comparison gives an indication on the effect of the substituents on the reaction, relative rates of reactions in competition experiments will be

carried out in the future to build a Hammett plot, in order to gain insight in the reaction mechanism and potentially tune the conditions.

During the reaction with mesitylene, aldehydes **a** and **b** were also produced in different ratios according to the choice of oxetanol (Table 5.9). The aldehydes were distinguished from one another using HSQC and HMBC NMR spectroscopy (Figure 10.1 in Appendix).



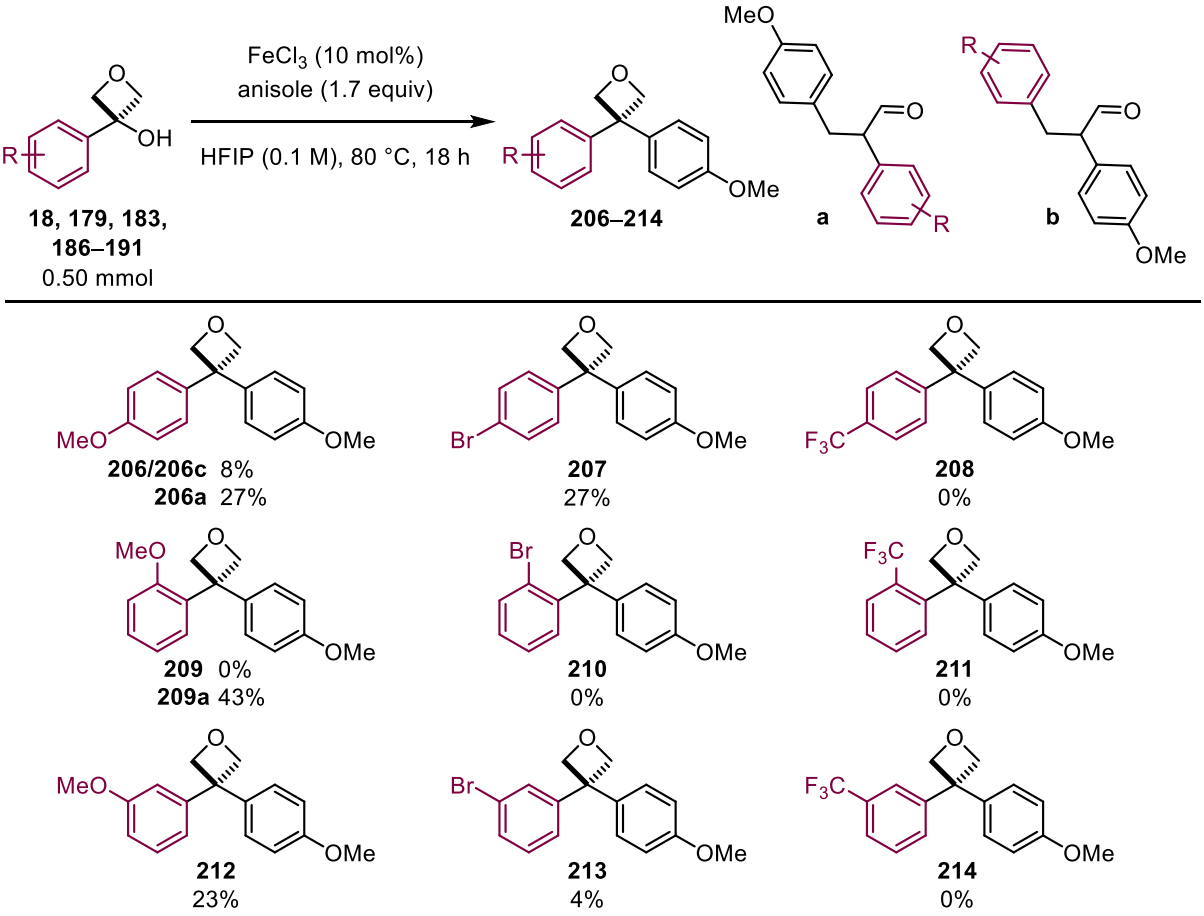
Entry	R=	N°	Ratio aldehydes a/b in crude product[a]	Ratio aldehydes a/b after purification	Yield aldehyde(s) (%)
1	H	**176**	30/70	24/76	10
2	*p*-Br	**193**	42/58	38/62	6
3	*p*-I	**194**	51/49	53/47	9
4	*p*-I[b]	**194**	1/99	3/97	1
5	*p*-Cl	**195**	38/62	39/61	7
6	*p*-F	**196**	1/99	7/93	7
7	*p*-CF_3	**197**	traces	-	-
8	*p*-OMe	**198**	-[c]	20/80	2
9	*p*-Me	**199**	16/84	16/84	6
10	*o*-Br	**200**	100/0	100/0	46
11	*o*-CF_3	**201**	100/0	100/0	1
12	*o*-OMe	**202**	traces	-	-
13	*m*-OMe	**203**	0	0	0
13	*m*-Br	**204**	traces	0	0
15	*m*-CF_3	**205**	traces	0	0

Table 5.9: Aldehydes **a** and **b** distribution for the Friedel–Crafts reaction of mesitylene with oxetanol. [a] Ratio determined integrating the peak of the two aldehydes in the ^{1}H NMR spectroscopy of the crude mixture. [b] 1 g scale. [c] The ratio could not be determined in the crude mixture.

Overall, aldehydes were only formed on substrates that were reactive to carbocation formation. For example, *para*-substituted oxetanols **18**,**179**–**182** and **192** gave a mixture of aldehydes **a** and **b** in 2% to 10% yields, with aldehyde **b** as major product in most cases (entries 1 to 9, Table 5.9). On the other hand, no aldehyde was formed with *para*-CF_3 substituted oxetanol **183**. In addition, *ortho*-substitution seems to be detrimental to the formation of aldehyde **b**, and aldehyde **200a** and **201a** were obtained exclusively with oxetanol **186** and **187** (entry 10 and 11). *meta*-Substituted oxetanols exclusively reacted towards the formation of 3,3-diaryloxetanes and no aldehyde products were obtained (entries 13 to 15). Finally, the distribution of aldehyde products was dependent on the scale, with only 1% of a 3:97 ratio of **194a**:**194b** on a 4.0 mmol scale compared to 9% of 53:47 mixture of **194a**:**194b** using 0.5 mmol of oxetanol **180**.

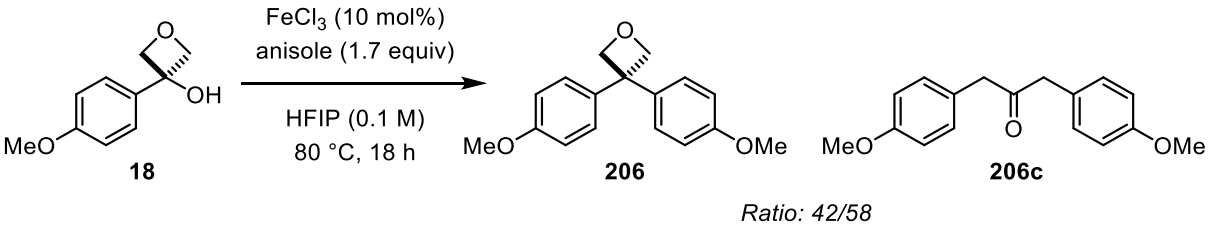
5.2.4.2 Scope of oxetanols with anisole and 2,6-dimethylphenol as nucleophiles

Anisole was a much less effective nucleophile (Scheme 5.6). Only *para*-Br, *meta*-Br and *meta*-OMe substituted oxetanol **179**, **188** and **190** produced the desired 3,3-diaryloxetanes **207**, **213** and **212** in 4% to 23% with complete consumption of the precursors.



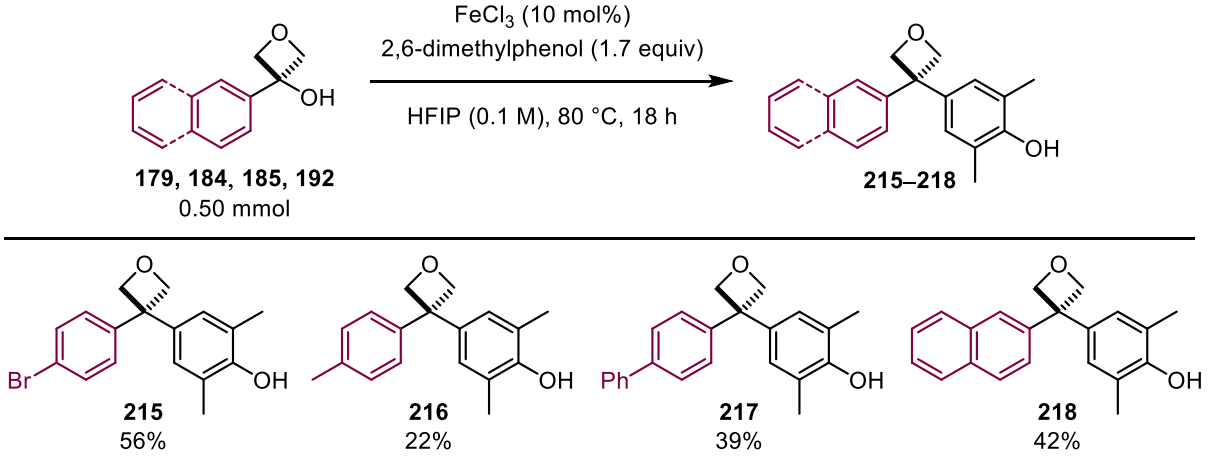
Scheme 5.6: Friedel–Crafts alkylation of anisole with oxetanols. General conditions: oxetanol (0.50 mmol), nucleophile (0.85 mmol), $FeCl_3$ (0.05 mmol), HFIP (5.0 mL).

The reaction was selective for the *para*-substituted product in all cases, as previously observed with oxetanol **170**. *para*-OMe and *ortho*-OMe substituted oxetanol **18** and **189** reacted unexpectedly towards preferential formation of aldehyde **206a** and **209a** in 27% and 43% yields respectively. Surprisingly, oxetane **206** was obtained as a mixture with a ketone **206c** (Scheme 5.7), for which the mechanism of formation will be discussed later (section 5.3). Finally, none of the CF_3-substituted oxetanols were reactive in presence of anisole with complete degradation of starting material.



Scheme 5.7: Formation of product **206c** during the Friedel–Crafts alkylation of anisole with oxetanol **18**.

The scope of oxetanols was further examined using 1.7 equivalents of 2,6-dimethylphenol (Scheme 5.8). Br- and Me-substituted oxetanols **179** and **192** afforded 3,3-diaryloxetanes **215** and **216** in 56% and 22% yields respectively. Phenyl group in *para*-position was electron-donating enough to stabilise the carbocation intermediate giving product **217** in 39% yield. Finally, naphthyl oxetanol **185** was also a suitable precursor producing oxetane **218** in 42% yield. Overall, these results are in agreement with the previous observations, where lower yields and significant mass loss were obtained with anisole and phenol compared to hydrocarbon nucleophiles. Although the reasons for the detrimental effect of oxygen-containing nucleophiles on the reaction remain unclear, the Lewis basic *O*-atom may assist in opening of the oxetane ring. Further investigations were then undertaken to understand the origin of the aldehyde side products.



Scheme 5.8: Friedel–Crafts alkylation of 2,6-dimethyphenol with oxetanols. General conditions: oxetanol (0.50 mmol), nucleophile (0.85 mmol), $FeCl_3$ (0.05 mmol), HFIP (5.0 mL).

5.3 Mechanistic Insights

To investigate potential degradation pathways, oxetanol **170** was subjected to the optimised reaction conditions in absence of nucleophile and was examined using ^{1}H NMR spectroscopy (Figure 5.4).

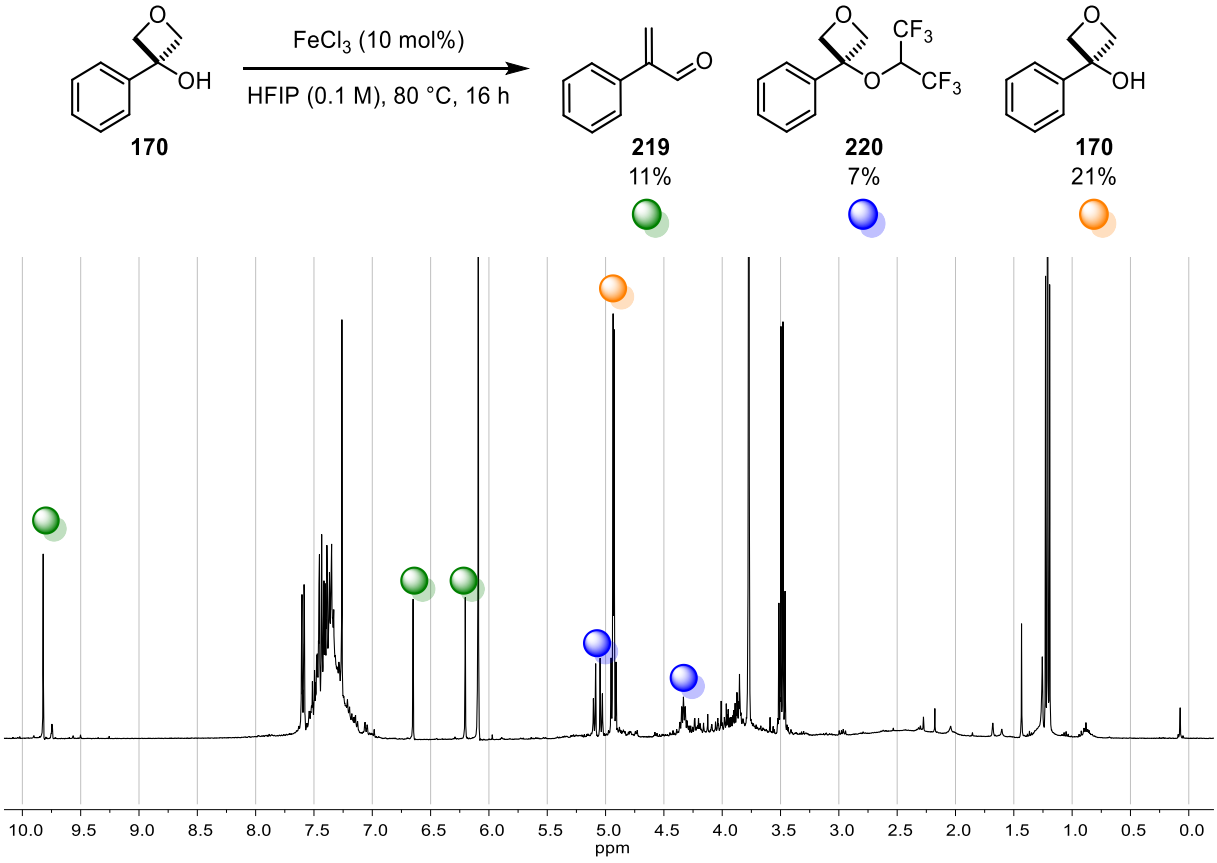
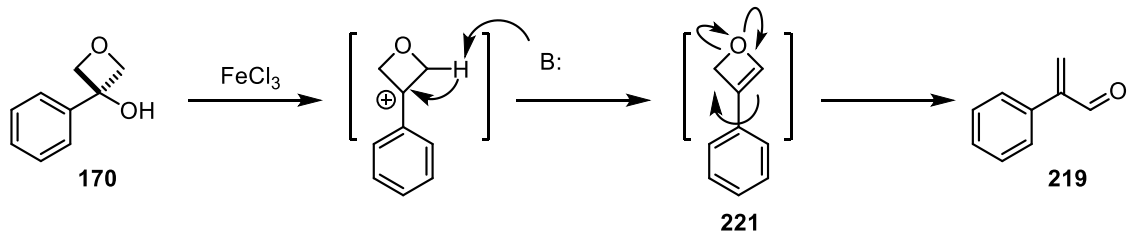


Figure 5.4: Product distribution for the reaction of oxetanol **170** in absence of nucleophile determined by ^{1}H NMR spectroscopy of the crude product using 1,3,5-trimethoxybenzene as the internal standard.

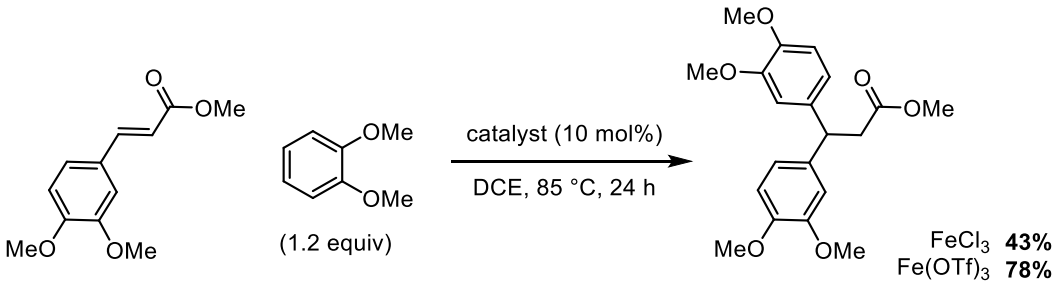
After 16 h, significant degradation of oxetanol **170** was observed with only 21% of precursor recovered and 18% of other two products which could not be isolated due to their instability despite several attempts. One of these products was identified as ether **220**, presenting two doublets for oxetane peaks (in blue, Figure 5.4) at δ_H = 5.10 ppm integrating for four protons and one heptet at δ_H = 4.3 ppm corresponding to the CH adjacent to the CF_3 groups. Ether **220** most likely resulted from the addition of HFIP to the oxetanyl carbocation intermediate. The second product had one aldehyde peak and two alkene signals at δ_H = 6.7 ppm and 6.3 ppm (in green) each integrating for one proton, which matched with previous ^{1}H NMR spectrum reported in the literature for atropaldehyde **219**.[145] A similar product was observed in previous work by the Bull group on the degradation pathways of oxetanol under lithium-catalysed Friedel–Crafts reaction without nucleophile.[52,88] The formation of this product was proposed through deprotonation of the carbocation intermediate, forming an unstable oxetene **221**

species which quickly rearranged into α,β–unsaturated aldehyde **219** *via* ring opening (Scheme 5.9).



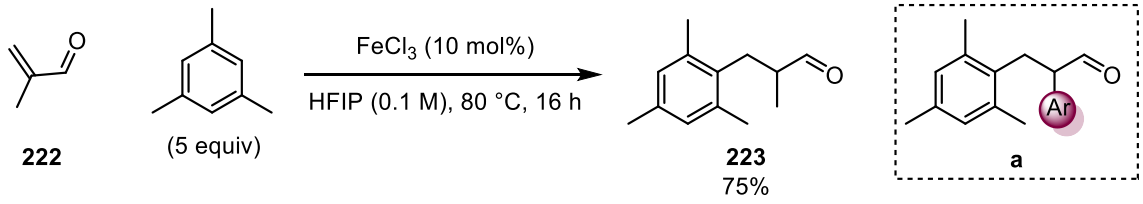
Scheme 5.9: Proposed mechanism for the formation of α,β-unsaturated aldehyde **219**.

Friedel–Crafts alkylation of aromatics with α,β–unsaturated carbonyls have been extensively investigated, using imine organocatalyst [146] or Lewis acid catalysts such as $Yb(OTf)_3$,[147] $AuCl_3$,[148] $InBr_3$,[149] Br_2,[150] $AlCl_3$,[151] $Bi(OTf)_3$[152] and $B(C_6F_5)_3$[153] as well as Brønsted acids[154]. More recently, Maji reported an $Fe(OTf)_3$-catalysed hydroarylation with α,β–unsaturated carbonyls and found that $FeCl_3$ was also a suitable catalyst although affording the product in lower yield (Scheme 5.10).[155]



Scheme 5.10: $Fe(OTf)_3$-hydroarylation with α,β–unsaturated carbonyls developed by Maji.[155]

Therefore, aldehyde **a** and **b** observed under the HFIP-mediated conditions, were thought to be formed through Friedel–Crafts alkylation of aromatics with atropaldehyde **219.** The latter could not be isolated as pure product due to instability. Instead, commercial methacrolein **222** was subjected to the reaction conditions giving aldehyde **223** in 75% yield, which supports the formation of aldehydes of type **a** through 1,4-addition of aromatics onto **219** (Scheme 5.11).

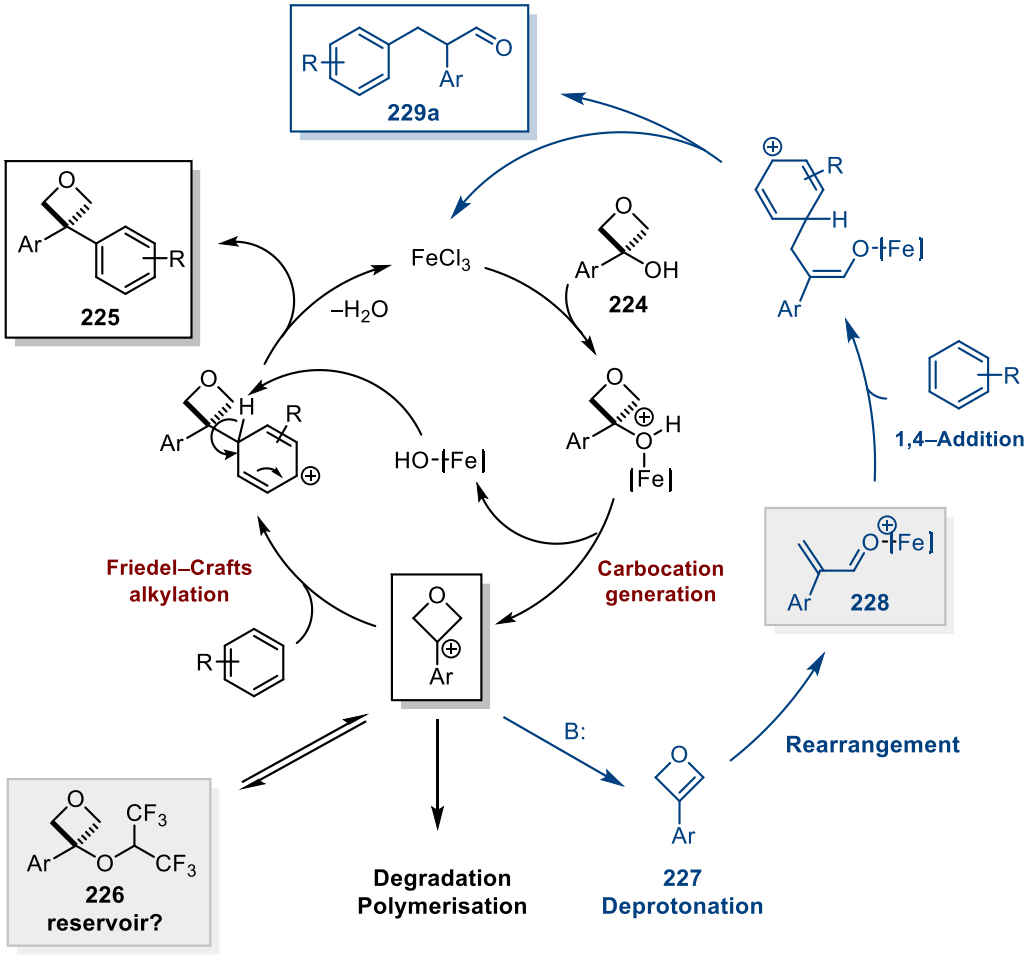


Scheme 5.11: Reaction of aldehyde **222** with mesitylene under the optimised conditions.

Friedel–Crafts alkylation of electron neutral or poor aromatics with an α,β-unsaturated carbonyl usually require excess amount of $AlCl_3$.[151] A few examples with non-activated aromatics were

reported in 1961 by Scriabine, using a combination of $BF_3{\cdot}OEt_2$ and stoichiometric amount of $TiCl_4$ at –30°C producing only 20% to 38% yield of products.[156] In 2010, Zhao reported a rare Rh-catalysed hydroarylation with α,β–unsaturated carbonyls and deficient perfluoroarenes.[157] However, this required the use of an expensive and precious metal catalyst and proceeded through a different mechanism than Friedel–Crafts reaction, involving an aromatic C–H activation step followed by olefin insertion. The current Lewis-acid catalysed Friedel–Crafts alkylation of aromatics with an α,β-unsaturated carbonyl are limited to heteroarenes such as indoles, pyrroles, furan or thiophene, or highly electron-donating aromatics.[146–155] Therefore, it appears that the combination of $FeCl_3$ with HFIP enables the difficult alkylation of non-activated aromatics with α,β–unsaturated aldehydes, and represent a new method to access useful 2,3-diarylpropanal products.

A plausible mechanism can be proposed from these investigations (Scheme 5.12). After coordination of the iron catalyst to the hydroxyl group of oxetanol **224**, this is ionised to form an oxetanyl carbocation intermediate. *C*-alkylation of the aromatic occurs to give 3,3-diaryloxetane **225**.



Scheme 5.12: Proposed catalytic cycle for the HFIP-mediated Friedel–Crafts reaction of aromatics with oxetanols and formation of aldehyde side products.

A competitive *O*-alkylation can take place with HFIP as the nucleophile to give oxetane ether **226**, which can reversibly regenerate the carbocation. The formation of this oxetane ether can act as a reservoir of oxetanyl carbocation. Alternatively, a base present in the reaction, can also α-deprotonate the carbocation to form an oxetene species **227**. Nucleophiles containing an oxygen atom, including anisole and phenol, can serve as a base through the oxygen, which could explained the lower yield of 3,3-diaryloxetane obtained with these nucleophiles and the detrimental effect using higher equivalents. Oxetene **227** is highly strained and quickly rearranges, opening the ring into acrolein derivative **228**. Coordination of the iron catalyst to the oxygen atom of the aldehyde, activates the system and allows 1,4-addition of the aromatic. Re-aromatisation followed by tautomerisation lead to aldehyde **229a**.

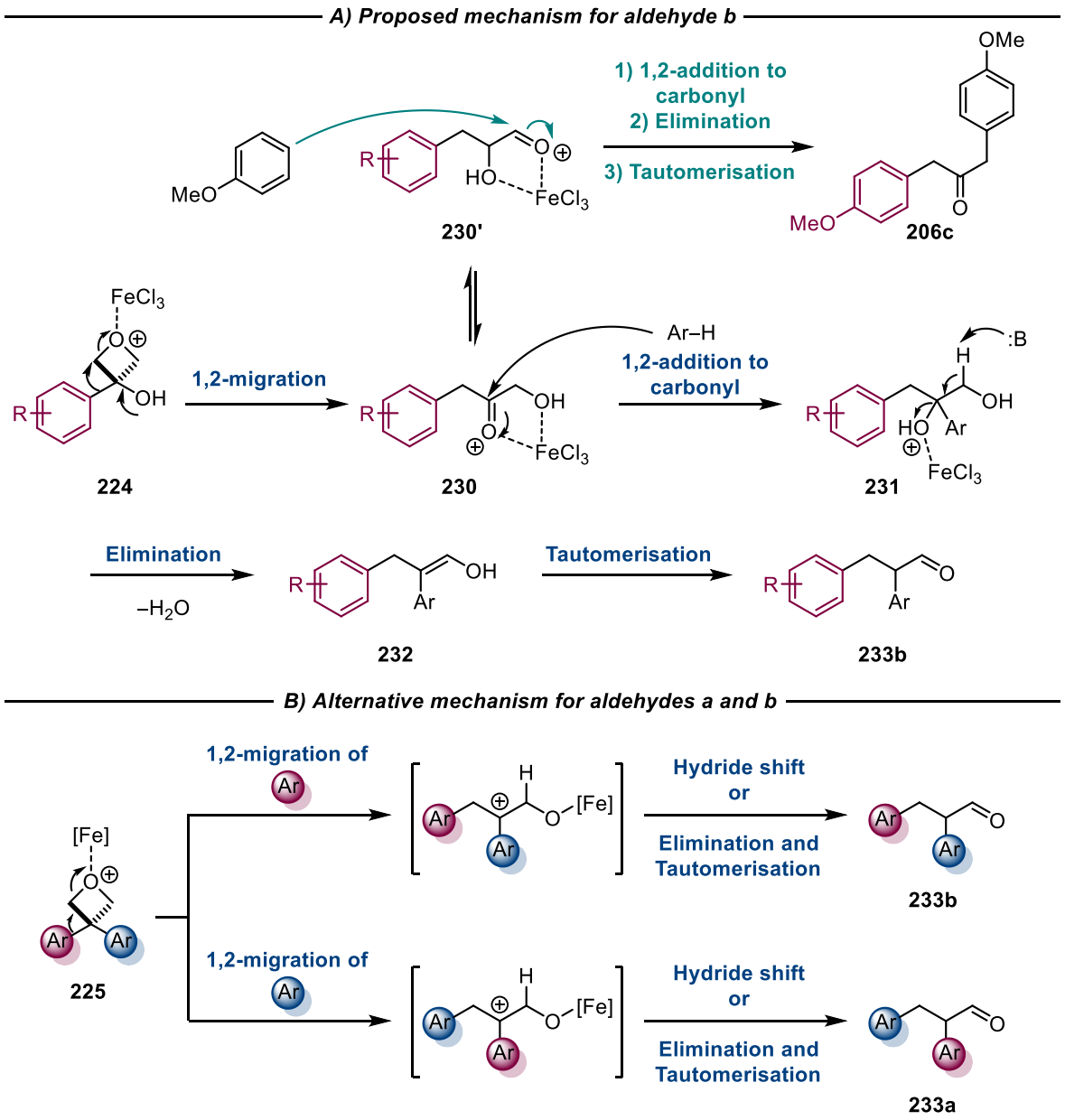
Alternatively, a $[FeCl_3+(HFIP)_n]^+$ complex, similar to that proposed by Moran and Leboeuf,[140,141] could activate the tertiary oxetanol's OH and α,β-unsaturated aldehyde, with the iron catalyst increasing the acidity of the HFIP OH (Scheme 5.13).



Scheme 5.13: Alternative activation of the oxetanol OH and α,β-unsaturated aldehyde.

On the other hand, the formation of aldehyde **b** is unclear. A possible mechanism could start with the 1,2-migration of the pre-installed aromatic with subsequent oxetane ring opening, upon activation of the oxetanol oxygen atom by the iron catalyst (Scheme 5.14, A). This would produce 1-hydroxy-3-aryl-propan-2-one species **230**. 1,2-Addition of an aromatic to ketone **230** can occur and lead to benzylic alcohol **231**, which after water elimination and tautomerisation could give aldehyde **233b**. This proposed mechanism would match with the formation of ketone **206c** observed during the Friedel–Crafts alkylation of anisole with *para*-OMe substituted oxetanol **18** (Scheme 5.7). Ketone **206c** could have been formed from 1,2-addition of anisole to ketone **230'** followed by elimination of water and tautomerisation (Scheme 5.14, A).

Alternatively, 1,2-migration of either aromatics could occur on the 3,3-diaryloxetane product **225** upon catalyst activation of the oxygen atom, which would open the oxetane ring (Scheme 5.14, B). Hydride shift or elimination and tautomerisation would lead to aldehydes **233a** and **233b**, according to which aromatic migrated.

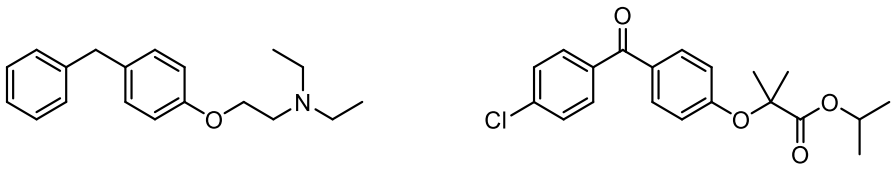


Scheme 5.14: Proposed mechanism for the formation of aldehydes **a** and **b** and ketone **206c**.

Further mechanistic investigations and DFT calculations could be undertaken in the future to: a) understand the importance of the Fe catalyst on the reaction, b) identify the active catalyst species, and c) establish the mechanism for the formation of aldehydes **a** and **b**. These will involve for example: resubjecting the 3,3-diaryloxetane product to the reaction conditions, and monitoring the evolution of the products with time by NMR experiments.

5.4 Synthesis of Medicinally Relevant 3,3-Diaryloxetanes

To demonstrate the utility of the method, the synthesis of two oxetane-containing drug analogues was targeted: antineoplastic agent Tesmilifene[158] and Fenofibrate which is used for the treatment of hypercholesterolemia (Scheme 5.15).[159]

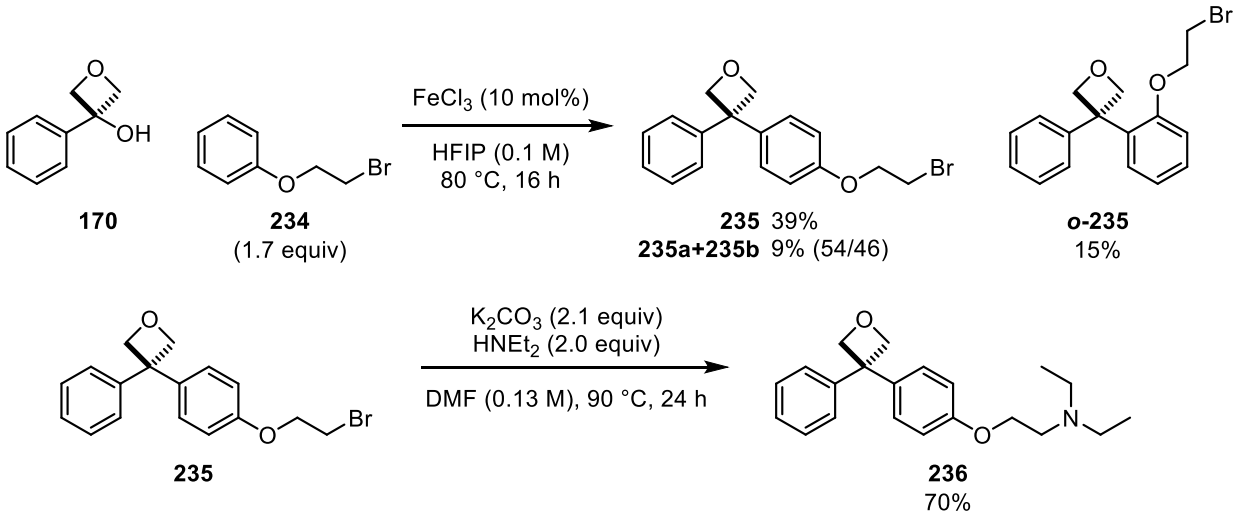


Tesmilifene
antineoplastic drug

Fenofibrate
treat primary hypercholesterolemia

Scheme 5.15: Structure of Tesmilifene and Fenofibrate.

The HFIP-mediated Friedel–Crafts conditions were applied to the reaction of oxetanol **170** with commercial β–bromophenetole **234** (Scheme 5.16). This nucleophile was compatible with the reaction conditions giving 3,3-diaryloxetane **235** in 39% yield, along with 15% of the *ortho*-product ***o*-235** and 9% of aldehydes **235a** and **235b**, all three product types separable by column chromatography. Nucleophilic substitution of bromide **235** with $HNEt_2$ provided 70% of oxetane derivative of Tesmilifene **236.**



170

234
(1.7 equiv)

235 39%
235a+235b 9% (54/46)

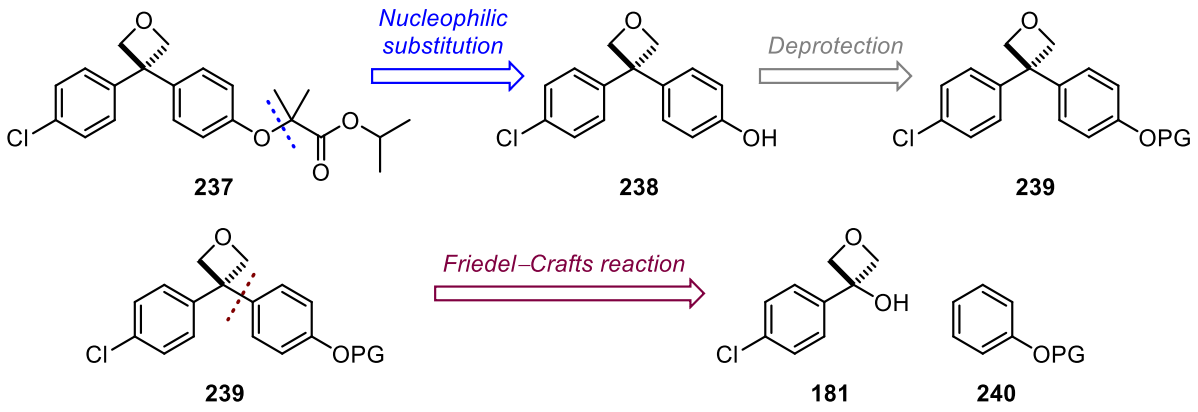
***o*-235**
15%

235

236
70%

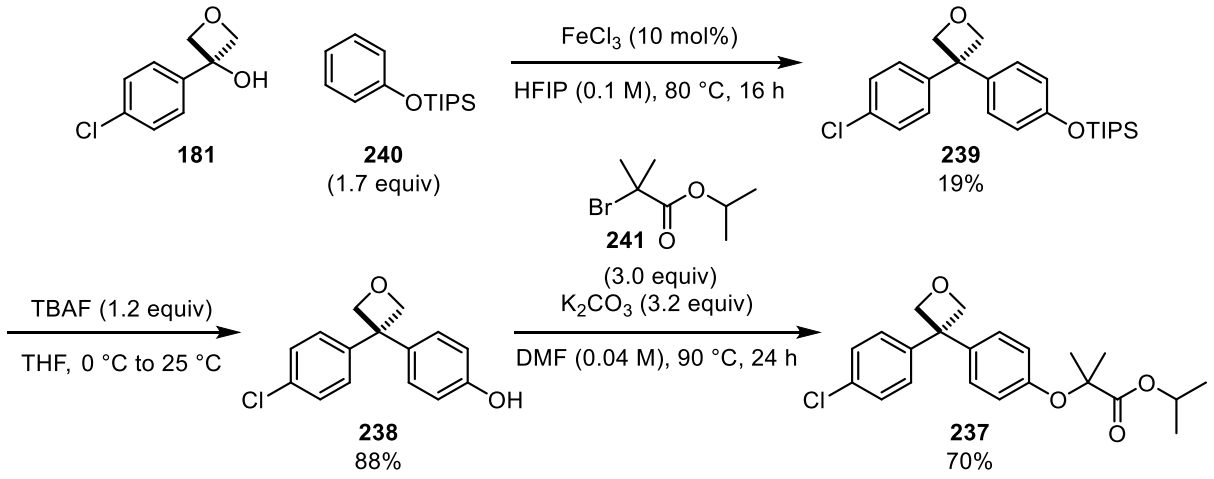
Scheme 5.16: Synthesis of oxetane-containing analogue **236** of Tesmilifene.

The synthesis of oxetane derivative of Fenofibrate **237** was envisaged through the nucleophilic substitution with phenol intermediate **238** (Scheme 5.17). Oxetane **238** cannot be accessed directly *via* the HFIP-mediated Friedel–Crafts reaction of oxetanol **181**, as phenol was shown to be an incompatible nucleophile. Instead, oxetane **238** could be made from oxetanol **181** and protected phenol **240** followed by deprotection step.



Scheme 5.17: Retrosynthesis of oxetane-containing Fenofibrate analogue **237**.

Pleasingly, TIPS-protected phenol **240** was a successful nucleophile in the Friedel–Crafts alkylation with oxetanol **181**, giving **239** in 19% yield, demonstrating the relative stability of TIPS protecting group under the reaction conditions and expanding the scope (Scheme 5.18). TIPS deprotection using TBAF afforded phenol **238** in 88% yield. Finally, oxetane **237** was obtained in 70% yield through nucleophilic substitution between phenol **238** and bromide **241**.

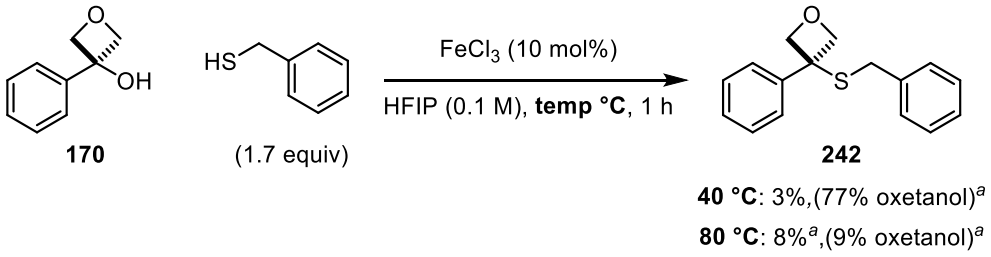


Scheme 5.18: Synthesis of oxetane-containing Fenofibrate analogue **237**.

The physicochemical properties and ADMET profile of oxetane analogues **236** and **237** will be measured at Pfizer and compared with those of Tesmilifene and Fenofibrate, completing the assessment of 3,3-diaryloxetanes as isosteres and potential bioisosteres for benzophenones and 1,1-diarylalkanes. The conditions were then applied to the synthesis of 3,3-diarylazetidines and 3-aryl-3-sulfanyl oxetanes. The previous methods towards these structures developed in this thesis (4.1) and by the Bull group currently limit the incorporation of phenyl, and electron-neutral or electron-poor aromatics on oxetanols.[51,111]

5.5 Synthesis of Oxetane Sulfides and 3,3-Diarylazetidines from Non-Activated Oxetanols and Azetidinols

Oxetanol **170** and benzylmercaptan were subjected to the HFIP-mediated Friedel–Crafts reaction developed in this chapter (Scheme 5.19). Careful control of the equivalents of thiols, temperature and time were key parameters in the previous methodology.[51] Therefore, the reaction was first attempted using 1.7 equivalents of thiol at 40 °C for 1 h, in order to prevent potential ring opening by excess nucleophile. Pleasingly, 3% of sulfide **242** was isolated and 77% of oxetanol **170** was recovered with small amount of side products formed. However, when the temperature was elevated to 80 °C, only 9% of the starting material remained and the yield for **242** was barely improved with a complex mixture of side products obtained. Control of the temperature and equivalents of the nucleophile will most likely play a pivotal role in optimising this reaction in the future.



170 (1.7 equiv) **242**

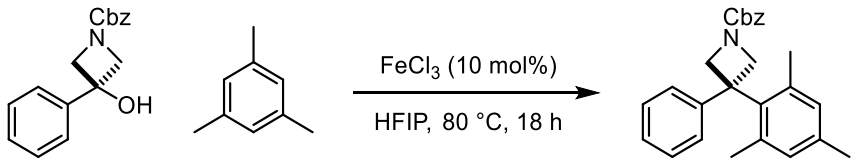
40 °C: 3%,(77% oxetanol)[a]

80 °C: 8%[a],(9% oxetanol)[a]

Scheme 5.19: Attempts towards the thiolalkylation of benzylmercaptan with oxetanol **170**.[a] Yields calculated by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as the internal standard.

Subjecting azetidinol **104** to the HFIP mediated and Fe-catalysed conditions, gave 3,3-diarylazetidine **243** in 5% isolated yield and 69% of azetidinol **104** was recovered. This indicates a relatively good stability of the starting material under the reaction conditions compared to oxetanols (Table 5.10, entry 1). Various Lewis and Brønsted acids were tested which all doubled the yield of **243** compared to $FeCl_3$, and $Ca(NTf_2)_2$ was the most efficient (entries 2 to 5). Increasing the loading of calcium triflimide to 20 mol% resulted in a small rise of the yield of **243** to 18% (entry 6), while heating the temperature to 100 °C did not improve the outcome. Co-solvents were also investigated in 1:1 ratio with HFIP, including CH_2Cl_2, toluene and EtOAc, which resulted in similar yields, and TFE was unsuccessful.

Other protected and unprotected azetidinols will be examined in the future to understand the role that the nitrogen substituent has on the reactivity.



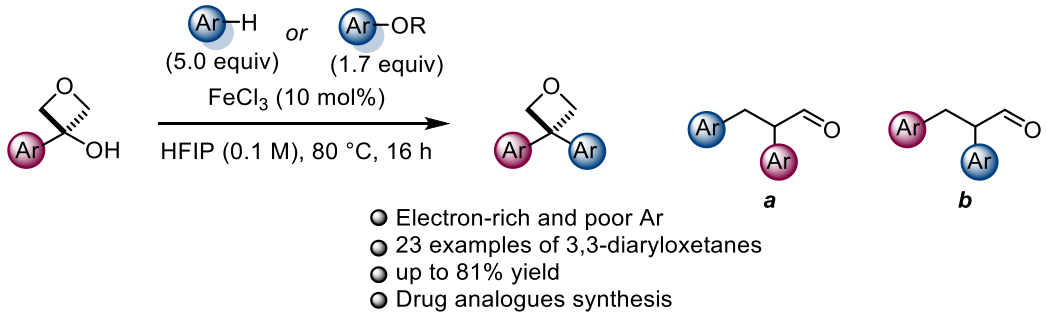
104 (5.0 equiv) **243**

Entry	Change in conditions	Yield 243 (%)[a]	Yield 104 (%)[a]	Total yield (%)[a]
1	standard	4 (5)	69	73
2	$Ca(NTf_2)_2$/nBu$_4$NPF$_6$	11	79	90
3	$Li(NTf_2)$/nBu$_4$NPF$_6$	9	84	93
4	$Bi(OTf)_3$ /-	10	81	91
5	TfOH	10	75	85
6	$Ca(NTf_2)_2$/nBu$_4$NPF$_6$ (20 mol%)	18	70	88
7	$Ca(NTf_2)_2$/nBu$_4$NPF$_6$ 100 °C	8	89	97

Table 5.10: Catalyst screen for the HFIP-mediated Friedel–Crafts alkylation of mesitylene with azetidinol **104**. [a] Yields calculated by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as the internal standard.

5.6 Conclusion and Remaining Challenges

The synthesis of new 3,3-diaryloxetanes containing electron-neutral or poor-aromatic groups was achieved in this chapter through a new Fe-catalysed Friedel–Crafts reaction in HFIP (Scheme 5.20). The iron catalyst was key to promote the reaction and prevent degradation of the starting material. The improved stabilisation of the carbocation intermediate by HFIP, enabled the generation of oxetanyl carbocations from inactivated oxetanol bearing a phenyl, or electron-donating, neutral, and poor groups on the pre-installed aromatics. In addition, substituents in both *para* and *meta* positions on the oxetanols were tolerated. Interestingly, CF_3-substituted oxetanol also gave traces amount of products, showing the possibility to form an oxetanyl carbocation in such an electron-poor system. Various non-oxygenated arenes and masked phenols were successful as nucleophiles under the reaction conditions. Intriguingly, the type of nucleophile had an important effect on the outcome. Aromatics containing oxygen atoms are suspected to act as a base, directing the carbocation intermediate into unproductive pathways. This led to lower yield and significant mass loss. As a result, using lower equivalents for this type of nucleophile was optimal, while non-oxygenated aromatics can be used in larger excess without detrimental effect.



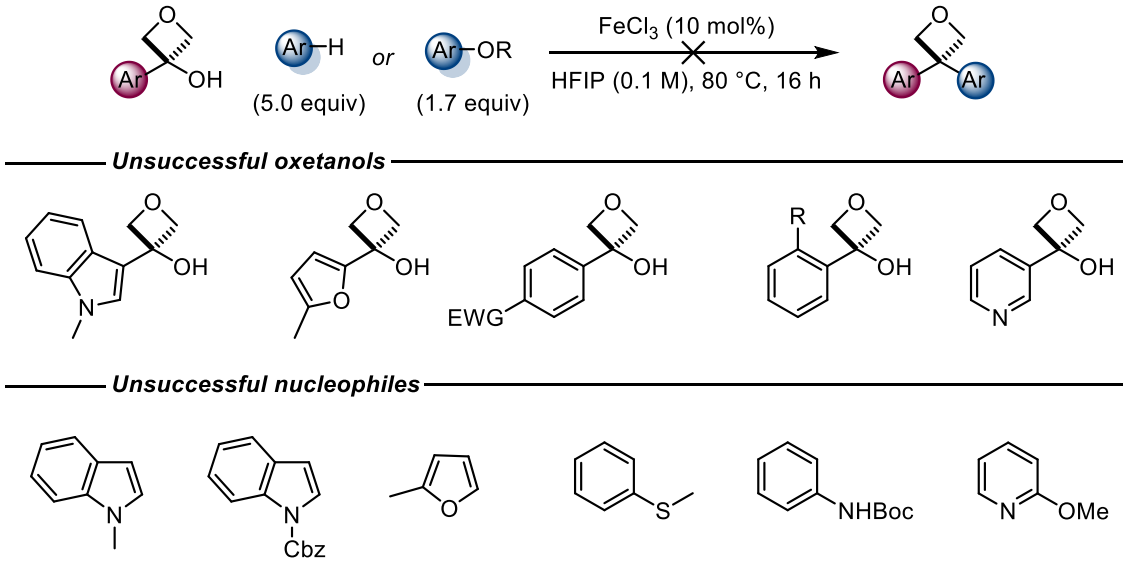
Scheme 5.20: HFIP-mediated Friedel–Crafts alkylation of aromatics with deactivated 3-aryloxetan-3-ols.

Overall, 20 examples of new 3,3-diaryloxetanes were synthesised in 22% to 81% yields and 6 examples with yields below 19%. The reaction could be scaled to 1 g without affecting dramatically the yield. Pleasingly, the reaction was shown to tolerate water and air with similar yields obtained without precautions taken to exclude moisture and oxygen. The usefulness of the method was demonstrated with the synthesis of oxetane analogues of Tesmilifene and Fenofibrate, and their physicochemical properties and ADMET profile are currently being measured by Pfizer.

Additionally, 25 examples of new 2,3-diarylpropanals were formed in this chapter, which represent interesting synthetic intermediates. Aldehydes **a** were proposed to form through deprotonation of the carbocation into oxetene species, followed by rearrangement to α,β-unsaturated aldehyde and 1,4-addition of aromatics. These represent rare examples of

catalytic Friedel–Crafts alkylation of non-activated aromatics with α,β-unsaturated aldehyde, which will be further developed in the future. Although the formation of aldehydes **b** remains unclear, this was proposed to occur *via* 1,2-aromatic migration with oxetanol ring opening, which represents an unexpected new reactivity for oxetanols.

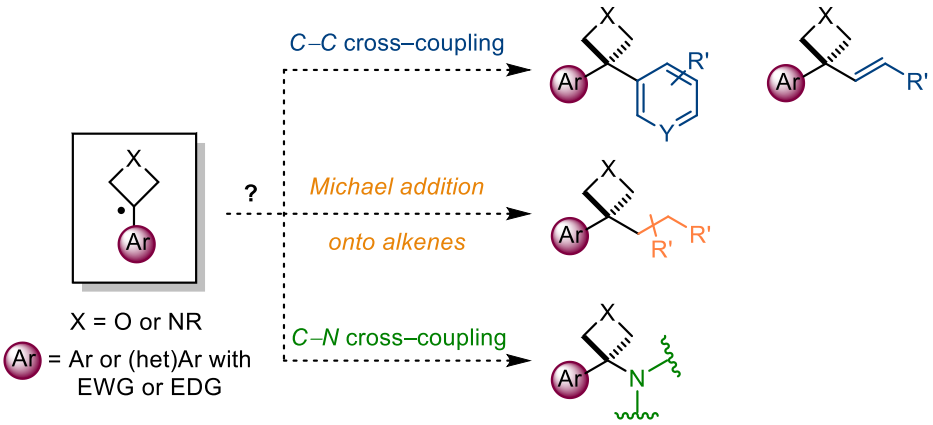
Although encouraging results were obtained for the thiolalkylation with oxetanol **170** and Friedel–Crafts alkylation with azetidinol **104**, these were rather challenging reactions due to ring opening by excess thiols and catalyst coordination or lack of reactivity respectively. Other limitations were found in the course of this work. Indoles and furan rings could not be incorporated into 3,3-diaryloxetanes using this methodology neither from oxetanols nor as nucleophiles, with complete degradation of the precursor (Scheme 5.21). However, the methodology seems to be complementary to the previous Friedel–Crafts reaction, as these rings were successfully introduced using the lithium-catalysed conditions (see section 3.3).[50,88] The new method is also sensitive to the steric and electronic nature of the substituent on the oxetanol aromatic. Therefore the introduction of highly electron-withdrawing groups and *ortho*-substitution are still not accessible through this method. Although anilines were not compatible nucleophiles, aniline-containing 3,3-diaryloxetanes can be access *via* cross–coupling reaction through the halides installed in this chapter. Finally, 3-pyridine-3-aryl oxetanes remain the most challenging limitation of the Friedel–Crafts reactions developed so far, with both pyridine-oxetanol and 2-methoxypyridine as nucleophile being unreactive in the HFIP-mediated reaction.



Scheme 5.21: Unsuccessful oxetanols and nucleophiles in the developed HFIP-mediated Friedel–Crafts reaction towards new 3,3-diaryloxetanes.

Pyridines are prevalent in pharmaceuticals. Consequently, these limitations restrict the incorporation of these motifs into medicinal chemistry programmes. The inability to form an oxetanyl carbocation intermediate from pyridine-oxetanol is attributed to the inherent electron-withdrawing effect of the pyridine ring, which can be exacerbated by catalyst coordination to the nitrogen atom. Therefore the synthesis of such pyridine motifs through another type of intermediate was considered.

3-Aryl-3-oxetanyl and azetidinyl radicals were envisaged as they would be stabilised by both mesomeric effect and hyperconjugation (Scheme 5.22). Such radical intermediates could react with a wide variety of reagents to give access to new 3,3-disubstituted oxetanes and azetidines and to new chemical space. Cross–coupling reaction of these oxetanyl and azetidinyl radicals with arenes or pyridine reagents would produce new 3,3-diaryloxetanes and azetidines inaccessible so far. However, the possibility to form a radical on such strained four-membered rings was a concern. The strain may destabilise the radical by reducing the hyperconjugation for instance, while the presence of inductively withdrawing oxygen and nitrogen atoms could decrease the overall stability of the intermediate.



Scheme 5.22: New strategy towards the synthesis of 3,3-disubstituted oxetanes and azetidines, through 3-aryl-3-oxetanyl and azetidinyl radicals.

6. Generation and Reaction of Oxetanyl and Azetidinyl Radicals

6.1 Approaches for Mild Radical Generation

6.1.1 The Emergence of Visible-Light Photoredox Catalysis

In 1912, Ciamician described “light” as an abundant and renewable source of energy to perform reactions.[160] Over the last twenty years, visible light mediated photoredox catalysis has emerged as one of the most promising tools in organic synthesis, enabling selective radical formation under mild conditions.[161] The usual inability of organic molecules to absorb visible light results in greater functional tolerance compared to previous methodology requiring UV light. In addition, the oxidative or reductive power of the metal or organic photocatalysts used is much milder than usual oxidants and reductants used in radical chemistry. This also results in a better functional group compatibility. Moreover, toxic reagents and energetic initiators are not required anymore leading to safer and more environmentally friendly reactions.

In photoredox-catalysed processes, selective excitation of a photocatalyst (PC) **244** can be achieved, upon photon absorption, to form an excited-state species **245** with stronger oxidative (Figure 6.1, A) or reductive power (Figure 6.1, B). The excited PC can undergo single electron transfer (SET) with a substrate R–X through oxidation (A) or reduction (B) reactions, generating a radical R•. The reduced or oxidised PC (**246** or **247**) can be regenerated into the initial PC **244** by reaction with an electron acceptor or donor through a second SET reaction. Importantly, the use of specific UV light equipment is not required anymore, and simple apparatus can be used to perform these processes.

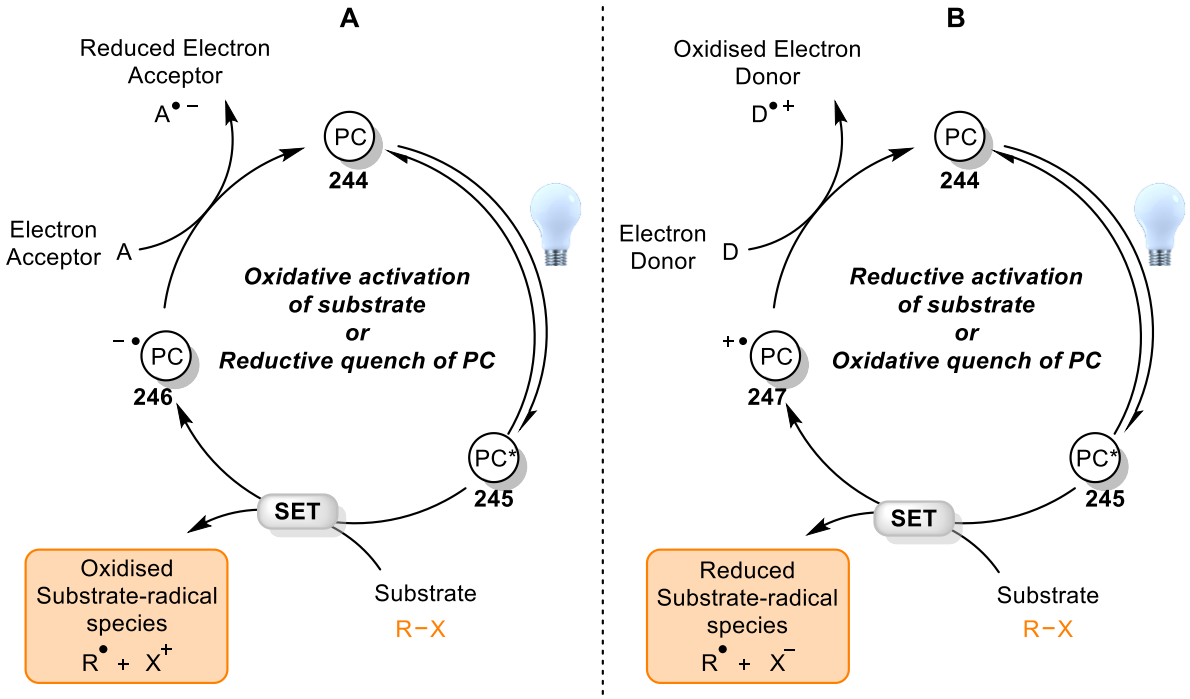
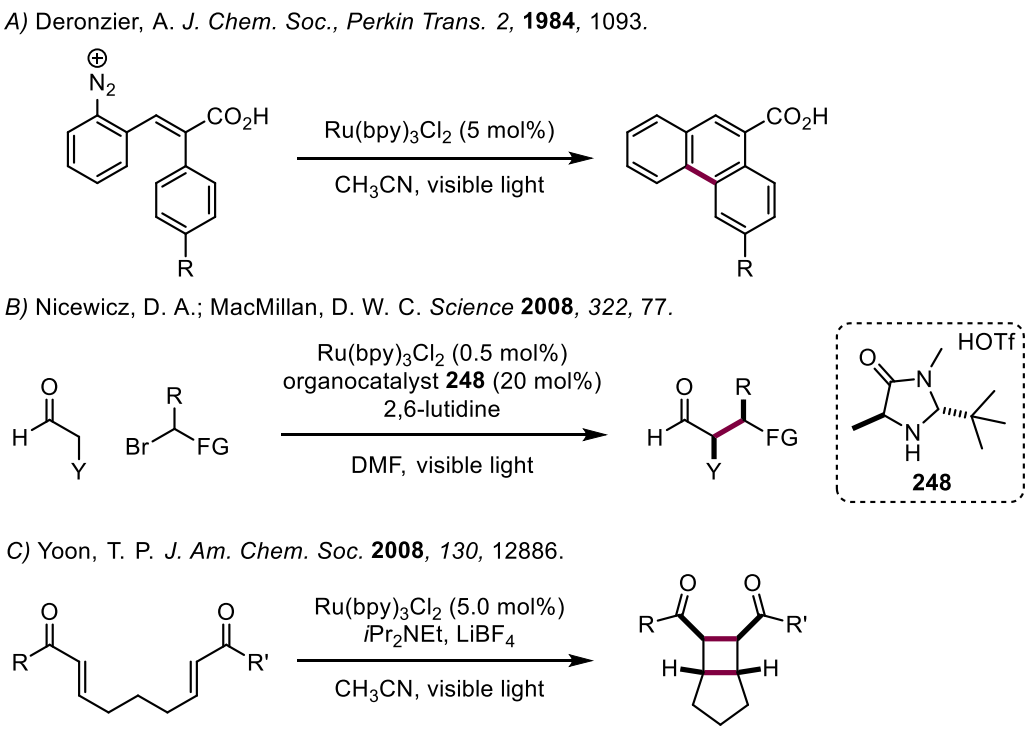


Figure 6.1: General description of visible-light mediated photoredox catalytic process.

One of the first examples of photoredox catalysis was reported in 1984 by Cano-Yelo and Deronzier.[162] They described the synthesis of phenanthrene *via* a photocatalytic Pschorr reaction using a ruthenium photocatalyst (Scheme 6.1, A). It is only in 2008 that photoredox catalysis made a breakthrough into organic synthesis landscape with the simultaneous works reported by MacMillan and Yoon (B and C).[163,164] MacMillan described the asymmetric alkylation of aldehydes using a combination of $Ru(bpy)_3Cl_2$ as the photocatalyst and a chiral organocatalyst **248**. Yoon developed a [2+2] enone intramolecular cycloaddition employing the same Ru photocatalyst. Following these reports, a growing number of photoredox-catalysed transformations have been developed and the field is expanding.[14,15,165,166]



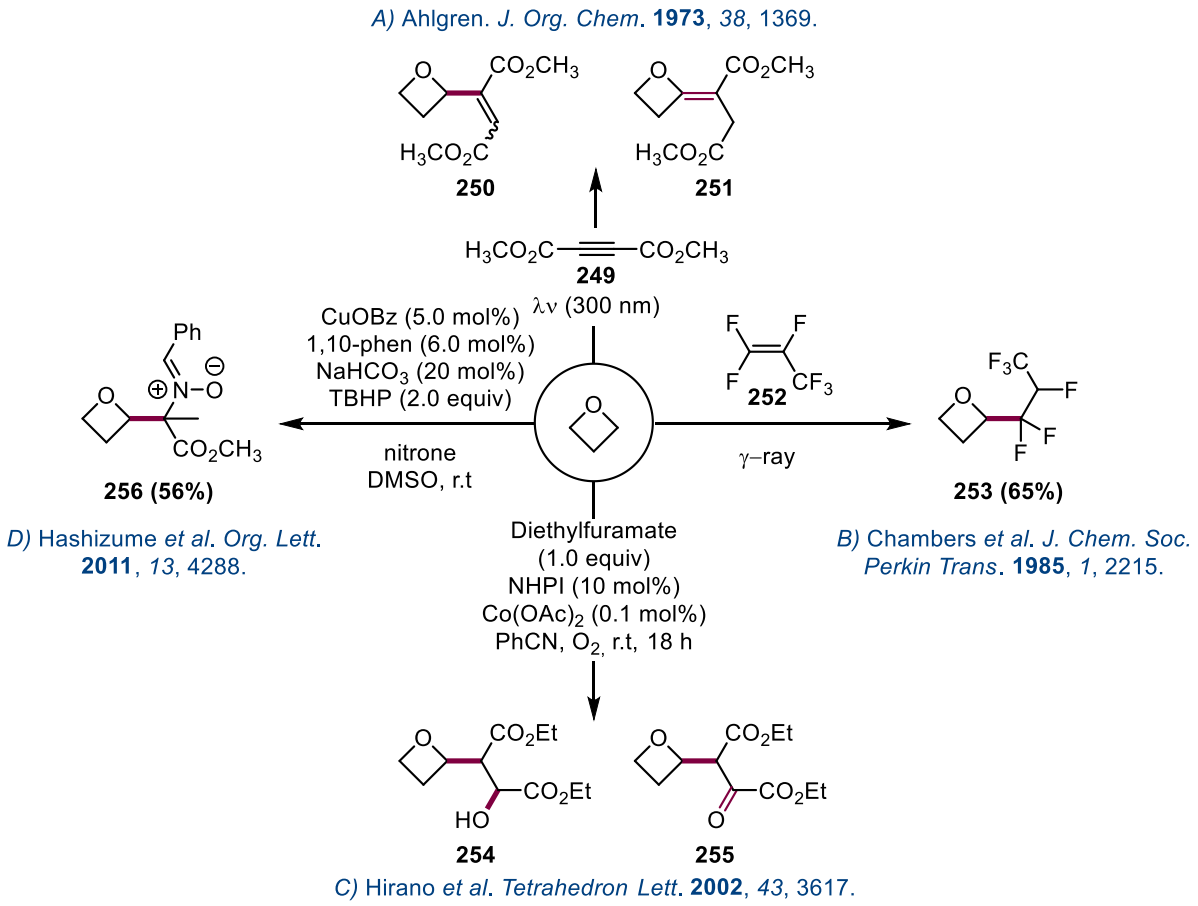
Scheme 6.1: First examples of visible-light photoredox-catalysed reactions.

Functionalisation of oxetanes and azetidines through photoredox–catalysed reactions have recently started to attract the attention of organic synthetic chemists.

6.1.3 Oxetanyl and Azetidinyl Radicals in Literature

2-Oxetanyl and azetidinyl radical species

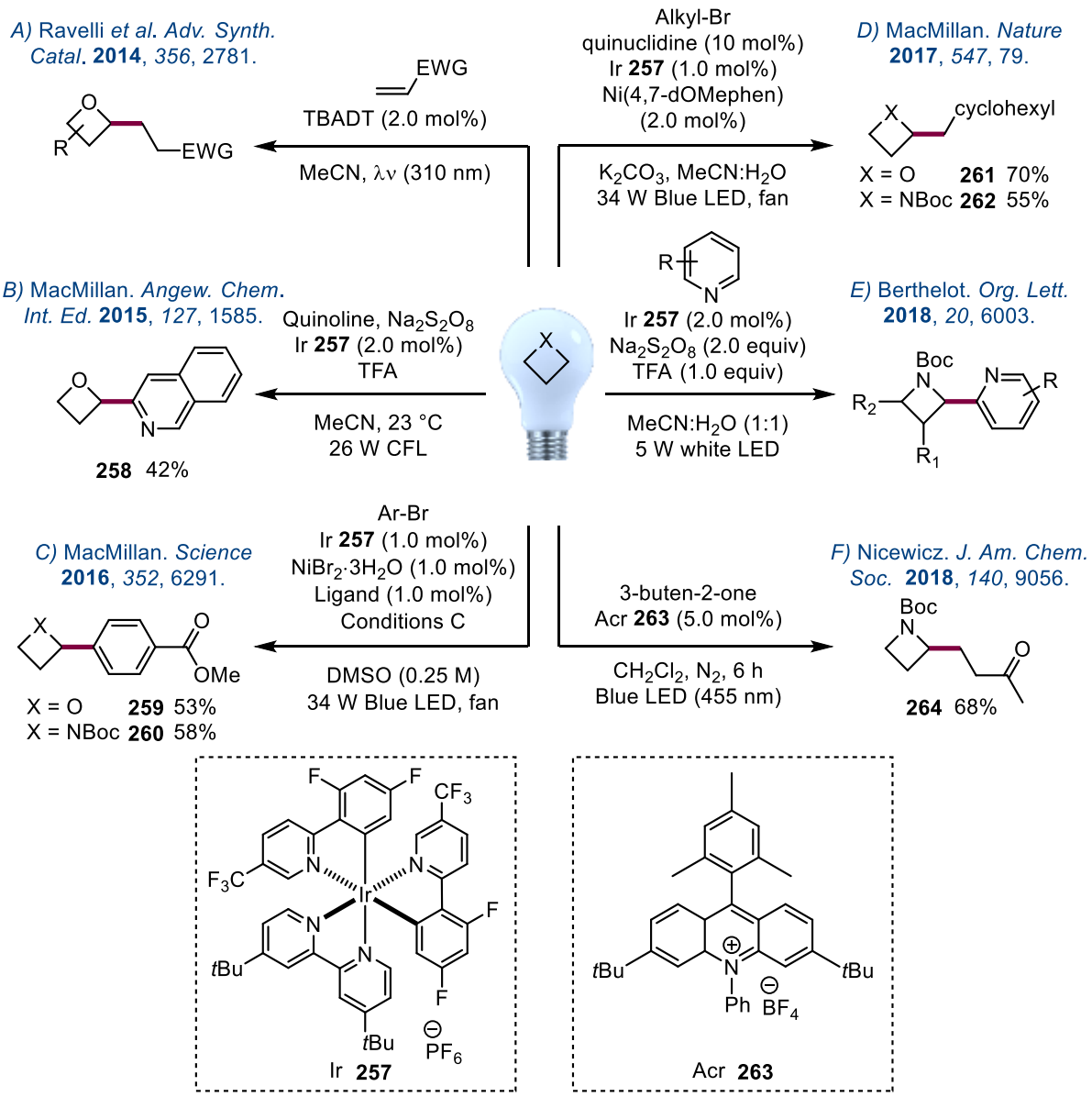
Few examples of 2-oxetanyl radicals can be found in the literature prior to the photoredox field's breakthrough. In 1973, Ahlgren described the synthesis of 2-substituted oxetanes **250** and **251** by irradiation of oxetane in presence of alkyne **249** (Scheme 6.2, A).[167] The formation of 2-oxetanyl radical species under irradiation is favoured due to stabilisation from the adjacent oxygen. In 1985, Chambers *et al*. used γ-ray to generate the same radical intermediate, which reacted with fluorinated alkene **252** to give product **253** in 65% yield (Scheme 6.2, B).[168]



Scheme 6.2: Formation and reactivity of 2-oxetanyl radicals prior to photoredox-mediated methodologies.

In 2002, the first example of catalytic formation of 2-oxetanyl radical was described by Hirano *et al* (Scheme 6.2, C).[169] In this work, the radical was generated using 0.1 mol% of a cobalt catalyst, 10 mol% *N*-hydroxyphthalimide and dioxygen. Addition to diethyl furamate gave oxetanes **254** and **255**. Hashizume *et al*. later developed a copper-catalysed migratory oxidative coupling of nitrones and heterocycles, reporting one example of an oxetane **256** (Scheme 6.2, D).[170] They proposed that a Fenton reaction between Cu(I) and *tert*-butylhydroperoxide leads to a *tert*-butoxy radical intermediate which can abstract a hydrogen atom at the 2-position of the oxetane, forming the desired radical.

In 2014, Ravelli *et al*. developed the first photoredox-catalysed α-CH functionalisation of oxetane using a photoredox catalyst under UV light (Scheme 6.3, A).[171] The oxetanyl radical was formed *via* hydrogen-atom-transfer (HAT) reaction with a photo-activated decatungstate catalyst (TBADT). Trapping of the radical with electron-withdrawing alkenes led to the synthesis of new 2-substituted oxetanes in good yields. In 2015, MacMillan reported an example of 2-substituted oxetane **258** synthesised in 42% yield through a Minisci reaction with quinoline using visible-light and an iridium photocatalyst **257** (Scheme 6.3, B).[172]

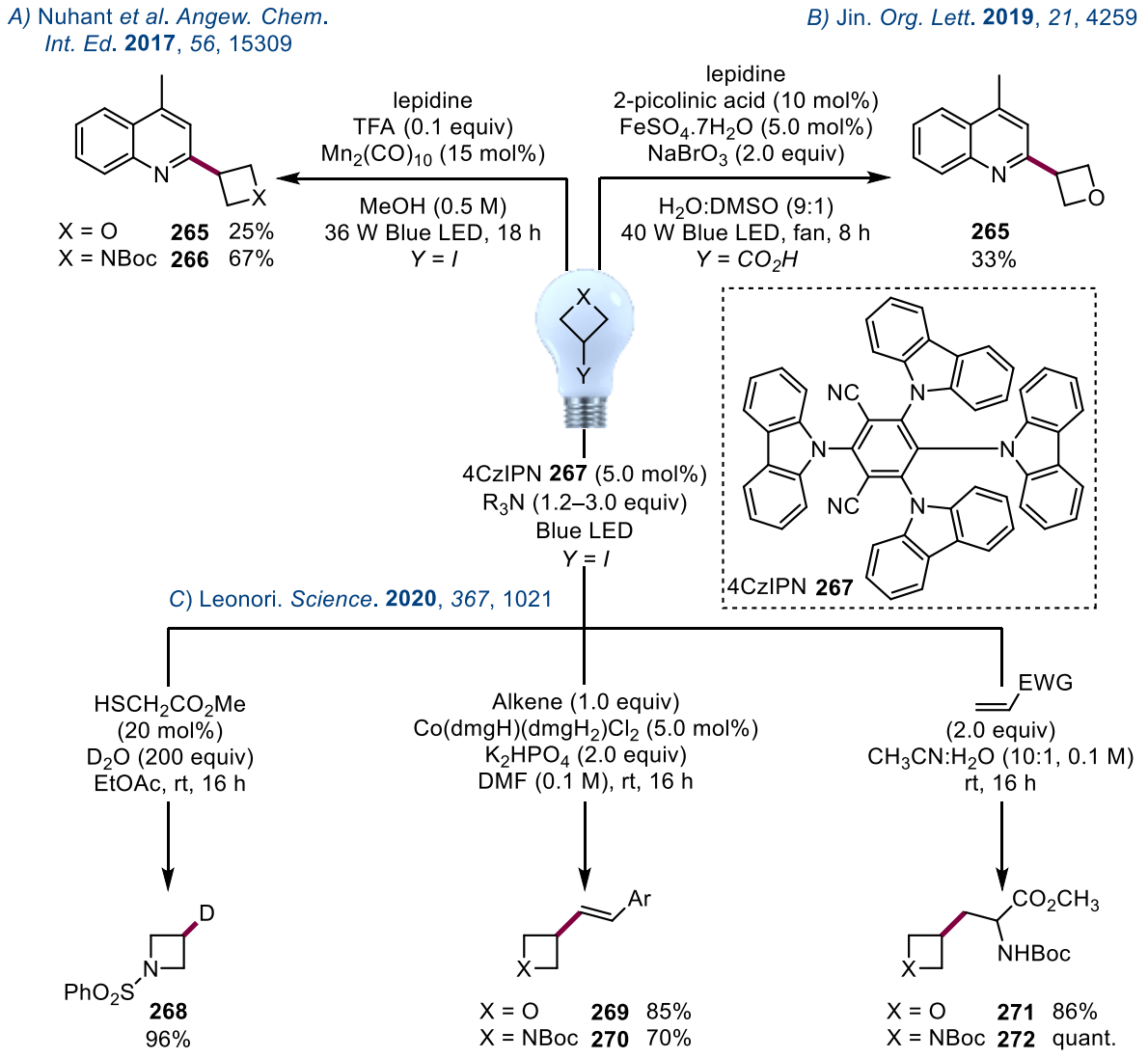


Scheme 6.3: 2-Oxetanyl and azetidinyl radical formation using photoredox catalytic reactions. Conditions C: 3-acetoxyquinuclidine (1.1 equiv), H_2O (40 equiv), ligand = 4,7-dOMe-phen.

In contrast with oxetane, 2-azetidinyl radicals were reported only recently. In 2016, MacMillan developed an α-CH arylation of heterocycles through HAT and cross–coupling reactions, merging both photoredox and nickel catalysis (Scheme 6.3, C).[173] Examples of 2-substituted oxetane **259** and azetidine **260** were reported in 53% and 58% yields respectively. A year later, the same group published a set of conditions to α-alkylate heterocycles using similar merged photocatalysed and nickel catalysed conditions (Scheme 6.3, D).[174] Oxetane **261** and azetidine **262** were synthesised in 70% and 55% yields through this method. In 2018, Berthelot developed a photoredox-catalysed Minisci reaction for the incorporation of *N*-heteroarene at the 2-position of azetidine rings (Scheme 6.3, E).[175] Finally, Nicewicz recently published the α-alkylation of azetidines with Michael acceptors and reported azetidine **264** in 68% yield (Scheme 6.3, F).[176]

3-Oxetanyl radical species

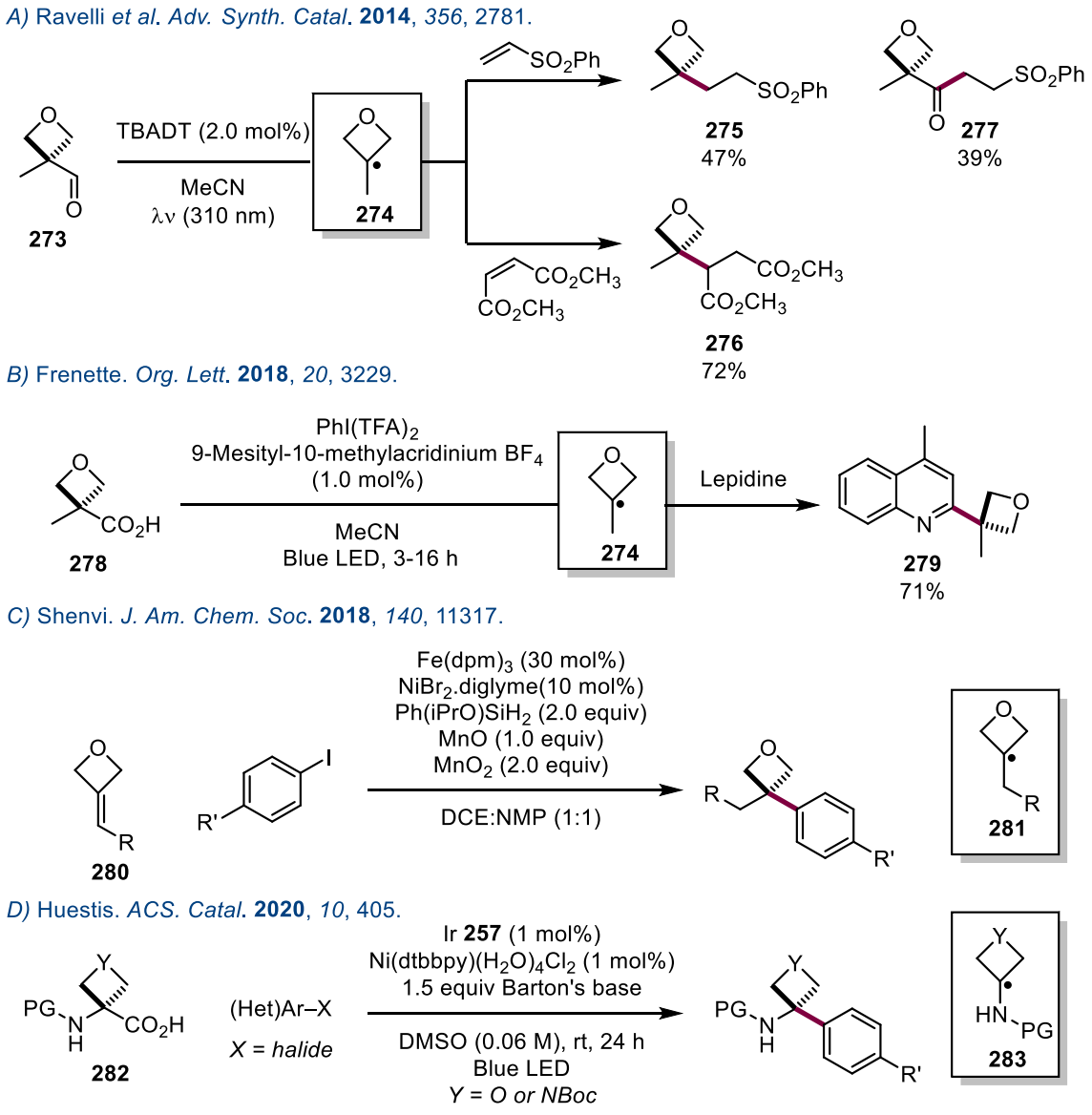
In contrast, a plethora of photoredox-catalysed reactions to synthesise 3-substituted oxetanes and azetidines have emerged in the last five years. These reactions involve the formation of 3-oxetanyl and azetidinyl radicals. For example, Nuhant *et al*. and Jin developed two photoredox-catalysed Minisci reactions separately, reporting the synthesis of 3-substituted oxetane **265** and azetidine **266** in 25% to 67% yields (Scheme 6.4, A and B). In these examples, 3-oxetanyl and azetidinyl radicals were generated from iodide and carboxylic acid precursors respectively.[177,178] The former methodology employed a manganese photocatalyst, whereas Jin used an iron photocatalyst, and both inexpensive and abundant metals represent alternatives to the usual iridium and ruthenium catalysts.



Scheme 6.4: 3-Oxetanyl and azetidinyl radical formation and reactivity through photoredox catalysed processes.

In 2020, Leonori reported conditions using 4-CzIPN **267** as photocatalyst and tertiary amine to functionalise 3-iodooxetane and azetidine through deuteration, Giese-type and olefination reactions (Scheme 6.4, C).[179] Reaction between the amine and the photo-activated 4-CzIPN **267** produces an α-aminoalkyl radical intermediate. This can undergo halide-atom transfer onto the iodo–precursor to form the reactive oxetanyl and azetidinyl radicals.

In comparison, reactions involving tertiary 3-substituted oxetanyl and azetidinyl radicals remain relatively underexplored, with only four radical reactions reported in the literature to date (Scheme 6.5).



Scheme 6.5: Tertiary 3-oxetanyl and azetidinyl radicals formation reported in the literature.

Both Ravelli and Frenette described the generation of 3-methyloxetanyl radical **274** under photoredox-catalysed decarbonylation and decarboxylation conditions (Scheme 6.5, A and B).[171,180] Interception of radical **274** with electron-poor alkenes led to the formation of 3-methyl-

3-alkylated oxetanes **275** and **276** in 47% and 72% yields (A). Interestingly, the oxetane acyl radical formed prior to decarbonylation of **273** also proved to react with alkenes to give ketone **277**. On the other hand, Frenette developed a rare metal-free and visible light mediated C–H alkylation of heteroaromatics *via* hypervalent-iodine-promoted decarboxylation. 3,3-Disubstituted oxetane **279** was obtained in 71% yield under these conditions (B). The use of an organophotocatalyst in this method brings an alternative to the use of expensive metal usually employed in Minisci reactions. In addition, it leverages the large choice of commercially available carboxylic acids. The same year, a non-photocatalytic method employing Fe/Ni dual catalysis for the formation of a quaternary centre was reported by Shenvi (Scheme 6.5, C).[181] In this work, an Fe catalyst can undergo HAT with alkene **280** to form 3-alkyl-oxetanyl radical **281**. This radical can then be intercepted by a Ni^0 species and coupled with an aryl iodide to give a variety of 3,3-disubstituted oxetane motifs in moderate to good yields. During the course of the research described in this thesis, Huestis reported the photoredox-catalysed decarboxylative arylation of oxetane and azetidine tertiary amines **282** through radical **283** (Scheme 6.5, D).[182] This represents a rare example of photoredox-catalysed decarboxylative coupling reaction on tertiary centre.

The lack of methodologies to synthesise 3,3-disubstituted oxetanes and azetidines *via* photoredox-catalysed processes is due to the difficulty of generating tertiary radicals at the 3-position. The C–H bonds at the α-position of the heteroatoms have a lower bond dissociation energy than Csp^3–H bonds at remote position. As a result, formation of radical species at C-3 requires the introduction of activating functional groups in order to compete with HAT process at the α-position. The installation of such groups requires additional synthetic steps, and methodologies to achieve this are not always available. In addition, the inherent stability and steric hindrance of tertiary radicals can make their functionalisation difficult while favouring unwanted side reactions.

To the best of our knowledge, no reaction involving a 3-aryl-3-oxetanyl and azetidinyl radical species have been reported so far. The generation and functionalisation of such radicals could give access to a range of new 3-aryl-3-substituted oxetanes and azetidines, and will be the subject of this chapter.

6.1.4 Project Aim and Challenges

The research in this section aims to develop new 3,3-disubstituted oxetanes and azetidines *via* generation and reaction of 3-aryl-3-oxetanyl and azetidinyl radicals using visible light-mediated photoredox catalysis. This is divided in two mains goals:

1) Development of a suitable radical precursor.

The first aim was to identify suitable 3-aryl-3-substituted oxetane and azetidine radical precursors **284** (Figure 6.2). These will have to be synthetically readily accessible.

2) Generation and reactivity of the radical intermediates.

Formation of radicals **285** under photoredox-catalysed conditions from the developed precursors would then be investigated. As a proof of concept, attempts to trap the radical with alkenes will first be made. Once conditions to form these radical intermediates have been obtained, their reactivity will be further explored to synthesise new 3,3-disubstituted oxetanes and azetidines **286**. This includes investigation towards the formation of Csp^3–Csp^2 bonds, to access new 3,3-diaryloxetanes and azetidines, especially containing pyridine and heteroaromatics groups.

The feasibility of forming a radical on a such strained ring was a concern at the start of this work. In addition, such benzylic and hindered radical species might be less reactive.

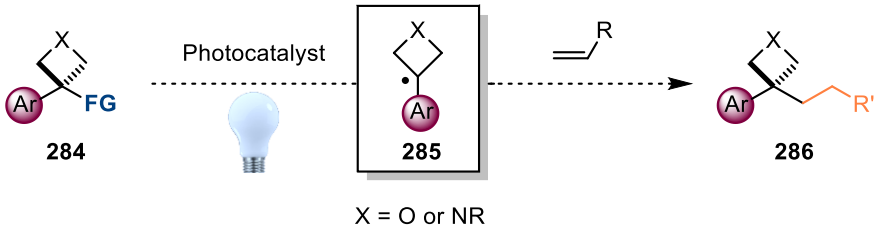


Figure 6.2: The initial goal consisted of finding suitable radical precursors, conditions to generate 3-aryl-3-oxetanyl and azetidinyl radicals, and trapping the intermediates with alkenes.

Aware of these challenges, investigation towards potential radical precursors were undertaken focusing first on the oxetane ring.

6.2 Investigating Viable Oxetanyl and Azetidinyl Radical Precursors

6.2.1 Recent C(sp^3)-Radical Precursors in Literature

Many functional groups have been recently developed for generation of C(sp^3)–radical centres (Figure 6.3).[183]

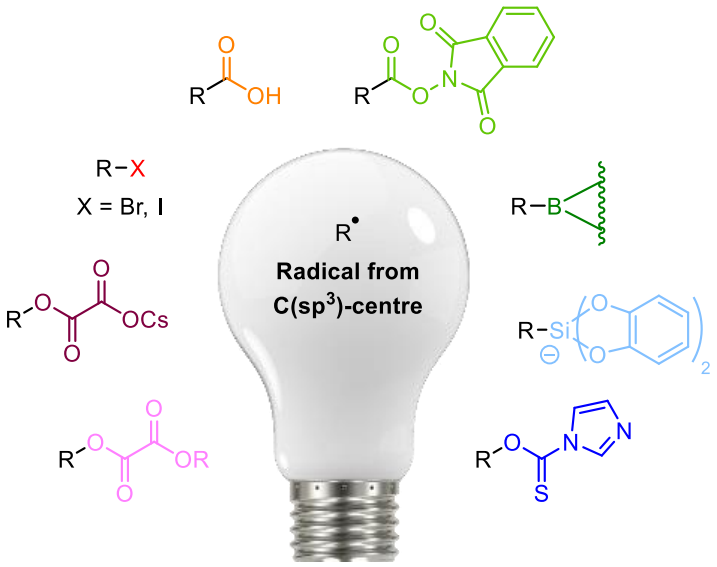
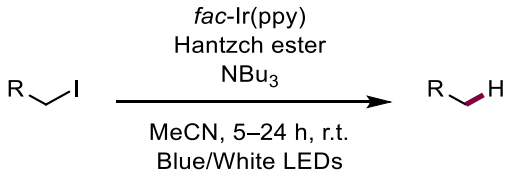


Figure 6.3: Precursors for generation of C(sp^3)–radical centres using photoredox catalysis.

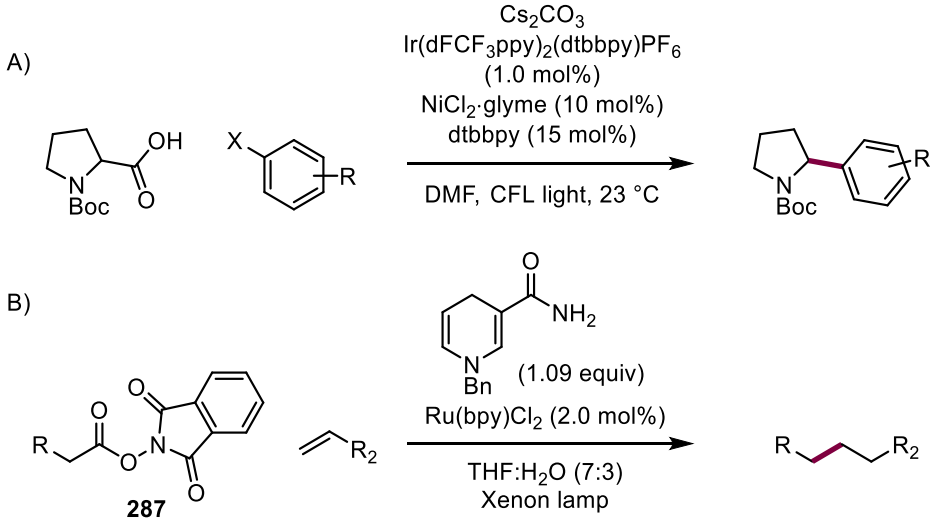
Readily available C(sp^3)–halides have been extensively used to generate radical centres. Stephenson reported the reductive dehalogenation of alkyl-iodide substrates using an iridium photocatalyst and visible light (Scheme 6.6).[184] This offers an attractive alternative to traditional radical dehalogenation reactions employing toxic tin reagents.



Scheme 6.6: Reductive dehalogenation of alkyl-iodide under visible-light.[184]

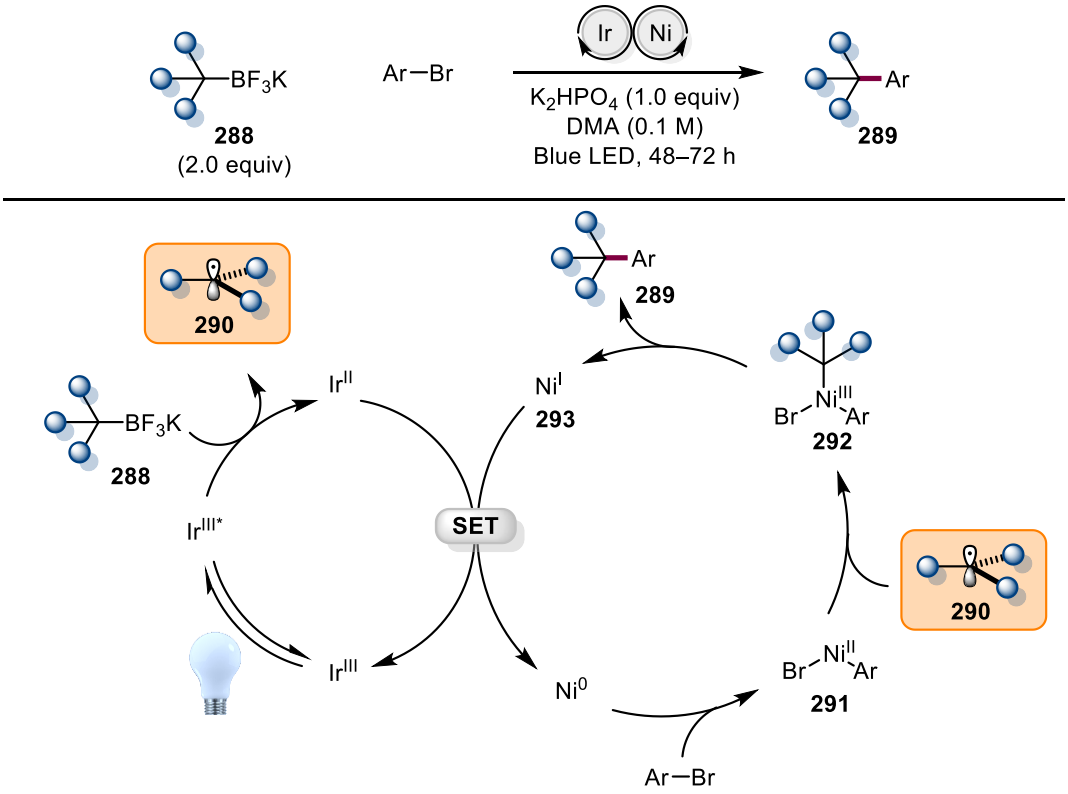
Carboxylic acids are also widely-commercialised and have proved to be successful C(sp^3)–radical precursors under photoredox catalytic process.[185] MacMillan and co-workers developed pioneering work on photoredox-catalysed decarboxylative alkylation,[186] olefination,[187] and C(sp^3)–C(sp^2) cross–coupling reactions.[188] In the latter, the authors demonstrated the power of photocatalysis to circumvent the usual risk of β-hydride elimination (Scheme 6.7, A). In this elegant work, the alkyl radical was formed through oxidation of the carboxylic acid using a base and an iridium photocatalyst under visible light. After decarboxylation, the radical can react with a nickel catalyst and be coupled with an aryl halide.

In 1991, Oda disclosed the first photoredox-catalysed decarboxylative alkylation reaction using a pre-functionalised carboxylic acid (Scheme 6.7, B).[189] In this work, the key radical intermediates were generated from *N*-(acyloxy)phthalimides **287** using a ruthenium photocatalyst.



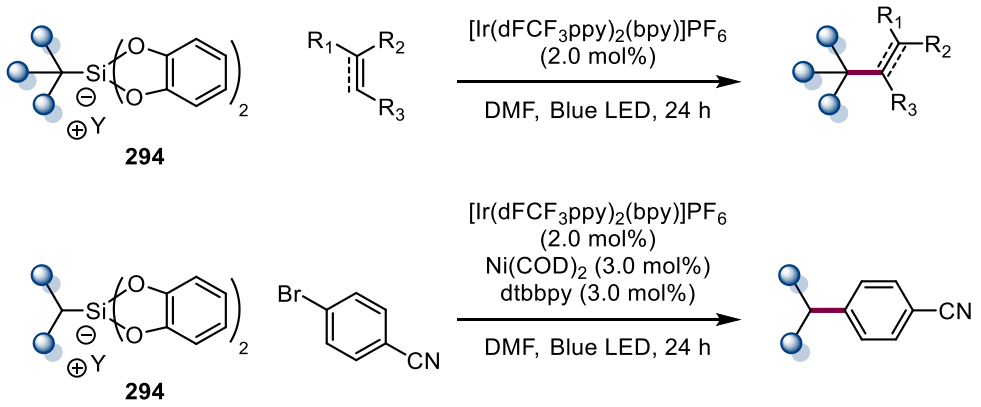
Scheme 6.7: Example of the generation and reaction of radicals formed from carboxylic acids derivatives.

Molander and co-workers have extensively contributed to the use of organoboron derivatives as C(sp^3)–radical precursors.[190,191,192,193] In particular, they have developed dual Ir/Ni catalysed conditions for the C(sp^3)–C(sp^2) cross–coupling reaction of tertiary radicals, usually challenging due to steric hindrance (Scheme 6.8).[193] The formation of a tertiary radical **290** was proposed *via* oxidation of the organoboron **288** by a photo-excited Ir(III) catalyst. The Ni(0) catalyst can then oxidatively add into the aryl bromide to give a Ni(II) complex **291**, which can in turn react with radical **290** to provide a Ni(III) complex **292**. The desired product **289** is then obtained after reductive elimination, producing Ni(I) catalyst **293**. SET between Ni(I) and Ir(II) allows regeneration of both initial catalysts. Although this is a rare example of photoredox-catalysed cross–coupling reaction with tertiary radicals, organoboron derivatives can be subject to instability and be difficult to synthesise.



Scheme 6.8: Photocatalysed C(sp^3)–C(sp^2) cross–coupling of organoboron derivatives and arylhalides. Ir = $[Ir(dFCF_3ppy)_2(bpy)]PF_6$ (1 mol%), Ni = $Ni(TMHD)_2$ (10 mol%). Ligand omitted for clarity.[193]

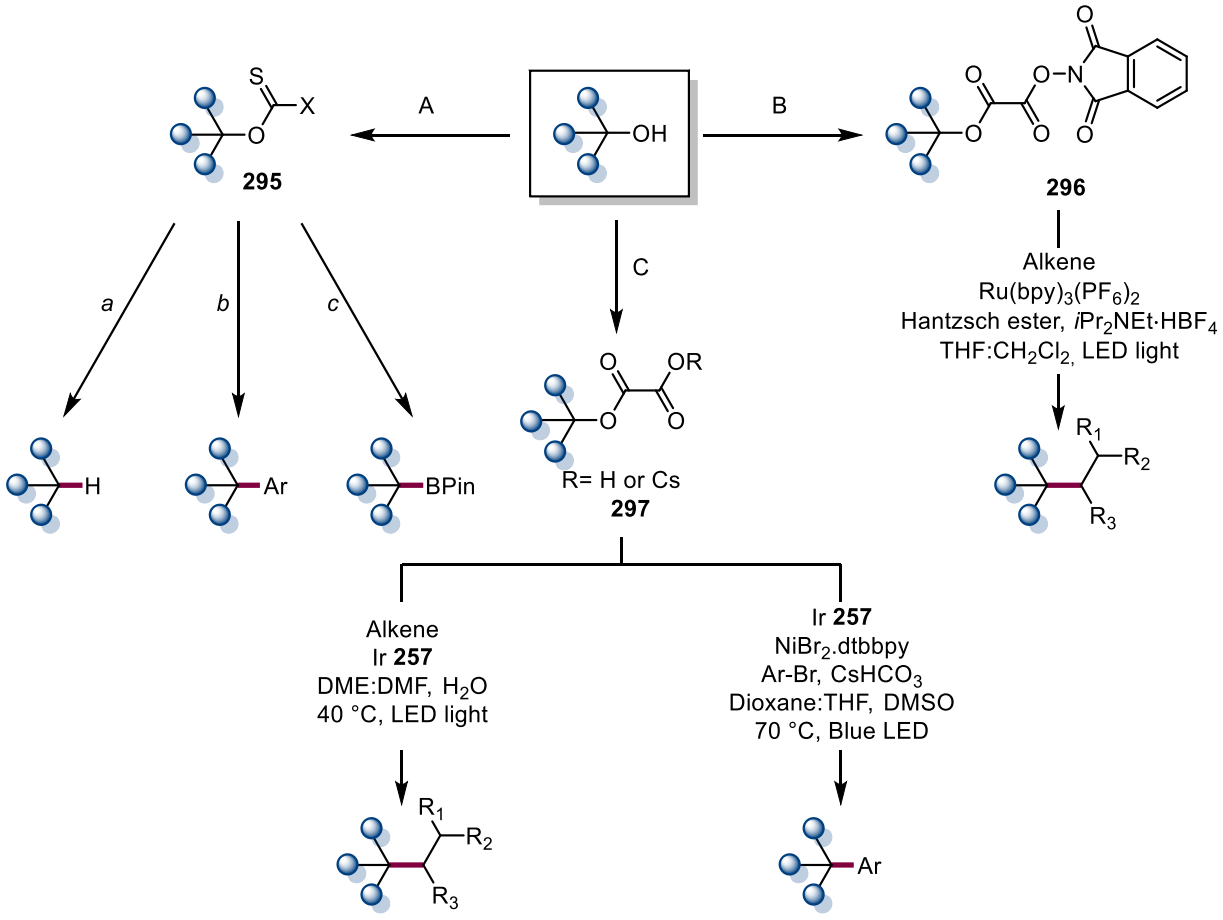
In 2015, silicon derivatives were shown to be suitable C(sp^3)–radical precursors (Scheme 6.9).[194] Indeed, hypervalent bis(catecholato)silicon derivatives **294** can be oxidised by an iridium photocatalyst under visible-light to form primary, secondary and tertiary radicals. These radicals can react with alkene and alkyne substrates as well as aryl halides through cross–coupling reactions in presence of a nickel catalyst.



Scheme 6.9: Photocatalysed C–C bond formation using organosilicon as radical precursors.[194]

Finally, alcohols as radical precursors have attracted recent attention as readily available starting materials. However, the strength of a C–O bond (96 kcal/mol) makes it difficult to cleave and therefore requires the installation of an activating group.[195] Xanthate and

thiocarbamate derivatives **295** are easily accessible from alcohols and were shown to readily generate radicals under photoredox-catalysed conditions. These were used in photoredox-catalysed deoxygenation, $C(sp^3)$–$C(sp^2)$ cross–coupling and borylation reactions (Scheme 6.10, A).[196] Although a few examples of tertiary xanthate esters have been used in these reports, they are usually unstable due to the well-known Chugaev elimination. Alternatively, Overman used *N*-phthalimidoyl oxalates **296**, readily accessible from the alcohol, to generate challenging tertiary radicals under ruthenium-catalysed photocatalysis (Scheme 6.10, B).[197,198] However, *N*-phthalimidoyl oxalates **296** are highly unstable molecules and thus challenging to purify.[197,198] To address this issue, MacMillan and Overman proposed alternative cesium oxalate salts **297** as alcohol-prefunctionalised intermediates (Scheme 6.10, C).[199,200] They showed that under visible-light, an excited iridium photocatalyst can oxidise the oxalate moiety in the presence of a base to form two molecules of CO_2 and the corresponding radical species. The route was exploited through Giese-type reaction with alkenes, and cross–coupling reactions using an Ir/Ni dual catalyst process.



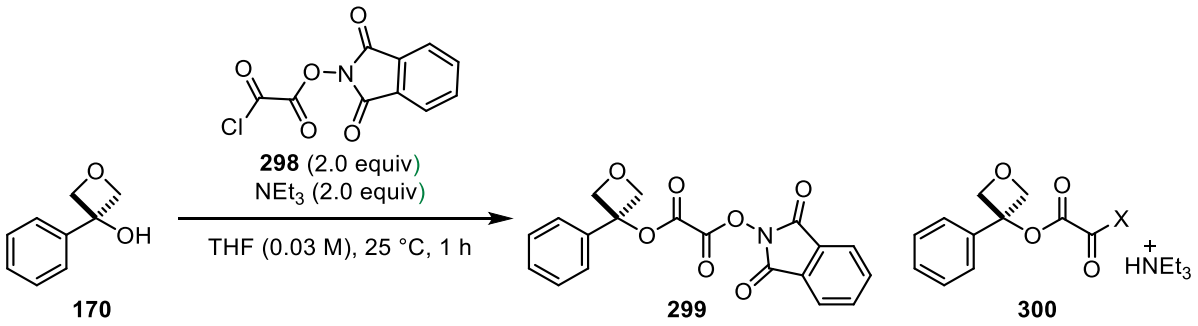
Scheme 6.10: Photoredox-catalysed reaction using functionalised alcohols as radical precursors. Conditions *a*: X = imidazole, $Ir(ppy)_3$, *i*Pr_2NEt, MeCN, Blue LED. Conditions *b*: X = SMe, arylbromide, $Ir[(dFCF_3ppy)_2(bpy)]PF_6$, $Ni(dtbbpy)(H_2O)_4Cl_2$, *sec*$BuBF_3K$, EtOAc, Blue LED. Conditions *c*: X = 1-iodo-2-alkoxybenzene, B_2cat_2, NEt_3, pinacol, DMF, Blue LED.

The use of functionalised alcohols as radical precursors was a particularly attractive approach for the generation of 3-aryl-3-oxetanyl radicals. Indeed, 3-aryl-3-oxetanols are readily available from commercial oxetanone, and this strategy was investigated first.

6.2.2 Synthesis of Oxetanyl Radical Precursors

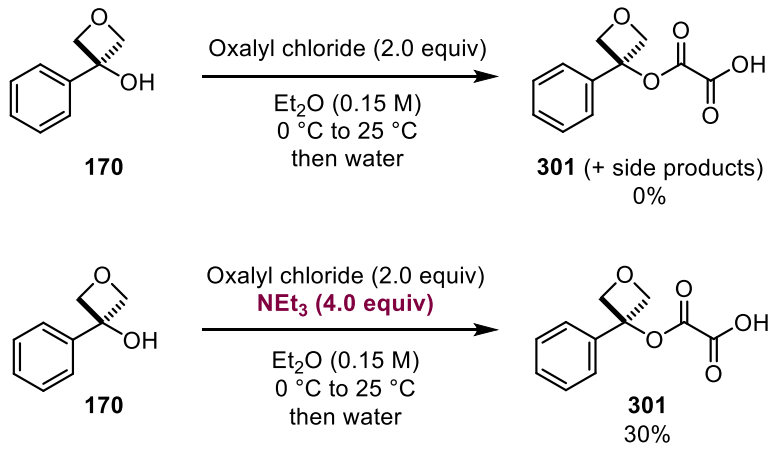
6.2.2.2 Oxetane Oxalates Derivatives

The synthesis of *N*-phthalimidoyl oxalate oxetane **299** was first attempted following Overman's procedure (Scheme 6.11).[197,198] Addition of *N*-phthalimidoyl chlorooxalate **298** to oxetanol **170** in presence of a base, resulted in complete consumption of the starting material with formation of oxalate **299** and a side product **300**, which could not be separated. Although the latter could not be characterised, it was proposed to result from the hydrolysis of the *N*-phthalimidoyl moiety.



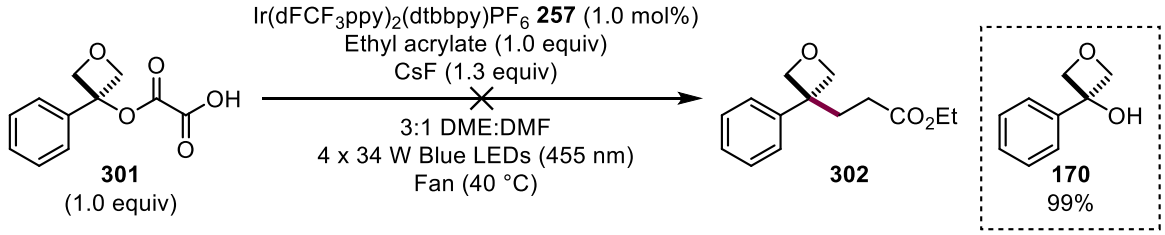
Scheme 6.11: Synthetic approach towards oxetane *N*-phthalimidoyl oxalate **299**.

The synthesis of oxetane oxalate **301** was envisaged as a more stable alternative to *N*-phthalimidoyl oxalate **299**. Following the procedure developed by MacMillan, two equivalents of oxalyl chloride were added to oxetanol **170** (Scheme 6.12).[200] An aqueous quench followed by work up afforded a mixture of oxalate **301** with two other oxetane products. Attempts to separate these products by flash column chromatography resulted in complete loss of material. This shows the high instability of oxetane oxalate **301** under acidic conditions. In addition, two equivalents of HCl are produced when water is added to oxalyl chloride and acyl chloride intermediates. Thus, oxalate **301** could have started to degrade under the reaction conditions, prior to purification, leading to ring opening of the oxetane. The addition of NEt_3 also resulted in a mixture of products, but recrystallisation from warm methanol gave oxalate **301** in 30% yield.



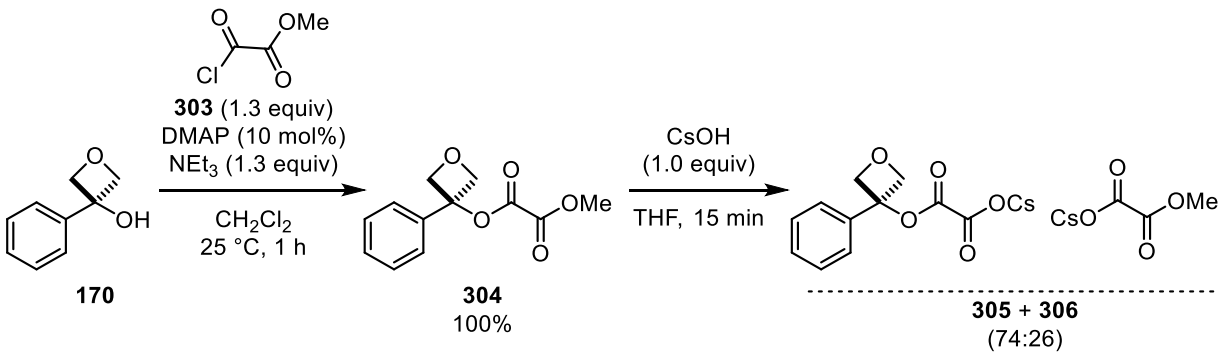
Scheme 6.12: Synthesis of 3-oxetanoxalate **301**.

The viability of oxalate **301** as a radical precursor was then assessed. It was subjected to the photoredox-catalysed reaction with ethyl acrylate developed by MacMillan and Overman, using Ir **257** and blue LEDs (Scheme 6.13).[199] No desired product **302** was observed and oxetanol **170** was obtained in nearly quantitative yield instead. Although the reaction is under basic conditions, oxalate **301** seemed to have been hydrolysed to oxetanol **170**, either during the reaction or the aqueous work up. Other precursors were then envisaged instead.



Scheme 6.13: Subjecting oxalate **301** to photoredox–catalysed addition to alkenes.

MacMillan and Overman proposed cesium oxalate salts as a stable alternative to oxalate and *N*-phthalimidoyl oxalate species.[199] Following their procedure, methyl oxalate **304** was first synthesised in quantitative yield from oxetanol **170** and commercial methyl oxalyl chloride **303** in presence of NEt_3 and DMAP (Scheme 6.14). Hydrolysis of **304** with an aqueous solution of CsOH in THF, unexpectedly produced a mixture of oxalate **305** and cesium salt **306** which could not be separated. This can be attributed to the attack of CsOH on the carbonyl group close to the oxetane ring resulting in the formation of oxetanol **170** and cesium salt **306**. Alternatively, deprotonation of α-CH on oxetane **304** by CsOH, followed by elimination of the oxalate moiety and attack of a hydroxide, can also form oxetanol **170**. The latter was easily removed due to high solubility in organic solvent compared to both cesium salts **305** and **306**.

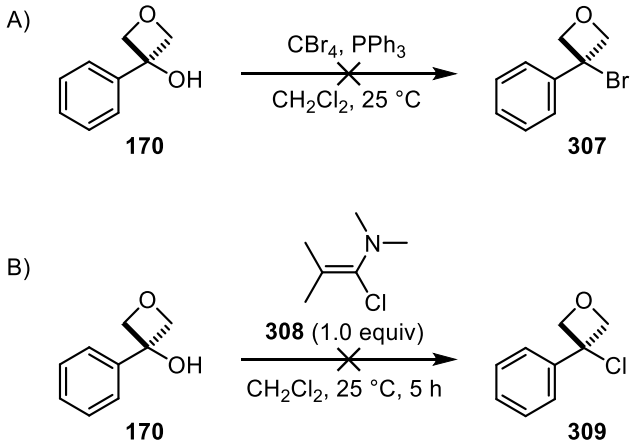


Scheme 6.14: Synthesis of cesium oxalate **305**.

The instability and difficult purification of oxetane-containing oxalate derivatives, make them unsuitable precursors to generate 3-aryl-3-oxetanyl radical species. The synthesis of 3-aryl-3-halo oxetanes was then investigated.

6.2.2.2 Oxetane Halide Derivatives

The synthesis of 3-aryl-3-bromo oxetane **307** from oxetanol **170** was first attempted *via* an Appel reaction (Scheme 6.15, A). Addition of triphenylphosphine and tetrabromomethane to oxetanol **170** led to a complex mixture of products, likely resulting from the opening of the oxetane ring. Although the desired compound **307** was detected by mass spectrometry, the product could not be isolated.



Scheme 6.15: Attempt to synthesise oxetane halides **307** and **309**.

The synthesis of 3-aryl-3-chloro oxetane **309** was then investigated, adding commercial Ghosez's reagent **308** to oxetanol **170** in dichloromethane (Scheme 6.15, B).[201] Although product **309** was detected by mass spectrometry, it could not be isolated from the complex crude mixture. Therefore the synthesis of other potential radical precursors were investigated. 3-Aryl-3-oxetane and azetidine carboxylic acids particularly attracted our attention, and their preparation will be discussed in the next section.

6.3 Oxetane & Azetidine Carboxylic Acids as Targeted Radical Precursors

The investigations discussed in this section have been published in *Org. Lett*.[202]

6.3.1 Oxetane and Azetidine Carboxylic Acids as Attractive Motifs

Recent examples of bioactive molecules containing 3-aryl-3-carboxylic acid oxetanes and azetidines were reported in the patent literature (Figure 6.4). These motifs were also used as building blocks to access bioactive esters and amide derivatives.[203,204,205,206]

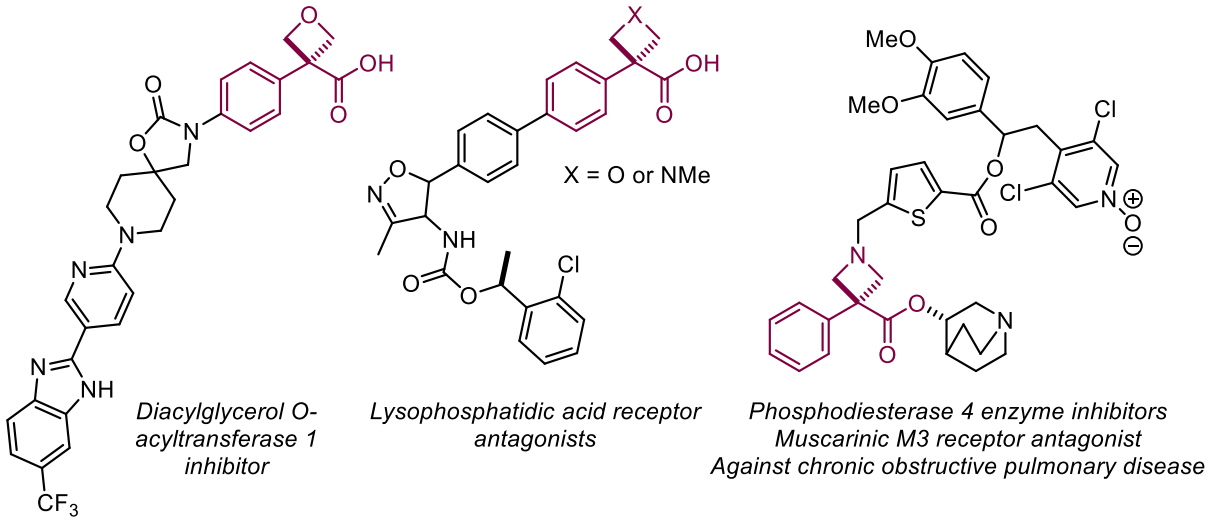


Figure 6.4: 3-Aryl-3-carboxylic acid oxetane and azetidine in biologically active compounds.

In addition, they present interesting structural similarities with 2-arylpropionic acids, but with an achiral centre α to the acid (Figure 6.5). 2-Arylalkanoic acids, such as ibuprofen, are an important class of nonsteroidal anti-inflammatory agents (NSAIDs).[207]

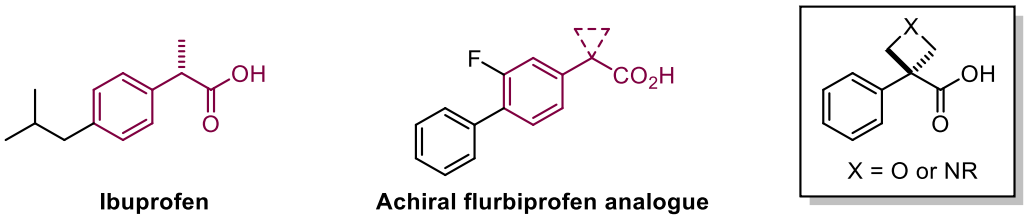


Figure 6.5: Chiral and achiral profens in the literature.

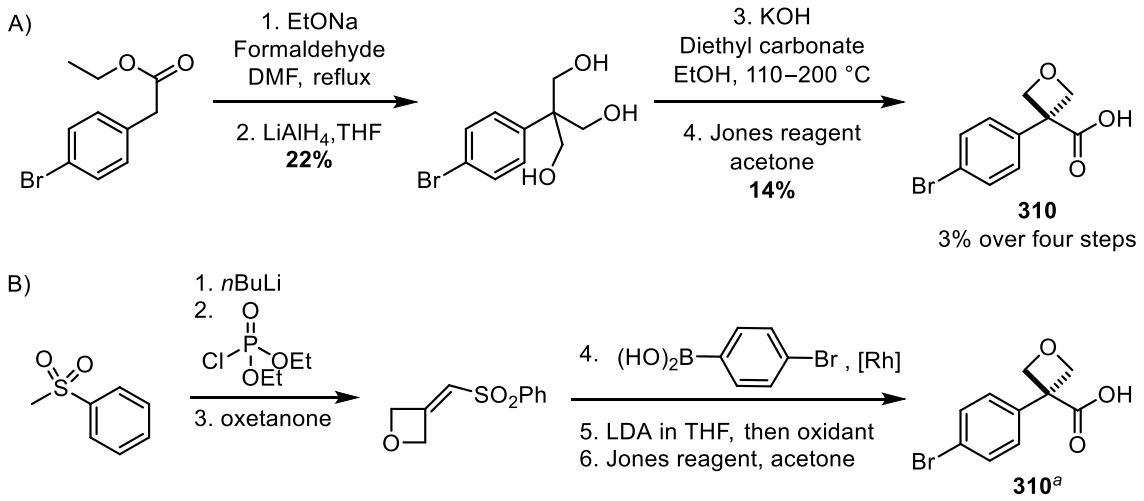
The prolonged use of NSAIDs has been associated with severe gastrointestinal complication through chronic inhibition of the cyclooxygenase-1 (COX-1) enzyme as well as acute myocardial infarction.[208] Recent studies focused on the development of new NSAIDs that selectively inhibit COX-2 while sparing COX-1 in order to reduce the toxicity.[208a] Interestingly, recent examples of achiral profens, such as desmethyl, dimethyl, and cyclopropyl profens (Figure 6.5) displayed substrate-selective COX-2 inhibition as well as inhibition of Aβ42

involved in Alzheimer's disease.[209,210] It was envisaged that incorporation of a four-membered ring into profens at the α-position of the acid would increase the steric bulk and prevent or decrease metabolic degradation. Therefore oxetane and azetidine acids can offer new possibilities for medicinal chemists.

Despite their attractive characteristics, a rather limited number of 3-aryl-3-carboxylic acid oxetanes and azetidines have been reported in the literature to date. This can be attributed to lengthy and low yielding synthetic approaches available.

6.3.2 Synthetic Approaches and Limitations

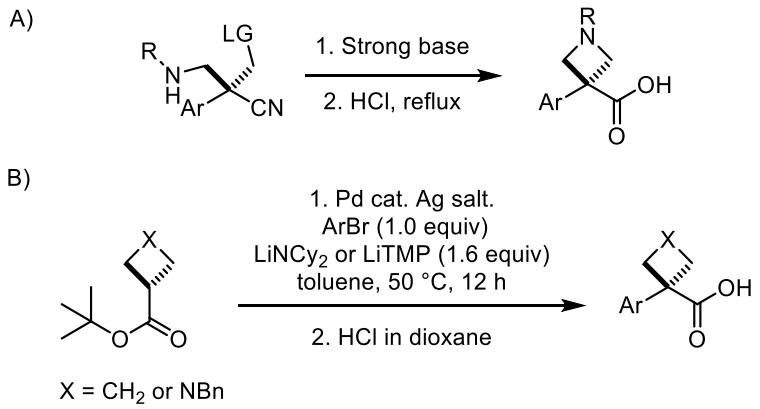
Two routes have been developed towards carboxylic acid oxetane **310** (Scheme 6.16).[203] The first methodology described a four step synthesis involving: a ring closure, and several oxidation and reduction reactions under harsh conditions (Scheme 6.16, A). The second methodology consists of six steps including a Wittig reaction, a Rh-catalysed addition of an aromatic to the formed alkene, followed by harsh oxidation/reduction steps (Scheme 6.16, B). Both methods are low yielding, lengthy and poorly functional group tolerant.



Scheme 6.16: Previous synthetic route towards 3-aryl-3-oxetane carboxylic acids. [a] Yields not given in the patent.

The synthesis of azetidine acids has been better studied. The most common strategy involves a ring closure step followed by hydrolysis of a cyanide group (Scheme 6.17, A).[211] Most recently, Hartwig developed an elegant palladium-catalysed α-arylation of azetidine and cyclobutane esters which provides the corresponding acid after hydrolysis (Scheme 6.17, B).[212] However, the use of strong bases and acids, or the expensive and inaccessible starting materials make the development of a complementary method attractive. In addition, there are only limited examples of these commercially available acids with very high cost. As a result, a

new synthetic method is needed to access these oxetane and azetidine derivatives efficiently, before testing their ability as radical precursors under photoredox conditions.



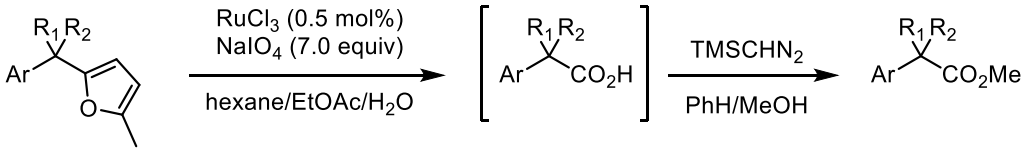
Scheme 6.17: Previous synthetic methods towards 3-aryl-3-carboxylic acid azetidines and cyclobutanes.

6.3.3 New Synthetic Approach towards Oxetane and Azetidine Acids

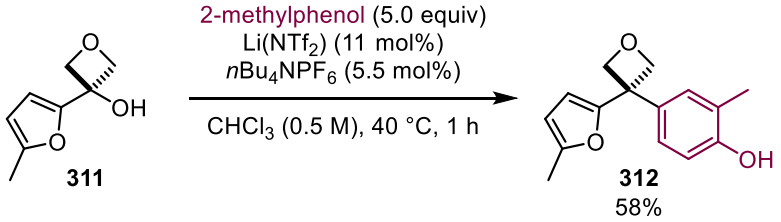
The introduction of a carboxylic acid into a molecule is traditionally achieved by hydrolysis of ester or nitrile groups. However, there are no available methods to install such groups from oxetanol for example. Another common way to incorporate carboxylic acids is by oxidative cleavage of a furan ring.[213]

In 2008, Ishii reported a two-step route to synthesise 2-arylalkanoic acids (Scheme 6.18, A).[214] In this work, 1-arylalkylfurans are first prepared *via* Friedel–Crafts alkylation of 2-methylfuran with 1-arylalkanols. The furans were then oxidatively cleaved to the carboxylic acid under Sharpless' ruthenium-catalysed conditions using $NaIO_4$ as an oxidant.[215] Ishii's cleavage step is run in a mixture of hexane, EtOAc and water, which are more environmentally friendly and safer than toxic CCl_4, usually employed for this type of transformation. Although none of the carboxylic acids were isolated, this mild and chemoselective method represents an appealing opportunity. Indeed, examples of 3-aryl-3-furanyl oxetanes and azetidines have been previously synthesised by the Bull group and in this thesis (section 4.1.5) *via* Friedel–Crafts alkylation with oxetanol **311** and azetidinol **83** (Scheme 6.18, B).[50,111]

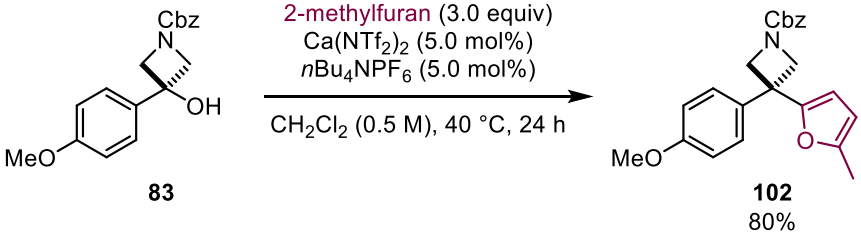
A) Ishii. *Synthesis* **2008**, 3835.



B) Bull, J. A. *Chem. Eur. J.* **2016**, *22*, 16271.

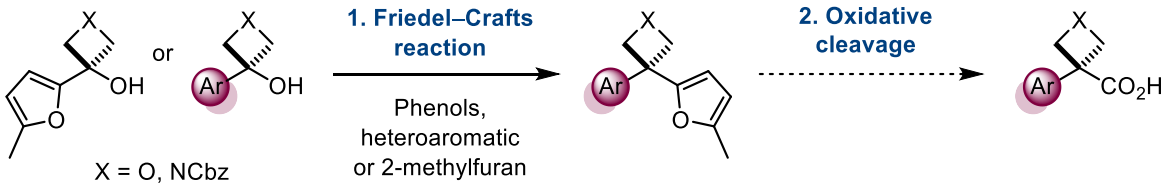


Part 4 & Bull, J. A. *Org. Lett*. **2019**, *21*, 300.



Scheme 6.18: Previous oxidative cleavage of furan and synthesis of 3-aryl-3-furanyl oxetanes and azetidines.

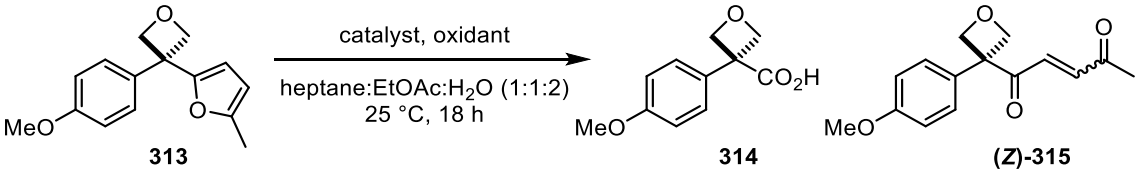
Oxidative cleavage of such furanyl oxetane and azetidine derivatives could give access to a variety of new 3-aryl-3-carboxylic acid oxetanes and azetidines (Scheme 6.19). However, ruthenium tetroxide, the active species generated by oxidation of $RuCl_3$, has been shown to oxidise carbons at the α–position of the heteroatom in cyclic ethers, oxetane and lactams.[216] Therefore concerns about the selectivity of the reaction, as well as the stability of the oxetane and azetidine rings towards oxidative cleavage, can be raised.



Scheme 6.19: Proposed two step synthesis of 3-aryl-3-carboxylic acid oxetanes and azetidines *via* oxidative cleavage of furan.

6.3.4 Oxidative Cleavage Optimisation

Oxidative cleavage conditions were first investigated on furanyl oxetane **313** which was prepared through the lithium-catalysed Friedel–Crafts reaction.[50] Using 5 mol% of $RuCl_3$ and 7.0 equivalents of sodium periodate in Ishii's solvent mixture of hexane:EtOAc:H_2O (1:1:2) produced the desired acid product **314** in 92% yield (entry 1, Table 6.1). Pleasingly, the oxetane ring was not oxidised under the reaction conditions and the product was stable. In addition, the reaction proceeded cleanly and did not require further purification after aqueous work up.



313 **314** (***Z***)-**315** (***E***)-**315**

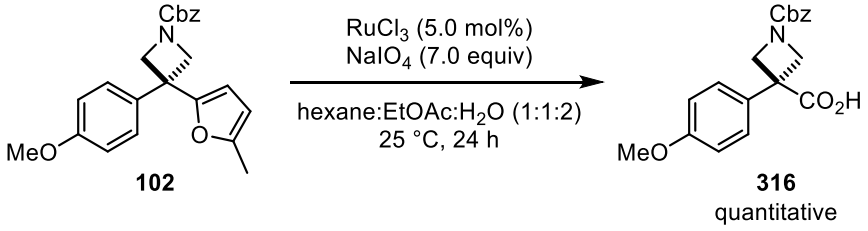
Entry	cat. (mol%)	Oxidant (equiv)	Concn (M)	Yield (%)[a]		
				314	(***Z***)-**315**	(***E***)-**315**
1[b]	$RuCl_3$ (5)	$NaIO_4$ (7)	0.04	92	0	0
2	$RuCl_3$ (5)	$NaIO_4$ (7)	0.04	92	0	0
3	$RuCl_3$ (0.5)	$NaIO_4$ (7)	0.04	93	0	0
4	$RuCl_3$ (0.5)	$NaIO_4$ (5)	0.04	70	0	0
5	$RuCl_3$ (5)	$NaIO_4$ (3.5)	0.04	79	0	0
6	$RuCl_3$ (0.5)	$NaIO_4$ (7)	0.1	75	0	0
7[c]	$RuCl_3$ (0.5)	$NaIO_4$ (7)	0.04	70	17	0
8	$RuCl_3$ (0.5)	H_5IO_6 (7)	0.04	99	0	0
9	$RuCl_3$ (0.5)	$NaBrO_3$ (7)	0.04	0	68 (51)	7 (15)
10[d]	-	*m*CPBA (1)	0.2	0	74 (67)	0
11[e]	-	NBS (1.2) and $NaHCO_3$ (2)	0.2	0	76	

Table 6.1: Optimisation of the oxidative cleavage of furan **313**. [a] Yields calculated by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as the internal standard. Yields in brackets are isolated [b] Solvent is hexane:EtOAc:H_2O. [c] Using MeCN:H_2O (1:1) as the solvent. [d] Using CH_2Cl_2 as the solvent. [e] Using acetone:H_2O (1:1) as the solvent.

Toxic hexane was replaced with heptane as a safer alternative solvent without affecting the yield (entry 2). Reduction of the catalyst loading to 0.5 mol% afforded a similar high yield of 93% (entry 3). The amount of oxidant can also be decreased to 5.0 equivalents albeit with a 20% drop in yield (entry 4). The equivalents of $NaIO_4$ can be lowered further to 3.5 equivalents when the loading of $RuCl_3$ is elevated to 5 mol%, giving acid **314** in 79% yield (entry 5). Concentrating the reaction to 0.1 M produced **314** in a slight lower yield of 75% due to the poor solubility of the oxidant (entry 6). Surprisingly, using MeCN instead of heptane/EtOAc gave 70% of the desired acid **314** along with 1,4-enedicarbonyl **(*Z*)-315** in 17% (entry 7). Such alkene products are useful precursors for the formation of cyclopentenone, but are usually obtained from acid-catalysed or oxidative ring opening of furan using peroxides, oxygen or halogens.[217] In addition, this type of oxetane alkene has not been reported in the literature prior to this work.

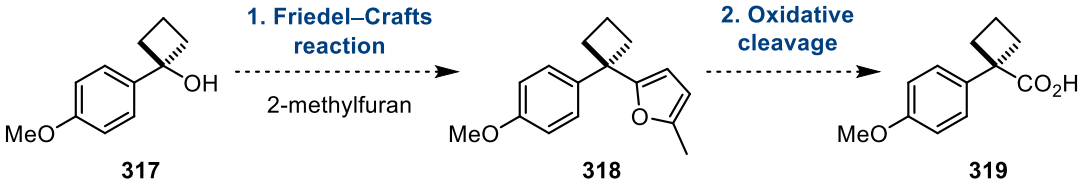
Other oxidants were investigated for this reaction. Although periodic acid was successful, this was accompanied by inorganic impurities which made the purification more difficult (entry 8). A combination of $RuCl_3$ and $NaBrO_3$ reacted exclusively towards the formation of 51% of alkene **(*Z*)-315** and 15% of alkene **(*E*)-315**, which were easily separated through flash column chromatography (entry 9). Interestingly, oxetane alkene **(*Z*)-315** can be selectively obtained using conditions developed by LeGoff and Kobayashi (entry 10).[218,219] Subjecting furan **313** to one equivalent of *m*CPBA in CH_2Cl_2 afforded **(*Z*)-315** in 67% isolated yield. NBS and bromine have been previously used to form selectively (*E*)-1,4-enedicarbonyl species.[217] However, subjecting furan **313** to NBS in presence of a base produced **(*Z*)-315** exclusively in 76% yield (entry 11).

Pleasingly, subjecting furanyl azetidine **102** to 5 mol% $RuCl_3$ and 7 equivalents of $NaIO_4$ also produced the desired azetidine acid **316** in quantitative yield, albeit with traces amount of inorganic impurities (Scheme 6.20). The reaction was then optimised by MRes student Milo Smith.[220] Similarly to the reaction for oxetane, hexane could be replaced with heptane. The catalyst loading could be lowered to 2.5 mol% without affecting adversely the yield. Finally, azetidine acid **316** was not successfully purified by acid and base work up and required a flash column chromatography or short filtration through silica to remove inorganic impurities.



Scheme 6.20: Initial synthesis of azetidine acid **316** through oxidative cleavage of furan **102**.

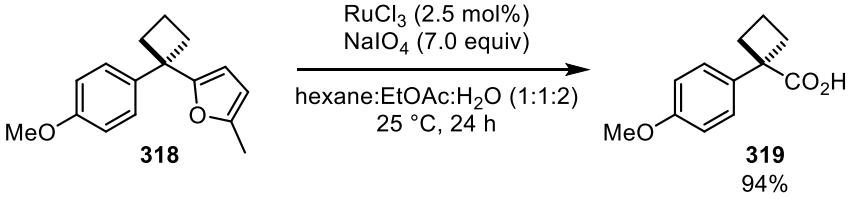
Finally, it was thought that 1-aryl-1-carboxylic acid cyclobutane **319** could also be accessed through this two–step strategy from cyclobutanol **317**[g] (Scheme 6.21). Example of bioactive molecules containing such carboxylic acid cyclobutane motifs have been recently reported in the literature.[221] These are currently synthesised through similar methodologies as azetidine acids, *via* palladium-catalysed α-arylation of cyclobutane esters or preparation of nitriles followed by hydrolysis.[212] An alternative method employing milder conditions and inexpensive starting materials and reagents would be valuable.



Scheme 6.21: Proposed synthetic route towards cyclobutane acid **319**.

Pleasingly, the previously developed lithium-catalysed and calcium-catalysed Friedel-Crafts conditions towards 3,3-diaryloxetanes[50] and azetidines,[111] could be extended to the synthesis of 1,1-diarylcyclobutanes (see Appendix, Table 10.5), but also to 5- and 6-membered *O*- and *N*-heterocycles. Investigations towards the syntheses of 1,1-diarylcyclobutanes, 4,4-diarylTHPs and piperidines as well as 3,3-diarylTHFs and pyrrolidines have been recently published in *Eur. J. Org. Chem*.[222] $Ca(NTf_2)_2$ was found to be the optimum catalyst for the Friedel–Crafts alkylation of aromatics with electron rich cyclobutanol such as **317** (see Appendix, Table 10.5).[222] Cyclobutanes displayed increased reactivity compared to oxetanes and azetidines, and less electron-rich cyclobutanols, such as phenyl and Cl-substituted, were successful precursors. This is attributed to the enhanced cyclobutanyl carbocation stability through transannular stabilising σCH–p interactions and in absence of inductive destabilisation from an oxygen or nitrogen atoms.[223] $FeCl_3$ was found to be the most efficient catalyst for less electron-activated cyclobutanols.

Pleasingly, subjecting furanyl cyclobutane **318** to the oxidative cleavage conditions afforded acid **319** in 94% yield (Scheme 6.22). The use of 2.5 mol% of $RuCl_3$ was necessary to reach completion.



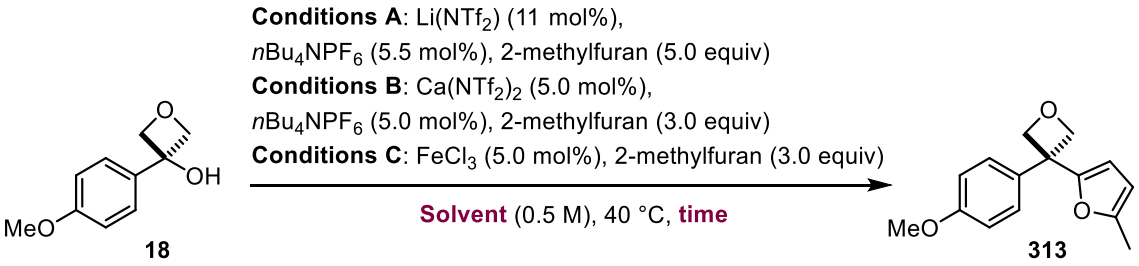
Scheme 6.22: Synthesis of cyclobutane acid **319** through oxidative cleavage of furan **318**.

[g] Previously synthesised within the Bull group.[222]

With the optimised oxidative cleavage conditions in hand, a collection of furan derivatives was then prepared.

6.3.5 Synthesis of Furan Intermediates

Initial synthesis of furanyl oxetane **313** using the previous lithium-catalysed Friedel–Crafts conditions was low yielding due to slow reaction (entry 1, Table 6.2).



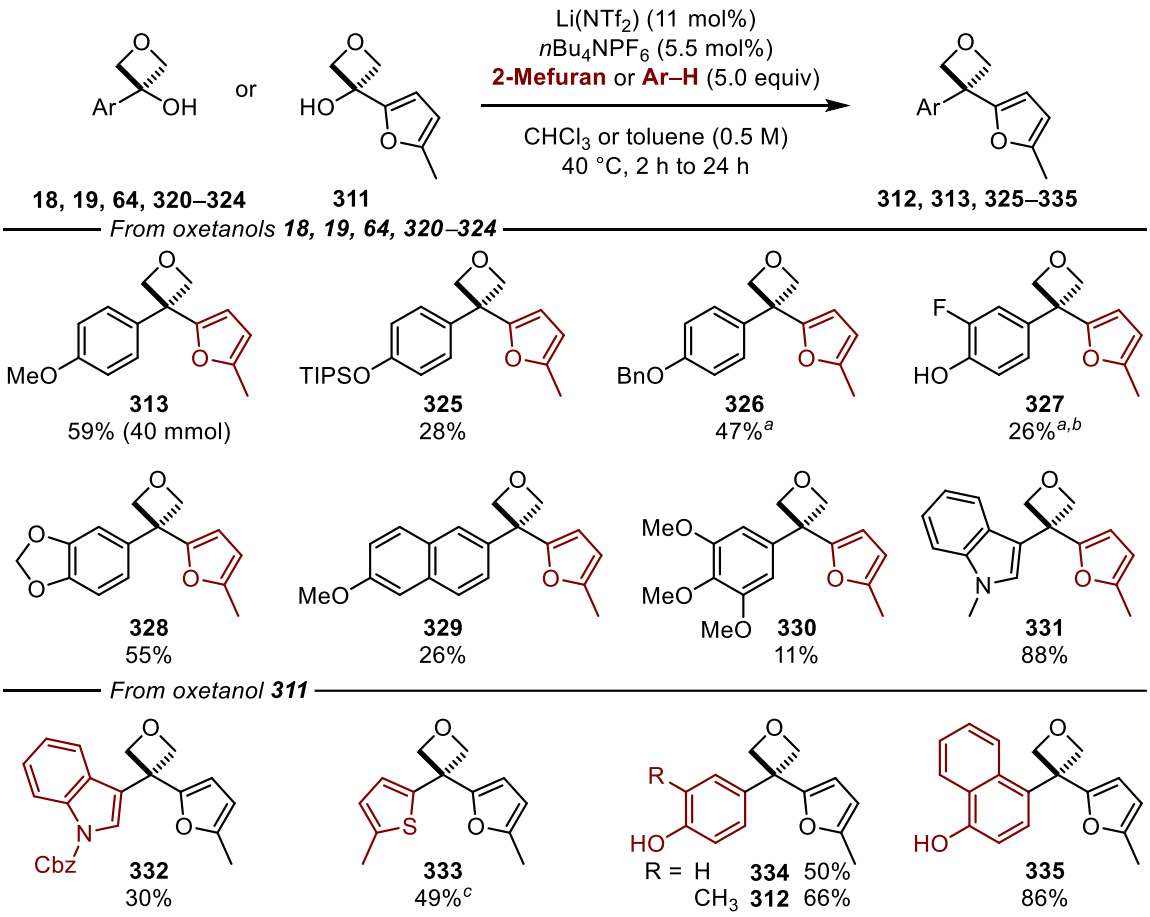
Entry	Conditions	Solvent	Time (h)	RSM 18 (%)[a]	Yield 313 (%)[a]
1	A (Li)	$CHCl_3$	1	87	5
2	A (Li)	$CHCl_3$	2	0	53
3	B (Ca)	CH_2Cl_2	2	0	43
4	C (Fe)	CH_2Cl_2	2	94	0
5	A (Li)	Toluene	2	0	71

Table 6.2: Optimisation for the Friedel–Crafts alkylation of 2-methylfuran with oxetanol **18**. Reactions were carried out on 0.25 mmol scale relative to the oxetanol. [a] Yields calculated by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as the internal standard.

Leaving the reaction for another hour increased significantly the yield of oxetane **313** to 53% (entry 2). Calcium- and iron-catalysed conditions were also tested, but led to lower yield or no reaction respectively (entry 3 and 4). Finally, the replacement of toxic chlorinated solvent with toluene led to a rise of the yield of 20%, affording **313** in 71% yield (entry 5).

The reaction could be scaled to 40 mmol, producing 5.8 g of furan **313** in 59% yield (Scheme 6.23). Some examples were synthesised in higher yield when the reaction was run for longer or when $CHCl_3$ was used as the solvent, due to higher solubility of the precursor or the nucleophile. A variety of furan derivatives could be prepared using 2-methylfuran as the nucleophile in a range of scales from 0.25 mmol to 40 mmol. TIPS and Bn protecting groups were well tolerated producing oxetanes **325** and **326** in 28% and 47% yields respectively. The latter example required higher temperature for Bn-protected oxetanol **321** to be solubilised. Interestingly, *meta*-F-substituted oxetanol **322** was a successful precursor despite the electron-withdrawing effect of the fluorine atom. The reaction needed to be heated to 50 °C

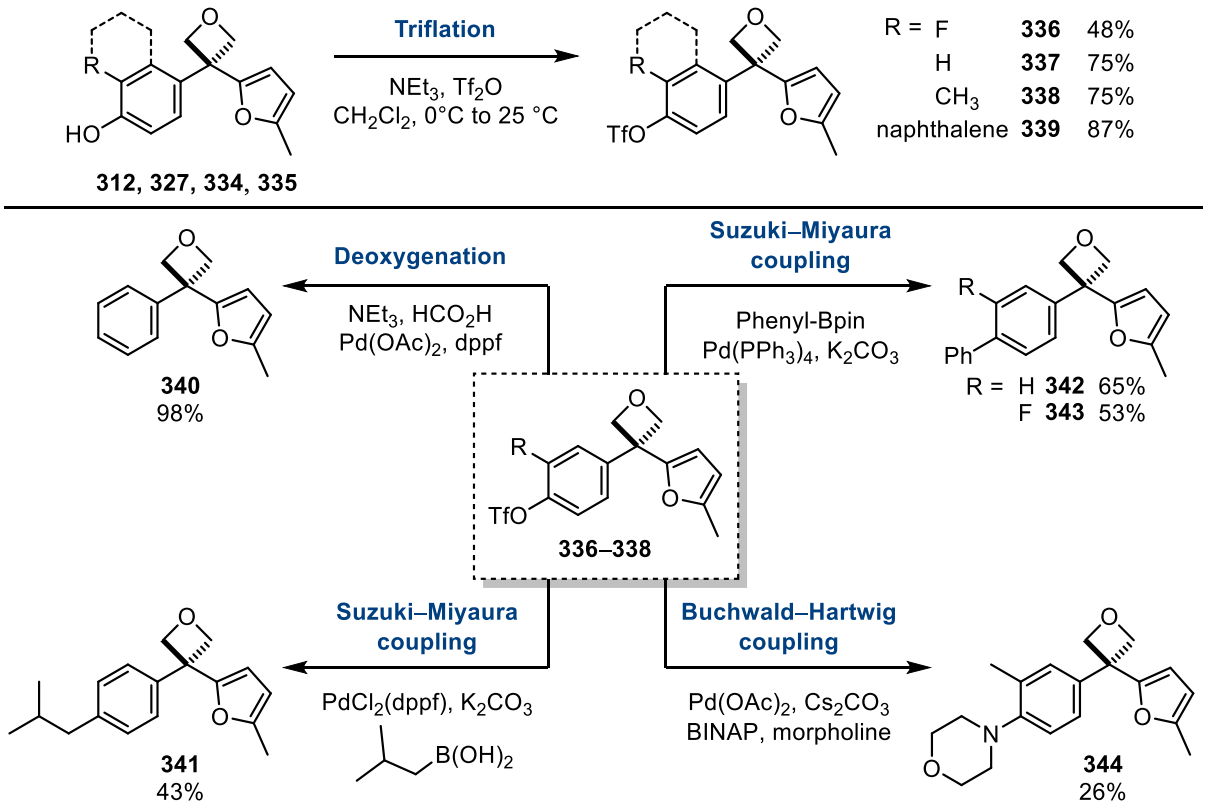
and diluted to give furan **327** in useful yield. Benzodioxole, methoxynaphthalene, trimethoxybenzene and 1-methylindole (**328**–**331**) were all successfully synthesised in 11% to 88% yields.



Scheme 6.23: Synthesis of 3-aryl-3-furanyl oxetanes through Friedel–Crafts reaction. [a] Reaction performed at 50 °C. [b] Concentration = 0.2 M. [c] $Ca(NTf_2)_2$ (5.0 mol%), nBu_4NPF_6 (5.0 mol%), 3.0 equiv of nucleophile used.

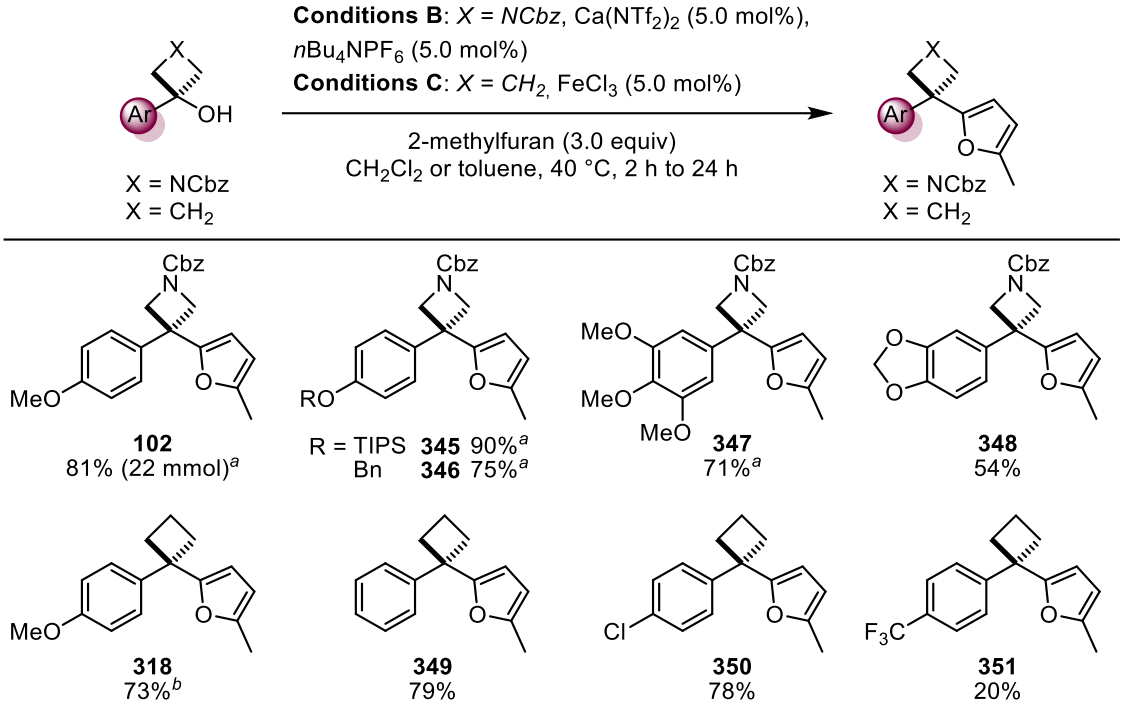
Further 3-aryl-3-furanyl oxetanes were prepared using 3-furan-3-oxetanol **311** as the precursor. Medicinally relevant Cbz-protected indole and thiophene were compatible nucleophiles giving furans **332** and **333** in 30% and 49% yields. Varied substituted phenols and naphthol aromatics were incorporated as the nucleophiles and **312**, **334** and **335** were prepared in good yields.

Although less electron-rich furanyl oxetane derivatives cannot be directly prepared *via* Friedel–Crafts reactions, they can be accessed taking advantage of the installed phenol groups (Scheme 6.24). Triflates **336** to **339** were obtained in high yields from their corresponding phenols precursors. Pd-catalysed deoxygenation of triflate **337** led to phenyl **340** in 98% yield. Finally, cross–coupling reactions of triflates **336**–**338** afforded isobutyl **341**, phenyls **342** and **343**, as well as morpholine **344** in 26% to 65% yields.



Scheme 6.24: Derivatisation of furanyl oxetane derivatives.

The synthesis of furanyl azetidine **102** was scaled to 22 mmol by Milo Smith and in 81% yield (Scheme 6.25).[220] TIPS and Bn-protected azetidinols produced furan **345** and **346** in 90% and 75% yields respectively.[220] Similarly to oxetane, chlorinated solvent could be replaced with toluene, and trimethoxybenzene **347**[220] and benzodioxole **348** reacted with 2-methylfuran in excellent yield. Finally, the cyclobutanes were synthesised in high yields using $FeCl_3$ or $Ca(NTf_2)_2$ as catalysts and 2-methylfuran as the nucleophile. Due to the increased stability of the carbocation intermediate, *para*-methoxybenzene (**318**) but also phenyl (**349**) and electron-withdrawing Cl and CF_3 groups (**350** and **351**) could be incorporated.



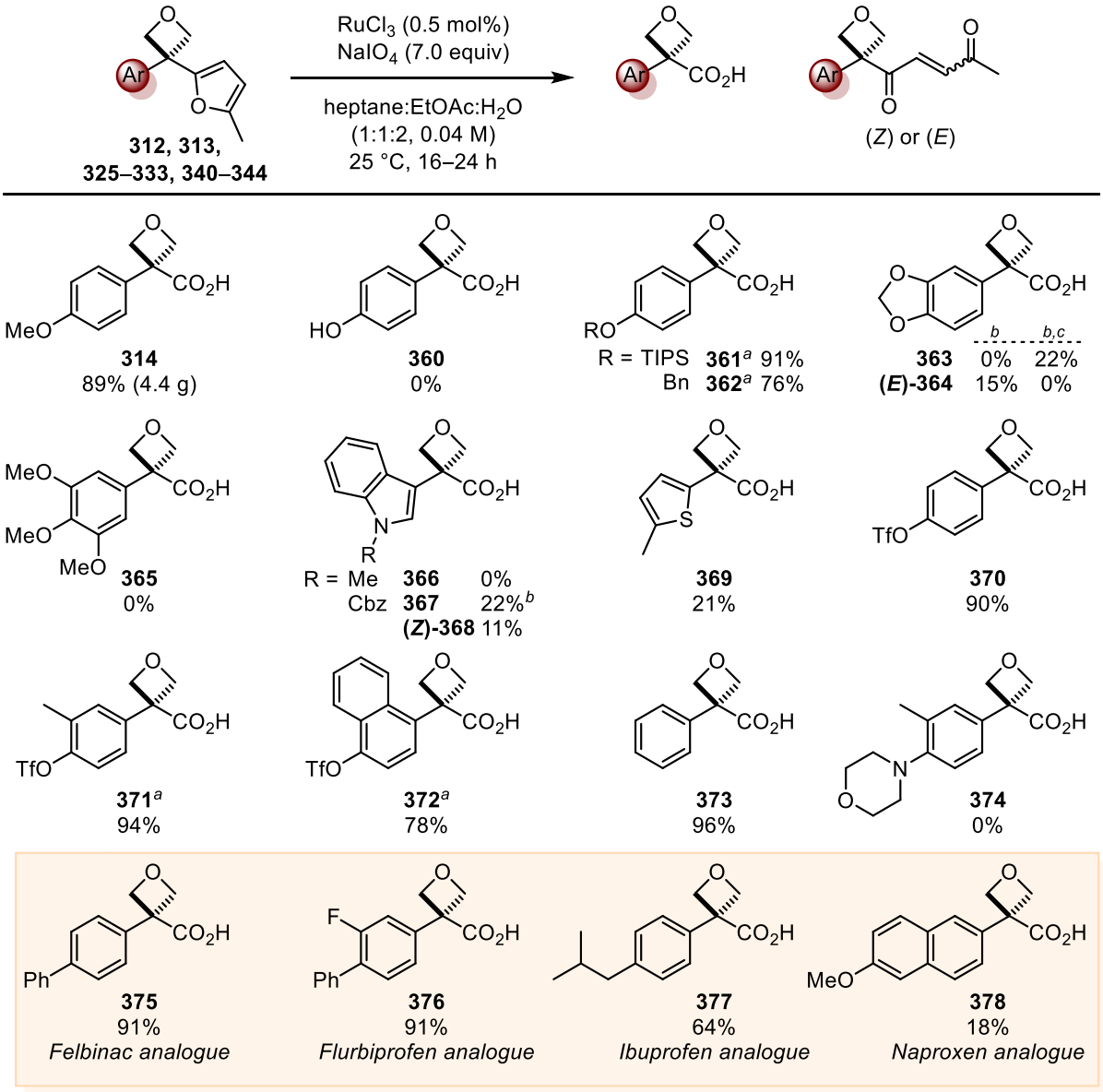
Scheme 6.25: Synthesis of furanyl azetidines and cyclobutanes through Friedel–Crafts reaction. [a] Synthesised by Milo Smith. [b] $Ca(NTf_2)_2$ (5.0 mol%), nBu_4NPF_6 (5.0 mol%) used.

6.3.6 Synthesis of Oxetane and Azetidine Carboxylic Acids

6.3.5.1 Reaction Scope

The synthesis of acid **314** was successfully scaled up to 4.4 g (23.6 mmol) in 89% yield (Scheme 6.26). Phenol **334** was not compatible with the reaction conditions, with complete degradation of the starting material. However, TIPS and Bn protecting groups were tolerated under the oxidative cleavage conditions, affording protected phenols **361** and **362** in 91% and 76% yields. These two examples required a higher catalyst loading of 2.5 mol% $RuCl_3$ to reach completion. The presence of protecting groups offers a valuable synthetic handle for further derivatisation through the oxygen atom. Intriguingly, benzodioxole **328** produced exclusively alkene **(*E*)-364** in 15% yield. The coordination of the Ru catalyst to the oxygen atoms of the benzodioxiole group and the oxetane ring might increase the electron-withdrawing properties of the furan moiety. This might favour acid-mediated ring opening of the furan and lead to alkene formation preferentially. Addition of four equivalents of $NaHCO_3$ prevented alkene formation and acid **363** was obtained in 22% yield. In comparison, trimethoxybenzene **330** was fully degraded in the reaction with no alkene nor acid **365** produced. This can be attributed to the lack of chemoselectivity of the cleavage as trimethoxybenzene is highly electron-rich. Methylindole **331** was similarly degraded under the oxidative cleavage conditions, but protecting the nitrogen with Cbz group allowed the cleavage of furan **332** to proceed giving

indole **367** in 22% yield and 11% of **(*Z*)-368**. Pleasingly, thiophene group could be incorporated and acid **369** was formed in 21% yield.

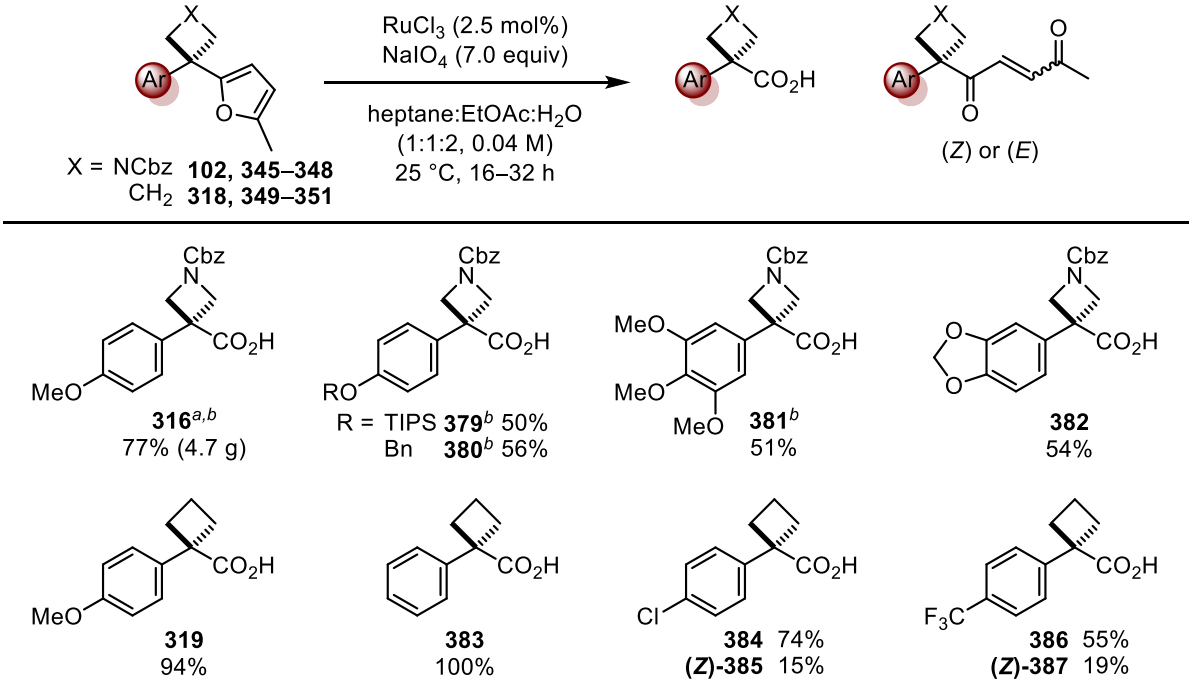


Scheme 6.26: Scope of the oxidative cleavage of furanyl oxetane derivatives. [a] 2.5 mol% $RuCl_3$ used. [b] 48 h. [c] Using 4 equiv of $NaHCO_3$.

Surprisingly, aryl triflates were compatible under the reaction conditions and oxetane acids **370** to **372** were prepared in high yields. These represent interesting oxetane building blocks, as a variety of functional groups could be directly installed from the triflate. Cleavage of unsubstituted phenyl **340** gave acid **373** in 96% yield which was characterised by X-ray crystallography (see Appendix, Figure 10.2). Finally, similarly as with trimethoxybenzene **330**, the cleavage of morpholine **344** suffered from chemoselectivity issues and acid **374** was not obtained. Importantly, the majority of the oxetane acid products were easily purified by simple acidic/basic work up, demonstrating the high stability of both triflate and oxetane groups.

The utility of the method for medicinal chemistry was demonstrated with the synthesis of four drug analogues. Felbinac, Flurbiprofen and Ibuprofen analogues **375**, **376** and **377** were made in 64% to 91% yields and purified by work-up procedures. Although highly electron-rich groups have previously been shown to be challenging for the oxidative cleavage, methoxynaphathalene could be installed, affording Naproxen analogue **378** in 18% yield. The physicochemical properties of the oxetane-containing drug analogues **375**–**378** will be measured in the near future by Pfizer and compared with the corresponding drugs.

The synthesis of azetidine acid **316** was also scaled to nearly 5 g in 77% yield by Milo Smith (Scheme 6.27).[220] $NaIO_4$ was replaced with periodic acid in this example, to facilitate the work up. TIPS and Bn protected phenols **345** and **346**, required longer reaction time to reach completion, affording azetidine **379** and **380** in 50% and 56% yields respectively.[220] Interestingly, the oxidative cleavage was selective for the furan moiety over the trimethoxybenzene in azetidine **347**, compared to oxetane **330**, producing 51% yield of acid **381**. In addition benzodioxole **348** was well tolerated giving acid **382** in 54% yield without formation of alkene.

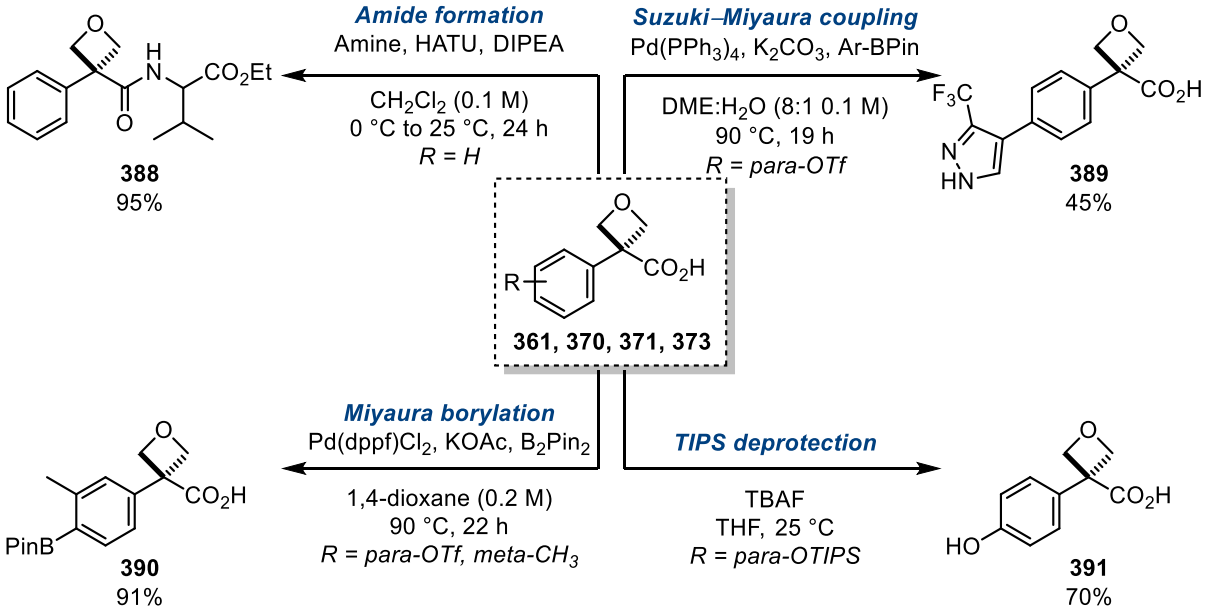


Scheme 6.27: Scope of the oxidative cleavage of furanyl azetidine and cyclobutane derivatives. [a] Periodic acid used. [b] Synthesised by Milo Smith.

Finally, furanyl cyclobutanes were also successfully cleaved to produce acids **319**, **383**, **384** and **386** in 100% to 55% yields (Scheme 6.27). Interestingly, the cleavage of furanyl cyclobutanes bearing electron-withdrawing groups Cl and CF_3 also resulted in the formation of **(*Z*)**-alkenes (**385** and **387**). Both acid and alkene products were easily separated by work-up procedures.

6.3.5.2 *Further Derivatisation of Oxetane Carboxylic Acids*

The potential of these acid motifs as building blocks for drug discovery programs was probed through various transformations commonly used in medicinal chemistry (Scheme 6.28). Amide formation proceeded smoothly under standard conditions to synthesise **388** in 95% yield. Triflates **370** and **371** were further functionalised through Pd-catalysed cross–coupling reactions to install a pyrazole and a BPin groups in 45% and 91% yields respectively. The latter product represents an attractive new building block. Finally, TIPS deprotection was carried out on acid **361**, accessing free phenol **391** in 70% yield.



Scheme 6.28: Derivatisation of 3-aryl-3-carboxylic acid oxetanes.

6.3.7 Conclusion

The synthesis of novel 3-aryl-3-carboxylic acid oxetanes and 4-membered rings has been achieved through a simple and rapid two steps procedure (Figure 6.6). This involved the installation of a furan ring *via* lithium, calcium or iron–catalysed Friedel–Crafts reactions with heterocyclic alcohol precursors. The furan derivatives were then oxidatively cleaved under mild Ru-catalysed conditions using $NaIO_4$ or periodic acid. Twenty-three examples of oxetane, azetidine and cyclobutane acids were synthesised from 18% to quantitative yield. Heteroaromatics such as thiophene and indoles, as well as electron-rich and poor aromatics could be incorporated. In addition, valuable functionalities were tolerated under the conditions, such as triflates and protecting groups including TIPS, Bn and Cbz. The reaction was applied on scales from 0.2 mmol up to 24 mmol (>4 g), and most of the products were purified by simple acidic/basic work-up procedures. This demonstrated the high stability of the oxetane acids in particular. The methodology was applied to the synthesis of four oxetane-containing profen analogues, made in 18% to 91% yields. The physicochemical properties of these new

profen analogues will be measured to evaluate the potential of these oxetane acid motifs for drug discovery. In addition, the use of these acid products as building block was demonstrated through derivatisation of the acid and the triflate groups.

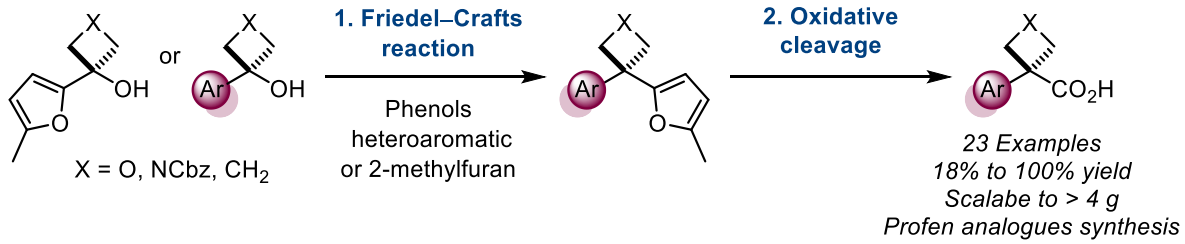
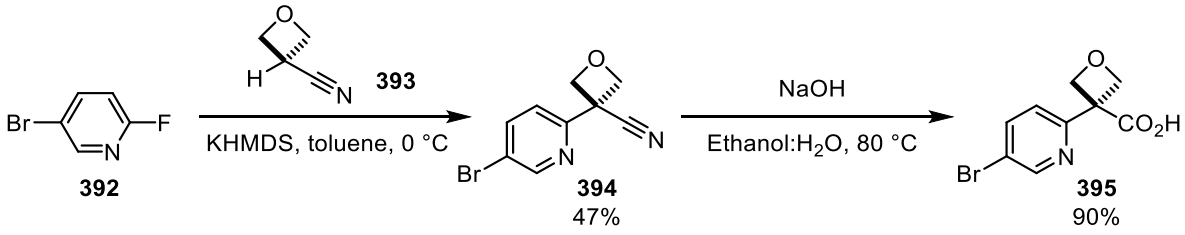


Figure 6.6: Synthesis of 3-aryl-3-carboxylic acid oxetanes, azetidines and cyclobutanes through a two-step process.

Due to the inherent limitations of the Friedel–Crafts reaction step, 3-pyridine-3-carboxylic acid derivatives cannot be accessed with this methodology. However, alternative methods have been previously described in the literature to prepare 3-pyridine-carboxylic acid azetidines and cyclobutanes.[211,212] In addition, Merck & Co reported a complementary method to access 3-pyridine-3-carboxylic acid oxetane **395** during the course of the research presented in this thesis (Scheme 6.29).[224] They showed that commercial nitrile **393**, can be directly deprotonated by KHMDS at low temperature, and can be added to fluoride **392**, affording intermediate **394** in 47% yield. Hydrolysis of **394** afforded the desired acid **395** in 90% yield.



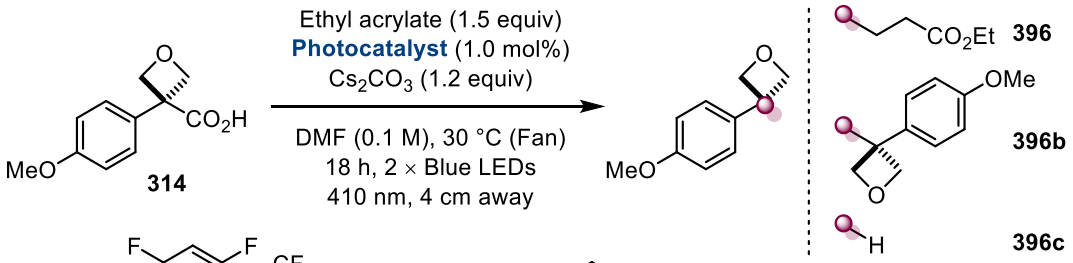
Scheme 6.29: Synthesis of 3-pyridine-3-carboxylic acid oxetane **395** by Merck & Co, through hydrolysis of carbonitrile **394**.[224]

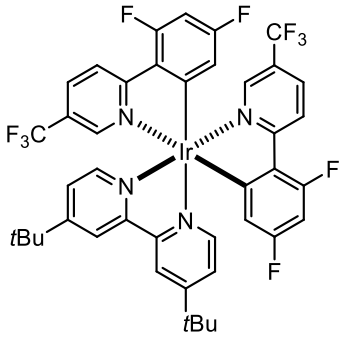
With a collection of 3-aryl-3-carboxylic acid oxetanes, azetidines and cyclobutanes in hand, their viability as radical precursors was then assessed.

6.4 New 3,3-Disubstituted Oxetanes and Azetidines *via* Radicals

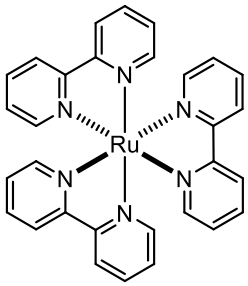
6.4.1 Decarboxylative Giese-Type Reaction: Initial Hit and Optimisation

As a proof of concept, the generation of a 3-aryl-3-oxetanyl radical was attempted, trapping with a Michael acceptor. Acid **314** was subjected to conditions inspired by MacMillan's investigations.[225] Photoredox-catalysed decarboxylative Giese reactions often require the alkene to be the limiting reagent, to prevent polymerisation reactions. However, 3-aryl-3-carboxylic acid oxetanes are more valuable compared to commercial alkenes. Therefore the reaction was first tested using acid **314** as the limiting reagent with 1.5 equivalents of ethyl acrylate (Table 6.3). Using Ir **257** in combination with Cs_2CO_3 in DMF using two LEDs lamps (410 nm), gave the desired product **396** in 47% yield (entry 1).

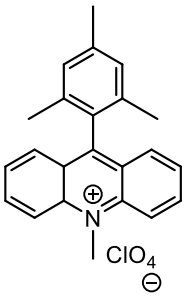




Ir[(dFCF$_3$ppy)$_2$(dtbbpy)]PF$_6$[a]
257



Ru(bpy)$_3$(PF$_6$)$_2$[a]
397



Mes-Acr$^+$
398

Entry	Photocatalyst	Yield (%)[b]		
		396	**396b**	**396c**
1	Ir **257**	47	6	3
2	Ru **397**	4	2	0
3	Mes-Acr$^+$ **398**	0	0	0

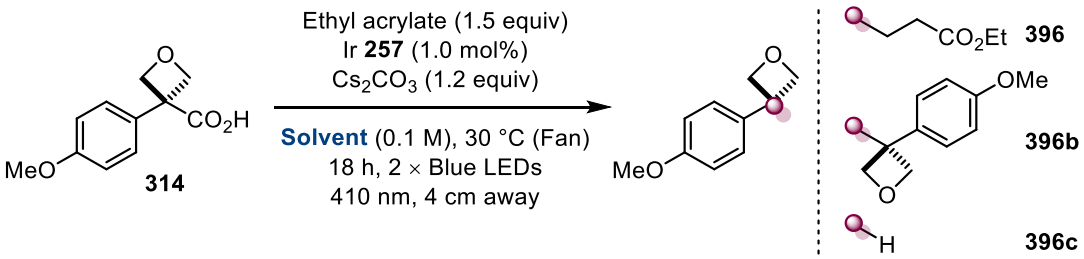
Table 6.3: Catalyst screen for the photoredox-catalysed decarboxylative Giese reaction of acid **314**. [a] PF_6 omitted in the structure for clarity. [b] Yields calculated by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as the internal standard.

Interestingly, bis-oxetane **396b** was also produced in 6% yield in the reaction, which likely formed from dimerization of the radical intermediate. Finally, oxetane **396c** was also observed in 3% yield. Ruthenium photocatalyst **397** and organocatalyst **398** were also tested, but these only resulted in poor yield or no product (entries 2 and 3).

A significant loss of ~30% between isolated and calculated yields was then observed when the product was isolated after flash column chromatography. The oxetane methylene protons (CH_2), as well as the alkane sets of methylene protons (CH_2) were found to be the slowest relaxing signals in product **396** compared to the internal standard.[h] Increasing the relaxation time to 25 s improved the calculated NMR yields accuracy with an average of 5% to 15% reduction compared to yields obtained with 1 s delay (see Appendix, Table 10.6). This disparity was found consistent throughout the following experiments. The stability of oxetane **396** through work up procedures and on different stationary phases was also investigated (see Appendix, Table 10.7). Treating the crude mixture with an aqueous work up procedure or a filtration through celite prior to ^{1}H NMR spectroscopy, resulted in more accurate calculated yield. It was proposed that an impurity present in the crude reaction mixture may affect the signals of **396** in the ^{1}H NMR spectrum. Finally the yield was not affected by stationary phases including silica, basified silica and alumina IV, and florasil, which shows the stability of oxetane **396**. Taken together, these experiments showed the role that the work up procedure and longer relaxing time play on the accuracy of the NMR yield calculation. Therefore, the yields throughout the early optimisation tables (Tables 6.3–6.6, and Tables 6.8–6.10) are approximate and are presented only to provide comparisons of the conditions, unless 25 s delay was used for ^{1}H NMR spectroscopy or isolated yields are reported.

Various solvents were then screened (Table 6.4). Replacing DMF with MeCN nearly halved the yield to 27% of oxetane **396** (entry 2). 1,4-Dioxane gave a similar yield of **396** but doubled the yield of dimer **396b** (entry 3). No desired product was observed when the reaction was run in methanol, and multiple unidentified side products were formed instead (entry 4). Acetone and EtOAc both yielded **396** but in lower yield (entries 5 and 6). DMF was chosen to continue the optimisation giving oxetane **396** in high yield while limiting side products.

[h] T_1 measured by NMR spectroscopist Pete Haycock. T_1 for oxetane **396**'s CH_2 is 5 seconds.

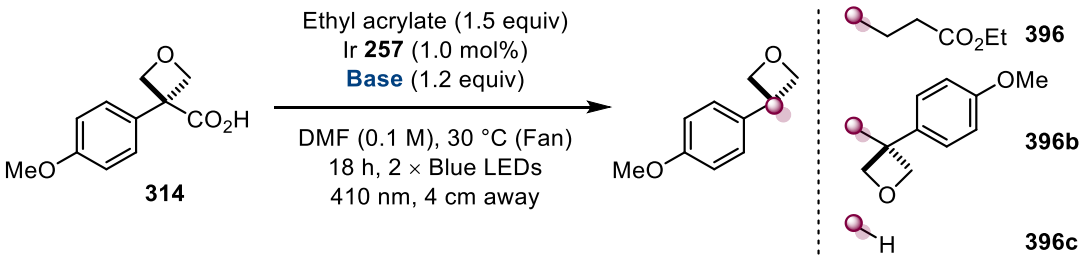


Entry	Solvent	Yield (%)[a]		
		396	396b	396c
1	DMF	47	6	3
2	MeCN	27	6	traces
3	Dioxane	51	12	traces
4	MeOH	0	0	0
5	Acetone	37	15	traces
6	EtOAc	12	5	6

Table 6.4: Solvent screen for the photoredox-catalysed decarboxylative Giese reaction of acid **314**. [a] Yields calculated by ^{1}H NMR spectroscopy, with 1 s delay, using 1,3,5-trimethoxybenzene as the internal standard.

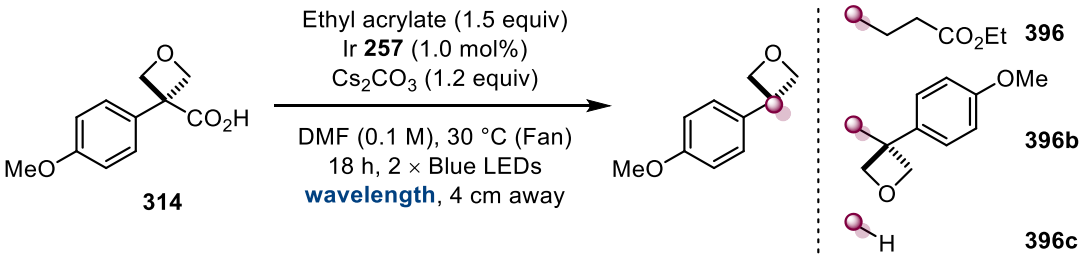
Different bases were then examined (Table 6.5). All the bases tested were successful under the reaction conditions giving product **396** in 41% to 50% yields. The possibility to use an organic base such as DBU in the reaction, opens opportunity to apply this reaction to flow chemistry. However, the reaction with Cs_2CO_3 was the cleanest among the other bases which makes the purification easier. Therefore the reaction was further investigated with this base.

The effect of the wavelength on the reaction was next studied (Table 6.6). Using 390 nm lamps instead of 410 nm resulted in a similar yield of oxetane **396**, but increased the amount of dimer **396b** formed (entry 2). When 467 nm lamps were used, an important rise in yield of **396** was observed while limiting the amount of side products (entry 3).



Entry	Base	Yield (%)[a]		
		396	396b	396c
1	Cs_2CO_3	47	6	3
2	K_2CO_3	48	6	7
3	Na_2CO_3	41	8	7
4	K_2HPO_4	43	11	14
5	DBU	50	7	8

Table 6.5: Base screen for the photoredox-catalysed decarboxylative Giese reaction of acid **314**. [a] Yields calculated by ^{1}H NMR spectroscopy, with 1 s delay, using 1,3,5-trimethoxybenzene as the internal standard.



Entry	Wavelength (nm)	Yield (%)[a]		
		396	396b	396c
1	410	47	6	3
2	390	53	13	5
3	467	65 (60)[b]	5	4

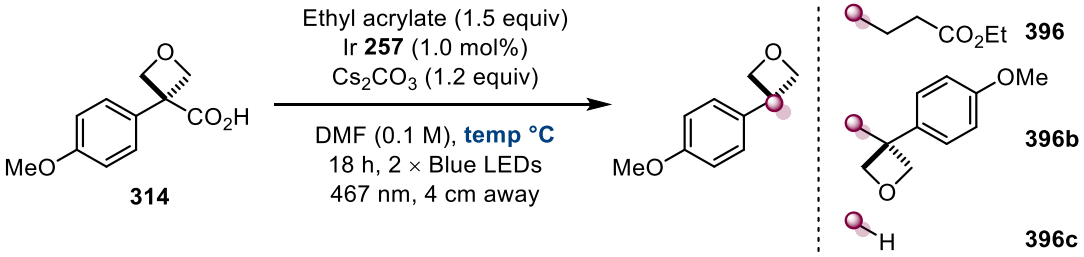
Table 6.6: LEDs wavelength screen for the photoredox-catalysed decarboxylative Giese reaction of acid **314**. [a] Yields calculated by ^{1}H NMR spectroscopy, with 1 s delay, using 1,3,5-trimethoxybenzene as the internal standard. [b] Yields calculated by ^{1}H NMR spectroscopy with 25 s delay.

Although a fan was used to keep the temperature near room temperature, the lamps generate heat differently according to the wavelength. In order to understand whether the rise in yield observed previously is indeed due to the change in wavelength, the temperature of the reaction conditions was measured (Table 6.7). A reaction vial was filled with the amount of DMF required for the reaction and a thermometer was introduced through a sealed cap. The vial was then irradiated with two lamps using the same set up as for the reaction. In presence of a fan, both set up with lamps at 410 nm and 467 nm wavelength resulted in similar 30 °C and 28 °C (entries 1 and 2). This indicates that the difference in yield can be attributed to the change of wavelength. Interestingly, when no fan was used, a sharp difference of 12 °C in temperature is observed between the two wavelengths (entries 3 and 4).

Entry	Wavelength (nm)	Fan (cm away from the vial)	Temperature in the vial (°C)
1	410	12	30
2	467	12	28
3	410	-	48
4	467	-	36

Table 6.7: Measurement of the temperature in the reaction vial filled with DMF, in presence of different wavelength LEDs and with or without fan. The temperature was reported after 30 min of irradiation.

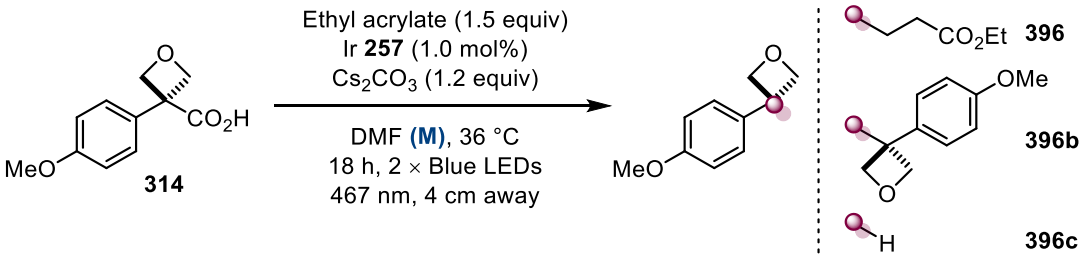
The effect of the temperature on the reaction was next investigated. A temperature of 36 °C was reached when running the reaction without fan using 467 nm LEDs, which led to an increased yield of oxetane **396** to 81% (Table 6.8).



Entry	Temperature (°C)	Yield (%)[a]		
		396	396b	396c
1	28	65	5	4
2	36	81	5	5

Table 6.8: Effect of the temperature on the photoredox-catalysed decarboxylative Giese reaction of acid **314**. [a] Yields calculated by ^{1}H NMR spectroscopy, with 1 s delay, using 1,3,5-trimethoxybenzene as the internal standard.

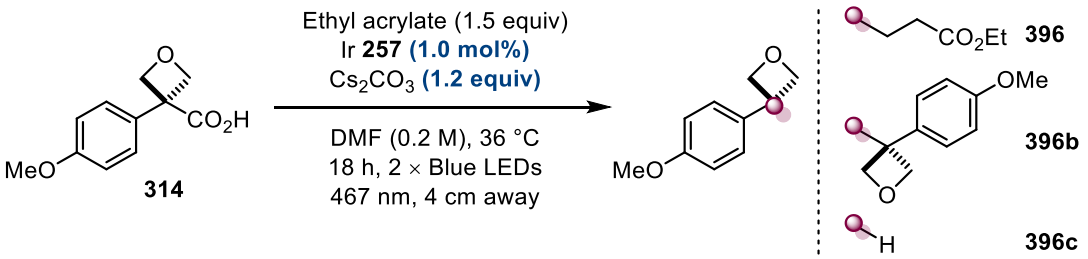
Attempts to reduce the amount of solvent were then undertaken (Table 6.9). Pleasingly, despite having a heterogenous reaction, the concentration was elevated to 0.2 M without adversely affecting the yield (entry 2). Increasing the concentration further resulted in a slightly lower yield but still afforded product **396** in 73% yield (entry 3).



Entry	Concentration (M)	Yield (%)[a]		
		396	396b	396c
1	0.1	81	5	5
2	0.2	81 (70)[b]	6	6
3	0.25	73 (62)[b]	6	7

Table 6.9: Effect of the concentration on the photoredox-catalysed decarboxylative Giese reaction of acid **314**. [a] Yields calculated by ^{1}H NMR spectroscopy, with 1 s delay, using 1,3,5-trimethoxybenzene as the internal standard. [b] Yields calculated by ^{1}H NMR spectroscopy with 25 s delay.

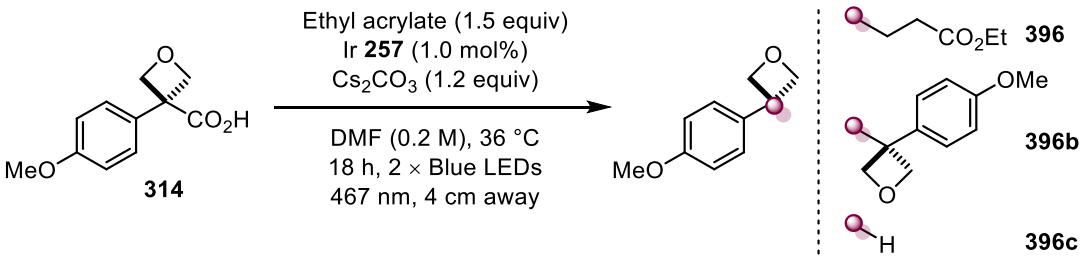
The equivalents of base can be reduced to 0.7 without detrimental effect on the reaction, and oxetane **396** was isolated in 58% yield (entry 2, Table 6.10). Lowering the photocatalyst loading to 0.5 mol% resulted in a similar outcome (entry 3). Combining both conditions gave 74% calculated yield of desired product **396**, but a lower isolated yield was obtained (entry 4). The best two set of conditions, using 1 and 0.5 mol% of photocatalyst were then repeated (entries 5 to 7). After an aqueous work up, the yield was calculated with 25 s delay for the ^{1}H NMR spectroscopy. Although the calculated yield varied between 58% to 70% between the two conditions, 57% isolated yield of oxetane **396** was obtained in all cases, showing the reproducibility of the method. In addition, the reaction run with 0.5 mol% of photocatalyst generated more impurities which made the purification slightly more difficult.



Entry	Change	Yield (%)[a]			
		396 (1 s delay)	396 (25 s delay)[b]	396b	396c
1	None	81	-	6	6
2	Cs_2CO_3 (0.7 equiv)	78 (58)	67	6	5
3	Ir **257** (0.5 mol%)	88	-	5	0
4	Cs_2CO_3 (0.7 equiv) Ir **257** (0.5 mol%)	74 (42)	64	4	3
5	Entry 3, with aqueous work up	-	64 (57)	n.d	n.d
6	Repeat entry 3, with aqueous work up	-	70 (57)	n.d	n.d
7	Entry 1, with aqueous work up	64	58 (57)	n.d	n.d

Table 6.10: Effect of the catalyst loading and equivalents of base on the photoredox-catalysed decarboxylative Giese reaction of acid **314**. [a] Yields calculated by ^{1}H NMR spectroscopy, with 1 s delay, using 1,3,5-trimethoxybenzene as the internal standard. [b] Yields calculated by ^{1}H NMR spectroscopy with 25 s delay. Yields in brackets are isolated.

The quality of the alkene was found to play a crucial role in the reproducibility and the yield of the reaction. When the reaction was repeated using 1 mol% of Ir **257** with a formerly distilled ethyl acrylate, only 47% isolated yield of product **396** was produced (entry 1, Table 6.11). Repeating this reaction with the same batch of alkene resulted in a nearly 10% drop in yield (entry 2). The ethyl acrylate being unstable under air and light can produce impurities which might dramatically affect the reaction. Taking the utmost care, ensuring the alkene was freshly distilled under argon and stored under constant cooled, dry, argon atmosphere, increased the yield by 10% (entry 3).

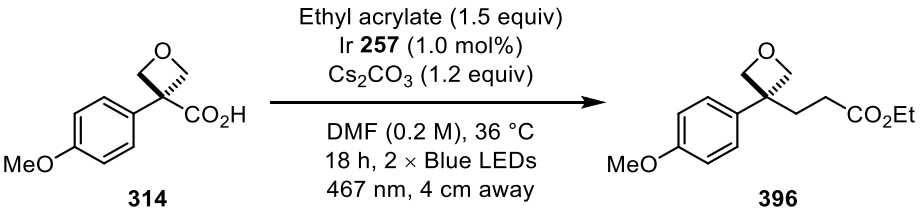


Entry	Change	Yield 396 (%)[a] 1 s delay	Yield 396 (%)[a] 25 s delay
1	Alkene distilled a month prior to the reaction. Alkene stored in a vial under argon and under dark, at 0 °C	52	47 (47)
2	Repeat of entry 1	45	41 (39)
3	Alkene freshly distilled prior to the reaction. Alkene stored in a sealed flask under argon and under dark at –20 °C.	64	58 (57)
4[b]	First repeat of entry 3	64	58 (58)
5[c]	Second repeat of entry 3	70	64
6	Reaction not degassed prior irradiation	44	44
7[d]	Reaction performed at 60 °C	69	64

Table 6.11: Effect of the quality of the alkene on the reproducibility of the photoredox-catalysed decarboxylative Giese reaction of acid **314**. [a] Yields calculated by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as the internal standard. Yields in brackets are isolated. [b] Repeated at 5 days interval. [c] Repeated at two weeks intervals. [d] Vial covered with aluminium and temperature measured in DMF prior to reaction.

This result was repeated both after 5 days (entry 4) and two weeks (entry 5) intervals affording reproducible yields. Running the reaction without exclusion of the oxygen prior to the reaction, led to a significant loss in yield (entry 6). This suggests that the oxygen present in the ethyl acrylate could have been the reason for the low yields in entries 1 and 2. Increasing the temperature to 60 °C did not improve the reaction further (entry 7). Importantly, performing the reaction in the absence of light, photocatalyst **257** or base led to no product formation (Table 6.12). Finally, the acid starting material **314** can be recovered in 79% yield, attesting to its stability under photoredox-catalysed conditions. The small loss of material was attributed to

the high solubility of the acid in the aqueous phase during the work up. With the optimum conditions in hand, the scope of the reaction was next explored.



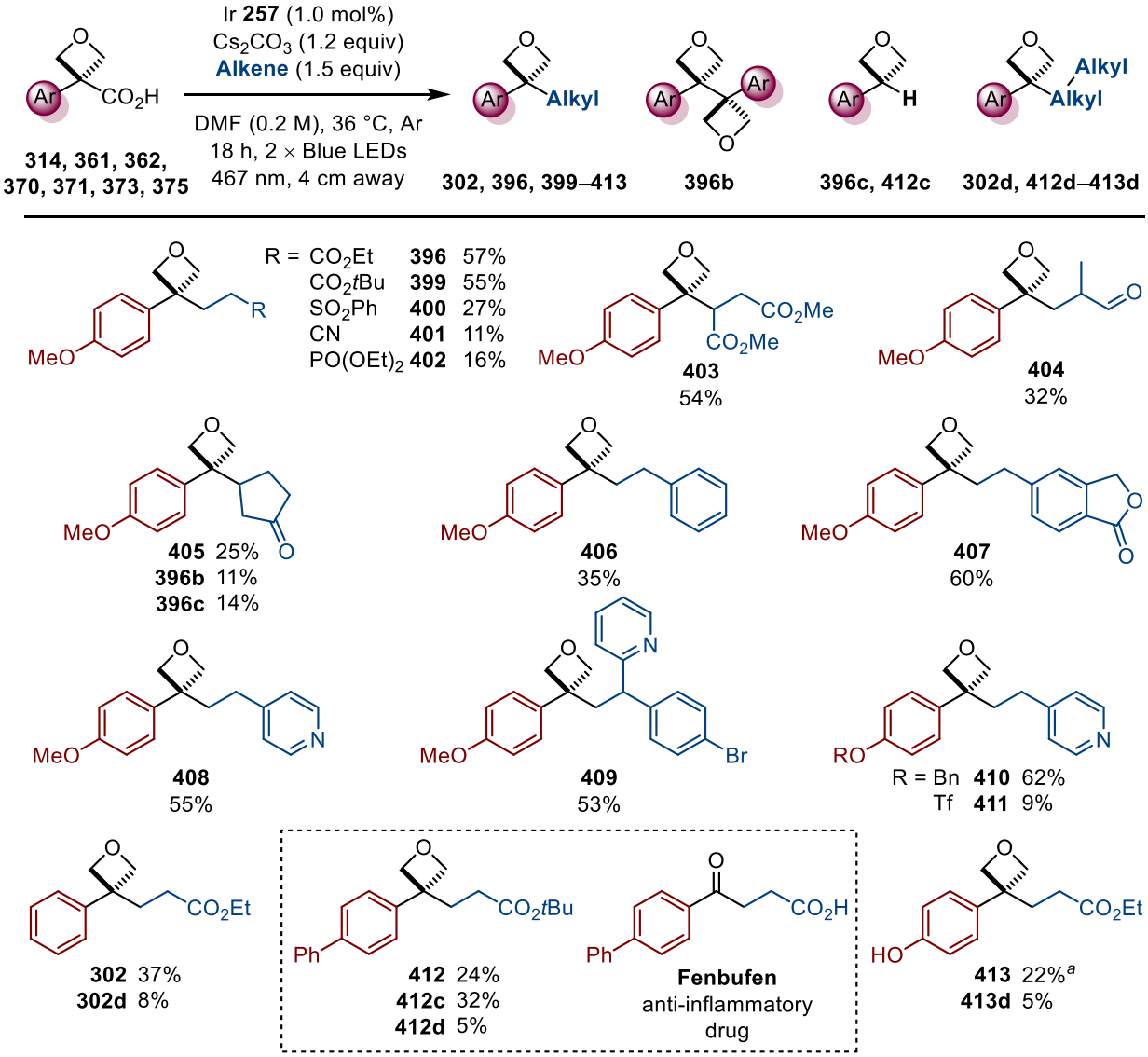
314 **396**

Entry	Change	Yield 396 (%)[a]
1	No light	0
2	No photocatalyst **257**	0
3	No base	0 (79% RSM)

Table 6.12: Control reactions for the synthesis of **396**. [a] Yields calculated by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as the internal standard, and 25 s delay.

6.4.2 Scope of 3-Aryl-3-Alkyl-Oxetanes and Azetidines

A variety of alkenes could be used in this reaction (Scheme 6.30). The reaction with *t*Bu-acrylate gave oxetane **399** in 55% yield. Phenyl vinylsulfone, acrylonitrile and diethyl vinylphosphonate were also successful Michael acceptors under the reaction conditions, although affording product **400**–**402** in lower yield. Additional substituents on the alkenes did not affect adversely the reaction despite increasing the steric bulk. Dimethyl maleate and α,β–unsaturated aldehyde afforded **403** and **404** in 54% and 32% yields respectively. Interestingly, a cyclic ketone was successfully incorporated (**405**) using cyclopentenone. In addition, 11% of dimer **396b** alongside 14% of oxetane **396c** were formed. This can be attributed to a slower radical addition onto this hindered and less electrophilic alkene, which favours dimerization and unproductive side reactions. Pleasingly, unactivated styrene and activated derivatives gave 32% and 60% yields of oxetanes **406** and **407** without side product formation. In addition, pyridines could be incorporated using vinylpyridines, which produced products **408** and **409** in 55% and 53% yield.

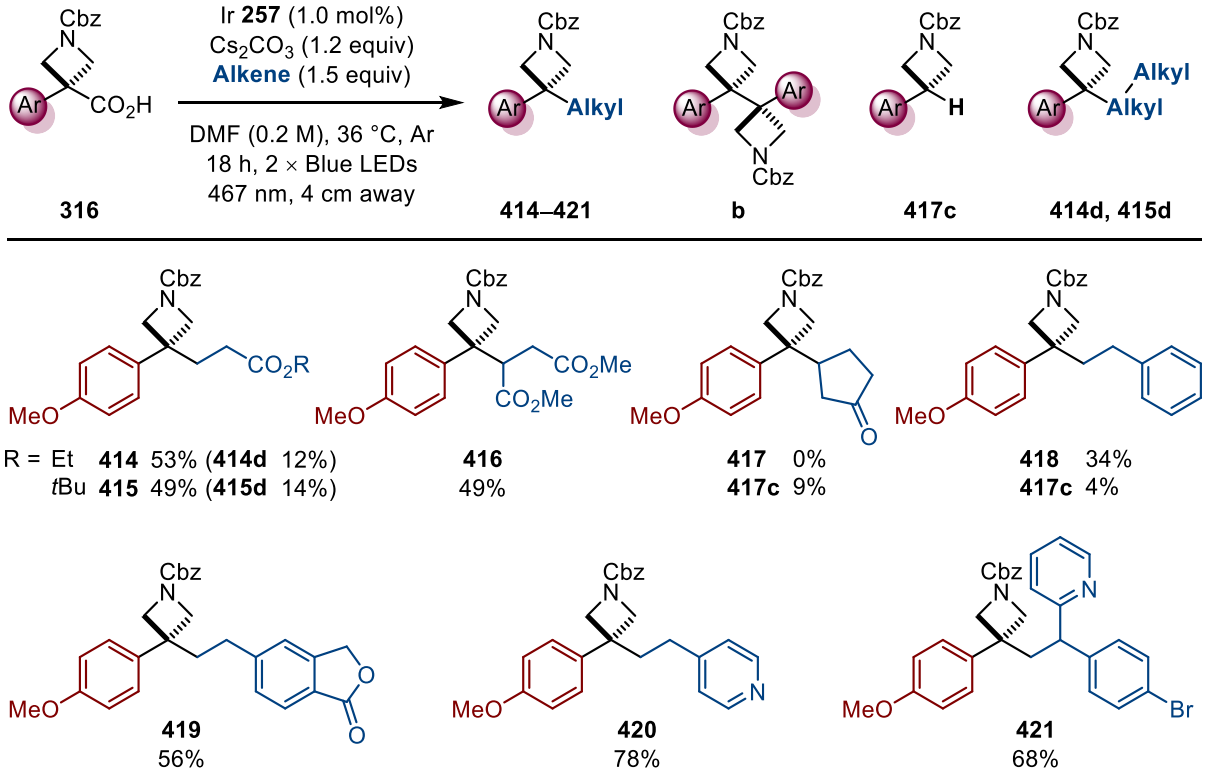


Scheme 6.30: Scope of the photoredox-catalysed decarboxylative Giese reaction of 3-aryl-3-carboxylic acid oxetanes and alkenes. General conditions: 0.20 mmol of acid used. [a] TIPS-protected acid **361** used as starting material.

The scope of oxetane acids was then examined (Scheme 6.30). A Bn-protecting group was well tolerated under the reaction conditions with vinylpyridine as the Michael acceptor, giving oxetane **410** in 62% yield. This offers the possibility to further elaborate this 3,3-disubstituted oxetane, through deprotection and functionalisation of the phenolic OH. Pleasingly, the presence of an electron-rich aromatic was not necessary for the radical formation. Indeed, electron-withdrawing OTf was tolerated and successfully produced oxetane **411**, although in only 9% yield. In addition, both phenyl and bi-phenyl substituted acids **373** and **375** were productive radical precursors, giving oxetanes **302** and **412** in 37% and 24% yields respectively. Oxetane **412** is now only one step away from the oxetane-containing analogue of anti-inflammatory drug Fenbufen. Intriguingly, these were the first two examples where a second alkene addition occurred, forming **302d** and **412d** in 8% and 5% yields. The reaction

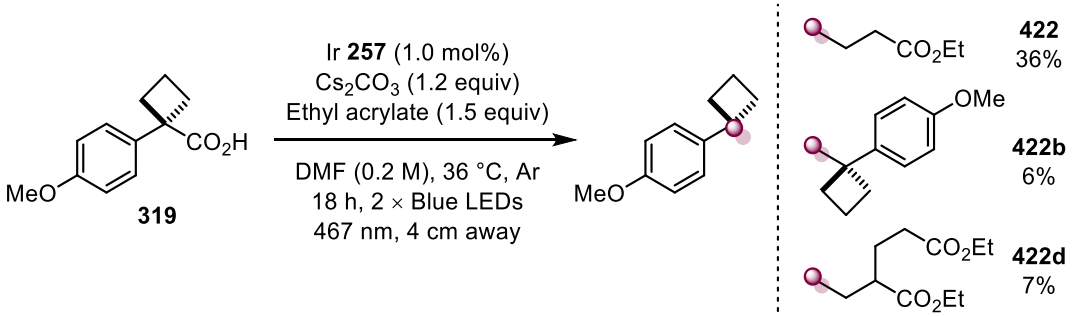
with bi-phenyl substituted acid **375** also produced oxetane **412c** as the major product. Finally, TIPS protecting group was unexpectedly removed when subjecting acid **361** to the reaction conditions, yielding 22% of phenol **413**. This was a surprise, as phenols are easily oxidised and are usually incompatible under these conditions. 3-Phenol-3-carboxylic acid oxetane will be also tested in the future as a precursor.

Azetidine acid **316** was then subjected to the reaction conditions developed for the oxetane ring (Scheme 6.31). Pleasingly, the 3-aryl-3-azetinyl radical can also be formed under these conditions, and can react with ethyl- and *t*Bu-acrylates, as well as methyl maleate to produce azetidines **414**, **415** and **416** in 49% to 53% yields. Interestingly, more di-addition of alkenes occurred in the case of azetidines, and 12% of **414d** and 14% of **415d** were also formed. The reaction with azetidinyl radicals seemed to be more sensitive to sterics than the oxetanyl radical, as cyclopentanone was unsuccessful and only produced 9% of azetidine **417c**. Styrenes can also be used as Michael acceptors with azetidine acid precursors, to give azetidines **418** and **419** in 34% and 56% yields respectively. Finally, the reaction of azetidine acid **316** with vinylpyridines was higher yielding than oxetane **314**, affording 78% and 68% yields of **420** and **421**.



Scheme 6.31: Scope of the photoredox-catalysed decarboxylative Giese reaction of 3-aryl-3-carboxylic acid azetidine **316** and alkenes. General conditions: 0.20 mmol of acid used.

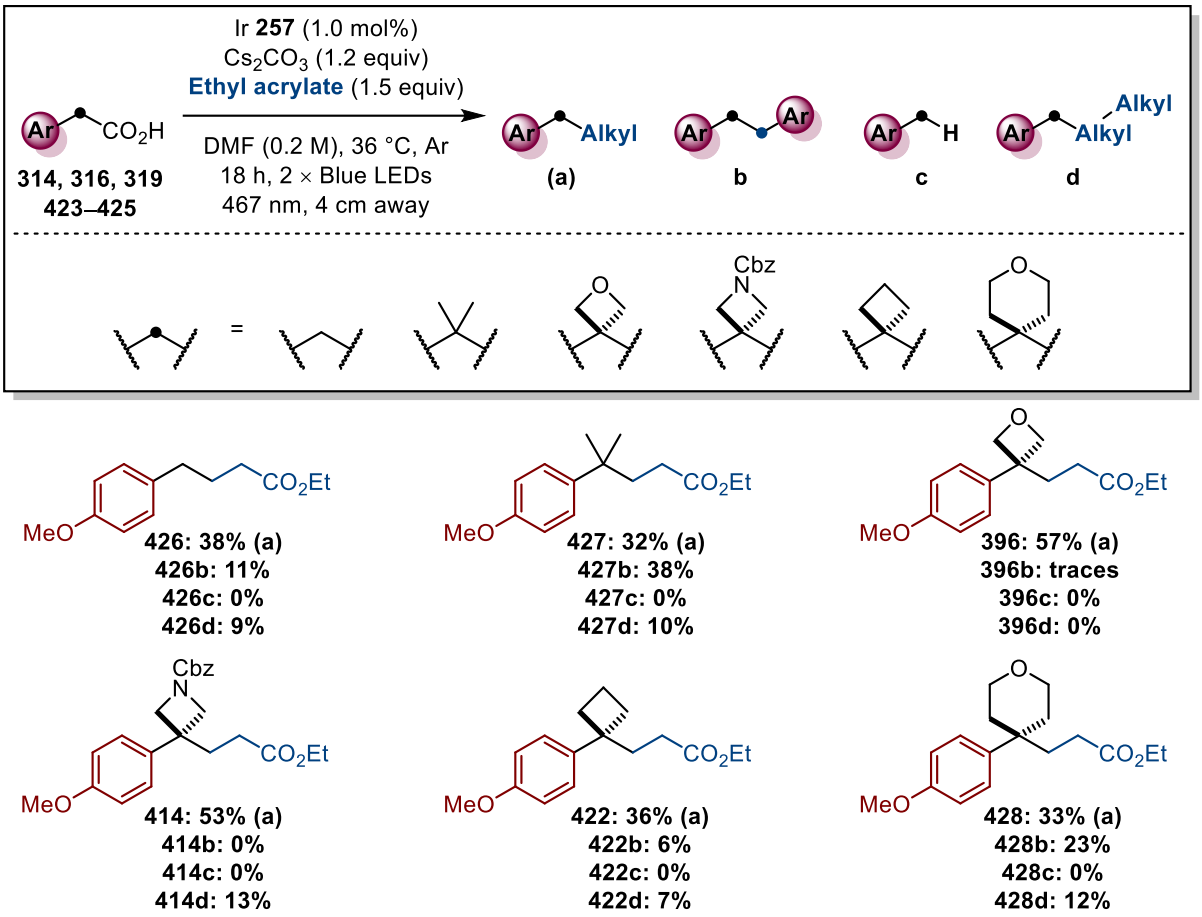
1-Aryl-1-cyclobutyl radicals were anticipated to be more easily formed than oxetanyl and azetidinyl radicals due to higher stabilisation through mesomery, hyperconjugation and σCH–p interaction. Subjecting cyclobutane acid **319** to the same reaction conditions, afforded 36% of product **422**, along with 6% of dimer **422b** and 7% of di-alkylated product **422d**. The enhanced reactivity of the oxetane and azetidine rings compared to cyclobutane was quite surprising, and this was further studied in the next section.



Scheme 6.32: Photoredox-catalysed decarboxylative Giese reaction of 3-aryl-3-carboxylic acid cyclobutane **319** with ethyl acrylate. General conditions: 0.20 mmol of acid used.

6.4.3 The Enhanced Reactivity of Oxetanes and Azetidines

The reactivity of the oxetane and azetidine rings was compared with methylene, *gem*-dimethyl and THP (Scheme 6.33). The reaction conditions developed for oxetanes and azetidines were applied to these linkers, reacting carboxylic acids **423**–**425** with ethyl acrylate. The product distribution for each linker is summarised in Figure 6.7, with product **a** represented in blue, dimers **b** in orange and di-alkylated products **d** in grey. Interestingly, product **c** was not observed for any of the linkers, while the three other products were formed in different ratios. Overall, higher yields for products **a** (>53%) and cleaner reaction were obtained for the oxetane and azetidine rings compared to all the other linkers. On average, 35% of products **a** were obtained with methylene, *gem*-dimethyl, cyclobutane and THP acids. Interestingly, none or a very low amount of dimer **b** is obtained for the 4-membered rings compared to the other linkers. The strain in such 4-membered rings seems to limit the formation of dimer **b**. Methylene, *gem*-dimethyl and THP radical centres do not suffer from such strain and could adopt a geometry that enhances the stabilisation of the radical intermediate through adjacent π system and hyperconjugation. This could result in longer radical life time and favour dimerisation.



Scheme 6.33: Photoredox-catalysed decarboxylative Giese reaction of acids **314**, **316**, **319**, **423–425** with ethyl acrylate. Yields are isolated.

On the other hand, the higher yields of products **a** for oxetane and azetidine cannot be explained by the strain of the ring alone, as cyclobutane gave a lower yield. The proximity of the oxygen and nitrogen atoms to the radical centre, changes the electronics *via* polarisation of the bonds. This may decrease the stability of the oxetanyl and azetidinyl radicals and increase their reactivity towards product **a** formation. To confirm this hypothesis, the reaction should be carried out on THF and pyrrolidine rings, which should give an outcome for product **a** similar to the oxetane and azetidine.

Finally, di-alkylation occurred with all linkers apart from oxetane, which is not yet well-understood. However, the formation of product **d** seems to be influenced by both the linkers and the pre-installed aromatic (Scheme 6.30 and 6.33).

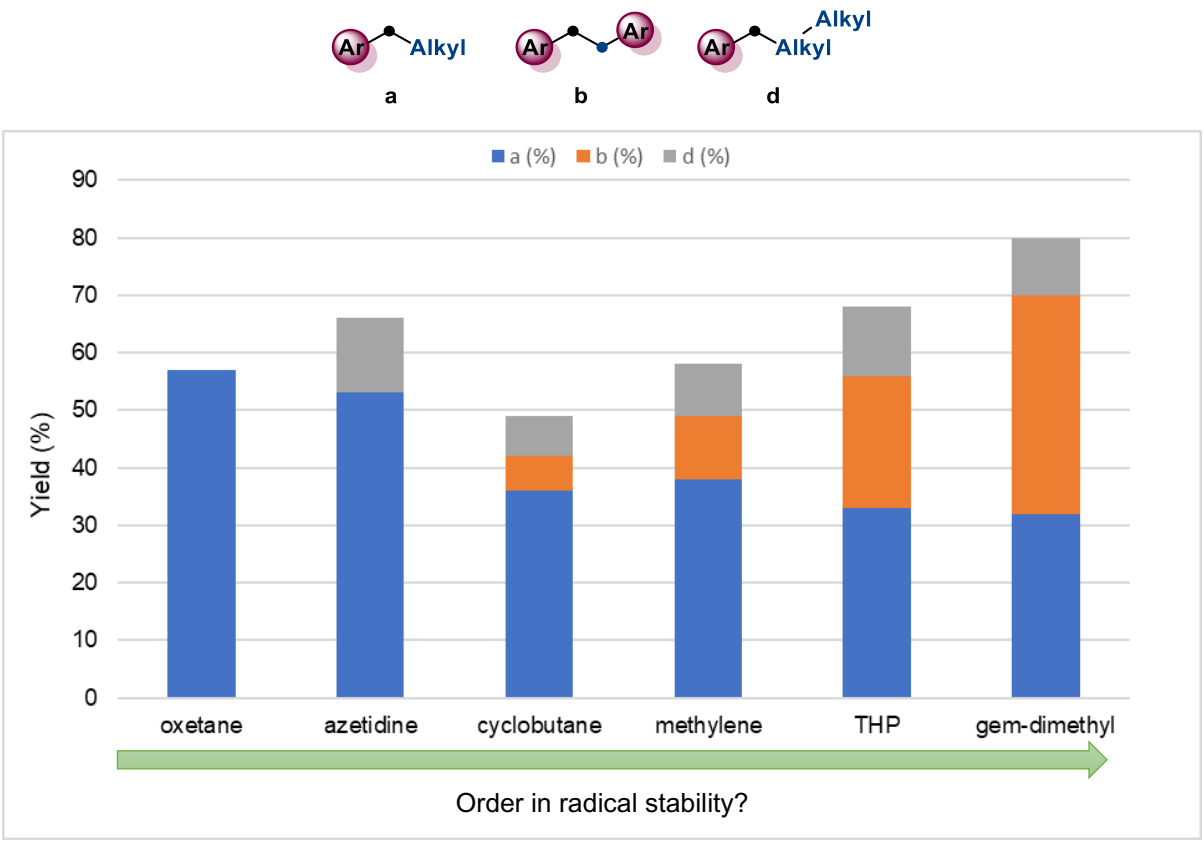
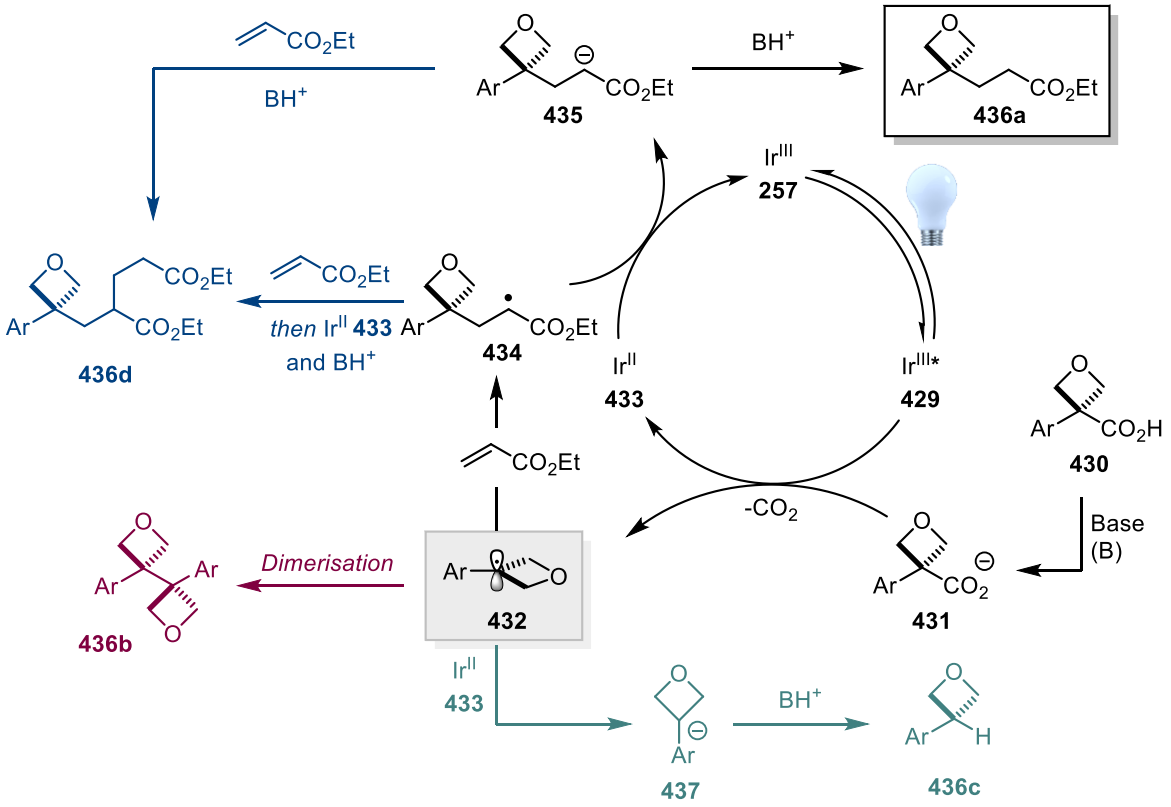


Figure 6.7: Product distribution for the photoredox-catalysed decarboxylative Giese reaction of acids **314**, **316**, **319**, **423–425** with ethyl acrylate.

6.4.4 Proposed Mechanism

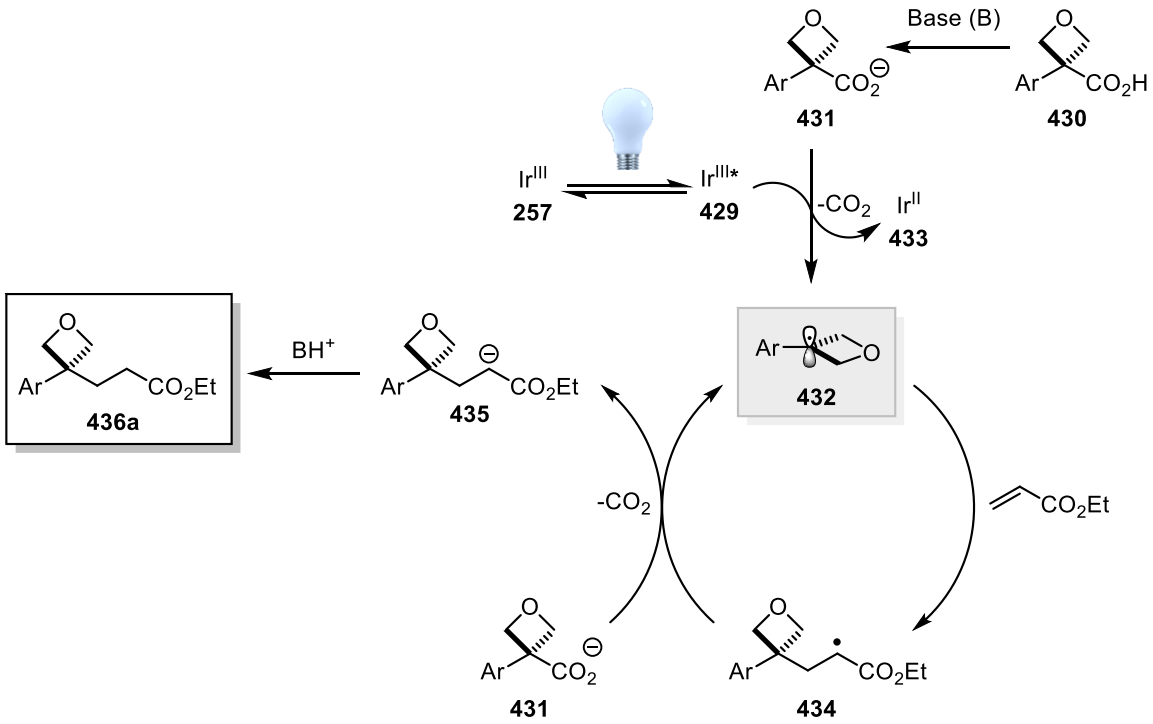
The mechanism of the photoredox-catalysed decarboxylative Giese reaction of carboxylic acids has been well documented.[225] Based on MacMillan's mechanism proposal, photocatalyst **257** can be excited by the blue light to give a stronger oxidant Ir^{III*} **429** species (Scheme 6.34). Deprotonation of acid **430**, SET oxidation with Ir^{III*} **429** and decarboxylation produces CO_2, oxetanyl radical **432** and the reduced Ir^{II} **433** complex. Radical **432** can then undergo conjugate addition with ethyl acrylate to form alkyl radical **434**. Reduction of intermediate **434** by SET with Ir^{II} **433**, followed by protonation of the corresponding carbanion **435** delivers the desired oxetane **436a** and regenerates photocatalyst **257**.



Scheme 6.34: Proposed mechanism for the photoredox-catalysed decarboxylative Giese reaction of acids **430** with ethyl acrylate.

If the pathway leading to product **436a** is slow, radical **432** can dimerise to produce **436b**. In addition, radical **434** and carbanion **435** can both react with a second equivalent of ethyl acrylate to give product **436d** after reduction and/or protonation. Although it is not clear how oxetane **436c** is formed, Ir^{II} **433** might be a sufficiently powerful reductant to undergo SET with radical **432** and generate carbanion **437**. Subsequent protonation would afford oxetane **436c**. Alternatively, radical **432** could abstract a hydrogen atom from DMF.

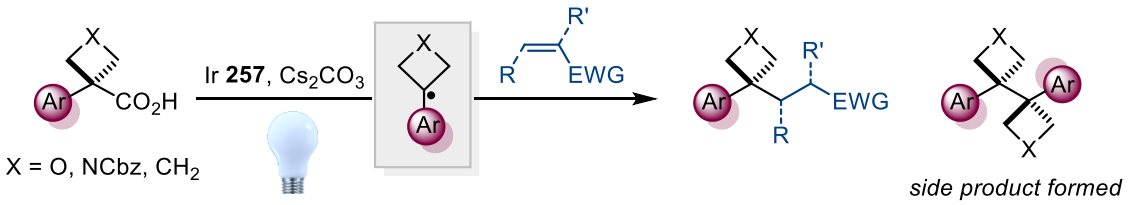
A second mechanism for the formation of oxetane **436a** can also be proposed involving a radical chain process (Scheme 6.35). In this case, the photocatalyst **257** would act as a radical initiator to generate radical **432** from carboxylate **431**. Conjugate addition of **432** to ethyl acrylate can then produce alkyl radical **434**. SET between carboxylate **431** and radical **434** would regenerate the initial radical **432** and form carbanion **435**. Product **436a** is then obtained after protonation. To discriminate between the two mechanisms, light/dark experiments and quantum yield measurements should be performed.[226]



Scheme 6.35: Proposed radical chain mechanism for the decarboxylative Giese reaction of acids **430** with ethyl acrylate.

6.4.5 Conclusion

The synthesis of new 3-aryl-3-alkyl oxetanes and azetidines has been achieved through a photoredox-catalysed decarboxylative Giese reaction (Scheme 6.36). This investigation showed that 3-aryl-3-oxetanyl and azetidinyl radicals can be formed in situ and used as synthetic intermediates. These radicals were generated from 3-aryl-3-carboxylic acid oxetanes and azetidines as precursors using an iridium photocatalyst and visible light. Due to the acid substituent, the radical formation was selective for the 3-position in the 4-membered ring over the favoured α-position to the heteroatom, with no 2-substituted oxetanes and azetidines formed. The choice of photocatalyst, wavelength, and quality of the alkenes used were key parameters to achieve high yields of products. Importantly, the valuable acid precursor can be recovered after the reaction without dramatic loss. It could also be used as the limiting reagent, without important formation of di-alkylated side product as usually observed for this type of transformation when excess alkene is employed.



Scheme 6.36: Synthesis of 3-aryl-3-alkyl oxetanes and azetidines through photoredox-catalysed decarboxylative Giese reaction.

A variety of cyclic and acyclic alkenes were used in this reaction, containing functionalities such as CN, sulfone, phosphonate, esters, ketones and aldehydes. Styrenes are usually low yielding substrates in Giese reactions, but proved to be suitable acceptors with both oxetanyl and azetidinyl radicals. Importantly, the presence of electron-rich aromatic group on the acid precursors is not essential for the radical to be formed. Thus, 3-aryl-3-alkyl oxetanes containing an unsubstituted phenyl, bi-phenyl or even phenyl-triflate, could be synthesised. This shows that the stability of 3-aryl-3-oxetanyl and azetidinyl radicals is greater than the corresponding carbocation species.

An interesting bis-oxetane side-product was also isolated in some cases. This likely resulted from the dimerisation of the radical intermediate. This bis-oxetane product is highly rich in sp^3 centres with increased 3-dimentional shape, and represents a new interesting motif for drug discovery programmes.

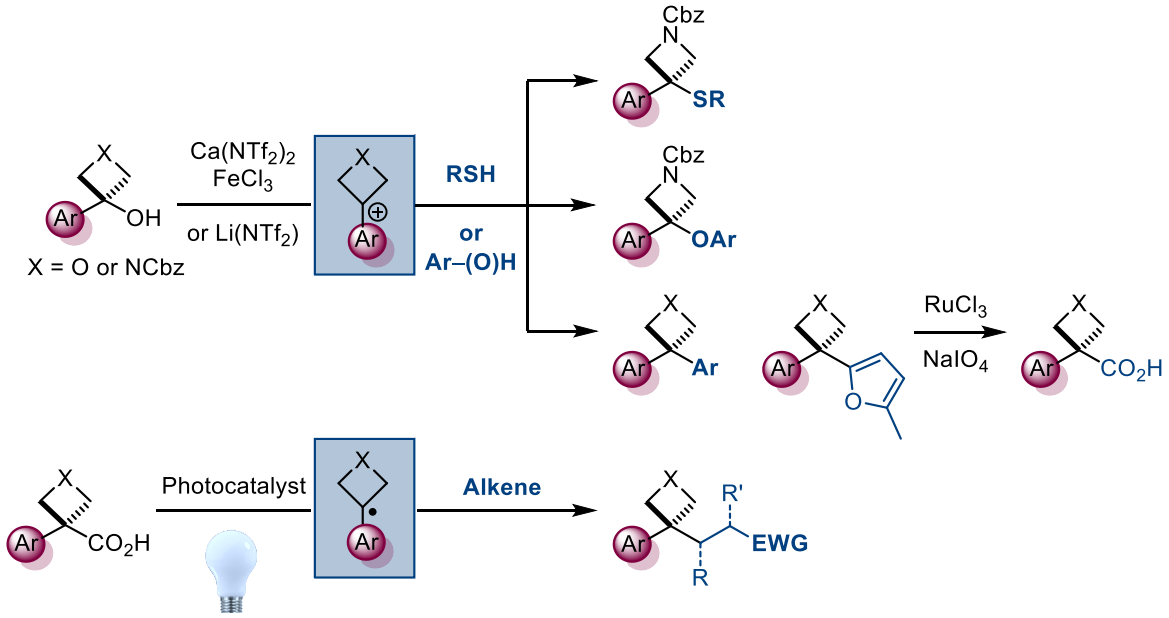
The methodology was also applied to cyclobutanes, though lower yield and more side products were obtained. A similar observation was made when the reaction was carried out with methylene, *gem*-dimethyl and THP carboxylic acid precursors. It was proposed that both the strain of the ring, and proximity of heteroatoms, prevent the oxetanyl and azetidinyl radicals following unproductive pathways. Computational studies should be undertaken to understand the enhanced reactivity observed for oxetane and azetidine rings in this reaction.

Now that the ability to form 3-aryl-3-oxetanyl and azetidinyl radicals has been demonstrated, the reactivity of these species with a variety of reagents will be investigated in order to access new 3,3-disubstituted oxetanes and azetidines. Minisci and cross–coupling reactions are of particular interest to synthesise 3,3-diaryloxetanes and azetidines containing pyridines which are inaccessible so far.

7. Conclusion and Future Work

3,3-Disubstituted oxetanes and azetidines are valuable motifs with attractive physicochemical properties and potential as replacement groups for liable functionalities. However, their incorporation and use in drug discovery programmes is currently undermined due to lack of synthetic methodologies. The development of robust methods to access such scaffolds is therefore highly desirable.

In this thesis, new divergent methods were developed to efficiently access a variety of novel 3,3-disubstituted oxetanes and azetidines. This was achieved through direct functionalisation on the intact ring through *in situ* generated oxetanyl and azetidinyl carbocations and radicals (Scheme 7.1). These intermediates were accessed from commercially available or readily accessible starting material, under catalytic and mild conditions. These strategies enable access to oxetanes and azetidines with new substitution patterns including: 3,3-diaryloxetanes and azetidines, 3-aryl-3-azetidine ethers, 3-arylsulfanyl azetidines, 3-aryl-3-carboxlic acid oxetanes and azetidines, as well as 3-aryl-3-alkyl oxetanes and azetidines. The relevance of these products for medicinal chemistry was also evaluated, through the measurement of their physicochemical properties.



Scheme 7.1: Overview of the synthesis of the new 3,3-disubstituted oxetanes and azetidines described in this thesis.

The potential of 3,3-diaryloxetanes as new motifs for drug discovery and new isosteres for diarylketones and 1,1-diarylalkanes was first evaluated. A matched molecular pair analysis of their physicochemical properties was performed. A total of 24 compounds divided in: 8 pairs of diarylketones and 3,3-diaryloxetanes; 6 pairs of 1,1-diarylalkanes and 3,3-diaryloxetanes; were designed to have desirable “drug-like” properties and were prepared in high yields. 3,3-

Diaryloxetanes were synthesised applying the lithium-catalysed Friedel–Crafts reaction previously developed by the Bull group. The physicochemical properties of these molecules was then measured by Pfizer. In this study, 3,3-diaryloxetanes exhibited high pH stability, low lipophilicity and metabolic degradation, acceptable cell permeability and no hERG inhibition issues. The replacement of diarylketones and 1,1-diarylalkanes with 3,3-diaryloxetanes resulted in similar or improved physicochemical properties, suggesting that these oxetanes would be suitable isosteres for incorporation in medicinal chemistry programmes. In addition, the preparation of four 3,3-diaryloxetane-containing drug analogues has been attempted. The physicochemical properties and ADMET parameters of the oxetane analogues and the parents molecules are currently being measured by Pfizer. This will allow further assessment of 3,3-diaryloxetanes as isosteres for benzophenones and 1,1-diarylalkanes in biologically active molecules.

With the promising results obtained on 3,3-diaryloxetanes, the synthesis of the aza–analogues: 3,3-diarylazetidines was investigated. These were prepared through *in situ* generation of an azetidinyl carbocation from readily prepared 3-arylazetidin-3-ols using an inexpensive and abundant calcium catalyst. Reaction with electron-rich phenols and heteroaromatics afforded new 3,3-diarylazetidines with excellent *para*-selectivity. Highly elaborated phenols were also used, demonstrating the possibility to apply this methodology to late-stage functionalisation. The azetidine ring was stable towards ring opening by adjacent phenolic OH, and 3,3-diarylazetidines formed through *ortho*-addition of phenol were also prepared. Interestingly, new 3-arylazetidin-3-ethers were selectively obtained when electron poor *para*-substituted phenols were used, which are also attractive motifs for medicinal chemistry. Importantly, the Cbz protecting group was crucial to the reactivity, potentially stabilising the azetidinyl carbocation *via* π–cation interaction. The Cbz protecting group could be easily removed under standard conditions, and medicinally relevant motifs were introduced through functionalisation of the nitrogen atoms or the phenol OH group.

Thiols were found to be suitable nucleophiles to react with azetidinyl carbocations formed from azetidinols using an iron catalyst. A range of new 3-aryl-3-sulfanyl azetidines were prepared through this methodology. The Cbz protecting group could not be removed using traditional methods, but mild and selective deprotection conditions were developed using Me_3SiI and MeOH at low temperature. Derivatisation of these scaffolds through amide bond formation, S_NAr, oxidations and cross–coupling reactions demonstrated their stability and produced new medicinally relevant molecules. This method was also extended to the preparation of piperidine and pyrrolidine sulfides in high yields.

The stabilisation of the azetidinyl and oxetanyl carbocations required so far highly electron-rich pre-installed aromatics on the alcohol precursors. Incorporation of simple phenyl and

aromatics bearing halides, EWG or *meta*-substitution, was therefore a limitation in the synthesis of 3,3-diaryloxetanes and azetidines as well as oxetane and azetidine sulfides. The stability of such carbocations was enhanced when HFIP was employed as solvent. This enabled the generation of oxetanyl carbocations with an iron catalyst, from oxetanol bearing a phenyl, or aromatics with EDGs to EWGs in *para* and *meta*-position. Reactions with 2,6-dimethylphenol, anisoles and non-activated aromatics afforded new 3,3-diaryloxetanes inaccessible with previous methodologies. The usefulness of the method was demonstrated with the synthesis of oxetane-containing drug analogues, and their physicochemical properties are currently being measured at Pfizer.

Interestingly, 2,3-diarylpropanals were also formed in the reaction and represent interesting synthetic intermediates. Some of these examples were formed through deprotonation of the carbocation into oxetene species, followed by rearrangement to α,β-unsaturated aldehyde and 1,4-addition of aromatics. These represent rare examples of catalytic Friedel–Crafts alkylation of non-activated aromatics with α,β-unsaturated aldehyde, which will be further developed in the future.

Unfortunately, highly electron-poor aromatics and pyridines could not be incorporated into these oxetane and azetidines motifs, using the methodologies involving carbocations. The synthesis of oxetanes and azetidines with such substitution patterns was envisaged through the generation and reaction of 3-aryl-3-oxetanyl and azetidinyl radicals instead.

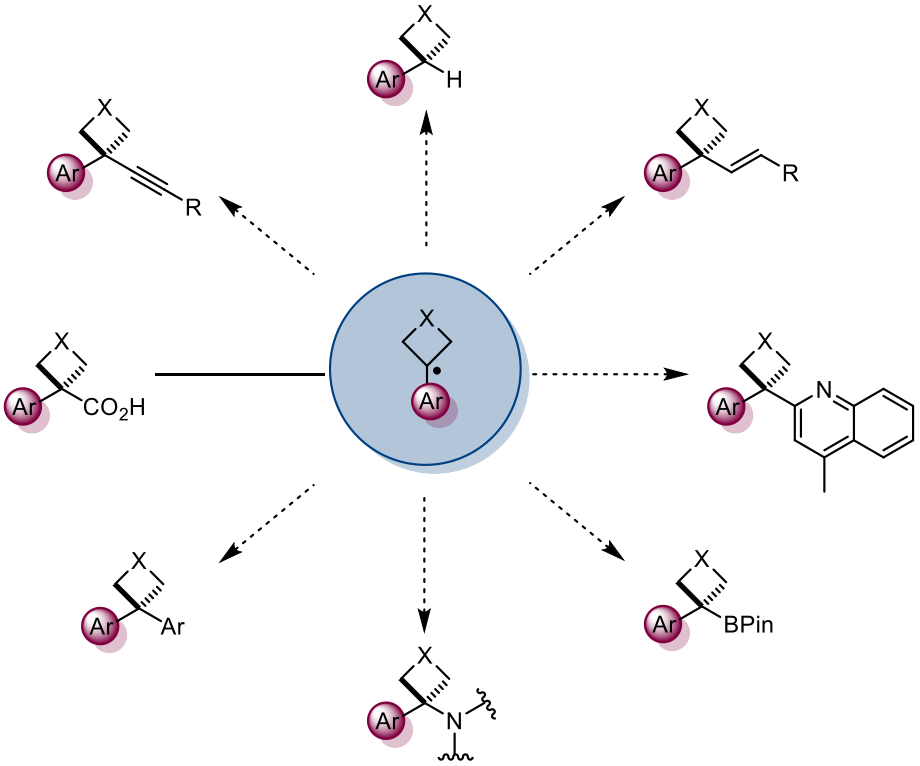
3-Aryl-3-carboxylic acid oxetanes and azetidines were found to generate these radical intermediates under visible-light mediated photoredox catalysis.

These acid precursors are valuable motifs for medicinal chemistry, presenting structural similarities with profen drugs. However, they were difficult to access due to limited and inefficient synthetic methods, and high cost associated to the few commercial examples. A new two–step protocol was developed to efficiently synthesised these scaffolds. This involved the installation of a furan ring *via* the previously developed catalysed Friedel–Crafts reactions followed by mild selective and catalytic oxidative cleavage. 3-Aryl-3-carboxylic acid oxetanes and azetidines containing heteroaromatic and aromatic triflates were prepared as well as profen drug analogues. The simple purification and derivatisation of the products demonstrated their high stability and relevance as building blocks.

In situ generation of oxetanyl and azetidinyl radicals was achieved through decarboxylation of the acid precursors in presence of a photocatalyst and visible light. Reaction with a variety of alkenes, produced new 3-aryl-3-alkyl oxetanes and azetidines. The reaction proceeded selectively at the three position, without degradation of the oxetane and azetidine rings through oxidation of α–CH bond. An interesting bis-oxetane side product was produced from

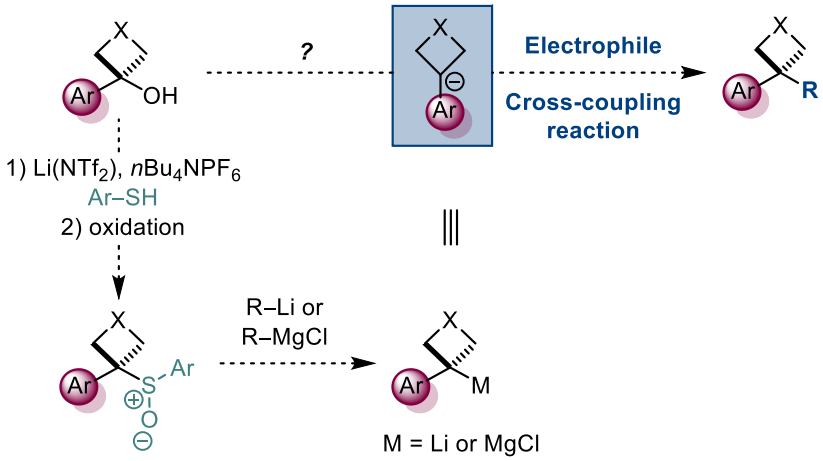
dimerisation of the radical intermediate, and represent an interesting 3-dimentional motif for drug discovery programmes. The oxetanyl and azetidinyl radicals exhibited enhanced reactivity towards product formation with limited side products, compared to other benzylic cyclic or linear radicals. Computational studies will be undertaken to rationalise this trend.

The reactivity of these radical species towards the synthesis of further new 3,3-disubstituted oxetanes and azetidines can be further explored. This represent the first main future project (Scheme 7.2). Photoredox-catalysed Minisci and cross–coupling reactions are of particular interest to synthesise 3,3-diaryloxetanes and azetidines containing pyridines which are inaccessible so far. Cross–coupling reactions to incorporate alkenes, alkynes and form C–N bonds would also give access to new oxetane and azetidine scaffolds of interested for medicinal chemistry.



Scheme 7.2: Future project 1 – exploring the potential of oxetanyl and azetidinyl radicals towards the synthesis of new 3,3-disubstituted motifs for medicinal chemistry.

The second main future project consists of investigating the *in situ* generation and reaction of oxetanyl and azetidinyl carbanion species (Scheme 7.3). Addition to electrophiles and cross–coupling reactions of such intermediates can give access to a new range of 3,3-disubstituted oxetane and azetidine products.



Scheme 7.3: Future project 2 – *in situ* generation and reaction of oxetanyl and azetidinyl carbanion species towards new 3,3-disubstituted oxetanes and azetidines.

Sulfoxide-metal exchange has been previously used within the Bull group to generate aziridinyl and cyclopropylmetal species.[227] Reaction with electrophiles and arylbromide through cross–coupling reactions delivered a variety of new compounds. The generation of oxetanyl and azetidinyl carbanions through sulfoxide-metal exchange protocol represent an attractive method. Indeed, sulfoxide azetidine and oxetane precursors have been synthesised in this thesis and previously in the group respectively.[51] Reaction with di-halides and aryl halides for instance, would enable the synthesis of 3,3-diaryl-, and 3-aryl-3-halo-oxetanes and azetidines which are currently inaccessible.

8. Experimental

8.1 General Experimental Considerations

All non-aqueous reactions were carried out under an inert atmosphere (argon) with flame-dried glassware, using standard techniques, unless specified. Friedel–Crafts reactions were carried out under inert atmosphere with flame-dried glassware, using standard techniques, using non-dried CH_2Cl_2, $CHCl_3$, toluene, EtOAc and HFIP. Anhydrous solvents were obtained by filtration through drying columns (THF, DMF, EtOH, MeCN) or used as supplied (1,4-dioxane, DME, CH_2Cl_2). Reactions in HFIP were carried out in sealed tubes using Biotage microwave vials (10-20 mL) and aluminium caps equipped with butyl septa.

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. Visualisation of the developed chromatogram was performed by UV absorbance (254 nm) and stained with aqueous potassium permanganate solution, phosphomolybdic acid solution, *para*-anisaldehyde solution or ninhydrin solution in ethanol. Infrared spectra (νmax, FTIR ATR) were recorded in reciprocal centimetres (cm^{-1}).

Nuclear magnetic resonance spectra were recorded on 400 or 500 MHz spectrometers. Chemical shifts for ^1H NMR spectra are recorded in parts per million (ppm) from tetramethylsilane with the solvent resonance as the internal standard ($CDCl_3$: δ = 7.27 ppm, DMSO-d_6: δ = 2.50 ppm, MeOD-d_4: δ = 3.35 ppm, acetone-d_6: δ = 2.05 ppm). Data is reported as follows: chemical shift (multiplicity [s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, h = heptet, m = multiplet and br = broad], coupling constant (in Hz), integration and assignment). ^{13}C NMR spectra were recorded with complete proton decoupling. Chemical shifts are reported in parts per million from tetramethylsilane with the solvent resonance as the internal standard ($^{13}CDCl_3$: δ = 77.0 ppm, $(^{13}CD_3)_2SO$: δ = 39.5 ppm, $^{13}CD_3OD$: δ = 49.0 ppm, $^{13}(CD_3)_2CO$: δ= 29.8 ppm). Assignments of ^1H and ^{13}C spectra were based upon the analysis of δ and *J* values, as well as DEPT, COSY, HSQC and HMBC experiments where appropriate. ^{19}F and ^{31}P NMR spectra were recorded with or without complete proton decoupling. Decoupling is indicated as $^{19}F\{^1H\}$ and $^{31}P\{^1H\}$ and where relevant this is stated in each assignment. ^{19}F, ^{11}B and ^{31}P NMR spectra are indirectly referenced to $CFCl_3$, $BF_3{\bullet}OEt_2$, and H_3PO_4 automatically *via* direct measurement of the absolute frequency of the deuterium lock signal by the spectrometer hardware.

Melting points were recorded using Optimelt MPA100 apparatus and are uncorrected.

The high resolution mass spectrometry (HRMS) analyses were performed using electrospray ion source (ESI), atmospheric pressure chemical ionisation (APCI), nanospray ionisation (NSI), or electron impact ionisation (EI). ESI was performed using a Waters LCT Premier equipped with an ESI source operated in positive or negative ion mode. In most cases the software used was MassLynx 4.1. This software does not account for the electron for +ESI and the calibrations/references are calculated accordingly, i.e. $[M+H]^+$ is detected and the mass is calibrated to output [M+H].

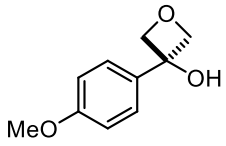
Reagents: Commercial reagents were used as supplied, or purified by standard techniques where necessary. Liquid alkenes, used for photoredox-catalysed reactions, were distilled under vacuum, argon, and in the dark, and were stored in a round bottom flash sealed with a septum, under argon, in the dark at –20 °C. Catalysts were purchased from the following suppliers, stored in a desiccator and used without further purification.

- Iron(III) chloride (98%, CAS: 7705-08-0) was purchased from Acros Organics, and stored under argon atmosphere.
- Bis(trifluoromethane)sulfonimide lithium salt (>99%, CAS: 90076-65-6) was purchased from Sigma-Aldrich.
- Calcium(II) bis(trifluoromethanesulfonyl)imide (> 97%, CAS: 165324-09-4) was purchased from TCI chemicals.
- $RuCl_3$ (CAS: 10049-08-8) was purchased from Sigma-Aldrich (Ru content 45-50%, product code: 208523-2G)
- $Ir(dFCF_3ppy)_2(dtbbpy)PF_6$ (**257**) was purchased from Sigma-Aldrich (CAS: 870987-63-6, product code: 747793-100MG).
- $NaIO_4$ was purchased from Fluorochem (> 99.8%, product code: 033232) or Sigma-Aldrich (> 99.8%, product code: 311448).

Procedure for purification with SCX® Column: SCX Cartridge 5 g/25 mL were purchased from ThermoScientific. The column was washed with three volumes of methanol. The sample was then loaded onto the column in a minimum amount of solvent (1:1 MeOH/DCM). The column was washed through with three column volumes of MeOH and then the free amine was eluted with three volumes of 5% NH_3 (28% aqueous solution)/MeOH.

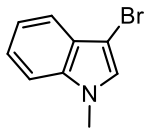
8.2 Experimental Details and Characterisation Data

8.2.1 Synthesis of the Matched Molecular Pairs (Part 3.2)



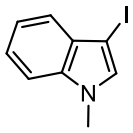
3-(4-Methyoxyphenyl) oxetan-3-ol (18)

*n*BuLi (1.53 M in hexane, 32.4 mL, 49.5 mmol) was added dropwise over 5 min to a solution of 4-bromoanisole (6.80 mL, 54.0 mmol) in THF (90 mL) at –78 °C. The reaction mixture was stirred at –78 °C for 40 min. Oxetan-3-one (2.90 mL, 45.0 mmol) was added dropwise to the reaction mixture. Following a further 40 min at –78 °C the reaction mixture was warmed to 25 °C then quenched with water (150 mL). EtOAc (150 mL) was added and the layers were separated. The aqueous portion was extracted with EtOAc (2 × 150 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography (20% EtOAc/pentane) afforded oxetanol **18** (7.30 g, 90%) as a white solid. R_f = 0.29 (45% EtOAc/hexane); mp = 53–55 °C [lit. 52–53 °C][50]; IR (film)/cm^{-1} 3313 (br, OH), 2995, 2949, 2882, 1607, 1581, 1511, 1462, 1440, 1300, 1236, 1217, 1178, 1028, 968, 950, 839, 815, 721, 663; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51–7.49 (m, 2 H, 2 × Ar-CH), 6.97–6.95 (m, 2 H, 2 × Ar-CH), 4.93 (d, *J* = 6.2 Hz, 2 H, CH*H*OCH*H*), 4.90 (d, *J* = 6.2 Hz, 2 H, C*H*HOC*H*H), 3.84 (s, 3 H, OCH_3), 2.47 (s, 1 H, OH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.3 (Ar-C_q-OCH_3), 134.5 (Ar-C_q-C_q), 125.9 (2 × Ar-CH), 114.0 (2 × Ar-CH), 85.5 (CH_2OCH_2), 75.7 (C_q (oxetane)), 55.3 (OCH_3). The observed spectroscopic data for this compound was consistent with that previously reported.[50]



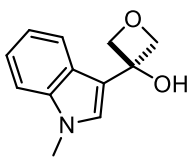
3-Bromo-1-methyl-1*H*-indole (S1)

A solution of 1,3-dibromo-5,5-dimethylhydantoin (1.89 g, 6.60 mmol) in 1,4-dioxane (30 mL) was added over 2 min to a solution of 1-methyl-1*H*-indole (1.50 mL, 12.0 mmol) in 1,4-dioxane (90 mL) at 10 ºC. The resulting solution was stirred for 10 min and then sat. aq. $NaHCO_3$ (100 mL) was added followed by water (100 mL) and Et_2O (200 mL). The layers were separated, and the aqueous portion was extracted with Et_2O (3 × 100 mL). The organic extract was dried over Na_2SO_4, filtered and concentrated under reduced pressure to give **S1** as a yellow brown oil (2.74 g, 100%). The crude product was used for the next step without further purification. R_f = 0.48 (2:1 hexane/Et_2O); IR (film)/cm^{-1} 3314, 1726, 1462, 1322, 1239, 946, 738; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, *J* = 7.6 Hz, 1 H, $Ar_{(indole)}$-CH), 7.34–7.27 (m, 2 H, 2 × $Ar_{(indole)}$-CH), 7.23–7.19 (m, 1 H, $Ar_{(indole)}$-CH), 7.09 (s, 1 H, N-Ar-CH), 3.80 (s, 3 H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.2 ($Ar_{(indole)}$-C_q), 127.6 ($Ar_{(indole)}$-CH), 127.2 ($Ar_{(indole)}$-C_q), 122.6 ($Ar_{(indole)}$-CH), 120.1 ($Ar_{(indole)}$-CH), 119.3 ($Ar_{(indole)}$-CH), 109.4 (N-Ar-CH), 89.3 ($Ar_{(indole)}$-C_q-Br), 33.0 (NCH_3). The observed spectroscopic data for this compound was consistent with that previously reported.[95]



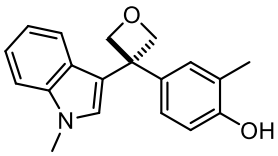
3-Iodo-1-methyl-1*H*-indole (20)

Using conditions developed by Larrosa,[97] MeCN (35 mL) was added to a flask containing flame dried K_2CO_3 (9.67 g, 7.00 mmol), I_2 (3.55 g, 14.0 mmol) and 1-methylindole-3-carboxylic acid (1.20 g, 7.00 mmol). The reaction mixture was stirred at 100 °C for 22 h then cooled to rt. A solution of 10% $Na_2S_2O_8$ (100 mL) and sat. aq. $NaHCO_3$ (100 mL) were added. The aqueous portion was extracted with Et_2O (3 × 180 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude was dissolved in 4% Et_2O/pentane and filtrated through celite to afford iodoaryl **20** (1.56 g, 86%) as a dark red oil. R_f = 0.16 (100% pentane); IR (film)/cm^{-1} 2939, 1509, 1438, 1420, 1355, 1330, 1314, 1237, 1128, 1104, 932, 763, 737; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46–7.44 (m, 1 H, $Ar_{(indole)}$-CH), 7.33–7.29 (m, 2 H, 2 × $Ar_{(indole)}$-CH), 7.23–7.19 (m, 1 H, $Ar_{(indole)}$-CH), 7.16 (s, 1 H, N-Ar-CH), 3.83 (s, 3 H, NCH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.7 ($Ar_{(indole)}$-C_q), 132.7 ($Ar_{(indole)}$-CH), 130.4 ($Ar_{(indole)}$-C_q), 122.6 ($Ar_{(indole)}$-CH), 121.1 ($Ar_{(indole)}$-CH), 120.2 ($Ar_{(indole)}$-CH), 109.4 (N-Ar-CH), 54.7 ($Ar_{(indole)}$-C_q-I), 33.1 (NCH_3). The observed characterisation data (^{1}H, ^{13}C NMR) was consistent with that previously reported.[228]



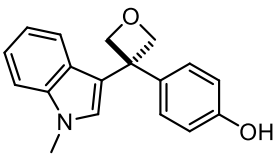
3-(1-Methyl-1*H*-indol-3-yl)oxetan-3-ol (19)

*n*BuLi (1.47 M in hexane, 6.50 mL, 9.54 mmol) was added dropwise over 5 min to a solution of 3-iodo-1-methyl-1*H*-indole **20** (2.68 g, 10.4 mmol) in THF (21 mL) at –78 °C. The reaction mixture was stirred at –78 °C for 40 min. Oxetan-3-one (556 µL, 8.67 mmol) was added dropwise to the reaction mixture. Following a further 30 min at –78 °C the reaction mixture was warmed to 25 °C for 17 h then quenched with water (80 mL). Et_2O (80 mL) was added and the layers were separated. The aqueous portion was extracted with Et_2O (2 × 80 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography (50 to 100% Et_2O/pentane) afforded oxetanol **19** (1.35 g, 77%) as a reddish oil. R_f = 0.15 (50% Et_2O/pentane); IR (film)/cm^{-1} 3365 (br, OH), 2948, 2873, 1728, 1553, 1229, 967, 738; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78–7.76 (m, 1 H, $Ar_{(indole)}$-CH), 7.37–7.35 (m, 1 H, $Ar_{(indole)}$-CH), 7.30 (ddd, *J* = 8.2, 7.0, 1.1 Hz, 1 H, $Ar_{(indole)}$-CH), 7.18 (ddd, *J* = 8.2, 7.0, 1.1 Hz, 1 H, $Ar_{(indole)}$-CH), 7.13 (s, 1 H, N-Ar-CH), 5.07 (d, *J* = 7.1 Hz, 2 H, C*H*HOC*H*H), 5.03 (d, *J* = 7.1 Hz, 2 H, CH*H*OCH*H*), 3.81 (s, 3 H, NCH_3), 2.51 (s, 1 H, OH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.6 ($Ar_{(indole)}$-C_q), 125.9 (N-Ar-CH), 125.3 ($Ar_{(indole)}$-C_q), 122.2 ($Ar_{(indole)}$-CH), 119.7 ($Ar_{(indole)}$-CH), 119.6 ($Ar_{(indole)}$-CH), 116.3 (N-Ar-CH-C_q), 109.6 ($Ar_{(indole)}$-CH), 84.8 (CH_2OCH_2), 72.9 (C_q), 32.7 (NCH_3); HRMS (+NSI) *m*/*z* calcd for $C_{12}H_{14}O_2N^+$ $[M+H]^+$: 204.1019, Found: 204.1019.



4-[3-(1-Methyl-1*H*-indol-3-yl)oxetan-3-yl]-2-methylphenol (16a)

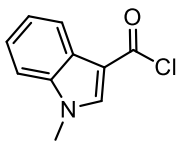
Lithium bis(trifluoromethane)sulfonimide (80.9 mg, 0.28 mmol) and tetrabutylammonium hexafluorophosphate (64.8 mg, 0.17 mmol) were added to a solution of oxetanol **19** (619 mg, 3.04 mmol) and 2-methylphenol (1.60 mL, 15.2 mmol) in $CHCl_3$ (6.1 mL). The reaction mixture was stirred at 40 °C for 1 h then sat. aq. $NaHCO_3$ (50 mL) was added followed by EtOAc (50 mL). The layers were separated and the aqueous portion was extracted with EtOAc (3 × 50 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography (30% Et_2O/pentane) afforded oxetane **16a** (594 mg, 67%) as a yellow solid. R_f = 0.15 (25% EtOAc/pentane); mp = 233–235 °C; IR (film)/cm^{-1} 3226 (br, OH), 2957, 1611, 1514, 1483, 1462, 1373, 1330, 1269, 1214, 1125, 967, 768, 734; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.18 (s, 1 H, OH), 7.40 (d, J = 8.5 Hz, 2 H, 2 × $Ar_{(indole)}$-CH), 7.16–7.12 (m, 1 H, $Ar_{(indole)}$-CH), 7.05 (d, J = 2.1 Hz, 1 H, Ar-CH), 7.00 (s, 1 H, N-Ar-CH), 6.98–6.91 (m, 2 H, $Ar_{(indole)}$-CH, Ar-CH), 6.72 (d, J = 8.3 Hz, 1 H, Ar-CH), 5.14–5.11 (m, 4 H, CH_2OCH_2), 3.73 (s, 3 H, NCH_3), 2.09 (s, 3 H, Ar-CH_3); ^{13}C NMR (101 MHz, DMSO-d_6) δ 153.7 (Ar-C_q-OH), 137.2 (Ar-C_q-C_q), 135.8 ($Ar_{(indole)}$-C_q), 128.4 (Ar-CH), 127.1 (N-Ar-CH), 125.5 ($Ar_{(indole)}$-C_q), 124.4 ($Ar_{(indole)}$-CH), 123.5 (Ar-C_q-CH_3), 121.2 ($Ar_{(indole)}$-CH), 119.4 (N-Ar-CH-C_q), 119.2 ($Ar_{(indole)}$-CH), 118.6 (Ar-CH), 114.1 (Ar-CH), 109.9 ($Ar_{(indole)}$-CH), 82.9 (CH_2OCH_2), 45.5 (C_q), 32.3 (NCH_3), 16.2 (Ar-CH_3); HRMS (+ESI) m/z calcd for $C_{19}H_{20}NO_2$ [M+H]: 294.1483, Found: 294.1494.



4-(3-(1-Methyl-1*H*-indol-3-yl)oxetan-3-yl)phenol (17a)

Lithium bis(trifluoromethane)sulfonimide (83.3 mg, 0.29 mmol) and tetrabutylammonium hexafluorophosphate (55.8 mg, 0.14 mmol) were added to a solution of oxetanol **19** (532 mg, 2.62 mmol) and phenol (1.23 g, 13.1 mmol) in $CHCl_3$ (5.2 mL). The reaction mixture was stirred at 40 °C for 3 h then sat. aq. $NaHCO_3$ (50 mL) was added followed by EtOAc (50 mL). The layers were separated, and the aqueous portion was extracted with EtOAc (3 × 50 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography (30% EtOAc/pentane) afforded oxetane **17a** (204 mg, 28%) as a yellow solid. R_f = 0.43 (50% EtOAc/pentane); mp = 207–209 °C; IR (film)/cm^{-1} 3477, 3131 (br, OH), 2953, 2880, 1516, 1374, 1218, 837, 814, 741; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.33 (s, 1 H, OH), 7.39 (dd, J = 14.0, 8.1 Hz, 2 H, 2 × $Ar_{(indole)}$-CH), 7.16–7.13 (m, 3 H, $Ar_{(indole)}$-CH, 2 × Ar-CH), 7.03 (s, 1 H, N-Ar-CH), 6.99–6.97 (m, 1 H, $Ar_{(indole)}$-CH), 6.73 (d, J = 8.6 Hz, 2 H, 2 × Ar-CH), 5.14 (dd, J = 13.9, 5.6 Hz, 4 H, CH_2OCH_2), 3.73 (s, 3 H, NCH_3); ^{13}C NMR (101 MHz, DMSO-d_6) δ 155.6 (Ar-C_q-OH), 137.2 (Ar-C_q-C_q), 136.0 ($Ar_{(indole)}$-C_q), 127.3 (2 × Ar-

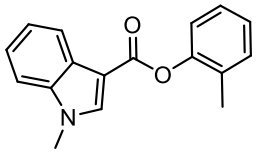
CH), 127.1 (N-Ar-CH), 125.6 ($Ar_{(indole)}$-C_q), 121.3 ($Ar_{(indole)}$-CH), 119.3 (N-Ar-CH-C_q), 119.3 ($Ar_{(indole)}$-CH), 118.7 ($Ar_{(indole)}$-CH), 115.0 (2 × Ar-CH), 110.0 ($Ar_{(indole)}$-CH), 83.0 (CH_2OCH_2), 45.5 (C_q), 32.3 (NCH_3); HRMS (+ESI) *m*/*z* calcd for $C_{18}H_{18}NO_2$ [M+H] : 280.1338, Found: 280.1346.



1-Methyl-1*H*-indole-3-carbonyl chloride (21)

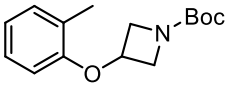
Oxalyl chloride (270 µL, 3.00 mmol) was added to a solution of 1-methylindole-3-carboxylic acid (350 mg, 2.00 mmol) in CH_2Cl_2 (8.0 mL) at 25 °C. The reaction mixture was stirred for 1 h before concentrating under reduced pressure giving acyl chloride **21** as a purple solid (387 mg, 100%). R_f = 0.34 (50% EtOAc/pentane); mp = 50–53 °C; IR(film)/cm^{-1} 3058, 1742, 1675, 1525, 1461, 1357, 1238, 1195, 1127, 1030, 788, 748, 722, 666; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (m, 1 H, $Ar_{(indole)}$-CH), 7.98 (s, 1 H, N-Ar-CH), 7.46–7.33 (m, 3 H, 3 × $Ar_{(indole)}$-CH), 3.91 (s, 3 H, NCH_3).* The observed spectroscopic data for this compound was consistent with that previously reported.[229]

** Acyl chloride **21** was too instable in solution over time to obtain ^{13}C NMR spectrum.*



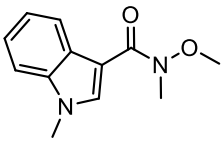
***o*-Tolyl 1-methyl-1*H*-indole-3-carboxylate (22)**

$AlCl_3$ (64.0 mg, 0.48 mmol) was added in four portions over 20 min to a solution of acyl chloride **21** (150 mg, 0.38 mmol) and 2-methylphenol (49.5 µL, 0.48 mmol) in CH_2Cl_2 (2.0 mL) at 0 °C. The reaction was stirred at 0 °C for 5 min and then at 25 °C for 3 h then H_2O (20 mL) was added followed by CH_2Cl_2 (20 mL). The layers were separated and the aqueous portion was extracted with CH_2Cl_2 (2 × 20 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography (100% chloroform) afforded ester **22** (137 mg, 100%) as a pink solid. R_f = 0.25 (50% Et_2O/pentane); mp = 104–106 °C; IR (film)/cm^{-1} 3121, 2914, 1702 (C=O), 1532, 1487, 1474, 1462, 1381, 1338, 1258, 1216, 1173, 1150, 1130, 1113, 1089, 1055, 979, 833, 766, 747, 734, 704; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (dd, *J* = 6.6, 1.8 Hz, 1 H, $Ar_{(indole)}$-CH), 7.99 (s, 1 H, N-Ar-CH), 7.43 (dd, *J* = 6.9, 1.8 Hz, 1 H, $Ar_{(indole)}$-CH), 7.39–7.32 (m, 2 H, 2 × $Ar_{(indole)}$-CH), 7.32–7.34 (m, 2 H, 2 × Ar-CH), 7.22–7.16 (m, 2 H, 2 × Ar-CH), 3.91 (s, 3 H, NCH_3), 2.28 (s, 3 H, Ar-CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.8 (C=O), 149.3 (Ar-C_q-O), 137.3 ($Ar_{(indole)}$-C_q), 136.1 ($Ar_{(indole)}$-CH), 131.0 ($Ar_{(indole)}$-CH), 130.7 ($Ar_{(indole)}$-C_q), 126.8 (Ar-CH), 126.8 (Ar-C_q-CH_3), 125.7 (Ar-CH), 123.1 (Ar-CH), 122.5 (Ar-CH), 122.2 ($Ar_{(indole)}$-CH), 121.8 ($Ar_{(indole)}$-CH), 109.9 (N-Ar-CH), 106.1 (N-Ar-CH-C_q), 33.5 (NCH_3), 16.3 (Ar-CH_3); HRMS (+ESI) *m*/*z* calcd for $C_{17}H_{18}NO_2$ [M+H] : 266.1181, Found: 266.1187.



tert-Butyl 3-(_o_-tolyloxy)azetidine-1-carboxylate (23)

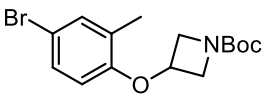
2-Methylphenol (105 µL, 1.02 mmol) was added to a solution of NaH (60% dispersion in mineral oil, 42.6 mg, 1.04 mmol) in DMF (4.8 mL) at 0 °C. The reaction mixture was stirred for 30 min at 0 °C and then *tert*-butyl-3-bromoazetidine-1-carboxylate (241 mg, 1.02 mmol) was added to the reaction mixture *via* syringe. The reaction mixture was heated to 80 °C for 3 h, then cooled to rt before addition of water (20 mL). Et_2O (20 mL) was added and the layers were separated. The aqueous portion was extracted with Et_2O (3 × 20 mL). The organic extracts were combined, washed with sat. aq. NaCl (20 mL) followed by aq. NaOH (1 M, 20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford **23** (243 mg, 90%) as a white solid. R_f = 0.41 (CH_2Cl_2); mp = 73–75 °C; IR (film)/cm^{-1} 2979, 1692 (C=O), 1491, 1389, 1382, 1362, 1239, 1192, 1161, 1152, 1116, 1099, 1011, 879, 853, 757; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21–7.08 (m, 2 H, 2 × Ar-CH), 6.91 (m, 1 H, Ar-CH), 6.45 (d, *J* = 8.0 Hz, 1 H, Ar-CH), 4.88 (tt, *J* = 6.4, 4.2 Hz, 1 H, OCH), 4.32 (ddd, *J* = 9.6, 6.4, 0.8 Hz, 2 H, C*H*HNC*H*H), 4.03 (dd, *J* = 9.6, 4.2 Hz, 2 H, CH*H*NCH*H*), 2.26 (s, 3 H, Ar-CH_3), 1.47 (s, 9 H, 3 × CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.1 (C=O), 154.7 (Ar-C_q-O), 131.1 (Ar-CH), 126.9 (Ar-C_q-CH_3), 126.7 (Ar-CH), 121.1 (Ar-CH), 110.6 (Ar-CH), 79.7 ($C_q(CH_3)_3$), 65.5 (OCH), 56.5 (CH_2NCH_2), 28.3 ($C_q(CH_3)_3$), 16.1 (Ar-CH_3); HRMS (+ESI) *m*/*z* calcd for $C_{15}H_{22}NO_3$ [M+H]: 264.1600, Found: 264.1607. Compound previously reported without characterisation data.[230]



_N_-Methoxy-_N_,1-dimethyl-1_H_-indole-3-carboxamide (26)

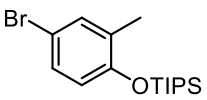
Pyridine (360 µL, 4.40 mmol) was added to a solution of 1-methyl-1*H*-indole-3-carbonyl chloride **21** (387 mg, 2.00 mmol) and *N*,*O*-dimethylhydroxylamine hydrochloride (234 mg, 2.40 mmol) in CH_2Cl_2 (4.0 mL) at 0 °C. The reaction mixture was then warmed up to 25 °C and stirred for 14 h 30 min. A solution of aqueous HCl (1 M, 25 mL) was then added followed by CH_2Cl_2 (20 mL). The layers were separated and the aqueous portion was extracted with CH_2Cl_2 (3 × 20 mL). The organic extracts were combined, washed with sat. aq. $NaHCO_3$ (60 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford amide **26** (404 mg, 93%) as a light purple solid. R_f = 0.34 (50% EtOAc/pentane); mp = 101–103 °C; IR (film)/cm^{-1} 3285, 2936, 1610 (C=O), 1463, 1419, 1374, 1125, 1089, 738; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48–8.35 (m, 1 H, $Ar_{(indole)}$-CH), 7.83 (s, 1 H, N-Ar-CH), 7.41–7.21 (m, 3 H, 3 × $Ar_{(indole)}$-CH), 3.84 (s, 3 H, $N_{(indole)}$-CH_3), 3.73 (s, 3 H, OCH_3), 3.40 (s, 3 H, NCH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.7 (C=O), 136.3 (N-Ar-CH), 133.7 ($Ar_{(indole)}$-C_q), 128.4 ($Ar_{(indole)}$-C_q), 122.6 ($Ar_{(indole)}$-CH), 122.6 ($Ar_{(indole)}$-CH), 121.5 ($Ar_{(indole)}$-CH), 109.2 ($Ar_{(indole)}$-CH), 107.2 (N-Ar-CH-C_q), 60.6 (OCH_3), 33.3 ($N_{(indole)}$-CH_3), 33.1 (NCH_3); HRMS (+ESI) *m*/*z* calcd for $C_{10}H_{15}N_2O_2$ [M+H] : 219.1134, Found:

219.1142. The observed characterisation data (^{1}H and ^{13}C NMR) for this compound was consistent with that previously reported.[231]



tert-Butyl 3-(4-bromo-2-methylphenoxy) azetidine-1-carboxylate (27)

A solution of 4-bromo-2-methylphenol (449 mg, 2.40 mmol) in DMF (6.0 mL) was added to a solution of NaH (60% dispersion in mineral oil, 96.0 mg, 2.40 mmol) in DMF (1.20 mL) at 0 °C. The reaction was stirred for 30 min and *tert*-butyl-3-bromoazetidine-1-carboxylate (472 mg, 2.00 mmol) was weighed intro a flask, dissolved in DMF (1.0 mL) and added to the reaction mixture *via* a syringe. DMF (5.0 mL) was then added to the previous flask and added to the reaction. The reaction mixture was heated to 80 °C and stirred for 21 h. The reaction was cooled down to room temperature and then water (80 mL) was added followed by Et_2O (80 mL). The layers were separated and the aqueous portion was extracted with Et_2O (2 × 80 mL). The organic extracts were combined and washed with aq. NaOH (1 M, 100 mL) and then dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography (20% Et_2O/pentane) afforded **27** (497 mg, 73%) as a white solid. R_f = 0.15 (20% Et_2O/hexane); mp = 52–55 °C; IR (film)/cm^{-1} 2976, 2883, 1701 (C=O), 1489, 1456, 1393, 1366, 1297, 1243, 1190, 1131, 1043, 860, 802, 773; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30–7.28 (d, *J* = 2.3 Hz, 1 H, Ar-CH), 7.24–7.19 (dd, *J* = 8.7, 2.3 Hz, 1 H, Ar-CH), 6.31 (d, *J* = 8.7 Hz, 1 H, Ar-CH), 4.87–4.80 (tt, *J* = 6.4, 4.1 Hz, 1 H, OCH), 4.33–4.28 (ddd, *J* = 9.7, 6.4, 0.8 Hz, 2 H, C*H*HNC*H*H), 4.02–3.97 (dd, *J* = 9.7, 4.1 Hz, 2 H, CH*H*NCH*H*), 2.22 (s, 3 H, Ar-CH_3), 1.45 (s, 9 H, 3 × CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.1 (C=O), 153.8 (Ar-C_q-O), 133.8 (Ar-CH), 129.4 (Ar-CH), 129.3 (Ar-C_q-CH_3), 113.4 (Ar-C_q-Br), 112.2 (Ar-CH), 79.9 ($C_q(CH_3)_3$), 65.8 (OCH), 56.1 (CH_2NCH_2), 28.3 ($C_q(CH_3)_3$), 16.0 (Ar-CH_3); HRMS (+NSI) *m*/*z* calcd for $C_{15}H_{20}O_3NBrNa^+$ [M+Na]$^+$: 364.0519, Found: 364.0521.

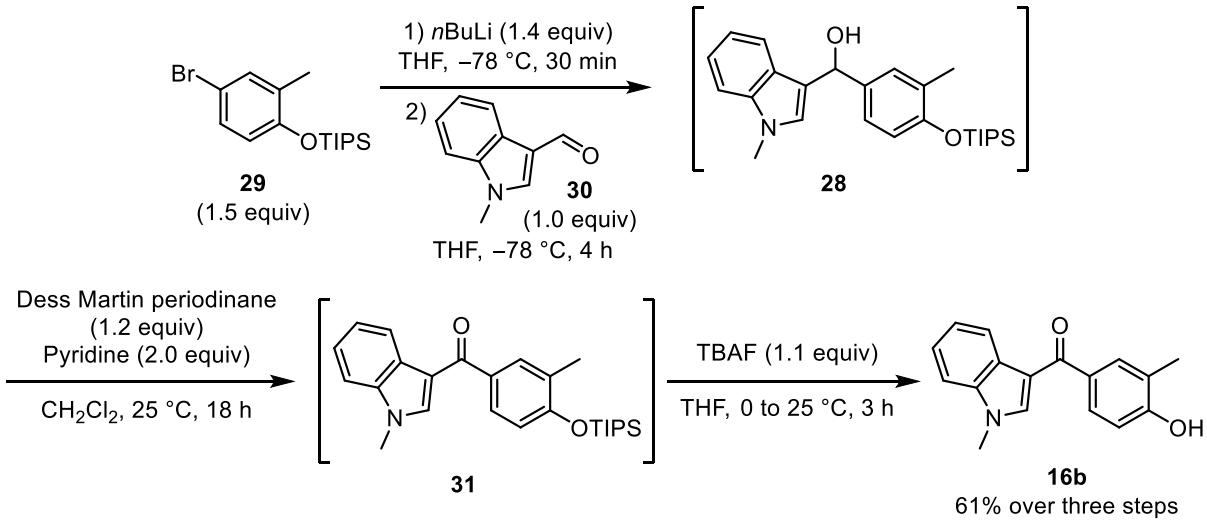


(4-Bromo-2-methylphenoxy)triisopropylsilane (29)

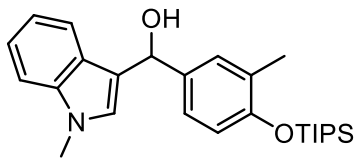
2,6-Lutidine (1.60 mL, 13.8 mmol) was added dropwise to a solution of 4-bromo 2-methylphenol (2.00 g, 10.7 mmol) and triisopropylsilyltrifluoromethanesulfonate (3.45 mL, 12.8 mmol) in CH_2Cl_2 (21.4 mL) at 0 °C. The reaction mixture was stirred for 30 min at 0 °C and then 5 h at 25 °C. Water (100 mL) was added followed by CH_2Cl_2 (80 mL). The layers were separated and the aqueous portion was extracted with CH_2Cl_2 (2 × 80 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography (100% pentane) afforded **29** (3.66 g, 99%) as a colourless oil. R_f = 0.63 (100% pentane); IR (film)/cm^{-1} 2945, 2867, 1487, 1394, 1283, 1269, 1186, 1125, 996, 882, 808, 702,

682; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (d, *J* = 2.6 Hz, 1 H, Ar-CH), 7.15 (dd, *J* = 8.6, 2.6 Hz, 1 H, Ar-CH), 6.66 (d, *J* = 8.6 Hz, 1 H, Ar-CH), 2.23 (s, 3 H, Ar-CH_3), 1.35–1.26 (m, 3 H, 3 × C*H*(CH_3)$_2$), 1.12 (d, *J* = 7.3 Hz, 18 H, 3 × CH(C*H*$_3$)$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.5 (Ar-C_q-OTIPS), 133.5 (Ar-CH), 131.0 (Ar-*C*$_q$-CH_3), 129.2 (Ar-CH), 119.4 (Ar-CH), 112.5 (Ar-C_q-Br), 18.0 (Ar-CH_3), 16.9 (3 × CH(*C*H$_3$)$_2$), 13.0 (3 × *C*H(CH_3)$_2$). The observed spectroscopic and physical data (^{1}H) for this compound was consistent with that previously reported.[232]

(4-Hydroxy-3-methylphenyl)(1-methyl-1*H*-indol-3-yl)methanone (16b)

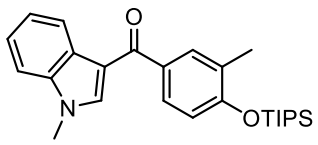


*n*BuLi (2.38 M in hexane, 590 µL, 1.40 mmol) was added dropwise in the solution of TIPS-protected bromo-phenol **29** (515 mg, 1.50 mmol) in THF (1.0 mL) at –78 °C and was stirred for 30 min. A solution of 1-methylindole-3-carboxaldehyde (159 mg, 1.00 mmol) in THF (2.3 mL) was added to the reaction mixture and stirred at –78 °C for further 4 h. The reaction was warmed to rt and then water (20 mL) was added followed by Et_2O (20 mL). The layers were separated and the aqueous portion was extracted with Et_2O (3 × 20 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give alcohol **28** which was used directly in the next step without further purification due to instability.



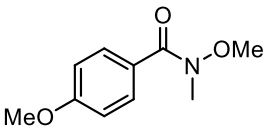
28: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, *J* = 8.0 Hz, 1 H, Ar$_{(indole)}$-CH), 7.31–7.29 (d, *J* = 8.2 Hz, 1 H, Ar$_{(indole)}$-CH), 7.26–7.21 (m, 2 H, Ar-CH, Ar$_{(indole)}$-CH), 7.17–7.14 (dd, *J* = 8.2, 2.2 Hz, 1 H, Ar-CH), 7.10–7.06 (m, 1 H, Ar$_{(indole)}$-CH), 6.83 (s, 1 H, N-Ar-CH), 6.77 (d, *J* = 8.2 Hz, 1 H, Ar-CH) , 6.09 (d, *J* = 4.1 Hz, 1 H, OH), 3.74 (s, 3 H, NCH_3), 2.25 (s, 3 H, Ar-CH_3), 2.09 (d, *J* = 4.1 Hz, 1 H, C*H*OH), 1.35–1.25 (m, 3 H, 3 × C*H*(CH_3)$_2$), 1.13 (d, *J* = 7.3 Hz, 18 H, 3 × CH(C*H*$_3$)$_2$). Compound was too unstable over time in solution to obtain ^{13}C NMR.

Dess-Martin periodinane (509 mg, 1.20 mmol) was added to a solution of alcohol **28** and pyridine (162 µL, 2.00 mmol) in CH_2Cl_2 (5.0 mL). The reaction mixture was stirred at 25 °C for 18 h and then sat. aq. sodium thiosulfate (20 mL) was added followed by CH_2Cl_2 (20 mL). The layers were separated and the aqueous portion was extracted with CH_2Cl_2 (2 × 20 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography (20% Et_2O/pentane) afforded TIPS protected ketone **31** with an impurity. The mixture was used without further purification.



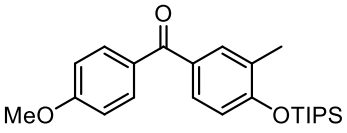
31: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (dd, *J* = 6.3, 2.2 Hz, 1 H, $Ar_{(indole)}$-CH), 7.70 (d, *J* = 2.3 Hz, 1 H, Ar-CH), 7.64–7.55 (m, 2 H, Ar-CH, N-Ar-CH), 7.40–7.33 (m, 3 H, 3 × $Ar_{(indole)}$-CH), 6.85 (d, *J* = 8.3 Hz, 1 H, Ar-CH), 3.88 (s, 3 H, NCH_3), 2.32 (s, 3 H, Ar-CH_3), 1.40–1.32 (m, 3 H, 3 × C*H*$(CH_3)_2$), 1.15 (d, *J* = 7.47 Hz, 18 H, 3 × CH(C*H*$_3)_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.4 (C=O), 157.5 (Ar-C_q-O), 141.8 (N-Ar-CH), 137.4 ($Ar_{(indole)}$-C_q), 133.3 (Ar-CH), 133.2 (Ar-*C*$_q$-CO), 132.0 ($Ar_{(indole)}$-CH), 128.6 ($Ar_{(indole)}$-C_q), 128.3 ($Ar_{(indole)}$-CH), 127.3 (Ar-*C*$_q$-CH_3), 123.4 ($Ar_{(indole)}$-CH), 122.4 (Ar-CH), 117.3 (Ar-CH), 115.7 (N-Ar-CH-*C*$_q$), 109.5 ($Ar_{(indole)}$-CH), 33.5 (NCH_3), 18.0 (3 × CH(*C*$H_3)_2$), 17.1 (Ar-CH_3), 13.0 (3 × *C*H$(CH_3)_2$); HRMS (+ESI) m/z calcd for $C_{26}H_{36}NO_2Si$ [M+H]: 422.2515, Found: 422.2515.

A solution of TBAF (1 M in THF, 1.10 mL, 1.10 mmol) was added to a solution of TIPS-protected ketone **31** in THF (3.0 mL) at 0 °C and stirred at 25 °C for 3 h and water (20 mL) was added followed by EtOAc (20 mL). The layers were separated and the aqueous portion was extracted with EtOAc (2 × 20 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography (30% to 50 EtOAc/pentane) afforded **16b** as a yellow solid (162 mg, 61% over three steps). R_f = 0.23 (40% EtOAc/pentane); mp = 239–241 °C; IR (film)/cm^{-1} 3124 (br, OH), 3051, 2925, 1608 (C=O), 1563, 1522, 1510, 1468, 1368, 1340, 1229, 1273, 1250, 1199, 1168, 1156, 1127, 1081, 1045, 1011, 949, 940, 933, 820, 741, 710; ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 10.0 (s, 1 H, OH), 8.23–8.21 (m, 1 H, $Ar_{(indole)}$-CH), 7.99 (s, 1 H, N-Ar-CH), 7.59 (d, *J* = 1.5 Hz, 1 H, Ar-CH), 7.56–7.53 (m, 2 H, $Ar_{(indole)}$-CH, Ar-CH), 7.32–7.23 (m, 2 H, 2 × $Ar_{(indole)}$-CH), 6.90 (d, *J* = 8.3 Hz, 1 H, Ar-CH), 3.88 (s, 3 H, NCH_3), 2.20 (s, 3 H, Ar-CH_3); ^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ 188.4 (C=O), 158.6 (Ar-C_q-OH), 138.2 (N-Ar-CH), 137.1 ($Ar_{(indole)}$-C_q), 131.5 (Ar-CH), 131.3 (Ar-*C*$_q$-CO), 128.2 ($Ar_{(indole)}$-CH), 126.9 ($Ar_{(indole)}$-C_q), 123.8 (Ar-*C*$_q$-CH_3), 122.8 ($Ar_{(indole)}$-CH), 121.8 (Ar-CH), 121.6 ($Ar_{(indole)}$-CH), 114.0 (Ar-CH), 113.9 (N-Ar-CH-*C*$_q$), 110.4 ($Ar_{(indole)}$-CH), 33.0 (NCH_3), 16.0 (Ar-CH_3); HRMS (+ESI) m/z calcd for $C_{17}H_{16}NO_2$ [M+H]: 266.1181, Found: 266.1183.



***N*,4-Dimethoxy-*N*-methylbenzamide (32)**

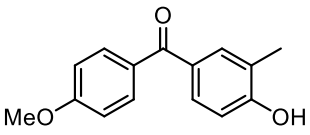
Pyridine (510 μL, 6.30 mmol) was added to the solution of 4-methoxy benzoyl chloride (512 mg, 3.00 mmol) and *N*,*O*-dimethylhydroxylamine (307 mg, 1.05 mmol) in CH_2Cl_2 (5.0 mL) at 0 °C. The reaction mixture was warmed to rt and then stirred for 15 h. A solution of HCl (3 M, 10 mL) was added dropwise, followed by water (30 mL), and the reaction mixture was then extracted with CH_2Cl_2 (5 × 40 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography (40% Et_2O/pentane) afforded Weinreb amide **32** (577 mg, 99%) as yellow oil. R_f = 0.15 (40% Et_2O/pentane); IR (film)/cm^{-1} 3470, 2936, 2840, 1632 (C=O), 1606, 1575, 1511, 1460, 1420, 1372, 1250, 1215, 1171, 1112, 1027, 994, 976, 840, 796, 755, 702, 676; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76–7.72 (m, 2 H, 2 × Ar-CH), 6.93–6.89 (m, 2 H, 2 × Ar-CH), 3.86 (s, 3 H, Ar-OCH_3), 3.57 (s, 3 H, OCH_3), 3.36 (s, 3 H, NCH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.1 (C=O), 161.3 (Ar-C_q-OCH_3), 130.3 (2 × Ar-CH), 125.8 (Ar-C_q-CO), 113.0 (2 × Ar-CH), 60.6 (OCH_3), 55.1 (Ar-OCH_3), 33.7 (NCH_3). The observed spectroscopic data for this compound was consistent with that previously reported.[233]



(4-Methoxyphenyl)(3-methyl-4 ((triisopropylsilyl)oxy)phenyl)methanone (33)

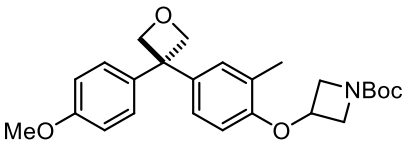
*n*BuLi (2.26 M in hexane, 1.24 mL, 2.82 mmol) was added dropwise over 5 min to a solution of **29** (1.06 g, 3.07 mmol) in THF (5.2 mL) at –78 °C. The reaction mixture was stirred at –78 °C for 40 min. A solution of amide **32** (505 mg, 2.59 mmol) in THF (5.0 mL) was added dropwise to the reaction mixture. Following a further 3 h 30 min at –78 °C the reaction mixture was warmed to 25 °C then quenched with water (50 mL). Et_2O (50 mL) was added and the layers were separated. The aqueous portion was extracted with Et_2O (3 × 50 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography (10% Et_2O/hexane) afforded ketone **33** (851 mg, 83%) as a colourless oil. R_f = 0.17 (10% Et_2O/pentane); IR (film)/cm^{-1} 2945, 2866, 1646, 1598 (C=O), 1497, 1462, 1304, 1275, 1250, 1168, 968, 916, 881, 844, 823, 707, 683; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81–7.78 (m, 2 H, 2 × Ar-CH), 7.65 (d, *J* = 2.4 Hz, 1 H, Ar-CH), 7.54 (dd, *J* = 8.4, 2.4 Hz, 1 H, Ar-CH), 6.98–6.95 (m, 2 H, 2 × Ar-CH), 6.83 (d, *J* = 8.4 Hz, 1 H, Ar-CH), 3.89 (s, 3 H, OCH_3), 2.29 (s, 3 H, Ar-CH_3), 1.39–1.29 (m, 3 H, 3 × C*H*(CH_3)$_2$), 1.14 (d, *J* = 7.5 Hz, 18 H, 3 × CH(C*H*$_3$)$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 194.8 (C=O), 162.7 (Ar-C_q-OCH_3), 158.2 (Ar-C_q-OTIPS), 133.1 (Ar-CH), 132.2 (2 × Ar-CH), 130.9 (Ar$_{(OMe)}$-C_q-CO), 130.6 (Ar$_{(OTIPS)}$-C_q-CO), 129.6 (Ar-CH), 128.6 (Ar-C_q-CH_3), 117.2 (Ar-CH), 113.4 (2 × Ar-CH), 55.4

(OCH_3), 18.0 (Ar-CH_3), 17.0 (3 × $CH(CH_3)_2$), 13.0 (3 × $CH(CH_3)_2$); HRMS (+ESI) m/z calcd for $C_{24}H_{35}O_3Si$ [M+H]: 399.2355, Found: 399.2364.



(4-Methoxyphenyl)(3-methy-4)(triisopropylsilyl)oxy)phenyl)-methanone (11b)

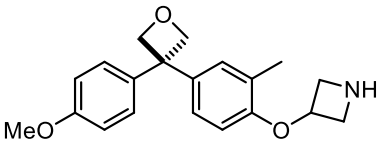
A solution of TBAF (1 M in THF, 2.70 mL, 2.70 mmol) was added dropwise to a solution of **33** (831 mg, 2.08 mmol) in THF (6.9 mL) at 0 °C. The reaction mixture was stirred for 30 min at 0 °C and then 4 h at 25 °C. Water (60 mL) was then added followed by Et_2O (60 mL). The layers were separated and the aqueous portion was extracted with Et_2O (3 × 60 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography (40% Et_2O/pentane) afforded ketone **11b** (476 mg, 94%) as a pink solid. R_f = 0.22 (0.15% Et_2O/pentane); mp = 186–187 °C; IR (film)/cm^{-1} 3100 (br, OH), 1630 (C=O), 1602, 1579, 1560, 1505, 1459, 1449, 1316, 1282, 1255, 1172, 1150, 1108, 1025, 904, 863, 834, 757, 729, 679; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.26 (s, 1 H, OH), 7.70–7.66 (m, 2 H, 2 × Ar-CH), 7.51 (d, J = 2.2 Hz, 1 H, Ar-CH), 7.45–7.42 (dd, J = 8.4, 2.2 Hz, 1 H, Ar-CH), 7.08–7.04 (m, 2 H, 2 × Ar-CH), 6.89 (d, J = 8.4 Hz, 1 H, Ar-CH), 3.85 (s, 3 H, OCH_3), 2.17 (s, 3 H, Ar-CH_3); ^{13}C NMR (101 MHz, DMSO-d_6) δ 193.2 (C=O), 162.2 (Ar-C_q-OCH_3), 159.7 (Ar-C_q-OH), 132.6 (Ar-CH), 131.6 (2 × Ar-CH), 130.4 ($Ar_{(OMe)}$-C_q-CO), 129.7 (Ar-CH), 128.4 ($Ar_{(OH)}$-C_q-CO), 124.0 (Ar-C_q-CH_3), 114.1 (Ar-CH), 113.6 (2 × Ar-CH), 55.4 (OCH_3), 15.9 (Ar-CH_3); HRMS (+ESI) m/z calcd for $C_{15}H_{15}O_3$ [M+H]: 243.1021, Found: 243.1021.



***tert*-Butyl-3-(4-(3-(4-methoxyphenyl)oxetan-3-yl)-2-methylphenoxy) azetidine-1-carboxylate (34a)**

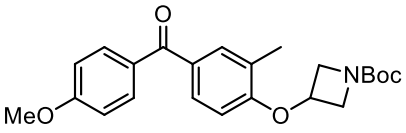
A solution of oxetane **11a**[97] (135 mg, 0.50 mmol) in DMF (1.3 mL) was added dropwise to a solution of NaH (60% dispersion in mineral oil, 26.0 mg, 0.65 mmol) in DMF (300 µL) at 0 °C. The reaction mixture was stirred for 30 min at 0 °C and then *tert*-butyl 3-bromoazetidine-1-carboxylate (236 mg, 1.00 mmol) was weighed into a flask, dissolved in DMF (100 µL) and added to the reaction mixture *via* syringe. DMF (900 µL) was added to the previous flask and then added to the reaction. The reaction mixture was then heated to 80 °C for 20 h. The reaction was cooled down to rt and then water (30 mL) was added followed by EtOAc (30 mL). The layers were separated and the aqueous portion was extracted with EtOAc (3 × 30 mL). The organic extracts were combined and washed with a solution of NaOH (1 M, 80 mL) and then dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography (40% Et_2O/pentane) afforded oxetane **34a** (195 mg, 92%) as a white solid. R_f = 0.20 (40% Et_2O/pentane); mp = 107–109 °C; IR (film)/cm^{-1} 2956, 2879, 1699 (C=O),1611,

1512, 1403, 1367, 1297, 1247, 1180, 1133, 1032, 988, 907, 831, 808, 728; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14–7.07 (m, 2 H, 2 × Ar-CH), 7.07 (d, *J* = 2.4 Hz, 1 H, Ar-CH), 6.91–6.86 (m, 3 H, 3 × Ar-CH), 6.40 (d, *J* = 8.4 Hz, 1 H, Ar-CH), 5.19 (s, 4 H, C*H*$_2$OC*H*$_2$), 4.89–4.84 (m, 1 H, OCH), 4.33–4.29 (dd, *J* = 9.6, 6.4 Hz, 2 H, C*H*HNC*H*H), 4.03–4.00 (dd, *J* = 9.6, 4.2 Hz, 2 H, CH*H*NCH*H*), 3.82 (s, 3 H, OCH_3) , 2.24 (s, 3 H, Ar-CH_3), 1.46 (s, 9 H, 3 × CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.2 (Ar-*C*$_q$-OCH_3), 156.1 (C=O), 153.4 (Ar-*C*$_q$-OCH), 138.8 (Ar$_{(OMe)}$-*C*$_q$-C$_q$), 138.1 (Ar$_{(OCH)}$-*C*$_q$-C$_q$), 129.3 (Ar-CH), 127.6 (2 × Ar-CH), 127.2 (Ar-*C*$_q$-CH_3), 124.8 (Ar-CH), 113.9 (2 × Ar-CH), 110.5 (Ar-CH), 84.9 (*C*H_2O*C*H_2), 79.8 (*C*$_q$(CH_3)$_3$), 65.7 (OCH), 56.8 (*C*H_2N*C*H_2), 55.3 (OCH_3), 50.3 (C$_q$), 28.4 (C$_q$(*C*H_3)$_3$), 16.4 (Ar-CH_3); HRMS (+ESI) m/z calcd for $C_{25}H_{32}NO_5$ [M+H]: 426.2280, Found: 426.2281.



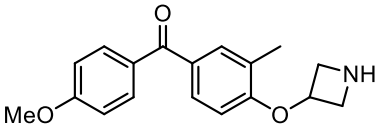
3-(4-(3-(4-Methoxyphenyl)oxetan-3-yl)-2-methylphenoxy) azetidine (8a)

Trifluoroacetic acid (128 µL, 1.67 mmol) was added to a solution of **34a** (71.0 mg, 0.17 mmol) in CH_2Cl_2 (0.9 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 20 min and then at 25 °C for 24 h. A solution of aq. NaOH (1 M, 20 mL) was added and the reaction mixture was stirred for 5 min. EtOAc (20 mL) was then added and the layers were separated. The aqueous portion was extracted with EtOAc (4 × 20 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by SCX column (see general procedure) gave amine **8a** (52.1 mg, 96%) as a white solid. R_f = 0.07 (95:5:1 CH_2Cl_2/Methanol/NEt_3); mp = 108–115 °C, IR (film)/cm^{-1} 2949, 2872, 1609, 1503, 1464, 1243, 1180, 1149, 1028, 988, 829, 806. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14–7.12 (m, 2 H, 2 × Ar-CH), 7.08 (d, *J* = 2.4 Hz, 1 H, Ar-CH), 6.90–6.85 (m, 3 H, 3 × Ar-CH), 6.46 (d, *J* = 8.4 Hz, 1 H, Ar-CH), 5.19 (s, 4 H, C*H*$_2$OC*H*$_2$), 5.01–4.98 (m, 1 H, OCH), 3.99–3.95 (m, 2 H, C*H*HNC*H*H), 3.86–3.82 (m, 5 H, CH*H*NCH*H*, OCH_3), 2.23 (s, 3 H, Ar-CH_3), 1.94 (br, s, 1 H, NH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.2 (Ar-*C*$_q$-OCH_3), 153.7 (Ar-*C*$_q$-OCH), 138.4 (Ar$_{(OMe)}$-*C*$_q$-C$_q$), 138.2 (Ar$_{(OCH)}$-*C*$_q$-C$_q$), 129.2 (Ar-CH), 127.6 (2 × Ar-CH), 127.1 (Ar-*C*$_q$-CH_3), 124.8 (Ar-CH), 113.9 (2 × Ar-CH), 110.8 (Ar-CH), 84.9 (*C*H_2O*C*H_2), 70.2 (OCH), 55.3 (OCH_3), 54.8 (*C*H_2N*C*H_2), 50.3 (C$_q$), 16.4 (Ar-CH_3); HRMS (+ESI) m/z calcd for $C_{20}H_{24}NO_3$ [M+H]:326.1756, Found: 326.1770.



***tert*-Butyl-3-(4-(4-methoxybenzoyl)-2-methylphenoxy) azetidine-1-carboxylate (34b)**

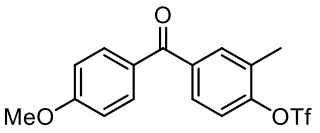
A solution of ketone **11b** (75.0 mg, 0.31 mmol) in DMF (800 µL) was added dropwise to a solution of NaH (60% dispersion in mineral oil, 16.0 mg, 0.40 mmol) in DMF (300 µL) at 0 °C. The reaction mixture was stirred for 30 min at 0 °C and then *tert*-butyl 3-bromoazetidine-1-carboxylate (146 mg, 0.62 mmol) was weighed into a flask, dissolved in DMF (100 µL) and added to the reaction mixture *via* syringe. DMF (400 µL) was added to the previous flask and then added to the reaction. The reaction mixture was heated to 80 °C for 20 h. The reaction was cooled down to rt and a solution of NaOH (1 M, 20 mL) was added followed by Et_2O (30 mL). The layers were separated and the aqueous portion was extracted with Et_2O (3 × 30 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography (40% Et_2O/pentane) afforded ketone **34b** (115 mg, 93%) as a white solid. R_f = 0.43 (25% EtOAc/pentane); mp = 107–108 °C; IR (film)/cm^{-1} 2973, 1702 (C=O), 1647 (C=O), 1601, 1403, 1313, 1254, 1171,1123, 1031, 769; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81–7.77 (m, 2 H, 2 × Ar-CH), 7.66 (s, 1 H, Ar-CH), 7.60–7.57 (dd, *J* = 8.4, 2.2 Hz, 1 H, Ar-CH), 6.99–6.95 (m, 2 H, 2 × Ar-CH), 6.49 (d, *J* = 8.4 Hz, 1 H, Ar-CH), 4.99–4.94 (tt, *J* = 6.4, 4.1 Hz, 1 H, OCH), 4.38–4.34 (dd, *J* = 10.2, 6.4 Hz, 2 H, C*H*HNC*H*H), 4.07–4.04 (dd, *J* = 10.2, 4.1 Hz, 2 H, CH*H*NCH*H*), 3.90 (s, 3 H, OCH_3), 2.29 (s, 3 H, Ar-CH_3), 1.47 (s, 9 H, 3 × CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 194.5 (C=O), 162.9 (Ar-C_q-OCH_3), 157.9 (Ar-C_q-OCH), 156.1 (C=$O_{(boc)}$), 133.0 (Ar-CH), 132.2 (2 × Ar-CH), 131.2 ($Ar_{(OMe)}$-C_q-CO), 130.6 ($Ar_{(OCH)}$-C_q-CO), 129.8 (Ar-CH), 127.0 (Ar-C_q-CH_3), 113.4 (2 × Ar-CH), 109.8 (Ar-CH), 80.0 ($C_q(CH_3)_3$), 65.9 (OCH), 56.5 (CH_2NCH_2), 55.5 (OCH_3), 28.4 ($C_q(CH_3)_3$), 16.2 (Ar-CH_3); HRMS (+ESI) m/z calcd for $C_{23}H_{28}NO_5$ [M+H]: 398.1967, Found: 398.1967.



(4-(Azetidin-3-yloxy)-3-methylphenyl)(4-methoxyphenyl) methanone (8b)

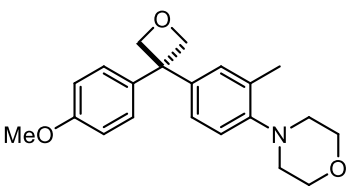
Trifluoroacetic acid (220 µL, 2.90 mmol) was added to a solution of **34b** (115 mg, 0.29 mmol) in CH_2Cl_2 (1.5 mL) at 0 °C and stirred for 30 min. The reaction mixture was then stirred at 25 °C for 18 h. A solution of NaOH (1 M, 20 mL) was added and the reaction mixture was stirred for 5 min. The mixture was extracted with Et_2O (2 × 20 mL) followed by EtOAc (2 × 20 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford amine **8b** (82.9 mg, 96%) as a pale yellow sticky solid. R_f = 0.04 (95:5:1 CH_2Cl_2/Methanol/NEt_3); mp = 99–103 °C; IR (film)/cm^{-1} 2949, 2868, 1640 (C=O), 1598, 1572, 1509, 1497, 1417, 1292, 1270, 1248, 1171,1119, 1029, 767, 729; ^{1}H NMR (400 MHz, $CDCl_3$)

δ 7.81–7.77 (m, 2 H, 2 × Ar-CH), 7.66 (d, *J* = 1.3 Hz, 1 H, Ar-CH), 7.60–7.57 (dd, *J* = 8.4, 2.2 Hz, 1 H, Ar-CH), 6.98–6.95 (m, 2 H, 2 × Ar-CH), 6.54 (d, *J* = 8.4 Hz, 1 H, Ar-CH), 5.13–5.07 (m, 1 H, OCH), 4.03 (m, 2 H, C*H*HNC*H*H), 3.90–3.86 (m, 5 H, CH*H*NCH*H*, OCH_3), 2.29 (s, 3 H, Ar-CH_3), 1.92 (br, s, 1 H, NH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 194.6 (C=O), 162.8 (Ar-C_q-OCH_3), 158.4 (Ar-C_q-OCH), 132.9 (Ar-CH), 132.2 (2 × Ar-CH), 130.8 ($Ar_{(OMe)}$-C_q-CO), 130.7 ($Ar_{(OCH)}$-C_q-CO), 129.9 (Ar-CH), 126.8 (Ar-C_q-CH_3), 113.4 (2 × Ar-CH), 110.1 (Ar-CH), 70.6 (OCH), 55.5 (OCH_3), 54.6 (CH_2NCH_2), 16.3 (Ar-CH_3); HRMS (+ESI) m/z calcd for $C_{18}H_{20}NO_3$ [M+H]: 298.1443, Found: 298.1453.



4-(4-Methoxybenzoyl)-2-methylphenyl trifluoromethanesulfonate (35b)

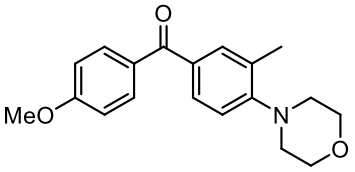
Pyridine (0.61 mL, 7.50 mmol) followed by triflic anhydride (0.84 mL, 5.00 mmol) was added to a solution of ketone **11b** (606 mg, 2.50 mmol) in CH_2Cl_2 (5.0 mL) at 0 °C. The reaction mixture was stirred at rt for 4 h. Water (20 mL) was added followed by extraction with CH_2Cl_2 (3 × 15 mL). The combined organic layers were washed with water (30 mL), then sat. aq. NaCl (2 × 25 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford triflate **35b** (814 mg, 87%) as a brown solid. R_f = 0.58 (40% Et_2O/pentane); mp = 45–47 °C; IR (film)/cm^{-1} 2988, 1651 (C=O), 1599, 1509, 1488, 1437, 1421, 1409, 1394, 1305, 1250, 1215, 1183, 1155, 1084, 1022, 950, 906, 896, 845, 829, 818, 793, 764, 737, 720, 690, 659; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84–7.80 (m, 2 H, 2 × Ar-CH), 7.72 (d, *J* = 2.2 Hz, 1 H, Ar-CH), 7.65–7.63 (dd, *J* = 8.5, 2.2 Hz, 1 H, Ar-CH), 7.36 (d, *J* = 8.5 Hz, 1 H, Ar-CH), 7.01–6.97 (m, 2 H, 2 × Ar-CH), 3.91 (s, 3 H, OCH_3), 2.46 (s, 3 H, Ar-CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.8 (C=O), 163.6 (Ar-C_q-OCH_3), 150.5 (Ar-C_q-OTf), 138.2 ($Ar_{(OTf)}$-C_q-CO), 133.4 (Ar-CH), 132.5 (2 × Ar-CH), 131.2 (Ar-C_q-CH_3), 129.4 ($Ar_{(OMe)}$-C_q-CO), 129.1 (Ar-CH), 121.1 (Ar-CH), 118.6 (q, $^1J_{C\text{-}F}$ = 320.1 Hz, CF_3), 113.8 (2 × Ar-CH), 55.5 (OCH_3), 16.4 (Ar-CH_3); ^{19}F{^{1}H} NMR (377 MHz, $CDCl_3$) δ –73.7; HRMS (+ESI) m/z calcd for $C_{16}H_{14}F_3O_5S$ [M+H]: 375.0514, Found: 375.0509.



4-(4-(3-(4-Methoxyphenyl)oxetan-3-yl)-2-methylphenyl) morpholine (9a)

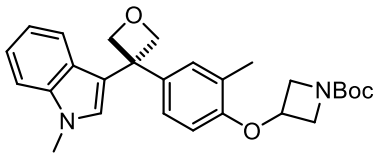
Using conditions developed by Buchwald,[99] triflated oxetane **35a**[94] (50.0 mg, 0.12 mmol), $Pd(OAc)_2$ (1.3 mg, 0.006 mmol), BINAP (5.6 mg, 0.009 mmol) and Cs_2CO_3 (55.4 mg, 0.17 mmol) were added to a reaction vial. The reaction vial was evacuated and then refilled with nitrogen three times. Morpholine (20 µL, 0.24 mmol) followed by toluene (240 µL) were added via syringe into the vial. The reaction mixture was stirred at 100 °C for 23 h then cooled to rt. Et_2O

(25 mL) was added and the reaction mixture was filtered through celite®. The organic layer was then washed with a solution of aq. NaOH (1 M, 3 × 20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography (10% to 20% EtOAc/pentane) afforded morpholine substituted oxetane **9a** (30 mg, 74%) as a white solid. R_f = 0.21 (20% EtOAc/pentane); mp = 133–135 °C; IR (film)/cm^{-1} 2962, 2930, 2895, 2862, 2813, 1608, 1580, 1513, 1500, 1439, 1298, 1251, 1228, 1184, 1114, 1068, 993, 934, 829, 799; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17–7.13 (m, 2 H, 2 × Ar-CH), 7.08 (d, *J* = 1.93 Hz, 1 H, Ar-CH), 7.01–6.96 (m, 2 H, 2 × Ar-CH), 6.92–6.88 (m, 2 H, 2 × Ar-CH), 5.23-5.20 (m, 4 H, C*H*$_2$OC*H*$_2$), 3.87–3.85 (m, 4 H, C*H*$_2$*C*H$_2$N*C*H$_2$C*H*$_2$), 3.82 (s, 3 H, OCH_3), 2.93–2.91 (m, 4 H, C*H*$_2$NC*H*$_2$), 2.32 (s, 3 H, Ar-CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.1 (Ar-*C*$_q$-OCH_3), 149.7 (Ar-*C*$_q$-N), 140.9 (Ar$_{(OMe)}$-*C*$_q$-C$_q$), 138.2 (Ar$_{(N)}$-*C*$_q$-C$_q$), 132.7 (Ar-*C*$_q$-CH_3), 129.3 (Ar-CH), 127.6 (2 × Ar-CH), 124.7 (Ar-CH), 118.8 (Ar-CH), 113.9 (2 × Ar-CH), 84.8 (*C*H$_2$O*C*H$_2$), 67.4 (CH$_2$*C*H$_2$O*C*H$_2$CH$_2$), 55.3 (OCH_3), 52.2 (*C*H$_2$N*C*H$_2$), 50.4 (C_q), 18.1 (Ar-CH_3); HRMS (+ESI) m/z calcd for $C_{21}H_{26}NO_3$ [M+H]: 340.1913, Found: 340.1920.



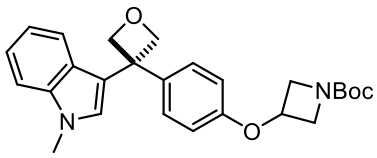
(4-Methoxyphenyl)(3-methyl-4-morpholinophenyl)methanone (9b)

Using conditions developed by Buchwald,[99] triflate **35b** (187 mg, 0.50 mmol), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), BINAP (23.4 mg, 0.037 mmol) and Cs_2CO_3 (228 mg, 0.70 mmol) were added to a reaction vial. The reaction vial was evacuated and then refilled with nitrogen three times. Morpholine (87.5 µL, 1.00 mmol) followed by toluene (1.0 mL) were added via syringe into the vial. The reaction mixture was stirred at 100 °C for 24 h then cooled to rt. Et_2O(15 mL) was added and the reaction mixture was filtered through celite® and then concentrated under reduced pressure. Purification by flash column chromatography (10% to 20% EtOAc/pentane) afforded morpholine ketone **9b** (136 mg, 87%) as a yellow oil. R_f = 0.22 (30% EtOAc/hexane); IR (film)/cm^{-1} 2958, 2851, 1645 (C=O), 1597, 1574, 1445, 1417, 1372, 1305, 1273, 1249, 1227, 1206, 1168, 1147, 1113, 1069, 1046, 1029, 971, 921, 864, 846, 829, 770, 698; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83–7.79 (m, 2 H, 2 × Ar-CH), 7.66 (d, *J* = 2.2 Hz, 1 H, Ar-CH), 7.62–7.59 (dd, *J* = 8.2, 2.2 Hz, 1 H, Ar-CH), 7.03 (d, *J* = 8.2 Hz, 1 H, Ar-CH), 6.98–6.95 (m, 2 H, 2 × Ar-CH), 3.90–3.87 (m, 7 H, OCH_3, C*H*$_2$OC*H*$_2$), 3.02–3.00 (m, 4 H, C*H*$_2$NC*H*$_2$), 2.36 (s, 3 H, Ar-CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 194.9 (C=O), 162.8 (Ar-*C*$_q$-OCH_3), 154.8 (Ar-C$_q$-N), 133.1 (Ar-CH), 132.6 (Ar$_{(N)}$-*C*$_q$-CO), 132.3 (2 × Ar-CH), 131.7 (Ar-*C*$_q$-CH_3), 130.7 (Ar$_{(OMe)}$-*C*$_q$-CO), 129.2 (Ar-CH), 117.8 (Ar-CH), 113.4 (2 × Ar-CH), 67.2 (*C*H$_2$O*C*H$_2$), 55.4 (OCH_3), 51.7 (*C*H$_2$N*C*H$_2$), 18.4 (Ar-CH_3); HRMS (+ESI) m/z calcd for $C_{19}H_{22}NO_3$ [M+H]: 312.1600, Found: 312.1603.



tert-Butyl-3-(2-methyl-4-(3-(1-methyl-1*H*-indol-3-yl)oxetan-3-yl)azetidine-1-carboxylate (36a)

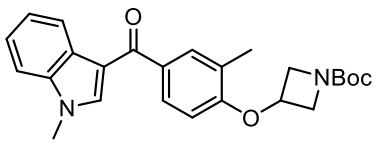
A solution of oxetane **16a** (249 mg, 1.04 mmol) in DMF (3.5 mL) was added to a solution of NaH (60% dispersion in mineral oil, 50 mg, 1.25 mmol) in DMF (0.5 mL) at 0 °C. The reaction mixture was stirred for 30 min at 0 °C and *tert*-butyl-3-bromoazetidine-1-carboxylate (504 mg, 2.10 mmol) was weighed into a flask, dissolved in DMF (0.2 mL) and added to the reaction mixture *via* syringe. DMF (0.5 mL) was then added to the previous flask and added to the reaction. The reaction mixture was heated up to 80 °C and stirred for 29 h. Water (20 mL) was added followed by EtOAc (20 mL). The layers were separated and the aqueous portion was extracted with EtOAc (3 × 20 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography (15% EtOAc/pentane to 50% EtOAc/pentane) afforded oxetane **36a** (332 mg, 71%) as a white powder. R_f = 0.29 (60% Et_2O/pentane); mp = 69–71 °C; IR (film)/cm^{-1} 2952, 2876, 1697 (C=O), 1391, 1365, 1239, 1128, 986, 740; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.0 Hz, 1 H, $Ar_{(indole)}$-CH), 7.34 (d, *J* = 8.0 Hz, 1 H, $Ar_{(indole)}$-CH), 7.29–7.25 (m, 1 H, $Ar_{(indole)}$-CH), 7.20 (d, *J* = 1.9 Hz, 1 H, Ar-CH), 7.13–7.09 (m, 1 H, $Ar_{(indole)}$-CH), 6.99 (dd, *J* = 8.3, 1.9 Hz, 1 H, Ar-CH), 6.50 (s, 1 H, N-Ar-CH), 6.41 (d, *J* = 8.3 Hz, 1 H, Ar-CH), 5.38 (d, *J* = 5.5 Hz, 2 H, C*H*HOC*H*H), 5.28 (d, *J* = 5.5 Hz, 2 H, CH*H*OCH*H*), 4.91–4.86 (m, 1 H, OCH), 4.34–4.30 (m, 2 H, C*H*HNC*H*H), 4.04 (dd, *J* = 9.9, 4.1 Hz, 2 H, CH*H*NCH*H*), 3.74 (s, 3 H, NCH_3), 2.26 (s, 3 H, Ar-CH_3), 1.47 (s, 9 H, 3 × CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.2 (C=O), 153.3 (Ar-C_q-OCH), 138.3 (Ar-C_q-C_q), 137.6 ($Ar_{(indole)}$-C_q), 129.3 (Ar-CH), 127.0 (N-Ar-CH), 127.0 ($Ar_{(indole)}$-C_q), 126.1 (Ar-C_q-CH_3), 124.8 (Ar-CH), 121.9 ($Ar_{(indole)}$-CH), 120.0 ($Ar_{(indole)}$-CH), 119.8 (N-Ar-CH-C_q), 119.3 ($Ar_{(indole)}$-CH), 110.3 (Ar-CH), 109.5 ($Ar_{(indole)}$-CH), 84.2 (CH_2OCH_2), 79.8 ($C_q(CH_3)_3$), 65.7 (OCH), 56.5 (br, CH_2NCH_2), 46.1 (C_q), 32.7 (NCH_3), 28.3 ($C_q(CH_3)_3$), 16.4 (Ar-CH_3); HRMS (+ESI) *m*/*z* calcd for $C_{27}H_{33}N_2O_4$ [M+H] : 449.2440, Found: 449.2447.



tert-Butyl 3-(4-(3-(1-methyl-1*H*-indol-3-yl)oxetan-3-yl)phenoxy)azetidine-1-carboxylate (37a)

A solution of oxetane **17a** (163 mg, 0.58 mmol) in DMF (1.5 mL) was added to a solution of NaH (60% dispersion in mineral oil, 59.0 mg, 1.48 mmol) in DMF (0.3 mL) at 0 °C. The reaction mixture was stirred for 30 min at 0 °C and then *tert*-butyl-3-bromoazetidine-1-carboxylate (274 mg, 1.16 mmol) was weighed into a flask, dissolved in DMF (0.3 mL) and added to the reaction mixture *via* syringe. DMF (0.7 mL) was added to the previous flask and then added to the reaction. The reaction mixture was heated to 80 °C. After 24 h, additional *tert*-butyl-3-bromoazetidine-1-carboxylate (137 mg,

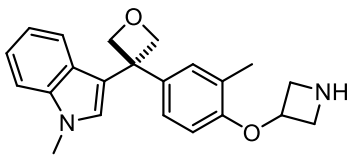
0.58 mmol) was added to the reaction mixture *via* syringe and the reaction mixture was stirred at 80 °C for 22 h before addition of NaH (60% dispersion in mineral oil, 12 mg, 0.29 mmol). The reaction mixture was stirred for a further 23 h and then water (20 mL) was added followed by EtOAc (20 mL). The layers were separated and the aqueous portion was extracted with EtOAc (3 × 20 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography (15% EtOAc/pentane to 30% EtOAc/pentane) afforded oxetane **37a** (199 mg, 79%) as a white powder. R_f = 0.14 (50% Et_2O/pentane); mp = 65–70 °C; IR (film)/cm^{-1} 2974, 1694 (C=O), 1595, 1523, 1465, 1383, 1364, 1264, 1246, 1135, 1111, 772, 748; ^1H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, *J* = 8.0 Hz, 1 H, $Ar_{(indole)}$-CH), 7.36 (d, *J* = 8.3 Hz, 1 H, $Ar_{(indole)}$-CH), 7.31–7.28 (m, 3 H, $Ar_{(indole)}$-CH, 2 × Ar-CH), 7.14–7.10 (m, 1 H, $Ar_{(indole)}$-CH), 6.75 (d, *J* = 8.7 Hz, 2 H, 2 × Ar-CH), 6.53 (s, 1 H, N-Ar-CH), 5.41 (d, *J* = 5.6 Hz, 2 H, C*H*HOC*H*H), 5.28 (d, *J* = 5.6 Hz, 2 H, CH*H*OCH*H*), 4.93–4.88 (m, 1 H, OCH), 4.32 (dd, *J* = 10.3, 6.4 Hz, 2 H, C*H*HNC*H*H), 4.05 (dd, *J* = 10.3, 4.1 Hz, 2 H, CH*H*NCH*H*), 3.76 (s, 3 H, NCH_3), 1.48 (s, 9 H, 3 × CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.1 (C=O), 155.2 (Ar-C_q-OCH), 138.8 (Ar-C_q-C_q), 137.6 ($Ar_{(indole)}$-C_q), 127.9 (2 × Ar-CH), 127.0 (N-Ar-CH), 126.1 ($Ar_{(indole)}$-C_q), 122.0 ($Ar_{(indole)}$-CH), 120.0 ($Ar_{(indole)}$-CH), 119.6 (N-Ar-CH-C_q), 119.3 ($Ar_{(indole)}$-CH), 114.4 (2 × Ar-CH), 109.5 ($Ar_{(indole)}$-CH), 84.2 (CH_2OCH_2), 79.8 ($C_q(CH_3)_3$), 65.7 (OCH), 56.3 (br, CH_2NCH_2), 46.1 (C_q), 32.7 (NCH_3), 28.3 ($C_q(CH_3)_3$); HRMS (+ESI) *m*/*z* calcd for $C_{26}H_{31}N_2O_4$ [M+H]$^+$: 435.2284, Found: 435.2284.



tert-Butyl-3-(2-methyl-4-(1-methyl-1H-indole-3-carbonyl)phenoxy)azetidine-1-carboxylate (36b)

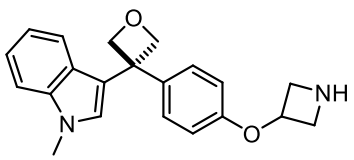
A solution of ketone **16b** (124 mg, 0.47 mmol) in DMF (1.80 mL) was added to a solution of NaH (60% dispersion in mineral oil, 22.5 mg, 0.56 mmol) in DMF (0.20 mL) at 0 °C. The reaction mixture was stirred for 30 min at 0 °C and *tert*-butyl-3-bromoazetidine-1-carboxylate (221 mg, 0.94 mmol) in DMF (0.50 mL) was added to the reaction mixture *via* syringe. The reaction mixture was then heated up to 80 °C and stirred for 19 h before addition of further NaH (60% dispersion in mineral oil, 18.6 mg, 0.47 mmol) and *tert*-butyl-3-bromoazetidine-1-carboxylate (110 mg, 0.47 mmol). The reaction mixture was stirred for 24 h and then water (30 mL) was added followed by Et_2O (20 mL). The layers were separated and the aqueous portion was extracted with Et_2O (3 × 30 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography (30% Et_2O/pentane) afforded ketone **36b** (169 mg, 86%) as a white powder. R_f = 0.25 (40% EtOAc/pentane); mp = 75–80 °C; IR (film)/cm^{-1} 2952, 2876, 1697 (C=O), 1391, 1365, 1239, 1128, 986, 740; ^1H NMR (400 MHz, $CDCl_3$) δ 8.38 (m, 1 H, $Ar_{(indole)}$-CH), 7.71 (d, *J* = 2.2 Hz,

1 H, Ar-CH), 7.64 (dd, *J* = 8.3, 2.2 Hz, 1 H, Ar-CH), 7.54 (s, 1 H, N-Ar-CH), 7.42–7.30 (m, 3 H, 3 × $Ar_{(indole)}$-CH), 6.51 (d, *J* = 8.3 Hz, 1 H, Ar-CH), 4.96 (m, 1 H, OCH), 4.36 (m, 2 H, C*H*HNC*H*H), 4.06 (m, 2 H, CH*H*NCH*H*), 3.86 (s, 3 H, NCH_3), 2.32 (s, 3 H, Ar-CH_3), 1.48 (s, 9 H, 3 × CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 189.8 (C=O), 157.3 ($C{=}O_{(boc)}$), 156.1 (Ar-C_q-OCH), 137.5 (Ar-C_q-CO), 137.1 (N-Ar-CH), 134.0 ($Ar_{(indole)}$-C_q), 131.9 (Ar-CH), 128.3 (Ar-CH), 127.3 ($Ar_{(indole)}$-C_q), 127.0 (Ar-C_q-CH_3), 123.5 ($Ar_{(indole)}$-CH), 122.7 ($Ar_{(indole)}$-CH), 122.5 ($Ar_{(indole)}$-CH), 115.7 (N-Ar-CH-C_q), 109.9 (Ar-CH), 109.5 ($Ar_{(indole)}$-CH), 79.9 ($C_q(CH_3)_3$), 65.9 (OCH), 56.5 (br, CH_2NCH_2), 33.5 (NCH_3), 28.4 ($C_q(CH_3)_3$),16.3 (Ar-CH_3). HRMS (+ESI) *m*/*z* calcd for $C_{25}H_{29}N_2O_4$ [M+H] : 421.2127, Found: 421.2126.



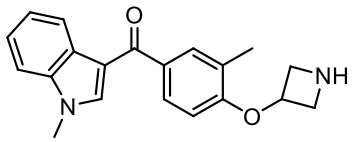
3-(3-(4-(Azetidin-3-yloxy)-3-methylphenyl)oxetan-3-yl)-1-methyl-1*H*-indole (12a)

Trifluoroacetic acid (430 µL, 5.70 mmol) was added dropwise to a solution of **36a** (301 mg, 0.67 mmol) in CH_2Cl_2 (3.0 mL) at 0 °C. The reaction mixture was stirred at 0 °C for further 30 min and then at 25 °C for 15 h. A solution of NaOH (1 M, 20 mL) was then added and the reaction mixture was stirred for 5 min. CH_2Cl_2 (20 mL) was then added and the layers were separated. The aqueous portion was extracted with CH_2Cl_2 (4 × 20 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by SCX column afforded amine **12a** (207 mg, 89%) as a yellow powder. R_f = 0.22 (95:5:1 CH_2Cl_2/Methanol/NEt_3); mp = 100–103 °C; IR (film)/cm^{-1} 2946 (NH), 2872, 1501, 1239, 1150, 984, 808, 737; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.0 Hz, 1 H, $Ar_{(indole)}$-CH), 7.34 (d, *J* = 8.2 Hz, 1 H, $Ar_{(indole)}$-CH), 7.29–7.25 (m, 1 H, $Ar_{(indole)}$-CH), 7.19 (d, *J* = 2.0 Hz, 1 H, Ar-CH), 7.13–7.09 (m, 1 H, $Ar_{(indole)}$-CH), 6.98 (dd, *J* = 8.3, 2.4 Hz, 1 H, Ar-CH), 6.50 (s, 1 H, N-Ar-CH), 6.48 (d, *J* = 8.3 Hz, 1 H, Ar-CH), 5.38 (d, *J* = 5.5 Hz, 2 H, C*H*HOC*H*H), 5.29 (d, *J* = 5.5 Hz, 2 H, CH*H*OCH*H*), 5.01 (p, *J* = 6.1 Hz, 1 H, OCH), 3.97–3.93 (m, 2 H, C*H*HNC*H*H), 3.86–3.82 (m, 2 H, CH*H*NCH*H*), 3.73 (s, 3 H, NCH_3), 2.26 (s, 3 H, Ar-CH_3), 1.93 (s, 1 H, NH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.8 (Ar-C_q-OCH), 137.8 (Ar-C_q-C_q), 137.6 ($Ar_{(indole)}$-C_q), 129.1 (Ar-CH), 127.0 (N-Ar-CH), 126.7 ($Ar_{(indole)}$-C_q), 126.2 (Ar-C_q-CH_3), 124.8 (Ar-CH), 121.9 ($Ar_{(indole)}$-CH), 120.1 ($Ar_{(indole)}$-CH), 119.9 (N-Ar-CH-C_q), 119.2 ($Ar_{(indole)}$-CH), 110.7 (Ar-CH), 109.4 ($Ar_{(indole)}$-CH), 84.3 (CH_2OCH_2), 70.6 (OCH), 55.0 (CH_2NCH_2), 46.1 (C_q), 32.6 (NCH_3), 16.4 (Ar-CH_3); HRMS (+ESI) *m*/*z* calcd for $C_{22}H_{25}N_2O_2$ [M+H] : 349.1916, Found: 349.1922.



***tert*-Butyl 3-(4-(3-(1-methyl-1*H*-indol-3-yl)oxetan-3-yl)phenoxy)azetidine-1-carboxylate (13a)**

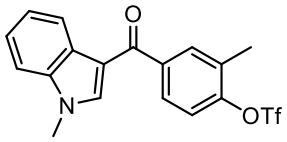
Trifluoroacetic acid (320 µL, 4.20 mmol) was added dropwise to a solution of **37a** (183 mg, 0.42 mmol) in CH_2Cl_2 (2.1 mL) at 0 °C. The reaction mixture was stirred at 0 °C for further 30 min and then at 25 °C for 18 h. A solution of NaOH (1 M, 20 mL) was then added and the reaction mixture was stirred for 5 min. CH_2Cl_2 (20 mL) was then added and the layers were separated. The aqueous portion was extracted with CH_2Cl_2 (4 × 20 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by SCX column afforded amine **13a** (125 mg, 89%) as a yellow powder. R_f = 0.18 (95:5:1 CH_2Cl_2/Methanol/NEt_3); mp = 100–103 °C; IR (film)/cm^{-1} 2942 (NH), 2872, 1508, 1237, 1181, 984, 828, 740; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, *J* = 8.0 Hz, 1 H, $Ar_{(indole)}$-CH), 7.32 (d, *J* = 8.2 Hz, 1 H, $Ar_{(indole)}$-CH), 7.25–7.22 (m, 3 H, $Ar_{(indole)}$-CH, 2 × Ar-CH), 7.09 (dd, *J* = 11.0, 3.9 Hz, 1 H, $Ar_{(indole)}$-CH), 6.74 (d, *J* = 8.7 Hz, 2 H, 2 × Ar-CH), 6.50 (s, 1 H, N-Ar-CH), 5.37 (d, *J* = 5.5 Hz, 2 H, C*H*HOC*H*H), 5.26 (d, *J* = 5.5 Hz, 2 H, CH*H*OCH*H*), 5.01–4.98 (m, 1 H, OCH), 3.93 (m, 2 H, C*H*HNC*H*H), 3.82 (m, 2 H, CH*H*NCH*H*), 3.72 (s, 3 H, NCH_3), 2.02 (br, s, 1 H, NH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.6 (Ar-C_q-OCH), 138.3 (Ar-C_q-C_q), 137.6 ($Ar_{(indole)}$-C_q), 127.8 (2 × Ar-CH), 127.0 (N-Ar-CH), 126.1 ($Ar_{(indole)}$-C_q), 121.9 ($Ar_{(indole)}$-CH), 120.0 ($Ar_{(indole)}$-CH), 119.7 (N-Ar-CH-C_q), 119.3 ($Ar_{(indole)}$-CH), 114.4 (2 × Ar-CH), 109.5 ($Ar_{(indole)}$-CH), 84.3 (*C*H_2O*C*H_2), 70.5 (OCH), 54.8 (*C*H_2N*C*H_2), 46.1 (C_q), 32.7 (NCH_3); HRMS (+ESI) *m*/*z* calcd for $C_{21}H_{23}N_2O_2$ [M+H] : 335.1760, Found: 335.1776.



(4-(Azetidin-3-yloxy)-3-methylphenyl)(1-methyl-1*H*-indol-3-yl)methanone (12b)

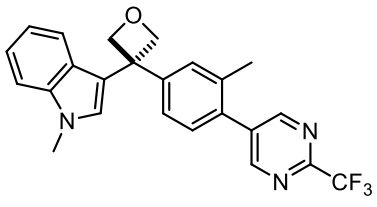
Trifluoroacetic acid (280 µL, 3.60 mmol) was added dropwise to a solution of **36b** (152 mg, 0.36 mmol) in CH_2Cl_2 (2.0 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min and then at 25 °C for 15 h. A solution of aq. NaOH (1 M, 20 mL) was added and the reaction mixture was stirred for 5 min. Et_2O (20 mL) was added and the layers were separated. The aqueous portion was extracted with Et_2O (3 × 20 mL) and EtOAc (20 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give amine **12b** (104 mg, 91%) as a white powder. R_f = 0.25 (95:5:1 CH_2Cl_2/Methanol/NEt_3); mp = 70–75 °C; IR (film)/cm^{-1} 3324 (br, NH), 2947, 1596 (C=O), 1520, 1463, 1362, 1263, 1245, 1199, 1145, 1126, 1112, 1075, 772, 748; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42–8.35 (m, 1 H, $Ar_{(indole)}$-CH), 7.70 (d, *J* = 1.3 Hz, 1 H, Ar-CH), 7.64 (dd, *J* = 8.4, 2.3 Hz, 1 H, Ar-CH), 7.54 (s, 1 H, N-Ar-CH), 7.38–7.31 (m, 3 H, 3 × $Ar_{(indole)}$-CH), 6.56 (d, *J* = 8.4 Hz, 1 H, Ar-CH), 5.09 (m, 1 H, OCH), 4.00 (m, 2 H, C*H*HNC*H*H), 3.85 (s, 5 H, CH*H*NCH*H,* NCH_3),

2.31 (s, 3 H, Ar-CH_3), 2.11 (br, s, 1 H, NH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 189.9 (C=O), 157.8 (Ar-C_q-OCH), 137.4 (Ar-C_q-CO), 137.0 (N-Ar-CH), 133.5 ($Ar_{(indole)}$-C_q), 131.7 (Ar-CH), 128.4 (Ar-CH), 127.3 ($Ar_{(indole)}$-C_q), 126.8 (Ar-C_q-CH_3), 123.4 ($Ar_{(indole)}$-CH), 122.7 ($Ar_{(indole)}$-CH), 122.4 ($Ar_{(indole)}$-CH), 115.7 (N-Ar-CH-C_q), 110.2 (Ar-CH), 109.5 ($Ar_{(indole)}$-CH), 70.7 (OCH), 54.8 (CH_2NCH_2), 33.5 (NCH_3), 16.3 (Ar-CH_3); HRMS (+ESI) *m*/*z* calcd for $C_{20}H_{21}N_2O_2$ [M+H]: 321.1603, Found: 321.1612.



2-Methyl-4-(1-methyl-1*H*-indole-3-carbonyl)phenyl trifluoromethanesulfonate (38b)

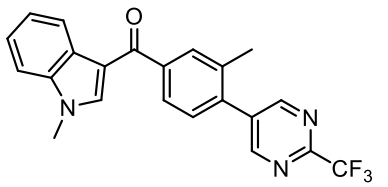
Pyridine (55.0 µL, 0.68 mmol) followed by triflic anhydride (172 µL, 1.02 mmol) was added to a solution of ketone **16b** (90.5 mg, 0.34 mmol) in CH_2Cl_2 (680 µL) at 0 °C. The reaction mixture was stirred at 25 °C for 3 h. Water (30 mL) was added followed by CH_2Cl_2 (30 mL). The layers were separated and the aqueous portion was extracted with CH_2Cl_2 (4 × 30 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography (30% Et_2O/pentane) afforded triflate **38b** (67.6 mg, 50%) as a white solid. R_f = 0.15 (20% Et_2O/pentane); mp = 157–159 °C; IR (film)/cm^{-1} 1612 (C=O), 1587, 1520, 1487, 1462, 1421, 1397, 1369, 1241, 1208, 1183, 1041, 1012, 908, 884, 823, 753, 726; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44–8.40 (m, 1 H, $Ar_{(indole)}$-CH), 7.76 (d, *J* = 2.1 Hz, 1 H, Ar-CH), 7.70–7.68 (dd, 1 H, *J* = 8.4, 2.1 Hz, Ar-CH), 7.52 (s, 1 H, $Ar_{(indole)}$-CH), 7.42–7.35 (m, 4 H, 2 × $Ar_{(indole)}$-CH, Ar-CH, N-Ar-CH), 3.88 (s, 3 H, NCH_3), 2.47 (s, 3 H, Ar-CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 188.8 (C=O), 149.9 (Ar-C_q-OTf), 140.8 (Ar-C_q-CO), 137.9 (N-Ar-CH), 137.6 ($Ar_{(indole)}$-C_q), 132.3 (Ar-CH), 131.2 (Ar-C_q-CH_3), 127.9 (Ar-CH), 127.0 ($Ar_{(indole)}$-C_q), 123.9 ($Ar_{(indole)}$-CH), 123.0 ($Ar_{(indole)}$-CH), 122.6 ($Ar_{(indole)}$-CH), 121.1 (Ar-CH), 118.6 (q, $^1J_{C-F}$ = 319.9 Hz, CF_3), 115.2 (N-Ar-CH-C_q), 109.7 ($Ar_{(indole)}$-CH), 33.6 (NCH_3), 16.4 (Ar-CH_3); ^{19}F{^{1}H} NMR (377 MHz, $CDCl_3$) δ –73.7; HRMS (+ESI) m/z calcd for $C_{18}H_{15}F_3NO_4S$ [M+H]: 398.0674, Found: 398.0668.



1-Methyl-3-(3-(3-methyl-4-(2-(trifluoromethyl)pyrimidin-5-yl)phenyl)oxetan-3-yl)-1*H*-indole (15a)

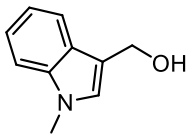
Triflate **38a**[94] (44.2 mg, 0.10 mmol), pyrimidine pinacol ester (41.1 mg, 0.15 mmol), $Pd(OAc)_2$ (1.1 mg, 0.005 mmol), SPhos (4.1 mg, 0.010 mmol) and K_3PO_4 (42.4 mg, 0.20 mmol) were added to a reaction vial. The reaction vial was evacuated and then refilled with nitrogen three times. Dioxane/water (4:1, 1.0 mL) was added *via* syringe. The reaction mixture was stirred at 65 °C for 23 h then cooled to rt. Et_2O (20 mL) was added and the crude mixture was filtered through celite® and then concentrated under reduced pressure. Purification by flash column

chromatography (10% to 20% EtOAc/hexane) afforded oxetane **15a** (29.4 mg, 70%) as a white solid. R_f = 0.29 (30% Et_2O/pentane); mp = 181–182 °C; IR (film)/cm^{-1} 3052, 2962, 2883, 1611, 1551, 1469, 1351, 1209, 1145, 1113, 970, 814, 742, 732; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.92 (s, 2 H, 2 × $Ar_{(pyrimidine)}$-CH), 7.66–7.63 (dt, *J* = 7.9, 1.0, 1 H, $Ar_{(indole)}$-CH), 7.42 (d, *J* = 1.1 Hz, 1 H, Ar-CH), 7.38–7.36 (m, 1 H, $Ar_{(indole)}$-CH), 7.32–7.27 (m, 2 H, Ar-CH, $Ar_{(indole)}$-CH), 7.23 (d, *J* = 8.0 Hz, 1 H, Ar-CH), 7.15–7.11 (ddd, *J* = 7.9, 6.9, 1.0 Hz, 1 H, $Ar_{(indole)}$-CH), 6.64 (s, 1 H, N-Ar-CH), 5.44 (d, *J* = 5.7 Hz, 2 H, C*H*HOC*H*H), 5.33 (d, *J* = 5.7 Hz, 2 H, CH*H*OCH*H*), 3.79 (s, 3 H, NCH_3), 2.34 (s, 3 H, Ar-CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.6 (2 × $Ar_{(pyrimidine)}$-CH), 155.0 (q, $^2J_{C\text{-}CF3}$ = 37.2 Hz, C_q-CF_3), 147.4 (Ar-C_q-C_q), 137.6 ($Ar_{(indole)}$-C_q), 137.0 ($C_{q(pyrimidine)}$), 135.9 (Ar-C_q-CH_3), 131.2 (Ar-C_q-$C_{q(pyrimidine)}$), 129.9 (Ar-CH), 129.1 (Ar-CH), 126.9 (N-Ar-CH), 125.9 ($Ar_{(indole)}$-C_q), 125.0 (Ar-CH), 122.1 ($Ar_{(indole)}$-CH), 119.8 ($Ar_{(indole)}$-CH), 119.7 (q, $^1J_{C\text{-}F}$ = 273.8 Hz, CF_3), 119.4 ($Ar_{(indole)}$-CH), 118.8 (N-Ar-CH-C_q), 109.6 ($Ar_{(indole)}$-CH), 83.9 (CH_2OCH_2), 46.5 (C_q), 32.8 (NCH_3), 20.5 (Ar-CH_3); ^{19}F{^{1}H} NMR (377 MHz, $CDCl_3$) δ –70.1; HRMS (+ESI) m/z calcd for $C_{24}H_{21}F_3N_3O$ [M+H]: 424.1637, Found: 424.1632.



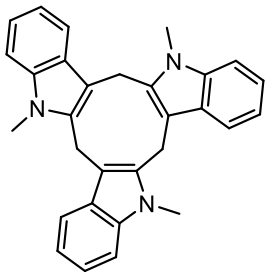
(1-Methyl-1*H*-indol-3-yl)(3-methyl-4-(2-(trifluoromethyl)pyrimidin-5-yl)phenyl)methanone (15b)

Triflate **38b** (64.1 mg, 0.161 mmol), pyrimidine pinacol ester (66.2 mg, 0.242 mmol), $Pd(OAc)_2$ (1.8 mg, 0.008 mmol), SPhos (6.6 mg, 0.016 mmol) and K_3PO_4 (65.4 mg, 0.308 mmol) were added to a reaction vial. The reaction vial was evacuated and then refilled with nitrogen three times. Dioxane/water (4:1, 1.6 mL) was added *via* syringe. The reaction mixture was stirred at 65 °C for 22 h then cooled to rt. Et_2O (20 mL) was added and the crude mixture was filtered through celite® and then concentrated under reduced pressure. Purification by flash column chromatography (20% Et_2O/pentane) afforded oxetane **15b** (63 mg, 99%) as a yellow solid. R_f = 0.29 (30% Et_2O/pentane); mp = 185–187 °C; IR (film)/cm^{-1} 3057, 1598 (C=O), 1521, 1464, 1367, 1350, 1231, 1186, 1141, 1118, 1106, 1077, 812, 773, 742, 733; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.94 (s, 2 H, 2 × $Ar_{(pyrimidine)}$-CH), 8.48–8.40 (m, 1 H, $Ar_{(indole)}$-CH), 7.81 (s, 1 H, Ar-CH), 7.76 (d, *J* = 7.6 Hz, 1 H, Ar-CH), 7.59 (s, 1 H, N-Ar-CH), 7.45–7.32 (m, 4 H, 3 × $Ar_{(indole)}$-CH, Ar-CH), 3.89 (s, 3 H, NCH_3), 2.40 (s, 3 H, Ar-CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 189.7 (C=O), 157.4 (2 × $Ar_{(pyrimidine)}$-CH), 155.4 (q, $^2J_{C\text{-}CF3}$ = 36.8 Hz, C_q-CF_3), 142.1 (Ar-C_q-CO), 137.8 (N-Ar-CH), 137.6 ($Ar_{(indole)}$-C_q), 136.6 ($C_{q\ (pyrimidine)}$), 136.1 (Ar-C_q-CH_3), 135.3 (Ar-$C_{q\ (pyrimidine)}$), 131.1 (Ar-CH), 129.7 (Ar-CH), 127.0 ($Ar_{(indole)}$-C_q), 126.8 (Ar-CH), 123.8 ($Ar_{(indole)}$-CH), 122.9 ($Ar_{(indole)}$-CH), 122.7 ($Ar_{(indole)}$-CH), 119.6 (q, $J_{C\text{-}F}$ = 275.9 Hz, CF_3), 115.4 (N-Ar-CH-C_q), 109.7 ($Ar_{(indole)}$-CH), 33.6 (NCH_3), 20.3 (Ar-CH_3); ^{19}F{^{1}H} NMR (377 MHz, $CDCl_3$) δ –70.1; HRMS (+ESI) m/z calcd for $C_{22}H_{17}F_3N_3O$ [M+H]: 396.1324, Found: 396.1344.



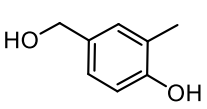
(1-Methyl-1*H*-indol-3-yl)methanol (39)

$NaBH_4$ (214 mg, 5.65 mmol) was added portionwise to a solution of 1-methyl-1*H*-3-carbaldehyde (300 mg, 1.88 mmol) in dry ethanol (15.7 mL) at 25 °C. The reaction mixture was stirred for 2 h then the solvent was removed under reduced pressure followed by the addition of water (30 mL). The aqueous layer was extracted with Et_2O (3 × 30 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford alcohol **39** (297 mg, 98%) as a yellow oil. R_f = 0.30 (100% Et_2O); IR (film)/cm^{-1} 3317 (br, OH), 2931, 2874, 1474, 1328, 1127, 1064, 1025, 982, 781, 735, 675; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77–7.68 (m, 1 H, $Ar_{(indole)}$-CH), 7.34 (d, *J* = 8.2 Hz, 1 H, $Ar_{(indole)}$-CH), 7.30–7.25 (m, 1 H, $Ar_{(indole)}$-CH), 7.20–7.15 (m, 1 H, $Ar_{(indole)}$-CH), 7.09 (s, 1 H, N-Ar-CH), 4.88 (s, 2 H, CH_2), 3.79 (s, 3 H, NCH_3), 1.40, (br, s, 1 H, OH)*; HRMS (+EI) *m*/*z* calcd for $C_{10}H_{11}NO^{\bullet+}$ $[M]^{\bullet+}$: 161.0841, Found: 161.0835. Compound previously reported without characterisation data.[234] ** ^{13}CNMR could not be obtained due to the instability of the product.*



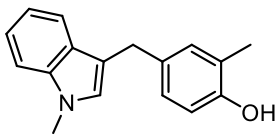
1,4,7-Trihydrocyclononano[2,3-b:5,6-b:8,9-b]tri-1-methylindole (40)

$FeCl_3$ (4.90 mg, 0.03 mmol) was added to a solution of **39** (98.0 mg, 0.61 mmol) in CH_2Cl_2 (1.20 mL) at 25 °C. The reaction mixture was stirred for 1 h then sat. aq $NaHCO_3$ (15 mL) was added followed by CH_2Cl_2 (15 mL). The layers were separated and the aqueous portion was extracted with CH_2Cl_2 (2 × 15 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford trimer **40** (83.5 mg, 96%) as a beige powder. R*f* = 0.69 (50% Et_2O/pentane); mp = 275–282 °C [lit. = 278–281 °C][101], coloration into a black solid from 235 °C; IR (film)/cm^{-1} 2925, 1469, 1434, 1363, 1176, 1130, 1013, 731; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, *J* = 7.8 Hz, 3 H, 3 × $Ar_{(indole)}$-CH), 7.29 (d, *J* = 8.1 Hz, 3 H, 3 × $Ar_{(indole)}$-CH), 7.21–7.14 (m, 3 H, 3 × $Ar_{(indole)}$-CH), 7.13–7.05 (m, 3 H, 3 × $Ar_{(indole)}$-CH), 4.07 (s, 6 H, 3 × CH_2), 3.76 (s, 9 H, 3 × CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.3 (3 × $Ar_{(indole)}$-C_q), 136.0 (3 × $Ar_{(indole)}$-C_q), 127.5 (3 × N-Ar-C_q), 120.8 (3 × $Ar_{(indole)}$-CH), 118.9 (3 × $Ar_{(indole)}$-CH), 117.2 (3 × $Ar_{(indole)}$-CH), 108.9 (3 × $Ar_{(indole)}$-CH), 107.0 (3 × N-Ar-C_q-C_q), 29.7 (3 × NCH_3), 20.4 (3 × CH_2); HRMS (+APCI) *m*/*z* calcd for $C_{30}H_{28}N_3^+$ $[M+H]^+$: 430.2278, Found: 430.2278. The observed spectroscopic and physical data (^{1}H, ^{13}C, mp) for this compound was consistent with that previously reported.[101]



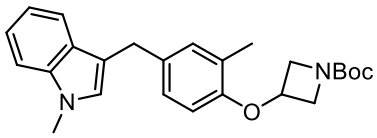
4-(Hydroxymethyl)-2-methylphenol (41)

$NaBH_4$ (471 mg, 12.4 mmol) was added to a solution of 4-hydroxy-3-methylbenzaldehyde (847 mg, 6.22 mmol) in dry ethanol (12.4 mL) at –5 °C. The reaction mixture was stirred for a further 30 min then the solvent was removed under reduced pressure. EtOAc (50 mL) and water (50 mL) were added. The layers were separated and then the aqueous layer was extracted with EtOAc (3 × 50 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford alcohol **41** (804 mg, 94%) as a pale pink solid. R_f = 0.50 (100% Et_2O); mp = 86–88 °C; IR (film)/cm^{-1} 3405 (br, OH), 3182 (br, OH), 2868, 1739, 1611, 1509, 1472, 1458, 1420, 1352, 1250, 1208, 1114, 1002, 820; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.10 (s, 1 H, Ar-OH), 6.98 (s, 1 H, Ar-CH), 6.91 (dd, *J* = 8.1, 1.9 Hz, 1 H, Ar-CH), 6.70 (d, *J* = 8.1 Hz, 1 H, Ar-CH), 4.89 (t, *J* = 5.7 Hz, 1 H, CH_2OH), 4.32 (d, *J* = 5.7 Hz, 2 H, CH_2), 2.10 (s, 3 H, CH_3); ^{13}C NMR (101 MHz, DMSO-d_6) δ 154.2 (Ar-C_q-OH), 132.7 (Ar-C_q-CH_2), 129.5 (Ar-CH), 125.4 (Ar-CH), 123.3 (Ar-C_q-CH_3), 114.3 (Ar-CH), 63.0 (CH_2), 16.2 (Ar-CH_3); HRMS (+EI) *m*/*z* calcd for $C_8H_{10}O_2^{\bullet}$ [M]$^{\bullet}$: 138.0681, Found: 138.0677. Compound previously reported.[235]



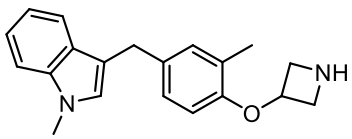
2-Methyl-4((1-methyl-1*H*-indol-3-yl)methyl)phenol (16c)

Calcium(II) bis(trifluoromethanesulfonimide) (174 mg, 0.29 mmol) and tetrabutylammonium hexafluorophosphate (112 mg, 0.29 mmol) were added to a solution of 4-(hydroxymethyl)-2-methylphenol **41** (799 mg, 5.78 mmol) and 1-methyl-1*H*-indole (2.20 mL,17.4 mmol) in CH_2Cl_2 (19.3 mL). The reaction mixture was stirred at 40 °C for 2 h then sat. aq. $NaHCO_3$ (30 mL) was added followed by CH_2Cl_2 (30 mL). The layers were separated and the aqueous portion was extracted with CH_2Cl_2 (2 × 30 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography (10% EtOAc/hexane) afforded diarylmethane **16c** (947 mg, 65%) as a light pink powder. R_f = 0.48 (50% Et_2O/pentane); mp = 77–79 °C; IR (film)/cm^{-1} 3407 (br, OH), 2904, 1506,1483, 1251, 1108, 736; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, *J* = 7.9 Hz, 1 H, $Ar_{(indole)}$-CH), 7.30 (d, *J* = 8.2 Hz, 1 H, $Ar_{(indole)}$-CH), 7.24–7.20 (m, 1 H, $Ar_{(indole)}$-CH), 7.10–7.05 (m, 2 H, $Ar_{(indole)}$-CH, Ar-CH), 7.00 (dd, *J* = 8.0, 2.0 Hz, 1 H, Ar-CH), 6.75 (s, 1 H, N-Ar-CH), 6.69 (d, *J* = 8.0 Hz, 1 H, Ar-CH), 4.52 (s, 1 H, OH), 3.99 (s, 2 H, CH_2), 3.74 (s, 3 H, NCH_3), 2.22 (s, 3 H, Ar-CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.8 (Ar-C_q-OH), 137.1 (Ar-C_q-CH_2), 133.6 ($Ar_{(indole)}$-C_q), 131.2 (Ar-CH), 127.8 (Ar-C_q-CH_3), 127.1 (Ar-CH), 127.0 (N-Ar-CH), 123.4 ($Ar_{(indole)}$-C_q), 121.5 ($Ar_{(indole)}$-CH), 119.2 ($Ar_{(indole)}$-CH), 118.7 ($Ar_{(indole)}$-CH), 114.8 (N-Ar-CH-C_q), 114.7 (Ar-CH), 109.1 ($Ar_{(indole)}$-CH), 32.6 (NCH_3), 30.6 (CH_2), 15.7 (Ar-CH_3); HRMS (+ESI) *m*/*z* calcd for $C_{17}H_{18}NO$ [M+H] : 252.1388, Found: 252.1393.



tert-Butyl-3-(2-methyl-4-((1-methyl-1*H*-indol-3-yl)methyl)phenoxy)azetidine-1-carboxylate (36c)

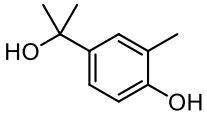
A solution of **16c** (251 mg, 0.99 mmol) in DMF (2.5 mL) was added to a solution of NaH (60% dispersion in mineral oil, 47.7 mg, 1.20 mmol) in DMF (0.5 mL) at 0 °C. The reaction mixture was stirred for 30 min at 0 °C and then a solution of *tert*-butyl-3-bromoazetidine-1-carboxylate (468 mg, 1.98 mmol) in DMF (1.0 mL) added to the reaction mixture *via* syringe. The reaction was heated up to 80 °C, stirred for 32 h and then water (20 mL) was added followed by EtOAc (20 mL). The layers were separated and the aqueous portion was extracted with EtOAc (3 × 20 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography (5% to 10% Acetone/pentane) afforded the ether **36c** (330 mg, 82%) as a white solid. R_f = 0.28 (10% acetone/pentane); mp = 44–47 °C; IR (film)/cm^{-1} 2973, 1696 (C=O), 1391, 1365, 1248, 1218, 1147, 1127, 738; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, *J* = 7.9 Hz, 1 H, $Ar_{(indole)}$-CH), 7.30 (d, *J* = 8.2 Hz, 1 H, $Ar_{(indole)}$-CH), 7.24–7.20 (m, 1 H, $Ar_{(indole)}$-CH), 7.10–7.06 (m, 2 H, $Ar_{(indole)}$-CH, Ar-CH), 7.02 (dd, *J* = 8.2, 1.9 Hz, 1 H, Ar-CH), 6.76 (s, 1 H, N-Ar-CH), 6.36 (d, *J* = 8.2 Hz, 1 H, Ar-CH), 4.84 (m, 1 H, OCH), 4.29 (dd, *J* = 9.6, 6.4 Hz, 2 H, C*H*HNC*H*H), 4.01 (m, *J* = 4.3 Hz, 4 H, CH*H*NCH*H,* CH_2), 3.74 (s, 3 H, NCH_3), 2.21 (s, 3 H, Ar-CH_3), 1.46 (s, 9 H, 3 × CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.2 (C=O), 153.0 (Ar-C_q-OCH), 137.2 (Ar-C_q-CH_2), 134.1 ($Ar_{(indole)}$-C_q), 131.5 (Ar-CH), 127.8 (Ar-CH), 126.9 ($Ar_{(indole)}$-C_q), 126.7 (Ar-C_q-CH_3), 126.6 (N-Ar-CH), 121.5 ($Ar_{(indole)}$-CH), 119.2 ($Ar_{(indole)}$-CH), 118.7 ($Ar_{(indole)}$-CH), 114.6 (N-Ar-CH-C_q), 110.7 (Ar-CH), 109.1 ($Ar_{(indole)}$-CH), 79.7 ($C_q(CH_3)_3$), 65.6 (OCH), 56.3 (br, CH_2NCH_2), 32.6 (NCH_3), 30.6 (CH_2), 28.4 ($C_q(CH_3)_3$), 16.2 (Ar-CH_3); HRMS (+ESI) *m*/*z* calcd for $C_{25}H_{31}N_2O_3$ [M+H] : 404.2335, Found: 407.2337.



3-(4-(Azetidin-3-yloxy)-3-methylbenzyl)-1-methyl-1*H*-indole (12c)

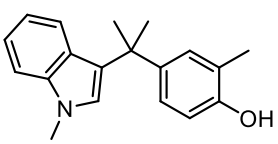
Trifluoroacetic acid (600 µL, 7.80 mmol) was added dropwise to a solution of **36c** (318 mg, 0.78 mmol) in CH_2Cl_2 (3.9 mL) at 0 °C. The reaction mixture was stirred at 0 °C for further 30 min and then at 25 °C for 6 h. A solution of NaOH (1 M, 20 mL) was then added and the reaction mixture was stirred for 5 min. CH_2Cl_2 (20 mL) was added and the layers were separated. The aqueous portion was then extracted with CH_2Cl_2 (4 × 20 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by SCX column afforded amine **12c** (231 mg, 97%) as a beige solid. R_f = 0.26 (95:5:1 CH_2Cl_2/Methanol/NEt_3); mp = 80–82 °C; IR (film)/cm^{-1} 2943 (NH), 1499, 1471, 1248, 1217, 1148, 737; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, *J* = 7.8 Hz, 1 H, $Ar_{(indole)}$-CH), 7.32 (d, *J* = 8.1 Hz, 1 H, $Ar_{(indole)}$-CH), 7.28–7.24 (m, 1 H, $Ar_{(indole)}$-CH), 7.14–7.10 (m , 2 H,

$Ar_{(indole)}$-CH, Ar-CH), 7.05 (d, *J* = 8.4 Hz, 1 H, Ar-CH), 6.78 (s, 1 H, N-Ar-CH), 6.45 (d, *J* = 8.2 Hz, 1 H, Ar-CH), 4.99 (m, 1 H, OCH), 4.05 (s, 2 H, CH_2), 3.96 (m, 2 H, C*H*HNC*H*H), 3.84 (m, 2 H, CH*H*NCH*H*), 3.75 (s, 3 H, NCH_3), 2.72 (br, s, 1 H, NH), 2.25 (s, 3 H, Ar-CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.3 (Ar-C_q-OCH), 137.1 (Ar-C_q-CH_2), 133.6 ($Ar_{(indole)}$-C_q), 131.3 (Ar-CH), 127.7 ($Ar_{(indole)}$-C_q), 126.9 (N-Ar-CH), 126.5 (Ar-CH), 126.5 (Ar-C_q-CH_3), 121.4 ($Ar_{(indole)}$-CH), 119.1 ($Ar_{(indole)}$-CH), 118.6 ($Ar_{(indole)}$-CH), 114.6 (N-Ar-CH-C_q), 111.0 (Ar-CH), 109.0 ($Ar_{(indole)}$-CH), 70.3 (OCH), 54.9 (CH_2NCH_2), 32.5 (NCH_3), 30.5 (CH_2), 16.2 (Ar-CH_3); HRMS (+ESI) *m*/*z* calcd for $C_{20}H_{23}N_2O$ [M+H]: 307.1810, Found: 307.1816.



4-(2-Hydroxypropan-2-yl)-2-methylphenol (42)

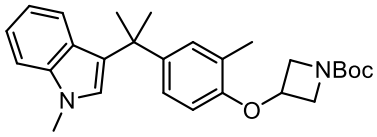
A solution of methylmagnesium bromide (2.1 M in THF, 2.85 mL, 6.0 mmol) was added dropwise over 5 min to a solution of 4′-Hydroxy-3′-methylacetophenone (300 mg, 2.0 mmol) in THF (7.0 mL) at 0 °C. The reaction mixture was stirred for 30 min at 0 °C and then 16 h 30 min at 25 °C and then 15 mL of sat. aq. NH_4Cl (15 mL) was added followed by Et_2O (15 mL). The layers were separated and the aqueous portion was extracted with Et_2O (2 × 15 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give alcohol **42** (332 mg, 100%) as a yellow brown powder. R_f = 0.24 (50% Et_2O/pentane); mp = 137–140 °C; IR (film)/cm^{-1} 3309 (br, OH), 2972 (br, OH), 1508, 1361, 1281, 1152, 1104, 951, 832, 824; ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 9.00 (s, 1 H, Ar-OH), 7.13 (s, 1 H, Ar-CH), 7.04 (d, *J* = 8.0 Hz, 1 H, Ar-CH), 6.66 (d, *J* = 8.0 Hz, 1 H, Ar-CH), 4.75 (s, 1 H, OH), 2.10 (s, 3 H, Ar-CH_3), 1.36 (s, 6 H, C*H*$_3$CC*H*$_3$); ^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ 153.4 (Ar-C_q-OH), 140.8 (Ar-C_q-CH_3), 126.9 (Ar-CH), 122.7 (Ar-CH), 122.5 (Ar-C_q-$C(CH_3)_2$), 113.7 (Ar-CH), 70.2 ($C_q(CH_3)_2$), 32.1 ($C_q(CH_3)_2$), 16.3 (Ar-CH_3). HRMS (EI+) *m*/*z* calcd for $C_{10}H_{14}O_2^{\bullet}$ [M]$^{\bullet}$: 166.0994, Found: 166.0988. Compound previously reported without characterisation data.[236]



2-Methyl-4-(2-(1-methyl-1*H*-indol-3-yl)propan-2-yl)phenol (16d)

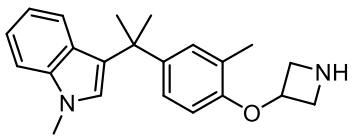
Calcium(II) bis(trifluoromethanesulfonimide) (99.0 mg, 0.17 mmol) and tetrabutylammonium hexafluorophosphate (63.9 mg, 0.17 mmol) were added to a solution of **42** (548 mg, 3.30 mmol) and 1-methyl-1*H*-indole (824 µL, 6.60 mmol) in CH_2Cl_2 (15.0 mL). The reaction mixture was stirred at 40 °C for 3 h then sat. aq. $NaHCO_3$ (50 mL) was added followed by CH_2Cl_2 (50 mL). The layers were separated and the aqueous portion was extracted with CH_2Cl_2 (3 × 50 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography (5% EtOAc/pentane) afforded *gem*-dimethyl derivative **16d** (850 mg, 92%) as a yellow solid. R_f = 0.80 (50% Et_2O/pentane); mp = 110–112 °C; IR (film)/cm^{-1} 3517 (br, OH),

2958, 2929, 1506, 1482, 1324, 1103, 818, 750; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (d, *J* = 8.2 Hz, 1 H, $Ar_{(indole)}$-CH), 7.18–7.11 (m, 3 H, 2 × $Ar_{(indole)}$-CH, Ar-CH), 7.05 (dd, *J* = 8.3, 2.4 Hz, 1 H, Ar-CH), 6.94 (s, 1 H, N-Ar-CH), 6.92–6.88 (m, 1 H, $Ar_{(indole)}$-CH), 6.65 (d, *J* = 8.3 Hz, 1 H, Ar-CH), 4.53 (s, 1 H, OH), 3.79 (s, 3 H, NCH_3), 2.21 (s, 3 H, Ar-CH_3), 1.75 (s, 6 H, C*H*$_3$CC*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.5 (Ar-C_q-OH), 142.4 (Ar-*C*$_q$-C$(CH_3)_2$), 137.8 ($Ar_{(indole)}$-C_q), 129.0 (Ar-CH), 126.4 ($Ar_{(indole)}$-C_q), 125.4 (N-Ar-CH), 125.1 (Ar-CH), 124.9 (Ar-*C*$_q$-CH_3), 122.8 (N-Ar-CH-*C*$_q$), 121.5 ($Ar_{(indole)}$-CH), 121.1 ($Ar_{(indole)}$-CH), 118.2 ($Ar_{(indole)}$-CH), 114.3 (Ar-CH), 109.0 ($Ar_{(indole)}$-CH), 38.2 (*C*$_q$$(CH_3)_2$), 32.6 ($NCH_3$), 31.0 ($C_q$(*C*$H_3)_2$), 16.0 (Ar-$CH_3$); HRMS (+ESI) *m*/*z* calcd for $C_{19}H_{22}NO$ [M+H]$^+$: 280.1701, Found: 280.1715.



tert-Butyl-3-(2-methyl-4-(2-(1-methyl-1*H*-indol-3-yl)propan-2-yl)phenoxy)azetidine-1-carboxylate (36d)

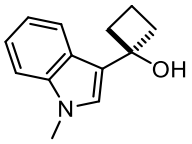
A solution of **16d** (500 mg, 1.79 mmol) in DMF (4.7 mL) was added to a solution of NaH (60% dispersion in mineral oil, 85.9 mg, 2.15 mmol) in DMF (1.1 mL) at 0 °C. The reaction mixture was stirred for 30 min at 0 °C and then *tert*-butyl-3-bromoazetidine-1-carboxylate (845 mg, 3.58 mmol) was weighed into a flask, dissolved in DMF (0.5 mL) and then added to the reaction mixture *via* a syringe. DMF (1.4 mL) was added to the previous flask and then added to the reaction. The reaction mixture was then heated to 85 °C for further 24 h, then water (30 mL) was added followed by EtOAc (40 mL). The layers were separated and the aqueous portion was extracted with EtOAc (3 × 40 mL). The organic extracts were combined and washed with sat. aq. NaCl (100 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography (5% EtOAc/pentane) afforded the ether **36d** (757 mg, 97%) as a white solid. R_f = 0.10 (5% EtOAc/pentane); mp = 60–63 °C; IR (film)/cm^{-1} 2964, 1700 (C=O), 1501, 1400, 1365, 1248, 1130, 738; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (d, *J* = 8.2 Hz, 1 H, $Ar_{(indole)}$-CH), 7.18–7.05 (m, 4 H, 3 × $Ar_{(indole)}$-CH, Ar-CH), 6.93–6.88 (m, 2 H, Ar-CH, N-Ar-CH), 6.32 (d, *J* = 12 Hz, 1 H, Ar-CH), 4.85–4.82 (m, 1 H, OCH), 4.28 (dd, *J* = 9.5, 6.4, 2 H, C*H*HNC*H*H), 4.01 (dd, *J* = 9.5, 4.1 Hz, 2 H, CH*H*NCH*H*), 3.79 (s, 3 H, NCH_3), 2.19 (s, 3 H, Ar-CH_3), 1.74 (s, 6 H, C*H*$_3$CC*H*$_3$), 1.47 (s, 9 H, 3 × CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.2 (C=O), 152.6 (Ar-*C*$_q$-OCH), 142.7 (Ar-*C*$_q$-C$(CH_3)_2$), 137.7 ($Ar_{(indole)}$-C_q), 129.3 (Ar-CH), 126.4 ($Ar_{(indole)}$-C_q), 126.0 (Ar-*C*$_q$-CH_3), 125.4 (N-Ar-CH), 124.6 (N-Ar-CH-*C*$_q$), 124.5 ($Ar_{(indole)}$-CH), 121.4 ($Ar_{(indole)}$-CH), 121.1 ($Ar_{(indole)}$-CH), 118.2 (Ar-CH), 110.1 (Ar-CH), 109.0 ($Ar_{(indole)}$-CH), 79.7 (*C*$_q$$(CH_3)_3$), 65.5 (OCH), 56.6 (*C*$H_2$N*C*$H_2$), 38.2 ($CH_3$*C*$CH_3$), 32.6 ($NCH_3$), 30.9 (*C*$_q$$(CH_3)_2$), 28.3 ($C_q$(*C*$H_3)_3$), 16.4 (Ar-$CH_3$); HRMS (+ESI) *m*/*z* calcd for $C_{27}H_{35}N_2O_3$ [M+H]$^+$: 435.2648, Found: 435.2667.



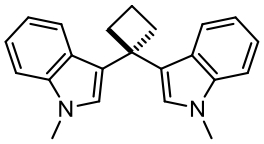
3-(2-(4-(Azetidin-3-yloxy)-3-methylphenyl)propan-2-yl)-1-methyl-1*H*-indole (12d)

A solution of HCl (4 M in dioxane, 1.7 mL, 6.90 mmol) was added to a solution of **36d** (301 mg, 0.69 mmol) in dioxane (2.7 mL) at 25 °C. The reaction mixture was stirred for 20 h and then a solution of aqueous NaOH (1 M, 50 mL) was added until the colour of the mixture changed, followed by the addition of Et_2O (50 mL). The layers were separated and the aqueous portion was extracted with Et_2O (3 × 50 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by SCX column gave amine **12d** (168 mg, 81%) as a white solid. R_f = 0.35 (95:5:1 CH_2Cl_2/MeOH/NEt_3); mp = 75–80 °C; IR (film)/cm^{-1} 2959 (br, NH), 1499, 1359, 1248, 1149, 1108, 807, 738; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30–7.25 (m, 1 H, $Ar_{(indole)}$-CH), 7.18–7.09 (m, 3 H, 2 × $Ar_{(indole)}$-CH, Ar-CH), 7.05 (dd, *J* = 8.4, 2.4 Hz, 1 H, $Ar_{(indole)}$-CH), 6.94–6.86 (m, 2 H, Ar-CH, N-Ar-CH), 6.38 (d, *J* = 8.5 Hz, 1 H, Ar-CH), 4.99–4.91 (m, 1 H, OCH), 3.94–3.87 (m, 2 H, C*H*HNC*H*H), 3.85–3.78 (m, 2 H, CH*H*NCH*H*), 3.78 (s, 3 H, NCH_3), 2.18 (s, 3 H, Ar-CH_3), 1.96 (br, s, 1 H, NH), 1.74 (s, 6 H, CH_3CCH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.0 (Ar-C_q-OCH), 142.3 (Ar-C_q-C$(CH_3)_2$), 137.7 ($Ar_{(indole)}$-C_q), 129.1 (Ar-CH), 126.4 ($Ar_{(indole)}$-C_q), 125.8 (Ar-C_q-CH_3), 125.4 (N-Ar-CH), 124.8 (N-Ar-CH-C_q), 124.5 ($Ar_{(indole)}$-CH), 121.5 ($Ar_{(indole)}$-CH), 121.1 ($Ar_{(indole)}$-CH), 118.2 (Ar-CH), 110.5 (Ar-CH), 109.0 ($Ar_{(indole)}$-CH), 70.5 (OCH), 55.1 (CH_2NCH_2), 38.2 ($C_q(CH_3)_2$), 32.6 (NCH_3), 30.9 ($C_q(CH_3)_2$), 16.5 (Ar-CH_3); HRMS (+ESI) *m*/*z* calcd for $C_{22}H_{27}N_2O$ [M+H]: 335.2123, Found: 335.2133.

1-(1-Methyl-1*H*-indol-3-yl)cyclobutan-1-ol (44) and **3,3'-(cyclobutane-1,1-diyl)bis(1-methyl-1*H*-indole) (45)**



44

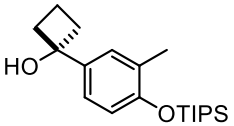


45

*n*BuLi (2.30 M in hexane, 2.60 mL, 5.93 mmol) was added dropwise over 5 min to a solution of 3-bromo-1-methyl-1*H*-indole **S1** (1.34 g, 5.93 mmol) in THF (21 mL) at –78 °C. The reaction mixture was stirred at –78 °C for 1 h. Cyclobutanone (665 µL, 8.90 mmol) was added dropwise to the reaction mixture. Following a further 2 h at –78 °C, the reaction mixture was warmed to 25 °C for 17 h then quenched with water (80 mL). EtOAc (80 mL) was added and the layers were separated. The aqueous portion was extracted with EtOAc (2 × 80 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography (5 to 10% EtOAc/pentane) afforded cyclobutane **45** (205 g, 11%) as a white solid, followed by cyclobutanol **44** (396 mg, ~60% pure, 33%) as a purple oil.

Cyclobutane **45**: R_f = 0.52 (10% EtOAc/pentane); mp = 145–149 °C (coloration at 99 °C into a pink then black solid); IR (film)/cm^{-1} 3325 (br, OH), 3046, 2975, 2936 1483, 1462 1378, 1324, 1234, 1156, 1012, 737, 696; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, J = 8.0 Hz, 2 H, 2 × $Ar_{(indole)}$-CH), 7.32 (d, J = 8.2 Hz, 2 H, 2 × $Ar_{(indole)}$-CH), 7.22 (m, 2 H, 2 × $Ar_{(indole)}$-CH), 7.05 (m, 2 H, 2 × $Ar_{(indole)}$-CH), 6.97 (s, 2 H, 2 × N-Ar-CH), 3.77 (s, 6 H, 2 × NCH_3), 2.96 (t, J = 7.7 Hz, 4 H, CH_2CH$_2$CH_2), 2.22 (t, J = 7.7 Hz, 2 H, CH$_2$CH_2CH$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.8 (2 × $Ar_{(indole)}$-C_q), 126.7 (2 × $Ar_{(indole)}$-C_q), 125.9 (2 × N-Ar-CH), 122.6 (2 × N-Ar-CH-C_q), 121.1 (2 × $Ar_{(indole)}$-CH), 120.8 (2 × $Ar_{(indole)}$-CH), 118.1 (2 × $Ar_{(indole)}$-CH), 109.2 (2 × $Ar_{(indole)}$-CH), 40.8 ($C_{q(cyclobutane)}$), 34.6 (CH_2CH$_2$CH_2), 32.6 (2 × NCH_3), 17.2 (CH$_2$CH_2CH$_2$); HRMS (-ESI) m/z calcd for $C_{22}H_{21}N_2^{\bullet+}$ [M-H]$^{\bullet+}$: 313.1705, Found: 313.1708.

Cyclobutanol **44**: R_f = 0.23 (10% EtOAc/pentane); IR (film)/cm^{-1} 3309 (br, OH), 2933, 1474, 1460, 1416, 1326, 1245, 1217, 1145, 1119, 1095, 953, 820, 737; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83–7.76 (m, 1 H, $Ar_{(indole)}$-CH), 7.34 (dt, J = 8.3, 1.1 Hz, 1 H, $Ar_{(indole)}$-CH), 7.31–7.25 (m, 1 H, $Ar_{(indole)}$-CH), 7.15 (ddd, J = 8.0, 6.9, 1.1 Hz, 1 H, $Ar_{(indole)}$-CH), 7.07 (s, 1 H, N-Ar-CH), 3.80 (s, 3 H, NCH_3), 2.68–2.58 (m, 2 H, CHHCH$_2$CHH), 2.55–2.45 (m, 2 H, CHHCH$_2$CHH), 1.96–1.84 (m, 1 H, CH$_2$CHHCH$_2$), 1.72–1.57 (m, 1 H, CH$_2$CHHCH$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.9 ($Ar_{(indole)}$-C_q), 125.7 (N-Ar-CH), 124.4 ($Ar_{(indole)}$-C_q), 121.9 ($Ar_{(indole)}$-CH), 120.6 ($Ar_{(indole)}$-CH), 119.8 (N-Ar-CH-C_q), 119.2 ($Ar_{(indole)}$-CH), 109.4 ($Ar_{(indole)}$-CH), 73.1 ($C_{q(cyclobutane)}$), 36.8 (CH_2CH$_2$CH_2), 32.7 (NCH_3), 13.3 (CH$_2$CH_2CH$_2$). Compound unstable, HRMS not obtained.

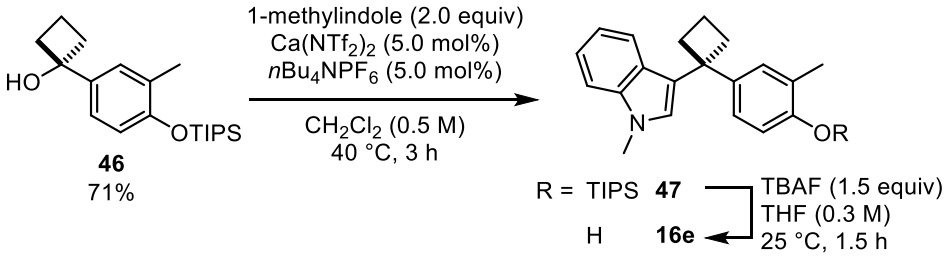


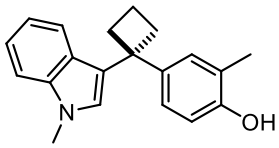
1-(3-Methyl-4-((triisopropylsilyl)oxy)phenyl)cyclobutan-1-ol (46)

*n*BuLi (2.3 M in THF, 970 µL, 2.24 mmol) was added dropwise over 5 min to a solution of **29** (698 mg, 2.03 mmol) in THF (6.7 mL) at –78 °C. The reaction mixture was stirred at –78 °C for 30 min. Cyclobutanone (200 µL, 3.04 mmol) was added dropwise to the reaction mixture. Following a further 1 h 30 min at –78 °C the reaction mixture was warmed to 25 °C then quenched with water (30 mL). Et_2O (30 mL) was added and the layers were separated. The aqueous portion was extracted with Et_2O (3 × 30 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography (10% Et_2O/hexane) afforded cyclobutanol **46** (480 mg, 71%) as a white crystalline solids. R_f = 0.18 (10% Et_2O/pentane); IR (film)/cm^{-1} 3325 (br, OH), 2944, 2866, 1501, 1263, 1245, 1134, 1120, 940, 883, 817, 782, 720, 681; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (d, J = 2.2 Hz, 1 H, Ar-CH), 7.16 (dd, J = 8.3, 2.2 Hz, 1 H, Ar-CH), 6.77 (d, J = 8.3 Hz, 1 H, Ar-CH), 2.58–2.52 (m, 2 H, CHHCH$_2$CHH), 2.38–2.30 (m, 2 H, CHHCH$_2$CHH), 2.26 (s, 3 H, Ar-CH_3), 1.99–1.95 (m, 1 H, CH$_2$CHHCH$_2$), 1.94 (s, 1 H, OH), 1.68–1.59 (m, 1 H, CH$_2$CHHCH$_2$), 1.35–1.26 (m, 3 H, 3 × CH(CH_3)$_2$), 1.13 (d, J = 7.31 Hz, 18 H, 3 × CH(CH_3)$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.5 (Ar-C_q-OTIPS), 138.2

(Ar-C_q-C_q), 128.4 (Ar-C_q-CH_3), 127.8 (Ar-CH), 123.2 (Ar-CH), 117.5 (Ar-CH), 76.8 (C_q), 36.7 ($CH_2CH_2CH_2$), 18.0 (3 × $CH(CH_3)_2$), 17.2 (Ar-CH_3), 13.0 (3 × $CH(CH_3)_2$), 12.9 ($CH_2CH_2CH_2$); HRMS (+ESI) *m*/*z* calcd for $C_{20}H_{33}OSi^{\bullet}$ $[M\text{-}OH]^{\bullet}$: 317.2301, Found: 317.2313.

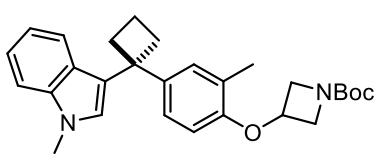
2-Methyl-4-(1-(1-methyl-1*H*-indol-3-yl)cyclobutyl)phenol (16e)





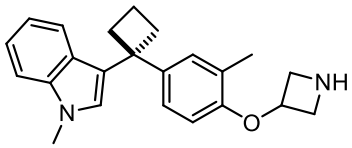
Calcium(II) bis(trifluoromethanesulfonimide) (27.2 mg, 0.04 mmol) and tetrabutylammonium hexafluorophosphate (15.5 mg, 0.04 mmol) were added to a solution of **46** (273 mg, 0.81 mmol) and 1-methyl-1*H*-indole (206 µL, 1.63 mmol) in CH_2Cl_2 (2.8 mL). The reaction mixture was stirred at 40 °C for 3 h then sat. aq. $NaHCO_3$ (30 mL) was added followed by CH_2Cl_2 (30 mL). The layers were separated and the aqueous portion was extracted with CH_2Cl_2 (4 × 30 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Attempted purification by flash column chromatography (100 % pentane) afforded inseparable mixture of product **47** containing unidentified impurity. The mixture was taken on the next step without further purification. A solution of TBAF (1 M in THF, 1.20 mL, 1.20 mmol) was added dropwise over two min to a solution of **47** (363 mg, 0.81 mmol) in THF (2.7 mL) at 0 °C. The reaction mixture was stirred for 10 min at 0 °C and then 1 h 30 min at 25 °C. Water (40 mL) was added followed by Et_2O (40 mL). The layers were separated and the aqueous portion was extracted with Et_2O (3 × 40 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography (20% Et_2O/hexane) afforded cyclobutane **16e** (218 mg, 92% over 2 steps) as a white solid. R_f = 0.46 (50% Et_2O/pentane); mp = 120–121 °C; IR (film)/cm^{-1} 3532 (OH), 2980, 2944, 1507, 1481, 1324, 1271, 1113, 817, 748, 726; ^1H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, *J* = 8.0 Hz, 1 H, $Ar_{(indole)}$-CH), 7.28 (d, *J* = 8.3 Hz, 1 H, $Ar_{(indole)}$-CH), 7.20–7.11 (m, 3 H, $Ar_{(indole)}$-CH, 2 × Ar-CH), 7.01–6.97 (m, 1 H, $Ar_{(indole)}$-CH), 6.95 (s, 1 H, N-Ar-CH), 6.68 (d, *J* = 8.2 Hz, 1 H, Ar-CH), 4.52 (s, 1 H, OH), 3.78 (s, 3 H, NCH_3), 2.76–2.72 (m, 4 H, $CH_2CH_2CH_2$), 2.22 (s, 3 H, Ar-CH_3), 2.14–1.97 (m, 2 H, $CH_2CH_2CH_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.4 (Ar-C_q-OH), 142.0 (Ar-C_q-C_q), 137.8 ($Ar_{(indole)}$-C_q), 129.0 (Ar-CH), 126.5 ($Ar_{(indole)}$-C_q), 125.7 (N-Ar-CH), 124.8 (Ar-CH), 123.1 (Ar-C_q-CH_3), 123.0 (N-Ar-CH-C_q), 121.3 ($Ar_{(indole)}$-CH), 120.7 ($Ar_{(indole)}$-CH), 118.4 ($Ar_{(indole)}$-CH), 114.3 (Ar-CH), 109.2 ($Ar_{(indole)}$-CH), 45.4

(C_q), 34.9 ($CH_2CH_2CH_2$), 32.6 (NCH_3), 17.0 ($CH_2CH_2CH_2$), 16.0 (Ar-CH_3). HRMS (+ESI) *m*/*z* calcd for $C_{20}H_{22}NO$ [M+H] : 292.1700, Found: 292.1696.



***tert*-Butyl-3-(2-methyl-4-(1-(1-methyl-1*H*-indol-3-yl)cyclobutyl)phenoxy)azetidine-1-carboxylate (36e)**

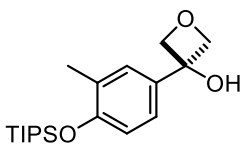
A solution of **16e** (363 mg, 0.81 mmol) in DMF (2.7 mL) was added to a solution of NaH (60% dispersion in mineral oil, 32.7 mg, 0.74 mmol) in DMF (0.3 mL) at 0 °C. The reaction mixture was stirred for 30 min at 0 °C and then *tert*-butyl-3-bromoazetidine-1-carboxylate (293 mg, 1.24 mmol) was weighed into a flask, dissolved in DMF (0.1 mL) and added to the reaction mixture *via* syringe. DMF (0.5 mL) was added to the previous flask and then added to the reaction. The reaction mixture was then heated to 85 °C for 24 h. The reaction was cooled down to rt and water (25 mL) was added followed by EtOAc (50 mL). The layers were separated and the aqueous portion was extracted with EtOAc (3 × 20 mL). The organic extracts were combined and washed with sat. aq. NaCl (80 mL) and then dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography (5% to 20% EtOAc/pentane) afforded cyclobutane **36e** (262 mg, 94%) as a white powder. R_f = 0.08 (5% EtOAc/pentane); mp = 148 °C; IR (film)/cm^{-1} 2972, 2950, 1692 (C=O), 1502, 1417, 1364, 1241, 1229, 1167, 1146, 1132, 1012, 813, 742; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, *J* = 7.9 Hz, 1 H, $Ar_{(indole)}$-CH), 7.28 (d, *J* = 6.2 Hz, 1 H, $Ar_{(indole)}$-CH), 7.19–7.12 (m, 3 H, 2 × $Ar_{(indole)}$-CH, Ar-CH), 7.00–6.95 (m, 2 H, Ar-CH, N-Ar-CH), 6.34 (d, *J* = 8.3 Hz, 1 H, Ar-CH), 4.82 (m, 1 H, OCH), 4.28 (dd, *J* = 9.2, 6.7 Hz, 2 H, C*H*HNC*H*H), 4.00 (dd, *J* = 9.2, 3.9 Hz, 2 H, CH*H*NCH*H*), 3.78 (s, 3 H, NCH_3), 2.75–2.72 (m, 4 H, $CH_2CH_2CH_2$), 2.20 (s, 3 H, Ar-CH_3), 2.13–1.99 (m, 2 H, $CH_2CH_2CH_2$), 1.46 (s, 9 H, 3 × CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.2 (C=O), 152.5 (Ar-C_q-OCH), 142.4 (Ar-C_q-C_q), 137.8 ($Ar_{(indole)}$-C_q), 129.3 (Ar-CH), 126.5 ($Ar_{(indole)}$-C_q), 126.3 (Ar-C_q-CH_3), 125.7 (N-Ar-CH), 124.2 (Ar-CH), 123.0 (N-Ar-CH-C_q), 121.3 ($Ar_{(indole)}$-CH), 120.7 ($Ar_{(indole)}$-CH), 118.4 ($Ar_{(indole)}$-CH), 110.2 (Ar-CH), 109.2 ($Ar_{(indole)}$-CH), 79.6 ($C_q(CH_3)_3$), 65.6 (OCH), 56.2 (CH_2NCH_2), 45.4 (C_q), 34.8 ($CH_2CH_2CH_2$), 32.6 (NCH_3), 28.4 ($C_q(CH_3)_3$), 17.0 ($CH_2CH_2CH_2$), 16.4 (Ar-CH_3); HRMS (+ESI) *m*/*z* calcd for $C_{28}H_{35}N_2O_3$ [M+H] : 447.2648, Found: 447.2645.



3-(1-(4-(Azetidin-3-yloxy)-3-methylphenyl)cyclobutyl)-1-methyl-1*H*-indole (12e)

A solution of HCl (4 M in dioxane, 1.40 mL, 5.60 mmol) was added to a solution of **36e** (252 mg, 0.56 mmol) in dioxane (2.5 mL) at 25 °C. The reaction mixture was stirred for 23 h and a solution of aqueous NaOH (1 M, 15 mL) was added until the colour of the mixture has changed, followed by the addition of Et_2O (30 mL). The layers were separated and the aqueous portion was extracted with Et_2O (4 × 30 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by SCX column gave cyclobutane **12e** (188 mg, 97%) as a white solid. R_f = 0.18 (95:5:1 CH_2Cl_2/MeOH/NEt_3); mp = 46–50 °C; IR (film)/cm^{-1} 2939 (br, NH), 2864, 1499, 1483, 1465, 1372, 1247, 1236, 1148, 1128, 807, 736; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, *J* = 8.0 Hz, 1 H, $Ar_{(indole)}$-CH), 7.28 (d, *J* = 6.0 Hz, 1 H, $Ar_{(indole)}$-CH), 7.20–7.12 (m, 3 H, 2 × $Ar_{(indole)}$-CH, Ar-CH), 7.01–6.96 (m, 2 H, Ar-CH, N-Ar-CH), 6.42 (d, *J* = 8.4 Hz, 1 H, Ar-CH), 4.95 (p, *J* = 6.2 Hz, 1 H, OCH), 3.93–3.89 (m, 2 H, C*H*HNC*H*H), 3.83–3.78 (m, 5 H, CH*H*NCH*H*, NCH_3), 2.74 (t, *J* = 7.5 Hz, 4 H, $CH_2CH_2CH_2$), 2.21 (s, 3 H, Ar-CH_3), 2.12–1.99 (m, 2 H, $CH_2CH_2CH_2$), 1.93 (br, s, 1 H, NH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.9 (Ar-C_q-OCH), 142.0 (Ar-C_q-C_q), 137.7 ($Ar_{(indole)}$-C_q), 129.0 (Ar-CH), 126.5 ($Ar_{(indole)}$-C_q), 126.1 (Ar-C_q-CH_3), 125.7 (N-Ar-CH), 124.2 (Ar-CH), 123.1 (N-Ar-CH-C_q), 121.3 ($Ar_{(indole)}$-CH), 120.7 ($Ar_{(indole)}$-CH), 118.3 ($Ar_{(indole)}$-CH), 110.5 (Ar-CH), 109.2 ($Ar_{(indole)}$-CH), 70.5 (OCH), 55.1 (CH_2NCH_2), 45.4 (C_q), 34.9 ($CH_2CH_2CH_2$), 32.6 (NCH_3), 17.0 ($CH_2CH_2CH_2$), 16.4 (Ar-CH_3); HRMS (+ESI) *m*/*z* calcd for $C_{23}H_{27}N_2O$ [M+H]$^+$: 347.2123, Found: 347.2138.

8.2.2 Synthesis of Oxetane-Containing-Drug Analogues (Part 3.3)

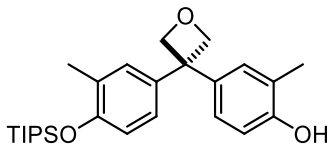


3-(3-Methyl-4-((triisopropylsilyl)oxy)phenyl)oxetan-3-ol (59)

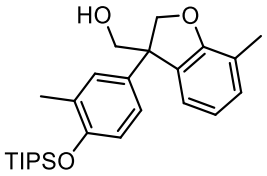
*n*BuLi (2.26 M in THF, 3.4 mL, 7.66 mmol) was added dropwise over 5 min to a solution of **29** (2.87 g, 8.36 mmol) in THF (23.2 mL) at –78 °C. The reaction mixture was stirred at –78 °C for 30 min. Oxetan-3-one (447 µL, 6.97 mmol) was added dropwise to the reaction mixture. Following a further 2 h 30 min at –78 °C the reaction mixture was warmed to rt and then quenched with water (80 mL). Et_2O (80 mL) was added and the layers were separated. The aqueous portion was extracted with Et_2O (2 × 80 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography (30% Et_2O/pentane) afforded oxetanol **59** (2.25 g, 96%) as a white solid. R_f = 0.15 (30% Et_2O/pentane); IR (film)/cm^{-1} 3323 (OH), 2944, 2867, 1504, 1298, 1261, 1195, 1126, 964, 932, 879, 844, 825, 703, 681; mp = 63–65 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (dd, *J* = 2.6, 0.8 Hz, 1 H, Ar-CH), 7.21 (ddd, *J* = 8.4, 2.6, 0.8 Hz, 1 H, Ar-CH), 6.81 (d, *J* = 8.4 Hz, 1 H, Ar-CH), 4.93

(d, *J* = 7.4 Hz, 2 H, C*H*HOC*H*H), 4.88 (d, *J* = 7.4 Hz, 2 H, CH*H*OCH*H*), 2.53 (s, 1 H, OH), 2.28 (s, 3 H, Ar-CH_3), 1.36–1.27 (m, 3 H, 3 × C*H*$(CH_3)_2$), 1.13 (d, *J* = 7.3 Hz, 18 H, 3 × CH(C*H*$_3)_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.1 (Ar-C_q-OTIPS), 134.3 (Ar-*C*$_q$-C_q), 128.9 (Ar-*C*$_q$-CH_3), 127.3 (Ar-CH), 122.8 (Ar-CH), 117.8 (Ar-CH), 85.4 (*C*H_2O*C*H_2), 75.8 (C_q), 18.0 (3 × CH(*C*$H_3)_2$), 17.2 (Ar-CH_3), 13.0 (3 × *C*H$(CH_3)_2$); HRMS (+ESI) *m*/*z* calcd for $C_{19}H_{31}O_2Si^{\bullet}$ [M-OH]$^{\bullet}$: 319.2093, Found: 319.2096.

(7-Methyl-3-(3-methyl-4-((triisopropylsilyl)oxy)phenyl)-2,3-dihydrobenzofuran-3-yl)methanol (60') and **2-methyl-4-(3-(3-methyl-4-((triisopropylsilyl)oxy)phenyl)oxetan-3-yl)phenol (60)**



60

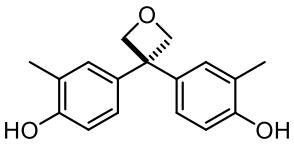


60'

Lithium bis(trifluoromethane)sulfonimide (233 mg, 0.81 mmol) and tetrabutylammonium hexafluorophosphate (130 mg, 0.33 mmol) were added to a solution of oxetanol **59** (2.24 g, 6.65 mmol) and 2-methylphenol (3.59 g, 33.2 mmol) in $CHCl_3$ (13.3 mL). The reaction mixture was stirred at 40 °C for 1 h 30 min. The reaction mixture was cooled to rt and water (80 mL) was added followed by Et_2O (80 mL). The layers were separated and the aqueous portion was extracted with Et_2O (3 × 80 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash columns chromatography (10% Et_2O/pentane) afforded dihydrobenzofuran **60'** (49.4 mg, 2%) as a colourless oil and oxetane **60** (1.74 g, 61%) as a white solid.

Dihydrobenzofuran **60'**: R_f = 0.38 (20% Et_2O/pentane); IR (film)/cm^{-1} 2943 (OH), 2867, 1502, 1462, 1266, 1131, 978, 937, 917, 881, 815, 745, 707, 678; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.07–7.05 (m, 3 H, 3 × Ar-CH), 6.98–6.96 (dd, *J* = 8.4, 2.6 Hz, 1 H, Ar-CH), 6.87 (m, 1 H, Ar-CH), 6.75 (d, *J* = 8.4 Hz, 1 H, Ar-CH), 4.77 (d, *J* = 8.9 Hz, 1 H, OC*H*HC_q), 4.61 (d, *J* = 8.9 Hz, 1 H, OCH*H*C_q), 4.07 (d, *J* = 11.3 Hz, 1 H, C*H*HOH), 3.99 (d, *J* = 11.3 Hz, 1 H, CH*H*OH), 2.27 (s, 3 H, Ar-CH_3), 2.24 (s, 3 H, Ar-CH_3), 1.61 (s, 1 H, OH), 1.35–1.25 (m, 3 H, 3 × C*H*$(CH_3)_2$), 1.12 (d, *J* = 7.5 Hz, 18 H, 3 × CH(C*H*$_3)_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.1 (Ar$_{(DHBF)}$-*C*$_q$-OCH_2), 153.2 (Ar-C_q-OTIPS), 134.5 (Ar-*C*$_q$-CH_3), 130.2 (Ar-CH), 129.3 (Ar-CH), 129.2 (Ar$_{(DHBF)}$-*C*$_q$-CH_3), 128.7 (Ar$_{(OTIPS)}$-*C*$_q$-C_q), 125.0 (Ar-CH), 122.6 (Ar-CH), 120.5 (Ar-CH), 120.3 (Ar$_{(DHBF)}$-*C*$_q$-C_q), 117.8 (Ar-CH), 81.0 (O*C*H_2C_q), 67.9 (CH_2OH), 56.0 (C_q), 18.0 (3 × CH(*C*$H_3)_2$), 17.2 (Ar-CH_3), 15.2 (Ar-CH_3), 12.9 (3 × *C*H$(CH_3)_2$); HRMS (+NSI) *m*/*z* calcd for $C_{26}H_{39}O_3Si$ [M+H]$^+$: 427.2663, Found: 427.2664.

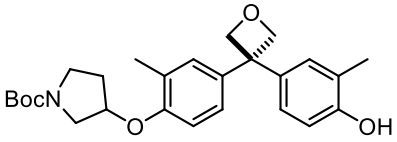
Oxetane **60**: R_f = 0.16 (20% Et_2O /pentane); IR (film)/cm^{-1} 3311 (OH), 2947, 2866, 1504, 1275, 1123, 975, 921, 882, 825, 814, 704, 678; mp = 124–126 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.00–6.98 (m, 2 H, 2 × Ar-CH), 6.90 (dd, *J* = 8.3, 2.4 Hz, 1 H, Ar-CH), 6.81 (dd, *J* = 8.4, 2.5 Hz, 1 H, Ar-CH), 6.74 (2 × d, *J* = 8.4, 8.3 Hz, 2 H, 2 × Ar-CH), 5.21 (d, *J* = 5.5 Hz, 2 H, C*H*HOC*H*H), 5.18 (d, *J* = 5.5 Hz, 2 H, CH*H*OCH*H*), 4.97 (s, 1 H, OH), 2.24 (s, 6 H, 2 × Ar-CH_3), 1.35–1.27 (m, 3 H, 3 × C*H*(CH_3)$_2$), 1.13 (d, *J* = 7.4 Hz, 18 H, 3 × CH(C*H*$_3$)$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.9 (Ar-C_q-OTIPS), 152.4 (Ar-C_q-OH), 138.5 (Ar-*C*$_q$-C_q), 138.0 (Ar-*C*$_q$-C_q), 129.2 (Ar-CH), 129.0 (Ar-CH), 128.5 (Ar-*C*$_q$-CH_3), 125.3 (Ar-CH), 124.7 (Ar-CH), 123.7 (Ar-*C*$_q$-CH_3), 117.7 (Ar-CH), 114.7 (Ar-CH), 85.1 (*C*H_2O*C*H_2), 50.3 (C_q), 18.0 (3 × CH(*C*H_3)$_2$), 17.2 (Ar-CH_3), 15.9 (Ar-CH_3), 13.0 (3 × *C*H(CH_3)$_2$); HRMS (+ESI) *m*/*z* calcd for $C_{26}H_{39}O_3Si$ [M+H]: 427.2668, Found: 427.2666.



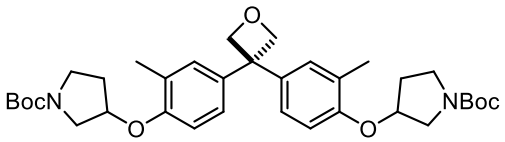
4,4'-(Oxetane-3,3-diyl)bis(2-methylphenol) (61)

A solution of TBAF (1 M in THF, 2.80 mL, 2.80 mmol) was added to a solution of TIPS-protected oxetane **60** (1.00 g, 2.34 mmol) in THF (7.5 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 20 min and at 25 °C for 4 h 30 min. Water (60 mL) was added followed by EtOAc (90 mL). The layers were separated and the aqueous portion was extracted with EtOAc (3 × 60 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography (30% EtOAc/pentane) afforded **61** as a white solid (608 mg, 96%). R_f = 0.41 (40% EtOAc/pentane); mp = 235–239°C; IR (film)/cm^{-1} 3347, 3109, 1508, 1275, 1255, 1221, 1180, 1168, 1125, 970, 891, 830, 773, 666; ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 9.19 (s, 2 H, 2 × OH), 6.94 (d, *J* = 2.4 Hz, 2 H, 2 × Ar-CH), 6.83 (dd, *J* = 8.3, 2.4 Hz, 2 H, 2 × Ar-CH), 6.70 (d, *J* = 8.3 Hz, 2 H, 2 × Ar-CH), 5.02 (s, 4 H, C*H*$_2$OC*H*$_2$), 2.08 (s, 6 H, 2 × Ar-CH_3); ^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ 153.6 (2 × Ar-C_q-OH), 137.1 (2 × Ar-*C*$_q$-CH_3), 128.3 (2 × Ar-CH), 124.3 (2 × Ar-CH), 123.6 (2 × Ar-*C*$_q$-C_q), 114.3 (2 × Ar-CH), 83.4 (*C*H_2O*C*H_2), 50.0 (C_q), 16.2 (2 × Ar-CH_3); HRMS (+EI) *m*/*z* calcd for $C_{17}H_{18}O_3$ $[M]^+$: 270.1256, Found: 270.1263.

***tert*-Butyl-3-(4-(3-(4-hydroxy-3-methylphenyl)oxetan-3-yl)-2-methylphenoxy)pyrrolidine-1-carboxylate (62-mono)** and **di-*tert*-butyl-3,3'-((oxetane-3,3-diylbis(2-methyl-4,1-phenylene))bis(oxy))bis(pyrrolidine-1-carboxylate) (62)**



62-mono



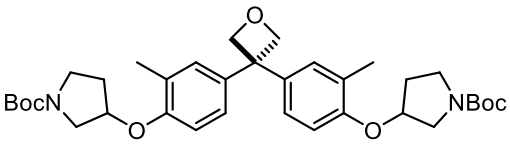
62

tert-butyl-3-bromopyrrolidine-1-carboxylate (500 mg, 2.00 mmol) was added to a solution of oxetane **61** (216 mg, 0.80 mmol) and K_2CO_3 (442 mg, 3.20 mmol) in DMF (4.0 mL). The reaction mixture was stirred for 29 h at 80 °C and then *tert*-butyl-3-bromopyrrolidine-1-carboxylate (250 mg, 1.00 mmol) was added to the reaction mixture. The reaction mixture was stirred at 80 °C for a further 24 h, then cooled to rt before addition of H_2O (40 mL). EtOAc (40 mL) was added and the layers were separated. The aqueous portion was extracted with EtOAc (3 × 40 mL). The organic extracts were combined, washed with aq. NaOH (1 M, 2 × 100 mL) dried over Na_2SO_4, filtered and concentrated under reduced pressure to give **62-mono** (118 mg, 32%) as a white solid, followed by oxetane **60** (25.8 mg, 5%) as a white solid.

Oxetane **62-mono**: R_f = 0.29 (70% Et_2O/pentane); mp = 74–81°C; IR (film)/cm^{-1} 3279 (br, OH), 2972, 2877, 1663 (C=O), 1502, 1412, 1365, 1238, 1163, 1122, 984, 813, 770; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.05 (d, *J* = 5.9 Hz, 1 H, Ar-CH), 7.00 (s, 1 H, Ar-CH), 6.96–6.89 (m, 1 H, Ar-CH), 6.86–6.82 (m, 1 H, Ar-CH), 6.76–6.74 (m, 2 H, 2 × Ar-CH), 5.20 (d, *J* = 5.5 Hz, 4 H, C*H*$_2$OC*H*$_2$), 4.88 (s, 1 H, OCH), 3.67–3.47 (m, 4 H, CH(C*H*$_2$)$_2$N), 2.24 (s, 3 H, Ar-CH_3), 2.18–2.05 (m, 5 H, Ar-CH_3, CHC*H*$_2$N), 1.48 (s, 9 H, 3 × CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.7 (C=O), 153.8 (Ar-*C*$_q$-OCH), 152.8 (Ar-C_q-OH), 138.6 (Ar-*C*$_q$-CH_3), 137.8 (Ar-*C*$_q$-CH_3), 129.2 (Ar-CH), 129.0 (Ar-CH), 127.9 (Ar$_{(p\text{-OCH})}$-*C*$_q$-C_q), 125.1 (Ar-CH), 124.7 (Ar-CH), 124.1 (Ar$_{(p\text{-OH})}$-*C*$_q$-C_q), 114.7 (Ar-CH), 112.2 (Ar-CH), 84.9 (*C*H$_2$O*C*H$_2$), 79.6 (*C*$_q$(CH_3)$_3$), 75.8 (OCH), 51.8 and 51.4 (CHCH$_2$*C*H$_2$N), 50.3 (C_q), 44.3 and 43.9 (CH*C*H$_2$CH$_2$N), 31.7 and 31.0 (CH*C*H$_2$N), 28.5 (C_q(*C*H$_3$)$_3$), 16.4 (Ar-CH_3), 16.0 (Ar-CH_3); HRMS (+ESI) *m*/*z* calcd for $C_{26}H_{34}NO_5$ [M+H]: 440.2437, Found: 440.2441.

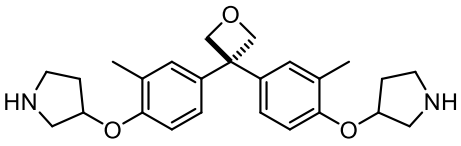
Oxetane **62**: R_f = 0.24 (70% Et_2O/pentane); mp = 64–69°C; IR (film)/cm^{-1} 2972, 1690 (C=O), 1501, 1401, 1364, 1239, 1164, 1133, 1114, 987, 771; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.05–7.04 (m, 2 H, 2 × Ar-CH), 6.92–6.90 (m, 2 H, 2 × Ar-CH), 6.74 (d, *J* = 8.5 Hz, 2 H, 2 × Ar-CH), 5.19 (s, 4 H, C*H*$_2$OC*H*$_2$), 4.88 (tt, *J* = 4.6, 2.3 Hz, 2 H, 2 × OCH), 3.58 (m, 8 H, 2 × CHCH$_2$C*H*$_2$N, 2 × CH*C*H$_2$N), 2.18 (m, 10 H, 2 × Ar-CH_3, 2 × CHC*H*$_2$CH$_2$N), 1.48 (s, 18 H, 6 × CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.6 (2 × C=O), 153.8 (2 × Ar-*C*$_q$-OCH), 138.4 (2 × Ar-*C*$_q$-CH_3), 129.2 (2 × Ar-CH), 128.0 (2 × Ar$_{(p\text{-OCH})}$-*C*$_q$-C_q), 124.7 (2 × Ar-CH), 112.1 (2 × Ar-CH), 84.8 (*C*H$_2$O*C*H$_2$), 79.4 (2 × *C*$_q$(CH_3)$_3$), 75.8 (2 × OCH), 51.7 and 51.4 (2 × CH*C*H$_2$N), 50.3 (C_q), 44.2

and 43.9 (2 × $CHCH_2CH_2N$), 31.8 and 31.0 (2 × $CHCH_2CH_2N$), 30.3 and 28.5 (2 × $C_q(CH_3)_3$), 16.4 (2 × Ar-CH_3); HRMS (+ESI) *m*/*z* calcd for $C_{35}H_{49}N_2O_7$ [M+H]: 609.3540, Found: 609.3558.



di-*tert*-butyl-3,3'-((oxetane-3,3-diylbis(2-methyl-4,1-phenylene))bis(oxy))bis(pyrrolidine-1-carboxylate) (62)

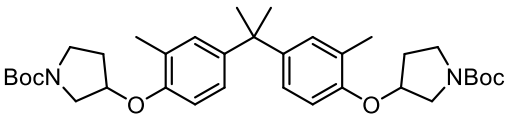
DIAD (1.00 mL, 5.16 mmol) was added dropwise to a solution of oxetane **61** (350 mg, 1.29 mmol), 1-boc-3-pyrrolidinol (966 mg, 5.16 mmol) and PPh_3 (1.35 g, 5.16 mmol) in THF (8.0 mL) at 0 °C. The reaction mixture was stirred for 5 min at 0 °C and allowed to warm to rt gradually. The reaction was stirred at 25 °C for 32 h and DIAD (510 µL, 2.60 mmol), 1-boc-3-pyrrolidinol (487 mg, 2.60 mmol) and PPh_3 (682 mg, 2.60 mmol) were then added. The reaction mixture was stirred for a further 15 h and a solution of NaOH (1 M, 50 mL) followed by EtOAc (50 mL) was added. The layers were separated and the aqueous portion was extracted with EtOAc (3 × 50 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography (50% to 70% Et_2O/pentane followed by 5% to 15% Et_2O/CH_2Cl_2) afforded oxetane **62** (607 mg, 77%) as a white solid. Identical spectroscopic data were obtained.



3,3'-((Oxetane-3,3-diylbis(2-methyl-4,1-phenylene))bis(oxy))dipyrrolidine (49)

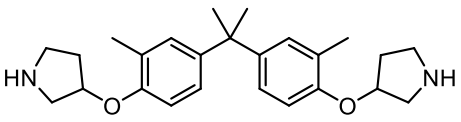
Trifluoroacetic acid (375 µL, 4.90 mmol) was added dropwise to a solution of **62** (300 mg, 0.49 mmol) in CH_2Cl_2 (2.5 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 20 min and then at 25 °C for 29 h. A solution of NaOH (1 M, 30 mL) was added and the reaction mixture was stirred for 5 min. EtOAc (30 mL) was added and the layers were separated. The aqueous portion was extracted with EtOAc (3 × 30 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by SCX column afforded the amine **49** (154.2 mg, 77%) as an off white solid. R_f = 0.06 (95:5:1 CH_2Cl_2/Methanol/NEt_3); mp = 51–58 °C; IR (film)/cm^{-1} 3311, 2944, 2872, 1498, 1237, 1186, 1133, 1039, 983, 890, 807, 737; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.04 (d, *J* = 2.4 Hz, 2 H, 2 × Ar-CH), 6.90 (dd, *J* = 8.4, 2.4 Hz, 2 H, 2 × Ar-CH), 6.73 (d, *J* = 8.4 Hz, 2 H, 2 × Ar-CH), 5.19 (s, 4 H, C*H*$_2$OC*H*$_2$), 4.83 (tt, *J* = 4.6, 2.0 Hz, 2 H, 2 × OCH), 3.22–3.15 (m, 4 H, 2 × CHC*H*HN, 2 × $CHCH_2$C*H*HN), 3.04 (dd, *J* = 12.6, 4.8 Hz, 2 H, 2 × CHCH*H*N), 2.97–2.90 (m, 2 H, 2 × $CHCH_2$CH*H*N), 2.33 (s, br, 2 H, 2 × NH), 2.18 (s, 6 H, 2 × Ar-CH_3), 2.14–2.04 (m, 2 H, 2 × CHC*H*HCH_2N), 2.02–1.95 (m, 2 H, 2 × CHCH*H*CH_2N); ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.2 (2 × Ar-C_q-OCH), 137.9 (2 × Ar-

C_q-CH_3), 129.0 (2 × Ar-CH), 127.4 (2 × $Ar_{(p\text{-}OCH)}$-C_q-C_q), 124.6 (2 × Ar-CH), 111.7 (2 × Ar-CH), 84.9 (CH_2OCH_2), 78.2 (2 × OCH), 53.7 (2 × $CHCH_2N$), 50.2 (C_q), 46.1 (2 × $CHCH_2CH_2N$), 33.5 (2 × $CHCH_2CH_2N$), 16.5 (2 × Ar-CH_3); HRMS (+ESI) *m*/*z* calcd for $C_{25}H_{33}N_2O_3$ [M+H]: 409.2491, Found: 409.2507.



Di-*tert*-butyl 3,3'-((propane-2,2-diylbis(2-methyl-4,1-phenylene))bis(oxy))bis(pyrrolidine-1-carboxylate) (63)

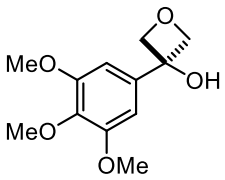
DIAD (1.48 mL, 7.50 mmol) was added dropwise to a solution of bisphenol C (385 mg, 2.50 mmol), 1-Boc-3-pyrrolidinol (1.40 g, 7.50 mmol) and PPh_3 (1.97 g, 7.50 mmol) in THF (15.0 mL) at 0 °C. The reaction mixture was stirred for 5 min at 0 °C and allowed to warm to rt gradually. The reaction was stirred at 25 °C for 19 h followed by 20 h at 40 °C. A solution of NaOH (1 M, 50 mL) followed by Et_2O (50 mL) was added. The layers were separated and the aqueous portion was extracted with Et_2O (2 × 50 mL). The organic extracts were combined, washed with sat. aq. NaCl (100 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography (5% Acetone/pentane) *gem*-dimethyl **63** (260 mg, 17%). R_f = 0.37 (15% Acetone/pentane); mp = 49–54°C; IR (film)/cm^{-1} 2973, 1692 (C=O), 1499, 1401, 1363, 1240, 1165, 1111, 875, 770; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.01–6.97 (m, 4 H, 4 × Ar-CH), 6.66 (d, *J* = 8.4 Hz, 2 H, 2 × Ar-CH), 4.86 (dt, *J* = 5.1, 2.7 Hz, 2 H, 2 × OCH), 3.58–3.48 (m, 8 H, 2 × $CHCH_2CH_2N$, 2 × $CHCH_2N$), 2.22–2.04 (m, 10 H, 2 × Ar-CH_3, 2 × $CHCH_2CH_2N$), 1.62 (s, 6 H, CH_3CCH_3), 1.47 (s, 18 H, 6 × CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.6 (2 × C=O), 153.0 (2 × Ar-C_q-OCH), 143.2 (2 × Ar-C_q-CH_3), 129.5 (2 × Ar-CH), 126.9 (2 × $Ar_{(p\text{-}OCH)}$-C_q-C_q), 124.7 (2 × Ar-CH), 111.6 (2 × Ar-CH), 79.3 (2 × $C_q(CH_3)_3$), 76.0 (2 × OCH), 51.6 (2 × $CHCH_2N$), 44.1 (2 × $CHCH_2CH_2N$), 41.5 ($CH_3C_qCH_3$), 31.5 (2 × $CHCH_2CH_2N$), 31.1 ($CH_3C_qCH_3$), 28.5 (2 × $C_q(CH_3)_3$), 16.5 (2 × Ar-CH_3); HRMS (+ESI) *m*/*z* calcd for $C_{35}H_{51}N_2O_6$ [M+H]: 595.3747, Found: 595.3743.



3,3'-((Propane-2,2-diylbis(2-methyl-4,1-phenylene))bis(oxy))dipyrrolidine (48)

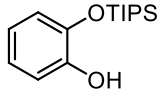
Trifluoroacetic acid (190 µL, 2.50 mmol) was added dropwise to a solution of **63** (150 mg, 0.25 mmol) in CH_2Cl_2 (1.3 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min and then at 25 °C for 18 h. A solution of NaOH (1 M, 20 mL) was added and the reaction mixture was stirred for 5 min. EtOAc (20 mL) was added and the layers were separated. The aqueous portion was extracted with EtOAc (3 × 20 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by SCX column afforded the amine **48** (85.5 mg, 87%) as beige

sticky paste. R_f = 0.15 (95:5:1 CH_2Cl_2/Methanol/NEt_3; IR (film)/cm^{-1} 2956 (NH), 1497, 1239, 1135, 906, 810, 724; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.99–6.97 (m, 4 H, 4 × Ar-CH), 6.67 (d, *J* = 8.2 Hz, 2 H, 2 × Ar-CH), 4.81–4.78 (m, 2 H, 2 × OCH), 3.21–3.15 (m, 4 H, 2 × CHC*H*HN, 2 × $CHCH_2C$*H*HN), 3.02 (dd, *J* = 12.5, 4.8 Hz, 2 H, 2 × CHCH*H*N), 2.95–2.90 (m, 2 H, 2 × $CHCH_2CH$*H*N), 2.76 (s, br, 2 H, 2 × NH), 2.14 (s, 6 H, 2 × Ar-CH_3), 2.10–1.95 (m, 4 H, 2 × CH*C*H_2CH_2N), 1.62 (s, 6 H, C*H*$_3$CC*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.4 (2 × Ar-*C*$_q$-OCH), 142.6 (2 × Ar-*C*$_q$-CH_3), 129.4 (2 × Ar-CH), 126.3 (2 × Ar$_{(p\text{-OCH})}$-*C*$_q$-C$_q$), 124.5 (2 × Ar-CH), 111.3 (2 × Ar-CH), 78.0 (2 × OCH), 53.7 (2 × CH*C*H_2N), 46.0 (2 × $CHCH_2$*C*H_2N), 41.4 (CH_3*C*$_q$$CH_3$), 33.4 (2 × CH*C*$H_2CH_2$N), 31.0 (*C*$H_3C_q$*C*$H_3$), 16.5 (2 × Ar-$CH_3$); HRMS (+ESI) *m*/*z* calcd for $C_{25}H_{35}N_2O_2$ [M+H]: 395.2699, Found: 395.2702. Compound previously reported without characterisation.[106]



3-(3,4,5-Trimethoxyphenyl)oxetan-3-ol (64)

*n*BuLi (2.42 M in THF, 1.5 mL, 3.60 mmol) was added dropwise over 5 min to a solution of 5-Bromo-1,2,3-trimethoxybenzene (964 mg, 3.90 mmol) in THF (10.0 mL) at –78 °C. The reaction mixture was stirred at –78 °C for 30 min. Oxetan-3-one (193 µL, 3.00 mmol) was added dropwise to the reaction mixture. Following a further 3 h at –78 °C the reaction mixture was warmed to rt and then quenched with water (40 mL). EtOAc (40 mL) was added and the layers were separated. The aqueous portion was extracted with EtOAc (2 × 40 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography (30% to 50% EtOAc /pentane) afforded oxetanol **64** (663 mg, 92%) as a white solid. R_f = 0.15 (50% EtOAc /pentane); IR (film)/cm^{-1}; mp = 120–126 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.84 (s, 2 H, 2 × Ar-CH), 4.92 (s, 4 H, C*H*$_2$OC*H*$_2$), 3.91 (s, 6 H, 2 × OCH_3), 3.87 (s, 3 H, OCH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.4 (2 × Ar-*C*$_q$-OCH_3), 138.1 (Ar-*C*$_q$-OCH_3), 137.5 (Ar-*C*$_q$-C$_q$), 101.7 (2 × Ar-CH), 85.7 (*C*H_2O*C*H_2), 75.8 (C$_q$), 60.8 (OCH_3), 56.2 (2 × OCH_3). The observed characterisation data (^{1}H and ^{13}C NMR) for this compound was consistent with that previously reported.[88]

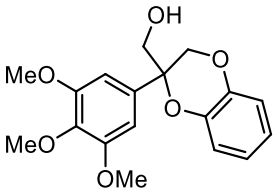


2-((Triisopropylsilyl)oxy)phenol (S2)

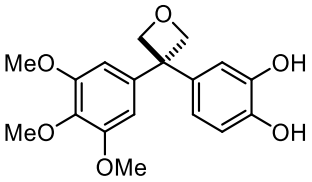
2,6-Lutidine (0.64 mL, 5.20 mmol) was added dropwise to a solution of catechol (440 mg, 4.00 mmol) and triisopropylsilyltrifluoromethanesulfonate (1.20 mL, 4.40 mmol) in CH_2Cl_2 (8.0 mL) at 0 °C. The reaction mixture was stirred for 15 min at 0 °C and then 1 h 30 min at 25 °C. Water (60 mL) was added followed by CH_2Cl_2 (60 mL). The layers were separated and the aqueous portion was extracted with CH_2Cl_2 (2 × 60 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced

pressure. Purification by flash column chromatography (20% Et_2O/pentane) afforded **S2** (1.06 g, 100%) as a light yellow oil. R_f = 0.8 (40% Et_2O /pentane); IR (film)/cm^{-1} 3541 (br, OH), 2945, 2867,1498, 1463, 1266, 1224, 1192, 1101, 912, 881, 808, 742, 678; ^1H NMR (400 MHz, $CDCl_3$) δ 6.95–6.93 (m, 1 H, Ar-CH), 6.88–6.84 (m, 2 H, 2 × Ar-CH), 6.76–6.72 (m, 1 H, Ar-CH), 5.62 (s, 1 H, OH), 1.39–1.29 (m, 3 H, (3 × C*H*$(CH_3)_2$)), 1.14 (d, *J* = 7.3 Hz, 18 H, 3 × CH(C*H*$_3)_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.1 (Ar-C_q-OTIPS), 142.7 (Ar-C_q-OH), 121.9 (Ar-CH), 119.9 (Ar-CH), 117.4 (Ar-CH), 114.7 (Ar-CH), 17.9 (3 × CH(*C*$H_3)_2$), 12.8 (3 × *C*H$(CH_3)_2$). The observed characterisation data (^1H and ^{13}C NMR) for this compound was consistent with that previously reported.[237]

(2-(3,4,5-Trimethoxyphenyl)-2,3-dihydrobenzo[b][1,4]dioxin-2-yl)methanol (70) and **4-(3-(3,4,5-trimethoxyphenyl)oxetan-3-yl)benzene-1,2-diol (67)**



70

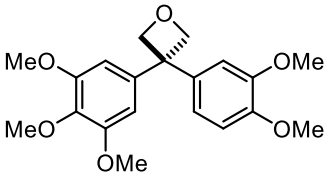


67

Lithium bis(trifluoromethane)sulfonimide (142 mg, 0.49 mmol) and tetrabutylammonium hexafluorophosphate (96.9 mg, 0.25 mmol) were added to a solution of oxetanol **64** (1.19 g, 4.95 mmol) and catechol (4.53 g, 22.6 mmol) in $CHCl_3$ (10.0 mL). The reaction mixture was stirred at 60 °C for 5 h. The reaction mixture was cooled to rt and water (60 mL) was added followed by EtOAc (70 mL). The layers were separated and the aqueous portion was extracted with EtOAc (3 × 80 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash columns chromatography (30% to 50% EtOAc/pentane, followed by 30% to 40% Acetone/pentane) afforded dihydrobenzodioxan **70** (769 mg, 47%) as a light pink solid and oxetane **67** (501 mg, 31%) as an off white solid.

Dihydrobenzodioxan **70**: R_f = 0.35 (50% EtOAc/pentane); mp = 40–45 °C; IR (film)/cm^{-1} 3469 (br, OH), 2936, 1590, 1492, 1453, 1413, 1333, 1260, 1241, 1116, 1101, 1042, 1001, 841, 746, 659; ^1H NMR (400 MHz, $CDCl_3$) δ 7.05 (dt, *J* = 7.9, 1.1 Hz, 1 H, Ar-CH), 6.93–6.85 (m, 3 H, 3 × Ar-CH), 6.68 (s, 2 H, 2 × Ar-CH), 4.47 (d, *J* = 11.8 Hz, 1 H, OC*H*HC_q), 4.43 (d, *J* = 11.8 Hz, 1 H, OCH*H*C_q), 3.95 (d, *J* = 12.2 Hz, 1 H, C*H*HOH), 3.88–3.82 (m, 10 H, CH*H*OH, 3 × OCH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.3 (3 × Ar-C_q-OCH_3), 142.8 (Ar-C_q-O), 142.3 (Ar-C_q-O), 133.5 (Ar-C_q-C_q), 121.9 (Ar-CH), 121.6 (Ar-CH), 117.4 (Ar-CH), 117.2 (Ar-CH), 103.3 (2 × Ar-CH), 78.8 (OCH_2C_q), 67.6 (O*C*H_2C_q), 66.3 (CH_2OH), 60.7 (OCH_3), 56.1 (2 × OCH_3); HRMS (+ESI) *m*/*z* calcd for $C_{18}H_{20}O_6$ [M+H]: 333.1333, Found: 333.1330.

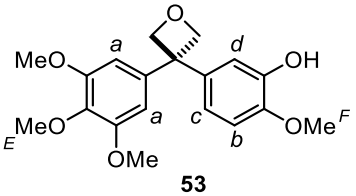
Oxetane **67**: R_f = 0.15 (50% EtOAc/pentane); mp = 145–149 °C; IR (film)/cm^{-1} 3328 (br, OH), 2961, 1589, 1511, 1459, 1415, 1333, 1243, 1126, 732; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.83 (s, 2 H, 2 × OH), 6.70–6.67 (m, 2 H, 2 × Ar-CH), 6.61–6.57 (m, 1 H, Ar-CH), 6.50 (s, 2 H, 2 × Ar-CH), 5.12 (d, *J* = 6.0 Hz, 2 H, C*H*HOC*H*H), 4.98 (d, *J* = 6.0 Hz, 2 H, CH*H*OCH*H*), 3.74 (d, *J* = 2.1 Hz, 6 H, 2 × OCH_3), 3.64 (d, *J* = 2.1 Hz, 3 H, OCH_3); ^{13}C NMR (101 MHz, DMSO-d_6) δ 152.7 (2 × Ar-C_q-OCH_3), 145.0 (Ar-C_q-OH), 143.7 (Ar-C_q-OH), 142.3 (Ar-C_q-C_q), 137.4 (Ar-C_q-C_q), 135.8 (Ar-C_q-OCH_3), 116.8 (Ar-CH), 115.3 (Ar-CH), 113.8 (Ar-CH), 104.0 (2 × Ar-CH), 83.2 (CH_2OCH_2), 59.9 (OCH_3), 55.9 (2 × OCH_3), 50.9 (C_q); HRMS (-ESI) *m*/*z* calcd for $C_{18}H_{19}O_6$ [M–H]$^-$: 331.1182, Found: 331.1180.



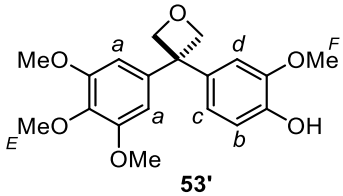
3-(3,4-Dimethoxyphenyl)-3-(3,4,5-trimethoxyphenyl)oxetane (54)

K_2CO_3 (124 mg, 0.90 mmol) followed by MeI (74.7 µL, 1.20 mmol) was added to a solution of oxetane **67** (99.7 mg, 0.30 mmol) in DMF (1.50 mL). The reaction mixture was stirred for 24 h at 80 °C and MeI (37 µL, 0.60 mmol) was added. The reaction was stirred for a further 13 h at 80 °C. The reaction was cooled to rt and water (30 mL) was added followed by EtOAc (30 mL). The layers were separated and the aqueous portion was extracted with EtOAc (3 × 30 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash columns chromatography (20% to 30% Et_2O/hexane) afforded oxetane **54** (91.4 mg, 85%) as a white solid. R_f = 0.30 (50% EtOAc/pentane); mp = 124–125 °C; IR (film)/cm^{-1} 2941, 2876, 2836, 1586, 1511, 1412, 1331, 1239, 1145, 1126, 987, 955, 807, 768, 665; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.86–6.84 (m, 2 H, 2 × Ar-CH), 6.68 (dd, *J* = 8.3, 2.1 Hz, 1 H, Ar-CH), 6.43 (s, 2 H, 2 × Ar-CH), 5.21 (m, 4 H, CH_2OCH_2), 3.89 (s, 3 H, OCH_3), 3.86 (s, 6 H, 2 × OCH_3), 3.81 (s, 6 H, 2 × OCH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.2 (2 × Ar-C_q-OCH_3), 149.1 (Ar-C_q-OCH_3), 147.9 (Ar-C_q-OCH_3), 141.5 (Ar-C_q-OCH_3), 138.1 (Ar-C_q-C_q), 136.8 (Ar-C_q-C_q), 119.0 (Ar-CH), 110.9 (Ar-CH), 109.9 (Ar-CH), 104.1 (2 × Ar-CH), 84.8 (CH_2OCH_2), 60.8 (OCH_3), 56.2 (2 × OCH_3), 56.0 (OCH_3), 55.9 (OCH_3), 51.4 (C_q); HRMS (+ESI) *m*/*z* calcd for $C_{20}H_{25}O_6$ [M+H]: 361.1651, Found: 361.1668.

2-Methoxy-5-(3-(3,4,5-trimethoxyphenyl)oxetan-3-yl)phenol (53) and **2-methoxy-4-(3-(3,4,5-trimethoxyphenyl)oxetan-3-yl)phenol (53')**



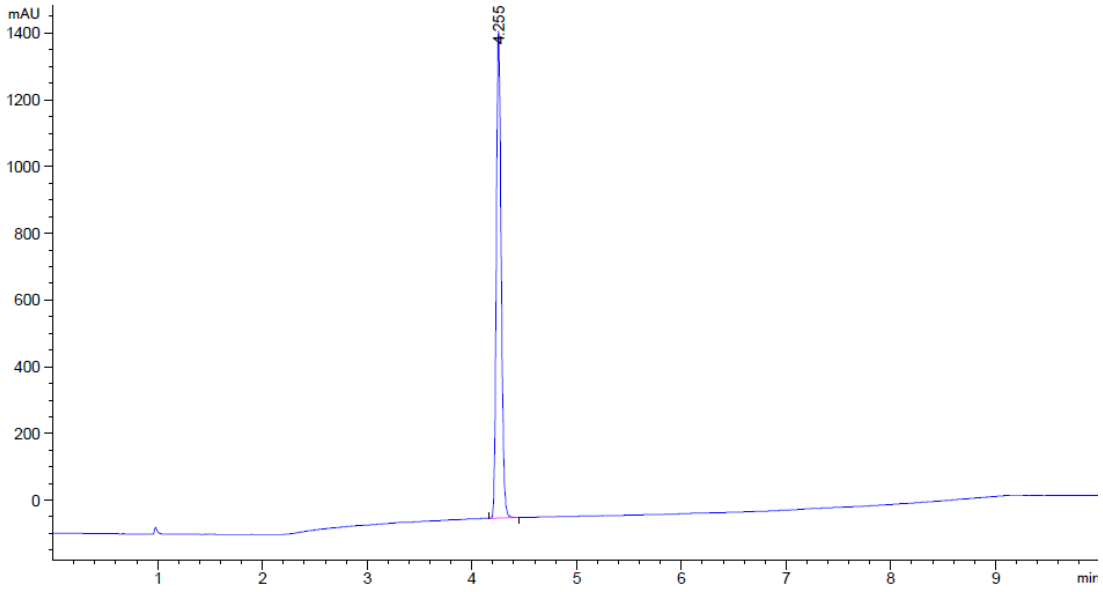
53



53'

A solution of oxetane **67** (131.4 mg, 0.40 mmol) in DMF (1.80 mL) was added to a solution of NaH (60% dispersion in mineral oil, 33.6 mg, 0.84 mmol) in DMF (0.20 mL) at 0 °C. The reaction mixture was stirred for 40 min at 0 °C and MeI (27.4 µL, 0.44 mmol) was added. The reaction mixture was stirred for 30 min at 0 °C and then heated to 80 °C and stirred for 28 h. The reaction was cooled to rt and then water (40 mL) was added followed by EtOAc (40 mL). The layers were separated and the aqueous portion was extracted with EtOAc (3 × 40 mL). The organic extracts were combined, washed with sat. aq. NaCl (100 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography (10% EtOAc/CH_2Cl_2) afforded a mixture of oxetane **53**, **53'** and **54** (64.9 mg, estimated ^{1}H NMR ratio is 45:44:11) as a yellow solid. Purification by preparative HPLC (Phenomenex Amylose-1 250 mm × 10.0 mm 5µ, 95% to 50% CO_2/MeOH, flow rate: 10 mL.min^{-1}, pressure: 100 bar, UV detection wavelength: 210 nm) afforded **54** (retention time: 3.64 min, 1.0 mg, 0.7%), oxetane **53'** (retention time: 4.26 min, 5.1 mg, 3.7%) as yellow gum and oxetane **53** (retention time: 5.24 min, 6.0 mg, 4.3%) as a white gum.

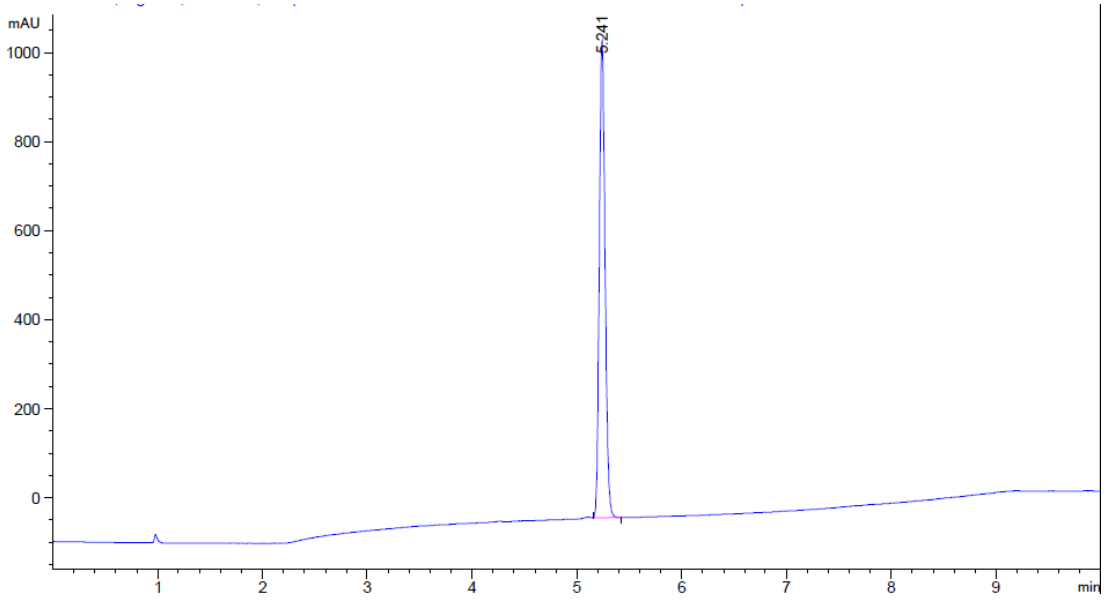
Oxetane **53'**: R_f = 0.24 (10% EtOAc/CH_2Cl_2); IR (film)/cm^{-1} 3291 (br, OH), 2938, 2837, 1587, 1511, 1461, 1414, 1331, 1242, 1217, 1124, 1030, 1004, 983, 953, 914, 816, 781, 729, 688; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.90 (d, *J* = 8.2 Hz, 1 H, Ar-CH_b), 6.80 (d, *J* = 2.1 Hz, 1 H, Ar-CH_d), 6.66 (dd, *J* = 8.2, 2.1 Hz, 1 H, Ar-CH_c), 6.43 (s, 2 H, 2 × Ar-CH_a), 5.63 (s, 1 H, OH), 5.22 (d, *J* = 5.6 Hz, 2 H, C*H*HOC*H*H), 5.19 (d, *J* = 5.6 Hz, 2 H, CH*H*OCH*H*), 3.87 (2 × s, 2 × 3 H, $OCH_{3,E}$, $OCH_{3,F}$), 3.81 (s, 6 H, 2 × OCH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.2 (2 × Ar-C_q-OCH_3), 146.7 (Ar-C_q-$OCH_{3,F}$), 144.5 (Ar-C_q-OH), 141.6 (Ar-C_q-CH_a), 137.5 (Ar-C_q-CH_c), 136.8 (Ar-C_q-$OCH_{3,E}$), 119.7 (Ar-CH_c), 114.1 (Ar-CH_b), 109.1 (Ar-CH_d), 104.1 (2 × Ar-CH_a), 84.9 (CH_2OCH_2), 60.9 ($OCH_{3,E}$), 56.2 (2 × OCH_3), 56.0 ($OCH_{3,F}$), 51.4 (C_q); HRMS (+ESI) *m*/*z* calcd for $C_{19}H_{23}O_6$ $[M+H]^+$: 347.1495, Found: 347.1504. Preparative HPLC traces:



Signal 1: DAD1 A, Sig=210,4 Ref=360,100

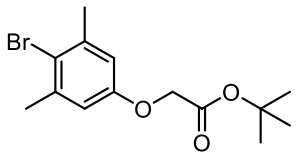
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.255	BB	0.0495	4698.44189	1462.57275	100.0000

Oxetane **53**: R_f = 0.24 (10% EtOAc/CH_2Cl_2); IR (film)/cm^{-1} 3273 (br, OH), 2937, 2880, 2837, 1585, 1511, 1452, 1414, 1326, 1287, 1244, 1179, 1128, 1020, 1007, 974, 923, 836, 809, 738, 659, 630; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.85 (s, 1 H, Ar-CH_d), 6.84 (d, *J* = 6.0 Hz, 1 H, Ar-CH_b), 6.72 (dd, *J* = 8.3, 2.3 Hz, 1 H, Ar-CH_c), 6.41 (s, 2 H, 2 × Ar-CH_a), 5.67 (s, 1 H, OH), 5.21 (d, *J* = 5.6 Hz, 2 H, C*H*HOC*H*H), 5.17 (d, *J* = 5.6 Hz, 2 H, CH*H*OCH*H*), 3.90 (s, 3 H, $OCH_{3,E}$), 3.86 (s, 3 H, $OCH_{3,F}$), 3.82 (s, 6 H, 2 × OCH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.2 (2 × Ar-C_q-OCH_3), 145.6 (Ar-C_q-OH), 145.3 (Ar-C_q-$OCH_{3,2}$), 141.5 (Ar-C_q-CH_a), 139.0 (Ar-C_q-CH_c), 136.7 (Ar-C_q-$OCH_{3,1}$), 118.0 (Ar-CH_c), 113.1 (Ar-CH_d), 110.5 (Ar-CH_b), 104.0 (2 × Ar-CH_a), 84.6 (CH_2OCH_2), 60.9 ($OCH_{3,E}$), 56.2 (2 × OCH_3), 56.0 ($OCH_{3,F}$), 51.3 (C_q); HRMS (+ESI) *m*/*z* calcd for $C_{19}H_{23}O_6$ $[M+H]^+$: 347.1495, Found: 347.1504. Preparative HPLC traces:



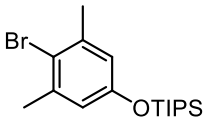
Signal 1: DAD1 A, Sig=210,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
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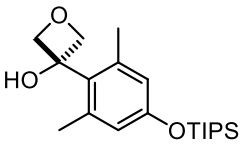
tert-Butyl 2-(4-bromo-3,5-dimethylphenoxy)acetate (76)

tert-Butyl-chloro-acetate (572 µL, 4.00 mmol) was added to a solution of 4-bromo-3,5-dimethyl phenol (1.20 g, 6.00 mmol) and K_2CO_3 (1.10 g, 8.00 mmol) in DMF (13 mL) at 25 °C. The reaction mixture was stirred at 80 °C for 66 h. The reaction was allowed to cooled to rt. Water (60 mL) followed by Et_2O (60 mL) was added and the layers were separated. The aqueous portion was extracted with Et_2O (3 × 60 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography (5 to 10% Et_2O/pentane) afforded aryl bromide **76** (1.08 g, 86%) as a white off solid. R_f = 0.44 (10% Et_2O/pentane); mp = 49–50 °C; IR (film)/cm^{-1} 2983, 2921, 1750 (C=O), 1589, 1471, 1435, 1399, 1367, 1324, 1229, 1151, 1097, 1008, 856, 762; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.65 (s, 2 H, 2 × Ar-CH), 4.47 (s, 2 H, OCH_2), 2.38 (s, 6 H, 2 × Ar-CH_3), 1.50 (s, 9 H, 3 × CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.9 (C=O), 156.3 (Ar-C_q-OCH_2), 139.2 (2 × Ar-C_q-CH_3), 119.1 (Ar-C_q-Br), 114.5 (2 × Ar-CH), 82.2 ($C_q(CH_3)_3$), 65.7 (OCH_2), 28.0 ($C_q(CH_3)_3$), 24.1 (2 × Ar-CH_3); HRMS (+EI) m/z calcd for $C_{14}H_{19}O_3Br^{\bullet}$ $[M]^{\bullet}$: 314.0518, Found: 314.0520.



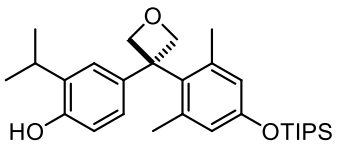
(4-Bromo-3,5-dimethylphenoxy)triisopropylsilane (76')

2,6-Lutidine (905 μL, 7.80 mmol) was added dropwise to a solution of 4-bromo-3,5-dimethylphenol (1.20 g, 6.00 mmol) and triisopropylsilyltrifluoromethanesulfonate (1.90 mL, 7.20 mmol) in CH_2Cl_2 (12 mL) at 0 °C. The reaction mixture was stirred for 30 min at 0 °C and then 2 h at 25 °C. Water (60 mL) was then added followed by CH_2Cl_2 (50 mL). The layers were separated and the aqueous portion was extracted with CH_2Cl_2 (2 × 50 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography (100% pentane) afforded **76'** (2.10 g, 100%) as a colourless oil. R_f = 0.92 (10% Et_2O/pentane); IR (film)/cm^{-1} 2944, 2866, 1580, 1463, 1324, 1171, 1017, 881, 860, 800; ^1H NMR (400 MHz, $CDCl_3$) δ 6.63 (s, 2 H, 2 × Ar-CH), 2.35 (s, 6 H, 2 × Ar-CH_3), 1.29–1.20 (m, 3 H, 3 × C*H*$(CH_3)_2$), 1.11 (d, *J* = 7.3 Hz, 18 H, 3 × CH(C*H*$_3)_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.6 (Ar-C_q-OTIPS), 138.2 (2 × Ar-*C*$_q$-CH_3), 119.7 (2 × Ar-CH), 118.5 (Ar-C_q-Br), 23.9 (2 × Ar-CH_3), 17.9 (3 × CH(*C*$H_3)_2$), 12.7 (3 × *C*H$(CH_3)_2$). The observed spectroscopic and physical data (^1H) for this compound was consistent with that previously reported.[238]



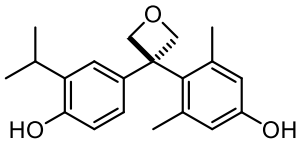
3-(2,6-Dimethyl-4-((triisopropylsilyl)oxy)phenyl)oxetan-3-ol (75')

*n*BuLi (2.38 M in THF, 2.1 mL, 4.98 mmol) was added dropwise over 5 min to a solution of **76'** (1.95 g, 5.40 mmol) in THF (8.0 mL) at –78 °C. The reaction mixture was stirred at –78 °C for 40 min. Oxetan-3-one (266 μL, 4.15 mmol) was added dropwise to the reaction mixture. Following a further 3 h at –78 °C the reaction mixture was warmed to rt and then quenched with water (80 mL). Et_2O (80 mL) was added and the layers were separated. The aqueous portion was extracted with Et_2O (2 × 80 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography (30% Et_2O/pentane) afforded oxetanol **75'** (935 mg, 64%) as a white solid. R_f = 0.19 (30% Et_2O/pentane); mp = 126 °C; IR (film)/cm^{-1} 3290 (br, OH), 2941, 2865, 1367, 1160, 994, 974, 881, 858, 709, 683; ^1H NMR (400 MHz, $CDCl_3$) δ 6.51 (s, 2 H, 2 × Ar-CH), 5.22 (d, *J* = 8.1 Hz, 2 H, C*H*HOC*H*H), 4.76 (d, *J* = 8.1 Hz, 2 H, CH*H*OCH*H*), 2.74 (s, 1 H, OH), 2.12 (s, 6 H, 2 × Ar-CH_3), 1.29–1.20 (m, 3H, 3 × C*H*$(CH_3)_2$), 1.11 (d, *J* = 7.1 Hz, 18 H, 3 × CH(C*H*$_3)_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.4 (Ar-C_q-OTIPS), 137.4 (2 × Ar-*C*$_q$-CH_3), 130.9 (Ar-*C*$_q$-C_q), 120.2 (2 × Ar-CH), 84.6 (*C*H_2O*C*H_2), 79.6 (C_q), 19.9 (3 × *C*H$(CH_3)_2$), 17.9 (3 × CH(*C*$H_3)_2$), 12.7 (2 × Ar-CH_3); HRMS (+ESI) *m*/*z* calcd for $C_{20}H_{33}O_2Si^•$ [M-OH]$^•$: 333.2250, Found: 333.2264.



4-(3-(2,6-Dimethyl-4-((triisopropylsilyl)oxy)phenyl)oxetan-3-yl)-2-isopropylphenol (78)

Lithium bis(trifluoromethane)sulfonimide (55.2 mg, 0.19 mmol) and tetrabutylammonium hexafluorophosphate (42.0 mg, 0.11 mmol) were added to a solution of oxetanol **75'** (677 mg, 1.93 mmol) and 2-isopropylphenol (1.30 mL, 9.65 mmol) in $CHCl_3$ (3.9 mL). The reaction mixture was stirred at 40 °C for 2 h then water (40 mL) was added followed by Et_2O (40 mL). The layers were separated and the aqueous portion was extracted with Et_2O (3 × 40 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash columns chromatography (10% EtOAc/pentane, followed by 80% CH_2Cl_2/pentane) afforded oxetane **78** (413 mg, 44%) as a white solid. R_f = 0.30 (10% EtOAc/pentane); mp = 172–174 °C; IR (film)/cm^{-1} 3257 (br, OH), 2946, 2867, 1600, 1505, 1464, 1425, 1315, 1269, 1162, 979, 881, 801, 681; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30–7.27 (m, 1 H, Ar-CH), 7.14 (dd, *J* = 8.4, 1.4 Hz, 1 H, Ar-CH), 6.69 (d, *J* = 9.4 Hz, 1 H, Ar-CH), 6.59 (s, 2 H, 2 × Ar-CH), 5.40 (d, *J* = 4.6 Hz, 2 H, C*H*HOC*H*H), 5.03 (s, 1 H, OH), 4.79 (d, *J* = 4.6 Hz, 2 H, CH*H*OCH*H*), 3.19 (h, *J* = 6.6 Hz, 1 H, Ar-C*H*$(CH_3)_2$), 1.83 (s, 6 H, 2 × Ar-CH_3), 1.33–1.24 (m, 3H, 3 × C*H*$(CH_3)_2$), 1.19–1.13 (2 × d, *J* = 6.6 Hz, *J* = 7.8 Hz, 24 H, Ar-CH(C*H*$_3)_2$, 3 × CH(C*H*$_3)_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.3 (Ar-C_q-OTIPS), 151.8 (Ar-C_q-OH), 137.4 (Ar-*C*$_q$-CH$(CH_3)_2$), 137.3 (2 × Ar-*C*$_q$-CH_3), 134.3 (Ar-*C*$_q$-C_q), 133.9 (Ar-*C*$_q$-C_q), 124.0 (Ar-CH), 123.9 (Ar-CH), 120.1 (2 × Ar-CH), 115.2 (Ar-CH), 85.6 (*C*H_2O*C*H_2), 52.0 (C_q), 27.1 (Ar-*C*H$(CH_3)_2$), 22.5 (Ar-CH(*C*$H_3)_2$), 20.4 (2 × Ar-CH_3), 18.0 (3 × CH(*C*$H_3)_2$), 12.7 (3 × *C*H$(CH_3)_2$); HRMS (+ESI) *m*/*z* calcd for $C_{29}H_{45}O_3Si$ [M+H]: 469.3138, Found: 469.3146.

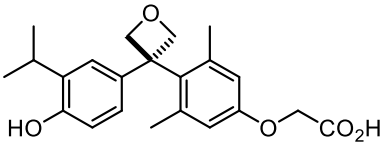


4-(3-(4-Hydroxy-3-isopropylphenyl)oxetan-3-yl)-3,5-dimethylphenol (77)

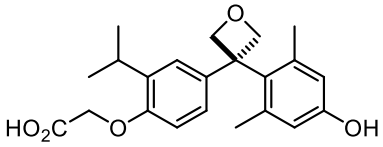
A solution of TBAF (1 M in THF, 1.10 mL, 1.10 mmol) was added to a solution of TIPS-protected oxetane **78** (399 mg, 0.85 mmol) in THF (2.8 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min and at 25 °C for 1 h 30 min. Water (50 mL) was added followed by EtOAc (50 mL). The layers were separated and the aqueous portion was extracted with EtOAc (3 × 50 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography (15% EtOAc/pentane) afforded **77** as a white solid (268 mg, 100%). R_f = 0.58 (50% EtOAc/pentane); mp = 192–194 °C; IR (film)/cm^{-1} 3124 (br, OH), 3051, 2925, 1608 (C=O), 1563, 1522, 1510, 1468, 1368, 1340, 1229, 1273, 1250, 1199, 1168, 1156, 1127, 1081, 1045, 1011, 949, 940, 933, 820, 741, 710; ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 9.19 (s, 1 H, OH), 9.12 (s, 1 H, OH), 7.25 (d, *J* = 2.5 Hz, 1 H, Ar-CH), 6.84 (dd, *J* = 8.4, 2.5 Hz, 1 H, Ar-CH), 6.69

(d, *J* = 8.4 Hz, 1 H, Ar-CH), 6.45 (s, 2 H, 2 × Ar-CH), 5.19 (d, *J* = 5.4 Hz, 2 H, C*H*HOC*H*H), 4.59 (d, *J* = 5.4 Hz, 2 H, CH*H*OCH*H*), 3,16 (h, *J* = 6.8 Hz, 1 H, Ar-C*H*$(CH_3)_2$) 1.73 (s, 6 H, 2 × Ar-CH_3), 1.08 (d, *J* = 7.2 Hz, 6 H, Ar-CH(C*H*$_3)_2$); ^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ 155.8 (Ar-C_q-OH), 153.7 (Ar-C_q-OH), 137.4 (2 × Ar-*C*$_q$-CH_3), 135.9 (Ar-*C*$_q$-CH$(CH_3)_2$), 134.4 (Ar-*C*$_q$-C_q), 132.2 (Ar-*C*$_q$-C_q), 123.8 (Ar-CH), 123.3 (Ar-CH), 115.8 (2 × Ar-CH), 115.1 (Ar-CH), 85.1 (CH_2OCH_2), 51.7 (C_q), 27.0 (*C*H$(CH_3)_2$), 23.0 (CH(*C*H$_3)_2$), 20.4 (2 × Ar-CH_3); HRMS (+ESI) *m*/*z* calcd for $C_{20}H_{25}O_3$ [M+H]: 313.1803, Found: 313.1804.

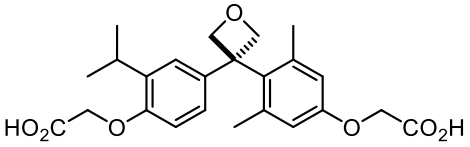
2-(4-(3-(4-Hydroxy-3-isopropylphenyl)oxetan-3-yl)-3,5-dimethylphenoxy)acetic acid (58), **2-(4-(3-(4-hydroxy-2,6-dimethylphenyl)oxetan-3-yl)-2-isopropylphenoxy)acetic acid (58')** and **2-(4-(3-(4-(Carboxymethoxy)-2,6-dimethylphenyl)oxetan-3-yl)-2-isopropylphenoxy)acetic acid (58-di)**



58



58'



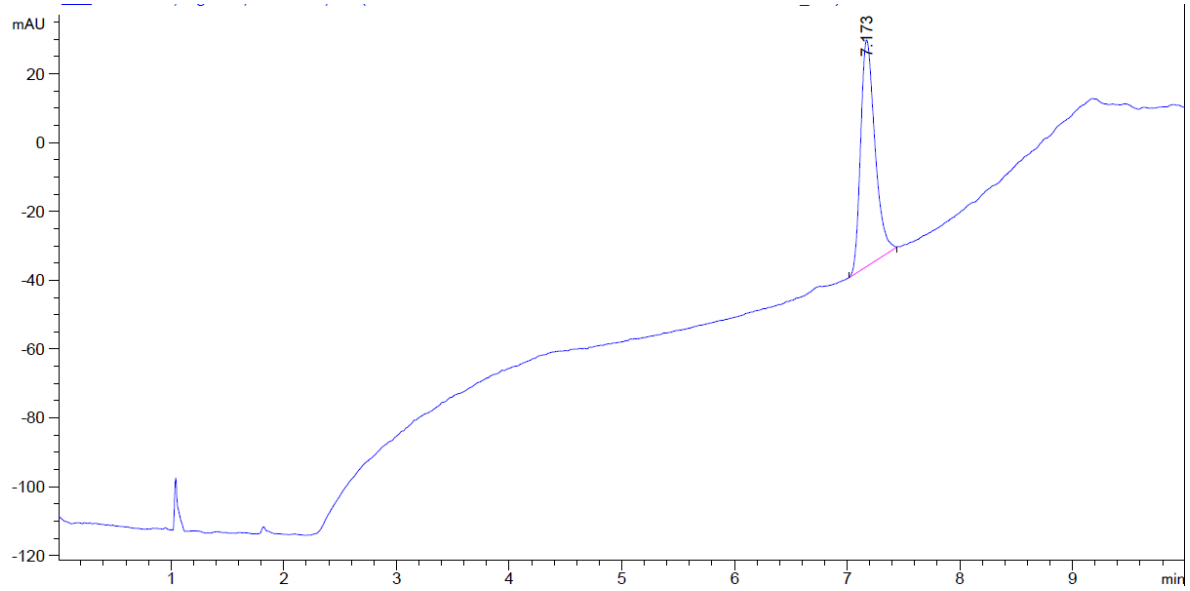
58-di

A solution of NaOH (1 M, 640 µL, 0.64 mmol) was added to a solution of oxetane **77** (100 mg, 0.32 mmol) in water (1.0 mL). The reaction mixture was stirred at 25 °C for 20 min and then at 100 °C for 10 min. A solution of NaOH (1 M, 320 µL, 0.32 mmol) was added to a solution of bromoacetic acid (48.6 mg, 0.35 mmol) in water (1.0 mL) and the solution was stirred for 10 min at 25 °C. This solution was added to the previous reaction mixture. The reaction was stirred at 100 °C for 32 h and was then cooled to 0 °C. A solution of HCl (1 M) was then added dropwise at 0 °C until pH = 2 was obtained. Water (40 mL) was added followed by EtOAc (40 mL). The layers were separated and the aqueous portion was extracted with EtOAc (4 × 40 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash columns chromatography (30% to 50% Et_2O/pentane containing 0.5% TFA) afforded a mixture of oxetane **58** and **58'** (53.0 mg, 45%) as a yellow solid and oxetane **58-di** (26.0 mg, 20%) as a white solid. Purification of the mixture of **58** and **58'** by preparative HPLC (Chiral Tech OD-H 250 mm × 10.0 mm 5µ, 60% CO_2/MeOH, flow rate: 10 mL. min^{-1}, pressure: 120 bar, UV detection wavelength: 210 nm), afforded **58'** (5 mg, 4%) as a yellow gum.

Oxetane **58-di**: R_f = 0.40 (50% Et_2O/pentane + 0.5% TFA); IR (film)/cm^{-1} 2959 (OH), 1712 (C=O), 1604, 1496, 1430, 1306, 1201, 1155, 1094, 798, 723; ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ

13.01 (s, 2 H, 2 × CO_2H), 7.39 (s, 1 H, Ar-CH), 6.90–6.87 (m, 1 H, Ar-CH), 6.75 (d, *J* = 8.4 Hz, 1 H, Ar-CH), 6.62 (s, 2 H, 2 × Ar-CH), 5.23 (s, 2 H, OCH_2CO), 4.66–4.63 (m, 6 H, CH_2OCH_2, OCH_2CO), 3.27 (m, 1 H, $CH(CH_3)_2$), 1.79 (s, 6 H, 2 × Ar-CH_3), 1.13 (d, *J* = 6.6 Hz, 6 H, $CH(CH_3)_2$); ^{13}C NMR (101 MHz, DMSO-d_6) δ 170.2 (2 × C=O), 155.9 (Ar-C_q-O), 153.8 (Ar-C_q-O), 137.14 (2 × Ar-C_q-CH_3), 137.08 (Ar-C_q-C_q), 136.2 (Ar-C_q-C_q), 133.5 (Ar-C_q-$CH(CH_3)_2$), 124.9 (Ar-CH), 123.4 (Ar-CH), 122.8 (Ar-CH), 114.4 (2 × Ar-CH), 84.2 (CH_2OCH_2), 64.6 (OCH_2CO), 64.3 (OCH_2CO), 51.2 (C_q), 26.6 ($CH(CH_3)_2$), 22.5 ($CH(CH_3)_2$), 20.0 (2 × Ar-CH_3);^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, *J* = 2.5 Hz, 1 H, Ar-CH), 6.86 (dd, *J* = 8.5, 2.5 Hz, 1 H, Ar-CH), 6.61 (s, 2 H, 2 × Ar-CH), 6.59 (d, *J* = 8.6 Hz, 1 H, Ar-CH), 5.39 (d, *J* = 5.5 Hz, 2 H, CHHOCHH), 4.80 (d, *J* = 5.4 Hz, 2 H, CHHOCHH), 4.70 (d, *J* = 5.8 Hz, 4 H, 2 × OCH_2CO), 3.37 (h, *J* = 6.9 Hz, 1 H, $CH(CH_3)_2$), 1.86 (s, 6 H, 2 × Ar-CH_3), 1.23 (d, *J* = 6.9 Hz, 6 H, $CH(CH_3)_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.8 (2 × C=O), 155.8 (Ar-C_q-O), 153.8 (Ar-C_q-O), 138.0 (2 × Ar-C_q-CH_3), 134.8 (2 × Ar-C_q-C_q), 125.5 (Ar-C_q-$CH(CH_3)_2$), 124.1 (Ar-CH), 123.8 (Ar-CH), 114.7 (2 × Ar-CH), 110.8 (Ar-CH), 85.3 (CH_2OCH_2), 65.1 (OCH_2CO), 64.7 (OCH_2CO), 51.8 (C_q), 27.3 ($CH(CH_3)_2$), 22.7 ($CH(CH_3)_2$), 20.6 (2 × Ar-CH_3); HRMS (-ESI) *m*/*z* calcd for $C_{24}H_{27}O_7$ $[M–H]^-$: 427.1757, Found: 427.1762.

Oxetane **58'**: R_f = 0.80 (50% Et_2O/pentane + 0.5% TFA); IR (film)/cm^{-1} 3359 (OH), 2958 (OH), 2926, 2872, 2359, 2342, 1682 (C=O), 1606, 1495, 1457, 1306, 1203, 1153, 1028, 948, 857, 829, 586; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, *J* = 2.5 Hz, 1 H, Ar-CH), 7.04 (dd, *J* = 8.6, 2.5 Hz, 1 H, Ar-CH), 6.65 (d, *J* = 8.6 Hz, 1 H, Ar-CH), 6.55 (s, 2 H, 2 × Ar-CH), 5.38 (d, *J* = 5.4 Hz, 2 H, CHHOCHH), 4.78 (d, *J* = 5.4 Hz, 2 H, CHHOCHH), 4.67 (s, 2 H, OCH_2CO), 3.37 (h, *J* = 6.9 Hz, 1 H, $CH(CH_3)_2$), 1.83 (s, 6 H, 2 × Ar-CH_3), 1.21 (d, *J* = 6.9 Hz, 6 H, $CH(CH_3)_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.7 (C=O), 153.9 (Ar-C_q-O), 153.8 (Ar-C_q-O), 138.5 (Ar-C_q-C_q), 137.9 (2 × Ar-C_q-CH_3), 137.7 (Ar-C_q-$CH(CH_3)_2$), 133.4 (Ar-C_q-C_q), 124.04 (Ar-CH), 124.00 (Ar-CH), 115.6 (2 × Ar-CH), 111.2 (Ar-CH), 85.4 (CH_2OCH_2), 65.3 (OCH_2CO), 51.9 (C_q), 27.2 ($CH(CH_3)_2$), 22.7 ($CH(CH_3)_2$), 20.3 (2 × Ar-CH_3). Preparative HPLC traces:



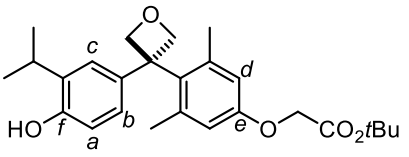
Signal 1: DAD1 A, Sig=210,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
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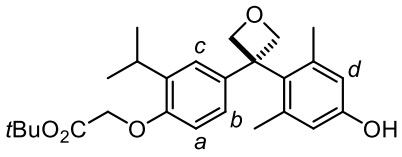
Oxetane **58**: R_f = 0.80 (50% Et_2O/pentane + 0.5% TFA); ^{1}H NMR* (400 MHz, $CDCl_3$) δ 7.48 (d, *J* = 2.4 Hz, 1 H, Ar-CH), 6.90 (dd, *J* = 8.3, 2.4 Hz, 1 H, Ar-CH), 6.67–6.62 (m, 3 H, 3 × Ar-CH), 5.40 (d, *J* = 5.5 Hz, 2 H, C*H*HOC*H*H), 4.83 (d, *J* = 5.5 Hz, 2 H, CH*H*OCH*H*), 4.71 (s, 2 H, OCH_2CO), 3.22 (h, *J* = 6.8 Hz, 1 H, C*H*$(CH_3)_2$), 1.87 (s, 6 H, 2 × Ar-CH_3), 1.22 (d, *J* = 6.8 Hz, 6 H, CH(C*H*$_3)_2$); ^{13}C NMR* (101 MHz, $CDCl_3$) δ 173.2 (C=O), 155.7 (Ar-C_q-O), 152.1 (Ar-C_q-O), 137.9 (2 × Ar-*C*$_q$-CH_3), 137.8 (Ar-*C*$_q$-C_q), 136.7 (Ar-*C*$_q$-C_q), 134.9 (Ar-*C*$_q$-$CH(CH_3)_2$), 124.1 (Ar-CH), 123.7 (Ar-CH), 115.0 (Ar-CH), 114.8 (2 × Ar-CH), 85.6 (CH_2OCH_2), 64.7 (OCH_2CO), 51.8 (C_q), 27.3 (*C*H$(CH_3)_2$), 22.5 (CH(*C*H$_3)_2$), 20.5 (2 × Ar-CH_3); HRMS† (–ESI) *m*/*z* calcd for $C_{24}H_{27}O_7$ $[M-H]^-$: 427.1757, Found: 427.1762.

Assigned comparing ^{1}H and ^{13}C NMR of pure **58', with ^{1}H and ^{13}C NMR of mixture of **58**+**58'**, plus HMBC and HSQC experiments.* †*Obtained on the mixture of **58**+**58'**.*

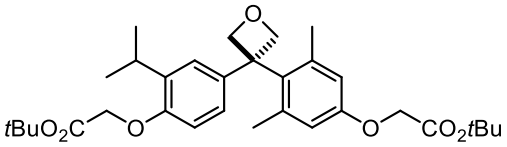
***tert*-Butyl-2-(4-(3-(4-hydroxy-3-isopropylphenyl)oxetan-3-yl)-3,5-dimethylphenoxy)acetate (74), *tert*-butyl 2-(4-(3-(4-hydroxy-2,6-dimethylphenyl)oxetan-3-yl)-2-isopropylphenoxy)acetate (74') and *tert*-butyl 2-(4-(3-(4-(2-(tert-butoxy)-2-oxoethoxy)-2,6-dimethylphenyl)oxetan-3-yl)-2-isopropylphenoxy)acetate (74-di)**.



74



74'



74-di

K_2CO_3 (8.4 mg, 0.06 mmol) was added to a solution of oxetane **77** (16.0 mg, 0.05 mmol) in DMF (510 µL). The reaction mixture was stirred for 30 min at 25 °C and *tert*-butyl chloroacetate was added. The reaction mixture was stirred for 24 h at 80 °C. The reaction was cooled down to rt and water (15 mL) was added followed by Et_2O (15 mL). The layers were separated and the aqueous portion was extracted with Et_2O (3 × 15 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash columns chromatography (20% to 50% Et_2O/pentane) afforded a mixture of oxetane **74** and **74'** (6.7 mg, 31%) as a white solid and oxetane **74-di** (8.8 mg, 32%) as a yellow oil.

Oxetane **74** and **74'**: R_f = 0.35 (40% Et_2O/pentane); IR (film)/cm^{-1} 3375 (br, OH), 2958, 1730 (C=O), 1604, 1506, 1316, 1226, 1150, 1100, 833. HRMS (+ESI) *m*/*z* calcd for $C_{26}H_{35}O_5$ [M+H]: 427.2491, Found: 427.2484.

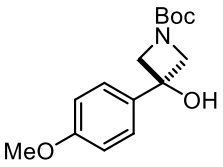
74: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, *J* = 2.4 Hz, 1 H, Ar-CH_c), 6.98 (dd, *J* = 8.4, 2.4 Hz, 1 H, Ar-CH_b), 6.66 (d, *J* = 8.4 Hz, 1 H, Ar-CH_a), 6.60 (s, 2 H, 2 × Ar-CH_d), 5.36 (d, *J* = 5.3 Hz, 2 H, C*H*HOC*H*H), 4.83 (s, 1 H, OH), 4.77 (d, *J* = 5.4 Hz, 2 H, CH*H*OCH*H*), 4.53 (s, 2 H, OCH_2CO), 3.20 (h, *J* = 6.8 Hz, 1 H, C*H*$(CH_3)_2$), 1.86 (s, 6 H, 2 × Ar-CH_3), 1.52 (s, 9 H, 3 × CH_3), 1.22 (d, *J* = 6.8 Hz, 6 H, CH(C*H*$_3)_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.2 (C=O), 156.2 (Ar-$C_{q(e)}$-OCH_2), 151.8 (Ar-$C_{q(f)}$-OH), 137.7 (2 × Ar-C_q-CH_3), 137.3 (Ar-C_q-C_q), 134.6 (Ar-C_q-$CH(CH_3)_2$), 134.5 (Ar-C_q-C_q), 124.1 (Ar-CH_b), 123.8 (Ar-CH_c), 115.0 (Ar-CH_a), 114.8 (2 × Ar-CH_d), 85.5 (CH_2OCH_2), 82.3 ($C_q(CH_3)_3$), 65.7 (OCH_2CO), 52.0 (C_q), 28.1 ($C_q(CH_3)_3$), 27.4 ($CH(CH_3)_2$), 22.5 ($CH(CH_3)_2$), 20.5 (2 × Ar-CH_3).

74': ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, *J* = 2.5 Hz, 1 H, Ar-CH_c), 7.02 (dd, *J* = 8.6, 2.5 Hz, 1 H, Ar-CH_b), 6.58 (d, *J* = 8.6 Hz, 1 H, Ar-CH_a), 6.55 (s, 2 H, 2 × Ar-CH_d), 5.37 (d, *J* = 5.8 Hz, 2 H, C*H*HOC*H*H), 4.78 (d, *J* = 5.8 Hz, 2 H, CH*H*OCH*H*), 4.52 (s, 2 H, OCH_2CO), 3.39 (h, *J* = 7.1 Hz, 1 H, C*H*$(CH_3)_2$), 1.83 (s, 6 H, 2 × Ar-CH_3), 1.48 (s, 9 H, 3 × CH_3), 1.21 (d, *J* = 7.0 Hz,

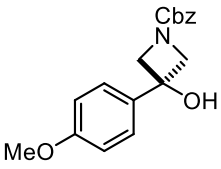
6 H, CH(CH_3)$_2$). *Carbon peaks for compound **74'** was too low in the ^{13}C NMR spectrum of the mixture **74**+**74'** to be able to assign them.*

Oxetane **74-di**: R_f = 0.35 (40% Et_2O/pentane); IR (film)/cm^{-1} 2958, 2870, 1753 (C=O), 1730 (C=O), 1495, 1367, 1313, 1220, 1147, 1095, 845; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, *J* = 2.4 Hz, 1 H, Ar-CH), 7.00 (dd, *J* = 8.5, 2.4 Hz, 1 H, Ar-CH), 6.60–6.57 (m, 3 H, 3 × Ar-CH), 5.36 (d, *J* = 5.5 Hz, 2 H, C*H*HOC*H*H), 4.77 (d, *J* = 5.5 Hz, 2 H, CH*H*OCH*H*), 4.52 (m, 4 H, 2 × OCH_2CO), 3.39 (h, *J* = 6.6 Hz, 1 H, C*H*(CH_3)$_2$), 1.85 (s, 6 H, 2 × Ar-CH_3), 1.51 (s, 9 H, 3 × CH_3), 1.48 (s, 9 H, 3 × CH_3), 1.21 (d, *J* = 6.6 Hz, 6 H, CH(CH_3)$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.23 (C=O), 168.19 (C=O), 156.2 (Ar-C_q-OCH_2), 154.3 (Ar-C_q-OCH_2), 137.7 (2 × Ar-C_q-CH_3), 137.6 (Ar-C_q-C_q), 137.5 (Ar-C_q-C_q), 134.5 (Ar-C_q-CH(CH_3)$_2$), 123.81 (Ar-CH), 123.8 (Ar-CH), 114.8 (2 × Ar-CH), 110.7 (Ar-CH), 85.4 (CH_2OCH_2), 82.2 (C_q(CH_3)$_3$), 82.1 (C_q(CH_3)$_3$), 66.0 (OCH_2CO), 65.7 (OCH_2CO), 52.0 (C_q), 28.1 (2 × C_q(CH_3)$_3$), 27.3 (*C*H(CH_3)$_2$), 22.6 (CH(*C*H_3)$_2$), 20.5 (2 × Ar-CH_3); HRMS (+ESI) *m*/*z* calcd for $C_{32}H_{45}O_7$ [M+H]: 541.3156, Found: 541.3165.

8.2.3 Synthesis of 3,3-Diarylazetidines, Precursors and Derivatives (Part 4.1)



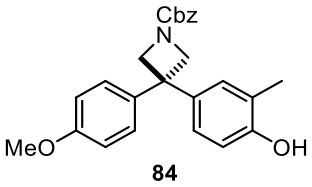
***tert*-Butyl 3-hydroxy-3-(4-methoxyphenyl)azetidine-1-carboxylate (81)** *n*BuLi (1.55 M in THF, 3.10 mL, 4.80 mmol) was added dropwise over 5 min to a solution of 4-bromoanisole (653 µL, 5.20 mmol) in THF (4.0 mL) at –78 °C. The reaction mixture was stirred at –78 °C for a further 30 min. 1-Boc-3-azetidinone (685 mg, 4.00 mmol) in THF (4.0 mL) 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 (40 mL). The layers were separated and the aqueous portion extracted with Et_2O (3 × 40 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash chromatography (10% to 70% Et_2O/pentane) afforded azetidinol **81** (8049 mg, 73%) as a white solid. R_f = 0.30 (30% EtOAc/hexane); mp = 86–88°C; IR (film)/cm^{-1} 3402 (br, OH), 2976, 1670 (C=O), 1513, 1460, 1398, 1367, 1153, 1166, 1119, 1101, 1048, 1031, 872, 854, 836, 807, 776; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42–7.38 (m, 2 H, 2 × Ar-CH), 6.93–6.89 (m, 2 H, 2 × Ar-CH), 4.23 (d, *J* = 9.2 Hz, 2 H, C*H*HNC*H*H), 4.14 (d, *J* = 9.2 Hz, 2 H, CH*H*NCH*H*), 3.82 (s, 3 H, OCH_3), 3.02 (br s, 1 H, OH), 1.45 (s, 9 H, 3 × CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.3 (Ar-C_q-OCH_3), 156.6 (C=O), 135.5 (Ar-C_q-C_q), 126.1 (2 × Ar-CH), 114.1 (2 × Ar-CH), 80.0 (C_q(CH_3)$_3$), 71.3 (C_q), 64.4 (br, CH_2NCH_2), 55.5 (OCH_3), 28.5 (3 × CH_3); HRMS (+ESI) *m*/*z* calcd for $C_{15}H_{22}NO_4$ [M+H]: 280.1556, Found: 280.1549. Compound previously reported without characterisation data.[239]



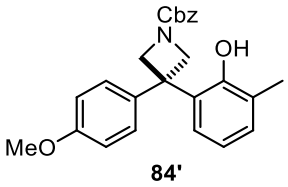
Benzyl 3-hydroxy-3-(4-methoxyphenyl)azetidine-1-carboxylate (83)

4-Methoxyphenylmagnesium bromide (0.5 M solution in THF, 100 mL, 50 mmol) was added dropwise to a solution of 1-Cbz-3-azetidinone (7.90 g, 38.5 mmol) in THF (50 mL) at 0 °C. The reaction mixture was stirred for 19 h at 25 °C, then cooled to 0 °C and quenched with sat. aq. NH_4Cl (300 mL). The aqueous portion was extracted with Et_2O (3 × 300 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash chromatography (70% Et_2O/hexane) afforded azetidinol **83** (9.22 g, 76%) as a white solid. R_f = 0.30 (30% EtOAc/hexane); mp = 80–82 °C; IR (film)/cm^{-1} 3308 (br, OH), 1674 (C=O), 1657, 1517, 1458, 1438, 1357, 1249, 1177, 1106, 1026, 949, 827, 756, 702; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41–7.30 (m, 7 H, 7 × Ar-CH), 6.93–6.89 (m, 2 H, 2 × Ar-CH), 5.11 (s, 2 H, CH_2Ph), 4.32 (d, *J* = 9.2 Hz, 2 H, C*H*HNC*H*H), 4.23 (d, *J* = 9.2 Hz, 2 H, CH*H*NCH*H*), 3.81 (s, 3 H, OCH_3), 3.06 (s, 1 H, OH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.4 (Ar-C_q-OCH_3), 156.7 (C=O), 136.6 (Ar-C_q-CH_2), 135.2 (Ar-C_q-C_q), 128.6 (2 × Ar-CH), 128.2 (Ar-CH), 128.1 (2 × Ar-CH), 126.1 (2 × Ar-CH), 114.2 (2 × Ar-CH), 71.7 (C_q), 67.0 (CH_2Ph), 64.5 (br, *C*H_2N*C*H_2), 55.5 (OCH_3); HRMS (+ESI) *m*/*z* calcd for $C_{18}H_{20}NO_4$ [M+H]: 314.1392, Found: 314.1396.

Benzyl 3-(4-hydroxy-3-methylphenyl)-3-(4-methoxyphenyl)azetidine -1-carboxylate (84) and **benzyl 3-(2-hydroxy-3-methylphenyl)-3-(4-methoxyphenyl)azetidine-1-carboxylate (84')**



84



84'

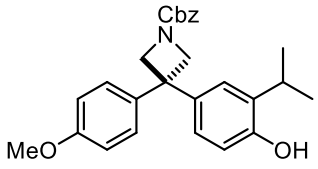
Calcium(II) bis(trifluoromethanesulfonimide) (120 mg, 0.20 mmol) and tetrabutylammonium hexafluorophosphate (77.5 mg, 0.20 mmol) were added to a solution of azetidinol **83** (1.25 g, 4.00 mmol) and 2-methylphenol (1.20 mL, 12.0 mmol) in CH_2Cl_2 (8.0 mL). The reaction mixture was stirred at 40 °C for 3 h then sat. aq. $NaHCO_3$ (80 mL) was added. The aqueous portion was extracted with EtOAc (3 × 80 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash chromatography (20% EtOAc/hexane) afforded azetidine **84'** (63.6 mg, 4%) as a white solid followed by azetidine **84** (1.49 g, 93%) as a white solid.

84': R_f = 0.37 (30% EtOAc/hexane); mp = 163–170 °C; IR (film)/cm^{-1} 3295 (br, OH), 2952, 1690 (C=O), 1608, 1593, 1578, 1510, 1461, 1430, 1351, 1318, 1305, 1250, 1209, 1179, 1123, 1026, 955, 912, 828, 803, 777, 758, 747, 694; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37–7.31 (m, 5 H, 5 × Ar-CH), 7.25–7.23 (m, 2 H, 2 × Ar-CH), 7.09 (ddd, *J* = 7.4, 1.6, 0.8 Hz, 1 H, Ar-CH), 7.04

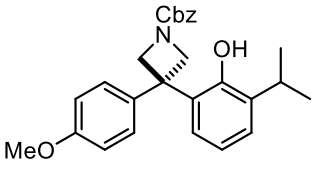
(dd, *J* = 7.8, 1.6 Hz, 1 H, Ar-CH), 6.93–6.89 (m, 1 H, Ar-CH), 6.84–6.82 (m, 2 H, 2 × Ar-CH), 5.17 (s, 1 H, OH), 5.12 (s, 2 H, CH_2Ph), 4.71 (d, *J* = 8.8 Hz, 2 H, C*H*HNC*H*H), 4.47 (d, *J* = 8.8 Hz, 2 H, CH*H*NCH*H*), 3.78 (s, 3 H, OCH_3), 2.23 (s, 3 H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.3 (Ar-C_q-OCH_3), 156.6 (C=O), 151.6 (Ar-C_q-OH), 137.6 (Ar-C_q-C_q), 136.6 (Ar-C_q-CH_2), 130.6 (Ar-C_q-C_q), 129.8 (Ar-CH), 128.4 (2 × Ar-CH), 128.01 (Ar-CH), 127.97 (2 × Ar-CH), 127.0 (2 × Ar-CH), 125.6 (Ar-CH), 123.9 (Ar-C_q-CH_3), 120.4 (Ar-CH), 113.9 (2 × Ar-CH), 66.8 (CH_2Ph), 62.6 (CH_2NCH_2), 55.2 (OCH_3), 43.8 (C_q), 15.7 (CH_3); HRMS (+ESI) *m*/*z* calcd for $C_{25}H_{26}NO_4$ [M+H]: 404.1862, Found: 404.1855.

84: R_f = 0.37 (30% EtOAc/hexane); mp = 148 °C; IR (film)/cm^{-1} 3309 (br, OH), 2958, 1676 (C=O), 1609, 1509, 1421, 1354, 1247, 1179, 1117, 1026, 827, 697; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38–7.30 (m, 5 H, 5 × Ar-CH), 7.12–7.08 (m, 2 H, 2 × Ar-CH), 6.94 (d, *J* = 1.8 Hz, 1 H, Ar-CH), 6.88–6.84 (m, 3 H, 3 × Ar-CH), 6.72 (d, *J* = 8.3 Hz, 1 H, Ar-CH), 5.13 (s, 2 H, CH_2Ph), 4.85 (s, 1 H, OH), 4.55 (d, *J* = 8.3 Hz, 2 H, C*H*HNC*H*H), 4.54 (d, *J* = 8.3 Hz, 2 H, CH*H*NCH*H*), 3.80 (s, 3 H, OCH_3), 2.22 (s, 3 H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.3 (Ar-C_q-OCH_3), 156.7 (C=O), 153.0 (Ar-C_q-OH), 138.5 (Ar-C_q-C_q), 138.0 (Ar-C_q-C_q), 136.6 (Ar-C_q-CH_2), 129.3 (Ar-CH), 128.6 (2 × Ar-CH), 128.2 (Ar-CH), 128.2 (2 × Ar-CH), 127.8 (2 × Ar-CH), 125.2 (Ar-CH), 124.3 (Ar-C_q-CH_3), 114.9 (Ar-CH), 114.0 (2 × Ar-CH), 67.1 (CH_2Ph), 63.9 and 63.2 (CH_2NCH_2), 55.4 (OCH_3), 45.0 (C_q), 16.1 (CH_3); HRMS (+ESI) *m*/*z* calcd for $C_{25}H_{26}NO_4$ [M+H]: 404.1867, Found: 404.1862.

Benzyl 3-(4-hydroxy-3-isopropylphenyl)-3-(4-methoxyphenyl)azetidine-1-carboxylate (86) and **benzyl 3-(2-hydroxy-3-isopropylphenyl)-3-(4-methoxyphenyl)azetidine-1-carboxylate (86')**



86



86'

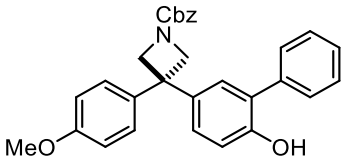
Calcium(II) bis(trifluoromethanesulfonimide) (15.0 mg, 0.025 mmol) and tetrabutylammonium hexafluorophosphate (9.7 mg, 0.025 mmol) were added to a solution of azetidinol **83** (157 mg, 0.50 mmol) and 2-isopropylphenol (202 µL, 1.50 mmol) in CH_2Cl_2 (1.0 mL). The reaction mixture was stirred at 40 °C for 2 h then sat. aq. $NaHCO_3$ (30 mL) was added followed by CH_2Cl_2 (30 mL). The layers were separated and the aqueous portion was extracted with EtOAc (3 × 30 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash chromatography (20%

acetone/pentane) afforded azetidine **86'** (14.4 mg, 7%) as a white solid followed by azetidine **86** (186 mg, 86%) as a white solid.

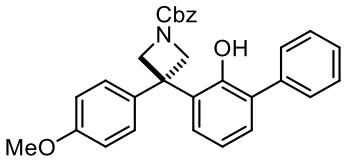
86': R_f = 0.42 (20% acetone/pentane); mp = 51–55 °C; IR (film)/cm^{-1} 3323 (br, OH), 2961, 1684 (C=O), 1511, 1439, 1355, 1305, 1248, 1207, 1181, 1128, 1027, 959, 828, 798, 779, 697; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.32 (m, 5 H, 5 × Ar-CH), 7.25–7.23 (m, 2 H, 2 × Ar-CH), 7.18 (dd, *J* = 7.4, 1.9 Hz, 1 H, Ar-CH), 7.05–6.97 (m, 2 H, 2 × Ar-CH), 6.86–6.83 (m, 2 H, 2 × Ar-CH), 5.13 (s, 2 H, CH_2Ph), 4.99 (s, 1 H, OH), 4.71 (d, *J* = 8.8 Hz, 2 H, C*H*HNC*H*H), 4.46 (d, *J* = 8.8 Hz, 2 H, CH*H*NCH*H*), 3.78 (s, 3 H, OCH_3), 3.06 (h, *J* = 6.8 Hz, 1 H, C*H*$(CH_3)_2$), 1.25 (d, *J* = 6.8 Hz, 6 H, CH(C*H*$_3)_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.4 (Ar-*C*$_q$-OCH_3), 156.6 (C=O), 150.5 (Ar-C_q-OH), 137.4 (Ar-*C*$_q$-CH$(CH_3)_2$), 136.6 (Ar-*C*$_q$-CH_2), 134.7 (Ar-*C*$_q$-C_q), 130.8 (Ar-*C*$_q$-C_q), 128.5 (2 × Ar-CH), 128.03 (Ar-CH), 128.00 (2 × Ar-CH), 127.0 (2 × Ar-CH), 125.2 (Ar-CH), 125.0 (Ar-CH), 120.8 (Ar-CH), 114.0 (2 × Ar-CH), 66.8 (CH_2Ph), 62.7 (br, *C*H_2N*C*H_2), 55.2 (OCH_3), 43.9 (C_q), 26.7 (*C*H$(CH_3)_2$), 22.7 (CH(*C*$H_3)_2$); HRMS (+ESI) *m*/*z* calcd for $C_{27}H_{30}NO_4$ [M+H]: 432.2175, Found: 432.2171.

86: R_f = 0.25 (20% acetone/pentane); mp = 137–139 °C; IR (film)/cm^{-1} 3320 (br, OH), 2958, 1676 (C=O), 1608, 1509, 1421, 1355, 1247, 1180, 1125, 826, 756; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.32 (m, 5 H, 5 × Ar-CH), 7.12–7.09 (m, 2 H, 2 × Ar-CH), 6.99 (d, *J* = 2.4 Hz, 1 H, Ar-CH), 6.88–6.85 (m, 2 H, 2 × Ar-CH), 6.82 (dd, *J* = 8.2, 2.4 Hz, 1 H, Ar-CH), 6.71 (d, *J* = 8.2 Hz, 1 H, Ar-CH), 5.45 (s, 1 H, OH), 5.15 (s, 2 H, CH_2Ph), 4.61–4.55 (m, 4 H, C*H*$_2$NC*H*$_2$), 3.81 (s, 3 H, OCH_3), 3.21 (h, *J* = 6.9 Hz, 1 H, C*H*$(CH_3)_2$), 1.22 (d, *J* = 6.9 Hz, 6 H, CH(C*H*$_3)_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.2 (Ar-*C*$_q$-OCH_3), 156.5 (C=O), 151.7 (Ar-C_q-OH), 138.6 (Ar-*C*$_q$-C_q), 137.9 (Ar-*C*$_q$-CH$(CH_3)_2$), 136.5 (Ar-*C*$_q$-CH_2), 134.6 (Ar-*C*$_q$-C_q), 128.5 (2 × Ar-CH), 128.1 (Ar-CH), 128.0 (2 × Ar-CH), 127.6 (2 × Ar-CH), 124.8 (Ar-CH), 124.7 (Ar-CH), 115.2 (Ar-CH), 113.8 (2 × Ar-CH), 66.9 (CH_2Ph), 64.0 and 63.2 (*C*H_2N*C*H_2), 55.3 (OCH_3), 45.0 (C_q), 27.3 (*C*H$(CH_3)_2$), 22.5 (CH(*C*$H_3)_2$); HRMS (+ESI) *m*/*z* calcd for $C_{27}H_{30}NO_4$ [M+H]: 432.2175, Found: 432.2166.

Benzyl 3-(6-hydroxy-[1,1'-biphenyl]-3-yl)-3-(4-methoxyphenyl)azetidine-1-carboxylate (87) and **benzyl 3-(2-hydroxy-[1,1'-biphenyl]-3-yl)-3-(4-methoxyphenyl)azetidine-1-carboxylate (87')**



87



87'

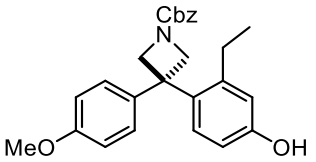
Calcium(II) bis(trifluoromethanesulfonimide) (15.0 mg, 0.025 mmol) and tetrabutylammonium hexafluorophosphate (9.7 mg, 0.025 mmol) were added to a solution of azetidinol **83** (157 mg, 0.50 mmol) and 2-phenylphenol (255 mg, 1.50 mmol) in CH_2Cl_2 (1.0 mL). The reaction mixture was stirred at 40 °C for 4 h then sat. aq. $NaHCO_3$ (30 mL) was added followed by CH_2Cl_2 (30 mL). The layers were separated and the aqueous portion was extracted with EtOAc (3 × 30 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash chromatography (20% to 30% EtOAc/hexane) afforded azetidine **87'** (18.3 mg, 8%) as a white solid followed by azetidine **87** (207 mg, 89%) as a white solid.

87': R_f = 0.29 (20% EtOAc/hexane); mp = 51–54 °C; IR (film)/cm^{-1} 3311 (br, OH), 3032, 2955, 2835, 1691 (C=O), 1510, 1453, 1429, 1353, 1296, 1247, 1215, 1180, 1131, 1094, 1029, 1006, 962, 907, 828, 800, 758, 728, 697; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51–7.47 (m, 2 H, 2 × Ar-CH), 7.43–7.28 (m, 10 H, 10 × Ar-CH), 7.22–7.19 (m, 2 H, 2 × Ar-CH), 7.08–7.06 (m, 1 H, Ar-CH), 6.86–6.84 (m, 2 H, 2 × Ar-CH), 5.38 (s, 1 H, OH), 5.13 (s, 2 H, CH_2Ph), 4.77 (d, *J* = 8.8 Hz, 2 H, C*H*HNC*H*H), 4.50 (d, *J* = 8.8 Hz, 2 H, CH*H*NCH*H*), 3.78 (s, 3 H, OCH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.2 (Ar-C_q-OCH_3), 156.5 (C=O), 149.8 (Ar-C_q-OH), 137.8 (Ar-C_q-C_q), 136.6 (Ar-C_q-CH_2), 136.3 (Ar-C_q-C_q), 131.0 (Ar-C_q-C_q), 129.5 (2 × Ar-CH), 129.1 (2 × Ar-CH), 129.0 (Ar-CH), 128.8 (Ar-C_q-C_q), 128.4 (2 × Ar-CH), 128.2 (2 × Ar-CH), 128.0 (2 × Ar-CH), 127.4 (Ar-CH), 127.0 (2 × Ar-CH), 120.5 (Ar-CH), 113.7 (2 × Ar-CH), 66.7 (CH_2Ph), 62.9 and 62.1 (CH_2NCH_2), 55.2 (OCH_3), 44.0 (C_q); HRMS (+NSI) *m*/*z* calcd for $C_{30}H_{28}NO_4^+$ $[M+H]^+$: 466.2013, Found: 466.2018.

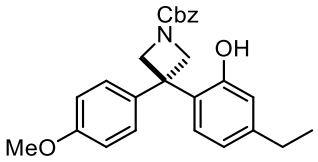
87: R_f = 0.07 (20% EtOAc/hexane); mp = 58–66 °C; IR (film)/cm^{-1} 3293 (br, OH), 2956, 1676 (C=O), 1608, 1511, 1490, 1407, 1354, 1247, 1180, 1127, 1018, 1003, 958, 827, 755, 733, 696; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51–7.30 (m, 10 H, 10 × Ar-CH), 7.16–7.13 (m, 2 H, 2 × Ar-CH), 7.09 (d, *J* = 2.4 Hz, 1 H, Ar-CH), 7.05 (dd, *J* = 8.4, 2.5 Hz, 1 H, Ar-CH), 6.95 (d, *J* = 8.4 Hz, 1 H, Ar-CH), 6.90–6.86 (m, 2 H, 2 × Ar-CH), 5.49 (s, 1 H, OH), 5.13 (s, 2 H, CH_2Ph), 4.63–4.57 (m, 4 H, CH_2NCH_2), 3.81 (s, 3 H, OCH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.2 (Ar-C_q-OCH_3), 156.5 (C=O), 151.2 (Ar-C_q-OH), 138.4 (Ar-C_q-C_q), 138.1 (Ar-C_q-C_q), 136.9 (Ar-C_q-C_q), 136.5 (Ar-C_q-CH_2), 129.2 (2 × Ar-CH), 129.1 (2 × Ar-CH), 128.5 (2 × Ar-CH), 128.3 (Ar-CH),

128.2 (Ar-C_q-C_q), 128.1 (Ar-CH), 128.0 (2 × Ar-CH), 127.9 (Ar-CH), 127.6 (2 × Ar-CH), 127.3 (Ar-CH), 115.9 (Ar-CH), 114.0 (2 × Ar-CH), 66.9 (CH_2Ph), 63.7 (br, CH_2NCH_2), 55.3 (OCH_3), 44.9 (C_q); HRMS (+NSI) *m*/*z* calcd for $C_{30}H_{28}NO_4^+$ $[M+H]^+$: 466.2013, Found: 466.2016.

Benzyl 3-(4-ethyl-2-hydroxyphenyl)-3-(4-methoxyphenyl)azetidine-1-carboxylate (90') and **benzyl 3-(2-ethyl-4-hydroxyphenyl)-3-(4-methoxyphenyl)azetidine-1-carboxylate (90)**



90



90'

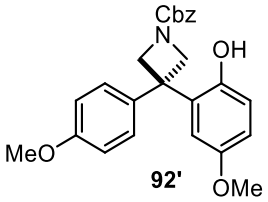
Calcium(II) bis(trifluoromethanesulfonimide) (15.0 mg, 0.025 mmol) and tetrabutylammonium hexafluorophosphate (9.7 mg, 0.025 mmol) were added to a solution of azetidinol **83** (157 mg, 0.50 mmol) and 3-ethylphenol (183 µL, 1.50 mmol) in CH_2Cl_2 (1.0 mL). The reaction mixture was stirred at 40 °C for 4 h then sat. aq. $NaHCO_3$ (30 mL) was added followed by CH_2Cl_2 (30 mL). The layers were separated and the aqueous portion was extracted with EtOAc (3 × 30 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash chromatography (15% to 20% acetone/pentane) afforded azetidine **90'** (146 mg, 70%) as a white solid followed by azetidine **90** (45 mg, 22%) as a white solid.

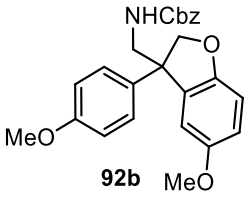
90': R_f = 0.25 (20% acetone/pentane); mp = 131–133 °C; IR (film)/cm^{-1} 2961 (br, OH), 1688 (C=O), 1589, 1512, 1402, 1357, 1249, 1213, 1188, 1163, 1106, 1034, 1029, 815, 702, 684; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (s, 1 H, OH), 7.39–7.34 (m, 5 H, 5 × Ar-CH), 7.27–7.24 (m, 2 H, 2 × Ar-CH), 7.02 (dd, *J* = 7.7, 1.4 Hz, 1 H, Ar-CH), 6.83–6.81 (m, 2 H, 2 × Ar-CH), 6.76 (d, *J* = 7.7 Hz, 1 H, Ar-CH), 6.69 (s, 1 H, Ar-CH), 5.17 (s, 2 H, CH_2Ph), 4.76 (d, *J* = 9.0 Hz, 2 H, C*H*HNC*H*H), 4.57–4.40 (m, 2 H, CH*H*NCH*H*), 3.77 (d, *J* = 1.4 Hz, 3 H, OCH_3), 2.59 (q, *J* = 7.6 Hz, 2 H, CH_2CH_3), 1.23 (t, *J* = 7.6 Hz, 3 H, CH_2CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.1 (Ar-C_q-OCH_3), 157.0 (C=O), 154.0 (Ar-C_q-OH), 144.8 (Ar-C_q-CH_2CH_3), 138.1 (Ar-C_q-C_q), 136.4 (Ar-C_q-CH_2), 128.5 (2 × Ar-CH), 128.1 (Ar-CH), 128.0 (2 × Ar-CH), 127.7 (Ar-C_q-C_q), 127.3 (Ar-CH), 127.0 (2 × Ar-CH), 119.3 (Ar-CH), 115.7 (Ar-CH), 113.7 (2 × Ar-CH), 67.0 (CH_2Ph), 62.9 (CH_2NCH_2), 55.2 (OCH_3), 43.5 (C_q), 28.4 (CH_2CH_3), 15.4 (CH_2CH_3); HRMS (+ESI) *m*/*z* calcd for $C_{26}H_{28}NO_4$ [M+H]: 418.2018, Found: 418.2026.

90: R_f = 0.17 (20% acetone/pentane); mp = 55–60 °C; IR (film)/cm^{-1} 3681, 3319 (br, OH), 2965, 1676 (C=O), 1607, 1509, 1424, 1354, 1248, 1181, 1134, 1055, 1032, 827, 810, 751, 697; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39–7.33 (m, 5 H, 5 × Ar-CH), 7.13–7.11 (m, 2 H, 2 × Ar-CH),

6.98 (d, *J* = 8.3 Hz, 1 H, Ar-CH), 6.82–6.79 (m, 2 H, 2 × Ar-CH), 6.78 (d, *J* = 2.7 Hz, 1 H, Ar-CH), 6.72 (dd, *J* = 8.3, 2.7 Hz, 1 H, Ar-CH), 5.75 (s, 1 H, OH), 5.17 (s, 2 H, CH_2Ph), 4.64 (d, *J* = 8.3 Hz, 2 H, C*H*HNC*H*H), 4.36 (d, *J* = 8.3 Hz, 2 H, CH*H*NCH*H*), 3.78 (s, 3 H, OCH_3), 2.05 (q, *J* = 7.5 Hz, 2 H, C*H*$_2$CH$_3$), 0.99 (t, *J* = 7.5 Hz, 3 H, CH_2CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.3 (Ar-*C*$_q$-OCH_3), 156.7 (C=O), 155.1 (Ar-C_q-OH), 143.9 (Ar-*C*$_q$-CH_2CH_3), 138.7 (Ar-*C*$_q$-C_q), 136.4 (Ar-*C*$_q$-CH_2), 133.7 (Ar-*C*$_q$-C_q), 128.5 (2 × Ar-CH), 128.4 (Ar-CH), 128.13 (Ar-CH), 128.07 (2 × Ar-CH), 126.8 (2 × Ar-CH), 116.0 (Ar-CH), 113.8 (2 × Ar-CH), 112.5 (Ar-CH), 67.0 (CH_2Ph), 63.3 (br, *C*H$_2$N*C*H$_2$), 55.2 (OCH_3), 44.9 (C_q), 24.9 (*C*H$_2$CH$_3$), 14.0 (CH_2*C*H$_3$); HRMS (+ESI) *m*/*z* calcd for $C_{26}H_{28}NO_4$ [M+H]: 418.2018, Found: 418.2020.

Benzyl 3-(2-hydroxy-5-methoxyphenyl)-3-(4-methoxyphenyl)azetidine-1-carboxylate (92') and **benzyl ((5-methoxy-3-(4-methoxyphenyl)-2,3-dihydrobenzofuran-3-yl)methyl)carbamate (92b)**



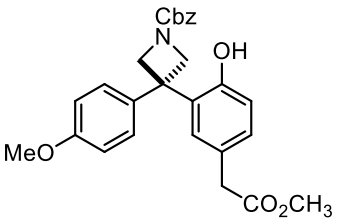


Calcium(II) bis(trifluoromethanesulfonimide) (15.0 mg, 0.025 mmol) and tetrabutylammonium hexafluorophosphate (9.7 mg, 0.025 mmol) were added to a solution of azetidinol **83** (157 mg, 0.50 mmol) and 4-methoxyphenol (186 mg, 1.50 mmol) in CH_2Cl_2 (1.0 mL). The reaction mixture was stirred at 40 °C for 4 h then sat. aq. $NaHCO_3$ (30 mL) was added followed by CH_2Cl_2 (30 mL). The layers were separated and the aqueous portion was extracted with EtOAc (3 × 30 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash chromatography (50% Et_2O/pentane) afforded dihydrobenzofuran **92b** (14.5 mg, 7%) as a colourless oil followed by azetidine **92'** (150 mg, 72%) as a white solid.

92b: R_f = 0.32 (50% Et_2O/pentane); IR (film)/cm^{-1} 3357 (br, NH), 2953, 1707 (C=O), 1511, 1486, 1464, 1234, 1227, 1180, 1028, 977, 828, 807, 755, 735, 697; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.30 (m, 5 H, 5 × Ar-CH), 7.22 (d, *J* = 8.9 Hz, 2 H, 2 × Ar-CH), 6.90–6.86 (m, 2 H, 2 × Ar-CH), 6.82–6.76 (m, 2 H, 2 × Ar-CH), 6.67 (d, *J* = 2.4 Hz, 1 H, Ar-CH), 5.10 (d, *J* = 12.2 Hz, 1 H, C*H*HPh), 5.05 (d, *J* = 12.2 Hz, 1 H, CH*H*Ph), 4.68–4.63 (m, 2 H, N*H*CH_2C_q, OC*H*HC_q), 4.49 (d, *J* = 9.0 Hz, 1 H, OCH*H*C_q), 4.05 (dd, *J* = 13.7, 8.0 Hz, 1 H, NC*H*HC_q), 3.80 (s, 3 H, OCH_3), 3.75 (m, 4 H, OCH_3, NCH*H*C_q); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.6 (Ar-*C*$_q$-OCH_3), 156.6 (C=O), 154.7 ($Ar_{(DHBF)}$-*C*$_q$-OCH_2), 154.4 (Ar-*C*$_q$-OCH_3), 136.3 (Ar-*C*$_q$-CH_2), 134.6 (Ar-*C*$_q$-C_q), 131.1 ($Ar_{(DHBF)}$-*C*$_q$-C_q), 128.5 (2 × Ar-CH), 128.2 (Ar-CH), 128.1 (2 × Ar-CH), 127.8

(2 × Ar-CH), 114.3 (Ar-CH), 114.2 (2 × Ar-CH), 110.7 (Ar-CH), 110.4 (Ar-CH), 82.2 (OCH_2C_q), 66.9 (CH_2Ph), 56.0 (OCH_3), 55.3 (OCH_3), 54.7 (C_q), 47.4 (NCH_2C_q); HRMS (+NSI) *m*/*z* calcd for $C_{25}H_{25}NO_5Na^+$ $[M+Na]^+$: 442.1625, Found: 442.1623.

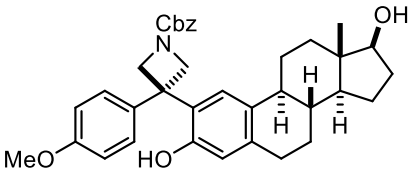
92': R_f = 0.15 (50% Et_2O/pentane); mp = 66–74 °C; IR (film)/cm^{-1} 3220 (br, OH), 2955, 1674 (C=O), 1509, 1456, 1420, 1358, 1248, 1208, 1180, 1128, 1029, 828, 759, 738, 697; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40–7.32 (m, 5 H, 5 × Ar-CH), 7.27–7.20 (m, 3 H, 2 × Ar-CH, OH), 6.84–6.79 (m, 2 H, 2 × Ar-CH), 6.75–6.73 (m, 1 H, Ar-CH), 6.70–6.68 (m, 2 H, 2 × Ar-CH), 5.15 (s, 2 H, CH_2Ph), 4.74 (d, *J* = 9.0 Hz, 2 H, C*H*HNC*H*H), 4.55–4.39 (m, 2 H, CH*H*NCH*H*), 3.77 (s, 3 H, OCH_3), 3.76 (s, 3 H, OCH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.2 (Ar-C_q-OCH_3), 157.0 (C=O), 153.1 (Ar-C_q-OCH_3), 148.1 (Ar-C_q-OH), 137.6 (Ar-C_q-C_q), 136.4 (Ar-C_q-CH_2), 131.4 (Ar-C_q-C_q), 128.5 (2 × Ar-CH), 128.1 (Ar-CH), 128.0 (2 × Ar-CH), 127.0 (2 × Ar-CH), 116.7 (Ar-CH), 113.82 (Ar-CH), 113.78 (2 × Ar-CH), 112.8 (Ar-CH), 67.1 (CH_2Ph), 62.8 (CH_2NCH_2), 55.8 (OCH_3), 55.2 (OCH_3), 43.9 (C_q); HRMS (+ESI) *m*/*z* calcd for $C_{25}H_{26}NO_5$ [M+H]: 420.1811, Found: 420.1797.



Benzyl 3-(2-hydroxy-5-(2-methoxy-2-oxoethyl)phenyl)-3-(4-methoxyphenyl)azetidine-1-carboxylate (93')

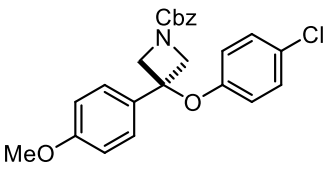
Calcium(II) bis(trifluoromethanesulfonimide) (15.0 mg, 0.025 mmol) and tetrabutylammonium hexafluorophosphate (9.7 mg, 0.025 mmol) were added to a solution of azetidinol **83** (157 mg, 0.50 mmol) and methyl 4-hydroxyphenylacetate (249 mg, 1.50 mmol) in CH_2Cl_2 (1.0 mL). The reaction mixture was stirred at 40 °C for 24 h then sat. aq. $NaHCO_3$ (30 mL) was added. The aqueous portion was extracted with Et_2O (3 × 30 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash chromatography (7% Et_2O/CH_2Cl_2) afforded azetidine **93'** (136 mg, 59%) as a white solid. R_f = 0.34 (10% Et_2O/CH_2Cl_2); mp = 53–60 °C; IR (film)/cm^{-1} 3243 (br, OH), 2952, 1732 (C=O), 1672 (C=O), 1610, 1510, 1428, 1354, 1279, 1248, 1180, 1121, 1025, 1007, 827, 807, 754, 697; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (s, 1 H, OH), 7.41–7.32 (m, 5 H, 5 × Ar-CH), 7.25–7.22 (m, 2 H, 2 × Ar-CH), 7.04 (dd, *J* = 8.2, 2.2 Hz, 1 H, Ar-CH), 7.00 (d, *J* = 2.2 Hz, 1 H, Ar-CH), 6.83–6.76 (m, 3 H, 3 × Ar-CH), 5.15 (d, *J* = 2.9 Hz, 2 H, CH_2Ph), 4.74 (br m, 2 H, C*H*HNC*H*H), 4.56 and 4.38 (2 × br m, 2 H, CH*H*NCH*H*), 3.76 (s, 3 H, OCH_3), 3.70 (s, 3 H, OCH_3), 3.56 (s, 2 H, $CH_2CO_2CH_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.4 (C=O, ester), 158.1 (Ar-C_q-OCH_3), 157.0 (C=O), 153.3 (Ar-C_q-OH), 137.7 (Ar-C_q-$CH_2CO_2CH_3$), 136.3 (Ar-C_q-CH_2), 130.4 (Ar-C_q-C_q), 129.1 (Ar-CH), 128.5 (2 × Ar-CH), 128.4 (Ar-CH), 128.2 (Ar-CH), 128.0 (2 × Ar-CH), 127.0 (2 × Ar-CH), 125.0 (Ar-C_q-C_q), 116.3 (Ar-CH), 113.7 (2 × Ar-CH), 67.1

(CH_2Ph), 62.9 (CH_2NCH_2), 55.2 (OCH_3), 52.0 ($CH_2CO_2CH_3$), 43.6 (C_q), 40.4 ($CH_2CO_2CH_3$); HRMS (+NSI) *m*/*z* calcd for $C_{27}H_{28}NO_6$ $[M+H]^+$: 462.1911, Found: 462.1914.



Benzyl 3-(3,17-dihydroxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-2-yl)-3-(4-methoxyphenyl)azetidine-1-carboxylate (94')

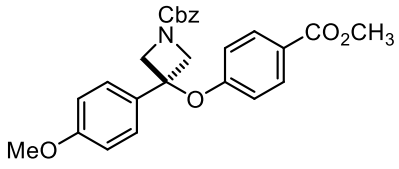
Calcium(II) bis(trifluoromethanesulfonimide) (7.50 mg, 0.0125 mmol) and tetrabutylammonium hexafluorophosphate (4.80 mg, 0.0125 mmol) were added to a solution of azetidinol **83** (78.3 mg, 0.25 mmol) and β-estradiol (204 mg, 0.75 mmol) in CH_2Cl_2 (1.0 mL). The reaction mixture was stirred at 40 °C for 4 h then sat. aq. $NaHCO_3$ (30 mL) was added followed by EtOAc (30 mL). The layers were separated and the aqueous portion was extracted with EtOAc (3 × 30 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash chromatography (60% to 100% Et_2O/pentane) afforded azetidine **94'** (71.9 mg, 51%) as a white solid. R_f = 0.44 (100% Et_2O); mp = 146–152 °C; IR (film)/cm^{-1} 3282 (br, OH), 2929, 1679 (C=O), 1520, 1417, 1354, 1246, 1181, 1116, 1032, 1007, 827, 753, 729, 696; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39–7.32 (m, 5 H, 5 × Ar-CH), 7.28–7.24 (m, 2 H, 2 × Ar-CH), 7.01 (s, 1 H, Ar-CH), 6.84–6.80 (m, 2 H, 2 × Ar-CH), 6.54 (s, 1 H, Ar-CH), 5.15 (s, 2 H, CH_2Ph), 4.75 (d, *J* = 8.8 Hz, 2 H, C*H*HNC*H*H), 4.47 (m, 2 H, CH*H*NCH*H*), 3.77 (m, 4 H, OCH_3, C*H*OH), 2.82–2.78 (m, 2 H, CH_2), 2.31–2.27 (m, 1 H, CH), 2.23–2.09 (m, 2 H, 2 × CH), 1.97–1.86 (m, 2 H, 2 × CH), 1.75–1.67 (m, 1 H, CH), 1.55–1.17 (m, 8 H, 7 × CH, OH), 0.80 (s, 3 H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.1 (Ar-C_q-OCH_3), 156.9 (C=O), 151.8 (Ar-C_q-OH), 138.2 (Ar-C_q-C_q), 136.8 (Ar-C_q-CH_2-O), 136.4 (Ar-C_q-CH_2), 131.6 (Ar-C_q-CH), 128.5 (2 × Ar-CH), 128.1 (Ar-CH), 128.0 (2 × Ar-CH), 127.8 (Ar-C_q-C_q), 127.0 (2 × Ar-CH), 124.4 (Ar-CH), 116.1 (Ar-CH), 113.7 (2 × Ar-CH), 81.9 (CHOH), 67.0 (CH_2Ph), 63.0 (CH_2NCH_2), 55.2 (OCH_3), 50.0 (CH_3-C_q-CH), 44.0 (Ar-C_q-CH), 43.7 (C_q), 43.2 (CH_3-C_q-CH), 38.9 (Ar-C_q-CH-CH), 36.7 (CH_2), 30.6 (CH_2), 29.3 (Ar-C_q-CH_2), 27.2 (CH_2), 26.5 (CH_2), 23.1 (CH_2), 11.1 (CH_3); HRMS (+NSI) *m*/*z* calcd for $C_{36}H_{42}NO_5^+$ $[M+H]^+$: 568.3057, Found: 568.3055.



Benzyl 3-(4-chlorophenoxy)-3-(4-methoxyphenyl)azetidine-1-carboxylate (95)

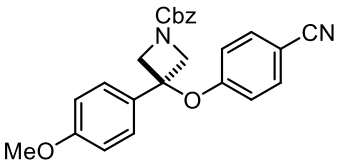
Calcium(II) bis(trifluoromethanesulfonimide) (15.0 mg, 0.025 mmol) and tetrabutylammonium hexafluorophosphate (9.7 mg, 0.025 mmol) were added to a solution of azetidinol **83** (157 mg, 0.50 mmol) and 4-chlorophenol (199 mg, 1.50 mmol) in CH_2Cl_2 (1.0 mL). The reaction mixture was stirred at 40 °C for 2 h then sat. aq. $NaHCO_3$ (30 mL) was added followed by CH_2Cl_2 (30 mL). The layers

were separated and the aqueous portion was extracted with EtOAc (3 × 30 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash chromatography (20 to 30% Et_2O/pentane) afforded azetidine ether **95** (97.7 mg, 46%) as a colourless oil. R_f = 0.24 (30% Et_2O/pentane); IR (film)/cm^{-1} 2956, 1704 (C=O), 1515, 1416, 1352, 1248, 1232, 1177, 1118, 1093, 1025, 1007, 906, 824, 727, 696, 688; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40–7.32 (m, 7 H, 7 × Ar-CH), 7.15–7.11 (m, 2 H, 2 × Ar-CH), 6.92–6.88 (m, 2 H, 2 × Ar-CH), 6.52–6.48 (m, 2 H, 2 × Ar-CH), 5.16 (s, 2 H, CH_2Ph), 4.44 (d, *J* = 9.8 Hz , 2 H, C*H*HNC*H*H), 4.37 (d, *J* = 9.8 Hz , 2 H, CH*H*NCH*H*), 3.81 (s, 3 H, OCH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.3 (Ar-C_q-OCH_3), 156.4 (C=O), 153.2 (Ar-C_q-OC_q), 136.3 (Ar-C_q-CH_2), 131.8 (Ar-C_q-C_q), 129.3 (2 × Ar-CH), 128.5 (2 × Ar-CH), 128.1 (Ar-CH), 128.0 (2 × Ar-CH), 126.3 (Ar-C_q-Cl), 126.0 (2 × Ar-CH), 117.9 (2 × Ar-CH), 114.3 (2 × Ar-CH), 76.6 (C_q), 67.0 (CH_2Ph), 62.0 (CH_2NCH_2), 55.2 (OCH_3); HRMS (+NSI) *m*/*z* calcd for $C_{24}H_{23}NO_4{}^{35}Cl^+$ $[M+H]^+$: 424.1310, Found: 424.1307.



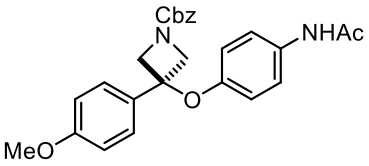
Benzyl 3-(4-(methoxycarbonyl)phenoxy)-3-(4-methoxyphenyl)azetidine-1-carboxylate (96)

Calcium(II) bis(trifluoromethanesulfonimide) (15.0 mg, 0.025 mmol) and tetrabutylammonium hexafluorophosphate (9.7 mg, 0.025 mmol) were added to a solution of azetidinol **83** (157 mg, 0.50 mmol) and methylparaben (228 mg, 1.50 mmol) in CH_2Cl_2 (1.0 mL). The reaction mixture was stirred at 40 °C for 2 h then sat. aq. $NaHCO_3$ (30 mL) was added followed by CH_2Cl_2 (30 mL). The layers were separated and the aqueous portion was extracted with EtOAc (3 × 30 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash chromatography (30% Et_2O/pentane) afforded azetidine ether **96** (77.5 mg, 35%) as a white solid. R_f = 0.11 (30% Et_2O/pentane); mp = 127–128 °C; IR (film)/cm^{-1} 2952, 1702 (C=O), 1606, 1508, 1446, 1371, 1283, 1242, 1172, 1148, 1116, 1097, 1023, 846, 822, 765, 723, 693, 653; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89–7.86 (m, 2 H, 2 × Ar-CH), 7.38–7.27 (m, 7 H, 7 × Ar-CH), 6.91–6.88 (m, 2 H, 2 × Ar-CH), 6.61–6.58 (m, 2 H, 2 × Ar-CH), 5.16 (s, 2 H, CH_2Ph), 4.48–4.37 (m, 4 H, CH_2NCH_2), 3.85–3.80 (2 × s, 6 H, 2 × OCH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.5 (CO_2CH_3), 159.4 (Ar-C_q-OCH_3), 158.5 (Ar-C_q-OC_q), 156.4 (C=O), 136.3 (Ar-C_q-CH_2), 131.5 (Ar-C_q-C_q), 131.4 (2 × Ar-CH), 128.5 (2 × Ar-CH), 128.2 (Ar-CH), 128.1 (2 × Ar-CH), 125.9 (2 × Ar-CH), 123.2 (Ar-C_q-CO_2CH_3), 116.3 (2 × Ar-CH), 114.4 (2 × Ar-CH), 76.9 (C_q), 67.1 (CH_2Ph), 62.2 (CH_2NCH_2), 55.3 (OCH_3), 51.9 (CO_2CH_3); HRMS (+NSI) *m*/*z* calcd for $C_{26}H_{26}NO_6^+$ $[M+H]^+$: 448.1755, Found: 448.1751.



Benzyl 3-(4-cyanophenoxy)-3-(4-methoxyphenyl)azetidine-1-carboxylate (97)

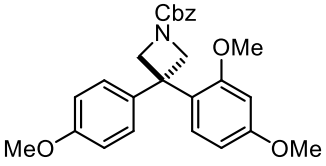
Calcium(II) bis(trifluoromethanesulfonimide) (15.0 mg, 0.025 mmol) and tetrabutylammonium hexafluorophosphate (9.7 mg, 0.025 mmol) were added to a solution of azetidinol **83** (157 mg, 0.50 mmol) and 4-cyanophenol (179 mg, 1.50 mmol) in CH_2Cl_2 (1.0 mL). The reaction mixture was stirred at 40 °C for 2 h then sat. aq. $NaHCO_3$ (30 mL) was added followed by CH_2Cl_2 (30 mL). The layers were separated and the aqueous portion was extracted with EtOAc (3 × 30 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash chromatography (30% Et_2O/pentane) afforded azetidine ether **97** (64.9 mg, 31%) as a white solid. R_f = 0.21 (50% Et_2O/pentane); mp = 43–49 °C; IR (film)/cm^{-1} 2952, 2225 (CN), 1706 (C=O), 1603, 1502, 1410, 1352, 1244, 1171, 1095, 1024, 829, 755, 697; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50–7.46 (m, 2 H, 2 × Ar-CH), 7.38–7.29 (m, 7 H, 7 × Ar-CH), 6.92–6.88 (m, 2 H, 2 × Ar-CH), 6.65–6.62 (m, 2 H, 2 × Ar-CH), 5.15 (s, 2 H, CH_2Ph), 4.45–4.39 (m, 4 H, C*H*$_2$NC*H*$_2$), 3.81 (s, 3 H, OCH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.5 (Ar-*C*$_q$-OCH_3), 158.1 (Ar-*C*$_q$-OC_q), 156.4 (C=O), 136.2 (Ar-*C*$_q$-CH_2), 133.8 (2 × Ar-CH), 130.9 (Ar-*C*$_q$-C_q), 128.5 (2 × Ar-CH), 128.2 (Ar-CH), 128.1 (2 × Ar-CH), 125.9 (2 × Ar-CH), 118.8 (Ar-*C*$_q$-CN), 117.3 (2 × Ar-CH), 114.5 (2 × Ar-CH), 104.8 (Ar-C_q-*C*N), 77.3 (C_q), 67.2 (CH_2Ph), 62.0 (*C*H_2N*C*H_2), 55.3 (OCH_3); HRMS (+NSI) *m*/*z* calcd for $C_{25}H_{23}N_2O_4^+$ $[M+H]^+$: 415.1652, Found: 415.1652.



Benzyl 3-(4-acetamidophenoxy)-3-(4-methoxyphenyl)azetidine-1-carboxylate (98)

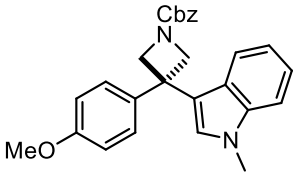
Calcium(II) bis(trifluoromethanesulfonimide) (7.5 mg, 0.0125 mmol) and tetrabutylammonium hexafluorophosphate (4.80 mg, 0.0125 mmol) were added to a solution of azetidinol **83** (78.3 mg, 0.25 mmol) and 4′-hydroxyacetanilide (113 mg, 0.75 mmol) in CH_2Cl_2 (0.5 mL). The reaction mixture was stirred at 60 °C for 28 h then sat. aq. $NaHCO_3$ (15 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 extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash chromatography (30% Et_2O/CH_2Cl_2) afforded azetidine ether **98** (36.4 mg, 33%) as a white solid. R_f = 0.24 (30% Et_2O/CH_2Cl_2); mp = 56–66 °C; IR (film)/cm^{-1} 3300, 2955, 1705 (C=O), 1505, 1410, 1353, 1249, 1226, 1177, 1098, 1025, 827, 750, 697; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.31 (m, 7 H, 7 × Ar-CH), 7.29–7.25 (m, 2 H, 2 × Ar-CH), 7.21 (s, 1 H, NHAc), 6.89–6.85 (m, 2 H, 2 × Ar-CH), 6.52–6.48 (m, 2 H, 2 × Ar-CH), 5.15 (s, 2 H, CH_2Ph), 4.43 (d, *J* = 9.8 Hz, 2 H, C*H*HNC*H*H), 4.34 (d, *J* = 9.8 Hz, 2 H,

CH*H*NCH*H*), 3.80 (s, 3 H, OCH_3), 2.11 (s, 3 H, HNCOC*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.1 (HN*C*OCH$_3$), 159.2 (Ar-*C*$_q$-OCH_3), 156.5 (C=O), 151.2 (Ar-*C*$_q$-OC_q), 136.3 (Ar-*C*$_q$-CH_2), 132.2 (Ar-*C*$_q$-C_q), 131.5 (Ar-*C*$_q$-NHCO), 128.5 (2 × Ar-CH), 128.1 (Ar-CH), 128.0 (2 × Ar-CH), 126.1 (2 × Ar-CH), 121.6 (2 × Ar-CH), 117.0 (2 × Ar-CH), 114.2 (2 × Ar-CH), 76.4 (C_q), 67.0 (CH_2Ph), 62.1 (*C*H$_2$N*C*H$_2$), 55.3 (OCH_3), 24.3 (HNCO*C*H$_3$); HRMS (+NSI) *m*/*z* calcd for $C_{26}H_{27}N_2O_5^+$ $[M+H]^+$: 447.1914, Found: 447.1913.



Benzyl 3-(2,4-dimethoxyphenyl)-3-(4-methoxyphenyl)azetidine-1-carboxylate (99)

Calcium(II) bis(trifluoromethanesulfonimide) (15.0 mg, 0.025 mmol) and tetrabutylammonium hexafluorophosphate (9.7 mg, 0.025 mmol) were added to a solution of azetidinol **83** (157 mg, 0.50 mmol) and 1,3-dimethoxybenzene (194 µL, 1.50 mmol) in CH_2Cl_2 (1.0 mL). The reaction mixture was stirred at 40 °C for 2 h then sat. aq. $NaHCO_3$ (30 mL) was added followed by CH_2Cl_2 (30 mL). The layers were separated and the aqueous portion was extracted with EtOAc (3 × 30 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash chromatography (40% Et_2O/pentane) afforded azetidine **99** (117 mg, 54%) as a white solid. R_f = 0.42 (70% Et_2O/pentane); mp = 107–109 °C; IR (film)/cm^{-1} 2955, 2835, 1701 (C=O), 1609, 1583, 1507, 1454, 1403, 1352, 1246, 1208, 1181, 1159, 1140, 1105, 1029, 1013, 1000, 897, 828, 751; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.32 (m, 5 H, 5 × Ar-CH), 7.19–7.17 (m, 2 H, 2 × Ar-CH), 7.05 (d, *J* = 8.4 Hz, 1 H, Ar-CH), 6.82–6.80 (m, 2 H, 2 × Ar-CH), 6.53 (dd, *J* = 8.4, 2.4 Hz, 1 H, Ar-CH), 6.47 (d, *J* = 2.4 Hz, 1 H, Ar-CH), 5.13 (s, 2 H, CH_2Ph), 4.62 (d, *J* = 8.7 Hz, 2 H, C*H*HNC*H*H), 4.42 (d, *J* = 8.7 Hz, 2 H, CH*H*NCH*H*), 3.83 (s, 3 H, OCH_3), 3.78 (s, 3 H, OCH_3), 3.68 (s, 3 H, OCH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.1 (Ar-*C*$_q$-OCH_3), 158.01 (Ar-*C*$_q$-OCH_3), 157.96 (Ar-*C*$_q$-OCH_3), 156.5 (C=O), 138.7 (Ar-*C*$_q$-C_q), 136.7 (Ar-*C*$_q$-CH_2), 128.4 (Ar-CH), 127.99 (4 × Ar-CH), 127.97 (Ar-CH), 126.9 (2 × Ar-CH), 125.1 (Ar-*C*$_q$-C_q), 113.4 (2 × Ar-CH), 104.0 (Ar-CH), 99.2 (Ar-CH), 66.6 (CH_2Ph), 62.6 (br, *C*H$_2$N*C*H$_2$), 55.4 (OCH_3), 55.23 (OCH_3), 55.20 (OCH_3), 43.4 (C_q); HRMS (+ESI) *m*/*z* calcd for $C_{26}H_{28}NO_5$ [M+H]: 434.1967, Found: 434.1963.

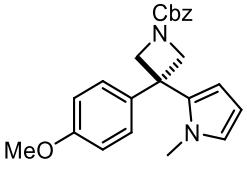


Benzyl 3-(4-methoxyphenyl)-3-(1-methyl-1*H*-indol-3-yl)azetidine-1-carboxylate (100)

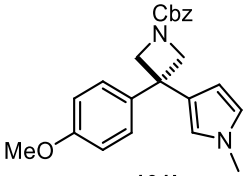
Calcium(II) bis(trifluoromethanesulfonimide) (7.5 mg, 0.0125 mmol) and tetrabutylammonium hexafluorophosphate (4.80 mg, 0.0125 mmol) were added to a solution of azetidinol **83** (78.3 mg, 0.25 mmol) and 1-methylindole (93.7 µL, 0.75 mmol) in toluene (0.5 mL). The reaction mixture was stirred at

80 °C for 24 h then sat. aq. $NaHCO_3$ (15 mL) was added. The aqueous portion was extracted with Et_2O (3 × 15 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash chromatography (40% Et_2O/hexane) afforded azetidine **100** (48.4 mg, 45%) as a yellow solid. R_f = 0.58 (70% Et_2O/hexane); mp = 175–182 °C; IR (film)/cm^{-1} 2954, 2885, 1698 (C=O), 1511, 1442, 1413, 1352, 1330, 1245, 1180, 1144, 1116, 1021, 907, 829, 728, 697; ^1H NMR (400 MHz, $CDCl_3$) δ 7.49 (dt, *J* = 7.9, 0.9 Hz, 1 H, $Ar_{(indole)}$-CH), 7.42–7.32 (m, 6 H, $Ar_{(indole)}$-CH, 5 × Ar-CH), 7.29–7.24 (m, 3 H, 2 × Ar-CH, $Ar_{(indole)}$-CH), 7.08 (ddd, *J* = 8.0, 6.9, 1.1 Hz, 1 H, $Ar_{(indole)}$-CH), 6.92–6.88 (m, 2 H, 2 × Ar-CH), 6.55 (s, 1 H, N-$Ar_{(indole)}$-CH), 5.18 (s, 2 H, CH_2Ph), 4.75 (d, *J* = 8.4 Hz, 2 H, C*H*HNC*H*H), 4.65 (d, *J* = 8.4 Hz, 2 H, CH*H*NCH*H*), 3.83 (s, 3 H, NCH_3), 3.73 (s, 3 H, OCH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.2 (Ar-C_q-OCH_3), 156.4 (C=O), 137.65 ($Ar_{(indole)}$-C_q), 137.63 (Ar-C_q-C_q), 136.6 (Ar-C_q-CH_2), 128.4 (2 × Ar-CH), 128.0 (Ar-CH), 127.9 (2 × Ar-CH), 127.7 (2 × Ar-CH), 127.2 (N-Ar-CH), 125.9 ($Ar_{(indole)}$-C_q), 122.0 ($Ar_{(indole)}$-CH), 119.89 (N-Ar-CH-C_q), 119.88 ($Ar_{(indole)}$-CH), 119.3 ($Ar_{(indole)}$-CH), 113.7 (2 × Ar-CH), 109.5 ($Ar_{(indole)}$-CH), 66.7 (CH_2Ph), 63.1 and 62.4 (CH_2NCH_2), 55.3 (OCH_3), 40.7 (C_q), 32.7 (NCH_3); HRMS (+ESI) *m*/*z* calcd for $C_{27}H_{27}N_2O_3$ [M+H]: 427.2022, Found: 427.2029.

Benzyl 3-(4-methoxyphenyl)-3-(1-methyl-*1H*-pyrrol-2-yl)azetidine-1-carboxylate (101a) and **benzyl 3-(4-methoxyphenyl)-3-(1-methyl-1*H*-pyrrol-3-yl)azetidine-1-carboxylate (101b)**



101a



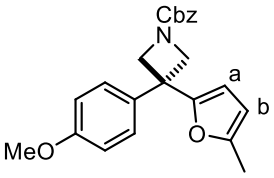
101b

CH_2Cl_2 (1.0 mL) was added to calcium(II) bis(trifluoromethanesulfonimide) (15.0 mg, 0.025 mmol), tetrabutylammonium hexafluorophosphate (9.7 mg, 0.025 mmol), azetidinol **83** (157 mg, 0.50 mmol) and 1-methylpyrrole (133 µL, 1.50 mmol). The reaction mixture was stirred at 60 °C for 24 h then sat. aq. $NaHCO_3$ (30 mL) was added followed by CH_2Cl_2 (30 mL). The layers were separated and the aqueous portion was extracted with EtOAc (3 × 30 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash chromatography (30% Et_2O/pentane) afforded azetidine **101a** (62.4 mg, 33%) as a yellow oil followed by azetidine **101b** (22.5 mg, 12%) as a yellow solid.

101a: R_f = 0.48 (70% Et_2O/pentane); IR (film)/cm^{-1} 2955, 2887, 1703 (C=O), 1510, 1441, 1408, 1350, 1307, 1297, 1247, 1180, 1120, 1027, 987, 829, 810, 767, 711, 697; ^1H NMR (400 MHz,

$CDCl_3$) δ 7.39–7.32 (m, 5 H, 5 × Ar-CH), 7.11–7.06 (m, 2 H, 2 × Ar-CH), 6.88–6.84 (m, 2 H, 2 × Ar-CH), 6.65–6.63 (m, 1 H, $N_{(pyrrole)}$-C*H*-CH), 6.18–6.16 (m, 1 H, $Ar_{(pyrrole)}$-CH), 6.15–6.13 (m, 1 H, $Ar_{(pyrrole)}$-CH), 5.15 (s, 2 H, CH_2Ph), 4.61 (d, *J* = 8.1 Hz, 2 H, C*H*HNC*H*H), 4.37 (d, *J* = 8.1 Hz, 2 H, CH*H*NCH*H*), 3.80 (s, 3 H, OCH_3), 3.16 (s, 3 H, NCH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.5 (Ar-C_q-OCH_3), 156.4 (C=O), 136.8 (Ar-C_q-C_q), 136.5 (Ar-C_q-CH_2), 134.4 ($Ar_{(pyrrole)}$-C_q-C_q), 128.5 (2 × Ar-CH), 128.1 (Ar-CH), 128.0 (2 × Ar-CH), 126.8 (2 × Ar-CH), 123.1 ($N_{(pyrrole)}$-*C*H-CH), 114.0 (2 × Ar-CH), 107.4 ($Ar_{(pyrrole)}$-CH), 106.7 ($Ar_{(pyrrole)}$-CH), 66.8 (CH_2Ph), 62.7 and 62.0 (CH_2NCH_2), 55.2 (OCH_3), 40.2 (C_q), 34.4 (NCH_3); HRMS (+NSI) *m*/*z* calcd for $C_{23}H_{25}N_2O_3^+$ $[M+H]^+$: 377.1860, Found: 377.1859.

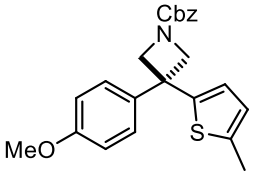
101b: R_f = 0.42 (70% Et_2O/pentane); mp = 91–93 °C; IR (film)/cm^{-1} 2955, 2884, 1700 (C=O), 1611, 1513, 1414, 1346, 1296, 1276, 1248, 1177, 1119, 1036, 1020, 959, 833, 805, 785, 759, 698, 666; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39–7.30 (m, 5 H, 5 × Ar-CH), 7.19–7.15 (m, 2 H, 2 × Ar-CH), 6.92–6.88 (m, 2 H, 2 × Ar-CH), 6.56 (t, *J* = 2.5 Hz, 1 H, $Ar_{(pyrrole)}$-CH), 6.09–6.07 (m, 2 H, 2 × $Ar_{(pyrrole)}$-CH), 5.13 (s, 2 H, CH_2Ph), 4.56 (d, *J* = 8.1 Hz, 2 H, C*H*HNC*H*H), 4.42 (d, *J* = 8.1 Hz, 2 H, CH*H*NCH*H*), 3.83 (s, 3 H, OCH_3), 3.56 (s, 3 H, NCH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.0 (Ar-C_q-OCH_3), 156.5 (C=O), 138.1 (Ar-C_q-C_q), 136.7 (Ar-C_q-CH_2), 131.2 ($Ar_{(pyrrole)}$-C_q-C_q), 128.4 (2 × Ar-CH), 127.94 (Ar-CH), 127.93 (2 × Ar-CH), 127.5 (2 × Ar-CH), 122.4 ($Ar_{(pyrrole)}$-CH), 119.5 ($Ar_{(pyrrole)}$-CH), 113.6 (2 × Ar-CH), 106.7 ($Ar_{(pyrrole)}$-CH), 66.6 (CH_2Ph), 64.1 and 63.3 (CH_2NCH_2), 55.3 (OCH_3), 40.8 (C_q), 36.1 (NCH_3); HRMS (+NSI) *m*/*z* calcd for $C_{23}H_{25}N_2O_3^+$ $[M+H]^+$: 377.1860, Found: 377.1859.



Benzyl 3-(4-methoxyphenyl)-3-(5-methylfuran-2-yl)azetidine-1-carboxylate (102)

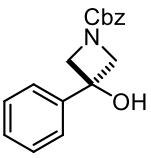
CH_2Cl_2 (1.0 mL) was added to calcium(II) bis(trifluoromethanesulfonimide) (15.0 mg, 0.025 mmol), tetrabutylammonium hexafluorophosphate (9.7 mg, 0.025 mmol), azetidinol **83** (157 mg, 0.50 mmol) and 2-methylfuran (135 µL, 1.50 mmol). The reaction mixture was stirred at 40 °C for 24 h then sat. aq. $NaHCO_3$ (30 mL) was added followed by CH_2Cl_2 (30 mL). The layers were separated and the aqueous portion was extracted with EtOAc (3 × 30 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash chromatography (20% Et_2O/pentane) afforded azetidine **102** (152 mg, 80%) as a yellow solid. R_f = 0.30 (30% Et_2O/pentane); mp = 77–88 °C; IR (film)/cm^{-1} 2960, 2884, 2840, 1708 (C=O), 1516, 1454, 1410, 1348, 1299, 1250, 1215, 1183, 1124, 1072, 1036, 1025, 1013, 956, 927, 834, 819, 805, 791, 764, 753, 694, 657; ^1H NMR (400 MHz, $CDCl_3$) δ 7.41–7.31 (m, 5 H, 5 × Ar-CH), 7.20–7.16 (m, 2 H, 2 × Ar-CH), 6.94–6.90 (m, 2 H, 2 × Ar-CH), 5.87 (dt, *J* = 3.1, 0.9 Hz, 1 H, Ar-CH_b), 5.69 (d, *J* = 3.1 Hz, 1 H, Ar-CH_a), 5.16 (s, 2 H,

CH_2Ph), 4.61 (d, *J* = 8.2 Hz, 2 H, C*H*HNC*H*H), 4.50 (d, *J* = 8.2 Hz, 2 H, CH*H*NCH*H*), 3.83 (s, 3 H, OCH_3), 2.30 (s, 3 H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.5 (Ar-C_q-OCH_3), 156.3 (C=O), 155.7 ($Ar_{(furan)}$-C_q-C_q), 151.9 ($Ar_{(furan)}$-C_q-CH_3), 136.6 (Ar-C_q-CH_2), 134.9 (Ar-C_q-C_q), 128.4 (2 × Ar-CH), 127.94 (Ar-CH), 127.87 (2 × Ar-CH), 127.7 (2 × Ar-CH), 113.8 (2 × Ar-CH), 107.7 ($Ar_{(furan)}$-CH), 106.0 ($Ar_{(furan)}$-CH), 66.7 (CH_2Ph), 61.0 and 60.4 (br, *C*H_2N*C*H_2), 55.2 (OCH_3), 41.5 (C_q), 13.5 ($Ar_{(furan)}$-CH_3); HRMS (+NSI) *m*/*z* calcd for $C_{23}H_{24}NO_4^+$ $[M+H]^+$: 378.1700, Found: 378.1699.



Benzyl 3-(4-methoxyphenyl)-3-(5-methylthiophen-2-yl)azetidine-1-carboxylate (103)

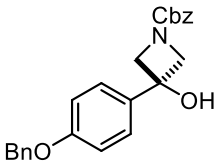
Calcium(II) bis(trifluoromethanesulfonimide) (15.0 mg, 0.025 mmol) and tetrabutylammonium hexafluorophosphate (9.7 mg, 0.025 mmol) were added to a solution of azetidinol **83** (157 mg, 0.50 mmol) and 2-methylthiophene (145 µL, 1.50 mmol) in CH_2Cl_2 (1.0 mL). The reaction mixture was stirred at 60 °C for 24 h then sat. aq. $NaHCO_3$ (30 mL) was added followed by CH_2Cl_2 (30 mL). The layers were separated and the aqueous portion was extracted with EtOAc (3 × 30 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash chromatography (20% Et_2O/pentane) afforded azetidine **103** (118 mg, 60%) as a white solid. R_f = 0.30 (30% Et_2O/pentane); mp = 99–102 °C; IR (film)/cm^{-1} 2963, 1708 (C=O), 1511, 1496, 1449, 1407, 1356, 1300, 1263, 1245, 1205, 1176, 1115, 1026, 963, 923, 830, 819, 798, 766, 754, 699; ^1H NMR (400 MHz, $CDCl_3$) δ 7.41–7.33 (m, 5 H, 5 × Ar-CH), 7.21–7.19 (m, 2 H, 2 × Ar-CH), 6.95–6.92 (m, 2 H, 2 × Ar-CH), 6.59–6.56 (m, 2 H, 2 × $Ar_{(thiophene)}$-CH), 5.17 (s, 2 H, CH_2Ph), 4.65 (d, *J* = 8.3 Hz, 2 H, C*H*HNC*H*H), 4.56 (d, *J* = 8.3 Hz, 2 H, CH*H*NCH*H*), 3.84 (s, 3 H, OCH_3), 2.44 (s, 3 H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.5 (Ar-C_q-OCH_3), 156.3 (C=O), 149.0 ($Ar_{(thiophene)}$-C_q-C_q), 139.1 ($Ar_{(thiophene)}$-C_q-CH_3), 136.7 (Ar-C_q-CH_2), 136.4 (Ar-C_q-C_q), 128.4 (2 × Ar-CH), 128.0 (Ar-CH), 127.9 (2 × Ar-CH), 127.5 (2 × Ar-CH), 124.6 ($Ar_{(thiophene)}$-CH), 124.2 ($Ar_{(thiophene)}$-CH), 113.8 (2 × Ar-CH), 66.7 (CH_2Ph), 63.8 (br, *C*H_2N*C*H_2), 55.2 (OCH_3), 43.3 (C_q), 15.2 ($Ar_{(thiophene)}$-CH_3); HRMS (+NSI) *m*/*z* calcd for $C_{23}H_{24}NO_3S^+$ $[M+H]^+$: 394.1471, Found: 394.1472.



Benzyl 3-hydroxy-3-phenylazetidine-1-carboxylate (104)

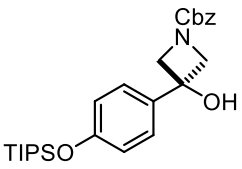
Phenylmagnesium bromide (2.63 M solution in THF, 2.00 mL, 5.20 mmol) was added dropwise to a solution of 1-Cbz-3-azetidinone (821 mg, 4.00 mmol) in THF (8.0 mL) at 0 °C. The reaction mixture was stirred for 19 h at 25 °C and then cooled to 0 °C and quenched with sat. aq. NH_4Cl (40 mL). The aqueous portion was extracted with EtOAc (3 × 40 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and

concentrated under reduced pressure. Purification by flash chromatography (60% to 70% Et_2O/pentane) afforded azetidinol **104** (949 mg, 86%) as a white solid. R_f = 0.36 (30% EtOAc/hexane); mp = 136–137 °C; IR (film)/cm^{-1} 3284 (br, OH), 2962, 1670 (C=O), 1653, 1476, 1456, 1439, 1361, 1241, 1195, 1017, 1118, 948, 761, 750, 700; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50–7.47 (m, 2 H, 2 × Ar-CH), 7.43–7.31 (m, 8 H, 8 × Ar-CH), 5.13 (s, 2 H, CH_2Ph), 4.35 (d, *J* = 9.3 Hz, 2 H, C*H*HNC*H*H), 4.26 (d, *J* = 9.3 Hz, 2 H, CH*H*NCH*H*), 3.01 (s, 1 H, OH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.6 (C=O), 142.8 (Ar-C_q-C_q), 136.4 (Ar-C_q-CH_2), 128.7 (2 × Ar-CH), 128.5 (2 × Ar-CH), 128.1 (2 × Ar-CH), 128.0 (2 × Ar-CH), 124.5 (2 × Ar-CH), 71.7 (C_q), 66.9 (CH_2Ph), 64.4 (br, CH_2NCH_2). The observed characterisation data (^{1}H, ^{13}C NMR) was consistent with that previously reported in the literature.[240]



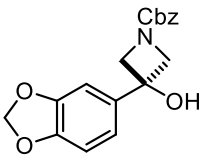
Benzyl 3-(4-(benzyloxy)phenyl)-3-hydroxyazetidine-1-carboxylate (105)

*i*PrMgCl•LiCl (1.09 M in THF, 2.20 mL, 2.40 mmol) was added dropwise over 5 min to a solution of 1-(benzyloxy)-4-iodobenzene (806 mg, 2.60 mmol) in THF (1.7 mL) at 0 °C. The reaction mixture was stirred at 0 °C for a further 10 min and warmed to 25 °C for 2 h. A solution of 1-Cbz-3-azetidinone (411 mg, 2.00 mmol) in THF (4.9 mL) was added dropwise to the reaction mixture at 0 °C. Following a further 19 h at 25 °C the reaction mixture was cooled to 0 °C then quenched with sat. aq. NH_4Cl (50 mL). The aqueous portion was extracted with Et_2O (3 × 50 mL). The organic extracts were combined, washed with sat. aq. NaCl (100 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash chromatography (70% Et_2O/pentane) afforded azetidinol **105** (545 mg, 70%) as a white solid. R_f = 0.36 (30% EtOAc/hexane); mp = 143 °C; IR (film)/cm^{-1} 3309 (br, OH), 1671 (C=O), 1655, 1475, 1461, 1440, 1361, 1233, 1108, 1002, 829, 754, 697; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45–7.32 (m, 12 H, 12 × Ar-CH), 7.01–6.97 (m, 2 H, 2 × Ar-CH), 5.12 (s, 2 H, CH_2Ph), 5.08 (s, 2 H, CH_2Ph), 4.33 (d, *J* = 9.3 Hz, 2 H, C*H*HNC*H*H), 4.23 (d, *J* = 9.3 Hz, 2 H, CH*H*NCH*H*), 2.82 (s, 1 H, OH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.4 (Ar-C_q-OBn), 156.6 (C=O), 136.7 (Ar-C_q-CH_2), 136.4 (Ar-C_q-CH_2), 135.2 (Ar-C_q-C_q), 128.6 (2 × Ar-CH), 128.5 (2 × Ar-CH), 128.1 (Ar-CH), 128.07 (Ar-CH), 128.02 (2 × Ar-CH), 127.4 (2 × Ar-CH), 126.0 (2 × Ar-CH), 115.0 (2 × Ar-CH), 71.6 (C_q), 70.0 (CH_2Ph), 66.9 (CH_2Ph), 64.2 (br, CH_2NCH_2); HRMS (+ESI) *m*/*z* calcd for $C_{24}H_{24}NO_4$ [M+H]: 390.1705, Found: 390.1715.



Benzyl 3-hydroxy-3-(4-((triisopropylsilyl)oxy)phenyl)azetidine-1-carboxylate (106)

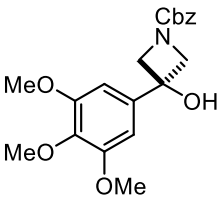
*i*PrMgCl•LiCl (1.09 M in THF, 2.10 mL, 2.28 mmol) was added dropwise over 5 min to a solution of (4-Iodophenoxy)triisopropylsilane[241] (941 mg, 2.50 mmol) in THF (1.5 mL) at 0 °C. The reaction mixture was stirred at 25 °C for 3 h. A solution of 1-Cbz-3-azetidinone (390 mg, 1.90 mmol) in THF (3.5 mL) was added dropwise to the reaction mixture at 0 °C. Following a further 23 h at 25 °C the reaction mixture was cooled to 0 °C then quenched with sat. aq. NH_4Cl (40 mL). The aqueous portion was extracted with Et_2O (3 × 40 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash chromatography (40% Et_2O/pentane) afforded azetidinol **106** (689 mg, 80%) as a white solid. R_f = 0.32 (5% Et_2O/CH_2Cl_2); mp = 39–44 °C; IR (film)/cm^{-1} 3395 (br, OH), 2945, 2867, 1685 (C=O), 1607, 1512, 1427, 1264, 1171, 1099, 911, 882, 835, 738; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37–7.30 (m, 7 H, 7 × Ar-CH), 6.91–6.87 (m, 2 H, 2 × Ar-CH), 5.12 (s, 2 H, CH_2Ph), 4.33 (d, *J* = 9.3 Hz, 2 H, C*H*HNC*H*H), 4.23 (d, *J* = 9.3 Hz, 2 H, CH*H*NCH*H*), 3.00 (s, 1 H, OH), 1.31–1.22 (m, 3 H, 3 × CH), 1.11 (d, *J* = 7.2 Hz, 18 H, 6 × CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.6 (Ar-C_q-OTIPS), 155.8 (C=O), 136.4 (Ar-C_q-CH_2), 135.3 (Ar-C_q-C_q), 128.5 (2 × Ar-CH), 128.0 (Ar-CH), 128.0 (2 × Ar-CH), 125.8 (2 × Ar-CH), 119.9 (2 × Ar-CH), 71.6 (C_q), 66.9 (CH_2Ph), 64.3 (br, CH_2NCH_2), 17.9 (3 × $CH(CH_3)_2$), 12.6 (3 × $CH(CH_3)_2$); HRMS (+ESI) *m*/*z* calcd for $C_{26}H_{38}NO_4Si$ [M+H]: 456.2570, Found: 456.2576.



Benzyl 3-(benzo[*d*][1,3]dioxol-5-yl)-3-hydroxyazetidine-1-carboxylate (107)

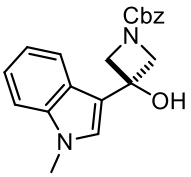
*i*PrMgCl•LiCl (1.09 M in THF, 2.20 mL, 2.40 mmol) was added dropwise over 5 min to a solution of 5-iodo-1,3-benzodioxole (941 mg, 2.50 mmol) in THF (1.5 mL) at 0 °C. The reaction mixture was stirred at 25 °C for 3 h. A solution of 1-Cbz-3-azetidinone (390 mg, 1.90 mmol) in THF (3.5 mL) was added dropwise to the reaction mixture at 0 °C. Following a further 23 h at 25 °C the reaction mixture was cooled to 0 °C then quenched with sat. aq. NH_4Cl (40 mL). The aqueous portion was extracted with Et_2O (3 × 40 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash chromatography (70% Et_2O/pentane) afforded azetidinol **107** (506 mg, 77%) as a white solid. R_f = 0.20 (30% EtOAc/hexane); mp = 68–70 °C; IR (film)/cm^{-1} 3264 (br, OH), 2884, 1649 (C=O), 1455, 1363, 1250, 1208, 1190, 1096, 1039, 916, 877, 808, 748, 701; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36–7.30 (m, 5 H, 5 × Ar-CH), 6.96 (d, *J* = 1.8 Hz, 1 H, Ar-CH), 6.93 (dd, *J* = 8.0, 1.8 Hz, 1 H, Ar-CH), 6.80 (d, *J* = 8.0 Hz, 1 H, Ar-CH), 5.97 (s, 2 H, OCH_2O), 5.12 (s, 2 H, CH_2Ph), 4.30 (d, *J* = 9.3 Hz, 2 H, C*H*HNC*H*H), 4.21 (d, *J* = 9.3 Hz, 2 H, CH*H*NCH*H*), 2.99 (s, 1 H, OH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.6 (C=O), 148.1 (Ar-C_q-

O), 147.3 (Ar-C_q-O), 136.9 (Ar-C_q-C_q), 136.4 (Ar-C_q-CH_2), 128.5 (2 × Ar-CH), 128.1 (Ar-CH), 128.0 (2 × Ar-CH), 118.0 (Ar-CH), 108.2 (Ar-CH), 105.6 (Ar-CH), 101.3 (OCH_2O), 71.7 (C_q), 66.9 (CH_2Ph), 64.4 (br, CH_2NCH_2); HRMS (+ESI) *m*/*z* calcd for $C_{18}H_{18}NO_5$ [M+H]: 328.1185, Found: 328.1180.



Benzyl 3-hydroxy-3-(3,4,5-trimethoxyphenyl)azetidine-1-carboxylate (109)

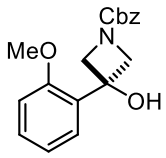
*i*PrMgCl•LiCl (1.09 M in THF, 2.20 mL, 2.40 mmol) was added dropwise over 5 min to a solution of 5-iodo-1,2,3-trimethoxybenzene (765 mg, 2.60 mmol) in THF (2.0 mL) at 0 °C. The reaction mixture was stirred at 25 °C for 3 h 30 min. A solution of 1-Cbz-3-azetidinone (410 mg, 2.00 mmol) in THF (4.6 mL) was added dropwise to the reaction mixture at 0 °C. Following a further 24 h at 25 °C the reaction mixture was cooled to 0 °C then quenched with sat. aq. NH_4Cl (60 mL). The aqueous portion was extracted with Et_2O (3 × 60 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash chromatography (80% Et_2O/pentane) afforded azetidinol **109** (552 mg, 94%) as a yellow sticky oil. R_f = 0.33 (100% Et_2O); IR (film)/cm^{-1} 3401 (br, OH), 2970, 2879, 1706, 1685 (C=O), 1589, 1511, 1453, 1414, 1352, 1234, 1181, 1109, 1066, 1003, 920, 827, 766, 734, 697, 655; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.32 (m, 5 H, 5 × Ar-CH), 6.69 (s, 2 H, 2 × Ar-CH), 5.15 (s, 2 H, CH_2Ph), 4.36 (d, *J* = 9.4 Hz, 2 H, C*H*HNC*H*H), 4.25 (d, *J* = 9.4 Hz, 2 H, CH*H*NCH*H*), 3.86 (m, 9 H, 3 × OCH_3), 2.54 (s, 1 H, OH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.6 (C=O), 154.0 (Ar-C_q-OCH_3), 153.4 (2 × Ar-C_q-OCH_3), 138.4 (Ar-C_q-C_q), 136.4 (Ar-C_q-CH_2), 128.5 (2 × Ar-CH), 128.2 (Ar-CH), 128.1 (2 × Ar-CH), 101.8 (2 × Ar-CH), 72.0 (C_q), 67.0 (CH_2Ph), 64.3 (br, CH_2NCH_2), 60.9 (OCH_3), 56.2 (2 × OCH_3); HRMS (+NSI) *m*/*z* calcd for $C_{20}H_{24}NO_6^+$ $[M+H]^+$: 374.1598, Found: 374.1598.



Benzyl 3-hydroxy-3-(1-methyl-1*H*-indol-3-yl)azetidine-1-carboxylate (110)

*i*PrMgCl•LiCl (1.09 M in THF, 5.40 mL, 5.90 mmol) was added dropwise over 5 min to a solution of 3-iodo-1-methyl-1*H*-indole **20** (1.56 g, 6.06 mmol) in THF (5.1 mL) at 0 °C. The reaction mixture was stirred at 25 °C for 3 h. A solution of 1-Cbz-3-azetidinone (964 mg, 4.70 mmol) in THF (10.5 mL) was added dropwise to the reaction mixture at 0 °C. Following a further 18 h at 25 °C the reaction mixture was cooled to 0 °C then quenched with sat. aq. NH_4Cl (60 mL). The aqueous portion was extracted with Et_2O (3 × 60 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash chromatography (70% Et_2O/pentane) afforded azetidinol **110**

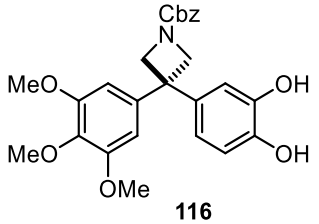
(1.52 g, 96%) as a yellow solid. R_f = 0.10 (70% Et_2O/pentane); mp = 120–123 °C; IR (film)/cm^{-1} 3383 (br, OH), 2940, 2877, 1683 (C=O), 1665, 1455, 1435, 1358, 1327, 1252, 1223, 1212, 1185, 1159, 1148, 1132, 1111, 1079, 954, 926, 829, 728, 702; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66–7.63 (dt, *J* = 8.0, 1.0 Hz, 1 H, Ar-CH), 7.36–7.26 (m, 7 H, 7 × Ar-CH), 7.15 (ddd, *J* = 8.1, 6.8, 1.2 Hz, 1 H, Ar-CH), 7.05 (s, 1 H, N-$Ar_{(indole)}$-CH), 5.11 (s, 2 H, CH_2Ph), 4.48 (d, *J* = 9.1 Hz, 2 H, C*H*HNC*H*H), 4.35 (d, *J* = 9.3 Hz, 2 H, CH*H*NCH*H*), 3.76 (s, 3 H, NCH_3), 2.78 (s, 1 H, OH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.6 (C=O), 137.7 ($Ar_{(indole)}$-C_q), 136.5 (Ar-C_q-CH_2), 128.4 (2 × Ar-CH), 128.0 (Ar-CH), 127.9 (2 × Ar-CH), 126.0 (N-*C*H-C_q), 125.1 ($Ar_{(indole)}$-C_q), 122.3 ($Ar_{(indole)}$-CH), 119.8 ($Ar_{(indole)}$-CH), 119.7 ($Ar_{(indole)}$-CH), 116.8 (N-Ar-CH-C_q), 109.7 ($Ar_{(indole)}$-CH), 68.8 (C_q), 66.8 (CH_2Ph), 63.5 (br, CH_2NCH_2), 32.8 (NCH_3); HRMS (+NSI) *m*/*z* calcd for $C_{20}H_{21}N_2O_3^+$ $[M+H]^+$: 337.1547, Found: 337.1545.



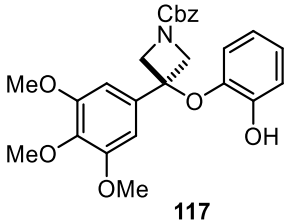
Benzyl 3-hydroxy-3-(2-methoxyphenyl)azetidine-1-carboxylate (111)

*i*PrMgCl•LiCl (1.05 M in THF, 2.30 mL, 2.40 mmol) was added dropwise over 5 min to a solution of 1-iodo-2-methoxybenzene (340 µL, 2.60 mmol) in THF (2.0 mL) at 0 °C. The reaction mixture was stirred at 25 °C for 4 h. A solution of 1-Cbz-3-azetidinone (410 mg, 2.00 mmol) in THF (4.7 mL) was added dropwise to the reaction mixture at 0 °C. Following a further 22 h at 25 °C the reaction mixture was cooled to 0 °C then quenched with sat. aq. NH_4Cl (40 mL). The aqueous portion was extracted with Et_2O (3 × 40 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash chromatography (50% Et_2O/pentane) afforded azetidinol **111** (318 mg, 51%) as a white solid. R_f = 0.20 (70% Et_2O/pentane); mp = 110–113 °C, IR (film)/cm^{-1} 3280 (br, OH), 1654 (C=O), 1476, 1431, 1353, 1241, 1125, 1095, 1021, 950, 760, 697; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37–7.27 (m, 7 H, 7 × Ar-CH), 7.00 (td, *J* = 7.5, 1.1 Hz, 1 H, Ar-CH), 6.94 (dd, *J* = 8.2, 1.1 Hz, 1 H, Ar-CH), 5.12 (s, 2 H, CH_2Ph), 4.46 (d, *J* = 9.5 Hz, 2 H, C*H*HNC*H*H), 4.24 (d, *J* = 9.5 Hz, 2 H, CH*H*NCH*H*), 3.88 (s, 3 H, OCH_3), 3.40 (s, 1 H, OH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.8 (C=O), 156.6 (Ar-C_q-OCH_3), 136.6 (Ar-C_q-CH_2), 129.8 (Ar-CH), 129.5 (Ar-C_q-C_q), 128.4 (2 × Ar-CH), 127.98 (Ar-CH), 127.96 (2 × Ar-CH), 126.0 (Ar-CH), 120.8 (Ar-CH), 111.0 (Ar-CH), 71.5 (C_q), 66.7 (CH_2Ph), 62.1 and 61.4 (br, CH_2NCH_2), 55.4 (OCH_3); HRMS (+ESI) *m*/*z* calcd for $C_{18}H_{20}NO_4$ [M+H]: 314.1392, Found: 314.1401.

Benzyl 3-(3,4-dihydroxyphenyl)-3-(3,4,5-trimethoxyphenyl)azetidine-1-carboxylate (116) and **benzyl 3-(2-hydroxyphenoxy)-3-(3,4,5-trimethoxyphenyl)azetidine-1-carboxylate (117)**



116



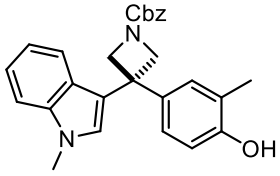
117

Calcium(II) bis(trifluoromethanesulfonimide) (15.0 mg, 0.025 mmol) and tetrabutylammonium hexafluorophosphate (9.7 mg, 0.025 mmol) were added to a solution of azetidinol **109** (187 mg, 0.50 mmol) and catechol (165 mg, 1.50 mmol) in CH_2Cl_2 (1.0 mL). The reaction mixture was stirred at 40 °C for 24 h then sat. aq. $NaHCO_3$ (30 mL) was added followed by Et_2O (30 mL). The layers were separated and the aqueous portion was extracted with Et_2O (2 × 30 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash chromatography (30 to 50% EtOAc/hexane) afforded ether azetidine **117** (10 mg, 5%) as a yellow solid followed by azetidine **116** (162 mg, 95%) as a white fluffy solid.

117: R_f = 0.53 (50% EtOAc/hexane); mp = 165–175 °C; IR (film)/cm^{-1} 3350 (br, OH), 2947, 1654 (C=O), 1498, 1416, 1355, 1059 (C-O ether), 744, 696; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41–7.32 (m, 5 H, 5 × Ar-CH), 6.98 (dd, *J* = 8.0, 1.6 Hz, 1 H, Ar-CH), 6.89–6.84 (m, 1 H, Ar-CH), 6.63–6.59 (m, 3 H, 3 × Ar-CH), 6.15 (dd, *J* = 8.0, 1.6 Hz, 1 H, Ar-CH), 5.72 (br, s, 1 H, OH), 5.16 (s, 2 H, CH_2Ph), 4.45 (d, *J* = 9.7 Hz, 2 H, C*H*HNC*H*H), 4.40 (d, *J* = 9.7 Hz, 2 H, CH*H*NCH*H*), 3.85 (s, 3 H, OCH_3), 3.79 (s, 6 H, 2 × OCH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.6 (C=O), 153.7 (3 × Ar-C_q-OCH_3), 146.3 (Ar-C_q-OC_q), 141.3 (Ar-C_q-OH), 136.1 (Ar-C_q-CH_2), 135.3 (Ar-C_q-C_q), 128.5 (2 × Ar-CH), 128.3 (Ar-CH), 128.2 (2 × Ar-CH), 122.7 (Ar-CH), 119.9 (Ar-CH), 115.6 (Ar-CH), 115.1 (Ar-CH), 101.9 (2 × Ar-CH), 77.8 (C_q), 67.2 (CH_2Ph), 61.9 (CH_2NCH_2), 60.9 (OCH_3), 56.3 (2 × OCH_3); HRMS (+ESI) *m*/*z* calcd for $C_{26}H_{28}NO_7$ [M+H]: 466.1866, Found: 466.1870.

116: R_f = 0.17 (50% EtOAc/hexane); mp = 76–79 °C; IR (film)/cm^{-1} 3366 (br, OH), 2957, 2836, 1675 (C=O), 1588, 1510, 1450, 1413, 1353, 1241, 1186, 1121, 1001, 923, 820, 765, 697, 665; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.30 (m, 5 H, 5 × Ar-CH), 6.79 (d, *J* = 8.3 Hz, 1 H, Ar-CH), 6.73 (d, *J* = 2.3 Hz, 1 H, Ar-CH), 6.56 (dd, *J* = 8.3, 2.3 Hz, 1 H, Ar-CH), 6.53 (s, 1 H, OH), 6.35 (s, 2 H, 2 × Ar-CH), 6.29 (s, 1 H, OH), 5.13 (s, 2 H, CH_2Ph), 4.57 (d, *J* = 8.4 Hz, 2 H, C*H*HNC*H*H), 4.51 (br, s, 2 H, CH*H*NCH*H*), 3.84 (s, 3 H, OCH_3), 3.77 (s, 6 H, 2 × OCH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.8 (C=O), 153.1 (2 × Ar-C_q-OCH_3), 144.0 (Ar-C_q-OCH_3), 142.9 (Ar-C_q-OH), 141.4 (Ar-C_q-OH), 138.2 (Ar-C_q-C_q), 136.7 (Ar-C_q-C_q), 136.1 (Ar-C_q-CH_2),

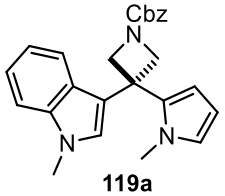
128.5 (2 × Ar-CH), 128.3 (Ar-CH), 128.1 (2 × Ar-CH), 118.6 (Ar-CH), 115.0 (Ar-CH), 113.6 (Ar-CH), 104.1 (2 × Ar-CH), 67.3 (CH_2Ph), 63.7 and 63.0 (CH_2NCH_2), 60.9 (OCH_3), 56.2 (2 × OCH_3), 45.8 (C_q); HRMS (+ESI) *m*/*z* calcd for $C_{26}H_{28}NO_7$ [M+H]: 466.1866, Found: 466.1868.



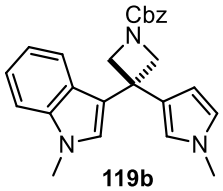
Benzyl 3-(4-hydroxy-3-methylphenyl)-3-(1-methyl-1*H*-indol-3-yl)azetidine-1-carboxylate (118)

Calcium(II) bis(trifluoromethanesulfonimide) (15.0 mg, 0.025 mmol) and tetrabutylammonium hexafluorophosphate (9.7 mg, 0.025 mmol) were added to a solution of azetidinol **110** (168 mg, 0.50 mmol) and 2-methylphenol (155 µL, 1.50 mmol) in CH_2Cl_2 (1.0 mL). The reaction mixture was stirred at 40 °C for 24 h then sat. aq. $NaHCO_3$ (30 mL) was added followed by Et_2O (30 mL). The layers were separated and the aqueous portion was extracted with Et_2O (3 × 30 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash chromatography (4% Et_2O/CH_2Cl_2) afforded azetidine **118** (147 mg, 69%) as a white solid. R_f = 0.27 (4% Et_2O/CH_2Cl_2); mp = 221–224 °C; IR (film)/cm^{-1} 3277 (br, OH), 2948, 2879, 1675 (C=O), 1459, 1446, 1418, 1363, 1331, 1301, 1282, 1222, 1205, 1184, 1160, 1148, 1136, 1118, 1087, 1053, 979, 823, 768, 742, 694; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (dt, *J* = 8.0, 1.0 Hz, 1 H, $Ar_{(indole)}$-CH), 7.41–7.30 (m, 6 H, 6 × Ar-CH), 7.27–7.23 (m, 1 H, $Ar_{(indole)}$-CH), 7.09–7.05 (m, 2 H, 2 × $Ar_{(indole)}$-CH), 6.97 (dd, *J* = 8.2, 2.5 Hz, 1 H, Ar-CH), 6.74 (d, *J* = 8.2 Hz, 1 H, Ar-CH), 6.52 (s, 1 H, N-Ar-CH), 5.39 (s, 1 H, OH), 5.17 (s, 2 H, CH_2Ph), 4.73 (d, *J* = 8.4 Hz, 2 H, C*H*HNC*H*H), 4.64 (d, *J* = 8.4 Hz, 2 H, CH*H*NCH*H*), 3.72 (s, 3 H, NCH_3), 2.24 (s, 3 H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.6 (C=O), 152.7 (Ar-C_q-OH), 137.7 ($Ar_{(indole)}$-C_q), 137.5 (Ar-C_q-C_q), 136.6 (Ar-C_q-CH_2), 129.2 ($Ar_{(indole)}$-CH), 128.5 (2 × Ar-CH), 128.02 (Ar-CH), 127.96 (2 × Ar-CH), 127.3 (N-Ar-CH), 125.9 ($Ar_{(indole)}$-C_q), 125.3 (Ar-CH), 123.8 (Ar-C_q-CH_3), 121.9 ($Ar_{(indole)}$-CH), 120.1 (N-Ar-CH-C_q), 119.9 ($Ar_{(indole)}$-CH), 119.3 ($Ar_{(indole)}$-CH), 114.6 (Ar-CH), 109.5 (Ar-CH), 66.8 (CH_2Ph), 63.1 and 62.4 (CH_2NCH_2), 40.8 (C_q), 32.7 (NCH_3), 16.0 (CH_3); HRMS (+ESI) *m*/*z* calcd for $C_{27}H_{27}N_2O_3$ [M+H]: 427.2022, Found: 427.2012.

Benzyl 3-(1-methyl-1*H*-indol-3-yl)-3-(1-methyl-1*H*-pyrrol-2-yl)azetidine-1-carboxylate (119a) and **benzyl 3-(1-methyl-1*H*-indol-3-yl)-3-(1-methyl-1*H*-pyrrol-3-yl)azetidine-1-carboxylate (119b)**

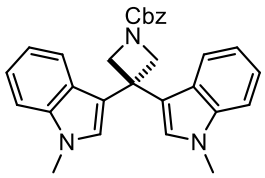


119a



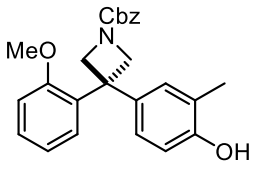
119b

CH_2Cl_2 (1.0 mL) was added to calcium(II) bis(trifluoromethanesulfonimide) (15.0 mg, 0.025 mmol), tetrabutylammonium hexafluorophosphate (9.7 mg, 0.025 mmol), azetidinol **110** (168 mg, 0.50 mmol) and 1-methylpyrrole (133 µL, 1.50 mmol). The reaction mixture was stirred at 40 °C for 24 h then sat. aq. $NaHCO_3$ (30 mL) was added followed by Et_2O (30 mL). The layers were separated and the aqueous portion was extracted with Et_2O (2 × 30 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash chromatography (50% Et_2O/hexane) afforded a mixture of azetidine **119a** and **119b** (136 mg, 68%, 85:15) as a white solid. R_f = 0.50 (50% Et_2O/hexane); mp = 148–154 °C; IR (film)/cm^{-1} 2950, 2889, 1702 (C=O), 1485, 1459, 1421, 1350, 1297, 1216, 1174, 1145, 1116, 1084, 972, 766, 756, 737, 712, 700; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (dt, J = 8.1, 1.0 Hz, $Ar_{(indole)}$-CH_{119a}), 7.45–7.30 (m, 5 × Ar-CH_{119a}, $Ar_{(indole)}$-CH_{119a}, 5 × Ar-CH_{119b}, 2 × $Ar_{(indole)}$-CH_{119b}), 7.28–7.24 (m, $Ar_{(indole)}$-CH_{119a}, $Ar_{(indole)}$-CH_{119b}), 7.10–7.01 (m, $Ar_{(indole)}$-CH_{119a}, $Ar_{(indole)}$-CH_{119b}), 6.85 (m, $N_{(indole)}$-Ar-CH_{119b}), 6.64 (t, J = 2.3 Hz, $Ar_{(pyrrole)}$-CH_{119a}), 6.57 (t, J = 2.5 Hz, $Ar_{(pyrrole)}$-CH_{119b}), 6.50 (s, $N_{(indole)}$-Ar-CH_{119a}), 6.29 (t, J = 2.1 Hz, $Ar_{(pyrrole)}$-CH_{119b}), 6.20 (d, J = 2.3 Hz, 2 × $Ar_{(pyrrole)}$-CH_{119a}), 6.17 (dd, J = 2.7, 1.9 Hz, $Ar_{(pyrrole)}$-CH_{119b}), 5.19–5.15 (m, CH_2Ph_{119a}, CH_2Ph_{119b}), 4.69–4.63 (m, CH_2NC$H_{2,119a}$, CHHNCHH_{119b}), 4.51 (d, J = 8.0 Hz, CHHNCHH$_{119b}$), 3.77 (s, $N_{(indole)}$-$CH_{3,119b}$), 3.71 (s, $N_{(indole)}$-$CH_{3,119a}$), 3.56 (s, $N_{(pyrrole)}$-$CH_{3,119b}$), 3.29 (s, $N_{(pyrrole)}$-$CH_{3\ 119a}$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.5 (C=O $_{119a}$), 156.3 (C=O_{119b}), 140.7 ($Ar_{(indole)}$-$C_{q\ 119b}$), 137.7 ($Ar_{(indole)}$-C_{q119a}), 136.6 (Ar-C_{q119a}-CH_2, Ar-C_{q119b}-CH_2), 135.2 ($Ar_{(pyrrole)}$-C_{q119a}-C_q), 129.9 ($Ar_{(pyrrole)}$-C_{q119b}-C_q), 128.5 (2 × Ar-CH_{119a}), 128.4 (2 × Ar-CH_{119b}), 128.02 (Ar-CH_{119a}), 127.98 (2 × Ar-CH_{119a}, Ar-$CH_{17'}$, $Ar_{(indole)}$-CH_{119b}), 127.9 (2 × Ar-CH_{119b}), 126.8 ($Ar_{(indole)}$-C_{q119b}), 126.7 (N-Ar-CH_{119a}), 126.4 (N-Ar-CH_{119b}), 125.7 ($Ar_{(indole)}$-C_{q119a}), 122.9 ($Ar_{(pyrrole)}$-CH_{119a}), 122.1 ($Ar_{(pyrrole)}$-CH_{119b}), 121.9 ($Ar_{(indole)}$-CH_{119a}), 120.3 ($Ar_{(indole)}$-CH_{119b}), 119.7 ($Ar_{(indole)}$-CH_{119a}, N-Ar-CH-C_{q119b}), 119.6 ($Ar_{(indole)}$-CH_{119a}), 119.5 ($Ar_{(pyrrole)}$-CH_{119b}), 118.9 ($Ar_{(indole)}$-CH_{119b}), 118.4 (N-Ar-CH-C_{q119a}), 109.44 ($Ar_{(indole)}$-CH_{119a}), 109.36 ($Ar_{(indole)}$-CH_{119b}), 106.8 ($Ar_{(pyrrole)}$-CH_{119b}), 106.7 ($Ar_{(pyrrole)}$-CH_{119a}), 106.6 ($Ar_{(pyrrole)}$-CH_{119a}), 66.8 (CH_2Ph_{119a}), 66.6 (CH_2Ph_{119b}), 63.8 ($CH_2NCH_{2,119b}$), 62.1 and 61.2 ($CH_2NCH_{2,119a}$), 36.54 (C_{q119a} and C_{q119b}), 36.53 ($N_{(pyrrole)}$-$CH_{3,119b}$), 34.6 ($N_{(pyrrole)}$-$CH_{3,119a}$), 32.7 ($N_{(indole)}$-$CH_{3,119a}$, $N_{(indole)}$-$CH_{3,119b}$); HRMS (+ESI) m/z calcd for $C_{25}H_{26}N_3O_2$ [M+H]: 400.2025, Found: 400.2012.



Benzyl 3,3-bis(1-methyl-1*H*-indol-3-yl)azetidine-1-carboxylate (120)

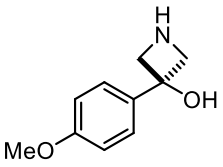
Calcium(II) bis(trifluoromethanesulfonimide) (7.50 mg, 0.0125 mmol) and tetrabutyl-ammonium hexafluorophosphate (4.80 mg, 0.0125 mmol) were added to a solution of azetidinol **110** (84.1 mg, 0.25 mmol) and 1-methylindole (93.7 µL, 0.75 mmol) in CH_2Cl_2 (0.5 mL). The reaction mixture was stirred at 60 °C for 24 h then sat. aq. $NaHCO_3$ (15 mL) was added followed by Et_2O (15 mL). The layers were separated and the aqueous portion was extracted with Et_2O (2 × 15 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash chromatography (30% Et_2O/pentane) afforded azetidine **120** (90.0 mg, 80%) as a white solid. R_f = 0.43 (70% Et_2O/pentane); mp = 193–196 °C; IR (film)/cm^{-1} 2947, 2880, 1706 (C=O), 1626, 1545, 1469, 1407, 1370, 1340, 1325, 1294, 1247, 1223, 1208, 1173, 1156, 1141, 1112, 1072, 1038, 960, 937, 919, 846, 815, 783, 761, 746; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60–7.58 (m, 2 H, 2 × $Ar_{(indole)}$-CH), 7.41–7.32 (m, 7 H, 5 × Ar-CH, 2 × $Ar_{(indole)}$-CH), 7.29–7.25 (m, 2 H, 2 × $Ar_{(indole)}$-CH), 7.11–7.07 (m, 2 H, 2 × $Ar_{(indole)}$-CH), 6.72 (2 × s, 2 H, 2 × N-Ar-CH), 5.19 (s, 2 H, CH_2Ph), 4.82 (d, *J* = 2.1 Hz, 4 H, CH_2NCH_2), 3.72 (2 × s, 6 H, 2 × NCH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.6 (C=O), 137.7 (2 × $Ar_{(indole)}$-C_q), 136.8 (Ar-C_q-CH_2), 128.4 (2 × Ar-CH), 127.93 (Ar-CH), 127.92 (2 × Ar-CH), 127.1 (2 × N-Ar-CH), 126.1 (2 × $Ar_{(indole)}$-C_q), 121.8 (2 × $Ar_{(indole)}$-CH), 120.1 (2 × $Ar_{(indole)}$-CH), 119.2 (2 × $Ar_{(indole)}$-CH), 119.1 (2 × N-Ar-CH-C_q), 109.5 (2 × $Ar_{(indole)}$-CH), 66.7 (CH_2Ph), 62.8 and 61.8 (CH_2NCH_2), 36.4 (C_q), 32.7 (2 × NCH_3); HRMS (+ESI) *m*/*z* calcd for $C_{29}H_{28}N_3O_2$ [M+H]: 450.2182, Found: 450.2195.



Benzyl 3-(4-hydroxy-3-methylphenyl)-3-(2-methoxyphenyl)azetidine-1-carboxylate (121)

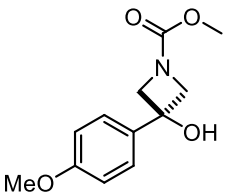
Calcium(II) bis(trifluoromethanesulfonimide) (7.5 mg, 0.0125 mmol) and tetrabutylammonium hexafluorophosphate (4.8 mg, 0.0125 mmol) were added to a solution of azetidinol **111** (78.3 mg, 0.25 mmol) and 2-methylphenol (77.2 µL, 0.75 mmol) in CH_2Cl_2 (0.5 mL). The reaction mixture was stirred at 40 °C for 2 h then sat. aq. $NaHCO_3$ (15 mL) was added followed by Et_2O (15 mL). The layers were separated and the aqueous portion was extracted with Et_2O (3 × 15 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash chromatography (50% Et_2O/pentane) afforded azetidine **121** (89.5 mg, 89%) as a white solid. R_f = 0.20 (50% Et_2O/pentane); mp = 148–152 °C; IR (film)/cm^{-1} 3317 (br, OH), 2952, 1673 (C=O), 1606, 1490, 1453, 1423, 1353, 1267, 1177, 1118, 1025, 820, 752, 697; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40–7.26 (m, 6 H, 6 × Ar-CH), 7.15 (dd, *J* = 7.6, 1.7 Hz, 1 H, Ar-CH), 7.03–6.98 (m, 2 H, 2 × Ar-CH), 6.92 (dd, *J* = 8.4, 2.5 Hz, 1 H, Ar-CH), 6.88 (dd, *J* = 8.4, 1.1 Hz,

1 H, Ar-CH), 6.66 (d, *J* = 8.4 Hz, 1 H, Ar-CH), 5.42 (s, 1 H, OH), 5.13 (s, 2 H, CH_2Ph), 4.65 (d, *J* = 8.7 Hz, 2 H, C*H*HNC*H*H), 4.45 (d, *J* = 8.7 Hz, 2 H, CH*H*NCH*H*), 3.71 (s, 3 H, OCH_3), 2.19 (s, 3 H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.9 (Ar-C_q-OCH_3), 156.7 (C=O), 152.6 (Ar-C_q-OH), 138.0 (Ar-C_q-C_q), 136.6 (Ar-C_q-CH_2), 132.6 (Ar-C_q-C_q), 128.5 (2 × Ar-CH), 128.4 (2 × Ar-CH), 128.3 (Ar-CH), 128.0 (2 × Ar-CH), 127.6 (Ar-CH), 124.4 (Ar-CH), 123.7 (Ar-C_q-CH_3), 120.5 (Ar-CH), 114.5 (Ar-CH), 111.2 (Ar-CH), 66.8 (CH_2Ph), 63.1 and 62.4 (CH_2NCH_2), 55.2 (OCH_3), 43.8 (C_q), 16.0 (CH_3); HRMS (+ESI) *m*/*z* calcd for $C_{25}H_{26}NO_4$ [M+H]: 404.1862, Found: 404.1852.



3-(4-Methoxyphenyl)azetidin-3-ol (124)

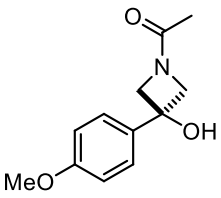
Palladium on carbon (10 mol% w/w, 31 mg) was added to a solution of azetidinol **83** (470 mg, 1.50 mmol) in ethanol (6.0 mL). The reaction mixture was stirred under atmosphere of hydrogen at 25 °C for 17 h. The reaction mixture was filtered through celite, washed through with ethanol and then concentrated under reduced pressure to afford 3-(4-methoxyphenyl)azetidin-3-ol **124** (273 mg, 100%) as a light yellow solid. mp = 145–153 °C; IR (film)/cm^{-1} 3299 (br, NH), 2940, 2873, 2836, 2624, 1608, 1578, 1510, 1456, 1443, 1338, 1317, 1299, 1243, 1187, 1174, 1146, 1105, 1083, 1021, 988, 949, 933, 865, 828, 811, 797, 721; ^{1}H NMR (400 MHz, MeOD-*d*$_4$) δ 7.49–7.45 (m, 2 H, 2 × Ar-CH), 6.94–6.90 (m, 2 H, 2 × Ar-CH), 3.88 (d, *J* = 9.8 Hz, 2 H, C*H*HNC*H*H), 3.82 (d, *J* = 9.8 Hz, 2 H, CH*H*NCH*H*), 3.78 (s, 3 H, OCH_3); ^{13}C NMR (101 MHz, MeOD-*d*$_4$) δ 160.4 (Ar-C_q-OCH_3), 138.0 (Ar-C_q-C_q), 127.3 (2 × Ar-CH), 114.7 (2 × Ar-CH), 76.2 (C_q), 61.8 (br, CH_2NCH_2), 55.7 (OCH_3); HRMS (+ESI) *m*/*z* calcd for $C_{10}H_{14}NO_2$ [M+H]: 180.1025, Found: 180.1022. Compound previously reported without characterisation data.[115a]



Methyl 3-hydroxy-3-(4-methoxyphenyl)azetidine-1-carboxylate (125)

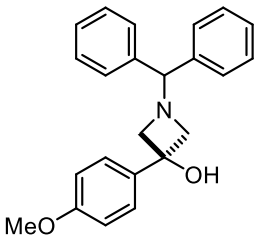
Methylchloroformate (238 µL, 3.08 mmol) was added to a solution of amine **124** (265 mg, 1.54 mmol) in THF and sat. aq. $NaHCO_3$ (1:1, 6.0 mL) at 0 °C. The reaction mixture was stirred for 10 min at 0 °C followed by 23 h at 25 °C. The aqueous portion was extracted with EtOAc (3 × 30 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give carbamate **125** (325 mg, 89%) as a white solid. R_f = 0.15 (70% Et_2O/pentane); mp = 93–97 °C; IR (film)/cm^{-1} 3424 (br, OH), 3365, 2960, 1674 (C=O), 1613, 1509, 1455, 1394, 1371, 1304, 1294, 1276, 1249, 1203, 1176, 1160, 1144, 1116, 1103, 1046, 1028, 972, 832, 825, 814, 795, 762; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42–7.38 (m, 2 H, 2 × Ar-CH), 6.94–6.90 (m, 2 H, 2 × Ar-CH), 4.30 (d, *J* = 9.5 Hz, 2 H, C*H*HNC*H*H), 4.21 (dd, *J* = 9.5, 1.0 Hz, 2 H, CH*H*NCH*H*), 3.82 (s, 3 H, OCH_3), 3.69 (s, 3 H, OCH_3), 3.03 (s, 1 H, OH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.2

(Ar-C_q-OCH_3), 157.2 (C=O), 135.1 (Ar-C_q-C_q), 125.9 (2 × Ar-CH), 114.0 (2 × Ar-CH), 71.5 (C_q), 64.3 (br, CH_2NCH_2), 55.3 (OCH_3), 52.5 (OCH_3); HRMS (+ESI) *m*/*z* calcd for $C_{12}H_{16}NO_4$ [M+H]: 238.1079, Found: 238.1082.



1-(3-Hydroxy-3-(4-methoxyphenyl)azetidin-1-yl)ethan-1-one (126)

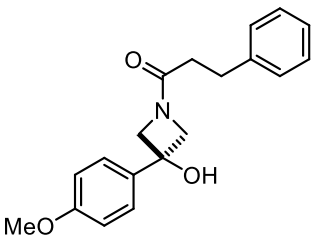
Acetic anhydride (73.7 µL, 0.78 mmol) was added to a solution of amine **124** (68.0 mg, 0.39 mmol) and NEt_3 (163 µL, 1.17 mmol) in CH_2Cl_2 (2.0 mL) at 0 °C. The reaction mixture was stirred for 1 h at 0 °C and then 16 h at 25 °C. The reaction mixture was then quenched with sat. aq. $NaHCO_3$ (20 mL). The aqueous portion was extracted with Et_2O (2 × 20 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash chromatography (100% EtOAc) afforded azetidinol **126** (43.9 mg, 53%) as a white solid. R_f = 0.15 (100% EtOAc); mp = 141–142 °C; IR (film)/cm^{-1} 3278 (br, OH), 3004, 2958, 1606, 1583, 1513, 1477, 1451, 1426, 1362, 1305, 1288, 1239, 1184, 1111, 1037, 1024, 1003, 972, 932, 916, 901, 862, 823, 793, 763, 673; ^{1}H NMR (400 MHz, MeOD-d_4) δ 7.44–7.40 (m, 2 H, 2 × Ar-CH), 6.95–6.91 (m, 2 H, 2 × Ar-CH), 4.47 (dd, *J* = 9.3, 1.3 Hz, 1 H, C*H*HNCHH), 4.31 (dd, *J* = 9.3, 1.3 Hz, 1 H, CH*H*NCHH), 4.24 (ddd, *J* = 10.4, 1.3, 0.6 Hz, 1 H, CHHNC*H*H), 4.09 (ddd, *J* = 10.4, 1.3, 0.6 Hz, 1 H, CHHNCH*H*), 3.78 (s, 3 H, OCH_3), 1.93 (s, 3 H, CH_3); ^{13}C NMR (101 MHz, MeOD-d_4) δ 173.6 (C=O), 160.7 (Ar-C_q-OCH_3), 136.8 (Ar-C_q-C_q), 127.2 (2 × Ar-CH), 114.9 (2 × Ar-CH), 71.1 (C_q), 66.8 (CH_2NCH_2), 64.1 (CH_2NCH_2), 55.7 (OCH_3), 18.9 (CH_3); HRMS (+ESI) *m*/*z* calcd for $C_{12}H_{16}NO_3$ [M+H]: 222.1130, Found: 222.1127.



1-Benzhydryl-3-(4-methoxyphenyl)azetidin-3-ol (127)

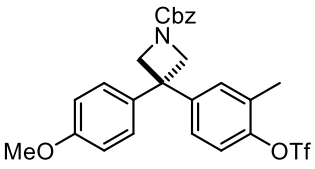
4-Methoxyphenylmagnesium bromide (0.5 M solution in THF, 2.40 mL, 1.20 mmol) was added dropwise to a solution of 1-benzhydrylazetidin-3-one (236 mg, 0.99 mmol) in THF (2.0 mL) at 0 °C. The reaction mixture was stirred for 23 h at 25 °C and then cooled to 0 °C and quenched with sat. aq. NH_4Cl (60 mL). The aqueous portion was extracted with Et_2O (3 × 60 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash chromatography (40% Et_2O/hexane) afforded azetidinol **127** (279 g, 81%) as a white solid. R_f = 0.40 (50% EtOAc/hexane); mp = 39–44 °C; IR (film)/cm^{-1} 3370 (br, OH), 3060, 3026, 2935, 2833, 1611, 1582, 1512, 1491, 1451, 1344, 1303, 1244, 1211, 1175, 1108, 1075, 1064, 1028, 889, 858, 829, 742, 696; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54–7.52 (m, 2 H, 2 × Ar-CH), 7.48–7.45 (m, 4 H, 4 × Ar-CH), 7.31–7.26 (m, 4 H, 4 × Ar-CH), 7.22–7.18 (m, 2 H, 2 × Ar-CH), 6.96–6.94 (m, 2 H, 2 × Ar-CH), 4.48 (s, 1 H, C*H*$(Ph)_2$), 3.84 (s, 3 H, OCH_3), 3.60–3.57 (m, 2 H, C*H*HNC*H*H), 3.41–3.38 (m, 2 H, CH*H*NCH*H*), 2.52 (s, 1 H,

OH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.0 (Ar-C_q-OCH_3), 142.2 (2 × Ar-C_q-CH), 136.4 (Ar-C_q-C_q), 128.4 (4 × Ar-CH), 127.4 (4 × Ar-CH), 127.1 (2 × Ar-CH), 126.2 (2 × Ar-CH), 113.8 (2 × Ar-CH), 78.1 (C_q), 71.3 ($CH(Ph)_2$), 67.6 (CH_2NCH_2), 55.3 (OCH_3); HRMS (+ESI) *m*/*z* calcd for $C_{23}H_{24}NO_2$ [M+H]: 346.1807, Found: 346.1815. Compound previously reported without characterisation data.[115a]



1-(3-Hydroxy-3-(4-methoxyphenyl)azetidin-1-yl)-3-phenylpropan-1-one (128)

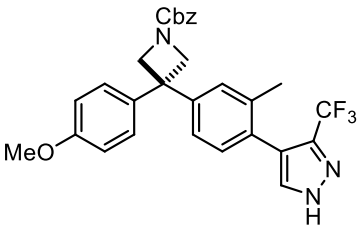
DMAP (122 mg, 1.00 mmol) followed by EDC•HCl (230 mg, 1.20 mmol) was added to a solution of azetidine **124** (172 mg, 1.00 mmol) and hydrocinnamic acid (165 mg, 1.10 mmol) in CH_2Cl_2 (10 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 10 min and then at 25 °C for 18 h. The reaction mixture was then quenched with sat. aq. $NaHCO_3$ (50 mL). The aqueous portion was extracted with CH_2Cl_2 (3 × 50 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash chromatography (80% EtOAc/pentane) afforded azetidine **128** (202 mg, 65%) as a white solid. R_f = 0.24 (80% EtOAc/pentane); mp = 120–121 °C; IR (film)/cm^{-1} 3201 (br, OH), 2959, 1595 (C=O), 1490, 1431, 1304, 1244, 1177 1021, 887, 827, 752, 704; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31–7.26 (m, 4 H, 4 × Ar-CH), 7.23–7.20 (m, 3 H, 3 × Ar-CH), 6.91–6.88 (m, 2 H, 2 × Ar-CH), 4.30 (d, *J* = 10.9 Hz, 1 H, C*H*HNCHH), 4.17–4.13 (m, 4 H, CH*H*NC*H*$_2$, OH), 3.82 (s, 3 H, OCH_3), 2.96 (t, *J* = 7.6 Hz, 2 H, CH_2), 2.43 (t, *J* = 7.6 Hz, 2 H, CH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.7 (C=O), 159.2 (Ar-C_q-OCH_3), 141.0 (Ar-C_q-CH_2), 134.9 (Ar-C_q-C_q), 128.5 (2 × Ar-CH), 128.4 (2 × Ar-CH), 126.3 (Ar-CH), 125.9 (2 × Ar-CH), 113.9 (2 × Ar-CH), 70.6 (C_q), 65.1 (CH_2NCH_2), 62.7 (CH_2NCH_2), 55.3 (OCH_3), 33.8 (CH_2), 31.2 (CH_2); HRMS (+ESI) *m*/*z* calcd for $C_{19}H_{21}NO_3Na^+$ [M+Na]$^+$: 334.1414, Found: 334.1419.



Benzyl-3-(4-methoxyphenyl)-3-(3-methyl-4-(((trifluoromethyl)sulfonyl)oxy)phenyl)azetidine-1-carboxylate (129)

NEt_3 (314 µL, 2.25 mmol) followed by Tf_2O (250 µL, 1.50 mmol) were added to a solution of azetidine **84** (306 mg, 0.75 mmol) in CH_2Cl_2 (1.5 mL) at 0 °C. The reaction mixture was stirred at 25 °C for 2 h then water (30 mL) was added at 0 °C. The aqueous portion was extracted with CH_2Cl_2 (4 × 30 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash chromatography (30% Et_2O/pentane) afforded azetidine **129** (355 mg, 88%) as a yellow sticky oil. R_f = 0.24 (30% Et_2O/pentane); IR (film)/cm^{-1} 2959, 2890, 1706 (C=O), 1610, 1512, 1495,

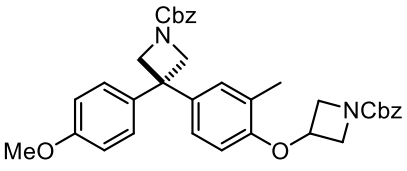
1413, 1352, 1296, 1248, 1207, 1181, 1137, 1087, 1029, 1004, 962, 910, 860, 828, 804, 767, 739, 697, 656; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39–7.31 (m, 5 H, 5 × Ar-CH), 7.18 (d, *J* = 8.6 Hz, 1 H, Ar-CH), 7.13 (dd, *J* = 2.4, 0.8 Hz, 1 H, Ar-CH), 7.10–7.04 (m, 3 H, 3 × Ar-CH), 6.91–6.88 (m, 2 H, 2 × Ar-CH), 5.14 (s, 2 H, CH_2Ph), 4.60 (d, *J* = 8.4 Hz, 2 H, C*H*HNC*H*H), 4.54 (d, *J* = 8.4 Hz, 2 H, CH*H*NCH*H*), 3.82 (s, 3 H, OCH_3), 2.35 (s, 3 H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.5 (Ar-C_q-OCH_3), 156.3 (C=O), 147.0 (Ar-C_q-OTf), 146.5 (Ar-C_q-C_q), 136.8 (Ar-C_q-C_q), 136.4 (Ar-C_q-CH_2), 131.0 (Ar-C_q-CH_3), 130.2 (Ar-CH), 128.4 (2 × Ar-CH), 128.1 (Ar-CH), 128.0 (2 × Ar-CH), 127.6 (2 × Ar-CH), 125.8 (Ar-CH), 121.3 (Ar-CH), 118.5 (q, *J* = 317.8 Hz, CF_3), 114.1 (2 × Ar-CH), 66.9 (CH_2Ph), 63.1 (CH_2NCH_2), 55.2 (OCH_3), 45.1 (C_q), 16.4 (CH_3); ^{19}F{^{1}H} NMR (377 MHz, $CDCl_3$) δ –73.8; HRMS (+ESI) *m*/*z* calcd for $C_{26}H_{25}NO_6SF_3$ [M+H]: 536.1355, Found: 536.1357.



Benzyl 3-(4-methoxyphenyl)-3-(3-methyl-4-(3-(trifluoromethyl)-1*H*-pyrazol-4-yl)phenyl)azetidine-1-carboxylate (130)

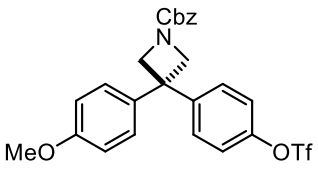
Triflated azetidine **129** (180 mg, 0.34 mmol), pyrazole pinacol ester (115 mg, 0.44 mmol), $Pd(PPh_3)_4$ (30.8 mg, 0.027 mmol) and K_2CO_3 (94.0 mg, 0.68 mmol) were added to a reaction vial. The reaction vial was evacuated and then refilled with nitrogen three times. DME/water (88:22, 3.4 mL) was added *via* syringe into the vial. The reaction mixture was stirred at 100 °C for 25 h then cooled to rt. and water (20 mL) was added. The aqueous portion was extracted with EtOAc (3 × 20 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography (4% Et_2O/CH_2Cl_2) afforded azetidine **130** (122 mg, 69%) as a white solid. R_f = 0.20 (4% Et_2O/CH_2Cl_2); mp = 90–98 °C; IR (film)/cm^{-1} 3187 (br, NH), 2956, 1688 (C=O), 1512, 1419, 1354, 1294, 1270, 1248, 1181, 1122, 1101, 1028, 1005, 978, 827, 804, 766, 748, 697; ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.67 (s, 1 H, NH), 7.61 (d, *J* = 1.2 Hz, 1 H, N-Ar-CH), 7.41–7.31 (m, 5 H, 5 × Ar-CH), 7.19 (d, *J* = 8.0 Hz, 1 H, Ar-CH), 7.17–7.13 (m, 2 H, 2 × Ar-CH), 7.11 (d, *J* = 2.0 Hz, 1 H, Ar-CH), 7.02 (dd, *J* = 8.0, 2.0 Hz, 1 H, Ar-CH), 6.92–6.88 (m, 2 H, 2 × Ar-CH), 5.15 (s, 2 H, CH_2Ph), 4.65 (d, *J* = 8.4 Hz, 2 H, C*H*HNC*H*H), 4.61 (d, *J* = 8.4 Hz, 2 H, CH*H*NCH*H*), 3.82 (s, 3 H, OCH_3), 2.17 (s, 3 H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.3 (Ar-C_q-OCH_3), 156.5 (C=O), 146.2 (Ar-C_q-$C_{q(pyrazole)}$), 140.1 (q, $J_{C\text{-}F}$ = 33.0 Hz, C_q-CF_3), 137.7 (Ar-C_q-C_q), 137.5 (Ar-C_q-C_q), 136.5 (Ar-C_q-CH_2), 131.0 (Ar-CH), 130.1 (br, N-Ar-CH), 128.5 (2 × Ar-CH), 128.2 (Ar-C_q-CH_3), 128.1 (Ar-CH), 128.0 (2 × Ar-CH), 127.7 (3 × Ar-CH), 123.7 (Ar-CH), 120.2 (q, $^{1}J_{C\text{-}F}$ = 268.9 Hz, CF_3), 119.7 (Ar-C_q-$C_{q(pyrazole)}$), 114.0 (2 × Ar-CH), 66.9 (CH_2Ph), 63.5 and 62.8 (CH_2NCH_2), 55.3 (OCH_3), 45.2 (C_q),

20.4 (CH_3); $^{19}F\{^1H\}$ NMR (377 MHz, $CDCl_3$) δ –60.1; HRMS (+ESI) *m*/*z* calcd for $C_{29}H_{27}N_3O_3F_3$ [M+H]: 522.2005, Found: 522.2004.



Benzyl 3-(4-((1-((benzyloxy)carbonyl)azetidin-3-yl)oxy)-3-methylphenyl)-3-(4-methoxyphenyl)azetidine-1-carboxylate (131)

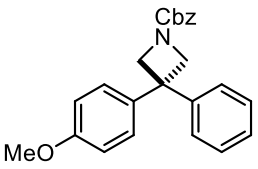
A solution of azetidine **84** (101 mg, 0.25 mmol), K_2CO_3 (87.1 mg, 0.63 mmol) and benzyl 3-((methylsulfonyl)oxy)azetidine-1-carboxylate[242] (79.9 mg, 0.28 mmol) in DMF (1.3 mL) was heated to 90 °C and stirred for 19 h. The reaction mixture was then cooled to rt and water (30 mL) was added. The aqueous portion was extracted with Et_2O (3 × 30 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash chromatography (30% EtOAc/pentane) afforded azetidine **131** (93.2 mg, 63%) as a white solid. R_f = 0.26 (30% EtOAc/pentane); mp = 48–52 °C; IR (film)/cm^{-1} 2950, 1704 (C=O), 1608, 1503, 1411, 1350, 1295, 1246, 1180, 1120, 1028, 829, 736, 696; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39–7.31 (m, 10 H, 10 × Ar-CH), 7.11–7.07 (m, 2 H, 2 × Ar-CH), 7.03–7.02 (m, 1 H, Ar-CH), 6.89–6.85 (m, 3 H, 3 × Ar-CH), 6.37 (d, *J* = 8.4 Hz, 1 H, Ar-CH), 5.13 (2 × s, 4 H, 2 × CH_2Ph), 4.90 (tt, *J* = 6.4, 4.1 Hz, 1 H, OCH), 4.55 (s, 4 H, C*H*$_2$NC*H*$_2$), 4.39 (ddd, *J* = 9.6, 6.4, 1.1 Hz, 2 H, C*H*H(OCH)C*H*H), 4.09 (ddd, *J* = 9.6, 4.1, 1.1 Hz, 2 H, CH*H*(OCH)CH*H*), 3.80 (s, 3 H, OCH_3), 2.21 (s, 3 H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.2 (Ar-C_q-OCH_3), 156.4 (C=O), 156.3 (C=O), 153.3 (Ar-C_q-OCH), 138.9 (Ar-C_q-C_q), 138.1 (Ar-C_q-C_q), 136.53 (Ar-C_q-CH_2), 136.46 (Ar-C_q-CH_2), 129.4 (Ar-CH), 128.48 (2 × Ar-CH), 128.47 (2 × Ar-CH), 128.09 (Ar-CH), 128.05 (Ar-CH), 128.0 (4 × Ar-CH), 127.6 (2 × Ar-CH), 127.3 (Ar-C_q-CH_3), 124.8 (Ar-CH), 113.9 (2 × Ar-CH), 110.4 (Ar-CH), 66.9 (CH_2Ph), 66.8 (CH_2Ph), 65.9 (OCH), 63.6 and 63.0 (*C*H_2N*C*H_2), 56.5 (*C*H_2N*C*H_2), 55.3 (OCH_3), 44.8 (C_q), 16.3 (CH_3); HRMS (+ESI) *m*/*z* calcd for $C_{36}H_{37}N_2O_6$ [M+H]: 593.2652, Found: 593.2651.



Benzyl 3-(4-methoxyphenyl)-3-(4-(((trifluoromethyl)sulfonyl)oxy)phenyl)azetidine-1-carboxylate (S3)

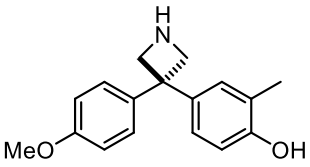
NEt_3 (83.6 µL, 0.60 mmol) followed by Tf_2O (67.3 µL, 0.40 mmol) were added to a solution of a mixture of azetidines **85** and **85'** (77.9 mg, 0.20 mmol, 80:20) in CH_2Cl_2 (0.4 mL) at 0 °C. The reaction mixture was stirred at 25 °C for 2 h then water (15 mL) was added at 0 °C. The aqueous portion was extracted with CH_2Cl_2 (4 × 15 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash chromatography (30% Et_2O/pentane) afforded azetidine triflate

S3 (86.1 mg, 83%) as a yellow sticky oil. R_f = 0.18 (30% Et_2O/pentane); IR (film)/cm^{-1} 2958, 2890, 1706 (C=O), 1611, 1513, 1499, 1416, 1352, 1248, 1207, 1183, 1134, 1033, 1014, 1003, 884, 831, 760, 734, 697; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.31 (m, 5 H, 5 × Ar-CH), 7.29–7.26 (m, 2 H, 2 × Ar-CH), 7.24–7.21 (m, 2 H, 2 × Ar-CH), 7.09–7.06 (m, 2 H, 2 × Ar-CH), 6.92–6.88 (m, 2 H, 2 × Ar-CH), 5.14 (s, 2 H, CH_2Ph), 4.62 (d, *J* = 8.4 Hz, 2 H, C*H*HNC*H*H), 4.53 (d, *J* = 8.4 Hz, 2 H, CH*H*NCH*H*), 3.82 (s, 3 H, OCH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.6 (Ar-C_q-OCH_3), 156.4 (C=O), 152.1 (Ar-C_q-OTf), 148.1 (Ar-C_q-C_q), 146.9 (Ar-C_q-C_q), 136.6 (Ar-C_q-CH_2), 128.5 (2 × Ar-CH), 128.4 (2 × Ar-CH), 128.2 (Ar-CH), 128.1 (2 × Ar-CH), 127.7 (2 × Ar-CH), 125.1 (CF_3)[i], 121.4 (2 × Ar-CH), 114.2 (2 × Ar-CH), 67.0 (CH_2Ph), 62.8 (CH_2NCH_2), 55.3 (OCH_3), 45.1 (C_q); ^{19}F{^{1}H} NMR (377 MHz, $CDCl_3$) δ –72.8; HRMS (+ESI) *m*/*z* calcd for $C_{25}H_{23}NO_6SF_3$ [M+H]: 522.1198, Found: 522.1200.



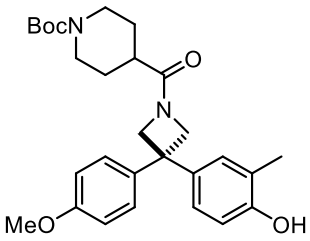
Benzyl 3-(4-methoxyphenyl)-3-phenylazetidine-1-carboxylate (132)
Based on conditions developed by Ortar,[126] triethylamine (41.8 µL, 0.30 mmol) then formic acid (7.50 µL, 0.20 mmol) were added to a solution of triflate **S3** (54.7 mg, 0.10 mmol), $Pd(OAc)_2$ (1.1 mg, 0.005 mmol), 1,1'-bis(diphenylphosphino)ferrocene (2.8 mg, 0.005 mmol) in DMF (1.0 mL). The reaction mixture was stirred at 60 °C for 2 h then sat. aq. NaCl (15 mL) was added followed by Et_2O (15 mL). The layers were separated and the aqueous portion was extracted with Et_2O (3 × 15 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash chromatography (20% Et_2O/pentane) afforded azetidine **132** (38.7 mg, 100%) as a colourless oil. R_f = 0.39 (30% Et_2O/pentane); IR (film)/cm^{-1} 2956, 2887, 1702 (C=O), 1610, 1511, 1495, 1446, 1408, 1351, 1295, 1247, 1180, 1158, 1120, 1082, 1027, 1004, 960, 921, 829, 809, 758, 726, 696; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42–7.32 (m, 7 H, 7 × Ar-CH), 7.29–7.25 (m, 1 H, Ar-CH), 7.23–7.20 (m, 2 H, 2 × Ar-CH), 7.16–7.12 (m, 2 H, 2 × Ar-CH), 6.91–6.87 (m, 2 H, 2 × Ar-CH), 5.16 (s, 2 H, CH_2Ph), 4.66–4.60 (m, 4 H, CH_2NCH_2), 3.81 (s, 3 H, OCH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.3 (Ar-C_q-OCH_3), 156.4 (C=O), 146.0 (Ar-C_q-C_q), 137.9 (Ar-C_q-C_q), 136.5 (Ar-C_q-CH_2), 128.5 (2 × Ar-CH), 128.4 (2 × Ar-CH), 128.01 (Ar-CH), 127.96 (2 × Ar-CH), 127.6 (2 × Ar-CH), 126.6 (Ar-CH), 126.5 (2 × Ar-CH), 113.9 (2 × Ar-CH), 66.8 (CH_2Ph), 63.2 (CH_2NCH_2), 55.2 (OCH_3), 45.5 (C_q); HRMS (+ESI) *m*/*z* calcd for $C_{24}H_{24}NO_3$ [M+H]: 374.1756, Found: 374.1759.

[i] The coupling was not observed due to low signal



4-(3-(4-Methoxyphenyl)azetidin-3-yl)-2-methylphenol (133)

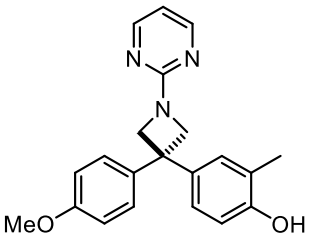
Palladium on carbon (10 mol% w/w, 150 mg) was added to a solution of azetidine **84** (605 mg, 1.50 mmol) in ethanol (7.5 mL). The reaction mixture was stirred under atmosphere of hydrogen at 25 °C for 21 h. The reaction mixture was filtered through celite, washed through with ethanol and then concentrated under reduced pressure to afford azetidine **133** (300 mg, 74%) as a yellow solid. mp = 163–170 °C; IR (film)/cm^{-1} 3293 (br, NH), 2954, 2572 (br, OH), 1606, 1510, 1459, 1275, 1248, 1181, 1130, 1032, 986, 824, 812, 771, 732; ^{1}H NMR (400 MHz, MeOD-*d*$_4$) δ 7.19–7.15 (m, 2 H, 2 × Ar-CH), 6.96 (d, *J* = 1.6 Hz, 1 H, Ar-CH), 6.90–6.87 (m, 1 H, Ar-CH), 6.85–6.82 (m, 2 H, 2 × Ar-CH), 6.67 (d, *J* = 8.3 Hz, 1 H, Ar-CH), 4.20–4.15 (m, 4 H, C*H*$_2$NC*H*$_2$), 3.73 (s, 3 H, OCH_3), 2.14 (s, 3 H, CH_3); ^{13}C NMR (101 MHz, MeOD-*d*$_4$) δ 159.3 (Ar-*C*$_q$-OCH_3), 154.8 (Ar-*C*$_q$-OH), 141.4 (Ar-*C*$_q$-C$_q$), 139.8 (Ar-*C*$_q$-C$_q$), 129.7 (Ar-CH), 128.5 (Ar-*C*$_q$-CH_3), 128.3 (2 × Ar-CH), 125.5 (Ar-CH), 115.4 (Ar-CH), 114.7 (2 × Ar-CH), 60.3 (*C*H_2N*C*H_2), 55.7 (OCH_3), 50.9 (C_q), 16.4 (CH_3); HRMS (+ESI) *m*/*z* calcd for $C_{17}H_{20}NO_2$ [M+H]: 270.1494, Found: 270.1497.



***tert*-Butyl 4-(3-(4-hydroxy-3-methylphenyl)-3-(4-methoxyphenyl)azetidine-1-carbonyl)piperidine-1-carboxylate (134)**

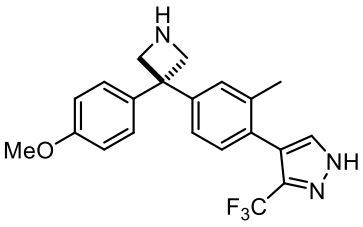
DMAP (91.6 mg, 0.75 mmol) followed by EDC.HCl (57.5 mg, 0.30 mmol) was added to a solution of azetidine **133** (67.3 mg, 0.25 mmol) and boc-Inp-OH (57.3 mg, 0.25 mmol) in CH_2Cl_2 (1.25 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 10 min and then at 25 °C for 19 h. The reaction mixture was then quenched with sat. aq. $NaHCO_3$ (20 mL). The aqueous portion was extracted with EtOAc (3 × 20 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash chromatography (60% EtOAc/pentane) afforded azetidine **134** (112 mg, 96%) as a white solid. R_f = 0.13 (50% EtOAc/pentane); mp = 210–213 °C; IR (film)/cm^{-1} 3185 (OH), 2952, 1694 (C=O), 1606 (C=O), 1510, 1492, 1417, 1364, 1251, 1234, 1169, 1120, 1034, 977, 850, 810, 769, 727, 612, 543, 516; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11–7.07 (m, 2 H, 2 × Ar-CH), 6.89–6.82 (m, 4 H, 4 × Ar-CH), 6.76 (d, *J* = 8.3 Hz, 1 H, Ar-CH), 4.72–4.67 (m, 2 H, C*H*$_2$NCH_2), 4.60–4.54 (m, 2 H, CH_2NC*H*$_2$), 4.16–4.07 (m, 2 H, CH_2C*H*HNC*H*HCH_2), 3.80 (s, 3 H, OCH_3), 2.76 (br, s, 2 H, CH_2CH*H*NCH*H*CH_2), 2.42–2.35 (m, 1 H, COC*H*), 2.21 (s, 3 H, CH_3), 1.74–1.69 (m, 4 H, C*H*$_2$$CH_2NCH_2$C*H*$_2$), 1.46 (s, 9 H, 3 × CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.6 (C=O), 158.2 (Ar-*C*$_q$-OCH_3), 154.7 (C=O), 153.5 (Ar-*C*$_q$-OH), 138.1 (Ar-*C*$_q$-C$_q$), 136.9 (Ar-*C*$_q$-C$_q$), 129.0 (Ar-CH), 127.5 (2 × Ar-CH), 124.8 (Ar-CH), 124.5 (Ar-*C*$_q$-CH_3), 114.8 (Ar-CH), 113.9 (2 × Ar-CH), 79.7 (*C*$_q$(CH_3)$_3$), 64.4 (*C*H_2NCH_2), 61.9

(CH_2NCH_2), 55.3 (OCH_3), 44.4 (C_q), 43.0 ($CH_2CH_2NCH_2CH_2$), 38.0 (CO*C*H), 28.4 (3 × CH_3), 27.64 ($CH_2CH_2NCH_2CH_2$), 27.58 ($CH_2CH_2NCH_2CH_2$), 16.1 (CH_3); HRMS (+ESI) *m*/*z* calcd for $C_{28}H_{37}N_2O_5$ [M+H]: 481.2702, Found: 481.2698.



4-(3-(4-Methoxyphenyl)-1-(pyrimidin-2-yl)azetidin-3-yl)-2-methylphenol (135)

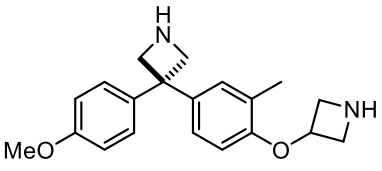
A solution of azetidine **133** (67.3 mg, 0.25 mmol), 2-chloropyrimidine (34.4 mg, 0.30 mmol) and KF (29.1 mg, 0.50 mmol) in water/MeCN (3:1, 1.0 mL) was stirred at 100 °C for 20 h. The reaction mixture was then cooled to rt and water (20 mL) was added. The aqueous portion was extracted with EtOAc (3 × 20 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash chromatography (70% Et_2O/pentane) afforded azetidine **135** (77.8 mg, 90%) as a white solid. R_f = 0.20 (50% EtOAc/pentane); mp = 206–208 °C; IR (film)/cm^{-1} 2949 (OH), 1583, 1555, 1491, 1470, 1458, 1412, 1376, 1288, 1271, 1244, 1214, 1180, 1152, 1130, 1116, 1031, 979, 837, 823, 810, 800, 768, 734, 721, 640, 608, 568, 550, 539, 526; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (d, *J* = 4.9 Hz, 2 H, 2 × $Ar_{(pyrimidine)}$-CH), 7.17–7.14 (m, 2 H, 2 × Ar-CH), 7.01 (dd, *J* = 8.3, 2.5 Hz, 1 H, Ar-CH), 6.90–6.85 (m, 3 H, 3 × Ar-CH), 6.72 (d, *J* = 8.3 Hz, 1 H, Ar-CH), 6.60 (t, *J* = 4.9 Hz, 1 H, $Ar_{(pyrimidine)}$-CH), 4.73–4.67 (m, 4 H, C*H*$_2$NC*H*$_2$), 3.80 (s, 3 H, OCH_3), 2.21 (s, 3 H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.3 (N-$C_{q(pyrimidine)}$), 158.0 (Ar-C_q-OCH_3), 157.9 (2 × $Ar_{(pyrimidine)}$-CH), 153.1 (Ar-C_q-OH), 138.6 (Ar-C_q-C_q), 138.2 (Ar-C_q-C_q), 129.3 (Ar-CH), 127.8 (2 × Ar-CH), 125.1 (Ar-CH), 124.1 (Ar-C_q-CH_3), 114.9 (Ar-CH), 113.8 (2 × Ar-CH), 110.5 ($Ar_{(pyrimidine)}$-CH), 64.4 (CH_2NCH_2), 55.3 (OCH_3), 45.0 (C_q), 16.1 (CH_3); HRMS (+ESI) *m*/*z* calcd for $C_{21}H_{22}N_3O_2$ [M+H]: 348.1712, Found: 348.1728.



4-(4-(3-(4-Methoxyphenyl)azetidin-3-yl)-2-methylphenyl)-3-(trifluoromethyl)-1*H*-pyrazole (136)

Palladium on carbon (10 mol% w/w, 23.5 mg) was added to a solution of azetidine **131** (56.1 mg, 0.11 mmol) in ethanol (1.0 mL). The reaction mixture was stirred under atmosphere of hydrogen at 25 °C for 24 h. The reaction mixture was filtered through celite, washed through with ethanol and then concentrated under reduced pressure. Purification by SCX column afforded impure azetidine **136** (36.0 mg, 86%, containing 10% impurity). R_f = 0.19 (10% MeOH/CH_2Cl_2); IR (film)/cm^{-1} 3248 (NH), 2953, 2497, 1986, 1612, 1504, 1514, 1479, 1463, 1362, 1293, 1249, 1180, 1162, 1126, 1027, 981, 929, 907, 810, 782, 747, 728, 716, 659; ^{1}H NMR (400 MHz, MeOD-d_4) δ 7.65 (s, 1 H, N-Ar-CH), 7.25–7.21 (m, 3 H, 3 × Ar-CH), 7.13–

7.12 (m, 2 H, 2 × Ar-CH), 6.88–6.85 (m, 2 H, 2 × Ar-CH), 4.88 (s, 3 H, OCH_3), 4.26 (q, *J* = 8.3 Hz, 4 H, CH_2NCH_2), 3.74–3.73 (m, 4 H, CH_3, NH); ^{13}C NMR (101 MHz, MeOD-*d*$_4$) δ 159.5 (Ar-C_q-OCH_3), 149.1 (Ar-C_q-$C_{q(pyrazole)}$), 140.8 (Ar-C_q-C_q), 138.5 (Ar-C_q-C_q), 132.1 (Ar-CH), 131.6 (br, N-Ar-CH), 129.6 (Ar-C_q-CH_3), 128.7 (Ar-CH), 128.3 (2 × Ar-CH), 124.5 (CF_3)[j], 124.3 (Ar-CH), 120.8 (Ar-C_q-$C_{q(pyrazole)}$), 114.9 (2 × Ar-CH), 60.1 (CH_2NCH_2), 55.7 (OCH_3), 51.4 (C_q), 20.5 (CH_3)[k]; $^{19}F\{^1H\}$ NMR (377 MHz, $CDCl_3$) δ –61.4, HRMS (+ESI) m/z calcd for $C_{21}H_{21}N_3OF_3$ [M+H]: 388.1637, Found: 388.1633.

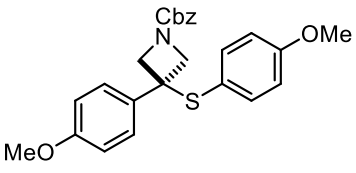


3-(4-(Azetidin-3-yloxy)-3-methylphenyl)-3-(4-methoxyphenyl)azetidine (137)

Palladium on carbon (10 mol% w/w, 17.5 mg) was added to a solution of azetidine **131** (61.3 mg, 0.10 mmol) in ethanol (1.0 mL). The reaction mixture was stirred under atmosphere of hydrogen at 25 °C for 24 h. The reaction mixture was filtered through celite, washed through with ethanol and then concentrated under reduced pressure. Purification by SCX column afforded impure azetidine **137** (28.2 mg, 87%, containing 10% impurity). R_f = 0.08 (10% MeOH/CH_2Cl_2); IR (film)/cm^{-1} 3385 (br, NH), 2952, 1609, 1504, 1399, 1295, 1244, 1180, 1137, 1031, 809; ^1H NMR (400 MHz, MeOD-*d*$_4$) δ 7.19–7.16 (m, 2 H, 2 × Ar-CH), 7.07 (d, *J* = 2.4 Hz, 1 H, Ar-CH), 7.00 (dd, *J* = 8.4, 2.5 Hz, 1 H, Ar-CH), 6.85–6.83 (m, 2 H, 2 × Ar-CH), 6.49 (d, *J* = 8.4 Hz, 1 H, Ar-CH), 4.97 (dt, *J* = 12.0, 5.9 Hz, 1 H, OCH), 4.23 (s, br, 4 H, CH_2NCH_2), 4.23 (s, 3 H, OCH_3), 3.94–3.90 (m, 2 H, CHH(OCH)CHH), 3.72–3.64 (m, 6 H, CHH(OCH)CHH, CH_3, NH); ^{13}C NMR (101 MHz, MeOD-*d*$_4$) δ 159.5 (Ar-C_q-OCH_3), 154.5 (Ar-C_q-OCH), 141.1 (Ar-C_q-C_q), 140.7 (Ar-C_q-C_q), 129.9 (Ar-CH), 128.3 (2 × Ar-CH), 127.9 (Ar-C_q-CH_3), 125.6 (Ar-CH), 114.9 (2 × Ar-CH), 112.2 (Ar-CH), 71.5 (OCH), 60.0 (CH_2NCH_2), 55.7 (OCH_3), 54.9 (CH_2NCH_2), 50.7 (C_q), 16.5 (CH_3); HRMS (+ESI) m/z calcd for $C_{20}H_{25}N_2O_2$ [M+H]: 325.1916, Found: 325.1917.

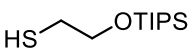
[j] The coupling was not observed due to low signal
[k] $Ar_{(pyrazole)}$-C_q-CF_3 was not observed

8.2.4 Synthesis of 3-Arylsulfanyl Azetidines and Derivatives (Part 4.2)



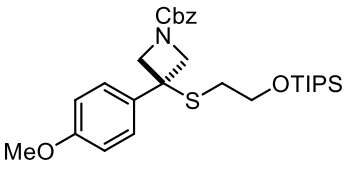
Benzyl 3-(4-methoxyphenyl)-3-((4-methoxyphenyl)thio)azetidine-1-carboxylate (150)

Azetidinol **83** (156 mg, 0.50 mmol) was added to a solution of $FeCl_3$ (6.1 mg, 0.0375 mmol) and methoxythiophenol (123 µL, 1.00 mmol) in toluene (1.0 mL). The reaction mixture was stirred at 80 °C for 15 h, then quenched with sat. aq. $NaHCO_3$ (20 mL). The layers were separated and the aqueous portion was extracted with CH_2Cl_2 (3 × 20 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography (20% Et_2O/pentane) afforded azetidine **150** (180 mg, 83%). R_f = 0.14 (20% Et_2O/pentane); mp = 122–123 °C; IR (film)/cm^{-1} 3027, 2938, 2841, 1707 (C=O), 1587, 1454, 1421, 1371, 1247, 1131, 1029, 823, 760, 738, 694; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42–7.30 (m, 5 H, 5 × Ar-CH), 7.14–7.11 (m, 2 H, 2 × Ar-CH), 6.90–6.86 (m, 2 H, 2 × Ar-CH), 6.82–6.80 (m, 2 H, 2 × Ar-CH), 6.78–6.75 (m, 2 H, 2 × Ar-CH), 5.07 (s, 2 H, CH_2Ph), 4.46 (d, *J* = 9.0 Hz, 2 H, C*H*HNC*H*H), 4.39 (d, *J* = 9.0 Hz, 2 H, CH*H*NCH*H*), 3.80 (s, 3 H, OCH_3), 3.79 (s, 3 H, OCH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.7 (Ar-C_q-OCH_3), 158.5 (Ar-C_q-OCH_3), 156.2 (C=O), 137.9 (2 × Ar-CH), 136.4 (Ar-C_q-CH_2), 134.7 (Ar-C_q-C_q), 128.4 (2 × Ar-CH), 128.01 (Ar-CH), 127.95 (2 × Ar-CH), 127.8 (2 × Ar-CH), 122.1 (S-C_q-Ar), 114.2 (2 × Ar-CH), 113.5 (2 × Ar-CH), 66.8 (CH_2Ph), 61.8 and 61.4 (CH_2NCH_2), 55.3 (OCH_3), 55.2 (OCH_3), 50.3 (C_q); HRMS (+ESI) *m*/*z* calcd for $C_{25}H_{26}NO_4S$ [M+H]: 436.1583, Found: 436.1587.



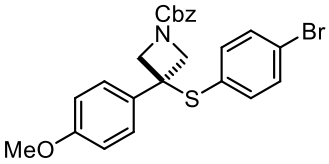
2-((Triisopropylsilyl)oxy)ethane-1-thiol (S4)

Triisopropylsilyl chloride (470 µL, 2.20 mmol) was added to a solution of 2-mercaptoethanol (140 µL, 2.00 mmol) in CH_2Cl_2 (4.0 mL). The reaction mixture was stirred at 40 °C for 4 h, then quenched with water (30 mL). The layers were separated and the aqueous portion was extracted with pentane (3 × 30 mL). The organic extracts were combined, dried over Na_2SO_4, filtered through a plug of silica and concentrated under reduced pressure to afford TIPS-protected thiol **S4** (453 mg, 97%) as a colourless oil. R_f=0.50 (100% pentane); IR (film)/cm^{-1} 2940, 2866, 1461, 1107, 1069, 995, 879, 801, 715, 682; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.82 (t, *J* = 6.4 Hz, 2 H, $SHCH_2CH_2O$), 2.67 (dt, *J* = 8.2, 6.4 Hz, 2 H, $SHCH_2CH_2O$), 1.61 (t, *J* = 8.2 Hz, 1 H, SH), 1.16–1.00 (m, 21 H, 3 × CH, 6 × CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 65.3 ($SHCH_2CH_2O$), 27.5 ($SHCH_2CH_2O$), 18.0 (3 × $CH(CH_3)_2$), 12.0 (3 × $CH(CH_3)_2$); HRMS (–ESI) *m*/*z* calcd for $C_{12}H_{27}O_3SSi^-$ [M-H+HCO_2H]$^-$: 279.1450, Found: 279.1443. Compound previously reported without characterisation data.[243]



Benzyl 3-(4-methoxyphenyl)-3-((2-((triisopropylsilyl)oxy)ethyl)thio)azetidine-1-carboxylate (151)

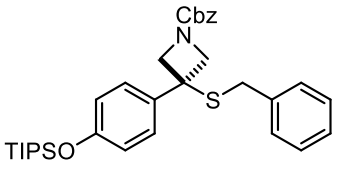
Azetidinol **83** (157 mg, 0.50 mmol) was added to a solution of $FeCl_3$ (6.1 mg, 0.0375 mmol) and thiol **S4** (235 mg, 1.0 mmol) in toluene (1.0 mL). The reaction mixture was stirred at 40 °C for 15 h, then quenched with sat. aq. $NaHCO_3$ (20 mL). The layers were separated and the aqueous portion was extracted with Et_2O (3 × 20 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography (20% Et_2O/pentane) afforded azetidine **151** (117 mg, 44%) as a colourless oil. R_f = 0.18 (20% Et_2O/pentane); IR (film)/cm^{-1} 2940, 2862, 1710 (C=O), 1513, 1463, 1412, 1353, 1297, 1248, 1177, 1114, 1032, 995, 879, 831, 730, 678; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37–7.31 (m, 5 H, 5 × Ar-CH), 7.19–7.15 (m, 2 H, 2 × Ar-CH), 6.90–6.86 (m, 2 H, 2 × Ar-CH), 5.11 (s, 2 H, CH_2Ph), 4.53 (d, *J* = 8.8 Hz, 2 H, C*H*HNC*H*H), 4.30 (d, *J* = 8.8 Hz, 2 H, CH*H*NCH*H*), 3.81 (s, 3 H, OCH_3), 3.56 (t, *J* = 7.2 Hz, 2 H, OC*H*$_2$CH$_2$S), 2.53 (t, *J* = 7.2 Hz, 2 H, OCH$_2$C*H*$_2$S), 1.04–0.97 (m, 21 H, 3 × CH, 6 × CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.7 (Ar-*C*$_q$-OCH_3), 156.2 (C=O), 136.4 (Ar-*C*$_q$-CH_2), 134.7 (Ar-*C*$_q$-C$_q$), 128.5 (2 × Ar-CH), 128.1 (Ar-CH), 128.0 (2 × Ar-CH), 127.6 (2 × Ar-CH), 113.9 (2 × Ar-CH), 66.9 (CH_2Ph), 62.6 (*C*H$_2$NCH$_2$), 55.3 (OCH_3), 47.0 (C$_q$), 32.9 (OCH$_2$CH$_2$S), 17.9 (3 × *C*H(CH$_3$)$_2$), 17.7 (OCH$_2$*C*H$_2$S), 11.9 (3 × CH(*C*H$_3$)$_2$); HRMS (+ESI) *m*/*z* calcd for $C_{29}H_{44}NO_4SSi$ [M+H]: 530.2760, Found: 530.2770.



Benzyl 3-((4-bromophenyl)thio)-3-(4-methoxyphenyl)azetidine-1-carboxylate (142)

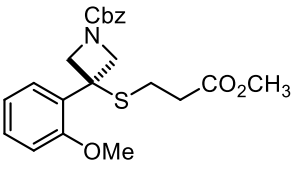
Azetidinol **83** (940 mg, 3.00 mmol) was added to a solution of $FeCl_3$ (36.5 mg, 0.225 mmol) and 4-bromothiophenol (1.10 g, 6.00 mmol) in toluene (6.0 mL). The reaction mixture was stirred at 40 °C for 15 h, then quenched with sat. aq. $NaHCO_3$ (40 mL). The layers were separated and the aqueous portion was extracted with CH_2Cl_2 (3 × 40 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography (20% Et_2O/pentane) afforded azetidine **142** (1.10 g, 76%) as a white solid. R_f = 0.23 (20% Et_2O/pentane); mp = 121–122 °C; IR (film)/cm^{-1} 2952, 2885, 1710 (C=O), 1610, 1513, 1415, 1354, 1250, 1180, 1129, 1009, 819, 698; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39–7.31 (m, 7 H, 7 × Ar-CH), 7.00 (d, *J* = 8.1 Hz, 2 H, 2 × Ar-CH), 6.93 (d, *J* = 8.4 Hz, 2 H, 2 × Ar-CH), 6.82 (d, *J* = 8.4 Hz, 2 H, 2 × Ar-CH), 5.09 (s, 2 H, CH_2Ph), 4.48 (d, *J* = 9.0 Hz, 2 H, C*H*HNC*H*H), 4.37 (d, *J* = 9.0 Hz, 2 H, CH*H*NCH*H*), 3.81 (s, 3 H, OCH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.8 (Ar-*C*$_q$-OCH_3), 156.2 (C=O), 137.0 (2 × Ar-CH), 136.4 (Ar-*C*$_q$-CH_2),

134.2 (Ar-C_q-C_q), 131.9 (2 × Ar-CH), 130.7 (S-C_q-Ar), 128.5 (2 × Ar-CH), 128.1 (Ar-CH), 128.0 (2 × Ar-CH), 127.8 (2 × Ar-CH), 123.9 (Ar-C_q-Br), 113.7 (2 × Ar-CH), 66.9 (CH_2Ph), 61.6 and 61.5 (CH_2NCH_2), 55.3 (OCH_3), 50.4 (C_q); HRMS (+ESI) *m*/*z* calcd for $C_{24}H_{23}BrNO_3S$ [M+H]: 484.0582, Found: 484.0605.



Benzyl 3-(benzylthio)-3-(4-((triisopropylsilyl)oxy)phenyl)azetidine-1-carboxylate (153)

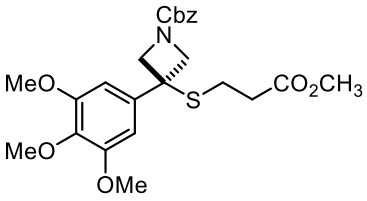
$FeCl_3$ (6.1 mg, 0.0375 mmol) was added to a solution of azetidinol **106** (228 mg, 0.50 mmol) and methyl 3-mercaptoproprionate (117 µL, 1.00 mmol) in toluene (1.0 mL). The reaction mixture was stirred at 40 °C for 15 h, then quenched with sat. aq. $NaHCO_3$ (20 mL). The layers were separated and the aqueous portion was extracted with CH_2Cl_2 (3 × 20 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography (10% Et_2O/pentane) afforded azetidine **153** (249 mg, 86%) as a colourless oil. R_f = 0.15 (10% Et_2O/pentane); IR (film)/cm^{-1} 2944, 2866, 1710 (C=O), 1602, 1509, 1453, 1408, 1350, 1259, 1177, 1125, 998, 909, 834, 752, 678; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38–7.32 (m, 5 H, 5 × Ar-CH), 7.29–7.22 (m, 3 H, 3 × Ar-CH), 7.19–7.17 (m, 2 H, 2 × Ar-CH), 7.14–7.11 (m, 2 H, 2 × Ar-CH), 6.92–6.89 (m, 2 H, 2 × Ar-CH), 5.10 (s, 2 H, CH_2Ph), 4.47 (d, *J* = 8.9 Hz, 2 H, C*H*HNC*H*H), 4.22 (d, *J* = 8.9 Hz, 2 H, CH*H*NCH*H*), 3.50 (s, 2 H, SCH_2Ph), 1.32–1.23 (m, 3 H, 3 × CH), 1.12 (d, *J* = 7.2 Hz, 18 H, 6 × CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.5 (Ar-C_q-OTIPS), 155.3 (C=O), 137.0 (Ar-C_q-CH_2), 136.4 (Ar-C_q-CH_2), 134.4 (Ar-C_q-C_q), 128.9 (2 × Ar-CH), 128.52 (2 × Ar-CH), 128.46 (2 × Ar-CH), 128.1 (Ar-CH), 128.0 (2 × Ar-CH), 127.7 (2 × Ar-CH), 127.2 (Ar-CH), 119.9 (2 × Ar-CH), 66.8 (CH_2Ph), 62.5 (CH_2NCH_2), 47.7 (C_q), 35.2 (SCH_2Ph), 17.9 (3 × $CH(CH_3)_2$), 12.6 (3 × $CH(CH_3)_2$); HRMS (+ESI) *m*/*z* calcd for $C_{33}H_{44}NO_3SSi$ [M+H]: 562.2811, Found: 562.2809.



Benzyl 3-((3-methoxy-3-oxopropyl)thio)-3-(2-methoxyphenyl)azetidine-1-carboxylate (155)

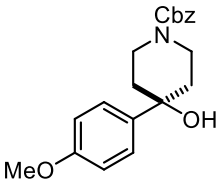
Azetidinol **111** (78.3 mg, 0.25 mmol) was added to a solution of $FeCl_3$ (3.1 mg, 0.019 mmol) and methyl 3-mercaptoproprionate (55.2 µL, 0.50 mmol) in toluene (0.5 mL). The reaction mixture was stirred at 40 °C for 15 h, then quenched with sat. aq. $NaHCO_3$ (15 mL). The layers were separated and the aqueous portion was extracted with CH_2Cl_2 (3 × 15 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography (40% Et_2O/pentane) afforded azetidine **155** (96.8 mg, 92%) as a yellow oil. R_f = 0.23 (40% Et_2O/pentane); IR (film)/cm^{-1} 2952, 1703 (C=O), 1490, 1408, 1349, 1248, 1174,

1125, 1025, 995, 752, 697; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37–7.26 (m, 6 H, 6 × Ar-CH), 7.00–6.93 (m, 2 H, 2 × Ar-CH), 6.90 (d, *J* = 8.2 Hz, 1 H, Ar-CH), 5.11 (s, 2 H, CH_2Ph), 4.57 (d, *J* = 9.3 Hz, 2 H, C*H*HNC*H*H), 4.28 (d, *J* = 9.3 Hz, 2 H, CH*H*NCH*H*), 3.84 (s, 3 H, OCH_3), 3.64 (s, 3 H, CO_2CH_3), 2.66 (t, *J* = 7.6 Hz, 2 H, SC$H_2$$CH_2CO_2Me$), 2.35 (t, *J* = 7.6 Hz, 2 H, $SCH_2CH_2CO_2Me$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.1 (CO_2CH_3), 156.5 (C=O, Ar-C_q-OCH_3), 136.5 (Ar-C_q-CH_2), 129.6 (Ar-C_q-C_q), 129.1 (Ar-CH), 128.4 (2 × Ar-CH), 128.03 (Ar-CH), 128.02 (2 × Ar-CH), 127.2 (Ar-CH), 120.3 (Ar-CH), 111.5 (Ar-CH), 66.8 (CH_2Ph), 62.2 (br, CH_2NCH_2), 55.4 (OCH_3), 51.7 (CO_2CH_3), 46.4 (C_q), 33.8 ($SCH_2CH_2CO_2CH_3$), 25.1 ($SCH_2CH_2CO_2CH_3$); HRMS (+ESI) *m*/*z* calcd for $C_{22}H_{26}NO_5S$ [M+H]: 416.1532, Found: 416.1533.



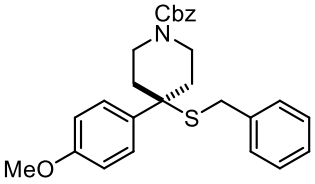
Benzyl 3-((3-methoxy-3-oxopropyl)thio)-3-(3,4,5-trimethoxyphenyl)azetidine-1-carboxylate (156)

Azetidinol **109** (93.4 mg, 0.25 mmol) was added to a solution of $FeCl_3$ (3.1 mg, 0.019 mmol) and methyl 3-mercaptoproprionate (55.2 µL, 0.50 mmol) in toluene (0.5 mL). The reaction mixture was stirred at 40 °C for 15 h, then quenched with sat. aq. $NaHCO_3$ (15 mL). The layers were separated and the aqueous portion was extracted with CH_2Cl_2 (3 × 15 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography (70% Et_2O/pentane) afforded azetidine **156** (80 mg, 67%) as a white solid. R_f = 0.40 (80% Et_2O/pentane); mp = 79–83 °C; IR (film)/cm^{-1} 2948, 1707 (C=O), 1587, 1505, 1453, 1408, 1353, 1241, 1215, 1174, 1121, 1002, 764, 697; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.32 (m, 5 H, 5 × Ar-CH), 6.44 (s, 2 H, 2 × Ar-CH), 5.11 (s, 2 H, CH_2Ph), 4.55 (d, *J* = 8.8 Hz, 2 H, C*H*HNC*H*H), 4.30 (d, *J* = 8.8 Hz, 2 H, CH*H*NCH*H*), 3.86–3.85 (m, 9 H, 3 × OCH_3), 3.66 (s, 3 H, CO_2CH_3), 2.65 (t, *J* = 7.4 Hz, 2 H, SC$H_2$$CH_2CO_2CH_3$), 2.39 (t, *J* = 7.4 Hz, 2 H, $SCH_2CH_2CO_2CH_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.9 (CO_2CH_3), 156.2 (C=O), 153.2 (3 × Ar-C_q-OCH_3), 137.8 (Ar-C_q-C_q), 136.3 (Ar-C_q-CH_2), 128.5 (2 × Ar-CH), 128.2 (Ar-CH), 128.1 (2 × Ar-CH), 103.7 (2 × Ar-CH), 67.0 (CH_2Ph), 62.8 (br, CH_2NCH_2), 60.9 (OCH_3), 56.3 (2 × OCH_3), 51.9 (CO_2CH_3), 48.0 (C_q), 33.7 ($SCH_2CH_2CO_2CH_3$), 25.4 ($SCH_2CH_2CO_2CH_3$); HRMS (+ESI) *m*/*z* calcd for $C_{24}H_{30}NO_7S$ [M+H]: 476.1743, Found: 476.1734.



Benzyl 4-hydroxy-4-(4-methoxyphenyl)piperidine-1-carboxylate (S5)

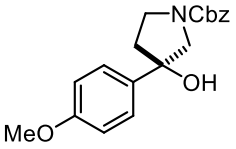
*i*PrMgCl•LiCl (1.05 M in THF, 3.20 mL, 3.40 mmol) was added dropwise over 5 min to a solution of 4-iodoanisole (843 mg, 3.60 mmol) in THF (2.8 mL) at 0 °C. The reaction mixture was stirred at 25 °C for 3 h. A solution of Benzyl 4-oxopiperidine-1-carboxylate (700 mg, 3.00 mmol) in THF (4.7 mL) was added dropwise to the reaction mixture at 0 °C. Following a further 24 h at 25 °C the reaction mixture was cooled to 0 °C then quenched with sat. aq. NH_4Cl (40 mL). The aqueous portion was extracted with Et_2O (3 × 40 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash chromatography (40% to 60% Et_2O/pentane) afforded piperidin-4-ol **S5** (449 mg, 45%) as a white solid. R_f = 0.34 (30% EtOAc/hexane); mp = 103−104 °C [Lit. mp = 102−104 °C][244]; IR (film)/cm^{-1} 3447 (OH), 2956, 1669 (C=O), 1513, 1471, 1427, 1275, 1246, 1216, 1176, 1072, 1022, 923, 825, 730, 694; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41–7.33 (m, 7 H, 7 × Ar-CH), 6.92–6.88 (m, 2 H, 2 × Ar-CH), 5.15 (s, 2 H, CH_2Ph), 4.10 (br s, 2 H, C*H*HNC*H*H), 3.81 (s, 3 H, OCH_3), 3.34 (br s, 2 H, CH*H*NCH*H*), 1.98 (br s, 2 H, C*H*HCC*H*H), 1.76 (br d, *J* = 13.2 Hz, 2 H, CH*H*CCH*H*), 1.68 (s, 1 H, OH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.7 (Ar-C_q-OCH_3), 155.3 (C=O), 140.0 (Ar-C_q), 136.8 (Ar-C_q), 128.5 (2 × Ar-CH), 127.9 (Ar-CH), 127.9 (2 × Ar-CH), 125.6 (2 × Ar-CH), 113.7 (2 × Ar-CH), 71.0 (C_q), 67.1 (CH_2Ph), 55.3 (OCH_3), 40.2 (2 × NCH_2), 38.0 (2 × NCH_2CH_2); HRMS (+ESI) *m*/*z* calcd for $C_{20}H_{23}NO_4$ [M+H]: 324.1594, Found: 324.1596.



Benzyl 4-(benzylthio)-4-(4-methoxyphenyl)piperidine-1-carboxylate (158)

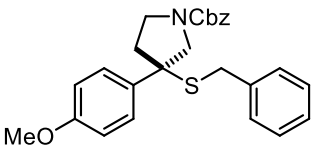
Benzyl 4-hydroxy-4-(4-methoxyphenyl)piperidine-1-carboxylate **S5** (171 mg, 0.50 mmol) was added to a solution of $FeCl_3$ (6.1 mg, 0.0375 mmol) and benzylmercaptan (120 µL, 1.00 mmol) in toluene (1.0 mL). The reaction mixture was stirred at 40 °C for 30 min, then quenched with sat. aq. $NaHCO_3$ (20 mL). The layers were separated and the aqueous portion was extracted with Et_2O (3 × 20 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography (20% Et_2O/pentane) afforded piperidine **158** (214 mg, 95%) as a colourless oil. R_f = 0.19 (20% Et_2O/hexane); IR (film)/cm^{-1} 2937, 1692 (C=O), 1509, 1423, 1349, 1278, 1233, 1177, 1110, 1069, 1021, 805, 760, 693; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43–7.38 (m, 2 H, 2 × Ar-CH), 7.40–7.28 (m, 5 H, 5 × Ar-CH), 7.27–7.13 (m, 3 H, 3 × Ar-CH), 7.12–7.07 (m, 2 H, 2 × Ar-CH), 6.95–6.89 (m, 2 H, 2 × Ar-CH), 5.13 (d, *J* = 1.6 Hz, 2 H, CH_2Ph), 3.85 (s, 3 H, OCH_3), 3.82–3.75 (m, 2 H, 2 × NC*H*HCH_2), 3.62–3.55 (m, 2 H, 2 × NCH*H*CH_2), 3.25 (d, *J* = 3.9 Hz, 2 H, SCH_2Ph), 2.07 (br s, 4 H, 2 × NCH_2CH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.3 (Ar-C_q-OCH_3), 155.2 (C=O),

137.8 (Ar-C_q-C_q), 136.8 (Ar-C_q-CH_2), 136.3 (Ar-C_q-CH_2), 128.8 (2 × Ar-CH), 128.5 (2 × Ar-CH), 128.3 (2 × Ar-CH), 127.9 (Ar-CH), 127.82 (2 × Ar-CH), 127.79 (2 × Ar-CH), 126.8 (Ar-CH), 113.6 (2 × Ar-CH), 55.3 (CH_2Ph), 51.0 (C_q), 40.5 (2 × NCH_2), 36.3 and 35.9 (2 × NCH_2CH_2), 33.3 (SCH_2Ph); HRMS (+ESI) *m*/*z* calcd for $C_{27}H_{29}NO_3SNa^+$ $[M+Na]^+$: 470.1766, Found: 470.1754.



Benzyl 3-hydroxy-3-(4-methoxyphenyl)pyrrolidine-1-carboxylate (S6)

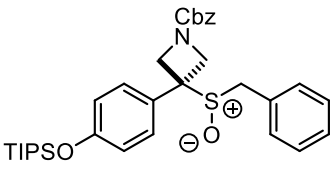
*n*BuLi (2.40 M in hexanes, 5.42 mL, 13.0 mmol) was added dropwise over 10 min to a solution of 4-bromoanisole (1.63 mL, 13.0 mmol) in THF (35 mL) at –78 ºC. The reaction mixture was stirred at –78 ºC for a further 30 min. A solution of benzyl 3-oxopyrrolidine-1-carboxylate (2.19 g, 10.0 mmol) in THF (5.0 mL) was added dropwise over 15 min to the reaction mixture. Following a further 15 min at –78 ºC the reaction mixture was warmed to rt, stirred for 1 h and then quenched with water (40 mL). The layers were separated and the aqueous portion was extracted with Et_2O (3 × 30 mL). The organic layers were combined, dried over Na_2SO_4 and concentrated under reduced pressure. Purification by flash chromatography (10% to 20% Et_2O/CH_2Cl_2) afforded pyrrolidinol **S6** (1.58 g, 48%) as a brown solid. R_f = 0.28 (20% Et_2O/CH_2Cl_2); mp = 94–96 ºC; IR (film)/cm^{-1} 3418 (br, OH), 2895, 1677 (C=O), 1514, 1423, 1360, 1249, 1179, 1104, 1132, 831, 698; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42–7.28 (m, 7 H, 7 × Ar-CH), 6.93–9.87 (m, 2 H, 2 × Ar-CH), 5.30–5.08 (m, 2 H, CH_2Ph), 3.87–3.58 (m, 7 H, OCH_3 and 2 × NCH_2), 2.40–2.14 (m, 3 H, OH and NCH_2CH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.1 (Ar-C_q-OCH_3), 155.1 and 154.9 (C=O), 136.8 and 136.7 (Ar-C_q), 134.73 and 134.65 (Ar-C_q), 128.4 (2 × Ar-CH), 127.9 (2 × Ar-CH), 127.8 (Ar-CH), 126.5 and 126.4 (2 × Ar-CH), 113.9 (2 × Ar-CH), 80.2 and 79.3 (C_q), 66.8 (CH_2Ph), 59.0 (NCH_2C_q), 55.3 (OCH_3), 45.1 and 44.9 (NCH_2), 39.2 and 38.5 (NCH_2CH_2); HRMS (+ESI) *m*/*z* calcd for $C_{19}H_{22}NO_4$ $[M+H]$ 328.1549, Found 328.1549.



Benzyl 3-(benzylthio)-3-(4-methoxyphenyl)pyrrolidine-1-carboxylate (159)

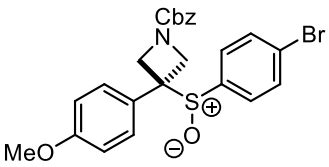
Benzyl 3-hydroxy-3-(4-methoxyphenyl)pyrrolidine-1-carboxylate **S6** (194 mg, 0.59 mmol) was added to a solution of $FeCl_3$ (7.2 mg, 0.044 mmol) and benzylmercaptan (140 µL, 1.19 mmol) in toluene (1.2 mL). The reaction mixture was stirred at 40 °C for 30 min, then quenched with sat. aq. $NaHCO_3$ (20 mL). The layers were separated and the aqueous portion was extracted with Et_2O (3 × 20 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography (20% to 30% Et_2O/pentane) afforded pyrrolidine **159** (240 mg, 93%) as a colourless oil. R_f = 0.11 (20% Et_2O/pentane); IR (film)/cm^{-1} 2948, 1699

(C=O), 1610, 1513, 1449, 1412, 1252, 1211, 1177, 1133, 1107, 1028, 827, 764, 693; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44–7.13 (m, 10 H, 10 × Ar-CH), 7.12–7.10 (m, 2 H, 2 × Ar-CH), 6.94–6.86 (m, 2 H, 2 × Ar-CH), 5.22–5.10 (m, 2 H, CH_2Ph), 4.04 (d, *J* = 11.7 Hz, 0.5 H, NC*H*HC_q), 3.89 (dd, *J* = 11.7 Hz, 0.5 H, NC*H*HC_q), 3.84 (m, 3 H, OCH_3), 3.80 (d, *J* = 11.7 Hz, 0.5 H, NCH*H*C_q), 3.77–3.69 (m, 1.5 H, NCH*H*C_q and NC*H*HCH_2), 3.58–3.48 (m, 1 H, NCH*H*CH_2), 3.47–3.34 (m, 2 H, SCH_2Ph), 2.37–2.23 (m, 2 H, NCH_2CH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.6 (Ar-C_q-OCH_3), 154.9 and 154.7 (C=O), 137.7 (Ar-C_q-CH_2), 137.4 (Ar-C_q-CH_2), 134.4 and 134.3 (Ar-C_q-C_q), 128.9 and 128.8 (2 × Ar-CH), 128.45 and 128.44 (2 × Ar-CH), 128.37 and 128.36 (2 × Ar-CH), 128.1 (2 × Ar-CH), 127.93 and 127.88 (Ar-CH), 127.89 and 127.8 (Ar-CH), 126.9 (2 × Ar-CH), 113.7 (2 × Ar-CH), 66.85 and 66.81 (CH_2Ph), 57.5 and 56.7 (C_q), 57.0 and 56.9 (N*C*H_2C_q), 55.3 (OCH_3), 44.9 and 44.5 (N*C*H_2CH_2), 37.2 and 36.2 (NCH_2CH_2), 34.7 and 34.6 (SCH_2Ph); HRMS (+ESI) *m*/*z* calcd for $C_{26}H_{27}NO_3SNa^+$ $[M+Na]^+$: 456.1609, Found: 456.1600.



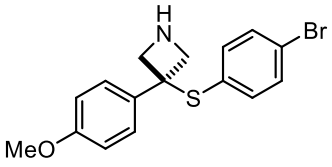
Benzyl 3-(benzylsulfinyl)-3-(4-((triisopropylsilyl)oxy)phenyl)azetidine-1-carboxylate (160)

*m*CPBA (45.3 mg, 0.26 mmol) was added in 3 portions over 30 min to a solution of azetidine **153** (141 mg, 0.25 mmol) in CH_2Cl_2 (2.5 mL). The reaction mixture was stirred at 0 ºC for 2.5 h then 1 M aq. K_2CO_3 (10 mL) and CH_2Cl_2 (15 mL) were added. The phases were separated and the aqueous portion was extracted with CH_2Cl_2 (2 × 15 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography (60% Et_2O/pentane) afforded sulfoxide **160** (122 mg, 84%) as a colourless oil. R_f = 0.06 (50% Et_2O/pentane); IR (film)/cm^{-1} 2944, 2866, 1707 (C=O), 1602, 1509, 1453, 1408, 1353, 1267, 1125, 1073, 905, 838, 752, 693; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37–7.29 (m, 8 H, 8 × Ar-CH), 7.14–7.10 (m, 4 H, 4 × Ar-CH), 7.02–6.98 (m, 2 H, 2 × Ar-CH), 5.11 (s, 2 H, CH_2Ph), 4.83 (d, *J* = 9.4 Hz, 1 H, C*H*HNCHH), 4.62–4.48 (m, 2 H, CH*H*NC*H*H), 4.36 (d, *J* = 9.3 Hz, 1 H, CHHNCH*H*), 3.43 (d, *J* = 12.7 Hz, 1 H, SC*H*HPh), 3.26 (s, 1 H, SCH*H*Ph), 1.34–1.25 (m, 3 H, 3 × CH), 1.13 (d, *J* = 7.4 Hz, 18 H, 6 × CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.6 (Ar-C_q-OTIPS), 155.9 (C=O), 136.1 (Ar-C_q-OCH_2), 130.3 (Ar-C_q-C_q), 130.3 (2 × Ar-CH), 128.8 (2 × Ar-CH), 128.4 (4 × Ar-CH), 128.2 (Ar-CH), 128.1 (Ar-CH), 128.0 (2 × Ar-CH), 126.3 (Ar-C_q-CH_2), 120.6 (2 × Ar-CH), 67.0 (CH_2Ph), 60.0 (C_q), 57.3 and 56.1 (CH_2NCH_2), 53.1 (br, $SOCH_2Ph$), 51.6 (CH_2NCH_2), 17.8 (3 × *C*H(CH_3)$_2$), 12.6 (3 × CH(*C*H_3)$_2$); HRMS (+ESI) *m*/*z* calcd for $C_{33}H_{44}NO_4SSi$ [M+H]: 578.2760, Found: 578.2770.



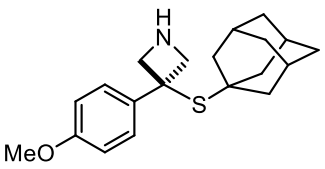
Benzyl 3-((4-bromophenyl)sulfinyl)-3-(4-methoxyphenyl)azetidine-1-carboxylate (161)

*m*CPBA (45.3 mg, 0.26 mmol) was added in 3 portions over 30 min to a solution of azetidine **142** (121 mg, 0.25 mmol) in CH_2Cl_2 (2.5 mL). The reaction mixture was stirred at 0 ºC for 2.5 h then aq. K_2CO_3 (1 M, 10 mL) and CH_2Cl_2 (15 mL) were added. The phases were separated and the aqueous portion was extracted with CH_2Cl_2 (2 × 15 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography (70% Et_2O/pentane) afforded sulfoxide **161** (100 mg, 80%) as a white solid. R_f = 0.30 (70% Et_2O/pentane); mp = 65–70 °C, IR (film)/cm^{-1} 2937, 1707 (C=O), 1610, 1513, 1408, 1353, 1252, 1181, 1129, 1084, 1051, 820, 764, 723; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45–7.42 (m, 2 H, 2 × Ar-CH), 7.37–7.32 (m, 5 H, 5 × Ar-CH), 6.84 (dd, *J* = 8.7, 2.9 Hz, 4 H, 4 × Ar-CH), 6.68 (d, *J* = 8.3 Hz, 2 H, 2 × Ar-CH), 5.11 (s, 2 H, CH_2Ph), 4.76–4.68 (m, 2 H, C*H*$_2$NCHH), 4.34 (d, *J* = 9.3 Hz, 1 H, CH_2NCHH), 4.16 (d, *J* = 9.3 Hz, 1 H, CH_2NCHH), 3.83 (s, 3 H, OCH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.9 (Ar-*C*$_q$-OCH_3), 155.9 (C=O), 137.6 (Ar-*C*$_q$-C_q), 136.2 (Ar-*C*$_q$-CH_2), 131.4 (2 × Ar-CH), 129.2 (2 × Ar-CH), 128.5 (2 × Ar-CH), 128.2 (Ar-CH), 128.1 (2 × Ar-CH), 127.1 (2 × Ar-CH), 126.4 (Ar-C_q-Br), 125.5 (Ar-C_q-SO), 113.9 (2 × Ar-CH), 67.1 (C_q, CH_2Ph), 62.6 (*C*H_2N*C*H_2), 55.4 (OCH_3); HRMS (+ESI) *m*/*z* calcd for $C_{24}H_{23}NO_4SBr$ [M+H]: 500.0531, Found: 500.0541.



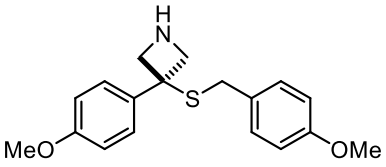
3-((4-Bromophenyl)thio)-3-(4-methoxyphenyl)azetidine (164)

MeSiI (1.2 mL, 8.5 mmol) was added to a solution of azetidine **142** (484 mg, 1.00 mmol) in MeCN (5.0 mL) at −10 °C. The reaction mixture was stirred for 4 h 30 min at −5 °C then quenched with MeOH (1.0 mL). After stirring for a further 10 min, the solvent was removed under reduced pressure. Purification by flash column chromatography (4% MeOH/CH_2Cl_2) afforded amine **164** (301 mg, 99 %) as a yellow solid. R_f = 0.23 (5% MeOH/CH_2Cl_2); mp = 142–146 °C; IR (film)/cm^{-1} 2896 (br, NH), 1610, 1513, 1468, 1438, 1297, 1244, 1177, 1036, 1006, 816, 730; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.34 (m, 2 H, 2 × Ar-CH), 7.07–7.04 (m, 2 H, 2 × Ar-CH), 6.79 (s, 4 H, 4 × Ar-CH), 5.70 (s, br, 1 H, NH), 4.59–4.56 (m, 2 H, C*H*HNC*H*H), 4.37–4.34 (m, 2 H, CH*H*NCH*H*), 3.80 (s, 3 H, OCH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.2 (Ar-*C*$_q$-OCH_3), 137.9 (2 × Ar-CH), 132.30 (2 × Ar-CH), 132.25 (Ar-*C*$_q$-C_q), 128.8 (S-C_q-Ar), 127.2 (2 × Ar-CH), 124.9 (Ar-C_q-Br), 114.0 (2 × Ar-CH), 56.4 (*C*H_2N*C*H_2), 55.4 (OCH_3), 52.5 (C_q); HRMS (+ESI) *m*/*z* calcd for $C_{16}H_{17}NOS$ [M+H]: 350.0214, Found: 350.0208.



3-(((3s,5s,7s)-Adamantan-1-yl)thio)-3-(4-methoxyphenyl)azetidine (165)

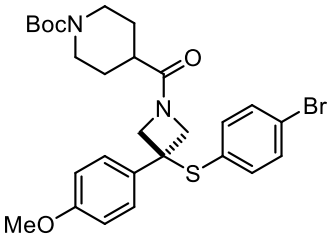
MeSiI (114 μL, 0.80 mmol) was added in three portions over 30 min to a solution of azetidine **148**[114] (92.7 mg, 0.20 mmol) in MeCN (1.2 mL) at −10 °C. The reaction mixture was stirred for 1 h then quenched with MeOH (50 μL). After stirring for a further 10 min, the solvent was removed under reduced pressure. Purification by flash column chromatography (2 to 4% MeOH/CH_2Cl_2) afforded amine **165** (64.6 mg, 98 %) as a pale yellow solid. R_f = 0.15 (5% MeOH/CH_2Cl_2); mp = 197 °C[l], IR (film)/cm^{-1} 2903 (br, NH), 2847, 1610, 1513, 1449, 1300, 1241, 1185, 1099, 1036, 916, 831, 775, 685; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29–7.26 (m, 2 H, 2 × Ar-CH), 6.91–6.87 (m, 2 H, 2 × Ar-CH), 6.30 (s, br, 1 H, NH), 4.63–4.60 (m, 2 H, C*H*HNC*H*H), 4.34–4.31 (m, 2 H, CH*H*NCH*H*), 3.83 (s, 3 H, OCH_3), 1.86 (s, 3 H, 3 × CH), 1.58–1.47 (m, 12 H, 6 × CH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.0 (Ar-C_q-OCH_3), 133.6 (Ar-C_q-C_q), 127.6 (2 × Ar-CH), 114.0 (2 × Ar-CH), 56.6 (CH_2NCH_2), 55.3 (OCH_3), 50.1 (C_q), 49.1 (S-$C_{q(adamantane)}$), 43.4 (3 × CH_2), 35.8 (3 × CH_2), 29.4 (3 × CH); HRMS (+ESI) *m*/*z* calcd for $C_{20}H_{28}NOS$ [M+H]: 330.1892, Found: 330.1896.



3-((4-Methoxybenzyl)thio)-3-(4-methoxyphenyl)azetidine (166)

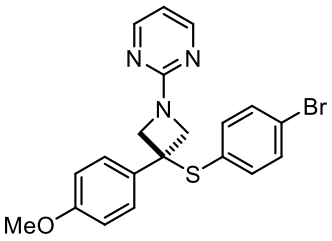
MeSiI (75 μL, 0.53 mmol) was added in three portions over 30 min to a solution of azetidine **140**[114] (90 mg, 0.20 mmol) in MeCN (1.2 mL) at −10 °C. The reaction mixture was stirred for 1 h then quenched with MeOH (50 μL). After stirring for a further 10 min, the solvent was removed under reduced pressure. Purification by flash column chromatography (2 to 8% MeOH/CH_2Cl_2) afforded amine **166** (62.0 mg, 98 %) as a pale yellow solid. R_f = 0.10 (5% MeOH/CH_2Cl_2); mp = 149–151 °C; IR (film)/cm^{-1} 3004 (br, NH), 2926, 2840, 1606, 1509, 1461, 1300, 1237, 1177, 1118, 1073, 1032, 808, 663; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16–7.11 (m, 4 H, 4 × Ar-CH), 6.96–6.92 (m, 2 H, 2 × Ar-CH), 6.83–6.80 (m, 2 H, 2 × Ar-CH), 4.45–4.42 (m, 2 H, C*H*HNC*H*H), 4.06–4.03 (m, 2 H, CH*H*NCH*H*), 3.85 (s, 3 H, OCH_3), 3.79 (s, 3 H, OCH_3), 3.48 (s, 2 H, SCH_2Ph); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.3 (Ar-C_q-OCH_3), 159.0 (Ar-C_q-OCH_3), 131.3 (Ar-C_q-C_q), 130.3 (2 × Ar-CH), 127.8 (Ar-C_q-CH_2), 127.4 (2 × Ar-CH), 114.4 (2 × Ar-CH), 114.2 (2 × Ar-CH), 56.8 (CH_2NCH_2), 55.4 (OCH_3), 55.3 (OCH_3), 50.0 (C_q), 34.8 (SCH_2Ph); HRMS (+ESI) *m*/*z* calcd for $C_{18}H_{22}NO_2S$ [M+H]: 316.1371, Found: 316.1380.

[l] Compound decomposes at 184 °C, becoming a black amorphous solid.



tert-Butyl 4-(3-((4-bromophenyl)thio)-3-(4-methoxyphenyl)azetidine-1-carbonyl)piperidine-1-carboxylate (167)

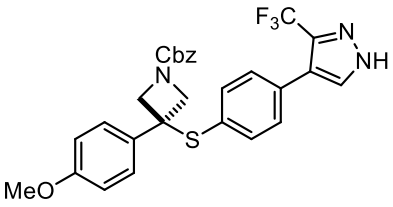
DMAP (30.5 mg, 0.25 mmol) followed by EDC•HCl (57.5 mg, 0.30 mmol) was added to a solution of amine **164** (75.3 mg, 0.25 mmol) and boc-Inp-OH (64.2 mg, 0.28 mmol) in CH_2Cl_2 (1.25 mL) at 25 °C. The reaction mixture was stirred at 25 °C for 24 h. The reaction mixture was then quenched with sat. aq. $NaHCO_3$ (20 mL). The aqueous portion was extracted with CH_2Cl_2 (3 × 20 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash chromatography (80% Et_2O/pentane) afforded azetidine **167** (85.8 mg, 61%) as a white solid. R_f = 0.12 (70% Et_2O/pentane); mp = 146–148 °C; IR (film)/cm^{-1} 2955, 2878, 1692 (C=O), 1636 (C=O), 1517, 1453, 1423, 1394, 1364, 1304, 1244, 1166, 1066, 1006, 931, 823; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.36 (m, 2 H, 2 × Ar-CH), 7.04–7.01 (m, 2 H, 2 × Ar-CH), 6.95–6.92 (m, 2 H, 2 × Ar-CH), 6.85–6.82 (m, 2 H, 2 × Ar-CH), 4.60 (d, *J* = 8.6 Hz, 1 H, C*H*HNCHH), 4.48–4.44 (m, 2 H, CH*H*NCH*H*), 4.39 (d, *J* = 9.8 Hz, 1 H, CHHNC*H*H), 4.12 (s, br, 2 H, C*H*HN$_{(piperidine)}$C*H*H), 3.81 (s, 3 H, OCH_3), 2.76–2.72 (m, 2 H, CH*H*N$_{(piperidine)}$CH*H*), 2.24 (tt, *J* = 10.5, 5.0 Hz, 1 H, CH), 1.68–1.57 (m, 4 H, 2 × N$_{(piperidine)}$CH$_2$C*H*$_2$), 1.46 (s, 9 H, 3 × CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.3 (C=O), 158.8 (Ar-*C*$_q$-OCH_3), 154.6 (C=O), 137.1 (2 × Ar-CH), 133.8 (Ar-*C*$_q$-C$_q$), 132.0 (2 × Ar-CH), 130.4 (S-C$_q$-Ar), 127.8 (2 × Ar-CH), 124.1 (Ar-C$_q$-Br), 113.8 (2 × Ar-CH), 79.6 (*C*$_q$(CH$_3$)$_3$), 62.6 (*C*H$_2$NCH$_2$), 60.3 (CH$_2$N*C*H$_2$), 55.3 (OCH_3), 49.8 (C$_q$), 42.7 (br, *C*H$_2$N$_{(piperidine)}$*C*H$_2$), 38.0 (CH), 28.4 (C$_q$(*C*H$_3$)$_3$), 27.6 (*C*H$_2$CH$_2$NCH$_2$CH$_2$), 27.5 (CH$_2$CH$_2$NCH$_2$*C*H$_2$); HRMS (+ESI) *m*/*z* calcd for $C_{27}H_{34}N_2O_4SBr$ [M+H]: 561.1423, Found: 561.1417.



2-(3-((4-Bromophenyl)thio)-3-(4-methoxyphenyl)azetidin-1-yl)pyrimidine (168)

A solution of amine **164** (75.3 mg, 0.25 mmol), 2-chloropyrimidine (34.4 mg, 0.30 mmol) and KF (19.1 mg, 0.33 mmol) in water/MeCN (2:1, 1.0 mL) was stirred at 80 °C for 22 h. The reaction mixture was then cooled to rt and water (20 mL) was added. The aqueous portion was extracted with CH_2Cl_2 (3 × 20 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash chromatography (40% Et_2O/pentane) afforded azetidine **168** (50.8 mg, 47%) as an off white solid. R_f = 0.13 (40% Et_2O/pentane); mp = 113–116 °C, IR (film)/cm^{-1} 2969, 2914, 2870, 1576, 1543, 1490, 1446, 1379, 1293, 1244, 1174, 1006, 820, 726; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (d, *J* = 4.8 Hz, 2 H,

2 × $Ar_{(pyrimidine)}$-CH), 7.34–7.31 (m, 2 H, 2 × Ar-CH), 7.07–7.04 (m, 2 H, 2 × Ar-CH), 7.03–6.99 (m, 2 H, 2 × Ar-CH), 6.85–6.81 (m, 2 H, 2 × Ar-CH), 6.57 (t, *J* = 4.8 Hz, 1 H, $Ar_{(pyrimidine)}$-CH), 4.61 (d, *J* = 9.4 Hz, 2 H, C*H*HNC*H*H), 4.55 (d, *J* = 9.4 Hz, 2 H, CH*H*NCH*H*), 3.81 (s, 3 H, OCH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.5 (N-$C_{q(pyrimidine)}$), 158.6 (Ar-C_q-OCH_3), 157.8 (2 × $Ar_{(pyrimidine)}$-CH), 137.1 (2 × Ar-CH), 134.7 (Ar-C_q-C_q), 131.8 (2 × Ar-CH), 131.0 (S-C_q-Ar), 127.9 (2 × Ar-CH), 123.7 (Ar-C_q-Br), 113.6 (2 × Ar-CH), 110.8 ($Ar_{(pyrimidine)}$-CH), 62.6 (CH_2NCH_2), 55.3 (OCH_3), 50.6 (C_q); HRMS (+ESI) *m*/*z* calcd for $C_{20}H_{19}N_3OSBr$ [M+H]: 428.0432, Found: 428.0422.

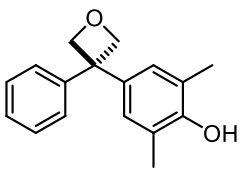


Benzyl 3-(4-methoxyphenyl)-3-((4-(3-(trifluoromethyl)-1*H*-pyrazol-4-yl)phenyl)thio)azetidine-1-carboxylate (169)

Azetidine **142** (121 mg, 0.25 mmol), pyrazole pinacol ester (83.9 mg, 0.32 mmol), $Pd(PPh_3)_4$ (28.9 mg, 0.025 mmol) and K_2CO_3 (69.1 mg, 0.50 mmol) were added to a reaction vial. The reaction vial was evacuated and then refilled with nitrogen three times. DME/water (88:22, 2.5 mL) was added *via* syringe into the vial. The reaction mixture was stirred at 100 °C for 18 h then cooled to rt. Et_2O (15 mL) was added and the crude mixture was filtered through celite and then concentrated under reduced pressure. Purification by flash column chromatography (8% Et_2O/pentane) afforded azetidine **169** (107 mg, 79%) as a white solid. R_f = 0.25 (8% Et_2O/pentane); mp = 67–72 °C; IR (film)/cm^{-1} 3172 (br, NH), 2952, 1684 (C=O), 1513, 1453, 1420, 1356, 1248, 1114, 1032, 976, 827, 730, 697; ^1H NMR (400 MHz, $CDCl_3$) δ 12.71 (s, 1 H, NH), 7.66 (d, *J* = 1.1 Hz, 1 H, N-Ar-CH), 7.29–7.19 (m, 7 H, 7 × Ar-CH), 7.13–7.10 (m, 2 H, 2 × Ar-CH), 6.88–6.85 (m, 2 H, 2 × Ar-CH), 6.75–6.71 (m, 2 H, 2 × Ar-CH), 5.02 (s, 2 H, CH_2Ph), 4.44 (d, *J* = 9.1 Hz, 2 H, C*H*HNC*H*H), 4.37 (d, *J* = 9.1 Hz, 2 H, CH*H*NCH*H*), 3.73 (s, 3 H, OCH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.7 (Ar-C_q-OCH_3), 156.3 (C=O), 136.3 (Ar-C_q-CH_2), 135.6 (2 × Ar-CH), 134.4 (Ar-C_q-C_q), 131.4 (Ar-C_q-$C_{q(pyrazole)}$), 131.1 (S-C_q-Ar), 129.7 (br, N-Ar-CH), 128.9 (2 × Ar-CH), 128.5 (2 × Ar-CH), 128.1 (Ar-CH), 128.0 (2 × Ar-CH), 127.8 (2 × Ar-CH), 121.7 (q, $^1J_{C\text{-}F}$ = 268.9 Hz, CF_3), 121.0 (Ar-C_q-$C_{q(pyrazole)}$), 113.6 (2 × Ar-CH), 67.0 (CH_2Ph), 61.7 (CH_2NCH_2), 55.3 (OCH_3), 50.4 (C_q);* $^{19}F\{^1H\}$ NMR (377 MHz, $CDCl_3$) δ –59.2; HRMS (+ESI) *m*/*z* calcd. for $C_{28}H_{25}N_3O_3SF_3$ [M+H]: 540.1569, Found: 540.1569.

*$Ar_{(pyrazole)}$-C_q-CF_3 was not observed on ^{13}C NMR.

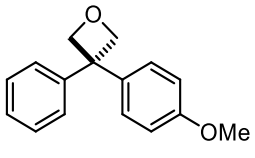
8.2.5 Synthesis of 3,3-Diaryloxetanes and Derivatives through HFIP-mediated Friedel–Crafts reaction (Part 5)



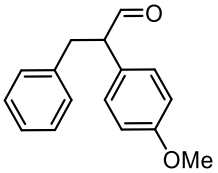
2,6-Dimethyl-4-(3-phenyloxetan-3-yl)phenol (171)

$FeCl_3$ (8.1 mg, 0.05 mmol) was weighed in a vial. 2,6-Dimethylphenol (104 mg, 0.85 mmol) and oxetanol **170**[m] (75.1 mg, 0.50 mmol) were added. The reaction vessel was sealed and HFIP (5.0 mL) was added. The reaction was stirred for 18 h at 80 °C, then cooled to rt and sat. aq. $NaHCO_3$ (20 mL) was added followed by Et_2O (20 mL). The layers were separated and the aqueous portion was extracted with Et_2O (2 × 20 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash chromatography (30% Et_2O/pentane) afforded oxetane **171** (91.8 mg, 72%) as a yellow solid. R_f = 0.23 (30% Et_2O/pentane); mp = 167–170 °C; IR (film)/cm^{-1} 3880 (br, OH), 2959, 2881, 2363, 1490, 1211, 1181, 976, 700; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41–7.33 (m, 2 H, 2 × Ar-CH), 7.32–7.20 (m, 3 H, 3 × Ar-CH), 6.82 (s, 2 H, 2 × Ar-CH), 5.24 (m, 4 H, C*H*$_2$OC*H*$_2$), 4.72 (m, 1 H, OH), 2.24 (s, 6 H, 2 × CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.8 (Ar-C_q-OH), 146.2 (Ar-*C*$_q$-C_q), 137.4 (Ar-*C*$_q$-C_q), 128.5 (2 × Ar-CH), 126.7 (2 × Ar-CH), 126.5 (Ar-CH), 126.4 (2 × Ar-CH), 123.1 (2 × Ar-*C*$_q$-CH_3), 84.8 (*C*H_2O*C*H_2), 50.8 (C_q), 16.1 (2 × Ar-CH_3); HRMS (–ESI) *m*/*z* calcd for $C_{17}H_{17}O_2$ [M–H]: 253.1229, Found: 253.1226.

3-(4-Methoxyphenyl)-3-phenyloxetane (173) and **2-(4-methoxyphenyl)-3-phenylpropanal (173b)**



173



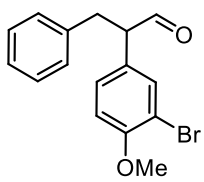
173b

$FeCl_3$ (8.1 mg, 0.05 mmol) was weighed in a vial. Oxetanol **170** (75.1 mg, 0.50 mmol) and anisole (92.4 µL, 0.85 mmol) were added. The reaction vessel was sealed and HFIP (5.0 mL) was added. The reaction was stirred for 18 h at 80 °C. The reaction was then cooled to rt and sat. aq. $NaHCO_3$ (20 mL) was added followed by Et_2O (20 mL). The layers were separated and the aqueous portion was extracted with Et_2O (2 × 20 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash chromatography (4 to 6% Et_2O/hexane) afforded aldehyde **173b** (13.7 mg, 11%) as a colourless oil followed by oxetane **173** (43.9 mg, 37%) as a yellow solid.

[m] Synthesised by Pfizer

Aldehyde **173b**: R_f = 0.23 (4% Et_2O/hexane); IR (film)/cm^{-1} 2938, 2832, 1722 (C=O), 1610, 1513, 1453, 1300, 1244, 1177, 1032, 823, 756, 700; ^1H NMR (400 MHz, $CDCl_3$) δ 9.75 (d, *J* = 1.6 Hz, 1 H, HC=O), 7.39–7.27 (m, 3 H, 3 × Ar-CH), 7.18–7.13 (m, 2 H, 2 × Ar-CH), 7.00–6.95 (m, 2 H, 2 × Ar-CH), 6.79–6.73 (m, 2 H, 2 × Ar-CH), 3.84–3.78 (m, 1 H, (C=O)-CH), 3.77 (s, 3 H, OCH_3), 3.42 (dd, *J* = 14.1, 6.8 Hz, 1 H, CH-C*H*H), 2.94 (dd, *J* = 14.1, 7.8 Hz, 1 H, CH-CH*H*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.1 (C=O), 158.0 (Ar-C_q-OCH_3), 135.8 (Ar-C_q), 130.7 (Ar-C_q), 130.0 (2 × Ar-CH), 128.99 (2 × Ar-CH), 128.98 (2 × Ar-CH), 127.6 (Ar-CH), 113.7 (2 × Ar-CH), 61.2 ((C=O)-*C*H), 55.2 (OCH_3), 35.3 (CH-*C*H_2); HRMS (+APCI) *m*/*z* calcd for $C_{16}H_{17}O_2^+$ $[M+H]^+$: 241.1223, Found: 241.1224.

Oxetane **173**: R_f = 0.14 (4% Et_2O/hexane); mp = 50–51 °C; IR (film)/cm^{-1} 2952, 2877, 1610, 1513, 1248, 1028, 991, 890, 812, 700; ^1H NMR (400 MHz, $CDCl_3$) δ 7.41–7.33 (m, 2 H, 2 × Ar-CH), 7.32–7.23 (m, 1 H, Ar-CH), 7.24–7.20 (m, 2 H, 2 × Ar-CH), 7.18–7.12 (m, 2 H, 2 × Ar-CH), 6.93–6.86 (m, 2 H, 2 × Ar-CH), 5.26 (d, *J* = 5.6 Hz, 2 H, C*H*HOC*H*H), 5.22 (d, *J* = 5.6 Hz, 2 H, CH*H*OCH*H*), 3.82 (s, 3 H, OCH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.2 (Ar-C_q-OCH_3), 146.0 (Ar-C_q-C_q), 138.0 (Ar-C_q-C_q), 128.5 (2 × Ar-CH), 127.6 (2 × Ar-CH), 126.6 (Ar-CH), 126.5 (2 × Ar-CH), 113.9 (2 × Ar-CH), 84.8 (*C*H_2O*C*H_2), 55.3 (OCH_3), 50.9 (C_q); HRMS (+APCI) *m*/*z* calcd for $C_{16}H_{17}O_2^+$ $[M+H]^+$: 241.1223, Found: 241.1224.

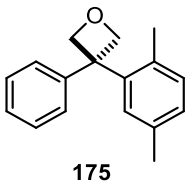


2-(3-Bromo-4-methoxyphenyl)-3-phenylpropanal (174b)

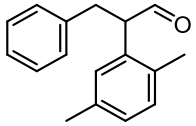
$FeCl_3$ (8.1 mg, 0.05 mmol) was weighed in a vial. Oxetanol **170** (75.1 mg, 0.50 mmol) and 2-bromoanisole (106 µL, 0.85 mmol) were added. The reaction vessel was sealed and HFIP (5.0 mL) was added. The reaction was stirred for 18 h at 80 °C. The reaction was then cooled to rt and sat. aq. $NaHCO_3$ (20 mL) was added followed by Et_2O (20 mL). The layers were separated and the aqueous portion was extracted with Et_2O (2 × 20 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash chromatography (4% Et_2O/pentane) afforded aldehyde **174b** (54.8 mg, 34%) as a yellow oil. R_f = 0.10 (4% Et_2O/hexane); IR (film)/cm^{-1} 2940, 2836, 2713, 1718 (C=O), 1602, 1494, 1438, 1282, 1181, 1051, 1021, 883, 808, 756, 700; ^1H NMR (400 MHz, $CDCl_3$) δ 9.74 (d, *J* = 1.6 Hz, 1 H, HC=O), 7.39–7.28 (m, 3 H, 3 × Ar-CH), 7.25 (d, *J* = 2.2 Hz, 1 H, Ar-CH), 7.15–7.10 (m, 2 H, 2 × Ar-CH), 6.93 (dd, *J* = 8.4, 2.2 Hz, 1 H, Ar-CH), 6.73 (d, *J* = 8.4 Hz, 1 H, Ar-CH), 3.85 (s, 3 H, OCH_3), 3.79 (ddd, *J* = 8.0, 6.8, 1.6 Hz, 1 H, (C=O)-CH), 3.39 (dd, *J* = 14.1, 6.8 Hz, 1 H, CH-C*H*H), 2.89 (dd, *J* = 14.1, 8.0 Hz, 1 H, CH-CH*H*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.6 (C=O), 154.3 (Ar-C_q-OCH_3), 135.4 (Ar-C_q), 133.7 (Ar-CH), 132.4 (Ar-C_q), 129.10 (2 × Ar-CH), 129.09 (Ar-CH), 129.0 (2 × Ar-CH), 127.8 (Ar-CH), 111.7 (Ar-CH), 111.3 (Ar-C_q-Br), 61.0 ((C=O)-*C*H),

56.2 (OCH_3), 34.9 (CH-CH_2); HRMS (+EI) *m*/*z* calcd for $C_{16}H_{15}O_2{}^{79}Br^{\bullet+}$ $[M]^{\bullet+}$: 318.0250, Found: 318.0261.

3-(2,5-Dimethylphenyl)-3-phenyloxetane (175) and **3-(2,5-dimethylphenyl)-2-phenylpropanal (175b)**



175



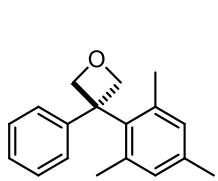
175b

$FeCl_3$ (8.1 mg, 0.05 mmol) was weighed in a vial. Oxetanol **170** (75.1 mg, 0.50 mmol) and *para*-xylene (309 µL, 2.50 mmol) were added. The reaction vessel was sealed and HFIP (5.0 mL) was added. The reaction was stirred for 18 h at 80 °C, then cooled to rt and sat. aq. $NaHCO_3$ (20 mL) was added followed by Et_2O (15 mL). The layers were separated and the aqueous portion was extracted with Et_2O (2 × 15 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash chromatography (4% Et_2O/hexane) afforded impure aldehyde **175b** (12.3 mg, ca. 10%) as a colourless oil followed by oxetane **175** (65.1 mg, 55%) as a yellow oil.

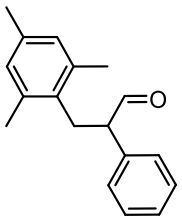
Aldehyde **175b**: R_f = 0.31 (4% Et_2O/hexane); IR (film)/cm^{-1} 3026, 2922, 1722 (C=O), 1498, 1453, 1140, 812, 752, 700; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.70 (d, *J* = 1.2 Hz, 1 H, HC=O), 7.25–7.17 (m, 3 H, 3 × Ar-CH), 7.25–7.17 (m, 4 H, 4 × Ar-CH), 6.90 (s, 1 H, Ar-CH), 4.09–4.01 (m, 1 H, (C=O)-CH), 3.49 (dd, *J* = 13.8, 6.7 Hz, 1 H, CH-C*H*H), 2.87 (dd, *J* = 13.8, 7.4 Hz, 1 H, CH-CH*H*), 2.33 (s, 3 H, CH_3), 2.08 (s, 3 H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.9 (C=O), 139.2 (Ar-C_q-CH_2), 136.1 (Ar-C_q-CH_3), 134.1 (Ar-C_q-CH and Ar-C_q-CH_3), 130.8 (Ar-CH), 129.1 (3 × Ar-CH), 128.9 (Ar-CH), 128.3 (2 × Ar-CH), 126.2 (Ar-CH), 56.9 ((C=O)-*C*H), 36.2 (CH-CH_2), 21.0 (Ar-CH_3), 19.1 (Ar-CH_3); HRMS (+EI) *m*/*z* calcd for $C_{17}H_{18}O$ [M]: 238.1358, Found: 238.1352.

Oxetane **175**: R_f = 0.26 (4% Et_2O/hexane); IR (film)/cm^{-1} 2952, 2873, 1494, 1446, 1028, 991, 890, 812, 700; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44–7.37 (m, 2 H, 2 × Ar-CH), 7.37–7.30 (m, 2 H, 2 × Ar-CH), 7.30–7.23 (m, 1 H, Ar-CH), 7.12–7.04 (m, 2 H, 2 × Ar-CH), 6.82 (s, 1 H, Ar-CH), 5.45 (d, *J* = 5.9 Hz, 2 H, C*H*HOC*H*H), 4.95 (d, *J* = 5.9 Hz, 2 H, CH*H*OCH*H*), 2.38 (s, 3 H, CH_3), 1.81 (s, 3 H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.6 (Ar-C_q-C_q), 141.8 (Ar-C_q-C_q), 135.5 (Ar-C_q-CH_3), 132.8 (Ar-C_q-CH_3), 131.1 (Ar-CH), 128.5 (2 × Ar-CH), 128.1 (Ar-CH), 127.8 (Ar-CH), 126.8 (Ar-CH), 125.8 (2 × Ar-CH), 84.4 (CH_2OCH_2), 51.7 (C_q), 21.0 (Ar-CH_3), 19.1 (Ar-CH_3); HRMS (+EI) *m*/*z* calcd for $C_{17}H_{18}O$ [M]: 238.1358, Found: 238.1355.

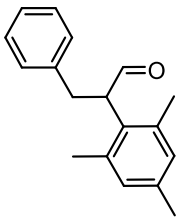
3-Mesityl-3-phenyloxetane (176), 3-mesityl-2-phenylpropanal (176a) and **2-mesityl-3-phenylpropanal (176b)**



176



176a



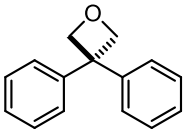
176b

$FeCl_3$ (8.1 mg, 0.05 mmol) was weighed in a vial. Oxetanol **170** (75.1 mg, 0.50 mmol) and mesitylene (348 µL, 2.50 mmol) were added. The reaction vessel was sealed and HFIP (5.0 mL) was added. The reaction was stirred for 18 h at 80 °C, then cooled to rt and sat. aq. $NaHCO_3$ (20 mL) was added followed by Et_2O (15 mL). The layers were separated and the aqueous portion was extracted with Et_2O (2 × 15 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash chromatography (4% Et_2O/pentane) afforded a mixture of aldehyde **176a** and **176b** (24:76, 12.9 mg, 10%) as a yellow solid, followed by oxetane **176** (91.6 mg, 73%) as a yellow solid.

Aldehyde **176a** and **176b**: R_f = 0.53 (4% Et_2O/pentane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.84 (d, *J* = 1.5 Hz, 1 H, H_aC=O), 9.79 (s, 1 H, H_bC=O), 7.39–7.31 (m, 3 H, 3 × Ar-CH_a), 7.26–7.16 (m, 3 H, 3 × Ar-CH_b), 7.12–7.08 (m, 2 H, 2 × Ar-CH_a), 7.05–7.00 (m, 2 H, 2 × Ar-CH_b), 6.87 (s, 2 H, 2 × Ar-CH_b), 6.80 (s, 2 H, 2 × Ar-CH_a), 3.97 (dd, *J* = 8.1, 4.9 Hz, 1 H, (C=O)-CH_b), 3.69 (dd, *J* = 13.6, 4.9 Hz, 1 H, CH-C*H*H_b), 3.69 (m, 1 H, (C=O)-CH_a), 3.53 (dd, *J* = 14.2, 5.6 Hz, 1 H, CH-C*H*H_a), 2.91 (dd, *J* = 14.2, 8.2 Hz, 1 H, CH-CH*H*$_a$), 2.85 (dd, *J* = 13.6, 8.1 Hz, 1 H, CH-CH*H*$_b$), 2.29 (s, 3 H, $CH_{3,b}$), 2.26 (s, 3 H, $CH_{3,a}$), 2.07 (m, 12 H, 2 × $CH_{3(a+b)}$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 201.6 (C_b=O), 200.3 (C_a=O), 140.0 (Ar-$C_{q,b}$), 137.2 (Ar-$C_{q,b}$), 136.6 (Ar-$C_{q,a}$), 136.5 (Ar-$C_{q,a}$), 135.6 (Ar-$C_{q,a}$), 132.6 (Ar-$C_{q,b}$), 130.6 (2 × Ar-CH_a), 129.9 (br, 4 × Ar-C_q-CH_3), 129.13 (2 × Ar-CH_b), 129.07 (2 × Ar-CH_b), 129.06 (2 × Ar-CH_a), 128.9 (2 × Ar-CH_a), 128.2 (2 × Ar-CH_b), 127.6 (Ar-CH_a), 126.1 (Ar-CH_b), 59.4 ((C=O)-*C*H_a), 57.0 ((C=O)-*C*H_b), 34.1 (CH-*C*$H_{2,b}$), 30.3 (CH-*C*$H_{2,a}$), 20.80 (Ar-$CH_{3,b}$), 20.78 (Ar-$CH_{3,a}$), 20.6 (2 × Ar-$CH_{3,b}$), 19.9 (2 × Ar-$CH_{3,a}$).

Oxetane **176**: R_f = 0.27 (4% Et_2O/pentane); mp = 96–99 °C; IR (film)/cm^{-1} 2952, 2870, 1610, 1490, 1446, 1379, 1189, 1032, 943, 849, 760, 700; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52–7.47 (m, 2 H, 2 × Ar-CH), 7.39–7.28 (m, 3 H, 3 × Ar-CH), 6.90 (s, 2 H, 2 × Ar-CH), 5.41 (d, *J* = 6.0 Hz, 2 H, C*H*HOC*H*H), 4.83 (d, *J* = 6.0 Hz, 2 H, CH*H*OCH*H*), 2.33 (s, 3 H, CH_3), 1.87 (s, 6 H, 2 × CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.9 (2 × Ar-C_q-C_q), 137.8 (Ar-C_q-CH_3), 136.2 (2 × Ar-C_q-CH_3), 129.8 (2 × Ar-CH), 128.6 (2 × Ar-CH), 127.0 (Ar-CH), 125.7 (2 × Ar-CH), 85.2

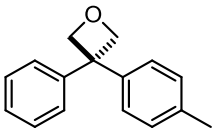
(CH_2OCH_2), 52.6 (C_q), 20.7 (Ar-CH_3), 20.2 (2 × Ar-CH_3); HRMS (+APCI) *m*/*z* calcd for $C_{18}H_{21}O^+$ $[M+H]^+$: 253.1587, Found: 253.1587.



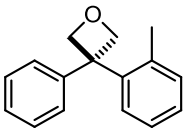
3,3-Diphenyloxetane (177)

$FeCl_3$ (8.1 mg, 0.05 mmol) was weighed in a vial. Oxetanol **170** (75.1 mg, 0.50 mmol) and benzene (222 µL, 2.50 mmol) were added. The reaction vessel was sealed and HFIP (5.0 mL) was added. The reaction was stirred for 18 h at 80 °C, then cooled to rt and sat. aq. $NaHCO_3$ (20 mL) was added followed by Et_2O (15 mL). The layers were separated and the aqueous portion was extracted with Et_2O (2 × 15 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash chromatography (4% Et_2O/pentane) afforded oxetane **177** (11.7 mg, 11%) as a yellow solid. R_f = 0.40 (4% Et_2O/pentane); mp = 72–74 °C; IR (film)/cm^{-1} 2955, 2881, 1490, 1084, 1021, 984, 935, 831, 760, 700; ^1H NMR (400 MHz, $CDCl_3$) δ 7.41–7.34 (m, 4 H, 4 × Ar-CH), 7.31–7.27 (m, 2 H, 2 × Ar-CH), 7.26–7.21 (m, 4 H, 4 × Ar-CH), 5.28 (s, 4 H, CH_2OCH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.8 (2 × Ar-C_q-C_q), 128.6 (4 × Ar-CH), 126.6 (2 × Ar-CH), 126.5 (4 × Ar-CH), 84.6 (CH_2OCH_2), 51.5 (C_q); HRMS (+EI) *m*/*z* calcd for $C_{15}H_{15}O^{\bullet+}$ $[M]^{\bullet+}$: 210.1039, Found: 210.1045.

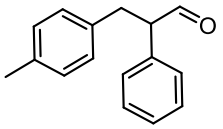
3-Phenyl-3-(*p*-tolyl)oxetane (*p*-178), 3-phenyl-3-(*o*-tolyl)oxetane (*o*-178) and **2-phenyl-3-(p-tolyl)propanal (178a).**



***p*-178**



***o*-178**



178a

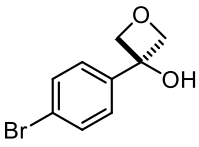
$FeCl_3$ (8.1 mg, 0.05 mmol) was weighed in a vial. Oxetanol **170** (75.1 mg, 0.50 mmol) and toluene (266 µL, 2.50 mmol) were added. The reaction vessel was sealed and HFIP (5.0 mL) was added. The reaction was stirred for 18 h at 80 °C, then cooled to rt and sat. aq. $NaHCO_3$ (20 mL) was added followed by Et_2O (15 mL). The layers were separated and the aqueous portion was extracted with Et_2O (2 × 15 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash chromatography (30% to 40% CH_2Cl_2/pentane) afforded aldehyde **178a** (88% pure, 31.5 mg, 28%) as a yellow oil, oxetane ***o*-178** (4.1 mg, 4%) as a yellow paste and oxetane ***p*-178** (11.7 mg, 12%) as an orange oil.

Aldehyde **178a**: R_f = 0.41 (30% CH_2Cl_2/pentane); IR (film)/cm^{-1} 3026, 2922, 2858, 2817, 1722 (C=O), 1513, 1453, 1136, 1028, 812, 760, 700; ^1H NMR (400 MHz, $CDCl_3$) δ 9.75 (d, *J* = 1.6 Hz,

1 H, HC=O), 7.39–7.28 (m, 3 H, 3 × Ar-CH), 7.18–7.13 (m, 2 H, 2 × Ar-CH), 7.04 (d, *J* = 7.7 Hz, 2 H, 2 × Ar-CH), 6.96 (d, *J* = 8.0 Hz, 2 H, 2 × Ar-CH), 3.83 (ddd, *J* = 8.2, 7.1, 1.6 Hz, 1 H, (C=O)-CH), 3.44 (dd, *J* = 14.1, 7.1 Hz, 1 H, CH-C*H*H), 2.95 (dd, *J* = 14.1, 8.2 Hz, 1 H, CH-CH*H*), 2.29 (s, 3 H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.1 (C=O), 135.8 (Ar-C_q), 135.6 (Ar-C_q), 129.01 (2 × Ar-CH), 129.00 (2 × Ar-CH), 128.99 (2 × Ar-CH), 128.9 (2 × Ar-CH), 128.3 (Ar-C_q-CH_3), 127.6 (Ar-CH), 61.0 ((C=O)-*C*H), 35.7 (CH-*C*H_2), 21.0 (Ar-CH_3); HRMS (–EI) *m*/*z* calcd for $C_{17}H_{18}O_3$ [M–H+HCO_2H]: 238.1358, Found: 238.1352.

Oxetane ***o*-178**: R_f = 0.29 (30% CH_2Cl_2/pentane); IR (film)/cm^{-1} 3056, 3022, 2952, 2922, 2873, 1490, 1446, 1032, 991, 756, 700; ^1H NMR (400 MHz, $CDCl_3$) δ 7.42–7.37 (m, 2 H, 2 × Ar-CH), 7.37–7.31 (m, 2 H, 2 × Ar-CH), 7.31–7.23 (m, 3 H, 3 × Ar-CH), 7.22–7.18 (m, 1 H, Ar-CH), 7.06 (dd, *J* = 7.0, 2.0 Hz, 1 H, Ar-CH), 5.45 (d, *J* = 5.8 Hz, 2 H, C*H*HOC*H*H), 4.97 (d, *J* = 5.8 Hz, 2 H, CH*H*OCH*H*), 1.85 (s, 3 H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.4 (Ar-C_q-C_q), 142.0 (Ar-C_q-C_q), 136.0 (Ar-C_q-CH_3), 131.3 (Ar-CH), 128.6 (2 × Ar-CH), 127.3 (Ar-CH), 127.2 (Ar-CH), 126.8 (Ar-CH), 126.0 (Ar-CH), 125.8 (2 × Ar-CH), 84.3 (*C*H_2O*C*H_2), 51.7 (C_q), 19.6 (Ar-CH_3); HRMS (+ESI) *m*/*z* calcd for $C_{16}H_{17}O^+$ $[M+H]^+$: 225.1274, Found: 225.1271.

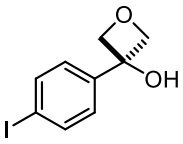
Oxetane ***p*-178**: R_f = 0.21 (30% CH_2Cl_2/pentane); IR (film)/cm^{-1} 3026, 2952, 2877, 1513, 1446, 1021, 991, 939, 816, 760, 700; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40–7.35 (m, 2 H, 2 × Ar-CH), 7.30–7.27 (m, 1 H, Ar-CH), 7.26–7.22 (m, 2 H, 2 × Ar-CH), 7.19 (d, *J* = 8.0 Hz, 2 H, 2 × Ar-CH), 7.15–7.11 (m, 2 H, 2 × Ar-CH), 5.29–5.24 (m, 4 H, C*H*$_2$OC*H*$_2$), 2.37 (s, 3 H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.9 (Ar-C_q-C_q), 142.8 (Ar-C_q-C_q), 136.3 (Ar-C_q-CH_3), 129.2 (2 × Ar-CH), 128.5 (2 × Ar-CH), 126.6 (Ar-CH), 126.43 (2 × Ar-CH), 126.35 (2 × Ar-CH), 84.7 (*C*H_2O*C*H_2), 51.1 (C_q), 21.0 (Ar-CH_3); HRMS (+EI) *m*/*z* calcd for $C_{16}H_{16}O^{\bullet+}$ $[M]^{\bullet+}$: 224.1196, Found: 224.1201.



3-(4-Bromophenyl)oxetan-3-ol (179)

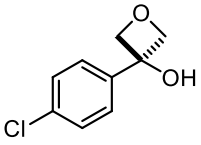
*n*BuLi (1.51 M in hexane, 7.20 mL, 11.0 mmol) was added dropwise over 5 min to a solution of 1-bromo-4-iodobenzene (3.39 g, 12.0 mmol) in THF (20 mL) at –78 °C. The reaction mixture was stirred at –78 °C for 30 min. Oxetan-3-one (640 µL, 10.0 mmol) was added dropwise to the reaction mixture. Following a further 30 min at –78 °C, the reaction was then warmed to rt and quenched with sat. aq. NH_4Cl (60 mL). Et_2O (40 mL) was added and the layers were separated. The aqueous portion was extracted with Et_2O (2 × 40 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography (10% acetone/pentane) afforded oxetanol **179** (2.04 g, 89%) as a white solid. R_f = 0.23 (10% acetone/pentane); mp = 91–93 °C [lit. 93–94° C][77]; IR (film)/cm^{-1} 3343 (br, OH), 2948, 2877, 1478, 1397, 1215, 1177, 1136, 1069, 1006, 980, 950, 872, 820; ^1H NMR

(400 MHz, $CDCl_3$) δ 7.58–7.54 (m, 2 H, 2 × Ar-CH), 7.53–7.49 (m, 2 H, 2 × Ar-CH), 4.95–4.88 (m, 2 H, C*H*HOC*H*H), 4.88–4.85 (m, 2 H, CH*H*OCH*H*), 2.59 (s, br, 1 H, OH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.3 (Ar-C_q-C_q), 131.8 (2 × Ar-CH), 126.2 (2 × Ar-CH), 121.9 (Ar-C_q-Br), 85.7 (CH_2OCH_2), 75.4 (C_q). The observed spectroscopic data for this compound (^{1}H and ^{13}C NMR) was consistent with that previously reported.[77]



3-(4-Iodophenyl)oxetan-3-ol (180)

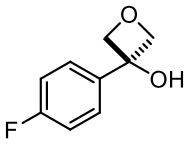
*n*BuLi (1.41 M in hexane, 5.50 mL, 7.70 mmol) was added dropwise over 5 min to a solution of 1,4-diiodobenzene (2.77 g, 8.40 mmol) in THF (14 mL) at –78 °C. The reaction mixture was stirred at –78 °C for 30 min. Oxetan-3-one (450 µL, 7.00 mmol) was added dropwise to the reaction mixture. Following a further 30 min at –78 °C, the reaction was then warmed to rt and then quenched with sat. aq. NH_4Cl (30 mL). Et_2O (40 mL) was added and the layers were separated. The aqueous portion was extracted with Et_2O (2 × 40 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography (40% Et_2O/pentane) afforded oxetanol **180** (1.80 g, 93%) as a white solid. R_f = 0.34 (50% Et_2O/pentane); mp = 106–110 °C; IR (film)/cm^{-1} 3365 (br, OH), 2967, 2877, 1587, 1483, 1408, 1211, 1181, 1062, 1002, 950, 872, 820; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80–7.71 (m, 2 H, 2 × Ar-CH), 7.41–7.34 (m, 2 H, 2 × Ar-CH), 4.92–4.88 (m, 2 H, C*H*HOC*H*H), 4.88–4.83 (m, 2 H, CH*H*OCH*H*), 2.73 (s, 1 H, OH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.0 (Ar-C_q-C_q), 137.7 (2 × Ar-CH), 126.4 (2 × Ar-CH), 121.9 (Ar-C_q-I), 85.7 (CH_2OCH_2), 75.5 (C_q); The observed spectroscopic data for this compound (^{1}H NMR) was consistent with that previously reported.[245]



3-(4-Chlorophenyl)oxetan-3-ol (181)

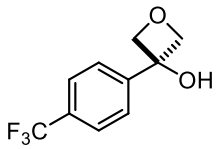
*n*BuLi (1.41 M in hexane, 5.50 mL, 7.70 mmol) was added dropwise over 5 min to a solution of 1-bromo-4-chlorobenzene (1.60 g, 8.40 mmol) in THF (14 mL) at –78 °C. The reaction mixture was stirred at –78 °C for 30 min. Oxetan-3-one (450 µL, 7.00 mmol) was added dropwise to the reaction mixture. Following a further 30 min at –78 °C, the reaction was then warmed to rt and then quenched with sat. aq. NH_4Cl (30 mL). Et_2O (40 mL) was added and the layers were separated. The aqueous portion was extracted with Et_2O (2 × 40 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography (40% Et_2O/pentane) afforded oxetanol **181** (1.20 g, 93%) as a white solid. R_f = 0.38 (50% Et_2O/pentane); mp = 63–65 °C; IR (film)/cm^{-1} 3343 (br, OH), 2967, 2881, 1490, 1416, 1218, 1177, 1088, 1013, 984, 954, 820; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59–7.53 (m, 2 H, 2 × Ar-CH), 7.43–7.37 (m, 2 H, 2 × Ar-CH), 4.93–4.89 (m, 2 H, C*H*HOC*H*H), 4.89–4.84 (m,

2 H, CH*H*OCH*H*), 2.85 (s, 1 H, OH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.8 (Ar-C_q-C_q), 133.8 (Ar-C_q-Cl), 128.8 (2 × Ar-CH), 125.9 (2 × Ar-CH), 85.8 (CH_2OCH_2), 75.4 (C_q); The observed spectroscopic data for this compound (^{1}H NMR) was consistent with that previously reported.[246]



3-(4-Fluorophenyl)oxetan-3-ol (182)

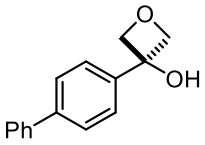
*n*BuLi (1.41 M in hexane, 5.50 mL, 7.70 mmol) was added dropwise over 5 min to a solution of 1-bromo-4-fluorobenzene (920 µL, 8.40 mmol) in THF (14 mL) at –78 °C. The reaction mixture was stirred at –78 °C for 30 min. Oxetan-3-one (450 µL, 7.02 mmol) was added dropwise to the reaction mixture. Following a further 30 min at –78 °C, the reaction was then warmed to rt and then quenched with sat. aq. NH_4Cl (30 mL). Et_2O (40 mL) was added and the layers were separated. The aqueous portion was extracted with Et_2O (2 × 40 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography (40% Et_2O/pentane) afforded oxetanol **182** (1.35 g, 100%) as a white solid. R_f = 0.38 (50% Et_2O/pentane); mp = 66–68 °C; IR (film)/cm^{-1} 3373 (br, OH), 2955, 2877, 1602, 1513, 1408, 1226, 1162, 1099, 969, 879, 834; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62–7.54 (m, 2 H, 2 × Ar-CH), 7.15–7.07 (m, 2 H, 2 × Ar-CH), 4.94–4.85 (m, 4 H, CH_2OCH_2), 2.87 (s, 1 H, OH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.3 (d, $^1J_{C\text{-}F}$ = 246.6 Hz, Ar-C_q-F), 138.1 (d, $^4J_{C\text{-}F}$ = 3.0 Hz, Ar-C_q-C_q), 126.3 (d, $^3J_{C\text{-}F}$ = 8.0 Hz, 2 × Ar-CH), 115.5 (d, $^2J_{C\text{-}F}$ = 21.5 Hz, 2 × Ar-CH), 85.8 (CH_2OCH_2), 75.4 (C_q); ^{19}F{^{1}H} NMR (377 MHz, $CDCl_3$) δ –114.4; HRMS (+APCI) *m*/*z* calcd for $C_9H_8FO_2^+$ [M–OH]$^+$: 151.0554, Found: 151.0555.



3-(4-(Trifluoromethyl)phenyl)oxetan-3-ol (183)

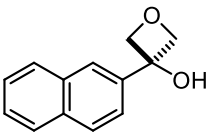
*n*BuLi (1.41 M in hexane, 5.50 mL, 7.70 mmol) was added dropwise over 5 min to a solution of 4-iodobenzotrifluoride (1.23 mL, 8.40 mmol) in THF (14 mL) at –78 °C. The reaction mixture was stirred at –78 °C for 30 min. Oxetan-3-one (450 µL, 7.00 mmol) was added dropwise to the reaction mixture. Following a further 30 min at –78 °C, the reaction was then warmed to rt and then quenched with sat. aq. NH_4Cl (30 mL). Et_2O (40 mL) was added and the layers were separated. The aqueous portion was extracted with Et_2O (2 × 40 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography (40% Et_2O/pentane) afforded oxetanol **183** (1.40 g, 92%) as a white solid. R_f = 0.29 (50% Et_2O/pentane); mp = 122–124 °C; IR (film)/cm^{-1} 3395 (br, OH), 1431, 1323, 1159, 984, 879; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81–7.75 (m, 2 H, 2 × Ar-CH), 7.73–7.67 (m, 2 H, 2 × Ar-CH), 4.97–4.92 (m, 2 H, C*H*HOC*H*H), 4.91–4.88 (m, 2 H, CH*H*OCH*H*), 2.85 (s, 1 H, OH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.1 (Ar-C_q-C_q), 130.2 (q, $^2J_{C\text{-}F}$ = 32.5 Hz, Ar-C_q-CF_3),

125.6 (q, $^{3}J_{C\text{-}F}$ = 3.8 Hz, 2 × Ar-CH), 124.8 (2 × Ar-CH), 124.0 (q, $^{1}J_{C\text{-}F}$ = 272.3 Hz, CF_3), 85.9 (CH_2OCH_2), 75.4 (C_q); $^{19}F\{^{1}H\}$ NMR (377 MHz, $CDCl_3$) δ –62.6; HRMS (+APCI) *m*/*z* calcd for $C_{10}H_8F_3O^+$ $[M–OH]^+$: 201.0522, Found: 201.0524. Compound previously reported without characterisation data.[247]



3-([1,1'-Biphenyl]-4-yl)oxetan-3-ol (184)

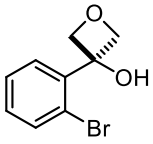
*n*BuLi (1.47 M in hexane, 1.50 mL, 2.20 mmol) was added dropwise over 5 min to a solution of 4-bromobiphenyl (559 mg, 2.40 mmol) in THF (4.0 mL) at –78 °C. The reaction mixture was stirred at –78 °C for 15 min. Oxetan-3-one (130 µL, 2.00 mmol) was added dropwise to the reaction mixture. Following a further 30 min at –78 °C, the reaction was then warmed to rt and then quenched with water (30 mL). Et_2O (30 mL) was added and the layers were separated. The aqueous portion was extracted with Et_2O (2 × 30 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography (40% Et_2O/pentane) afforded oxetanol **184** (347 mg, 77%) as a white solid. R_f = 0.46 (70% Et_2O/pentane); mp = 144–146 °C [lit. 139–142 °C][77]; IR (film)/cm^{-1} 3358 (br, OH), 1420, 1374, 1230, 961, 935, 879, 827, 760, 726, 697; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70–7.65 (m, 4 H, 4 × Ar-CH), 7.63–7.60 (m, 2 H, 2 × Ar-CH), 7.49–7.45 (m, 2 H, 2 × Ar-CH), 7.46–7.40 (m, 1 H, Ar-CH), 4.99–4.94 (m, 4 H, CH_2OCH_2), 2.85 (s, 1 H, OH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.2 (Ar-C_q-C_q), 140.9 (Ar-C_q-C_q), 140.4 (Ar-C_q-C_q), 128.8 (2 × Ar-CH), 127.5 (Ar-CH), 127.4 (2 × Ar-CH), 127.1 (2 × Ar-CH), 125.0 (2 × Ar-CH), 85.7 (CH_2OCH_2), 75.7 (C_q).The observed spectroscopic data for this compound (^{1}H and ^{13}C NMR) was consistent with that previously reported.[77]



3-(Naphthalen-2-yl)oxetan-3-ol (185)

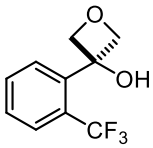
*n*BuLi (1.47 M in hexane, 5.50 mL, 7.70 mmol) was added dropwise over 5 min to a solution of 2-bromonapththalene (1.70 g, 8.40 mmol) in THF (14.0 mL) at –78 °C. The reaction mixture was stirred at –78 °C for 30 min. Oxetan-3-one (450 µL, 7.00 mmol) was added dropwise to the reaction mixture. Following a further 30 min at –78 °C, the reaction was then warmed to rt and then quenched with water (40 mL). Et_2O (40 mL) was added and the layers were separated. The aqueous portion was extracted with Et_2O (2 × 40 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography (50% Et_2O/pentane) afforded oxetanol **185** (1.29 g, 92%) as a white solid. R_f = 0.21 (40% Et_2O/pentane); mp = 109–110 °C; IR (film)/cm^{-1} 3343 (br, OH), 3058, 2963, 2888, 1602, 1423, 1271, 1230, 1192, 965, 902, 857, 748; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, *J* = 1.8 Hz, 1 H, Ar-CH), 7.93 (d, *J* = 8.6 Hz, 1 H, Ar-CH), 7.90–7.84 (m, 2 H, 2 × Ar-CH), 7.74 (dd, *J* = 8.6,

1.8 Hz, 1 H, Ar-CH), 7.56–7.48 (m, 2 H, 2 × Ar-CH), 5.03 (d, *J* = 6.9 Hz, 2 H, C*H*HOC*H*H), 4.99 (d, *J* = 6.9 Hz, 2 H, CH*H*OCH*H*), 2.91 (s, 1 H, OH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.4 (Ar-C_q-C_q), 132.9 (Ar-C_q-C_q), 132.8 (Ar-C_q-C_q), 128.8 (Ar-CH), 128.2 (Ar-CH), 127.6 (Ar-CH), 126.5 (Ar-CH), 126.3 (Ar-CH), 123.2 (Ar-CH), 122.6 (Ar-CH), 85.5 (CH_2OCH_2), 75.9 (C_q); HRMS (+APCI) *m*/*z* calcd for $C_{13}H_{11}O^+$ [M–OH]$^+$: 183.0804, Found: 183.0804.



3-(2-Bromophenyl)oxetan-3-ol (186)[248]

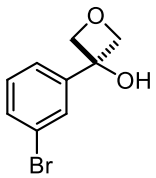
Following a procedure developed by Sun, *i*PrMgCl•LiCl (1.18 M in THF, 7.40 mL, 8.80 mmol) was added dropwise over 5 min to a solution of 1,2-dibromobenzene (1.10 mL, 9.10 mmol) in THF (14.0 mL) at –78 °C. The reaction mixture was warmed and stirred at 0 °C for 1 h. The reaction was then cooled to 0 °C and oxetan-3-one (450 µL, 7.00 mmol) was added. Following a further 1 h at 25 °C the reaction mixture was quenched with sat. aq. NH_4Cl (20 mL). The aqueous portion was extracted with Et_2O (3 × 50 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash chromatography (50% Et_2O/pentane) afforded oxetanol **186** (1.10 g, 69%) as a white solid. R_f = 0.26 (50% Et_2O/pentane); mp = 53–56 °C; IR (film)/cm^{-1} 3362 (br, OH), 2944, 2877, 1472, 1438, 1181, 1136, 1021, 976, 879, 760, 700; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (dd, *J* = 7.9, 1.2 Hz, 1 H, Ar-CH), 7.37 (ddd, *J* = 7.9, 7.5, 1.2 Hz, 1 H, Ar-CH), 7.29 (dd, *J* = 7.9, 1.7 Hz, 1 H, Ar-CH), 7.23 (ddd, *J* = 7.9, 7.5, 1.7 Hz, 1 H, Ar-CH), 5.25–5.16 (m, 2 H, C*H*HOC*H*H), 4.97–4.88 (m, 2 H, CH*H*OCH*H*), 3.15–3.03 (m, 1 H, OH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.4 (Ar-C_q-C_q), 133.9 (Ar-CH), 130.1 (Ar-CH), 127.8 (Ar-CH), 127.7 (Ar-CH), 121.6 (Ar-C_q-Br), 82.4 (CH_2OCH_2), 78.1 (C_q).



3-(2-(Trifluoromethyl)phenyl)oxetan-3-ol (187)

*n*BuLi (1.41 M in hexane, 4.50 mL, 7.70 mmol) was added dropwise over 5 min to a solution of 2-bromo-1-benzotrifluoride (1.15 mL, 8.40 mmol) in THF (14 mL) at –78 °C. The reaction mixture was stirred at –78 °C for 20 min. Oxetan-3-one (450 µL, 7.00 mmol) was added dropwise to the reaction mixture. Following a further 1 h 30 min at –78 °C, the reaction was then warmed to rt and then quenched with water (30 mL). Et_2O (40 mL) was added and the layers were separated. The aqueous portion was extracted with Et_2O (2 × 40 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography (50% Et_2O/pentane) afforded oxetanol **187** (1.38 g, 90%) as a white solid. R_f = 0.30 (50% Et_2O/pentane); mp = 66–69 °C; IR (film)/cm^{-1} 3369 (br, OH), 2955, 2885, 1312, 1170, 1110, 1077, 1032, 980, 887, 831, 767, 689; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75–7.70 (m, 1 H, Ar-CH), 7.63–7.56 (m, 1 H, Ar-CH), 7.54–7.44 (m, 1 H, Ar-CH), 7.30 (d, *J* = 7.8 Hz, 1 H, Ar-CH), 5.21

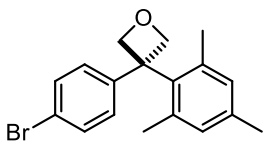
(d, *J* = 7.4 Hz, 2 H, C*H*HOC*H*H), 4.84 (d, *J* = 7.4 Hz, 2 H, CH*H*OCH*H*), 2.99 (d, *J* = 1.9 Hz, 1 H, OH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.1 (d, ^{3}J = 1.6 Hz, Ar-C_q-C_q), 132.4 (Ar-CH), 128.8 (Ar-CH), 128.2 (Ar-CH), 127.7 (q, $^{3}J_{C\text{-}F}$ = 6.0 Hz, Ar-CH), 127.1 (q, $^{2}J_{C\text{-}F}$ = 31.3 Hz, Ar-C_q-CF_3), 124.1 (q, $^{1}J_{C\text{-}F}$ = 273.2 Hz, CF_3), 82.8 (q, *J* = 3.6 Hz, CH_2OCH_2), 77.0 (C_q); ^{19}F{^{1}H} NMR (377 MHz, $CDCl_3$) δ –58.7; HRMS (+APCI) *m*/*z* calcd for $C_{10}H_8F_3O^+$ [M–OH]$^+$: 201.0522, Found: 201.0524.



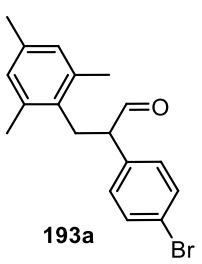
3-(3-Bromophenyl)oxetan-3-ol (188)

*i*PrMgCl•LiCl (1.18 M in THF, 7.40 mL, 8.80 mmol) was added dropwise over 5 min to a solution of 1,2-dibromobenzene (1.10 mL, 9.10 mmol) in THF (14.0 mL) at –78 °C. The reaction mixture was warmed and stirred at 0 °C for 1 h. The reaction was then cooled to 0 °C and oxetan-3-one (450 µL, 7.00 mmol) was added. Following a further 1 h at 25 °C the reaction mixture was quenched with sat. aq. NH_4Cl (20 mL). The aqueous portion was extracted with Et_2O (3 × 50 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash chromatography (40% Et_2O/pentane) afforded oxetanol **188** (723 mg, 45%) as a white solid. R_f = 0.42 (50% Et_2O/pentane); mp = 93–94 °C; IR (film)/cm^{-1} 3369 (br, OH), 2952, 2877, 1595, 1569, 1476, 1416, 1326, 1267, 1177, 1062, 969, 883, 782, 726, 700; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (ddd, *J* = 2.0, 1.8, 0.4 Hz, 1 H, Ar-CH), 7.57 (ddd, *J* = 7.9, 1.8, 1.0 Hz, 1 H, Ar-CH), 7.48 (ddd, *J* = 8.0, 2.0, 1.0 Hz, 1 H, Ar-CH), 7.31 (ddd, *J* = 8.0, 7.9, 0.4, 1 H, Ar-CH), 4.90 (d, *J* = 7.3 Hz, 2 H, C*H*HOC*H*H), 4.87 (d, *J* = 7.3 Hz, 2 H, CH*H*OCH*H*), 2.85 (s, 1 H, OH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.5 (Ar-C_q-C_q), 131.0 (Ar-CH), 130.3 (Ar-CH), 127.8 (Ar-CH), 123.1 (Ar-CH), 122.9 (Ar-C_q-Br), 85.7 (CH_2OCH_2), 75.3 (C_q); HRMS (+APCI) *m*/*z* calcd for $C_9H_8O^{79}Br^+$ [M–OH]$^+$: 210.9753, Found: 210.9755. Compound previously reported without characterisation data.[249]

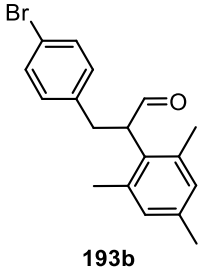
3-(4-Bromophenyl)-3-mesityloxetane (193), 2-(4-bromophenyl)-3-mesitylpropanal (193a) and **3-(4-bromophenyl)-2-mesitylpropanal (193b)**



193



193a



193b

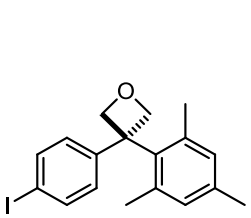
$FeCl_3$ (8.1 mg, 0.05 mmol) was weighed in a vial. Oxetanol **179** (114 mg, 0.50 mmol) and mesitylene (350 µL, 2.50 mmol) were added. The reaction vessel was sealed and HFIP (5.0 mL) was added. The reaction was stirred for 18 h at 80 °C, then cooled to rt and sat. aq.

$NaHCO_3$ (20 mL) was added followed by Et_2O (15 mL). The layers were separated and the aqueous portion was extracted with Et_2O (2 × 15 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash chromatography (4% Et_2O/pentane) afforded a mixture of aldehyde **193a** and **193b** (38:62, 10.2 mg, 6%) as a yellow oil, followed by oxetane **193** (125 mg, 76%) as a yellow oil.

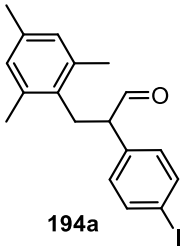
Aldehyde **193a** and **193b**: R_f = 0.40 (4% Et_2O/pentane); IR (film)/cm^{-1} 2918, 2862, 2810, 2713, 1722 (C=O), 1610, 1487, 1446, 1401, 1073, 1010, 853, 812, 711; ^1H NMR (400 MHz, $CDCl_3$) δ 9.79 (d, *J* = 1.4 Hz, 1 H, H_aC=O), 9.75 (s, 1 H, H_bC=O), 7.49–7.43 (m, 2 H, 2 × Ar-CH_a), 7.34–7.28 (m, 2 H, 2 × Ar-CH_b), 6.98–6.92 (m, 2 H, 2 × Ar-CH_a), 6.90–6.82 (m, 4 H, 4 × Ar-CH_b), 6.79 (s, 2 H, 2 × Ar-CH_a), 3.91 (dd, *J* = 8.2, 4.9 Hz, 1 H, (C=O)-CH_b), 3.68–3.63 (m, 1 H, (C=O)-CH_a), 3.61 (dd, *J* = 13.7, 4.9 Hz, 1 H, CH-C*H*H_b), 3.47 (dd, *J* = 14.2, 5.7 Hz, 1 H, CH-C*H*H_a), 2.88 (dd, *J* = 14.2, 8.3 Hz, 1 H, CH-CH*H*$_a$), 2.79 (dd, *J* = 13.7, 8.2 Hz, 1 H, CH-CH*H*$_b$), 2.28 (s, 3 H, $CH_{3,b}$), 2.24 (s, 3 H, $CH_{3,a}$), 2.12–1.95 (m, 12 H, 4 × $CH_{3(a+b)}$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 201.3 (C_b=O), 199.7 (C_a=O), 138.9 (Ar-$C_{q,b}$-CH_2), 137.4 (Ar-$C_{q,b}$-CH), 136.4 (Ar-$C_{q,a}$-CH_2), 135.8 (Ar-$C_{q,a}$-CH), 135.6 (Ar-$C_{q,a}$-CH_3), 132.4 (2 × Ar-$C_{q,a}$-CH_3), 132.1 (2 × Ar-$C_{q,b}$-CH_3), 132.0 (2 × Ar-CH_a), 131.3 (2 × Ar-CH_b), 130.9 (2 × Ar-CH_b), 130.7 (2 × Ar-CH_a), 130.1 (2 × Ar-CH_b and Ar-$C_{q,b}$-CH_3), 129.2 (2 × Ar-CH_a), 121.7 (Ar-$C_{q,a}$-Br), 120.3 (Ar-$C_{q,b}$-Br), 58.6 ((C=O)-*C*H_a), 56.7 ((C=O)-*C*H_b), 33.4 (CH-*C*$H_{2,b}$), 30.3 (CH-*C*$H_{2,a}$), 20.80 (Ar-$CH_{3,b}$), 20.78 (Ar-$CH_{3,a}$), 20.6 (2 × Ar-$CH_{3,b}$), 20.0 (2 × Ar-$CH_{3,a}$); HRMS (+APCI) *m*/*z* calcd. for $C_{18}H_{20}{}^{79}BrO^+$ $[M+H]^+$: 331.0692, Found: 331.0707.

Oxetane **193**: R_f = 0.36 (4% Et_2O/pentane); IR (film)/cm^{-1} 2952, 2870, 1487, 1387, 1036, 987, 943, 846, 767, 730; ^1H NMR (400 MHz, $CDCl_3$) δ 7.51–7.42 (m, 2 H, 2 × Ar-CH), 7.41–7.33 (m, 2 H, 2 × Ar-CH), 6.90 (s, 2 H, 2 × Ar-CH), 5.40 (d, *J* = 5.1 Hz, 2 H, C*H*HOC*H*H), 4.77 (d, *J* = 5.1 Hz, 2 H, CH*H*OCH*H*), 2.33 (s, 3 H, CH_3), 1.86 (s, 6 H, 2 × CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.1 (Ar-C_q-C_q), 137.1 (Ar-C_q-C_q), 136.5 (Ar-C_q-CH_3), 136.1 (2 × Ar-C_q-CH_3), 131.7 (2 × Ar-CH), 129.9 (2 × Ar-CH), 127.6 (2 × Ar-CH), 121.0 (Ar-C_q-Br), 84.9 (*C*H_2O*C*H_2), 52.4 (C_q), 20.7 (Ar-CH_3), 20.1 (2 × Ar-CH_3); HRMS (+APCI) *m*/*z* calcd for $C_{18}H_{20}{}^{79}BrO^+$ $[M+H]^+$: 331.0692, Found: 331.0698.

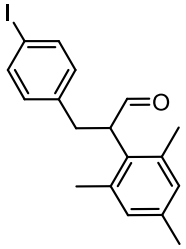
3-(4-Iodophenyl)-3-mesityloxetane (194), 2-(4-iodophenyl)-3-mesitylpropanal (194a) and **3-(4-iodophenyl)-2-mesitylpropanal (194b)**



194



194a



194b

$FeCl_3$ (8.1 mg, 0.05 mmol) was weighed in a vial. Oxetanol **180** (138 mg, 0.50 mmol) and mesitylene (350 µL, 2.50 mmol) were added. The reaction vessel was sealed and HFIP (5.0 mL) was added. The reaction was stirred for 18 h at 80 °C, then cooled to rt and sat. aq. $NaHCO_3$ (20 mL) was added followed by Et_2O (15 mL). The layers were separated and the aqueous portion was extracted with Et_2O (2 × 15 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash chromatography (4% Et_2O/pentane) afforded a mixture of aldehyde **194a** and **194b** (53:47, 16.4 mg, 9%) as a yellow oil, followed by oxetane **194** (148 mg, 78%) as a yellow oil.

The reaction was also scaled to 4.0 mmol and performed in a round bottom flask: $FeCl_3$ (64.9 mg, 0.40 mmol), oxetanol **180** (1.10 g, 4.00 mmol), mesitylene (2.8 mL, 20.0 mmol) and HFIP (40 mL). Purification by flash chromatography (4% Et_2O/pentane) afforded aldehyde **194b** (13.8 mg, 0.9%) as a yellow oil, followed by oxetane **194** (1.04 g, 69%) as a yellow sticky solid.

Aldehyde **194a**[n]: R_f = 0.29 (4% Et_2O/pentane); IR (film)/cm^{-1} 2955, 2918, 2862, 2814, 2717, 1725 (C=O), 1483, 1010, 853, 812; ^1H NMR (400 MHz, $CDCl_3$) δ 9.79 (d, *J* = 1.4 Hz, 1 H, HC=O), 7.70–7.61 (m, 2 H, 2 × Ar-CH), 6.85–6.81 (m, 2 H, 2 × Ar-CH), 6.80 (s, 2 H, 2 × Ar-CH), 3.66–3.62 (m, 1 H, (C=O)-CH), 3.47 (dd, *J* = 14.2, 5.7 Hz, 1 H, CH-C*H*H), 2.87 (dd, *J* = 14.2, 8.3 Hz, 1 H, CH-CH*H*), 2.24 (s, 3 H, CH_3), 2.06 (s, 6 H, 2 × CH_3);^{13}C NMR (101 MHz, $CDCl_3$) δ 199.7 (C=O), 138.0 (2 × Ar-CH), 136.3 (2 × Ar-C_q-CH_3), 136.2 (Ar-C_q-CH_2), 135.8 (Ar-C_q-CH), 132.1 (Ar-C_q-CH_3), 131.0 (2 × Ar-CH), 129.2 (2 × Ar-CH), 93.2 (Ar-C_q-I), 58.7 ((C=O)-*C*H), 30.2 (CH-*C*H_2), 20.8 (Ar-CH_3), 20.0 (2 × Ar-CH_3); HRMS (+APCI) *m*/*z* calcd for $C_{18}H_{18}IO^{+\bullet}$ $[M–H]^{+\bullet}$: 377.0397, Found: 377.0390.

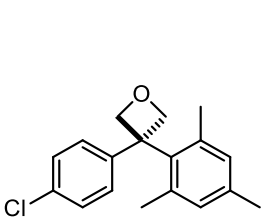
Aldehyde **194b**: R_f = 0.29 (4% Et_2O/pentane); IR (film)/cm^{-1} 2918, 2863, 2713, 1710 (C=O), 1483, 1446, 1401, 1062, 1006, 853, 808, 708; ^1H NMR (400 MHz, $CDCl_3$) δ 9.74 (s, 1 H, HC=O), 7.54–7.48 (m, 2 H, 2 × Ar-CH), 6.86 (s, 2 H, 2 × Ar-CH), 6.77–6.70 (m, 2 H, 2 × Ar-CH), 3.91 (dd, *J* = 8.2, 4.9 Hz, 1 H, (C=O)-CH), 3.60 (dd, *J* = 13.7, 4.9 Hz, 1 H, CH-C*H*H), 2.77

[n] Assigned comparing the ^1H and ^{13}C NMR spectra of aldehyde **194b** with the mixture of **194a**/**194b**.

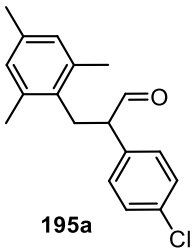
(dd, J = 13.7, 8.2 Hz, 1 H, CH-CHH), 2.28 (s, 3 H, CH_3), 2.04 (s, 6 H, 2 × CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 201.3 (C=O), 139.6 (Ar-C_q-CH_2), 137.4 (Ar-C_q-CH), 137.3 (2 × Ar-CH), 131.2 (2 × Ar-CH), 130.1 (2 × Ar-CH), 130.0 (br, 3 × Ar-C_q-CH_3), 91.4 (Ar-C_q-I), 56.7 ((C=O)-CH), 33.5 (CH-CH_2), 20.8 (Ar-CH_3), 20.6 (2 × Ar-CH_3). HRMS (+APCI) m/z calcd for $C_{18}H_{20}IO^+$ $[M+H]^+$: 379.0553, Found: 379.0544.

Oxetane **194**: R_f = 0.26 (4% Et_2O/pentane); mp = 41–42 °C; IR (film)/cm^{-1} 2962, 2870, 1610, 1476, 1453, 1073, 1032, 987, 943, 842, 764; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71–7.61 (m, 2 H, 2 × Ar-CH), 7.29–7.20 (m, 2 H, 2 × Ar-CH), 6.90 (s, 2 H, 2 × Ar-CH), 5.40 (dd, J = 5.0 , 1.1 Hz, 2 H, CHHOCHH), 4.76 (dd, J = 5.0, 1.3 Hz, 2 H, CHHOCHH), 2.33 (s, 3 H, CH_3), 1.85 (s, 6 H, 2 × CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.8 (Ar-C_q-C_q), 137.7 (2 × Ar-CH), 137.0 (Ar-C_q-C_q), 136.5 (Ar-C_q-CH_3), 136.1 (2 × Ar-C_q-CH_3), 129.8 (2 × Ar-CH), 127.9 (2 × Ar-CH), 92.6 (Ar-C_q-I), 84.8 (CH_2OCH_2), 52.4 (C_q), 20.7 (Ar-CH_3), 20.1 (2 × Ar-CH_3); HRMS (+APCI) m/z calcd for $C_{18}H_{20}IO^+$ $[M+H]^+$: 379.0553, Found: 379.0571.

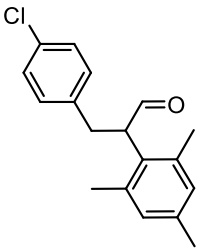
3-(4-Chlorophenyl)-3-mesityloxetane (195), 2-(4-chlorophenyl)-3-mesitylpropanal (195a) and **3-(4-chlorophenyl)-2-mesitylpropanal (195b)**



195



195a



195b

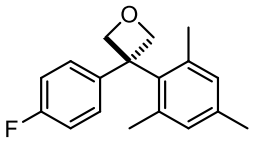
$FeCl_3$ (8.1 mg, 0.05 mmol) was weighed in a vial. Oxetanol **181** (92.3 mg, 0.50 mmol) and mesitylene (350 µL, 2.50 mmol) were added. The reaction vessel was sealed and HFIP (5.0 mL) was added. The reaction was stirred for 18 h at 80 °C, then cooled to rt and sat. aq. $NaHCO_3$ (20 mL) was added followed by Et_2O (15 mL). The layers were separated and the aqueous portion was extracted with Et_2O (2 × 15 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash chromatography (4% Et_2O/pentane) afforded a mixture of aldehyde **195a** and **195b** (39:61, 10.3 mg, 7%) as a yellow oil, followed by oxetane **195** (115 mg, 80%) as a yellow oil.

Aldehyde **195a** and **195b**: R_f = 0.59 (4% Et_2O/pentane); IR (film)/cm^{-1} 2955, 2922, 2862, 2810, 2717, 1725 (C=O), 1610, 1490, 1092, 1013, 853, 820, 719; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.80 (d, J = 1.4 Hz, 1 H, H_aC=O), 9.75 (s, 1 H, H_bC=O), 7.34–7.28 (m, 2 H, 2 × Ar-CH_a), 7.19–7.13 (m, 2 H, 2 × Ar-CH_b), 7.03–6.97 (m, 2 H, 2 × Ar-CH_a), 6.95–6.89 (m, 2 H, 2 × Ar-CH_b), 6.86 (s, 2 H, 2 × Ar-CH_b), 6.79 (s, 2 H, 2 × Ar-CH_a), 3.91 (dd, J = 8.3, 4.9 Hz, 1 H, (C=O)-CH_b), 3.70–

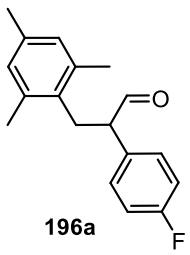
3.65 (m, 1 H, (C=O)-CH$_a$), 3.62 (dd, J = 13.7, 4.9 Hz, 1 H, CH-CHH$_b$), 3.47 (dd, J = 14.2, 5.6 Hz, 1 H, CH-CHH$_a$), 2.87 (dd, J = 14.2, 8.3 Hz, 1 H, CH-CHH_a), 2.81 (dd, J = 13.7, 8.3 Hz, 1 H, CH-CHH_b), 2.28 (s, 3 H, CH$_{3,b}$), 2.24 (s, 3 H, CH$_{3,a}$), 2.10 (s, 6 H, 2 × CH$_{3,a}$), 2.00 (s, br, 6 H, 2 × CH$_{3,b}$); ^{13}C NMR (101 MHz, CDCl$_3$) δ 201.3 (C$_b$=O), 199.8 (C$_a$=O), 138.4 (Ar-$C_{q,b}$-CH$_2$), 137.4 (Ar-$C_{q,b}$-CH), 136.4 (2 × Ar-$C_{q,a}$-CH$_3$), 135.8 (Ar-$C_{q,a}$-CH$_2$), 135.1 (Ar-$C_{q,a}$-CH), 133.7 (Ar-C$_{q,a}$-Cl), 132.2 (Ar-$C_{q,a}$-CH$_3$), 132.0 (Ar-C$_{q,b}$-Cl), 130.5 (2 × Ar-CH$_b$), 130.4 (2 × Ar-CH$_a$), 130.1 (2 × Ar-CH$_b$), 130.0 (br, 3 × Ar-C$_{q,b}$-CH$_3$), 129.2 (2 × Ar-CH$_a$), 129.1 (2 × Ar-CH$_a$), 128.3 (2 × Ar-CH$_b$), 58.6 ((C=O)-CH$_a$), 56.8 ((C=O)-CH$_b$), 33.4 (CH-CH$_{2,b}$), 30.3 (CH-CH$_{2,a}$), 20.80 (Ar-CH$_{3,b}$), 20.78 (Ar-CH$_{3,a}$), 20.6 (br, 2 × Ar-CH$_{3,b}$), 20.0 (2 × Ar-CH$_{3,a}$); HRMS (+APCI) m/z calcd for $C_{18}H_{18}{}^{35}ClO^{+\bullet}$ [M–H]$^{+\bullet}$: 285.1041, Found: 285.1044.

Oxetane **195**: R_f = 0.53 (4% Et$_2$O/pentane); IR (film)/cm^{-1} 2952, 2870, 1610, 1490, 1401, 1095, 1013, 849, 827, 771, 745, 674; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.46–7.38 (m, 2 H, 2 × Ar-CH), 7.34–7.28 (m, 2 H, 2 × Ar-CH), 6.90 (s, 2 H, 2 × Ar-CH), 5.39 (dd, J = 5.0, 1.1 Hz, 2 H, CHHOCHH), 4.77 (dd, J = 5.0, 1.2 Hz, 2 H, CHHOCHH), 2.32 (s, 3 H, CH$_3$), 1.85 (s, 6 H, 2 × CH$_3$); ^{13}C NMR (101 MHz, CDCl$_3$) δ 143.5 (Ar-C_q-C$_q$), 137.2 (Ar-C_q-C$_q$), 136.5 (Ar-C_q-CH$_3$), 136.1 (2 × Ar-C_q-CH$_3$), 132.9 (Ar-C$_q$-Cl), 129.9 (2 × Ar-CH), 128.7 (2 × Ar-CH), 127.2 (2 × Ar-CH), 85.0 (CH$_2$OCH$_2$), 52.3 (C$_q$), 20.7 (Ar-CH$_3$), 20.1 (2 × Ar-CH$_3$); HRMS (+APCI) m/z calcd for $C_{18}H_{20}{}^{35}ClO^{+}$ [M+H]$^{+}$: 287.1197, Found: 287.1192.

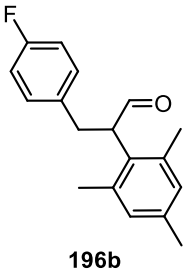
3-(4-Fluorophenyl)-3-mesityloxetane (196), 2-(4-fluorophenyl)-3-mesitylpropanal (196a) and **3-(4-fluorophenyl)-2-mesitylpropanal (196b)**



196



196a

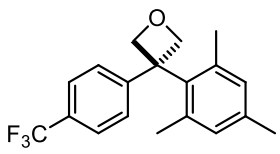


196b

$FeCl_3$ (8.1 mg, 0.05 mmol) was weighed in a vial. Oxetanol **182** (92.3 mg, 0.50 mmol) and mesitylene (350 µL, 2.50 mmol) were added. The reaction vessel was sealed and HFIP (5.0 mL) was added. The reaction was stirred for 18 h at 80 °C, then cooled to rt and sat. aq. $NaHCO_3$ (20 mL) was added followed by Et_2O (15 mL). The layers were separated and the aqueous portion was extracted with Et_2O (2 × 15 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash chromatography (4% Et_2O/pentane) afforded a mixture of aldehyde **196a** and **196b** (7:93, 10.0 mg, 7%) as a yellow oil, followed by oxetane **196** (109 mg, 81%) as a yellow oil.

Aldehyde **196a** and **196b**: R_f = 0.50 (4% Et_2O/pentane); IR (film)/cm^{-1} 2952, 2922, 2866, 1722 (C=O), 1602, 1509, 1483, 1449, 1222, 1159, 853, 782; ^1H NMR (400 MHz, $CDCl_3$) δ 9.81 (d, *J* = 1.4 Hz, 1 H, H_aC=O), 9.77 (s, 1 H, H_bC=O), 7.04 (s, 2 H, 2 × Ar-CH_a), 7.02 (s, 2 H, 2 × Ar-CH_a), 6.97–6.82 (m, 6 H, 6 × Ar-CH_b), 6.79 (s, 2 H, 2 × Ar-CH_a), 3.91 (dd, *J* = 8.3, 4.9 Hz, 1 H, (C=O)-CH_b), 3.70–3.66 (m, 1 H, (C=O)-CH_a), 3.63 (dd, *J* = 13.8, 4.9 Hz, 1 H, CH-C*H*H_b), 3.47 (dd, *J* = 14.2, 5.6 Hz, 1 H, CH-C*H*H_a), 2.93 (dd, *J* = 14.2, 8.3 Hz, 1 H, CH-CH*H*$_a$), 2.82 (dd, *J* = 13.8, 8.3 Hz, 1 H, CH-CH*H*$_b$), 2.28 (s, 3 H, $CH_{3,b}$), 2.24 (s, 3 H, $CH_{3,a}$), 2.10 (s, 6 H, 2 × $CH_{3,a}$), 2.05 (s, br, 6 H, 2 × $CH_{3,b}$); ^{13}C NMR (101 MHz, $CDCl_3$)[o] δ 201.5 (C_b=O), 200.8 (C_a=O), 161.5 (d, ^1J = 244.0 Hz, Ar-$C_{q,b}$-F), 137.4 (Ar-$C_{q,a}$-CH_2), 137.3 (Ar-$C_{q,b}$-CH), 136.4 (2 × Ar-$C_{q,a}$-CH_3), 135.5 (d, ^4J = 3.2 Hz, Ar-$C_{q,b}$-CH_2), 135.4 (d, ^4J = 2.7 Hz, Ar-$C_{q,a}$-CH), 130.6 (d, ^3J = 7.8 Hz, 2 × Ar-CH_b), 130.2 (2 × Ar-CH_b), 130.0 (br, 3 × Ar-$C_{q,b}$-CH_3), 129.1 (2 × Ar-CH_a), 115.9 (d, ^2J = 21.9 Hz, 2 × Ar-CH_a), 115.0 (d, ^2J = 21.4 Hz, 2 × Ar-CH_b), 58.4 ((C=O)-*C*H_a), 57.0 ((C=O)-*C*H_b), 33.2 (CH-*C*$H_{2,b}$), 30.3 (CH-*C*$H_{2,a}$), 20.80 (Ar-$CH_{3,b}$), 20.78 (Ar-$CH_{3,a}$), 20.6 (br, 2 × Ar-$CH_{3,b}$), 20.0 (2 × Ar-$CH_{3,a}$); $^{19}F\{^1H\}$ NMR (377 MHz, $CDCl_3$) δ –114.6 (F_a), –117.1 (F_b); HRMS (+APCI) *m*/*z* calcd for $C_{18}H_{18}FO^{+\bullet}$ $[M–H]^{+\bullet}$: 269.1336, Found: 269.1345.

Oxetane **196**: R_f = 0.44 (4% Et_2O/pentane); IR (film)/cm^{-1} 2955, 2873, 1632, 1505, 1453, 1222, 1162, 1036, 991, 834; ^1H NMR (400 MHz, $CDCl_3$) δ 7.50–7.42 (m, 2 H, 2 × Ar-CH), 7.07–6.99 (m, 2 H, 2 × Ar-CH), 6.91 (s, 2 H, 2 × Ar-CH), 5.41 (dd, *J* = 5.0, 1.1 Hz, 2 H, C*H*HOC*H*H), 4.79 (dd, *J* = 5.0, 1.2 Hz, 2 H, CH*H*OCH*H*), 2.33 (s, 3 H, CH_3), 1.87 (s, 6 H, 2 × CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.0 (d, ^1J = 245.4 Hz, Ar-C_q-F), 140.7 (d, ^4J = 3.3 Hz, Ar-C_q-C_q), 137.5 (Ar-C_q-C_q), 136.4 (Ar-C_q-CH_3), 136.1 (2 × Ar-C_q-CH_3), 129.8 (2 × Ar-CH), 127.4 (d, ^3J = 7.8 Hz, 2 × Ar-CH), 115.3 (d, ^2J = 21.1 Hz, 2 × Ar-CH), 85.2 (*C*H_2O*C*H_2), 52.3 (C_q), 20.7 (Ar-CH_3), 20.1 (2 × Ar-CH_3); $^{19}F\{^1H\}$ NMR (377 MHz, $CDCl_3$) δ –116.2; HRMS (+APCI) *m*/*z* calcd for $C_{18}H_{18}FO^+$ $[M–H]^+$: 269.1336, Found: 269.1344.



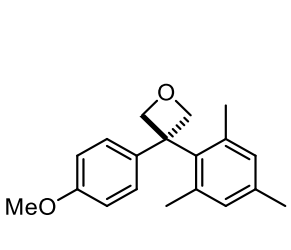
3-Mesityl-3-(4-(trifluoromethyl)phenyl)oxetane (197)

$FeCl_3$ (8.1 mg, 0.05 mmol) was weighed in a vial. Oxetanol **183** (109 mg, 0.50 mmol) and mesitylene (350 µL, 2.50 mmol) were added. The reaction vessel was sealed and HFIP (5.0 mL) was added. The reaction was stirred for 18 h at 80 °C, then cooled to rt and sat. aq. $NaHCO_3$ (20 mL) was added followed by Et_2O (15 mL). The layers were separated and the aqueous portion was extracted with Et_2O (2 × 15 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash chromatography (4% Et_2O/pentane) afforded oxetane **197** (4.5 mg, 3%) as a yellow oil. R_f = 0.45 (4% Et_2O/pentane);

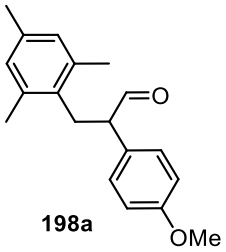
[o] The signal for Ar-$C_{q,a}$-F, 2 × Ar-CH_a and Ar-$C_{q,a}$-CH_3 were not observed due to the small amount of **196a** in the mixture.

IR (film)/cm^{-1} 2959, 2877, 1617, 1326, 1166, 1125, 1080, 1036, 842; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65–7.56 (m, 4 H, 4 × Ar-CH), 6.91 (s, 2 H, 2 × Ar-CH), 5.42 (dd, *J* = 5.0, 1.3 Hz, 2 H, C*H*HOC*H*H), 4.80 (dd, *J* = 5.0, 1.3 Hz, 2 H, CH*H*OCH*H*), 2.33 (s, 3 H, CH_3), 1.85 (s, 6 H, 2 × CH_3); ^{13}C NMR (101 MHz, $CDCl_3$)[p] δ 149.1 (Ar-C_q-C_q), 136.8 (Ar-C_q-C_q), 136.7 (Ar-C_q-CH_3), 136.1 (2 × Ar-C_q-CH_3), 130.0 (2 × Ar-CH), 126.1 (2 × Ar-CH), 125.6 (d, ^{3}J = 3.6 Hz, 2 × Ar-CH), 84.8 (CH_2OCH_2), 52.7 (C_q), 20.7 (Ar-CH_3), 20.1 (2 × Ar-CH_3); ^{19}F{^{1}H} NMR (377 MHz, $CDCl_3$) δ –62.4; HRMS (+APCI) *m*/*z* calcd for $C_{19}H_{20}F_3O^+$ [M+H]$^+$: 321.1461, Found: 321.1462.

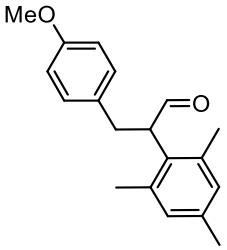
3-Mesityl-3-(4-methoxyphenyl)oxetane (198), 3-mesityl-2-(4-methoxyphenyl)propanal (198a) and **2-mesityl-3-(4-methoxyphenyl)propanal (198b)**



198



198a



198b

$FeCl_3$ (8.1 mg, 0.05 mmol) was weighed in a vial. Oxetanol **18** (90.0 mg, 0.50 mmol) and mesitylene (350 µL, 2.50 mmol) were added. The reaction vessel was sealed and HFIP (5.0 mL) was added. The reaction was stirred for 18 h at 80 °C, then cooled to rt and sat. aq. $NaHCO_3$ (20 mL) was added followed by Et_2O (15 mL). The layers were separated and the aqueous portion was extracted with Et_2O (2 × 15 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash chromatography (4% Et_2O/pentane) afforded a mixture of aldehyde **198a** and **198b** (20:80, 3.2 mg, 2%) as a yellow oil, followed by oxetane **198** (87.9 mg, 62%) as a colourless paste

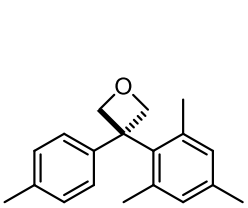
Aldehyde **198a** and **198b**: R_f = 0.38 (4% Et_2O/pentane); IR (film)/cm^{-1} 2952, 1722 (C=O), 1610, 1513, 1300, 1244, 1177, 1036, 849, 827; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.78 (d, *J* = 1.5 Hz, 1 H, H_aC=O), 9.77 (s, 1 H, H_bC=O), 7.00–6.97 (m, 2 H, 2 × Ar-CH_a), 6.93–6.89 (m, 2 H, 2 × Ar-CH_b), 6.89–6.87 (m, 2 H, 2 × Ar-CH_a), 6.85 (s, 2 H, 2 × Ar-CH_b), 6.78 (s, 2 H, 2 × Ar-CH_a), 6.76–6.71 (m, 2 H, 2 × Ar-CH_b), 3.91 (dd, *J* = 8.1, 5.0 Hz, 1 H, (C=O)-CH_b), 3.81 (s, 3 H, $OCH_{3,a}$), 3.77 (s, 3 H, $OCH_{3,b}$), 3.65–3.60 (m, 1 H, (C=O)-CH_a), 3.60 (dd, *J* = 13.7, 5.0 Hz, 1 H, CH-C*H*H_b), 3.47 (dd, *J* = 14.2, 5.6 Hz, 1 H, CH-C*H*H_a), 2.86 (dd, *J* = 14.2, 8.2 Hz, 1 H, CH-CH*H*$_a$), 2.78 (dd, *J* = 13.7, 8.1 Hz, 1 H, CH-CH*H*$_b$), 2.28 (s, 3 H, $CH_{3,b}$), 2.24 (s, 3 H, $CH_{3,a}$), 2.05 (s, 6 H, 2 × $CH_{3,a}$), 2.05 (s, br, 6 H, 2 × $CH_{3,b}$); ^{13}C NMR (101 MHz, $CDCl_3$)[q] δ 201.9 (C_b=O), 153.9 (Ar-$C_{q,b}$-OCH_3), 137.1 (Ar-$C_{q,b}$-CH), 132.0 (Ar-$C_{q,b}$-CH_2), 130.1 (4 × Ar-CH_b),

[p] The signal for Ar-C_q-CF_3 and CF_3 were not observed due to the small amount of product isolated.
[q] Only signals for **198b** could be attributed due to the low amount of material.

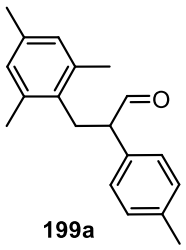
129.9 (br, 3 × Ar-$C_{q,b}$-CH_3), 113.6 (2 × Ar-CH_b), 57.2 ((C=O)-CH_b), 55.2 ($OCH_{3,b}$), 33.2 (CH-$CH_{2,b}$), 20.8 (Ar-$CH_{3,b}$), 20.7 (2 × Ar-$CH_{3,b}$); HRMS (+APCI) *m*/*z* calcd for $C_{19}H_{23}O_2^+$ $[M+H]^+$: 283.1693, Found: 283.1703.

Oxetane **198**: R_f = 0.30 (4% Et_2O/pentane); IR (film)/cm^{-1} 2952, 2870, 1610, 1509, 1461, 1297, 1248, 1185, 1036, 991, 943, 831; ^1H NMR (400 MHz, $CDCl_3$) δ 7.43–7.36 (m, 2 H, 2 × Ar-CH), 6.91–6.83 (m, 4 H, 4 × Ar-CH), 5.39 (dd, *J* = 5.0, 1.1 Hz, 2 H, C*H*HOC*H*H), 4.79 (dd, *J* = 5.0, 1.2 Hz, 2 H, CH*H*OCH*H*), 3.81 (s, 3 H, OCH_3), 2.32 (s, 3 H, CH_3), 1.87 (s, 6 H, 2 × CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.6 (Ar-C_q-OCH_3), 138.0 (Ar-C_q-C_q), 137.0 (Ar-C_q-C_q), 136.2 (Ar-C_q-CH_3), 136.1 (2 × Ar-C_q-CH_3), 129.7 (2 × Ar-CH), 126.9 (2 × Ar-CH), 113.9 (2 × Ar-CH), 85.4 (CH_2OCH_2), 55.2 (OCH_3), 52.1 (C_q), 20.7 (Ar-CH_3), 20.2 (2 × Ar-CH_3); HRMS (+ESI) *m*/*z* calcd for $C_{21}H_{26}NO_2$ [M+MeCN+H]: 324.1964, Found: 324.1959.

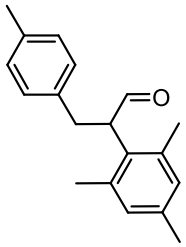
3-Mesityl-3-(*p*-tolyl)oxetane (199), 3-mesityl-2-(*p*-tolyl)propanal (199a) and **2-mesityl-3-(*p*-tolyl)propanal (199b)**



199



199a



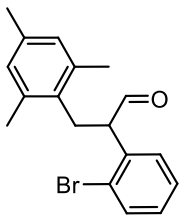
199b

$FeCl_3$ (8.1 mg, 0.05 mmol) was weighed in a vial. Oxetanol **192** (82.0 mg, 0.50 mmol) and mesitylene (350 µL, 2.50 mmol) were added. The reaction vessel was sealed and HFIP (5.0 mL) was added. The reaction was stirred for 18 h at 80 °C, then cooled to rt and sat. aq. $NaHCO_3$ (20 mL) was added followed by Et_2O (15 mL). The layers were separated and the aqueous portion was extracted with Et_2O (2 × 15 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash chromatography (4% Et_2O/pentane) afforded a mixture of aldehyde **199a** and **199b** (16:84, 7.4 mg, 6%) as a yellow oil, followed by oxetane **199** (108 mg, 81%) as a yellow oil

Aldehyde **199a** and **199b**: R_f = 0.63 (4% Et_2O/pentane); IR (film)/cm^{-1} 3004, 2922, 2862, 2810, 1725 (C=O), 1610, 1513, 1449, 1025, 853, 812; ^1H NMR (400 MHz, $CDCl_3$) δ 9.79 (d, *J* = 1.5 Hz, 1 H, H_aC=O), 9.77 (s, 1 H, H_bC=O), 7.16–7.13 (m, 2 H, 2 × Ar-CH_a), 7.03–6.99 (m, 2 H, 2 × Ar-CH_b), 6.99–6.96 (m, 2 H, 2 × Ar-CH_a), 6.92–6.89 (m, 2 H, 2 × Ar-CH_b), 6.86 (s, 2 H, 2 × Ar-CH_b), 6.79 (s, 2 H, 2 × Ar-CH_a), 3.94 (dd, *J* = 7.9, 5.2 Hz, 1 H, (C=O)-CH_b), 3.67–3.60 (m, 1 H, (C=O)-CH_a, and dd, *J* = 13.7, 5.2 Hz, 1 H, CH-C*H*H_b), 3.49 (dd, *J* = 14.3, 5.5 Hz, 1 H, CH-C*H*H_a), 2.87 (dd, *J* = 14.3, 7.9 Hz, 1 H, CH-CH*H*$_a$), 2.79 (dd, *J* = 13.7, 7.9 Hz, 1 H, CH-CH*H*$_b$), 2.35 (s, 3 H, $CH_{3,a}$), 2.30 (s, 3 H, $CH_{3,b}$), 2.28 (s, 3 H, $CH_{3,b}$), 2.24 (s, 3 H, $CH_{3,a}$),

2.06 (s, 6 H, 2 × $CH_{3,a}$), 2.06 (s, br, 6 H, 2 × $CH_{3,b}$); ^{13}C NMR (101 MHz, $CDCl_3$)[r] δ 201.8 (C_b=O), 201.7 (C_a=O), 137.1 (Ar-$C_{q,b}$-CH_2), 136.9 (Ar-$C_{q,b}$-CH), 135.6 (Ar-$C_{q,b}$-CH_3), 130.9 (2 × Ar-CH_a), 129.9 (br, 3 × Ar-$C_{q,b}$-CH_3), 129.6 (2 × Ar-CH_a), 129.04 (2 × Ar-CH_a), 128.97 (2 × Ar-CH_b), 128.9 (4 × Ar-CH_b), 59.0 ((C=O)-CH_a), 57.1 ((C=O)-CH_b), 33.7 (CH-$CH_{2,b}$), 30.3 (CH-$CH_{2,a}$), 21.0 (Ar-$CH_{3,b}$), 20.81 (Ar-$CH_{3,b}$), 20.79 (Ar-$CH_{3,a}$), 20.7 (2 × Ar-$CH_{3,b}$), 20.6 (Ar-$CH_{3,a}$), 20.0 (2 × Ar-$CH_{3,a}$); HRMS (+ESI) *m*/*z* calcd for $C_{19}H_{23}O$ [M+H]: 267.1749, Found: 267.1745.

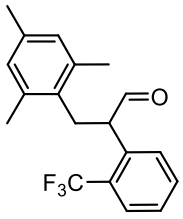
Oxetane **199**: R_f = 0.47 (4% Et_2O/pentane); IR (film)/cm^{-1} 2952, 2870, 1613, 1509, 1453, 1379, 1036, 991, 943, 849, 816, 719; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41–7.34 (m, 2 H, 2 × Ar-CH), 7.19–7.12 (m, 2 H, 2 × Ar-CH), 6.90 (s, 2 H, 2 × Ar-CH), 5.40 (d, *J* = 5.9 Hz, 2 H, C*H*HOC*H*H), 4.81 (d, *J* = 5.9 Hz, 2 H, CH*H*OCH*H*), 2.36 (s, 3 H, CH_3), 2.33 (s, 3 H, CH_3), 1.87 (s, 6 H, 2 × CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.9 (Ar-C_q-C_q), 138.0 (Ar-C_q-C_q), 136.6 (Ar-C_q-CH_3), 136.2 (2 × Ar-C_q-CH_3), 136.1 (Ar-C_q-CH_3), 129.7 (2 × Ar-CH), 129.3 (2 × Ar-CH), 125.6 (2 × Ar-CH), 85.3 (CH_2OCH_2), 52.3 (C_q), 21.0 (Ar-CH_3), 20.7 (Ar-CH_3), 20.2 (2 × Ar-CH_3); HRMS (+APCI) *m*/*z* calcd for $C_{19}H_{23}O^+$ [M+H]$^+$: 267.1743, Found: 267.1732.



2-(2-Bromophenyl)-3-mesitylpropanal (200a)

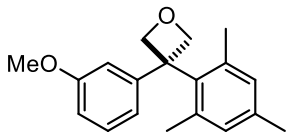
$FeCl_3$ (8.1 mg, 0.05 mmol) was weighed in a vial. Oxetanol **186** (115 mg, 0.50 mmol) and mesitylene (350 µL, 2.50 mmol) were added. The reaction vessel was sealed and HFIP (5.0 mL) was added. The reaction was stirred for 18 h at 80 °C, then cooled to rt and sat. aq. $NaHCO_3$ (20 mL) was added followed by Et_2O (15 mL). The layers were separated and the aqueous portion was extracted with Et_2O (2 × 15 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash chromatography (4% Et_2O/pentane) afforded a aldehyde **200a** (77.0 mg, 46%) as a yellow oil. R_f = 0.33 (4% Et_2O/pentane); IR (film)/cm^{-1} 2955, 2918, 2862, 2817, 2728, 1725 (C=O), 1610, 1472, 1028, 853, 756; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.79 (d, *J* = 0.6 Hz, 1 H, HC=O), 7.57 (dd, *J* = 8.0, 1.3 Hz, 1 H, Ar-CH), 7.32 (td, *J* = 7.5, 1.3 Hz, 1 H, Ar-CH), 7.21–7.11 (m, 2 H, 2 × Ar-CH), 6.79 (s, 2 H, 2 × Ar-CH), 4.17 (dd, *J* = 8.3, 5.7 Hz, 1 H, (C=O)-CH), 3.59 (dd, *J* = 14.2, 5.7 Hz, 1 H, CH-C*H*H), 2.98 (dd, *J* = 14.2, 8.3 Hz, 1 H, CH-CH*H*), 2.24 (s, 3 H, CH_3), 2.10 (s, 6 H, 2 × CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.7 (C=O), 136.9 (Ar-C_q-CH_2), 136.6 (2 × Ar-C_q-CH_3), 135.8 (Ar-C_q-CH), 133.3 (Ar-CH), 132.0 (Ar-C_q-CH_3), 131.1 (Ar-CH), 129.2 (Ar-CH), 129.1 (2 × Ar-CH), 127.8 (Ar-CH), 125.2 (Ar-C_q-Br), 58.1 ((C=O)-CH), 29.7 (CH-CH_2), 20.8 (Ar-CH_3), 19.9 (2 × Ar-CH_3); HRMS (–APCI) *m*/*z* calcd for $C_{18}H_{18}{}^{79}BrO^-$ [M–H]$^-$: 329.0536, Found: 329.0543.

[r] The Ar-C_q signals for **199a** were not observed due to the small amount of **199a** in the mixture.



3-Mesityl-2-(2-(trifluoromethyl)phenyl)propanal (201a)

$FeCl_3$ (8.1 mg, 0.05 mmol) was weighed in a vial. Oxetanol **187** (109 mg, 0.50 mmol) and mesitylene (350 µL, 2.50 mmol) were added. The reaction vessel was sealed and HFIP (5.0 mL) was added. The reaction was stirred for 18 h at 80 °C, then cooled to rt and sat. aq. $NaHCO_3$ (20 mL) was added followed by Et_2O (15 mL). The layers were separated and the aqueous portion was extracted with Et_2O (2 × 15 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash chromatography (4% Et_2O/pentane) afforded aldehyde **201a** (0.9 mg, 1%) as a yellow oil. R_f = 0.50 (4% Et_2O/pentane); IR (film)/cm^{-1} 2959, 2922, 1729 (C=O), 1453, 1312, 1159, 1121, 1062, 853, 767; ^1H NMR (400 MHz, $CDCl_3$) δ 9.67 (d, *J* = 1.3 Hz, 1 H, HC=O), 7.73–7.60 (m, 1 H, Ar-CH), 7.54 (d, *J* = 7.8 Hz, 1 H, Ar-CH), 7.48–7.38 (m, 2 H, 2 × Ar-CH), 6.83 (s, 2 H, 2 × Ar-CH), 4.34–4.23 (m, 1 H, (C=O)-CH), 3.59 (dd, *J* = 14.2, 7.7 Hz, 1 H, CH-C*H*H), 3.04 (dd, *J* = 14.2, 6.7 Hz, 1 H, CH-CH*H*), 2.25 (s, 3 H, CH_3), 2.19 (s, 6 H, 2 × CH_3); ^{13}C NMR (101 MHz, $CDCl_3$)[s] δ 199.4 (C=O), 136.4 (Ar-CH), 132.2 (Ar-CH), 130.7 (Ar-CH), 129.3 (2 × Ar-CH), 127.6 (Ar-CH), 54.0 ((C=O)-*C*H), 31.3 (CH-*C*H_2), 20.8 (Ar-CH_3), 20.1 (2 × Ar-CH_3); $^{19}F\{^1H\}$ NMR (377 MHz, $CDCl_3$) δ –58.4; HRMS (+APCI) *m*/*z* calcd for $C_{18}H_{16}F_3O^+$ $[M–CH_3]^+$: 305.1148, Found: 305.1145.

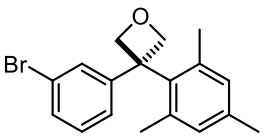


3-Mesityl-3-(3-methoxyphenyl)oxetane (203)

$FeCl_3$ (8.1 mg, 0.05 mmol) was weighed in a vial. Oxetanol **190** (90.0 mg, 0.50 mmol) and mesitylene (350 µL, 2.50 mmol) were added. The reaction vessel was sealed and HFIP (5.0 mL) was added. The reaction was stirred for 18 h at 80 °C, then cooled to rt and sat. aq. $NaHCO_3$ (20 mL) was added followed by Et_2O (15 mL). The layers were separated and the aqueous portion was extracted with Et_2O (2 × 15 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash chromatography (8% Et_2O/pentane) afforded oxetane **203** (110 mg, 78%) as a yellow solid. R_f = 0.42 (10% Et_2O/pentane); mp = 112–113 °C; IR (film)/cm^{-1} 2955, 2870, 1606, 1483, 1461, 1293, 1244, 1166, 1051, 991, 853, 782, 700; ^1H NMR (400 MHz, $CDCl_3$) δ 7.30–7.21 (m, 1 H, Ar-CH), 7.11–7.08 (m, 1 H, Ar-CH), 7.06 (ddd, *J* = 7.8, 1.8, 0.9 Hz, 1 H, Ar-CH), 6.88 (s, 2 H, 2 × Ar-CH), 6.83 (dd, *J* = 2.6, 0.9 Hz, 1 H, Ar-CH), 5.44–5.35 (m, 2 H, C*H*HOC*H*H), 4.86–4.78 (m, 2 H, CH*H*OCH*H*), 3.80 (s, 3 H, OCH_3), 2.31 (s, 3 H, CH_3), 1.87 (s, 6 H, 2 × CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.0 (Ar-C_q-OCH_3), 146.8 (Ar-C_q-C_q), 137.7 (Ar-C_q-C_q), 136.20 (Ar-C_q-CH_3), 136.16 (2 × Ar-C_q-CH_3), 129.8 (2 × Ar-CH), 129.5 (Ar-CH), 118.3 (Ar-CH), 112.1 (Ar-

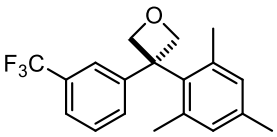
[s] The Ar-C_q, and CF_3 signals for **201a** were not observed due to the small amount of **201a** isolated.

CH), 111.8 (Ar-CH), 85.0 (*C*H_2O*C*H_2), 55.2 (OCH_3), 52.7 (C_q), 20.7 (Ar-CH_3), 20.2 (2 × Ar-CH_3); HRMS (+ESI) *m*/*z* calcd for $C_{21}H_{26}NO_2$ [M+MeCN+H]: 324.1964, Found: 324.1957.



3-(3-Bromophenyl)-3-mesityloxetane (204)

$FeCl_3$ (8.1 mg, 0.05 mmol) was weighed in a vial. Oxetanol **188** (115 mg, 0.50 mmol) and mesitylene (350 µL, 2.50 mmol) were added. The reaction vessel was sealed and HFIP (5.0 mL) was added. The reaction was stirred for 18 h at 80 °C, then cooled to rt and sat. aq. $NaHCO_3$ (20 mL) was added followed by Et_2O (15 mL). The layers were separated and the aqueous portion was extracted with Et_2O (2 × 15 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash chromatography (4% Et_2O/pentane) afforded oxetane **204** (23.7 mg, 14%) as a yellow solid. R_f = 0.33 (4% Et_2O/pentane); mp = 91–94 °C; IR (film)/cm^{-1} 2955, 2873, 1610, 1561, 1468, 1013, 943, 853, 697; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (t, *J* = 1.9 Hz, 1 H, Ar-CH), 7.43 (ddd, *J* = 7.9, 2.0, 1.9 Hz, 1 H, Ar-CH), 7.30 (ddd, *J* = 8.0, 1.9, 1.1 Hz, 1 H, Ar-CH), 7.22–7.14 (m, 1 H, Ar-CH), 6.90 (s, 2 H, 2 × Ar-CH), 5.43–5.32 (m, 2 H, C*H*HOC*H*H), 4.83–4.74 (m, 2 H, CH*H*OCH*H*), 2.33 (s, 3 H, CH_3), 1.86 (s, 6 H, 2 × CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.5 (Ar-C_q-C_q), 136.9 (Ar-C_q-C_q), 136.5 (Ar-C_q-CH_3), 136.1 (2 × Ar-C_q-CH_3), 130.3 (Ar-CH), 130.1 (Ar-CH), 129.9 (2 × Ar-CH), 128.7 (Ar-CH), 124.5 (Ar-CH), 123.2 (Ar-C_q-Br), 84.8 (*C*H_2O*C*H_2), 52.6 (C_q), 20.7 (Ar-CH_3), 20.2 (2 × Ar-CH_3); HRMS (+APCI) *m*/*z* calcd for $C_{18}H_{20}{}^{79}BrO^+$ [M+H]$^+$: 331.0692, Found: 331.0690.

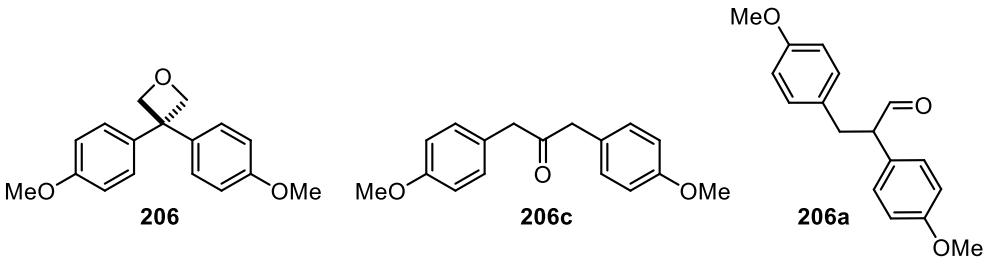


3-Mesityl-3-(3-(trifluoromethyl)phenyl)oxetane (205)

$FeCl_3$ (8.1 mg, 0.05 mmol) was weighed in a vial. Oxetanol **191** (109 mg, 0.50 mmol) and mesitylene (350 µL, 2.50 mmol) were added. The reaction vessel was sealed and HFIP (5.0 mL) was added. The reaction was stirred for 18 h at 80 °C, then cooled to rt and sat. aq. $NaHCO_3$ (20 mL) was added followed by Et_2O (15 mL). The layers were separated and the aqueous portion was extracted with Et_2O (2 × 15 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash chromatography (4% Et_2O/pentane) afforded oxetane **205** (5.5 mg, 3%) as a white solid. R_f = 0.47 (4% Et_2O/pentane); mp = 86–88 °C, IR (film)/cm^{-1} 2959, 2929, 2877, 1438, 1326, 1166, 1125, 1073, 805, 704; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (s, 1 H, Ar-CH), 7.59–7.49 (m, 2 H, 2 × Ar-CH), 7.47–7.38 (m, 1 H, Ar-CH), 6.91 (s, 2 H, 2 × Ar-CH), 5.48–5.35 (m, 2 H, C*H*HOC*H*H), 4.85–4.74 (m, 2 H, CH*H*OCH*H*), 2.33 (s, 3 H, CH_3), 1.85 (s, 6 H, 2 × CH_3); ^{13}C NMR (101 MHz,

$CDCl_3$)[t] δ 146.2 (Ar-C_q-C_q), 136.68 (Ar-C_q-C_q), 136.66 (Ar-C_q-CH_3), 136.1 (2 × Ar-C_q-CH_3), 131.3 (q, ^2J = 32.3 Hz, Ar-C_q-CF_3), 130.0 (2 × Ar-CH), 129.2 (Ar-CH), 129.0 (Ar-CH), 124.0 (q, ^3J = 3.5 Hz, Ar-CH), 122.4 (q, ^3J = 3.9 Hz, Ar-CH), 84.8 (CH_2OCH_2), 52.7 (C_q), 20.7 (Ar-CH_3), 20.1 (2 × Ar-CH_3); $^{19}F\{^1H\}$ NMR (377 MHz, $CDCl_3$) δ –62.4; HRMS (+APCI) *m*/*z* calcd for $C_{19}H_{20}F_3O^+$ $[M+H]^+$: 321.1461, Found: 321.1472.

3,3-Bis(4-methoxyphenyl)oxetane (206), 1,3-bis(4-methoxyphenyl)propan-2-one (206c) and **2,3-bis(4-methoxyphenyl)propanal (206a)**



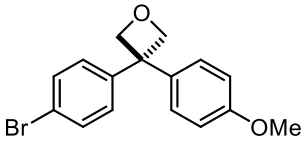
$FeCl_3$ (8.1 mg, 0.05 mmol) was weighed in a vial. Oxetanol **18** (90.0 mg, 0.50 mmol) and anisole (92.4 µL, 0.85 mmol) were added. The reaction vessel was sealed and HFIP (5.0 mL) was added. The reaction was stirred for 18 h at 80 °C, then cooled to rt and sat. aq. $NaHCO_3$ (20 mL) was added followed by Et_2O (15 mL). The layers were separated and the aqueous portion was extracted with Et_2O (2 × 15 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash chromatography (10% Et_2O/pentane) afforded aldehyde **206a** (37.1 mg, 27%) as a while solid, followed by a mixture of oxetane **206** and ketone **206c** (42:58, 10.5 mg, 8%) as a yellow oil.

Aldehyde **206a**: R_f = 0.19 (10% Et_2O/pentane); mp = 61–62 °C, IR (film)/cm^{-1} 2996, 2952, 2907, 2832, 1710 (C=O), 1610, 1461, 1300, 1244, 1174, 1107, 1028, 872, 812, 730; ^1H NMR (400 MHz, $CDCl_3$) δ 9.71 (d, *J* = 1.6 Hz, 1 H, HC=O), 7.08–7.01 (m, 2 H, 2 × Ar-CH), 6.99–6.93 (m, 2 H, 2 × Ar-CH), 6.91–6.84 (m, 2 H, 2 × Ar-CH), 6.80–6.72 (m, 2 H, 2 × Ar-CH), 3.81 (s, 3 H, OCH_3), 3.76 (s, 3 H, OCH_3), 3.76–3.71 (m, 1 H, (C=O)-CH), 3.37 (dd, *J* = 14.1, 6.7 Hz, 1 H, CH-C*H*H), 2.89 (dd, *J* = 14.1, 8.0 Hz, 1 H, CH-CH*H*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.2 (C=O), 160.0 (Ar-C_q-OCH_3), 159.1 (Ar-C_q-OCH_3), 130.9 (Ar-C_q-CH), 130.1 (2 × Ar-CH), 130.0 (2 × Ar-CH), 127.6 (Ar-C_q-CH_2), 114.4 (2 × Ar-CH), 113.7 (2 × Ar-CH), 60.3 ((C=O)-*C*H), 55.3 (OCH_3), 55.2 (OCH_3), 35.3 (CH-*C*H_2); HRMS (+ESI) *m*/*z* calcd for $C_{17}H_{19}O_3$ [M+H]: 271.1334, Found: 271.1334.

Oxetane **206** (ox) and ketone **206c** (ket): R_f = 0.09 (10% Et_2O/pentane); ^1H NMR (400 MHz, $CDCl_3$) δ 7.17–7.11 (m, 4 H, 4 × Ar-CH_{ox}), 7.10–7.05 (m, 4 H, 4 × Ar-CH_{ket}), 6.92–6.88 (m, 4 H,

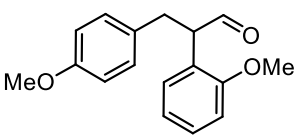
[t] The signal for CF_3 was not observed due to the small amount of product isolated.

4 × Ar-CH_{ox}), 6.88–6.84 (m, 4 H, 4 × Ar-CH_{ket}), 5.21 (s, 4 H, CH_2OCH_2), 3.82 (s, 6 H, 2 × $OCH_{3,ox}$), 3.81 (s, 6 H, 2 × $OCH_{3,ket}$), 3.66 (s, 4 H, 2 × Ar-CH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 206.5 (C=O), 158.6 (2 × Ar-C_q-$OCH_{3,ket}$), 158.2 (2 × Ar-C_q-$OCH_{3,ox}$), 138.2 (2 × Ar-C_q-$C_{q,ox}$), 130.5 (4 × Ar-CH_{ket}), 127.6 (4 × Ar-CH_{ox}), 126.1 (2 × Ar-C_q-$CH_{2,ket}$), 114.1 (4 × Ar-CH_{ket}), 113.9 (4 × Ar-CH_{ox}), 84.9 (CH_2OCH_2), 55.3 (2 × $OCH_{3,ox}$), 55.2 (2 × $OCH_{3,ket}$), 50.3 ($C_{q,ox}$), 48.0 (2 × $CH_{2,ket}$). The observed spectroscopic data for ketone **xxc** (^{1}H and ^{13}C NMR) was consistent with that previously reported.[250]



3-(4-Bromophenyl)-3-(4-methoxyphenyl)oxetane (207)

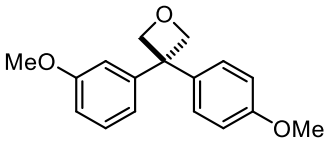
$FeCl_3$ (8.1 mg, 0.05 mmol) was weighed in a vial. Oxetanol **179** (114 mg, 0.50 mmol) and anisole (92.4 µL, 0.85 mmol) were added. The reaction vessel was sealed and HFIP (5.0 mL) was added. The reaction was stirred for 18 h at 80 °C, then cooled to rt and sat. aq. $NaHCO_3$ (20 mL) was added followed by Et_2O (15 mL). The layers were separated and the aqueous portion was extracted with Et_2O (2 × 15 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash chromatography (8% Et_2O/pentane) afforded oxetane **207** (43.8 mg, 27%) as a white solid. R_f = 0.19 (8% Et_2O/pentane); mp = 76–77 °C; IR (film)/cm^{-1} 3004, 2952, 2885, 2840, 1610, 1513, 1397, 1244, 1185, 1077, 1025, 997, 935, 812; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52–7.44 (m, 2 H, 2 × Ar-CH), 7.15–7.07 (m, 4 H, 4 × Ar-CH), 6.94–6.86 (m, 2 H, 2 × Ar-CH), 5.22 (d, *J* = 5.7 Hz, 2 H, C*H*HOC*H*H), 5.17 (d, *J* = 5.7 Hz, 2 H, CH*H*OCH*H*), 3.82 (s, 3 H, OCH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.3 (Ar-C_q-OCH_3), 145.1 (Ar-C_q-C_q), 137.1 (Ar-C_q-C_q), 131.6 (2 × Ar-CH), 128.3 (2 × Ar-CH), 127.5 (2 × Ar-CH), 120.5 (Ar-C_q-Br), 114.0 (2 × Ar-CH), 84.5 (CH_2OCH_2), 55.3 (OCH_3), 50.6 (C_q); HRMS (+APCI) *m*/*z* calcd for $C_{16}H_{16}{}^{79}BrO_2^+$ $[M+H]^+$: 319.0328, Found: 319.0314.



2-(2-Methoxyphenyl)-3-(4-methoxyphenyl)propanal (209a)

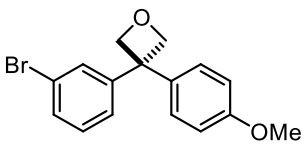
$FeCl_3$ (8.1 mg, 0.05 mmol) was weighed in a vial. Oxetanol **189** (90.0 mg, 0.50 mmol) and anisole (92.4 µL, 0.85 mmol) were added. The reaction vessel was sealed and HFIP (5.0 mL) was added. The reaction was stirred for 18 h at 80 °C. The reaction was then cooled to rt and sat. aq. $NaHCO_3$ (20 mL) was added followed by Et_2O (20 mL). The layers were separated and the aqueous portion was extracted with Et_2O (2 × 20 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash chromatography (8% Et_2O/pentane) afforded aldehyde **209a** (57.6 mg, 43%) as a yellow oil. R_f = 0.24 (8% Et_2O/hexane); IR (film)/cm^{-1} 2937, 2832, 1718 (C=O), 1610, 1513, 1461, 1283, 1241, 1177,

1103, 1028, 823, 752; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.74 (d, *J* = 0.7 Hz, 1 H, HC=O), 7.32–7.23 (m, 1 H, Ar-CH), 7.00–6.93 (m, 3 H, 3 × Ar-CH), 6.93–6.88 (m, 2 H, 2 × Ar-CH), 6.77–6.72 (m, 2 H, 2 × Ar-CH), 4.01 (dd, *J* = 7.9, 6.4 Hz, 1 H, (C=O)-CH), 3.78 (s, 3 H, OCH_3), 3.76 (s, 3 H, OCH_3), 3.42 (dd, *J* = 14.0, 6.4 Hz, 1 H, CH-C*H*H), 2.90 (dd, *J* = 14.0, 7.9 Hz, 1 H, CH-CH*H*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 201.0 (C=O), 157.9 (Ar-C_q-$OCH_{3,para}$), 157.3 (Ar-C_q-$OCH_{3,ortho}$), 131.6 (Ar-C_q), 130.3 (Ar-CH), 130.0 (2 × Ar-CH), 128.8 (Ar-CH), 125.1 (Ar-C_q), 120.8 (Ar-CH), 113.5 (2 × Ar-CH), 110.9 (Ar-CH), 55.6 (OCH_3), 55.4 (OCH_3), 55.2 (*C*H-CH_2), 33.8 (CH-*C*H_2); HRMS (+ESI) *m*/*z* calcd for $C_{17}H_{19}O_3$ [M+H]: 271.1334, Found: 271.1343.



3-(3-Methoxyphenyl)-3-(4-methoxyphenyl)oxetane (212)

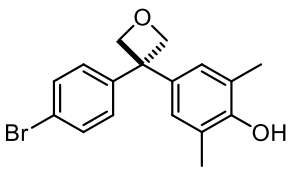
$FeCl_3$ (8.1 mg, 0.05 mmol) was weighed in a vial. Oxetanol **190** (90.0 mg, 0.50 mmol) and anisole (92.4 µL, 0.85 mmol) were added. The reaction vessel was sealed and HFIP (5.0 mL) was added. The reaction was stirred for 18 h at 80 °C, then cooled to rt and sat. aq. $NaHCO_3$ (20 mL) was added followed by Et_2O (15 mL). The layers were separated and the aqueous portion was extracted with Et_2O (2 × 15 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash chromatography (10% Et_2O/pentane) afforded oxetane **212** (31.5 mg, 23%) as a yellow oil. R_f = 0.19 (10% Et_2O/pentane); IR (film)/cm^{-1} 2952, 2873, 2832, 1602, 1513, 1289, 1244, 1177, 1028, 984, 943, 875, 827, 779, 700; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32–7.27 (m, 1 H, Ar-CH), 7.19–7.11 (m, 2 H, 2 × Ar-CH), 6.93–6.85 (m, 2 H, 2 × Ar-CH), 6.84–6.78 (m, 2 H, 2 × Ar-CH), 6.74 (dd, *J* = 2.5, 1.8 Hz, 1 H, Ar-CH), 5.25 (d, *J* = 5.7 Hz, 2 H, C*H*HOC*H*H), 5.20 (d, *J* = 5.7 Hz, 2 H, CH*H*OCH*H*), 3.81 (s, 3 H, OCH_3), 3.80 (s, 3 H, OCH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.7 (Ar-C_q-OCH_3), 158.2 (Ar-C_q-OCH_3), 147.6 (Ar-C_q-C_q), 137.8 (Ar-C_q-C_q), 129.6 (Ar-CH), 127.6 (2 × Ar-CH), 118.9 (Ar-CH), 113.9 (2 × Ar-CH), 112.8 (Ar-CH), 111.5 (Ar-CH), 84.6 (CH_2OCH_2), 55.3 (OCH_3), 55.2 (OCH_3), 50.9 (C_q); HRMS (+EI) *m*/*z* calcd for $C_{17}H_{18}O_3^{\bullet+}$ [M]$^{\bullet+}$: 270.1250, Found: 270.1258.



3-(3-Bromophenyl)-3-(4-methoxyphenyl)oxetane (213)

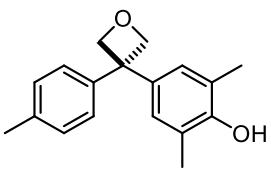
$FeCl_3$ (8.1 mg, 0.05 mmol) was weighed in a vial. Oxetanol **188** (114 mg, 0.50 mmol) and anisole (92.4 µL, 0.85 mmol) were added. The reaction vessel was sealed and HFIP (5.0 mL) was added. The reaction was stirred for 18 h at 80 °C, then cooled to rt and sat. aq. $NaHCO_3$ (20 mL) was added followed by Et_2O (15 mL). The layers were separated and the aqueous portion was extracted with Et_2O (2 × 15 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash chromatography (8% Et_2O/pentane) afforded oxetane **213** (7.1 mg, 4%) as a white solid. R_f = 0.24 (8%

Et_2O/pentane); mp = 68–70 °C; IR (film)/cm^{-1} 2955, 2877, 1610, 1513, 1461, 1297, 1248, 1181, 1118, 1028, 991, 831, 790; ^1H NMR (400 MHz, $CDCl_3$) δ 7.43–7.35 (m, 2 H, 2 × Ar-CH), 7.29–7.21 (m, 1 H, Ar-CH), 7.19–7.14 (m, 1 H, Ar-CH), 7.14–7.09 (m, 2 H, 2 × Ar-CH), 6.94–6.88 (m, 2 H, 2 × Ar-CH), 5.22 (d, *J* = 5.9 Hz, 2 H, C*H*HOC*H*H), 5.19 (d, *J* = 5.9 Hz, 2 H, CH*H*OCH*H*), 3.83 (s, 3 H, OCH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.4 (Ar-C_q-OCH_3), 148.4 (Ar-C_q-C_q), 137.0 (Ar-C_q-C_q), 130.1 (Ar-CH), 129.8 (Ar-CH), 129.6 (Ar-CH), 127.5 (2 × Ar-CH), 125.1 (Ar-CH), 122.8 (Ar-C_q-Br), 114.1 (2 × Ar-CH), 84.4 (CH_2OCH_2), 55.3 (OCH_3), 50.8 (C_q); HRMS (+APCI) *m*/*z* calcd for $C_{16}H_{16}{}^{79}BrO_2^+$ $[M+H]^+$: 319.0328, Found: 319.0329.



4-(3-(4-Bromophenyl)oxetan-3-yl)-2,6-dimethylphenol (215)

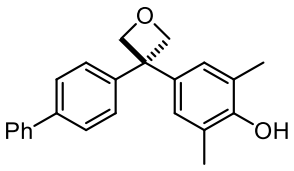
$FeCl_3$ (8.1 mg, 0.05 mmol) was weighed in a vial. Oxetanol **179** (114 mg, 0.50 mmol) and 2,6-dimethylphenol (104 mg, 0.85 mmol) were added. The reaction vessel was sealed and HFIP (5.0 mL) was added. The reaction was stirred for 18 h at 80 °C, then cooled to rt and sat. aq. $NaHCO_3$ (20 mL) was added followed by Et_2O (15 mL). The layers were separated and the aqueous portion was extracted with Et_2O (2 × 15 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash chromatography (20% Et_2O/pentane) afforded oxetane **215** (93.9 mg, 56%) as a yellow solid. R_f = 0.17 (20% Et_2O/pentane); mp = 164–166 °C; IR (film)/cm^{-1} 3339 (br, OH), 2959, 2877, 1487, 1394, 1312, 1203, 1077, 990, 976, 950, 905, 820, 730; ^1H NMR (400 MHz, $CDCl_3$) δ 7.51–7.44 (m, 2 H, 2 × Ar-CH), 7.15–7.09 (m, 2 H, 2 × Ar-CH), 6.77 (s, 2 H, 2 × Ar-CH), 5.23 (d, *J* = 5.7 Hz, 2 H, C*H*HOC*H*H), 5.14 (d, *J* = 5.7 Hz, 2 H, CH*H*OCH*H*), 4.70 (s, 1 H, OH), 2.24 (s, 6 H, 2 × CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.0 (Ar-C_q-OH), 145.4 (Ar-C_q-C_q), 136.6 (Ar-C_q-C_q), 131.6 (2 × Ar-CH), 128.3 (2 × Ar-CH), 126.6 (2 × Ar-CH), 123.2 (2 × Ar-C_q-CH_3), 120.4 (Ar-C_q-Br), 84.5 (CH_2OCH_2), 50.5 (C_q), 16.1 (2 × Ar-CH_3); HRMS (+EI) *m*/*z* calcd for $C_{16}H_{15}{}^{79}BrO_2^{\bullet+}$ $[M-CH_3+H]^{\bullet+}$: 318.0250, Found: 318.0259.



2,6-Dimethyl-4-(3-(p-tolyl)oxetan-3-yl)phenol (216)

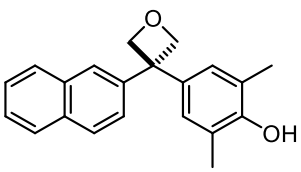
$FeCl_3$ (8.1 mg, 0.05 mmol) was weighed in a vial. Oxetanol **192** (82.0 mg, 0.50 mmol) and 2,6-dimethylphenol (104 mg, 0.85 mmol) were added. The reaction vessel was sealed and HFIP (5.0 mL) was added. The reaction was stirred for 18 h at 80 °C, then cooled to rt and sat. aq. $NaHCO_3$ (20 mL) was added followed by Et_2O (15 mL). The layers were separated and the aqueous portion was extracted with Et_2O (2 × 15 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash chromatography (20% Et_2O/pentane) afforded oxetane **216** (29.2 mg, 22%) as a yellow solid.

R_f = 0.30 (20% Et_2O/pentane); mp = 128–130 °C; IR (film)/cm^{-1} 3354 (br, OH), 2952, 2922, 2877, 1487, 1308, 1207, 1177, 1021, 976, 905, 816, 730; ^1H NMR (400 MHz, $CDCl_3$) δ 7.18 (d, *J* = 8.1 Hz, 2 H, 2 × Ar-CH), 7.13 (d, *J* = 8.1 Hz, 2 H, 2 × Ar-CH), 6.82 (s, 2 H, 2 × Ar-CH), 5.26–5.16 (m, 4 H, C*H*$_2$OC*H*$_2$), 4.79–4.68 (m, 1 H, OH), 2.36 (s, 3 H, CH_3), 2.24 (s, 6 H, 2 × CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.8 (Ar-C_q-OH), 143.3 (Ar-*C*$_q$-C_q), 137.5 (Ar-*C*$_q$-C_q), 136.1 (Ar-*C*$_q$-CH_3), 129.1 (2 × Ar-CH), 126.7 (2 × Ar-CH), 126.3 (2 × Ar-CH), 123.0 (2 × Ar-*C*$_q$-CH_3), 84.9 (*C*H$_2$O*C*H$_2$), 50.5 (C_q), 21.0 (Ar-CH_3), 16.1 (2 × Ar-CH_3); HRMS (+EI) *m*/*z* calcd for $C_{18}H_{20}O_2^{\bullet+}$ $[M]^{\bullet+}$: 268.1458, Found: 268.1469.



4-(3-([1,1'-Biphenyl]-4-yl)oxetan-3-yl)-2,6-dimethylphenol (217)

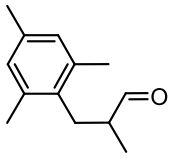
$FeCl_3$ (8.1 mg, 0.05 mmol) was weighed in a vial. Oxetanol **184** (113 mg, 0.50 mmol) and 2,6-dimethylphenol (104 mg, 0.85 mmol) were added. The reaction vessel was sealed and HFIP (5.0 mL) was added. The reaction was stirred for 18 h at 80 °C, then cooled to rt and sat. aq. $NaHCO_3$ (20 mL) was added followed by Et_2O (15 mL). The layers were separated and the aqueous portion was extracted with Et_2O (2 × 15 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash chromatography (25% Et_2O/pentane) afforded oxetane **217** (64.9 mg, 39%) as a yellow solid. R_f = 0.16 (20% Et_2O/pentane); mp = 160–164 °C; IR (film)/cm^{-1} 3369 (br, OH), 3026, 2955, 2881, 1487, 1312, 976, 909, 838, 697; ^1H NMR (400 MHz, $CDCl_3$) δ 7.63–7.57 (m, 4 H, 4 × Ar-CH), 7.50–7.42 (m, 2 H, 2 × Ar-CH), 7.40–7.29 (m, 3 H, 3 × Ar-CH), 6.86 (s, 2 H, 2 × Ar-CH), 5.33–5.20 (m, 4 H, C*H*$_2$OC*H*$_2$), 4.69 (s, 1 H, OH), 2.26 (s, 6 H, 2 × CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.9 (Ar-C_q-OH), 145.4 (Ar-*C*$_q$-C_q), 140.6 (Ar-*C*$_q$-C_q), 139.4 (Ar-*C*$_q$-C_q), 137.2 (Ar-*C*$_q$-C_q), 128.8 (2 × Ar-CH), 127.3 (Ar-CH), 127.2 (2 × Ar-CH), 127.0 (2 × Ar-CH), 126.8 (2 × Ar-CH), 126.7 (2 × Ar-CH), 123.1 (2 × Ar-*C*$_q$-CH_3), 84.8 (*C*H$_2$O*C*H$_2$), 50.7 (C_q), 16.1 (2 × Ar-CH_3); HRMS (+APCI) *m*/*z* calcd for $C_{23}H_{23}O_2^+$ $[M+H]^+$: 331.1693, Found: 331.1682.



2,6-Dimethyl-4-(3-(naphthalen-2-yl)oxetan-3-yl)phenol (218)

$FeCl_3$ (8.1 mg, 0.05 mmol) was weighed in a vial. Oxetanol **185** (100 mg, 0.50 mmol) and 2,6-dimethylphenol (104 mg, 0.85 mmol) were added. The reaction vessel was sealed and HFIP (5.0 mL) was added. The reaction was stirred for 18 h at 80 °C, then cooled to rt and sat. aq. $NaHCO_3$ (20 mL) was added followed by Et_2O (15 mL). The layers were separated and the aqueous portion was extracted with Et_2O (2 × 15 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash chromatography (20% Et_2O/pentane) afforded oxetane **218** (63.6 mg, 42%) as a yellow solid.

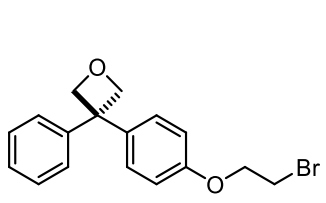
R_f = 0.16 (20% Et_2O/pentane); mp = 144–145 °C; IR (film)/cm^{-1} 3369 (br, OH), 3052, 2959, 2881, 1602, 1490, 1312, 1196, 980, 909, 861, 816, 749; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90–7.75 (m, 3 H, 3 × Ar-CH), 7.59 (d, *J* = 1.9 Hz, 1 H, Ar-CH), 7.53–7.45 (m, 2 H, 2 × Ar-CH), 7.42 (dd, *J* = 8.6, 1.9 Hz, 1 H, Ar-CH), 6.88 (s, 2 H, 2 × Ar-CH), 5.34 (d, *J* = 5.7 Hz, 2 H, C*H*HOC*H*H), 5.29 (d, *J* = 5.7 Hz, 2 H, CH*H*OCH*H*), 4.71–4.66 (m, 1 H, OH), 2.24 (s, 6 H, 2 × CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.9 (Ar-C_q-OH), 143.4 (Ar-C_q-C_q), 137.3 (Ar-C_q-C_q), 133.1 (Ar-C_q-C_q), 132.1 (Ar-C_q-C_q), 128.5 (Ar-CH), 127.9 (Ar-CH), 127.5 (Ar-CH), 126.8 (2 × Ar-CH), 126.3 (Ar-CH), 125.8 (Ar-CH), 125.0 (Ar-CH), 124.9 (Ar-CH), 123.1 (2 × Ar-C_q-CH_3), 84.5 (CH_2OCH_2), 51.0 (C_q), 16.1 (2 × Ar-CH_3); HRMS (–EI) *m*/*z* calcd for $C_{21}H_{19}O_2$ [M–H]: 303.1385, Found: 303.1394.



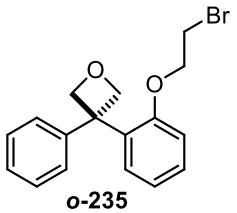
3-Mesityl-2-methylpropanal (223)

$FeCl_3$ (4.9 mg, 0.03 mmol) was weighed in a vial. Methacrolein (25 µL, 0.30 mmol) and mesitylene (209 µL, 1.50 mmol) were added. The reaction vessel was sealed and HFIP (5.0 mL) was added. The reaction was stirred for 23 h at 80 °C, then cooled to rt and sat. aq. $NaHCO_3$ (15 mL) was added followed by Et_2O (15 mL). The layers were separated and the aqueous portion was extracted with Et_2O (2 × 15 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash chromatography (4% Et_2O/pentane) afforded aldehyde **223** (43.1 mg, 75%) as a yellow oil. R_f = 0.43 (4% Et_2O/pentane); IR (film)/cm^{-1} 2963, 2922, 2873, 1722 (C=O), 1613, 1461, 1379, 920, 849; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.73 (d, *J* = 1.3 Hz, 1 H, HC=O), 6.88 (s, 2 H, 2 × Ar-CH), 3.11–2.96 (m, 1 H, CH-CH*H*), 2.75–2.59 (m, 2 H, CH-C*H*H, (C=O)-CH), 2.31 (s, 6 H, 2 × CH_3), 2.28 (s, 3 H, CH_3), 1.14 (d, *J* = 6.7 Hz, 3 H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 204.6 (C=O), 136.3 (2 × Ar-C_q-CH_3), 135.6 (Ar-C_q-CH_3), 132.6 (Ar-C_q-CH_2), 129.2 (2 × Ar-CH), 46.6 ((C=O)-*C*H), 29.8 (CH-*C*H_2), 20.7 (Ar-CH_3), 20.2 (2 × Ar-CH_3), 13.4 (CH_3); HRMS (+EI) *m*/*z* calcd for $C_{13}H_{18}O^{\bullet}$ $[M]^{\bullet}$: 190.1358, Found: 190.1363.

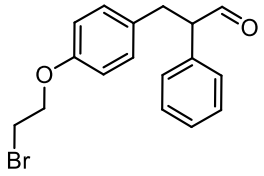
3-(4-(2-Bromoethoxy)phenyl)-3-phenyloxetane (235), 3-(2-(2-bromoethoxy)phenyl)-3-phenyloxetane (*o*-235), 3-(4-(2-bromoethoxy)phenyl)-2-phenylpropanal (235a) and **2-(4-(2-bromoethoxy)phenyl)-3-phenylpropanal (235b)**



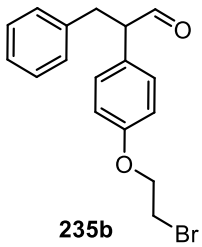
235



***o*-235**



235a



235b

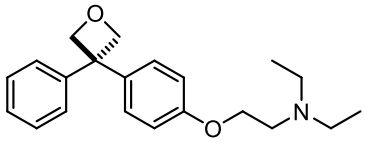
$FeCl_3$ (8.1 mg, 0.05 mmol) was weighed in a vial. Oxetanol **170** (75.1 mg, 0.50 mmol) and β–bromophenetole **234** (171 mg, 0.85 mmol) were added. The reaction vessel was sealed and HFIP (5.0 mL) was added. The reaction was stirred for 18 h at 80 °C, then cooled to rt and sat. aq. $NaHCO_3$ (20 mL) was added followed by Et_2O (15 mL). The layers were separated and the aqueous portion was extracted with Et_2O (2 × 15 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash chromatography (10% Et_2O/pentane) afforded a mixture of aldehyde **235a** and **235b** (54:46, 15.1 mg, 9%) as a colourless oil, followed by oxetane **235** (65.4 mg, 39%) as an off-white solid, and oxetane ***o*-235** (25.2 mg, 80% pure, 15%) as a yellow oil.

Aldehyde **235a** and **235b**: R_f = 0.55 (10% Et_2O/pentane); IR (film)/cm^{-1} 3060, 3026, 2926, 2821, 2721, 1722 (C=O), 1602, 1490, 1453, 1282, 1244, 1177, 1017, 752, 700; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.79 (d, *J* = 0.6 Hz, 1 H, H_aC=O), 9.75 (d, *J* = 1.6 Hz, 1 H, H_bC=O), 7.40–7.22 (m, 4 H, 4 × Ar-CH), 7.23–7.11 (m, 5 H, 5 × Ar-CH), 7.10–7.03 (m, 2 H, 2 × Ar-CH), 7.03–6.91 (m, 4 H, 4 × Ar-CH), 6.85 (dd, *J* = 8.2, 1.1 Hz, 1 H, Ar-CH), 6.80–6.74 (m, 2 H, 2 × Ar-CH_b), 4.32–4.24 (m, 1 H, OC*H*H_a), 4.24 (t, *J* = 6.3 Hz, 2 H, $OCH_{2,b}$), 4.19–4.10 (m, 2 H, OC*H*H_a, (C=O)-CH_a), 3.80 (dd, *J* = 7.9, 6.8, 1.6 Hz, 1 H, (C=O)-CH_b), 3.61 (t, *J* = 6.3 Hz, 2 H, $CH_{2,b}$Br), 3.56 (t, *J* = 6.0 Hz, 2 H, $CH_{2,a}$Br), 3.51 (dd, *J* = 13.9, 6.2 Hz, 1 H, CH-C*H*H_a), 3.42 (dd, *J* = 14.1, 6.8 Hz, 1 H, CH-C*H*H_b), 3.00 (dd, *J* = 13.9, 8.3 Hz, 1 H, CH-CH*H*$_a$), 2.94 (dd, *J* = 14.1, 7.9 Hz, 1 H, CH-CH*H*$_b$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.6 (C_a=O), 200.0 (C_b=O), 156.6 (Ar-$C_{q,b}$-O), 155.8 (Ar-$C_{q,a}$-O), 139.4 (Ar-$C_{q,a}$-CH_2), 135.9 (Ar-$C_{q,b}$-CH_2), 131.6 (Ar-$C_{q,b}$-CH), 130.6 (Ar-$C_{q,a}$-CH), 130.1 (2 × Ar-CH_b), 129.2 (2 × Ar-CH_a), 129.0 (2 × Ar-CH), 128.9 (2 × Ar-CH), 128.1 (2 × Ar-CH_a), 127.7 (Ar-CH), 126.1 (2 × Ar-CH_a), 121.6 (2 × Ar-CH_b), 114.6 (2 × Ar-CH_b), 111.7 (Ar-CH), 67.9 ($OCH_{2,a}$ and $OCH_{2,b}$), 61.1 ((C=O)-CH_b), 55.2 ((C=O)-CH_a), 35.3 (CH-$CH_{2,b}$), 35.0 (CH-$CH_{2,a}$), 29.1 ($CH_{2,a}$Br), 29.0 ($CH_{2,b}$Br); HRMS (+APCI) *m*/*z* calcd for $C_{17}H_{16}{}^{79}BrO_2^+$ $[M–H]^+$: 331.0328, Found: 331.0327.

Oxetane **235**: R_f = 0.38 (10% Et_2O/pentane); mp = 85–86 °C; IR (film)/cm^{-1} 2952, 2877, 1610, 1513, 1446, 1282, 1244, 1185, 1013, 967, 831, 760, 700; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42–

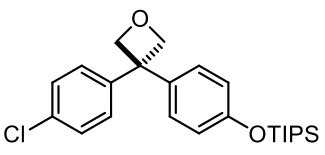
7.32 (m, 2 H, 2 × Ar-CH), 7.32–7.24 (m, 1 H, Ar-CH), 7.25–7.19 (m, 2 H, 2 × Ar-CH), 7.19–7.11 (m, 2 H, 2 × Ar-CH), 6.94–6.87 (m, 2 H, 2 × Ar-CH), 5.27 (d, *J* = 5.7 Hz, 2 H, C*H*HOC*H*H), 5.21 (d, *J* = 5.7 Hz, 2 H, CH*H*OCH*H*), 4.30 (t, *J* = 6.3 Hz, 2 H, OCH_2), 3.65 (t, *J* = 6.3 Hz, 2 H, CH_2Br); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.7 (Ar-C_q-O), 145.8 (Ar-C_q-C_q), 138.8 (Ar-C_q-C_q), 128.6 (2 × Ar-CH), 127.7 (2 × Ar-CH), 126.6 (Ar-CH), 126.4 (2 × Ar-CH), 114.8 (2 × Ar-CH), 84.7 (CH_2OCH_2), 67.9 (OCH_2), 50.9 (C_q), 29.1 (CH_2Br); HRMS (+APCI) *m*/*z* calcd for $C_{17}H_{16}{}^{79}BrO_2^+$ $[M–H]^+$: 331.0328, Found: 331.0339.

Oxetane ***o*-235**: R_f = 0.18 (10% Et_2O/pentane); IR (film)/cm^{-1} 3428, 3656, 2952, 2877, 1595, 1479, 1215, 1185, 1013, 969, 827, 749, 697; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35–7.33 (m, 3 H, 3 × Ar-CH), 7.26–7.21 (m, 2 H, 2 × Ar-CH), 7.01–6.94 (m, 2 H, 2 × Ar-CH), 6.91 (d, *J* = 8.0 Hz, 2 H, 2 × Ar-CH), 4.81 (d, *J* = 8.9 Hz, 2 H, C*H*HOC*H*H), 4.63 (d, *J* = 8.9 Hz, 2 H, CH*H*OCH*H*), 4.15 (dd, *J* = 11.2, 5.1 Hz, 2 H, OCH_2), 4.08 (dd, *J* = 11.2, 8.0 Hz, 2 H, CH_2Br); ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.8 (Ar-C_q-O), 142.7 (Ar-C_q-C_q), 129.8 (Ar-C_q-C_q), 129.3 (Ar-CH), 128.8 (2 × Ar-CH), 127.1 (Ar-CH), 126.9 (2 × Ar-CH), 125.2 (Ar-CH), 120.8 (Ar-CH), 110.2 (Ar-CH), 81.2 (CH_2OCH_2), 67.6 (OCH_2), 56.4 (C_q), 30.3 (CH_2Br); HRMS (+APCI) *m*/*z* calcd for $C_{17}H_{16}{}^{79}BrO_2^+$ $[M–H]^+$: 331.0328, Found: 331.0326.



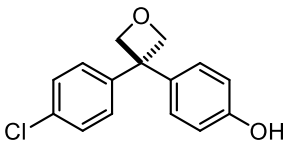
N,N-Diethyl-2-(4-(3-phenyloxetan-3-yl)phenoxy)ethan-1-amine (236)

Diethylamine (40.3 µL, 0.39 mmol) was added to a solution of oxetane **235** (65 mg, 0.20 mmol) and K_2CO_3 (56.6 mg, 0.41 mmol) in DMF (1.5 mL). The reaction mixture was stirred at 80 °C for 23 h, then cooled to rt and water (10 mL) was added followed by Et_2O (10 mL). The layers were separated and the aqueous portion was extracted with Et_2O (2 × 10 mL). The organic extracts were combined, washed with sat. aq. NaCl (2 × 5 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash chromatography (10% MeOH/CH_2Cl_2) afforded oxetane **236** (44.4 mg, 70%) as a light yellow paste. R_f = 0.34 (10% MeOH/CH_2Cl_2); IR (film)/cm^{-1} 2967, 2873, 1610, 1513, 1464, 1297, 1244, 1181, 1028, 987, 831, 760, 700; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40–7.32 (m, 2 H, 2 × Ar-CH), 7.31–7.24 (m, 1 H, Ar-CH), 7.24–7.18 (m, 2 H, 2 × Ar-CH), 7.17–7.10 (m, 2 H, 2 × Ar-CH), 6.93–6.85 (m, 2 H, 2 × Ar-CH), 5.25 (d, *J* = 5.6 Hz, 2 H, C*H*HOC*H*H), 5.21 (d, *J* = 5.6 Hz, 2 H, CH*H*OCH*H*), 4.13 (t, *J* = 6.3 Hz, 2 H, OCH_2), 2.98 (t, *J* = 6.3 Hz, 2 H, OCH_2CH_2N), 2.75 (q, *J* = 7.2 Hz, 4 H, 2 × NCH_2), 1.14 (t, *J* = 7.2 Hz, 6 H, 2 × NCH_2CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.2 (Ar-C_q-O), 145.9 (Ar-C_q-C_q), 138.1 (Ar-C_q-C_q), 128.5 (2 × Ar-CH), 127.6 (2 × Ar-CH), 126.5 (Ar-CH), 126.4 (2 × Ar-CH), 114.4 (2 × Ar-CH), 84.7 (CH_2OCH_2), 65.8 (OCH_2), 51.5 (OCH_2CH_2N), 50.8 (C_q), 47.6 (2 × NCH_2CH_3), 11.2 (2 × NCH_2CH_3); HRMS (+APCI) *m*/*z* calcd for $C_{21}H_{28}NO_2^+$ $[M+H]^+$: 326.2115, Found: 326.2119.



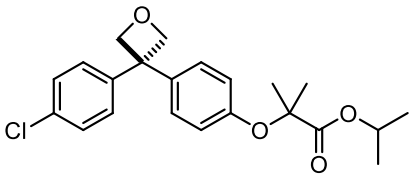
(4-(3-(4-Chlorophenyl)oxetan-3-yl)phenoxy)triisopropylsilane (239)

$FeCl_3$ (8.1 mg, 0.05 mmol) was weighed in a vial. Oxetanol **181** (92.3 mg, 0.50 mmol) and triisopropyl(phenoxy)silane **240**[251] (213 mg, 0.85 mmol) were added. The reaction vessel was sealed and HFIP (5.0 mL) was added. The reaction was stirred for 18 h at 80 °C, then cooled to rt and sat. aq. $NaHCO_3$ (20 mL) was added followed by Et_2O (15 mL). The layers were separated and the aqueous portion was extracted with Et_2O (2 × 15 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash chromatography (4% Et_2O/pentane) afforded oxetane **239** (40.1 mg, 19%) as a yellow oil. R_f = 0.34 (4% Et_2O/pentane); IR (film)/cm^{-1} 2944, 2870, 1729, 1600, 1513, 1464, 1267, 1177, 1155, 1095, 1013, 916, 834, 685; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35–7.30 (m, 2 H, 2 × Ar-CH), 7.19–7.13 (m, 2 H, 2 × Ar-CH), 7.04–6.98 (m, 2 H, 2 × Ar-CH), 6.90–6.84 (m, 2 H, 2 × Ar-CH), 5.22 (d, *J* = 5.7 Hz, 2 H, C*H*HOC*H*H), 5.15 (d, *J* = 5.7 Hz, 2 H, CH*H*OCH*H*), 1.32–1.20 (m, 3 H, 3 × CH), 1.11 (d, *J* = 7.3 Hz, 18 H, 6 × CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.9 (Ar-C_q-OTIPS), 144.7 (Ar-C_q-C_q), 137.4 (Ar-C_q-C_q), 132.4 (Ar-C_q-Cl), 128.6 (2 × Ar-CH), 128.0 (2 × Ar-CH), 127.5 (2 × Ar-CH), 119.9 (2 × Ar-CH), 84.7 (CH_2OCH_2), 50.6 (C_q), 17.9 (3 × $CH(CH_3)_2$), 12.6 (3 × $CH(CH_3)_2$); HRMS (+APCI) *Mass not found*.



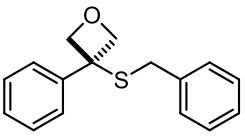
4-(3-(4-Chlorophenyl)oxetan-3-yl)phenol (238)

A solution of TBAF (1 M in THF, 145 µL, 0.145 mmol) was added dropwise to a solution of **239** (40.0 mg, 0.096 mmol) in THF (1.0 mL) at 25 °C. The reaction mixture was stirred for 1 h, and then water (10 mL) was added followed by Et_2O (10 mL). The layers were separated and the aqueous portion was extracted with Et_2O (2 × 10 mL). The organic extracts were combined, washed with sat. aq. NH_4Cl (2 × 5 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography (30% Et_2O/pentane) afforded oxetane **238** (21.9 mg, 88%) as a white solid. R_f = 0.25 (30% Et_2O/pentane); mp = 158–160 °C; IR (film)/cm^{-1} 3302 (br, OH), 2959, 2885, 1610, 1513, 1438, 1263, 1230, 1177, 1095, 976, 931, 827, 730; ^1H NMR (400 MHz, $CDCl_3$) δ 7.37–7.30 (m, 2 H, 2 × Ar-CH), 7.20–7.13 (m, 2 H, 2 × Ar-CH), 7.09–7.02 (m, 2 H, 2 × Ar-CH), 6.87–6.78 (m, 2 H, 2 × Ar-CH), 5.27 (br, s, 1 H, OH), 5.23 (d, *J* = 5.7 Hz, 2 H, C*H*HOC*H*H), 5.19 (d, *J* = 5.7 Hz, 2 H, CH*H*OCH*H*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.5 (Ar-C_q-OH), 144.4 (Ar-C_q-C_q), 137.2 (Ar-C_q-C_q), 132.5 (Ar-C_q-Cl), 128.7 (2 × Ar-CH), 127.9 (2 × Ar-CH), 127.7 (2 × Ar-CH), 115.5 (2 × Ar-CH), 84.6 (CH_2OCH_2), 50.5 (C_q); HRMS (–ESI) *m*/*z* calcd for $C_{15}H_{12}{}^{35}ClO_2$ [M–H]: 259.0526, Found: 259.0531.



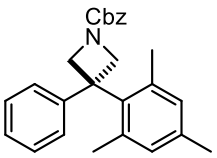
Isopropyl 2-(4-(3-(4-chlorophenyl)oxetan-3-yl)phenoxy)-2-methylpropanoate (237)

Isopropyl 2-bromo-2-methylpropanoate **241** (20.6 µL, 0.122 mmol) was added to a solution of oxetane **238** (10.6 mg, 0.041 mmol) and K_2CO_3 (18.0 mg, 0.13 mmol) in DMF (1.0 mL). The reaction mixture was stirred at 90 °C for 23 h, then cooled to rt and water (10 mL) was added followed by Et_2O (10 mL). The layers were separated and the aqueous portion was extracted with Et_2O (2 × 10 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash chromatography (30% Et_2O/pentane) afforded oxetane **237** (11.1 mg, 70%) as a colourless oil. R_f = 0.53 (30% Et_2O/pentane); IR (film)/cm^{-1} 2981, 2877, 1729 (C=O), 1509, 1382, 1285, 1241, 1177, 1148, 1103, 1013, 935, 827; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36–7.28 (m, 2 H, 2 × Ar-CH), 7.20–7.10 (m, 2 H, 2 × Ar-CH), 7.08–7.01 (m, 2 H, 2 × Ar-CH), 6.88–6.79 (m, 2 H, 2 × Ar-CH), 5.20 (d, *J* = 5.7 Hz, 2 H, C*H*HOC*H*H), 5.16 (d, *J* = 5.7 Hz, 2 H, CH*H*OCH*H*), 5.09 (h, *J* = 6.3 Hz, 1 H, C*H*(CH_3)$_2$), 1.60 (s, 6 H, 2 × CH_3), 1.23 (d, *J* = 6.3 Hz, 6 H, CH(C*H*$_3$)$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.6 (C=O), 154.3 (Ar-C_q-O), 144.4 (Ar-*C*$_q$-C_q), 138.4 (Ar-*C*$_q$-C_q), 132.5 (Ar-C_q-Cl), 128.6 (2 × Ar-CH), 127.9 (2 × Ar-CH), 127.2 (2 × Ar-CH), 118.9 (2 × Ar-CH), 84.6 (*C*H$_2$O*C*H$_2$), 79.1 (*C*$_q$(CH_3)$_2$), 69.0 (*C*H(CH_3)$_2$), 50.5 (C_q), 25.4 (C_q(*C*H$_3$)$_2$), 21.5 (CH(*C*H$_3$)$_2$); HRMS (+ESI) *m*/*z* calcd for $C_{22}H_{26}{}^{35}ClO_4^+$ [M+H]$^+$: 389.1514, Found: 389.1508.



3-(Benzylthio)-3-phenyloxetane (242)

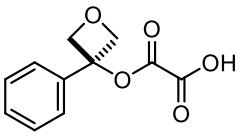
$FeCl_3$ (3.2 mg, 0.02 mmol) was weighed in a vial. Oxetanol **170** (30.0 mg, 0.20 mmol) and benzylmercaptan (40.0 µL, 0.34 mmol) were added. The reaction vessel was sealed and HFIP (2.0 mL) was added. The reaction was stirred for 1 h at 40 °C, then sat. aq. $NaHCO_3$ (10 mL) was added followed by Et_2O (10 mL). The layers were separated and the aqueous portion was extracted with Et_2O (2 × 10 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash chromatography (0 to 30% Et_2O/pentane) afforded sulfide **242** (1.5 mg, 3%) as a colourless oil. R_f = 0.16 (4% Et_2O/pentane); IR (film)/cm^{-1} 3060, 3026, 2929, 2870, 1494, 1453, 984, 700; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45–7.38 (m, 2 H, 2 × Ar-CH), 7.36–7.19 (m, 8 H, 8 × Ar-CH), 5.13 (d, *J* = 6.5 Hz, 2 H, C*H*HOC*H*H), 4.82 (d, *J* = 6.5 Hz, 2 H, CH*H*OCH*H*), 3.60 (s, 2 H, SCH_2Ph); ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.4 (Ar-*C*$_q$-CH_2), 134.1 (Ar-*C*$_q$-C_q), 129.0 (2 × Ar-CH), 128.6 (2 × Ar-CH), 128.5 (2 × Ar-CH), 127.3 (Ar-CH), 127.1 (Ar-CH), 126.4 (2 × Ar-CH), 82.7 (*C*H$_2$O*C*H$_2$), 52.9 (C_q), 35.0 (SCH_2Ph); HRMS (+APCI) *m*/*z* calcd for $C_{16}H_{17}OS^+$ [M+H]$^+$: 257.0995, Found: 257.0994.



Benzyl 3-mesityl-3-phenylazetidine-1-carboxylate (243)

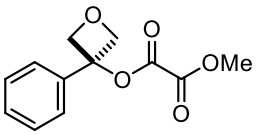
$FeCl_3$ (4.1 mg, 0.025 mmol) was weighed in a vial. Azetidinol **104** (70.8 mg, 0.25 mmol) and mesitylene (175 µL, 1.25 mmol) were added; The reaction vessel was sealed and HFIP (2.5 mL) was added. The reaction was stirred for 18 h at 80 °C, then cooled to rt and sat. aq. $NaHCO_3$ (10 mL) was added followed by Et_2O (10 mL). The layers were separated and the aqueous portion was extracted with Et_2O (2 × 10 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash chromatography (8% Et_2O/pentane) afforded azetidine **243** (4.5 mg, 5%) as a colourless oil. R_f = 0.22 (8% Et_2O/pentane); IR (film)/cm^{-1} 2959, 2885, 1714 (C=O), 1408, 1349, 1125, 760, 700; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43–7.22 (m, 10 H, 10 × Ar-CH), 6.90 (s, 2 H, 2 × Ar-CH), 5.16 (s, 2 H, CH_2Ph), 4.68 (d, *J* = 8.2 Hz, 2 H, C*H*HNC*H*H), 4.30 (d, *J* = 8.2 Hz, 2 H, CH*H*NCH*H*), 2.31 (s, 3 H, CH_3), 1.96 (s, 6 H, 2 × CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.7 (C=O), 145.1 (Ar-C_q-C_q), 138.0 (Ar-C_q-C_q), 136.53 (Ar-C_q-CH_2),136.50 (Ar-C_q-CH_3), 136.3 (2 × Ar-C_q-CH_3), 130.1 (2 × Ar-CH), 128.7 (2 × Ar-CH), 128.5 (2 × Ar-CH), 128.1 (2 × Ar-CH), 127.0 (2 × Ar-CH), 125.6 (2 × Ar-CH), 66.9 (CH_2Ph), 64.4 (br, *C*H_2N*C*H_2), 46.0 (C_q), 20.8 (Ar-CH_3), 20.6 (2 × Ar-CH_3); HRMS (+APCI) *m*/*z* calcd for $C_{26}H_{28}NO_2^+$ [M+H]$^+$: 386.2115, Found: 386.2110.

8.2.6 Synthesis of Oxetanyl and Azetidinyl Radical Precursors (Part 6.2 and 6.3)



2-Oxo-2-((3-phenyloxetan-3-yl)oxy)acetic acid (301)

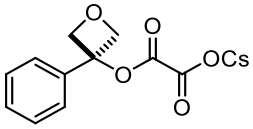
Oxalyl chloride (130 µL, 1.52 mmol) was added dropwise to a solution of oxetanol **170** (111 mg, 0.74 mmol) and NEt_3 (420 µL, 3.01 mmol) in Et_2O (5.0 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 10 min and then at 25 °C for 16 h. The reaction was then cooled to 0 °C and water (2.0 mL) was added. The reaction was stirred for 1 h at 20 °C and then water (20 mL) was added followed by EtOAc (15 mL). The layers were separated and the aqueous portion was extracted with EtOAc (2 × 20 mL). The organic extracts were combined, washed with sat. aq. NaCl (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. Recrystallisation from warm methanol afforded oxalate **301** (49.4 mg, 30%) as a white solid. mp = compound degraded under heat; IR (film)/cm^{-1} 3456 (br, OH), 2959, 1773 (C=O), 1746 (C=O), 1601, 1495, 1447, 1312, 1279, 1148, 1122, 1065, 979, 878, 752, 693; ^{1}H NMR (400 MHz, acetone-d_6) δ 7.62–7.56 (m, 2 H, 2 × Ar-CH), 7.50–7.43 (m, 2 H, 2 × Ar-CH), 7.43–7.36 (m, 1 H, Ar-CH), 5.14–5.09 (m, 2 H, C*H*HOC*H*H), 5.01–4.95 (m, 2 H, CH*H*OCH*H*); ^{13}C NMR (101 MHz, $(CD_3)_2CO$) δ 156.2 (2 × C=O), 139.1 (Ar-C_q-C_q), 129.6 (2 × Ar-CH), 129.4 (Ar-CH), 126.0 (2 × Ar-CH), 83.4 (C_q), 81.4 (*C*H_2O*C*H_2); HRMS (–APCI) *m*/*z* calcd for $C_{11}H_9O_5^-$ [M–H]$^-$: 221.0445, Found: 221.0448.



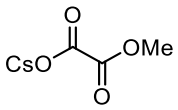
Methyl (3-phenyloxetan-3-yl) oxalate (304)

Following a procedure developed by MacMillan and Overman,[199] methyl chlorooxacetate **303** (120 µL, 1.31 mmol) was added dropwise to a solution of oxetanol **170** (151 mg, 1.00 mmol), NEt_3 (182 µL, 1.31 mmol), DMAP (12.2 mg, 0.10 mmol) in CH_2Cl_2 (10 mL) at 25 °C. The reaction was stirred for 1 h and sat. aq. NH_4Cl (30 mL) was added followed by CH_2Cl_2 (20 mL). The layers were separated and the aqueous portion was extracted with CH_2Cl_2 (20 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash chromatography (0% to 30% EtOAc/heptane) afforded oxalate **304** (238 mg, 100%) as a colourless oil. R_f = 0.29 (30% EtOAc/heptane); IR (film)/cm^{-1} 2956, 2923, 2852, 1771 (C=O), 1743 (C=O), 1497, 1449, 1322, 1285, 1202, 1154, 1110, 1067, 979, 880, 782, 758, 698, 548; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55–7.48 (m, 2 H, 2 × Ar-CH), 7.47–7.40 (m, 2 H, 2 × Ar-CH), 7.40–7.34 (m, 1 H, Ar-CH), 5.20–5.12 (m, 2 H, C*H*HOC*H*H), 5.08–5.01 (m, 2 H, CH*H*OCH*H*), 3.93 (s, 3 H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.6 (C=O), 155.8 (C=O), 137.4 (Ar-C_q-C_q), 128.82 (2 × Ar-CH), 128.76 (Ar-CH), 125.2 (2 × Ar-CH), 82.8 (C_q), 81.2 (CH_2OCH_2), 53.7 (CH_3); HRMS (+APCI) *m*/*z* calcd for $C_{12}H_{13}O_5^+$ $[M+H]^+$: 237.0757, Found: 237.0758.

Cesium 2-oxo-2-((3-phenyloxetan-3-yl)oxy)acetate (305) and **cesium 2-methoxy-2-oxoacetate (306)**



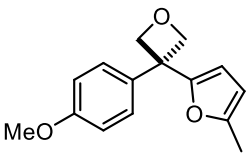
305



306

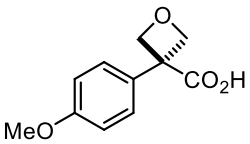
Following a procedure developed by MacMillan and Overman,[199] aq. CsOH (1 M, 1.01 mL, 1.01 mmol) was added dropwise to a solution of methyl oxalate **304** (238 mg, 1.00 mmol) in THF (2.0 mL) at 25 °C. The reaction was stirred for 30 min and aq. CsOH (1 M, 300 µL, 0.30 mmol) was added. After a further 20 min, the solvent was removed under reduced pressure. The crude product was dissolved in water (30 mL), washed with Et_2O (2 × 30 mL), and concentrated under reduced pressure to afford a mixture of oxalates **305** and **306** (74:26, 338 mg, 95%) as a white solid. mp = decomposed under heat; IR (film)/cm^{-1} 3346, 1729 (C=O), 1719 (C=O), 1688, 1652, 1568, 1295, 1217, 1198, 1167, 1161, 756; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.59–7.49 (m, 2 H, 2 × Ar-CH), 7.46–7.37 (m, 2 H, 2 × Ar-CH), 7.37–7.27 (m, 1 H, Ar-CH), 4.90 (d, *J* = 7.4 Hz, 2 H, C*H*HOC*H*H), 4.78 (d, *J* = 7.4 Hz, 2 H, CH*H*OCH*H*), 3.49 (s, 3 H, $CH_{3,\mathbf{306}}$); ^{13}C NMR (101 MHz, $(CD_3)_2SO$) δ 167.5 (C=O), 161.6 (C=O), 140.3 (Ar-C_q-C_q),

128.3 (2 × Ar-CH), 127.5 (Ar-CH), 124.3 (2 × Ar-CH), 81.7 (CH_2OCH_2), 78.1 (C_q), 49.6 (CH_3)[u]; HRMS (+APCI) not found.



2-(3-(4-Methoxyphenyl)oxetan-3-yl)-5-methylfuran (313)

2-Methylfuran (18.0 mL, 20.0 mmol) followed by toluene (80 mL) was added to a flask containing lithium bis(trifluoromethane)sulfonimide (1.26 g, 4.39 mmol), tetrabutylammonium hexafluorophosphate (852 mg, 2.20 mmol) and oxetanol **18** (7.21 g, 40.0 mmol). The reaction mixture was stirred at 40 °C for 2 h then sat. aq. $NaHCO_3$ (150 mL) was added followed by Et_2O (80 mL). The layers were separated and the aqueous portion was extracted with Et_2O (2 × 80 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash chromatography (5 to 10% Et_2O/pentane) afforded oxetane **313** (5.77 g, 59%) as a white solid. R_f = 0.53 (20% Et_2O/pentane); mp = 94–97 °C; IR (film)/cm^{-1} 2955, 2878, 1611, 1578, 1560, 1514, 1453, 1442, 1294, 1239, 1214, 1201, 1183, 1154, 1118, 1084, 1020, 993, 840, 820, 793, 743, 676, 655; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19–7.15 (m, 2 H, 2 × Ar-CH), 6.94–6.90 (m, 2 H, 2 × Ar-CH), 5.88 (dq, *J* = 3.1, 1.0 Hz, 1 H, $Ar_{(furan)}$-CH), 5.69 (d, *J* = 3.1 Hz, 1 H, $Ar_{(furan)}$-CH), 5.22 (d, *J* = 5.6 Hz, 2 H, C*H*HOC*H*H), 5.12 (d, *J* = 5.6 Hz, 2 H, CH*H*OCH*H*), 3.83 (s, 3 H, OCH_3), 2.31 (d, *J* = 1.0 Hz, 3 H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.5 (Ar-C_q-OCH_3), 155.8 ($Ar_{(furan)}$-C_q-C_q), 151.9 ($Ar_{(furan)}$-C_q-CH_3), 135.2 (Ar-C_q-C_q), 127.6 (2 × Ar-CH), 113.9 (2 × Ar-CH), 107.5 ($Ar_{(furan)}$-CH), 106.0 ($Ar_{(furan)}$-CH), 82.0 (CH_2OCH_2), 55.3 (OCH_3), 47.1 (C_q), 13.6 ($Ar_{(furan)}$-CH_3); HRMS (+ESI) *m*/*z* calcd. for $C_{15}H_{17}O_3$ [M+H]: 245.1172, Found: 245.1175.



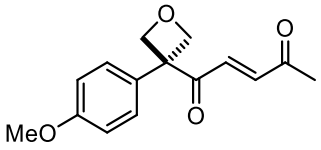
3-(4-Methoxyphenyl)oxetane-3-carboxylic acid (314)

$NaIO_4$ (35.3 g, 165.2 mmol) was added to a solution of oxetane furan **313** (5.77 g, 23.6 mmol) in heptane/EtOAc/H_2O (148 mL/148 mL/294 mL). The reaction mixture was stirred for 5 min at 25 °C, cooled to 0 °C and $RuCl_3$ (24.5 mg, 0.118 mmol) was added. The reaction mixture was stirred for 18 h at 25 °C. Water (250 mL) was added followed by EtOAc (250 mL) and the layers were separated. The aqueous portion was extracted with EtOAc (2 × 400 mL). The organic extracts were combined, dried over Na_2SO_4, filtered through celite® and concentrated under reduced pressure, affording carboxylic acid **314** (4.36 g, 89%) as an off-white solid. mp = 87–93 °C; IR (film)/cm^{-1} 3444 (br. COOH), 3131, 2967, 2896, 2766, 2620, 1722 (C=O), 1607, 1513, 1461, 1387, 1245, 1163, 1028, 958, 932, 887, 671; ^{1}H NMR (400 MHz, Acetone-d_6) δ 7.29–7.25 (m, 2 H, 2 × Ar-CH), 6.97–6.94 (m, 2 H, 2 × Ar-CH), 5.16 (d, *J* = 6.1 Hz, 2 H, C*H*HOC*H*H), 4.91 (d, *J* = 6.1 Hz, 2 H,

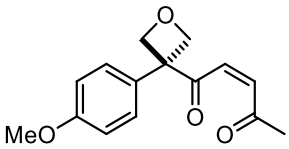
[u] The two C=O signals for **306** were not observed due to low intensities.

CH*H*OCH*H*), 3.80 (s, 3 H, OCH_3); ^{13}C NMR (101 MHz, $(CD_3)_2CO$) δ 175.0 (CO_2H), 159.9 (Ar-C_q-OCH_3), 133.0 (Ar-C_q-C_q), 128.1 (2 × Ar-CH), 114.8 (2 × Ar-CH), 80.0 (CH_2OCH_2), 55.5 (OCH_3), 53.2 (C_q); HRMS (–APCI) *m*/*z* calcd for $C_{11}H_{11}O_4^-$ $[M–H]^-$: 207.0663, Found: 207.0657.

(*E*)-1-(3-(4-Methoxyphenyl)oxetan-3-yl)pent-2-ene-1,4-dione ((*E*)-315) and **(*Z*)-1-(3-(4-methoxyphenyl)oxetan-3-yl)pent-2-ene-1,4-dione ((*Z*)-315)**



(*E*)-315



(*Z*)-315

Procedure using $RuCl_3$ and $NaBrO_3$

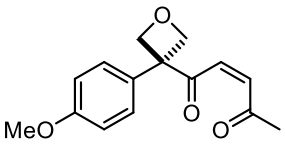
$NaBrO_3$ (211 mg, 1.40 mmol) was added to a solution of oxetane furan **313** (48.6 mg, 0.20 mmol) in heptane/EtOAc/H_2O (1.25 mL/1.25 mL /2.50 mL). The reaction mixture was stirred for 5 min at 25 °C and a solution of $RuCl_3$ (0.05 M in water, 20 µL, 0.001 mmol) was added. The reaction mixture was stirred for 18 h at 25 °C. Water (10 mL) was added followed by EtOAc (10 mL) and the layers were separated. The aqueous portion was extracted with EtOAc (2 × 10 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography (70% to 100% Et_2O/pentane) afforded alkene **(*E*)-315** (7.6 mg, 15%) as a yellow oil, followed by alkene **(*Z*)-315** (26.6 mg, 51%) as a colourless oil.

(*E*)-315: R_f = 0.50 (70% Et_2O/pentane); IR (film)/cm^{-1} 2959, 2881, 1684 (C=O), 1610 (C=O), 1513, 1360, 1293, 1254, 1181, 1028, 984, 834; ^1H NMR (400 MHz, $CDCl_3$) δ 7.14–7.10 (m, 2 H, 2 × Ar-CH), 7.02 (d, *J* = 15.8 Hz, 1 H, *H*C=CH), 6.96–6.92 (m, 2 H, 2 × Ar-CH), 6.83 (d, *J* = 15.8 Hz, 1 H, HC=C*H*), 5.20 (d, *J* = 6.2 Hz, 2 H, C*H*HOC*H*H), 5.01 (d, *J* = 6.2 Hz, 2 H, CH*H*OCH*H*), 3.82 (s, 3 H, OCH_3), 2.30 (s, 3 H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.3 (C=O), 196.2 (C=O), 159.4 (Ar-C_q-OCH_3), 138.5 (H*C*=CH), 132.4 (HC=*C*H), 129.2 (Ar-C_q-C_q), 127.5 (2 × Ar-CH), 114.9 (2 × Ar-CH), 77.6 (CH_2OCH_2), 57.9 (C_q), 55.3 (OCH_3), 29.1 (CH_3); HRMS (+APCI) *m*/*z* calcd for $C_{15}H_{17}O_4^+$ $[M+H]^+$: 261.1121, Found: 261.1116.

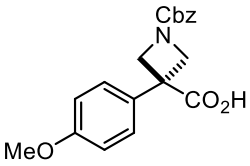
(*Z*)-315: R_f = 0.24 (70% Et_2O/pentane); IR (film)/cm^{-1} 2959, 2881, 1692 (C=O), 1610 (C=O), 1513, 1386, 1300, 1248, 1181, 1025, 984, 834; ^1H NMR (400 MHz, $CDCl_3$) δ 7.13–7.05 (m, 2 H, 2 × Ar-CH), 6.97–6.88 (m, 2 H, 2 × Ar-CH), 6.31 (d, *J* = 12.0 Hz, 1 H, *H*C=CH), 6.21 (d, *J* = 12.0 Hz, 1 H, HC=C*H*), 5.21 (d, *J* = 6.1 Hz, 2 H, C*H*HOC*H*H), 4.99 (d, *J* = 6.1 Hz, 2 H, CH*H*OCH*H*), 3.82 (s, 3 H, OCH_3), 2.30 (s, 3 H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 201.5 (C=O), 198.7 (C=O), 159.2 (Ar-C_q-OCH_3), 140.3 (H*C*=CH), 130.1 (Ar-C_q-C_q), 129.9 (HC=*C*H),

127.6 (2 × Ar-CH), 114.6 (2 × Ar-CH), 78.0 (CH_2OCH_2), 57.4 (C_q), 55.3 (OCH_3), 29.4 (CH_3); HRMS (+APCI) *m*/*z* calcd for $C_{15}H_{17}O_4$ $[M+H]^+$: 261.1121, Found: 261.1113.

Procedure using *m*CPBA

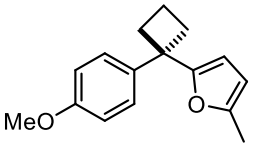


Washed *m*CPBA (34.5 mg, 0.20 mmol) was added to a solution of oxetane furan **313** (48.8 mg, 0.20 mmol) in CH_2Cl_2 (1.0 mL) at 0 °C. The reaction mixture was brought to 25 °C and stirred for 22 h. Sat. aq. $NaHCO_3$ (15 mL) was added followed by Et_2O (15 mL). The layers were separated and the aqueous portion was extracted with Et_2O (2 × 15 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography (70% Et_2O/pentane) afforded alkene **(*Z*)-315** (34.9 mg, 67%) as a colourless oil. Identical spectroscopic data were obtained.



1-((Benzyloxy)carbonyl)-3-(4-methoxyphenyl)azetidine-3-carboxylic acid (316)

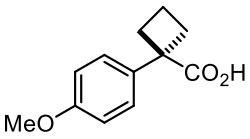
$NaIO_4$ (225 mg, 1.05 mmol) was added to a solution of azetidine furan **102** (56.6 mg, 0.15 mmol) in hexane/EtOAc/H_2O (2.5 mL/2.5 mL/5.0 mL). The reaction mixture was stirred for 5 min, and $RuCl_3$ (1.6 mg, 0.0077 mmol) was added. The reaction mixture was stirred for 24 h at 25 °C. Water (10 mL) was added followed by EtOAc (10 mL) and the layers were separated. The aqueous portion was extracted with EtOAc (2 × 10 mL). The organic extracts were combined, washed with sat. aq. NaCl (20 mL), dried over Na_2SO_4, filtered through celite® and concentrated under reduced pressure to afford carboxylic acid **316** (51.8 mg, 100%) as a brown paste. R_f = 0.31 (40% EtOAc/pentane + 1% AcOH); IR (film)/cm^{-1} 2959 (br. COOH), 1703 (br, 2 × C=O), 1610, 1583, 1513, 1424, 1355, 1247, 1179, 1144, 1101, 1024, 956, 829, 756, 696, 676; ^{1}H NMR (400 MHz, MeOD-*d*$_4$) δ 7.40–7.30 (m, 5 H, 5 × Ar-CH), 7.29–7.21 (m, 2 H, 2 × Ar-CH), 6.98–6.90 (m, 2 H, 2 × Ar-CH), 5.12 (s, 2 H, CH_2Ph), 4.64 (d, *J* = 8.7 Hz, 2 H, C*H*HOC*H*H), 4.32 (d, *J* = 8.7 Hz, 2 H, CH*H*OCH*H*), 3.80 (s, 3 H, OCH_3); ^{13}C NMR (101 MHz, CD_3OD) δ 176.5 (CO_2H), 160.5 (Ar-C_q-OCH_3), 158.2 (C=O), 137.8 (Ar-C_q-CH_2), 133.1 (Ar-C_q-C_q), 129.5 (2 × Ar-CH), 129.1 (Ar-CH), 128.9 (2 × Ar-CH), 128.5 (2 × Ar-CH), 115.1 (2 × Ar-CH), 68.1 (CH_2Ph), 59.8 (br, CH_2NCH_2), 55.8 (OCH_3), 48.4 (C_q); HRMS (+ESI) *m*/*z* calcd for $C_{19}H_{20}NO_5$ [M+H]: 342.1341, Found: 342.1336.



2-(1-(4-Methoxyphenyl)cyclobutyl)-5-methylfuran (318)

Toluene (2.0 mL) was added to calcium(II) bis(trifluoromethanesulfonimide) (30.0 mg, 0.05 mmol), tetrabutylammonium hexafluorophosphate (19.4 mg, 0.05 mmol),

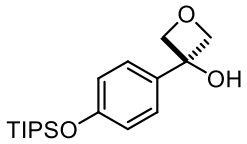
cyclobutanol **317**[v] (178 mg, 1.00 mmol) and 2-methylfuran (271 µL, 3.00 mmol). The reaction mixture was stirred at 40 °C for 2 h then sat. aq. $NaHCO_3$ (15 mL) was added followed by Et_2O (15 mL). The layers were separated and the aqueous portion was extracted with Et_2O (2 × 15 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash chromatography (2% Et_2O/pentane) afforded cyclobutane **318** (176 mg, 73%) as a colourless oil. R_f = 0.50 (2% Et_2O/pentane); IR (film)/cm^{-1} 2985, 2944, 1610, 1513, 1464, 1297, 1248, 1177, 1025, 831, 728; ^1H NMR (400 MHz, $CDCl_3$) δ 7.25–7.17 (m, 2 H, 2 × Ar-CH), 6.90–6.83 (m, 2 H, 2 × Ar-CH), 5.82 (dq, *J* = 3.0, 1.0 Hz, 1 H, $Ar_{(furan)}$-CH), 5.74 (d, *J* = 3.0 Hz, 1 H, $Ar_{(furan)}$-CH), 3.81 (s, 3 H, OCH_3), 2.72–2.63 (m, 2 H, CH_2), 2.63–2.52 (m, 2 H, CH_2), 2.25 (s, 3 H, CH_3), 2.19–2.05 (m, 1 H, C*H*H), 1.95–1.83 (m, 1 H, CH*H*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.8 (Ar-C_q-OCH_3), 157.6 ($Ar_{(furan)}$-C_q-C_q), 150.9 ($Ar_{(furan)}$-C_q-CH_3), 139.5 (Ar-C_q-C_q), 127.4 (2 × Ar-CH), 113.4 (2 × Ar-CH), 105.6 ($Ar_{(furan)}$-CH), 105.2 ($Ar_{(furan)}$-CH), 55.2 (OCH_3), 46.2 (C_q), 33.7 ($CH_2CH_2CH_2$), 16.6 ($CH_2CH_2CH_2$), 13.7 ($Ar_{(furan)}$-CH_3); HRMS (+APCI) *m*/*z* calcd for $C_{16}H_{19}O_2^+$ $[M+H]^+$: 243.1380, Found: 243.1388.



1-(4-Methoxyphenyl)cyclobutane-1-carboxylic acid (319)

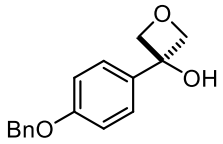
$NaIO_4$ (1.09 g, 5.10 mmol) was added to a solution of cyclobutane furan **318** (176 mg, 0.73 mmol) in heptane/EtOAc/H_2O (4.50 mL/ 4.50 mL/ 9.0 mL). The reaction mixture was stirred for 5 min and $RuCl_3$ (3.8 mg, 0.018 mmol) was added. The reaction mixture was stirred for 22 h at 25 °C. Water (15 mL) was added followed by EtOAc (15 mL) and the layers were separated. The aqueous portion was extracted with EtOAc (2 × 15 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude was dissolved in 5 mL of 50% Et_2O/pentane, filtrated through a pad of silica and concentrated under reduced pressure to afford cyclobutane **319** (142 mg, 94%) as a dark yellow solid. R_f = 0.32 (50% Et_2O/pentane); mp = 93–95 °C [lit.105–107 °C][252], IR (film)/cm^{-1} 2955 (br. COOH), 2899, 2836, 1692 (C=O), 1610, 1509, 1464, 1408, 1297, 1244, 1177, 1110, 1025, 939, 827, 734; ^1H NMR (400 MHz, $CDCl_3$) δ 7.25–7.22 (m, 2 H, 2 × Ar-CH), 6.92–6.85 (m, 2 H, 2 × Ar-CH), 3.81 (s, 3 H, OCH_3), 2.90–2.77 (m, 2 H, CH_2), 2.57–2.44 (m, 2 H, CH_2), 2.13–1.99 (m, 1 H, C*H*H), 1.95–1.80 (m, 1 H, CH*H*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 182.4 (CO_2H), 158.4 (Ar-C_q-OCH_3), 135.1 (Ar-C_q-C_q), 127.5 (2 × Ar-CH), 113.7 (2 × Ar-CH), 55.3 (OCH_3), 51.5 (C_q), 32.2 ($CH_2CH_2CH_2$), 16.5 ($CH_2CH_2CH_2$); HRMS (–APCI) *m*/*z* calcd for $C_{12}H_{13}O_3^-$ $[M-H]^-$: 205.0870, Found: 205.0864. Compound previously reported without characterisation data.[252]

[v] Previously synthesised in the Bull group



3-(4-((Triisopropylsilyl)oxy)phenyl)oxetan-3-ol (320)

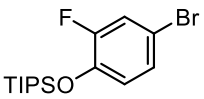
*n*BuLi (1.51 M in hexane, 17.7 mL, 26.7 mmol) was added dropwise over 5 min to a solution of (4-bromophenoxy)triisopropylsilane[253] (9.24 g, 28.1 mmol) in THF (51 mL) at –78 °C. The reaction mixture was stirred at –78 °C for 30 min. Oxetan-3-one (1.63 mL, 25.4 mmol) was added dropwise to the reaction mixture. Following a further 40 min at –78 °C the reaction mixture was warmed to 0 °C, then quenched with water (90 mL). Et_2O (80 mL) was added and the layers were separated. The aqueous portion was extracted with Et_2O (2 × 80 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography (40% to 50% Et_2O/hexane) afforded oxetanol **320** (7.03 g, 86%) as a white solid. R_f = 0.14 (30% Et_2O/hexane); mp = 60–63 °C [lit. 63–64 °C][50]; IR (film)/cm^{-1} 3404 (br, OH), 2945, 2868, 1605, 1513, 1251, 1171, 1076, 999, 977, 908, 881, 738, 727, 688; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45–7.38 (m, 2 H, 2 × Ar-CH), 6.95–6.90 (m, 2 H, 2 × Ar-CH), 4.95–4.91 (m, 2 H, CH*H*OCH*H*), 4.91–4.88 (m, 2 H, C*H*HOC*H*H), 1.32–1.20 (m, 3 H, 3 × C*H*(CH_3)$_2$), 1.11 (d, *J* = 7.3 Hz, 18 H, 3 × CH(C*H*$_3$)$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.9 (Ar-*C*$_q$-OTIPS), 134.7 (Ar-*C*$_q$-C$_q$), 125.8 (2 × Ar-CH), 119.9 (2 × Ar-CH), 85.3 (*C*H_2O*C*H_2), 75.7 (C$_q$), 17.9 (3 × CH(*C*H_3)$_2$), 12.6 (3 × *C*H(CH_3)$_2$). The observed spectroscopic (^{1}H and ^{13}C NMR) data for this compound were consistent with that previously reported.[50]



3-(4-(Benzyloxy)phenyl)oxetan-3-ol (321)

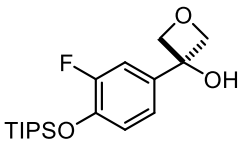
*n*BuLi (1.47 M in hexane, 12.2 mL, 17.9 mmol) was added dropwise over 5 min to a solution of 4-benzyloxybromobenzene (5.13 g, 19.5 mmol) in THF (50 mL) at –78 °C. The reaction mixture was stirred at –78 °C for 30 min. Oxetan-3-one (1.20 mL, 18.7 mmol) was added dropwise to the reaction mixture. Following a further 1 h at –78 °C the reaction mixture was warmed to 0 °C, then quenched with water (50 mL). Et_2O (70 mL) was added and the layers were separated. The aqueous portion was extracted with Et_2O (2 × 70 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography (60% Et_2O/pentane) afforded oxetanol **321** (3.96 g, 83%) as a white solid. R_f = 0.39 (60% Et_2O/pentane); mp = 113–115 °C [lit. 114–115 °C][50]; IR (film)/cm^{-1} 3394 (br. OH), 2974, 2877, 1609, 1580, 1458, 1399, 1239, 1179, 1043, 1008, 958, 843, 822, 733, 701, 656; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55–7.49 (m, 2 H, 2 × Ar-CH), 7.49–7.31 (m, 5 H, 5 × Ar-CH), 7.07–7.02 (m, 2 H, 2 × Ar-CH), 5.12 (s, 2 H, CH_2Ph), 4.95 (d, *J* = 6.9 Hz, 2 H, CH*H*OCH*H*), 4.92 (d, *J* = 6.9 Hz, 2 H, C*H*HOC*H*H), 2.46 (s, br, 1 H, OH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.3 (Ar-C$_q$-O), 136.7 (Ar-*C*$_q$-CH_2), 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 (*C*H_2O*C*H_2), 75.7 (C$_q$), 70.1 (CH_2Ph). The

observed spectroscopic (^{1}H and ^{13}C NMR) data for this compound were consistent with that previously reported.[50]



(4-Bromo-2-fluorophenoxy)triisopropylsilane (S7)

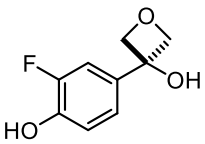
Triisopropylsilyl chloride (3.90 mL, 18.2 mmol) was added dropwise to a solution of 4-bromo-2-fluorophenol (1.64 mL, 15.0 mmol) and imidazole (1.84 g, 27.0 mmol) in CH_2Cl_2 (25.0 mL) at 25 °C. The reaction mixture was stirred for 3 h at 25 °C and then water (50 mL) was added followed by Et_2O (50 mL). The layers were separated and the aqueous portion was extracted with Et_2O (2 × 80 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was dissolved in pentane and filtrated through a plug of silica to afford **S7** (5.17 g, 99%) as a colourless oil. R_f = 0.87 (100% pentane); IR (film)/cm^{-1} 2944, 2868, 1495, 1463, 1297, 1204, 1119, 919, 881, 846, 810, 697, 684; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (dd, *J* = 10.1, 2.4 Hz, 1 H, Ar-CH), 7.10 (ddd, *J* = 8.7, 2.4; 1.5 Hz, 1 H, Ar-CH), 6.82 (dd, *J* = 8.7 Hz, 1 H, Ar-CH), 1.32–1.20 (m, 3 H, 3 × C*H*$(CH_3)_2$), 1.10 (d, *J* = 7.3 Hz, 18 H, 3 × CH(C*H*$_3)_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.9 (d, $^1J_{C\text{-}F}$ = 249.2 Hz, Ar-C_q-F), 143.4 (d, $^2J_{C\text{-}F}$ = 11.9 Hz, Ar-C_q-OTIPS), 127.2 (d, $^3J_{C\text{-}F}$ = 4.2 Hz, Ar-CH), 122.8 (d, $^4J_{C\text{-}F}$ = 1.9 Hz, Ar-CH), 119.9 (d, $^2J_{C\text{-}F}$ = 20.6 Hz, Ar-CH), 112.2 (d, $^3J_{C\text{-}F}$ = 8.1 Hz, Ar-C_q-Br), 17.7 (3 × CH(*C*$H_3)_2$), 12.6 (3 × *C*H$(CH_3)_2$); ^{19}F NMR (377 MHz, $CDCl_3$) δ –128.7 (m). The observed spectroscopic data (^{1}H and ^{19}F NMR) for this compound were consistent with that previously reported.[232]



3-(3-Fluoro-4-((triisopropylsilyl)oxy)phenyl)oxetan-3-ol (S8)

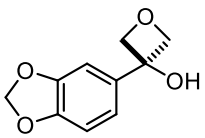
*n*BuLi (1.50 M in hexane, 9.63 mL, 14.4 mmol) was added dropwise over 5 min to a solution of bromo aryl **S7** (5.17 g, 14.9 mmol) in THF (30.0 mL) at –78 °C. The reaction mixture was stirred at –78 °C for 30 min. Oxetan-3-one (1.05 mL, 16.0 mmol) was added dropwise to the reaction mixture. Following a further 30 min at –78 °C the reaction mixture was warmed to 25 °C then quenched with water (80 mL). Et_2O (80 mL) was added and the layers were separated. The aqueous portion was extracted with Et_2O (2 × 80 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography (20% Et_2O/hexane) afforded oxetanol **S8** (3.30 g, 61%) as a white solid. R_f = 0.29 (30% Et_2O/pentane); mp = 49–50 °C; IR (film)/cm^{-1} 3391 (br, OH), 2944, 2870, 1520, 1464, 1304, 1125, 972, 939, 883, 820, 685; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (dd, *J* = 11.9, 2.4 Hz, 1 H, Ar-CH), 7.20 (ddd, *J* = 8.4, 2.4, 1.1 Hz, 1 H, Ar-CH), 6.98 (m, 1 H, Ar-CH), 4.88 (d, *J* = 6.6 Hz, 2 H, C*H*HOC*H*H), 4.86 (d, *J* = 6.6 Hz, 2 H, CH*H*OCH*H*), 2.79 (s, 1 H, OH), 1.35–1.22 (m, 3 H, 3 × C*H*$(CH_3)_2$), 1.11 (d, *J* = 7.3 Hz, 18 H, 3 × CH(C*H*$_3)_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.9 (d, $^1J_{C\text{-}F}$ = 245.2 Hz, Ar-C_q-F), 143.5 (d, $^2J_{C\text{-}F}$ = 12.2 Hz, Ar-C_q-OTIPS), 135.9 (d, $^3J_{C\text{-}F}$ = 5.9 Hz,

Ar-C_q-C_q), 121.7 (d, $^4J_{C\text{-}F}$ = 1.6 Hz, Ar-CH), 120.2 (d, $^3J_{C\text{-}F}$ = 3.5 Hz, Ar-CH), 113.0 (d, $^2J_{C\text{-}F}$ = 20.6 Hz, Ar-CH), 85.6 (CH_2OCH_2), 75.3 (C_q), 17.8 (3 × CH(CH_3)$_2$), 12.7 (3 × CH(CH_3)$_2$); ^{19}F NMR (377 MHz, $CDCl_3$) δ –130.8 (dd, *J* = 11.9, 8.4 Hz); HRMS (–ESI) *m*/*z* calcd for $C_{18}H_{28}FO_3Si$ [M–H]: 339.1792, Found: 339.1805.



3-(3-Fluoro-4-hydroxyphenyl)oxetan-3-ol (322)

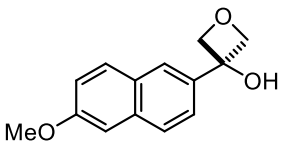
A solution of TBAF (1 M in THF, 12.6 mL, 12.6 mmol) was added dropwise to a solution of **S8** (3.30 g, 9.69 mmol) in THF (19.4 mL) at 0 °C. The reaction mixture was stirred for 10 min at 0 °C and then 3 h at 25 °C. Water (60 mL) was added followed by Et_2O (60 mL). The layers were separated and the aqueous portion was extracted with Et_2O (2 × 60 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography (70% Et_2O/hexane) afforded oxetanol **322** containing a tetrabutylammonium salt. The mixture was dissolved in Et_2O (40 mL) and washed with sat. aq. NH_4Cl (3 × 20 mL) to give oxetanol **322** (1.33 g, 75%) as a white solid. R_f = 0.23 (70% Et_2O/hexane); mp = 129–130 °C; IR (film)/cm^{-1} 3254 (br, OH), 2959, 2881, 2363, 1625, 1520, 1435, 1297, 1218, 1118, 969, 823, 775; ^{1}H NMR (400 MHz, MeOD-*d*$_4$) δ 7.34–7.27 (m, 2 H, 2 × Ar-CH), 6.98 (m, 1 H, Ar-CH), 4.88 (d, *J* = 6.6 Hz, 2 H, C*H*HOC*H*H), 4.83 (d, *J* = 6.6 Hz, 2 H, CH*H*OCH*H*); ^{13}C NMR (101 MHz, MeOD-*d*$_4$) δ 152.7 (d, $^1J_{C\text{-}F}$ = 240.3 Hz, Ar-C_q-F), 145.5 (d, $^2J_{C\text{-}F}$ = 13.0 Hz, Ar-C_q-OH), 136.7 (d, $^3J_{C\text{-}F}$ = 5.3 Hz, Ar-C_q-C_q), 121.8 (d, $^4J_{C\text{-}F}$ = 3.3 Hz, Ar-CH), 118.7 (d, $^3J_{C\text{-}F}$ = 3.2 Hz, Ar-CH), 113.7 (d, $^2J_{C\text{-}F}$ = 19.9 Hz, Ar-CH), 87.0 (CH_2OCH_2), 75.5 (C_q); ^{19}F NMR (377 MHz, MeOD-*d*$_4$) δ –139.2 (dd, *J* = 12.5, 9.1 Hz); HRMS (–ESI) *m*/*z* calcd for $C_9H_8FO_3$ [M–H]: 183.0457, Found: 183.0462.



3-(Benzo[d][1,3]dioxol-5-yl)oxetan-3-ol (323)

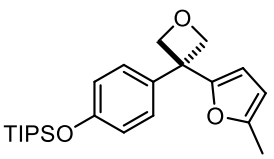
*n*BuLi (1.51 M in hexane, 13.9 mL, 21.0 mmol) was added dropwise over 5 min to a solution of 5-bromo-2H-1,3-benzodioxole (2.65 mL, 22.0 mmol) in THF (40 mL) at –78 °C. The reaction mixture was stirred at –78 °C for 1 h. Oxetan-3-one (1.28 mL, 20.0 mmol) was added dropwise to the reaction mixture. Following a further 3 h at –78 °C the reaction mixture was warmed to 0 °C then quenched with sat. aq. NH_4Cl (40 mL). Et_2O (40 mL) was added and the layers were separated. The aqueous portion was extracted with Et_2O (2 × 40 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography (40% Et_2O/hexane) afforded oxetanol **323** (3.34 g, 86%) as a white solid. R_f = 0.38 (70% Et_2O/pentane); mp = 85–87 °C [lit. 88–91 °C][50]; IR (film)/cm^{-1} 3333 (br, OH), 2971, 2875, 1736, 1435, 1248, 1035, 960, 857, 726; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.07 (d, *J* = 1.8 Hz, 1 H, Ar-CH), 7.05 (dd, *J* = 8.0, 1.8 Hz, 1 H, Ar-CH), 6.85 (d, *J* = 8.0 Hz, 1 H, Ar-CH), 6.00 (s, 2 H, Ar-

O-CH_2), 4.89 (s, 4 H, C*H*$_2$OC*H*$_2$), 2.50 (s, 1 H, OH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.0 (Ar-C_q-O), 147.2 (Ar-C_q-O), 136.3 (Ar-*C*$_q$-C_q), 117.8 (Ar-CH), 108.1 (Ar-CH), 105.4 (Ar-CH), 101.2 (OCH_2O), 85.5 (*C*H_2O*C*H$_2$), 75.7 (C_q). The observed spectroscopic (^{1}H and ^{13}C NMR) data for this compound was consistent with that previously reported.[50]



3-(6-Methoxynaphthalen-2-yl)oxetan-3-ol (324)

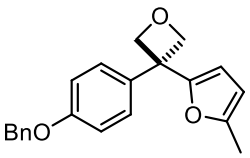
*n*BuLi (1.47 M in hexane, 4.00 mL, 5.88 mmol) was added dropwise over 5 min to a solution of 2-bromo-6-methoxy-naphthalene (1.50 g, 6.33 mmol) in THF (10 mL) at –78 °C. The reaction mixture was stirred at –78 °C for 2 h. Oxetan-3-one (312 µL, 4.87 mmol) was added dropwise to the reaction mixture at –78 C. The reaction mixture was warmed to 25 °C and stirred for 18 h, then quenched with water (50 mL). Et_2O (50 mL) was added and the layers were separated. The aqueous portion was extracted with Et_2O (2 × 50 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography (10% Et_2O/CH_2Cl_2) afforded oxetanol **324** (631 mg, 56%) as a white solid. R_f = 0.16 (10% Et_2O/CH_2Cl_2); mp = 166–169 °C; IR (film)/cm^{-1} 3309 (br, OH), 2877, 1605, 1461, 1257, 1203, 969, 924, 853, 816, 667; ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 8.00 (d, *J* = 1.9 Hz, 1 H, Ar-CH), 7.86 (d, *J* = 8.8 Hz, 2 H, 2 × Ar-CH), 7.72 (dd, *J* = 8.6, 1.9 Hz, 1 H, Ar-CH), 7.32 (d, *J* = 2.5 Hz, 1 H, Ar-CH), 7.17 (dd, *J* = 8.8, 2.5 Hz, 1 H, Ar-CH), 6.42 (s, 1 H, OH), 4.83 (d, *J* = 6.4 Hz, 2 H, C*H*HOC*H*H), 4.78 (d, *J* = 6.4 Hz, 2 H, CH*H*OCH*H*), 3.87 (s, 3 H, OCH_3); ^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ 157.2 (Ar-*C*$_q$-OCH_3), 139.1 (Ar-*C*$_q$-C_q), 133.4 (Ar-*C*$_q$-C_q), 129.5 (Ar-CH), 127.9 (Ar-*C*$_q$-C_q), 127.0 (Ar-CH), 123.7 (Ar-CH), 122.8 (Ar-CH), 118.7 (Ar-CH), 105.7 (Ar-CH), 85.1 (*C*H_2O*C*H$_2$), 74.1 (C_q), 55.1 (OCH_3); HRMS (–ESI) *m*/*z* calcd for $C_{14}H_{13}O_2^{\bullet}$ [M–OH]$^{\bullet}$: 213.0916, Found: 213.0922.



Triisopropyl(4-(3-(5-methylfuran-2-yl)oxetan-3-yl)phenoxy)silane (325)

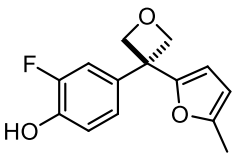
2-Methylfuran (3.20 mL, 35.0 mmol) followed by toluene (14.0 mL) was added to a flask containing lithium bis(trifluoromethane)sulfonimide (221 mg, 0.77 mmol), tetrabutylammonium hexafluorophosphate (149 mg, 0.38 mmol) and oxetanol **320** (2.26 g, 7.01 mmol). The reaction mixture was stirred at 40 °C for 19 h and then sat. aq. $NaHCO_3$ (60 mL) was added followed by Et_2O (70 mL) and the layers were separated. The aqueous portion was extracted with Et_2O (2 × 70 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography (4% Et_2O/pentane) afforded oxetane **325** (751 mg, 28%) as a colourless oil. R_f = 0.28 (4% Et_2O/pentane); IR (film)/cm^{-1} 2945, 2870, 1730, 1610, 1558, 1513, 1461, 1264, 995, 910, 883, 734, 686; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.09–7.05 (m, 2 H,

2 × Ar-CH), 6.90–6.87 (m, 2 H, 2 × Ar-CH), 5.86 (dq, *J* = 3.2, 1.1 Hz, 1 H, $Ar_{(furan)}$-CH), 5.62 (d, *J* = 3.2 Hz, 1 H, $Ar_{(furan)}$-CH), 5.22 (d, *J* = 5.6 Hz, 2 H, C*H*HOC*H*H), 5.11 (d, *J* = 5.6 Hz, 2 H, CH*H*OCH*H*), 2.32 (d, *J* = 1.1 Hz, 3 H, CH_3), 1.31–1.22 (m, 3 H, 3 × C*H*$(CH_3)_2$), 1.12 (d, *J* = 7.3 Hz, 18 H, 3 × CH(C*H*$_3)_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.8 (Ar-C_q-OTIPS), 154.9 ($Ar_{(furan)}$-*C*$_q$-C_q), 151.8 ($Ar_{(furan)}$-*C*$_q$-CH_3), 135.3 (Ar-*C*$_q$-C_q), 127.6 (2 × Ar-CH), 119.8 (2 × Ar-CH), 107.6 ($Ar_{(furan)}$-CH), 106.0 ($Ar_{(furan)}$-CH), 82.1 (*C*H_2O*C*H_2), 47.1 (C_q), 17.9 (3 × CH(*C*$H_3)_2$), 13.7 ($Ar_{(furan)}$-CH_3), 12.6 (3 × *C*H$(CH_3)_2$); HRMS (+ESI) *m*/*z* calcd for $C_{23}H_{35}O_3Si$ [M+H]: 387.2355, Found: 387.2360.



2-(3-(4-(Benzyloxy)phenyl)oxetan-3-yl)-5-methylfuran (326)

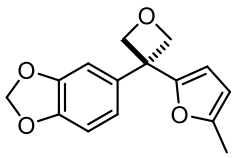
2-Methylfuran (1.40 mL, 15.0 mmol) followed by $CHCl_3$ (6.0 mL) was added to a flask containing lithium bis(trifluoromethane)sulfonimide (94.8 mg, 0.33 mmol), tetrabutylammonium hexafluorophosphate (63.9 mg, 0.165 mmol) and oxetanol **321** (769 mg, 3.00 mmol). The reaction mixture was stirred at 50 °C for 3 h then sat. aq. $NaHCO_3$ (40 mL) was added followed by Et_2O (40 mL). The aqueous portion was extracted with Et_2O (2 × 40 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography (10% Et_2O/pentane) afforded oxetane **326** (456 mg, 47%) as a white solid. R_f = 0.24 (10% Et_2O/pentane); mp = 88–89 °C; IR (film)/cm^{-1} 2952, 2877, 1606, 1513, 1453, 1386, 1233, 1064, 991, 954, 861, 831, 779, 741, 697; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50–7.30 (m, 5 H, 5 × Ar-CH), 7.20–7.13 (m, 2 H, 2 × Ar-CH), 7.03–6.96 (m, 2 H, 2 × Ar-CH), 5.88 (dq, *J* = 3.1, 1.0 Hz, 1 H, $Ar_{(furan)}$-CH), 5.69 (d, *J* = 3.1 Hz, 1 H, $Ar_{(furan)}$-CH), 5.23 (d, *J* = 5.6 Hz, 2 H, C*H*HOC*H*H), 5.12 (d, *J* = 5.6 Hz, 2 H, CH*H*OCH*H*), 5.09 (s, 2 H, OCH_2Ph), 2.32 (d, *J* = 1.0 Hz, 3 H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.7 (Ar-C_q-OBn), 155.7 ($Ar_{(furan)}$-*C*$_q$-C_q), 151.9 ($Ar_{(furan)}$-*C*$_q$-CH_3), 136.9 (Ar-*C*$_q$-CH_2), 135.4 (Ar-*C*$_q$-C_q), 128.6 (2 × Ar-CH), 128.0 (Ar-CH), 127.6 (2 × Ar-CH), 127.5 (2 × Ar-CH), 114.8 (2 × Ar-CH), 107.6 ($Ar_{(furan)}$-CH), 106.0 ($Ar_{(furan)}$-CH), 82.0 (*C*H_2O*C*H_2), 70.1 (OCH_2Ph), 47.1 (C_q), 13.7 ($Ar_{(furan)}$-CH_3); HRMS (+ESI) *m*/*z* calcd for $C_{21}H_{21}O_3$ [M+H]: 321.1491, Found: 321.1492.



2-Fluoro-4-(3-(5-methylfuran-2-yl)oxetan-3-yl)phenol (327)

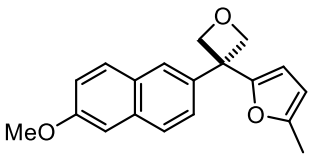
2-Methylfuran (3.00 mL, 33.1 mmol) followed by lithium bis(trifluoromethane)sulfonimide (209 mg, 0.728 mmol) and tetrabutylammonium hexafluorophosphate (141 mg, 0.364 mmol) was added to a solution of oxetanol **322** (1.22 g, 6.62 mmol) in $CHCl_3$ (33.1 mL) warmed at 55 °C. The reaction mixture was stirred at 55 °C for 25 h and then sat. aq. $NaHCO_3$ (30 mL) was added followed by Et_2O (30 mL) and the layers were separated. The aqueous portion was extracted with Et_2O (2 × 40 mL). The organic extracts were combined, dried over Na_2SO_4,

filtered and concentrated under reduced pressure. Purification by flash column chromatography (0% to 2% Et_2O/CH_2Cl_2) afforded oxetane **327** (421 mg, 26%) containing 7% of tetrabutylammonium hexafluorophosphate, as a white solid. R_f = 0.23 (70% Et_2O/hexane); mp = 129–130 °C; IR (film)/cm^{-1} 3254 (br, OH), 2959, 2881, 2363, 1625, 1520, 1435, 1297, 1218, 1118, 969, 823, 775; ^{1}H NMR (400 MHz, MeOD-d_4) δ 7.05–6.86 (m, 3 H, 3 × Ar-CH), 5.96 (dq, J = 3.1, 1.2 Hz, 1 H, $Ar_{(furan)}$-CH), 5.83 (d, J = 3.1 Hz, 1 H, $Ar_{(furan)}$-CH), 5.18 (d, J = 5.8 Hz, 2 H, C*H*HOC*H*H), 5.09 (d, J = 5.8 Hz, 2 H, CH*H*OCH*H*), 2.31 (s, 3 H, CH_3); ^{13}C NMR (101 MHz, MeOD-d_4) δ 156.6 ($Ar_{(furan)}$-C_q-C_q), 153.5 (d, $^1J_{C\text{-}F}$ = 240.4 Hz, Ar-C_q-F), 153.2 ($Ar_{(furan)}$-C_q-CH_3), 145.1 (d, $^2J_{C\text{-}F}$ = 12.8 Hz, Ar-C_q-OH), 136.1 (d, $^3J_{C\text{-}F}$ = 5.4 Hz, Ar-C_q-C_q), 123.7 (d, $^4J_{C\text{-}F}$ = 3.4 Hz, Ar-CH), 118.7 (d, $^3J_{C\text{-}F}$ = 2.9 Hz, Ar-CH), 115.4 (d, $^2J_{C\text{-}F}$ = 19.7 Hz, Ar-CH), 108.7 ($Ar_{(furan)}$-CH), 107.2 ($Ar_{(furan)}$-CH), 83.0 (CH_2OCH_2), 48.4 (C_q), 13.4 ($Ar_{(furan)}$-CH_3); ^{19}F NMR (377 MHz, MeOD-d_4) δ –138.9 (dd, J = 12.1, 8.5 Hz); HRMS (–ESI) m/z calcd for $C_{14}H_{12}FO_3$ [M–H]: 247.0770, Found: 247.0776.



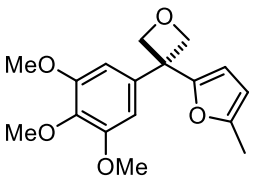
5-(3-(5-Methylfuran-2-yl)oxetan-3-yl)benzo[d][1,3]dioxole (328)

2-Methylfuran (3.50 mL, 38.6 mmol) followed by $CHCl_3$ (15.4 mL) was added to a flask containing lithium bis(trifluoromethane)sulfonimide (244 mg, 0.85 mmol), tetrabutylammonium hexafluorophosphate (165 mg, 0.425 mmol) and oxetanol **323** (1.50 g, 7.72 mmol). The reaction mixture was stirred at 40 °C for 2 h and then sat. aq. $NaHCO_3$ (80 mL) was added followed by Et_2O (80 mL) and the layers were separated. The aqueous portion was extracted with Et_2O (2 × 80 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography (10% Et_2O/hexane) afforded oxetane **328** (1.10 g, 55%) as a yellow oil. R_f = 0.15 (10% Et_2O/hexane); IR (film)/cm^{-1} 2952, 2878, 1610, 1558, 1487, 1439, 1349, 1241, 1036, 992, 932, 895, 783; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.82 (d, J = 8.0 Hz, 1 H, Ar-CH), 6.72 (d, J = 1.7 Hz, 1 H, Ar-CH), 6.99 (dd, J = 8.0, 1.7 Hz, 1 H, Ar-CH), 5.98 (s, 2 H, OCH_2O), 5.88 (dq, J = 3.1, 1.1 Hz, 1 H, $Ar_{(furan)}$-CH), 5.74 (d, J = 3.1 Hz, 1 H, $Ar_{(furan)}$-CH), 5.19 (d, J = 5.6 Hz, 2 H, C*H*HOC*H*H), 5.09 (d, J = 5.6 Hz, 2 H, CH*H*OCH*H*), 2.31 (d, J = 1.1 Hz, 3 H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.4 ($Ar_{(furan)}$-C_q-C_q), 151.9 ($Ar_{(furan)}$-C_q-CH_3), 147.7 (Ar-C_q-OCH_2), 146.4 (Ar-C_q-OCH_2), 136.9 (Ar-C_q-C_q), 119.7 (Ar-CH), 108.1 (Ar-CH), 107.5 (Ar-CH), 107.3 ($Ar_{(furan)}$-CH), 106.0 ($Ar_{(furan)}$-CH), 101.1 (CH_2), 81.9 (CH_2OCH_2), 47.4 (C_q), 13.6 (CH_3); HRMS (+ESI) m/z calcd for $C_{15}H_{15}O_4$ [M+H]: 259.0970, Found: 259.0971.



2-(3-(6-Methoxynaphthalen-2-yl)oxetan-3-yl)-5-methylfuran (329)

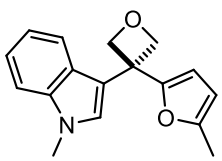
2-Methylfuran (113 µL, 1.25 mmol) followed by $CHCl_3$ (0.5 mL) was added to a flask containing lithium bis(trifluoromethane)sulfonimide (7.9 mg, 0.0275 mmol), tetrabutylammonium hexafluorophosphate (5.3 mg, 0.014 mmol) and oxetanol **324** (57.6 mg, 0.25 mmol). The reaction mixture was stirred at 40 °C for 4 h and then sat. aq. $NaHCO_3$ (20 mL) was added followed by Et_2O (20 mL). The aqueous portion was extracted with Et_2O (2 × 20 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography (10% Et_2O/pentane) afforded oxetane **329** (19.0 mg, 26%) as an off white solid. R_f = 0.30 (10% Et_2O/pentane); mp = 135–137 °C; IR (film)/cm^{-1} 2952, 2877, 1632, 1606, 1514, 1483, 1390, 1263, 1200, 1028, 991, 853, 786; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.6 Hz, 1 H, Ar-CH), 7.73 (d, *J* = 8.8 Hz, 1 H, Ar-CH), 7.62 (d, *J* = 1.9 Hz, 1 H, Ar-CH), 7.33 (dd, *J* = 8.6, 1.9 Hz, 1 H, Ar-CH), 7.20–7.16 (m, 2 H, 2 × Ar-CH), 5.89 (dq, *J* = 3.2, 1.0 Hz, 1 H, $Ar_{(furan)}$-CH), 5.70 (d, *J* = 3.2 Hz, 1 H, $Ar_{(furan)}$-CH), 5.32 (d, *J* = 5.6 Hz, 2 H, C*H*HOC*H*H), 5.26 (d, *J* = 5.6 Hz, 2 H, CH*H*OCH*H*), 3.94 (s, 3 H, OCH_3), 2.33 (d, *J* = 1.0 Hz, 3 H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.8 (Ar-C_q-OCH_3), 155.5 ($Ar_{(furan)}$-C_q-C_q), 151.9 ($Ar_{(furan)}$-C_q-CH_3), 137.9 (Ar-C_q-C_q), 133.4 (Ar-C_q-C_q), 129.4 (Ar-CH), 128.6 (Ar-C_q-C_q), 127.2 (Ar-CH), 125.3 (Ar-CH), 124.9 (Ar-CH), 119.1 (Ar-CH), 107.7 (Ar-CH), 106.1 ($Ar_{(furan)}$-CH), 105.6 ($Ar_{(furan)}$-CH), 81.8 (CH_2OCH_2), 55.3 (OCH_3), 47.6 (C_q), 13.7 ($Ar_{(furan)}$-CH_3); HRMS (+ESI) *m*/*z* calcd for $C_{19}H_{19}O_3$ [M+H]: 295.1334, Found: 295.1327.



2-Methyl-5-(3-(3,4,5-trimethoxyphenyl)oxetan-3-yl)furan (330)

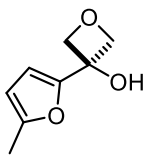
2-Methylfuran (451 µL, 5.00 mmol) followed by toluene (2.0 mL) was added to a flask containing lithium bis(trifluoromethane)sulfonimide (31.6 mg, 0.11 mmol), tetrabutylammonium hexafluorophosphate (21.3 mg, 0.055 mmol) and oxetanol **64** (240 mg, 1.00 mmol). The reaction mixture was stirred at 40 °C for 2 h and then sat. aq. $NaHCO_3$ (15 mL) was added followed by Et_2O (15 mL). The aqueous portion was extracted with Et_2O (2 × 15 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography (40% Et_2O/hexane) afforded oxetane **330** (32.2 mg, 11%) as a yellow oil. R_f = 0.30 (50% Et_2O/hexane); IR (film)/cm^{-1} 2940, 2877, 1587, 1509, 1453, 1412, 1334, 1241, 1125, 991, 782; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.44 (s, 2 H, 2 × Ar-CH), 5.89 (dq, *J* = 3.2, 1.1 Hz, 1 H, $Ar_{(furan)}$-CH), 5.75 (d, *J* = 3.2 Hz, 1 H, $Ar_{(furan)}$-CH), 5.22 (d, *J* = 5.6 Hz, 2 H, C*H*HOC*H*H), 5.13 (d, *J* = 5.6 Hz, 2 H, CH*H*OCH*H*), 3.86 (s, 3 H, OCH_3), 3.84 (s, 6 H, 2 × OCH_3), 2.32 (d, *J* = 1.1 Hz, 3 H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.2 ($Ar_{(furan)}$-C_q-C_q), 153.2 (2 × Ar-C_q-OCH_3), 151.9 ($Ar_{(furan)}$-C_q-CH_3), 138.6 (Ar-C_q-OCH_3), 136.9 (Ar-C_q-C_q), 107.7

($Ar_{(furan)}$-CH), 106.1 ($Ar_{(furan)}$-CH), 103.9 (2 × Ar-CH), 81.9 (CH_2OCH_2), 60.8 (OCH_3), 56.1 (2 × OCH_3), 47.8 (C_q), 13.6 ($Ar_{(furan)}$-CH_3); HRMS (+ESI) *m*/*z* calcd for $C_{17}H_{21}O_5^+$ $[M+H]^+$: 305.1384, Found: 305.1388.



1-Methyl-3-(3-(5-methylfuran-2-yl)oxetan-3-yl)-1*H*-indole (331)

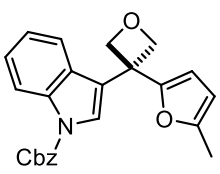
2-Methylfuran (340 µL, 3.75 mmol) followed by toluene (1.50 mL) was added to a flask containing lithium bis(trifluoromethane)sulfonimide (23.7 mg, 0.083 mmol), tetrabutylammonium hexafluorophosphate (16.0 mg, 0.041 mmol) and oxetanol **19** (152 mg, 0.75 mmol). The reaction mixture was stirred at 40 °C for 2 h and then sat. aq. $NaHCO_3$ (30 mL) was added followed by Et_2O (30 mL) and the layers were separated. The aqueous portion was extracted with Et_2O (2 × 30 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography (20% Et_2O/pentane) afforded oxetane **331** (176 mg, 88%) as a white solid. R_f = 0.23 (20% Et_2O/pentane); mp = 94–96 °C; IR (film)/cm^{-1} 2944, 2877, 1472, 1379, 1215, 1013, 991, 950, 805, 741; ^1H NMR (400 MHz, $CDCl_3$) δ 7.45 (dt, *J* = 8.0, 1.0 Hz, 1 H, $Ar_{(indole)}$-CH), 7.35 (dt, *J* = 8.2, 1.0 Hz, 1 H, $Ar_{(indole)}$-CH), 7.30–7.23 (m, 1 H, $Ar_{(indole)}$-CH), 7.09 (ddd, *J* = 8.0, 7.0, 1.1 Hz, 1 H, $Ar_{(indole)}$-CH), 6.93 (s, 1 H, N-Ar-CH-C_q), 5.90 (dq, *J* = 3.0, 1.0 Hz, 1 H, $Ar_{(furan)}$-CH), 5.85 (d, *J* = 3.0 Hz, 1 H, $Ar_{(furan)}$-CH), 5.33 (d, *J* = 5.5 Hz, 2 H, C*H*HOC*H*H), 5.11 (d, *J* = 5.5 Hz, 2 H, CH*H*OCH*H*), 3.81 (s, 3 H, NCH_3), 2.34 (d, *J* = 1.0 Hz, 3 H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.1 ($Ar_{(furan)}$-C_q-C_q), 151.5 ($Ar_{(furan)}$-C_q-CH_3), 137.5 ($Ar_{(indole)}$-C_q-C_q), 126.4 (N-Ar-*C*H-C_q), 126.4 ($Ar_{(indole)}$-C_q-C_q), 121.8 ($Ar_{(indole)}$-CH), 119.9 ($Ar_{(indole)}$-CH), 119.1 ($Ar_{(indole)}$-CH), 116.4 (N-Ar-CH-C_q), 109.5 ($Ar_{(indole)}$-CH), 107.2 ($Ar_{(furan)}$-CH), 106.1 ($Ar_{(furan)}$-CH), 82.0 (CH_2OCH_2), 42.5 (C_q), 32.8 (NCH_3), 13.7 ($Ar_{(furan)}$-CH_3); HRMS (+ESI) *m*/*z* calcd for $C_{17}H_{18}NO_2$ [M+H]: 268.1338, Found: 268.1341.



3-(5-Methylfuran-2-yl)oxetan-3-ol (311)

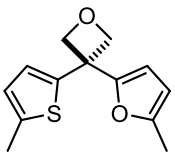
*n*BuLi (1.47 M in hexane, 7.50 mL, 11.0 mmol) was added dropwise over 5 min to a solution of 2-methylfuran (1.1 mL, 12.0 mmol) in THF (20 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h. Oxetan-3-one (640 µL, 10.0 mmol) was added dropwise to the reaction mixture at –78 °C. Following a further 1 h at –78 °C the reaction mixture was warmed to 25 °C, stirred for 23 h then quenched with water (80 mL). Et_2O (80 mL) was added and the layers were separated. The aqueous portion was extracted with Et_2O (2 × 80 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography (30% Et_2O/pentane) afforded oxetanol **311** (1.21 g, 78%) as a yellow solid. R_f = 0.21 (40% Et_2O/pentane); mp = 47–48 °C; 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 6.28 (d,

J = 3.1 Hz, 1 H, Ar-CH), 5.98 (dq, *J* = 3.1, 1.0 Hz, 1 H, Ar-CH), 4.92 (dd, *J* = 6.6, 0.9 Hz, 2 H, C*H*HOC*H*H), 4.83 (dd, *J* = 6.6, 0.9 Hz, 2 H, CH*H*OCH*H*), 2.67 (br, s, 1 H, OH), 2.32 (d, *J* = 1.0 Hz, 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 (Ar-CH_3). The observed characterisation data (^1H and ^{13}C NMR) were consistent with that previously reported.[50]



Benzyl 3-(3-(5-methylfuran-2-yl)oxetan-3-yl)-1*H*-indole-1-carboxylate (332)

Toluene (4.1 mL) was added to a flask containing lithium bis(trifluoromethane)sulfonimide (65.1 mg, 0.227 mmol), tetrabutylammonium hexafluorophosphate (43.9 mg, 0.113 mmol), benzyl 1*H*-indole-1-carboxylate[254] (2.58 g, 10.3 mmol) and oxetanol **311** (309 mg, 2.00 mmol). The reaction mixture was stirred at 40 °C for 2 h and then sat. aq. $NaHCO_3$ (30 mL) was added followed by Et_2O (30 mL) and the layers were separated. The aqueous portion was extracted with Et_2O (2 × 30 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography (4% to 20% Et_2O/pentane) afforded oxetane **332** (232 mg, 30%) as a white solid. R_f = 0.29 (20% Et_2O/hexane); mp = 117–120 °C; IR (film)/cm^{-1} 2952, 2877, 1733 (C=O), 1453, 1394, 1356, 1304, 1278, 1230, 1110, 1051, 987, 954, 786, 697; ^1H NMR (400 MHz, $CDCl_3$) δ 8.23 (s, 1 H, N-Ar-CH), 7.59 (s, 1 H, $Ar_{(indole)}$-CH), 7.55–7.48 (m, 2 H, 2 × Ar-CH), 7.48–7.37 (m, 3 H, 3 × Ar-CH), 7.34 (ddd, *J* = 8.4, 7.1, 1.3 Hz, 1 H, $Ar_{(indole)}$-CH), 7.27 (dt, *J* = 7.9, 1.1 Hz, 1 H, $Ar_{(indole)}$-CH), 7.19 (ddd, *J* = 8.0, 7.1, 1.0 Hz, 1 H, $Ar_{(indole)}$-CH), 5.88 (dq, *J* = 3.2, 1.1 Hz, 1 H, $Ar_{(furan)}$-CH), 5.83 (d, *J* = 3.2 Hz, 1 H, $Ar_{(furan)}$-CH), 5.48 (s, 2 H, OCH_2Ph), 5.31 (d, *J* = 5.6 Hz, 2 H, C*H*HOC*H*H), 5.14 (d, *J* = 5.6 Hz, 2 H, CH*H*OCH*H*), 2.31 (d, *J* = 1.1 Hz, 3 H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.4 ($Ar_{(furan)}$-C_q-C_q), 151.9 ($Ar_{(furan)}$-C_q-CH_3), 150.9 (C=O), 135.9 ($Ar_{(indole)}$-C_q-C_q), 135.0 (Ar-C_q-CH_2), 128.8 (3 × Ar-CH), 128.6 (2 × Ar-CH, $Ar_{(indole)}$-C_q-C_q), 124.9 ($Ar_{(indole)}$-CH), 123.0 ($Ar_{(indole)}$-CH), 122.9 ($Ar_{(indole)}$-CH), 122.7 (N-Ar-CH-C_q), 120.1 ($Ar_{(indole)}$-CH), 115.5 (N-Ar-*C*H-C_q), 107.6 ($Ar_{(furan)}$-CH), 106.2 ($Ar_{(furan)}$-CH), 81.1 (CH_2OCH_2), 68.8 (OCH_2Ph), 42.3 (C_q), 13.7 ($Ar_{(furan)}$-CH_3); HRMS (+ESI) *m*/*z* calcd for $C_{24}H_{22}NO_4$ [M+H]: 388.1549, Found: 388.1565.

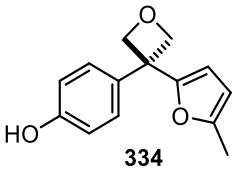


2-Methyl-5-(3-(5-methylthiophen-2-yl)oxetan-3-yl)furan (333)

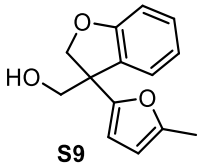
2-Methylthiophene (292 µL, 3.02 mmol) followed by toluene (2.0 mL) was added to a flask containing calcium(II) bis(trifluoromethanesulfonimide) (30.0 mg, 0.05 mmol), tetrabutylammonium hexafluorophosphate (19.4 mg, 0.05 mmol) and oxetanol **311** (150 mg, 0.97 mmol). The reaction mixture was stirred at 40 °C for 2 h then sat. aq. $NaHCO_3$ (15 mL) was added followed by Et_2O (15 mL). The layers were

separated and the aqueous portion was extracted with Et_2O (2 × 15 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash chromatography (4% Et_2O/hexane) afforded oxetane **333** (111 mg, 49%) as a colourless oil. R_f = 0.19 (4% Et_2O/hexane); IR (film)/cm^{-1} 2952, 2877, 1561, 1446, 1218, 1162, 1021, 987, 954, 786; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.73 (d, *J* = 3.4 Hz, 1 H, $Ar_{(thiophene)}$-CH), 6.64 (dq, *J* = 3.4, 1.1 Hz, 1 H, $Ar_{(thiophene)}$-CH), 6.02 (d, *J* = 3.1 Hz, 1 H, $Ar_{(furan)}$-CH), 5.94 (dq, *J* = 3.1, 1.1 Hz, 1 H, $Ar_{(furan)}$-CH), 5.18 (d, *J* = 5.7 Hz, 2 H, C*H*HOC*H*H), 5.03 (d, *J* = 5.7 Hz, 2 H, CH*H*OCH*H*), 2.47 (d, *J* = 1.1 Hz, 3 H, $Ar_{(thiophene)}$-CH_3), 2.31 (d, *J* = 1.0 Hz, 3 H, $Ar_{(furan)}$-CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.2 ($Ar_{(furan)}$-C_q-C_q), 152.0 ($Ar_{(furan)}$-C_q-CH_3), 144.2 ($Ar_{(thiophene)}$-C_q-C_q), 139.1 ($Ar_{(thiophene)}$-C_q-CH_3), 124.8 ($Ar_{(thiophene)}$-CH), 124.5 ($Ar_{(thiophene)}$-CH), 107.6 ($Ar_{(furan)}$-CH), 106.1 ($Ar_{(furan)}$-CH), 82.9 (CH_2OCH_2), 45.3 (C_q), 15.3 ($Ar_{(thiophene)}$-CH_3), 13.6 ($Ar_{(furan)}$-CH_3); HRMS (+ESI) *m*/*z* calcd for $C_{13}H_{15}O_2S$ [M+H]: 235.0787, Found: 235.0791.

4-(3-(5-Methylfuran-2-yl)oxetan-3-yl)phenol (334) and **(3-(5-methylfuran-2-yl)-2,3-dihydrobenzofuran-3-yl)methanol (S9)**



334



S9

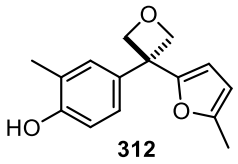
Phenol (4.70 g, 49.9 mmol) followed by toluene (20.0 mL) was added to a flask containing lithium bis(trifluoromethane)sulfonimide (315 mg, 1.10 mmol), tetrabutylammonium hexafluorophosphate (213 mg, 0.55 mmol) and oxetanol **311** (1.54 g, 10.0 mmol). The reaction mixture was stirred at 40 °C for 2 h and then sat. aq. $NaHCO_3$ (50 mL) was added followed by CH_2Cl_2 (50 mL) and the layers were separated. The aqueous portion was extracted with CH_2Cl_2 (2 × 50 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography (CH_2Cl_2) afforded dihydrobenzofuran **S9** (115 mg, 5%, containing 10% of phenol) as a white paste and oxetane **334** (1.14 g, 50%, containing 5% of tetrabutylammonium salt) as a white solid.

Dihydrobenzofuran **S9**: R_f = 0.38 (4% Et_2O/CH_2Cl_2); IR (film)/cm^{-1} 3396 (br. OH), 2952, 2881, 1595, 1558, 1480, 1219, 1021, 969, 910, 731; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (dd, *J* = 7.4, 1.4 Hz, 1 H, Ar-CH), 7.22 (td, *J* = 7.8, 1.4 Hz, 1 H, Ar-CH), 6.92 (td, *J* = 7.4, 1.0 Hz, 1 H, Ar-CH), 6.87 (d, *J* = 8.1 Hz, 1 H, Ar-CH), 6.04 (d, *J* = 3.1 Hz, 1 H, $Ar_{(furan)}$-CH), 5.92 (dq, *J* = 3.1, 1.1 Hz, 1 H, $Ar_{(furan)}$-CH), 4.76 (d, *J* = 9.0 Hz, 1 H, OC*H*HC_q), 4.70 (d, *J* = 9.0 Hz, 1 H, OCH*H*C_q), 4.00 (dd, *J* = 11.1, 6.4 Hz, 1 H, C*H*HOH), 3.93 (dd, *J* = 11.1, 6.7 Hz, 1 H, CH*H*OH), 2.29 (d, *J* = 1.1 Hz, 3 H, CH_3), 1.91–1.81 (m, 1 H, OH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.1 ($Ar_{(DHBF)}$-C_q-OCH_2), 153.0 ($Ar_{(furan)}$-C_q-C_q), 152.1 ($Ar_{(furan)}$-C_q-CH_3), 129.4 (Ar-CH), 128.4 ($Ar_{(DHBF)}$-C_q-C_q),

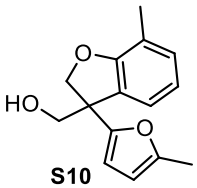
124.7 (Ar-CH), 120.7 (Ar-CH), 110.1 (Ar-CH), 107.5 ($Ar_{(furan)}$-CH), 106.2 ($Ar_{(furan)}$-CH), 77.8 (OCH_2C_q), 67.0 (CH_2OH), 53.0 (C_q), 13.6 (CH_3); HRMS (+ESI) *m*/*z* calcd for $C_{14}H_{15}O_3$ [M+H]: 231.1021, Found: 231.1017.

Oxetane **334**: R_f = 0.19 (4% Et_2O/CH_2Cl_2); mp = 116–118 °C; IR (film)/cm^{-1} 3291 (br. OH), 2956, 2885, 1614, 1517, 1439, 1353, 1271, 1215, 1018, 977, 947, 801; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14–7.05 (m, 2 H, 2 × Ar-CH), 6.88–6.80 (m, 2 H, 2 × Ar-CH), 5.87 (dq, *J* = 3.2, 1.1 Hz, 1 H, $Ar_{(furan)}$-CH), 5.68 (d, *J* = 3.2 Hz, 1 H, $Ar_{(furan)}$-CH), 5.45 (s, 1 H, OH), 5.24 (d, *J* = 5.6 Hz, 2 H, C*H*HOC*H*H), 5.12 (d, *J* = 5.6 Hz, 2 H, CH*H*OCH*H*), 2.31 (d, *J* = 1.1 Hz, 3 H, $Ar_{(furan)}$-CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.6 (Ar-C_q-OH), 154.7 ($Ar_{(furan)}$-C_q-C_q), 151.9 ($Ar_{(furan)}$-C_q-CH_3), 135.0 (Ar-C_q-C_q), 127.8 (2 × Ar-CH), 115.3 (2 × Ar-CH), 107.7 ($Ar_{(furan)}$-CH), 106.0 ($Ar_{(furan)}$-CH), 82.2 (CH_2OCH_2), 47.0 (C_q), 13.7 ($Ar_{(furan)}$-CH_3); HRMS (+ESI) *m*/*z* calcd for $C_{14}H_{15}O_3$ [M+H]: 231.1021, Found: 231.1030.

2-Methyl-4-[3-(5-methylfuran-2-yl)oxetan-3-yl]phenol (312) and **(7-Methyl-3-(5-methylfuran-2-yl)-2,3-dihydrobenzofuran-3-yl)methanol (S10)**



312



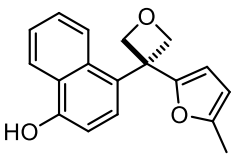
S10

2-Methylphenol (2.60 mL, 25.0 mmol) followed by toluene (10.0 mL) was added to a flask containing lithium bis(trifluoromethane)sulfonimide (158 mg, 0.55 mmol), tetrabutylammonium hexafluorophosphate (107 mg, 0.28 mmol) and oxetanol **311** (751 mg, 4.87 mmol). The reaction mixture was stirred at 40 °C for 2 h and then sat. aq. $NaHCO_3$ (40 mL) was added followed by Et_2O (40 mL) and the layers were separated. The aqueous portion was extracted with Et_2O (2 × 40 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography (CH_2Cl_2) afforded dihydrobenzofuran **S10** (47.5 mg, 4%) as a white paste and oxetane **312** (790 mg, 66%) as a white paste.

Dihydrobenzofuran **S10**: R_f = 0.29 (CH_2Cl_2); IR (film)/cm^{-1} 3421 (br. OH), 2922, 1595, 1476, 1259, 1215, 1189, 1080, 1021, 987, 834, 782, 745; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11 (dd, *J* = 7.5, 1.1 Hz, 1 H, Ar-CH), 7.04 (dt, *J* = 7.5, 1.1 Hz, 1 H, Ar-CH), 6.83 (dd, *J* = 7.5 Hz, 1 H, Ar-CH), 6.03 (d, *J* = 3.1 Hz, 1 H, Ar-$CH_{(furan)}$), 5.91 (dq, *J* = 3.1, 1.1 Hz, 1 H, Ar-$CH_{(furan)}$), 4.76 (d, *J* = 9.0 Hz, 1 H, OC*H*HC_q), 4.70 (d, *J* = 9.0 Hz, 1 H, OCH*H*C_q), 4.02–3.91 (m, 2 H, CH_2OH), 2.28 (d, *J* = 1.1 Hz, 3 H, $Ar_{(furan)}$-CH_3), 2.25 (s, 3 H, CH_3), 1.69 (dd, *J* = 6.9 Hz, 1 H, OH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.6 ($Ar_{(DHBF)}$-C_q-OCH_2), 153.3 ($Ar_{(furan)}$-C_q-C_q), 152.1 ($Ar_{(furan)}$-

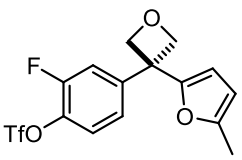
C_q-CH_3), 130.6 (Ar-CH), 127.5 ($Ar_{(DHBF)}$-C_q-CH_3), 122.0 (Ar-CH), 120.6 (Ar-CH), 120.3 ($Ar_{(DHBF)}$-C_q-C_q), 107.5 ($Ar_{(furan)}$-CH), 106.2 ($Ar_{(furan)}$-CH), 77.6 (O*C*H_2C_q), 67.1 (CH_2OH), 53.4 (C_q), 15.1 ($Ar_{(DHBF)}$-CH_3), 13.6 ($Ar_{(furan)}$-CH_3); HRMS (+ESI) *m*/*z* calcd for $C_{15}H_{17}O_3$ [M+H]: 245.1178, Found: 245.1184.

Oxetane **312**: R_f = 0.11 (CH_2Cl_2); 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; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.00 (d, *J* = 2.0 Hz, 1 H, $Ar_{(phenol)}$-CH), 6.93 (dd, *J* = 8.3, 2.0, Hz, 1 H, $Ar_{(phenol)}$-CH), 6.77 (d, *J* = 8.2 Hz, 1 H, $Ar_{(phenol)}$-CH), 5.87 (dq, *J* = 3.1, 1.0 Hz, 1 H, $Ar_{(furan)}$-CH), 5.69 (d, *J* = 3.1 Hz, 1 H, $Ar_{(furan)}$-CH), 5.21 (d, *J* = 5.5 Hz, 2 H, C*H*HOC*H*H), 5.11 (d, *J* = 5.5 Hz, 2 H, CH*H*OCH*H*), 4.74 (s, 1 H, OH), 2.31 (d, *J* = 1.0 Hz, 3 H, $Ar_{(furan)}$-CH_3), 2.27 (s, 3 H, $Ar_{(phenol)}$-CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.7 (Ar-C_q-OH), 153.0 ($Ar_{(furan)}$-C_q-C_q), 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). The observed spectroscopic data (^{1}H and ^{13}C NMR) for this compound was consistent with that previously reported.[50]



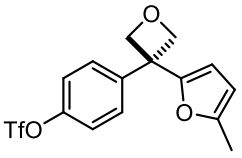
4-(3-(5-Methylfuran-2-yl)oxetan-3-yl)naphthalen-1-ol (335)

Toluene (1.50 mL) was added to a flask containing lithium bis(trifluoromethane)sulfonimide (23.8 mg, 0.083 mmol), tetrabutylammonium hexafluorophosphate (15.5 mg, 0.04 mmol), 1-naphthol (541 mg, 3.75 mmol) and oxetanol **311** (116 mg, 0.75 mmol). The reaction mixture was stirred at 40 °C for 2 h and then sat. aq. $NaHCO_3$ (20 mL) was added followed by CH_2Cl_2 (20 mL) and the layers were separated. The aqueous portion was extracted with CH_2Cl_2 (2 × 20 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography (2% Et_2O/CH_2Cl_2) afforded oxetane **335** (180 mg, 86%, containing 5% of tetrabutylammonium hexafluorophosphate) as a white solid. R_f = 0.11 (30% Et_2O/pentane); mp = 169–172 °C; IR (film)/cm^{-1} 3258 (br. OH), 2956, 2885, 1588, 1517, 1372, 1226, 1185, 1051, 764, 731; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30–8.28 (m, 1 H, Ar-CH), 7.48–7.37 (m, 2 H, 2 × Ar-CH), 7.18–7.08 (m, 2 H, 2 × Ar-CH), 6.83 (d, *J* = 7.8 Hz, 1 H, Ar-CH), 6.40 (s, 1 H, OH), 5.79 (dq, *J* = 3.1, 1.1 Hz, 1 H, $Ar_{(furan)}$-CH), 5.52–5.38 (m, 5 H, $Ar_{(furan)}$-CH, CH_2OCH_2), 2.34 (s, 3 H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.5 (Ar-C_q-OH), 151.6 ($Ar_{(furan)}$-C_q-C_q), 151.5 ($Ar_{(furan)}$-C_q-CH_3), 131.7 (Ar-C_q-C_q), 130.4 (Ar-C_q-C_q), 126.4 (Ar-CH), 125.2 (Ar-C_q-C_q), 125.0 (Ar-CH), 124.9 (Ar-CH), 124.7 (Ar-CH), 122.8 (Ar-CH), 107.9 (Ar-CH), 107.5 ($Ar_{(furan)}$-CH), 106.3 ($Ar_{(furan)}$-CH), 82.2 (CH_2OCH_2), 47.2 (C_q), 13.8 ($Ar_{(furan)}$-CH_3); HRMS (+ESI) *m*/*z* calcd for $C_{18}H_{17}O_3$ [M+H]: 281.1178, Found: 281.1173.



2-Fluoro-4-(3-(5-methylfuran-2-yl)oxetan-3-yl)phenyl trifluoromethanesulfonate (336)

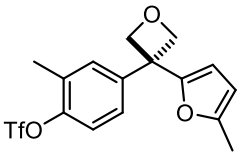
Triethylamine (710 µL, 5.09 mmol) followed by triflic anhydride (430 µL, 2.56 mmol) was added to a solution of oxetane **327** (421 mg, 1.70 mmol) in CH_2Cl_2 (6.0 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 2 h. Water (20 mL) was added followed by Et_2O (20 mL) and the layers were separated. The aqueous portion was extracted with Et_2O (2 × 20 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography (5% Et_2O/hexane) afforded triflate **336** (307 mg, 48%, 12% over two steps) as a yellow oil. R_f = 0.16 (5% Et_2O/hexane); IR (film)/cm^{-1} 2959, 2885, 1602, 1502, 1423, 1248, 1211, 1170, 1136, 991, 909, 864, 820, 786; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (dd, *J* = 8.5, 7.5 Hz, 1 H, Ar-CH), 7.22–7.11 (m, 2 H, 2 × Ar-CH), 5.94 (dq, *J* = 3.2, 1.1 Hz, 1 H, $Ar_{(furan)}$-CH), 5.86 (d, *J* = 3.1 Hz, 1 H, $Ar_{(furan)}$-CH), 5.23 (d, *J* = 5.9 Hz, 2 H, C*H*HOC*H*H), 5.04 (d, *J* = 5.9 Hz, 2 H, CH*H*OCH*H*), 2.31 (d, *J* = 1.1 Hz, 3 H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.3 ($Ar_{(furan)}$-C_q-C_q), 152.2 (d, $^1J_{C\text{-}F}$ = 254.0 Hz, Ar-C_q-F), 152.2 ($Ar_{(furan)}$-C_q-CH_3), 145.7 (d, $^2J_{C\text{-}F}$ = 5.8 Hz, Ar-C_q-OTf), 135.6 (Ar-C_q-C_q), 123.6 (Ar-CH), 123.1 (d, $^3J_{C\text{-}F}$ = 3.7 Hz, Ar-CH), 116.1 (d, $^2J_{C\text{-}F}$ = 19.1 Hz, Ar-CH), 117.1 (q, $^1J_{C\text{-}F}$ = 323.8 Hz, CF_3), 108.1 ($Ar_{(furan)}$-CH), 106.3 ($Ar_{(furan)}$-CH), 81.5 (CH_2OCH_2), 47.4 (C_q), 13.6 (CH_3); ^{19}F NMR (377 MHz, $CDCl_3$) δ –73.1 (d, *J* = 5.3 Hz, CF_3), –126.5 (ddd, *J* = 11.0, 8.5, 5.0 Hz, 1 F, Ar-C_q-F); HRMS (+APCI) *m*/*z* calcd for $C_{15}H_{13}O_5SF_4^+$ $[M+H]^+$: 381.0414, Found: 381.0417.



4-(3-(5-Methylfuran-2-yl)oxetan-3-yl)phenyl trifluoromethanesulfonate (337)

Triethylamine (2.10 mL, 14.9 mmol) followed by triflic anhydride (1.25 mL, 7.40 mmol) was added to a solution of oxetane **334** (1.14 g, 4.95 mmol) in CH_2Cl_2 (9.9 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 2 h. Water (30 mL) was added followed by Et_2O (30 mL) and the layers were separated. The aqueous portion was extracted with Et_2O (2 × 30 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography (5 to 10% Et_2O/pentane) afforded triflate **337** (1.35 g, 75%) as a colourless oil. R_f = 0.32 (10% Et_2O/pentane); IR (film)/cm^{-1} 2959, 2885, 1502, 1423, 1248, 1203, 1136, 1017, 883, 842, 782; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.33 (m, 2 H, 2 × Ar-CH), 7.33–7.28 (m, 2 H, 2 × Ar-CH), 5.91 (dq, *J* = 3.2, 1.1 Hz, 1 H, $Ar_{(furan)}$-CH), 5.77 (d, *J* = 3.2 Hz, 1 H, $Ar_{(furan)}$-CH), 5.25 (d, *J* = 5.7 Hz, 2 H, C*H*HOC*H*H), 5.09 (d, *J* = 5.7 Hz, 2 H, CH*H*OCH*H*), 2.31 (d, *J* = 1.1 Hz, 3 H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.2 ($Ar_{(furan)}$-C_q-C_q), 152.4 ($Ar_{(furan)}$-C_q-CH_3), 148.4 (Ar-C_q-OTf), 143.7 (Ar-C_q-C_q), 128.5 (2 × Ar-CH), 121.4 (2 × Ar-CH), 118.7 (q, $^1J_{C\text{-}F}$ = 320.9 Hz, CF_3), 107.9 ($Ar_{(furan)}$-CH), 106.2 ($Ar_{(furan)}$-CH), 81.7 (CH_2OCH_2), 47.3 (C_q), 13.6 (CH_3);

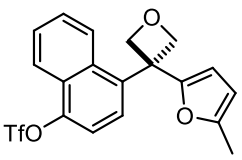
$^{19}F\{^{1}H\}$ NMR (377 MHz, $CDCl_3$) δ –72.8; HRMS (–ESI) *m*/*z* calcd for $C_{15}H_{12}O_5SF_3$ [M–H]: 361.0358, Found: 361.0360.



2-Methyl-4-(3-(5-methylfuran-2-yl)oxetan-3-yl)phenyl trifluoromethanesulfonate (338)

Triethylamine (1.50 mL, 10.8 mmol) followed by triflic anhydride (880 µL, 5.25 mmol) was added to a solution of oxetane **312** (790 mg, 3.29 mmol) in CH_2Cl_2 (12 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 2 h. Water (20 mL) was added followed by Et_2O (20 mL) and the layers were separated. The aqueous portion was extracted with Et_2O (2 × 20 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography (5 to 10% Et_2O/pentane) afforded triflate **338** (926 mg, 75%) as a yellow oil. R_f = 0.19 (5% Et_2O/pentane); IR (film)/cm^{-1} 2959, 2885, 1494, 1420, 1248, 1207, 1140, 1092, 991, 905, 861, 820, 786; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, *J* = 8.6 Hz, 1 H, Ar-CH), 7.20 (dd, *J* = 2.4, 0.8 Hz, 1 H, Ar-CH), 7.13 (ddd, *J* = 8.6, 2.4, 0.8 Hz, 1 H, Ar-CH), 5.91 (dq, *J* = 3.1, 1.0 Hz, 1 H, $Ar_{(furan)}$-CH), 5.76 (d, *J* = 3.1 Hz, 1 H, $Ar_{(furan)}$-CH), 5.23 (d, *J* = 5.8 Hz, 2 H, C*H*HOC*H*H), 5.09 (d, *J* = 5.8 Hz, 2 H, CH*H*OCH*H*), 2.40 (s, 3 H, Ar-CH_3), 2.31 (d, *J* = 1.0 Hz, 3 H, $Ar_{(furan)}$-CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.4 ($Ar_{(furan)}$-C_q-C_q), 152.3 ($Ar_{(furan)}$-C_q-CH_3), 147.2 (Ar-C_q-OTf), 143.3 (Ar-C_q-C_q), 131.0 (Ar-C_q-CH_3), 130.3 (Ar-CH), 125.9 (Ar-CH), 121.3 (Ar-CH), 107.8 ($Ar_{(furan)}$-CH), 106.2 ($Ar_{(furan)}$-CH), 81.6 (CH_2OCH_2), 47.3 (C_q), 16.5 (Ar-CH_3), 13.6 ($Ar_{(furan)}$-CH_3);* $^{19}F\{^{1}H\}$ NMR (377 MHz, $CDCl_3$) δ –73.8; HRMS (+APCI) *m*/*z* calcd for $C_{16}H_{16}O_5SF_3^+$ $[M+H]^+$: 377.0665, Found: 377.0665.

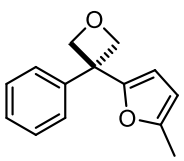
*CF_3 signal was not observed in the ^{13}C NMR spectrum.



4-(3-(5-Methylfuran-2-yl)oxetan-3-yl)naphthalen-1-yl trifluoromethanesulfonate (339)

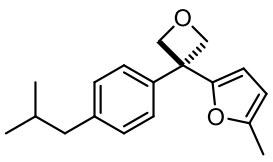
Triethylamine (271 µL, 1.92 mmol) followed by triflic anhydride (162 µL, 0.96 mmol) was added to a solution of oxetane **335** (180 mg, 0.64 mmol) in CH_2Cl_2 (3.1 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 2 h. Water (20 mL) was added followed by Et_2O (20 mL) and the layers were separated. The aqueous portion was extracted with Et_2O (2 × 20 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography (5 to 10% Et_2O/pentane) afforded triflate **339** (232 mg, 87%) as a colourless oil. R_f = 0.25 (10% Et_2O/pentane); IR (film)/cm^{-1} 2955, 2881, 1423, 1215, 1140, 1013, 857, 764; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (dt, *J* = 8.5, 0.9 Hz, 1 H, Ar-CH), 7.64 (ddd, *J* = 8.4, 6.9, 1.1 Hz, 1 H, Ar-CH), 7.54–7.49 (m, 1 H, Ar-CH), 7.51 (d, *J* = 8.0 Hz, 1 H, Ar-CH), 7.36 (d, *J* = 8.1 Hz, 1 H, Ar-CH), 7.27 (dt, *J* = 8.5, 0.9 Hz, 1 H, Ar-CH), 5.82 (dq, *J* = 3.1, 1.0 Hz, 1 H,

$Ar_{(furan)}$-CH), 5.54 (d, *J* = 3.1 Hz, 1 H, $Ar_{(furan)}$-CH), 5.42 (d, *J* = 5.7 Hz, 2 H, C*H*HOC*H*H), 5.39 (d, *J* = 5.7 Hz, 2 H, CH*H*OCH*H*), 2.33 (d, *J* = 1.0 Hz, 3 H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.5 ($Ar_{(furan)}$-C_q-C_q), 152.1 ($Ar_{(furan)}$-C_q-CH_3), 145.1 (Ar-C_q-OTf), 139.6 (Ar-C_q-C_q), 132.0 (Ar-C_q), 127.6 (Ar-CH), 127.4 (Ar-CH), 127.0 (Ar-C_q), 125.2 (Ar-CH), 124.0 (Ar-CH), 121.8 (Ar-CH), 118.7 (q, $^1J_{C\text{-}F}$ = 320.5 Hz, CF_3), 117.0 (Ar-CH), 108.0 ($Ar_{(furan)}$-CH), 106.4 ($Ar_{(furan)}$-CH), 81.7 (CH_2OCH_2), 47.7 (C_q), 13.7 (CH_3); $^{19}F\{^1H\}$ NMR (377 MHz, $CDCl_3$) δ –73.3; HRMS (+APCI) *m*/*z* calcd for $C_{19}H_{14}O_5SF_3^+$ $[M–H]^+$: 411.0509, Found: 411.0502.



2-Methyl-5-(3-phenyloxetan-3-yl)furan (340)

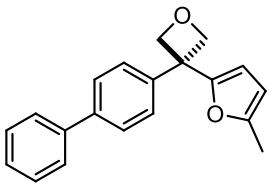
Based on conditions developed by Ortar,[126] triethylamine (630 μL, 4.52 mmol) followed by formic acid (114 μL, 3.01 mmol) were added to a solution of triflate **337** (546 mg, 1.51 mmol), $Pd(OAc)_2$ (16.9 mg, 0.075 mmol), 1,1'-bis(diphenylphosphino)ferrocene (41.7 mg, 0.075 mmol) in DMF (15.1 mL). The reaction mixture was stirred at 60 °C for 2 h then brine (20 mL) was added followed by Et_2O (20 mL). The layers were separated and the aqueous portion was extracted with Et_2O (2 × 20 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude was dissolved in 10% Et_2O/pentane and filtrated through a plug of silica to afford oxetane **340** (316 mg, 98%) as a colourless oil. R_f = 0.32 (10% Et_2O/pentane); IR (film)/cm^{-1} 2955, 2881, 1558, 1494, 1446, 1218, 1021, 991, 954, 782, 756, 700; ^1H NMR (400 MHz, $CDCl_3$) δ 7.43–7.36 (m, 2 H, 2 × Ar-CH), 7.34–7.28 (m, 1 H, Ar-CH), 7.26–7.22 (m, 2 H, 2 × Ar-CH), 5.88 (dq, *J* = 3.1, 1.0 Hz, 1 H, $Ar_{(furan)}$-CH), 5.68 (d, *J* = 3.1 Hz, 1 H, $Ar_{(furan)}$-CH), 5.25 (d, *J* = 5.6 Hz, 2 H, C*H*HOC*H*H), 5.17 (d, *J* = 5.6 Hz, 2 H, CH*H*OCH*H*), 2.31 (d, *J* = 1.0 Hz, 3 H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.5 ($Ar_{(furan)}$-C_q-C_q), 151.9 ($Ar_{(furan)}$-C_q-CH_3), 143.0 (Ar-C_q-C_q), 128.5 (2 × Ar-CH), 127.0 (Ar-CH), 126.5 (2 × Ar-CH), 107.6 ($Ar_{(furan)}$-CH), 106.1 ($Ar_{(furan)}$-CH), 81.9 (CH_2OCH_2), 47.6 (C_q), 13.7 (CH_3); HRMS (+APCI) *m*/*z* calcd for $C_{14}H_{15}O_2^+$ $[M+H]^+$: 215.1067, Found: 215.1060.



2-(3-(4-Isobutylphenyl)oxetan-3-yl)-5-methylfuran (341)

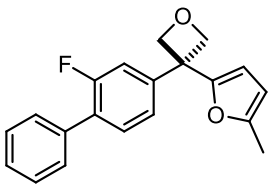
Triflate **337** (407 mg, 1.12 mmol), 2-methylpropylboronic acid (149 mg, 1.46 mmol), $Pd(dppf)Cl_2$ (41.0 mg, 0.056 mmol), and K_2CO_3 (310 mg, 2.24 mmol) were added to a reaction vial. The reaction vial was evacuated and then refilled with nitrogen three times. THF (7.0 mL) was then added via syringe. The reaction mixture was stirred at 70 °C for 20 h then cooled to rt. Et_2O (20 mL) was added and the crude mixture was filtered through celite® and then concentrated under reduced pressure. Purification by flash column chromatography (2 to 4% Et_2O/pentane) afforded oxetane **341** (129 mg, 43%) as a yellow oil. R_f = 0.45 (4% Et_2O/pentane); IR (film)/cm^{-1} 2952,

2877, 1513, 1464, 1218, 1021, 954, 842, 782; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20–7.10 (m, 4 H, 4 × Ar-CH), 5.87 (dq, *J* = 3.1, 1.0 Hz, 1 H, $Ar_{(furan)}$-CH), 5.67 (d, *J* = 3.1 Hz, 1 H, $Ar_{(furan)}$-CH), 5.24 (d, *J* = 5.5 Hz, 2 H, C*H*HOC*H*H), 5.15 (d, *J* = 5.5 Hz, 2 H, CH*H*OCH*H*), 2.49 (d, *J* = 7.2 Hz, 2 H, Ar-C_q-CH_2), 2.32 (d, *J* = 1.0 Hz, 3 H, $Ar_{(furan)}$-CH_3), 1.89 (th, *J* = 7.2, 6.8 Hz, 1 H, C*H*$(CH_3)_2$), 0.93 (d, *J* = 6.8 Hz, 6 H, CH(CH_3)$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.7 ($Ar_{(furan)}$-*C*$_q$-C_q), 151.8 ($Ar_{(furan)}$-*C*$_q$-CH_3), 140.4 (Ar-C_q), 140.2 (Ar-C_q), 129.2 (2 × Ar-CH), 126.2 (2 × Ar-CH), 107.6 ($Ar_{(furan)}$-CH), 106.0 ($Ar_{(furan)}$-CH), 82.1 (*C*H_2O*C*H_2), 47.3 (C_q), 45.0 (Ar-CH_2), 30.2 (*C*H$(CH_3)_2$), 22.4 (CH(*C*H_3)$_2$), 13.7 ($Ar_{(furan)}$-CH_3); HRMS (+ESI) *m*/*z* calcd for $C_{18}H_{23}O_2$ [M+H]: 271.1698, Found: 271.1688.



2-(3-([1,1'-Biphenyl]-4-yl)oxetan-3-yl)-5-methylfuran (342)

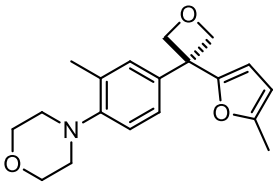
Triflate **337** (303 mg, 0.84 mmol), phenylboronic acid pinacol ester (223 mg, 1.09 mmol), $Pd(PPh_3)_4$ (48.5 mg, 0.042 mmol), and K_2CO_3 (232 mg, 1.68 mmol) were added to a reaction vial. The reaction vial was evacuated and then refilled with nitrogen three times. DME/water (8:1, 8.4 mL) was added *via* syringe. The reaction mixture was stirred at 90 °C for 24 h then cooled to rt. Et_2O (20 mL) was added and the crude mixture was filtered through celite® and then concentrated under reduced pressure. Purification by flash column chromatography (4 to 10% Et_2O/CH_2Cl_2) afforded oxetane **342** (158 mg, 65%) as a white solid. R_f = 0.19 (4% Et_2O/pentane); mp = 138–140 °C; IR (film)/cm^{-1} 2952, 2877, 1021, 991, 957, 842, 760, 738, 700; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68–7.59 (m, 4 H, 4 × Ar-CH), 7.52–7.44 (m, 2 H, 2 × Ar-CH), 7.42–7.31 (m, 3 H, 3 × Ar-CH), 5.92 (dq, *J* = 3.2, 1.1 Hz, 1 H, $Ar_{(furan)}$-CH), 5.79 (d, *J* = 3.2 Hz, 1 H, $Ar_{(furan)}$-CH), 5.29 (d, *J* = 5.6 Hz, 2 H, C*H*HOC*H*H), 5.21 (d, *J* = 5.6 Hz, 2 H, CH*H*OCH*H*), 2.35 (d, *J* = 1.1 Hz, 3 H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.3 ($Ar_{(furan)}$-*C*$_q$-C_q), 152.0 ($Ar_{(furan)}$-*C*$_q$-CH_3), 142.0 (Ar-*C*$_q$-C_q), 140.6 (Ar-*C*$_q$-C_q), 139.9 (Ar-*C*$_q$-C_q), 128.8 (2 × Ar-CH), 127.3 (Ar-CH), 127.2 (2 × Ar-CH), 127.0 (2 × Ar-CH), 126.9 (2 × Ar-CH), 107.7 ($Ar_{(furan)}$-CH), 106.1 ($Ar_{(furan)}$-CH), 81.9 (*C*H_2O*C*H_2), 47.4 (C_q), 13.6 (CH_3); HRMS (+APCI) *m*/*z* calcd for $C_{20}H_{19}O_2^+$ [M+H]$^+$: 291.1380, Found: 291.1377.



2-(3-(2-Fluoro-[1,1'-biphenyl]-4-yl)oxetan-3-yl)-5-methylfuran (343)

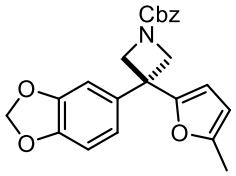
Triflate **336** (275 mg, 0.72 mmol), phenylboronic acid (106 mg, 0.87 mmol), $Pd(dppf)Cl_2$ (26.5 mg, 0.036 mmol), and Cs_2CO_3 (471 mg, 1.45 mmol) were added to a reaction vial. The reaction vial was evacuated and then refilled with nitrogen three times. 1,4-Dioxane (7.2 mL) was then added *via* syringe. The reaction mixture was stirred at 90 °C for 23 h then cooled to rt. Et_2O (20 mL) was added and the crude mixture was filtered through celite® and then concentrated under reduced pressure. Purification by flash column chromatography (10% Et_2O/hexane) afforded

oxetane **343** (118 mg, 53%) as a white solid. R_f = 0.45 (10% Et_2O/hexane); mp = 88–89 °C; IR (film)/cm^{-1} 2959, 2922, 2881, 1729, 1558, 1483, 1408, 1259, 1215, 1133, 1021, 991, 954, 820, 767, 723, 700; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61–7.55 (m, 2 H, 2 × Ar-CH), 7.51–7.43 (m, 3 H, 3 × Ar-CH), 7.43–7.36 (m, 1 H, Ar-CH), 7.14 (dd, *J* = 8.0, 1.9 Hz, 1 H, Ar-CH), 7.06 (dd, *J* = 11.7, 1.9 Hz, 1 H, Ar-CH), 5.94 (dq, *J* = 3.1, 1.1 Hz, 1 H, $Ar_{(furan)}$-CH), 5.86 (d, *J* = 3.1 Hz, 1 H, $Ar_{(furan)}$-CH), 5.26 (d, *J* = 5.7 Hz, 2 H, C*H*HOC*H*H), 5.15 (d, *J* = 5.7 Hz, 2 H, CH*H*OCH*H*), 2.33 (d, *J* = 1.1 Hz, 3 H, $Ar_{(furan)}$-CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.6 (d, $^1J_{C\text{-}F}$ = 248.9 Hz, Ar-C_q-F), 154.5 ($Ar_{(furan)}$-C_q-C_q), 152.2 ($Ar_{(furan)}$-C_q-CH_3), 144.5 (d, $^2J_{C\text{-}F}$ = 7.1 Hz, Ar-C_q-C_q), 135.3 (Ar-C_q-C_q), 130.8 (d, $^4J_{C\text{-}F}$ = 4.2 Hz, Ar-CH), 128.9 (d, $^4J_{C\text{-}F}$ = 3.1 Hz, 2 × Ar-CH), 128.5 (2 × Ar-CH), 127.7 (d, $^3J_{C\text{-}F}$ = 9.7 Hz, Ar-C_q-C_q), 127.7 (Ar-CH), 122.4 (d, $^3J_{C\text{-}F}$ = 3.3 Hz, Ar-CH), 114.5 (d, $^2J_{C\text{-}F}$ = 24.0 Hz, Ar-CH), 107.8 ($Ar_{(furan)}$-CH), 106.2 ($Ar_{(furan)}$-CH), 81.7 (CH_2OCH_2), 47.4 (C_q), 13.6 (CH_3); ^{19}F NMR (377 MHz, $CDCl_3$) δ –117.4 (dd, *J* = 11.7, 8.0 Hz); HRMS (+APCI) *m*/*z* calcd for $C_{20}H_{18}O_2F^+$ $[M+H]^+$: 309.1285, Found: 309.1279.



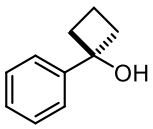
4-(2-Methyl-4-(3-(5-methylfuran-2-yl)oxetan-3-yl)phenyl)morpholine (344)

Using conditions developed by Buchwald,[99] triflate **338** (75.3 mg, 0.20 mmol), $Pd(OAc)_2$ (2.2 mg, 0.010 mmol), BINAP (9.3 mg, 0.015 mmol) and Cs_2CO_3 (91.2 mg, 0.28 mmol) were added to a reaction vial. The reaction vial was evacuated and then refilled with nitrogen three times. Morpholine (35 µL, 0.40 mmol) followed by toluene (0.6 mL) were added via syringe into the vial. The reaction mixture was stirred at 100 °C for 24 h then cooled to rt. Et_2O (15 mL) was added and the reaction mixture was filtered through celite® and then concentrated under reduced pressure. Purification by flash column chromatography (20% Et_2O/hexane) afforded morpholine oxetane **344** (16.0 mg, 26%) as a white solid. R_f = 0.11 (20% Et_2O/hexane); mp = 113–118 °C; IR (film)/cm^{-1} 2952, 2877, 2851, 1505, 1449, 1256, 1222, 1118, 1021, 991, 939, 786; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.10–7.04 (m, 1 H, Ar-CH), 7.04–7.01 (m, 2 H, 2 × Ar-CH), 5.88 (dq, *J* = 3.1, 1.1 Hz, 1 H, $Ar_{(furan)}$-CH), 5.71 (d, *J* = 3.1 Hz, 1 H, $Ar_{(furan)}$-CH), 5.21 (d, *J* = 5.6 Hz, 2 H, C*H*HOC*H*H), 5.13 (d, *J* = 5.6 Hz, 2 H, CH*H*OCH*H*), 3.92–3.79 (m, 4 H, $CH_2CH_2OCH_2CH_2$), 2.98–2.87 (m, 4 H, CH_2NCH_2), 2.33 (s, 3 H, Ar-CH_3), 2.31 (d, *J* = 1.1 Hz, 3 H, $Ar_{(furan)}$-CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.7 ($Ar_{(furan)}$-C_q-C_q), 151.8 ($Ar_{(furan)}$-C_q-CH_3), 150.1 (Ar-C_q-N), 137.8 (Ar-C_q-C_q), 132.6 (Ar-C_q-CH_3), 129.3 (Ar-CH), 124.7 (Ar-CH), 118.8 (Ar-CH), 107.5 ($Ar_{(furan)}$-CH), 106.0 ($Ar_{(furan)}$-CH), 82.0 (CH_2OCH_2), 67.4 ($CH_2CH_2OCH_2CH_2$), 52.2 (CH_2NCH_2), 47.1 (C_q), 18.0 (Ar-CH_3), 13.7 ($Ar_{(furan)}$-CH_3); HRMS (+ESI) *m*/*z* calcd for $C_{19}H_{24}NO_3$ [M+H]: 314.1756, Found: 314.1753.



Benzyl 3-(benzo[d][1,3]dioxol-5-yl)-3-(5-methylfuran-2-yl)azetidine-1-carboxylate (348)

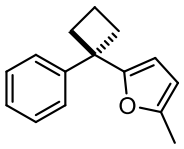
Toluene (1.0 mL) was added to calcium(II) bis(trifluoromethanesulfonimide) (15.0 mg, 0.025 mmol), tetrabutylammonium hexafluorophosphate (9.7 mg, 0.025 mmol), azetidinol **107** (164 mg, 0.5 mmol) and 2-methylfuran (135 µL, 1.50 mmol). The reaction mixture was stirred at 40 °C for 2 h then sat. aq. $NaHCO_3$ (20 mL) was added followed by Et_2O (20 mL). The layers were separated and the aqueous portion was extracted with Et_2O (2 × 20 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash chromatography (20% Et_2O/pentane) afforded azetidine **348** (106 mg, 54%) as a yellow solid. R_f = 0.40 (30% Et_2O/pentane); mp = 87–90 °C; IR (film)/cm^{-1} 2952, 2888, 1707 (C=O), 1490, 1420, 1360, 1244, 1181, 1144, 1103, 1039, 1013, 957, 793, 752, 697; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41–7.29 (m, 5 H, 5 × Ar-CH), 6.80 (s, 1 H, Ar-CH), 6.70 (m, 2 H, 2 × Ar-CH), 5.97 (s, 2 H, OCH_2O), 5.86 (dd, *J* = 2.6, 1.4 Hz, 1 H, $Ar_{(furan)}$-CH), 5.73 (d, *J* = 2.6 Hz, 1 H, $Ar_{(furan)}$-CH), 5.14 (s, 2 H, OCH_2Ph), 4.57 (d, *J* = 8.2 Hz, 2 H, C*H*HNC*H*H), 4.45 (d, *J* = 8.2 Hz, 2 H, CH*H*NCH*H*), 2.28 (s, 3 H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.3 (C=O), 155.4 ($Ar_{(furan)}$-C_q-C_q), 152.1 ($Ar_{(furan)}$-C_q-CH_3), 147.7 (Ar-C_q-OCH_2), 146.5 (Ar-C_q-OCH_2), 136.7 (Ar-C_q-C_q), 136.5 (Ar-C_q-CH_2), 128.4 (2 × Ar-CH), 128.0 (Ar-CH), 127.9 (2 × Ar-CH), 119.8 (Ar-CH), 108.0 (Ar-CH), 107.7 ($Ar_{(furan)}$-CH), 107.4 (Ar-CH), 106.0 ($Ar_{(furan)}$-CH), 101.1 (OCH_2O), 66.7 (OCH_2Ph), 61.1 and 60.4 (br, CH_2NCH_2), 41.9 (C_q), 13.6 ($Ar_{(furan)}$-CH_3); HRMS (+APCI) *m*/*z* calcd for $C_{23}H_{22}NO_5^+$ $[M+H]^+$: 392.1492, Found: 392.1504.



1-Phenylcyclobutan-1-ol (S11)

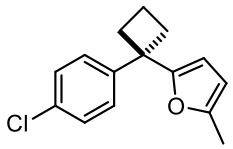
Phenylmagnesium bromide (2.63 M in Et_2O, 3.70 mL, 9.73 mmol) was added dropwise over 10 min to a solution of cyclobutanone (600 µL, 8.03 mmol) in THF (8.0 mL) at 0 °C. The reaction was stirred for 30 min at 0 °C and then 24 h at 25 °C. The reaction mixture was then cooled to 0 °C, and sat. aq. NH_4Cl (60 mL) was added. The layers were separated and the aqueous portion extracted with Et_2O (3 × 60 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography (20% Et_2O/pentane) afforded 1-phenylcyclobutan-1-ol **S11** (734 mg, 62%) as a white solid. R_f = 0.30 (25% EtOAc/hexane); mp = 40 °C [lit. mp = 40–41 °C][255]; IR (film)/ cm^{-1} 3303 (br, OH), 2989, 2940, 2869, 1495, 1446, 1423, 1246, 1185, 1132, 1110, 1074, 1026, 959, 913, 825, 760, 697, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57–7.47 (m, 2 H, 2 × Ar-CH), 7.46–7.35 (m, 2 H, 2 × Ar-CH), 7.35–7.22 (m, 1 H, Ar-CH), 2.67–2.50 (m, 2 H, C*H*HCH$_2$C*H*H), 2.50–2.28 (m, 2 H, CH*H*CH$_2$CH*H*), 2.11–1.98 (m, 1 H, CH$_2$C*H*HCH$_2$), 1.93 (br. s, 1 H, OH), 1.71 (dtt, *J* = 11.3, 8.8, 7.5 Hz, 1 H, CH$_2$CH*H*CH$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.3 (Ar-C_q), 128.4 (2 × Ar-CH), 127.2 (Ar-CH), 124.9 (2 × Ar-

CH), 77.1 (C_q), 36.8 ($CH_2CH_2CH_2$), 13.0 ($CH_2CH_2CH_2$). The spectroscopic data for this compound (^{1}H, ^{13}C NMR) are consistent with the literature.[256]



2-Methyl-5-(1-phenylcyclobutyl)furan (349)

Toluene (3.0 mL) was added to iron chloride (12.2 mg, 0.075 mmol), cyclobutanol **S11** (222 mg, 1.50 mmol) and 2-methylfuran (406 µL, 4.50 mmol). The reaction mixture was stirred at 40 °C for 2 h then sat. aq. $NaHCO_3$ (15 mL) was added followed by Et_2O (15 mL). The layers were separated and the aqueous portion was extracted with Et_2O (2 × 15 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash chromatography (pentane) afforded cyclobutane **349** (252 mg, 79%) as a colourless oil. R_f = 0.31 (pentane); IR (film)/cm^{-1} 2985, 2944, 1602, 1558, 1490, 1446, 1218, 1088, 1021, 954, 779, 752, 700; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36–7.25 (m, 4 H, 4 × Ar-CH), 7.24–7.17 (m, 1 H, Ar-CH), 5.83 (dq, *J* = 3.0, 1.0 Hz, 1 H, $Ar_{(furan)}$-CH), 5.78 (d, *J* = 3.0 Hz, 1 H, $Ar_{(furan)}$-CH), 2.75–2.57 (m, 4 H, C*H*$_2$CH$_2$C*H*$_2$), 2.25 (d, *J* = 1.0 Hz, 3 H, CH_3), 2.22–2.08 (m, 1 H, C*H*H), 1.96–1.84 (m, 1 H, CH*H*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.5 ($Ar_{(furan)}$-*C*$_q$-C_q), 151.0 ($Ar_{(furan)}$-*C*$_q$-CH_3), 147.4 (Ar-*C*$_q$-C_q), 128.0 (2 × Ar-CH), 126.3 (2 × Ar-CH), 125.8 (Ar-CH), 105.7 ($Ar_{(furan)}$-CH), 105.3 ($Ar_{(furan)}$-CH), 46.8 (C_q), 33.7 ($CH_2CH_2CH_2$), 16.8 ($CH_2CH_2CH_2$), 13.7 ($Ar_{(furan)}$-CH_3); HRMS (+APCI) *m*/*z* calcd for $C_{15}H_{17}O^+$ [M+H]$^+$: 213.1274, Found: 213.1269.

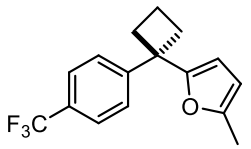


2-(1-(4-Chlorophenyl)cyclobutyl)-5-methylfuran (350)

Toluene (3.0 mL) was added to iron chloride (12.2 mg, 0.075 mmol), 1-(4-chlorophenyl)cyclobutan-1-ol[w] (274 mg, 1.50 mmol) and 2-methylfuran (406 µL, 4.50 mmol). The reaction mixture was stirred at 40 °C for 2 h then sat. aq. $NaHCO_3$ (15 mL) was added followed by Et_2O (15 mL). The layers were separated and the aqueous portion was extracted with Et_2O (2 × 15 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash chromatography (pentane) afforded cyclobutane **350** (288 mg, 78%) as a colourless oil. R_f = 0.48 (pentane); IR (film)/cm^{-1} 2981, 2944, 1558, 1490, 1218, 1092, 1031, 954, 827, 779; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31–7.25 (m, 2 H, 2 × Ar-CH), 7.24–7.18 (m, 2 H, 2 × Ar-CH), 5.83 (dq, *J* = 3.1, 1.0 Hz, 1 H, $Ar_{(furan)}$-CH), 5.80 (d, *J* = 3.1 Hz, 1 H, $Ar_{(furan)}$-CH), 2.73–2.62 (m, 2 H, CH_2), 2.62–2.51 (m, 2 H, CH_2), 2.24 (d, *J* = 1.0 Hz, 3 H, CH_3), 2.21–2.06 (m, 1 H, C*H*H), 1.96–1.83 (m, 1 H, CH*H*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.8 ($Ar_{(furan)}$-*C*$_q$-C_q), 151.2 ($Ar_{(furan)}$-*C*$_q$-CH_3), 147.5 (Ar-*C*$_q$-C_q), 131.5 (Ar-C_q-Cl), 128.1 (2 × Ar-CH), 127.8 (2 × Ar-CH), 105.7 ($Ar_{(furan)}$-CH), 105.4 ($Ar_{(furan)}$-CH), 46.4 (C_q), 33.6 ($CH_2CH_2CH_2$), 16.7 ($CH_2CH_2CH_2$), 13.7

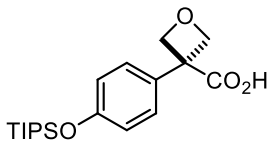
[w] Previously synthesised in the Bull group.

($Ar_{(furan)}$-CH_3); The observed spectroscopic data (IR, ^1H and ^{13}C NMR) for this compound was consistent with that previously reported.[114, 222]



2-Methyl-5-(1-(4-(trifluoromethyl)phenyl)cyclobutyl)furan (351)

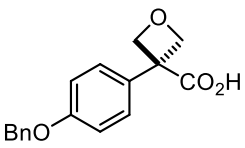
CH_2Cl_2 (3.0 mL) was added to iron chloride (12.2 mg, 0.075 mmol), 1-(4-(trifluoromethyl)phenyl)cyclobutan-1-ol[w] (324 mg, 1.50 mmol) and 2-methylfuran (406 µL, 4.50 mmol). The reaction mixture was stirred at 40 °C for 2 h then sat. aq. $NaHCO_3$ (15 mL) was added followed by Et_2O (15 mL). The layers were separated and the aqueous portion was extracted with Et_2O (2 × 15 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash chromatography (pentane) afforded cyclobutane **351** (86.1 mg, 20%) as a white solid. R_f = 0.49 (pentane); mp = 44–46 °C, IR (film)/cm^{-1} 2989, 2944, 1613, 1408, 1323, 1159, 1110, 1013, 931, 846, 782; ^1H NMR (400 MHz, $CDCl_3$) δ 7.60–7.55 (m, 2 H, 2 × Ar-CH), 7.42–7.37 (m, 2 H, 2 × Ar-CH), 5.86–5.84 (m, 2 H, 2 × $Ar_{(furan)}$-CH), 2.77–2.68 (m, 2 H, CH_2), 2.66–2.56 (m, 2 H, CH_2), 2.25 (d, *J* = 0.5 Hz, 3 H, CH_3), 2.23–2.12 (m, 1 H, C*H*H), 1.99–1.85 (m, 1 H, CH*H*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.2 ($Ar_{(furan)}$-C_q-C_q), 151.4 ($Ar_{(furan)}$-C_q-CH_3), 139.6 (Ar-C_q-C_q), 128.1 (q, $^2J_{C\text{-}F}$ = 32.3 Hz, Ar-C_q-CF_3), 126.6 (2 × Ar-CH), 126.2 (q, $^1J_{C\text{-}F}$ = 296.0 Hz, CF_3), 125.1 (q, $^3J_{C\text{-}F}$ = 3.8 Hz, 2 × Ar-CH), 105.8 ($Ar_{(furan)}$-CH), 105.6 ($Ar_{(furan)}$-CH), 46.8 (C_q), 33.5 ($CH_2CH_2CH_2$), 16.8 ($CH_2CH_2CH_2$), 13.6 ($Ar_{(furan)}$-CH_3); $^{19}F\{^1H\}$ NMR (377 MHz, $CDCl_3$) δ –62.3; HRMS (+APCI) *m*/*z* calcd for $C_{16}H_{16}F_3O^+$ $[M+H]^+$: 281.1148, Found: 281.1156.



3-(4-((Triisopropylsilyl)oxy)phenyl)oxetane-3-carboxylic acid (361)

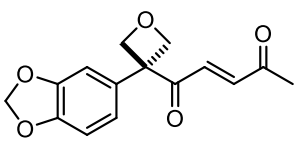
$NaIO_4$ (2.60 g, 12.2 mmol) was added to a solution of oxetane furan **325** (673 mg, 1.74 mmol) in heptane/EtOAc/H_2O (11.0 mL/11.0 mL/21.5 mL). The reaction mixture was stirred for 5 min and $RuCl_3$ (9.0 mg, 0.043 mmol) was added. The reaction mixture was stirred for 18 h at 25 °C. Water (10 mL) was added followed by EtOAc (10 mL) and the layers were separated. The aqueous portion was extracted with EtOAc (2 × 20 mL). The organic extracts were combined, dried over Na_2SO_4, filtered through a plug of silica and concentrated under reduced pressure. The crude was dissolved in 5 mL of Et_2O and transferred to a separating funnel. Hexane (15 mL) was added and the organic layer was extracted with aq. NaOH (1 M, 5 × 15 mL). The aqueous extracts were combined and acidified to pH ~ 1 with aq. HCl (1 M, ~50 mL). The aqueous portion was extracted with Et_2O (5 × 15 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford carboxylic acid **361** (556 mg, 91%) as a black paste. R_f = 0.13 (20% EtOAc/hexane + 0.5% AcOH); IR (film)/cm^{-1} 2944 (br. COOH), 2892, 2866, 1729 (C=O), 1606, 1513, 1461, 1263, 1162, 913, 834, 760, 682; ^1H NMR (400 MHz, $CDCl_3$) δ 7.13–7.09 (m, 2 H, 2 × Ar-CH), 6.93–6.84 (m, 2 H, 2 × Ar-

CH), 5.26 (d, *J* = 6.2 Hz, 2 H, C*H*HOC*H*H), 5.01 (d, *J* = 6.2 Hz, 2 H, CH*H*OCH*H*), 1.32–1.21 (m, 3 H, 3 × C*H*(CH_3)$_2$), ;1.11 (d, *J* = 7.3 Hz, 18 H, 3 × CH(C*H*$_3$)$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.0 (CO_2H), 155.7 (Ar-C_q-OTIPS), 131.0 (Ar-*C*$_q$-C_q), 127.2 (2 × Ar-CH), 120.1 (2 × Ar-CH), 79.6 (*C*H_2O*C*H_2), 52.4 (C_q), 17.9 (3 × CH(*C*H_3)$_2$), 12.6 (3 × *C*H(CH_3)$_2$); HRMS (–ESI) *m*/*z* calcd for $C_{19}H_{29}O_4Si$ [M–H]: 349.1835, Found: 349.1850.



3-(4-(Benzyloxy)phenyl)oxetane-3-carboxylic acid (362)

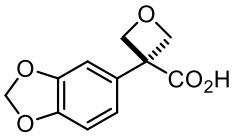
$NaIO_4$ (2.13 g, 9.96 mmol) was added to a solution of oxetane furan **326** (455 mg, 1.42 mmol) in heptane/EtOAc/H_2O (8.90 mL/8.90 mL/17.7 mL). The reaction mixture was stirred for 5 min and $RuCl_3$ (7.4 mg, 0.036 mmol) was added. The reaction mixture was stirred for 18 h at 25 °C. Water (30 mL) was added followed by EtOAc (30 mL) and the layers were separated. The aqueous portion was extracted with EtOAc (2 × 30 mL). The organic extracts were combined, dried over Na_2SO_4, filtered through celite® and concentrated under reduced pressure. The crude was dissolved in 5 mL of EtOAc and transferred to a separating funnel. Pentane (15 mL) was added and the organic layer was extracted with sat. aq. $NaHCO_3$ (3 × 10 mL). The aqueous extracts were combined and acidified to pH ~ 1 with aq. HCl (1 M, ~30 mL). The aqueous portion was extracted with EtOAc (3 × 30 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford carboxylic acid **362** (305 mg, 76%) as a light yellow solid. R_f = 0.20 (20% EtOAc/hexane + 0.5% AcOH); mp = 149–151 °C, IR (film)/cm^{-1} 2888 (br. COOH), 1692 (C=O), 1610, 1513, 1408, 1282, 1252, 1170, 1025, 980, 924, 846, 734, 697; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.14 (br s, 1 H, CO_2H), 7.51–7.30 (m, 5 H, 5 × Ar-CH), 7.24–7.13 (m, 2 H, 2 × Ar-CH), 7.06–6.93 (m, 2 H, 2 × Ar-CH), 5.26 (d, *J* = 6.2 Hz, 2 H, C*H*HOC*H*H), 5.08 (s, 2 H, OCH_2Ph), 5.02 (d, *J* = 6.2 Hz, 2 H, CH*H*OCH*H*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.0 (CO_2H), 158.4 (Ar-C_q-OBn), 136.7 (Ar-*C*$_q$-CH_2), 131.0 (Ar-*C*$_q$-C_q), 128.6 (2 × Ar-CH), 128.1 (Ar-CH), 127.42 (2 × Ar-CH), 127.37 (2 × Ar-CH), 115.2 (2 × Ar-CH), 79.5 (*C*H_2O*C*H_2), 70.1 (OCH_2Ph), 52.4 (C_q); HRMS (–ESI) *m*/*z* calcd for $C_{17}H_{15}O_4$ [M–H]: 283.0970, Found: 283.0977.



(*E*)-1-(3-(Benzo[d][1,3]dioxol-5-yl)oxetan-3-yl)pent-2-ene-1,4-dione (*(E)*-364)

$NaIO_4$ (299 mg, 1.40 mmol) was added to a solution of oxetane furan **328** (51.7 mg, 0.20 mmol) in heptane/EtOAc/H_2O (1.30 mL/1.30 mL/2.40 mL). The reaction mixture was stirred for 5 min and $RuCl_3$ (1.0 mg, 0.005 mmol) was added. The reaction mixture was stirred for 48 h at 25 °C. Water (15 mL) was added followed by EtOAc (10 mL) and the layers were separated. The aqueous portion was extracted with EtOAc (2 × 10 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced

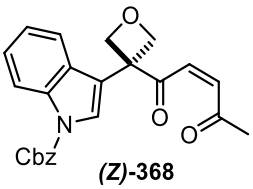
pressure. Purification by flash column chromatography (4% Et_2O/CH_2Cl_2) afforded alkene ***(E)*-364** (8.4 mg, 15%) as a yellow oil. R_f = 0.46 (4% Et_2O/CH_2Cl_2); IR (film)/cm^{-1} 2959, 2885, 1684 (C=O), 1610 (C=O), 1487, 1438, 1356, 1293, 1230, 1114, 1036, 984, 931, 812; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.04 (d, *J* = 15.8 Hz, 1 H, C*H*=CH), 6.84 (d, *J* = 8.6 Hz, 1 H, Ar-CH), 6.83 (d, *J* = 15.8 Hz, 1 H, CH=C*H*), 6.67–6.61 (m, 2 H, 2 × Ar-CH), 6.00 (s, 2 H, OCH_2O), 5.17 (d, *J* = 6.3 Hz, 2 H, C*H*HOC*H*H), 4.98 (d, *J* = 6.3 Hz, 2 H, CH*H*OCH*H*), 2.31 (s, 3 H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.2 (C=O), 195.8 (C=O), 148.7 (Ar-C_q-OCH_2), 147.6 (Ar-C_q-OCH_2), 138.6 (*C*H=CH), 132.2 (CH=*C*H), 130.9 (Ar-C_q-C_q), 119.9 (Ar-CH), 109.0 (Ar-CH), 106.6 (Ar-CH), 101.5 (OCH_2O), 77.4 (CH_2OCH_2), 58.2 (C_q), 29.2 (CH_3); HRMS (+APCI) *m*/*z* calcd for $C_{15}H_{15}O_5^+$ $[M+H]^+$: 275.0914, Found: 275.0910.



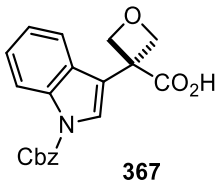
3-(Benzo[d][1,3]dioxol-5-yl)oxetane-3-carboxylic acid (363)

$NaIO_4$ (300 mg, 1.40 mmol) was added to a solution of oxetane furan **328** (51.7 mg, 0.20 mmol) and $NaHCO_3$ (67.2 mg, 0.80 mmol) in heptane/EtOAc/H_2O (1.25 mL/1.25 mL/2.50 mL). The reaction mixture was stirred for 5 min and a solution of $RuCl_3$ (0.05 M in water, 20 µL, 0.001 mmol) was added. The reaction mixture was stirred for 24 h at 25 °C. Water (15 mL) was added followed by EtOAc (15 mL) and the layers were separated. The aqueous portion was extracted with EtOAc (2 × 15 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography (50% Et_2O/pentane followed by 50% Et_2O/pentane + 0.5% AcOH) afforded oxetane **363** (9.3 mg, 22%) as a white solid. R_f = 0.29 (50% Et_2O/pentane + 0.5% AcOH); mp = 147–148 °C, IR (film)/cm^{-1} 2963 (br. COOH), 2911, 2769, 1722 (C=O), 1483, 1435, 1353, 1244, 1170, 1133, 1036, 961, 898, 697; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.82 (d, *J* = 8.0 Hz, 1 H, Ar-CH), 6.78–6.64 (m, 2 H, 2 × Ar-CH), 5.99 (s, 2 H, OCH_2O), 5.23 (d, *J* = 6.1 Hz, 2 H, C*H*HOC*H*H), 5.00 (d, *J* = 6.1 Hz, 2 H, CH*H*OCH*H*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.5 (CO_2H), 148.1 (Ar-C_q-OCH_2), 147.3 (Ar-C_q-OCH_2), 132.4 (Ar-C_q-C_q), 119.6 (Ar-CH), 108.5 (Ar-CH), 106.9 (Ar-CH), 101.4 (OCH_2O), 79.4 (CH_2OCH_2), 52.8 (C_q); HRMS (–ESI) *m*/*z* calcd for $C_{11}H_9O_5$ [M–H]: 221.0450, Found: 221.0452.

Benzyl (Z)-3-(3-(4-oxopent-2-enoyl)oxetan-3-yl)-1*H*-indole-1-carboxylate (*(Z)*-368) and **3-(1-((benzyloxy)carbonyl)-1*H*-indol-3-yl)oxetane-3-carboxylic acid (367)**



***(Z)*-368**



367

$NaIO_4$ (810 mg, 3.79 mmol) was added to a solution of oxetane furan **332** (207 mg, 0.54 mmol) in heptane/EtOAc/H_2O (3.40 mL/3.40 mL/6.70 mL). The reaction mixture was stirred for 5 min and a solution of $RuCl_3$ (0.05 M in water, 54 µL, 0.0027 mmol) was added. The reaction mixture was stirred for 48 h at 25 °C. Water (5 mL) was added followed by EtOAc (5 mL) and the layers were separated. The aqueous portion was extracted with EtOAc (2 × 10 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography (30 to 50% EtOAc/pentane, followed by 50% EtOAc/pentane + 0.5% AcOH) afforded alkene ***(Z)*-368** (24.8 mg, 90% pure, 11%) as a yellow paste, and oxetane acid **367** (42.3 mg, 22%) as a yellow solid.

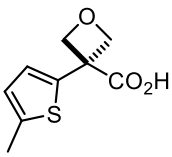
***(Z)*-368**: R_f = 0.24 (30% EtOAc/pentane); IR (film)/cm^{-1} 3421, 2955, 2982, 1736 (C=O), 1695 (C=O), 1610 (C=O), 1453, 1397, 1360, 1308, 1267, 1166, 1237, 1054, 987, 760; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (s, 1 H, N-Ar-CH), 7.60 (s, 1 H, $Ar_{(indole)}$-CH), 7.55–7.49 (m, 2 H, 2 × Ar-CH), 7.48–7.39 (m, 3 H, 3 × Ar-CH), 7.39–7.4 (m, 1 H, $Ar_{(indole)}$-CH), 7.24 (ddd, *J* = 8.0, 7.1, 1.1 Hz, 1 H, $Ar_{(indole)}$-CH), 7.20 (ddd, *J* = 7.9, 1.5, 0.8 Hz, 1 H, $Ar_{(indole)}$-CH), 6.27 (d, *J* = 12.0 Hz, 1 H, CH=C*H*), 6.21 (d, *J* = 12.0 Hz, 1 H, C*H*=CH), 5.49 (s, 2 H, OCH_2Ph), 5.32 (d, *J* = 6.0 Hz, 2 H, C*H*HOC*H*H), 5.00 (d, *J* = 6.0 Hz, 2 H, CH*H*OCH*H*), 2.26 (s, 3 H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 201.4 (C=O), 198.2 (C=O), 150.6 ($C=O_{(carbamate)}$)*, 140.8 (*C*H=CH), 135.8 ($Ar_{(indole)}$-C_q-C_q), 134.7 (Ar-C_q-CH_2), 129.5 (CH=*C*H), 129.0 (Ar-CH), 128.8 (2 × Ar-CH), 128.7 (2 × Ar-CH), 128.0 ($Ar_{(indole)}$-C_q-C_q), 125.6 ($Ar_{(indole)}$-CH), 123.6 ($Ar_{(indole)}$-CH), 123.2 ($Ar_{(indole)}$-CH), 119.3 ($Ar_{(indole)}$-CH), 119.1 (N-Ar-CH-C_q), 115.7 (N-Ar-*C*H-C_q), 77.3 (*C*H_2O*C*H_2), 69.2 (OCH_2Ph), 52.5 (C_q), 29.5 (CH_3); HRMS (+APCI) *m*/*z* calcd. for $C_{24}H_{22}NO_5^+$ $[M+H]^+$: 404.1492, Found: 404.1480.

*Found using a HMBC correlation experiment.

367: R_f = 0.29 (50% EtOAc/ CH_2Cl_2 + 0.5% AcOH); mp = 159–162 °C, IR (film)/cm^{-1} 2963 (br. COOH), 1733 (C=O), 1453, 1394, 1360, 1308, 1267, 1237, 1110, 1054, 984, 909, 745, 700; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (s, 1 H, N-Ar-CH), 7.63 (s, 1 H, $Ar_{(indole)}$-CH), 7.53–7.47 (m, 2 H, 2 × Ar-CH), 7.47–7.39 (m, 4 H, $Ar_{(indole)}$-CH, 3 × Ar-CH), 7.47–7.39 (m, 1 H, $Ar_{(indole)}$-CH), 7.47–7.39 (m, 1 H, $Ar_{(indole)}$-CH), 5.47 (s, 2 H, OCH_2Ph), 5.33 (d, *J* = 6.1 Hz, 2 H, C*H*HOC*H*H), 5.07 (d, *J* = 6.1 Hz, 2 H, CH*H*OCH*H*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.3 (CO_2H), 150.8

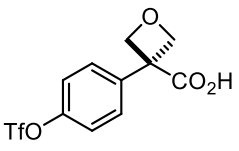
(C=$O_{(carbamate)}$)*, 135.7 ($Ar_{(indole)}$-C_q-C_q), 134.8 (Ar-C_q-CH_2), 128.9 (Ar-CH), 128.8 (2 × Ar-CH), 128.6 (2 × Ar-CH), 127.9 ($Ar_{(indole)}$-C_q-C_q), 125.3 ($Ar_{(indole)}$-CH), 123.4 ($Ar_{(indole)}$-CH), 123.1 ($Ar_{(indole)}$-CH), 119.6 ($Ar_{(indole)}$-CH), 119.1 (N-Ar-CH-C_q), 115.6 (N-Ar-*C*H-C_q), 78.5 (CH_2OCH_2), 69.0 (OCH_2Ph), 47.5 (C_q); HRMS (–APCI) *m*/*z* calcd for $C_{20}H_{16}NO_5^-$ [M–H]$^-$: 350.1034, Found: 350.1030.

* Found using a HMBC correlation experiment.



3-(5-Methylthiophen-2-yl)oxetane-3-carboxylic acid (369)

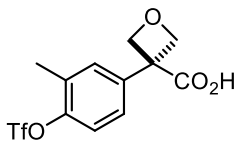
$NaIO_4$ (824 mg, 3.85 mmol) was added to a solution of oxetane furan **333** (81.3 mg, 0.35 mmol) in EtOAc/H_2O (6.90 mL/6.90 mL). The reaction mixture was stirred for 5 min and a solution of $RuCl_3$ (0.05 M in water, 55 µL, 0.00275 mmol) was added. The reaction mixture was stirred for 24 h at 25 °C. Water (15 mL) was added followed by EtOAc (15 mL) and the layers were separated. The aqueous portion was extracted with EtOAc (2 × 15 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude was dissolved in 5 mL of Et_2O and transferred in a separating funnel. Hexane (10 mL) was added and the organic layer was extracted with aq. NaOH (1 M, 2 × 10 mL). The aqueous extracts were combined and acidified to pH ~ 1 with aq. HCl (1 M, ~20 mL). The aqueous portion was extracted with EtOAc (3 × 20 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography (40% Et_2O/pentane + 0.5% AcOH) afforded oxetane **369** (14.8 mg, 21%) as a yellow solid. R_f = 0.30 (50% Et_2O/pentane + 0.5% AcOH); mp = 88–90 °C, IR (film)/cm^{-1} 2959 (br. COOH), 2888, 1733 (C=O), 1267, 1241, 1162, 1125, 969, 924, 797; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (s, br, 1 H, CO_2H), 6.83 (d, *J* = 3.5 Hz, 1 H, Ar-CH), 6.66 (dq, *J* = 3.5, 1.1 Hz, 1 H, Ar-CH), 5.24 (d, *J* = 6.3 Hz, 2 H, C*H*HOC*H*H), 4.96 (d, *J* = 6.3 Hz, 2 H, CH*H*OCH*H*), 2.48 (d, *J* = 1.1 Hz, 3 H, Ar-CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.5 (CO_2H), 140.2 (Ar-C_q-C_q), 138.5 (Ar-C_q-CH_3), 125.2 (Ar-CH), 125.1 (Ar-CH), 80.3 (CH_2OCH_2), 50.3 (C_q), 15.3 (Ar-CH_3); HRMS (–ESI) *m*/*z* calcd for $C_9H_9O_3S$ [M–H]: 197.0272, Found: 197.0279.



3-(4-(((Trifluoromethyl)sulfonyl)oxy)phenyl)oxetane-3-carboxylic acid (370)

$NaIO_4$ (1.50 g, 7.00 mmol) was added to a solution of oxetane furan **337** (363 mg, 1.00 mmol) in heptane/EtOAc/H_2O (6.30 mL/6.30 mL/12.4 mL). The reaction mixture was stirred for 5 min and $RuCl_3$ (1.0 mg, 0.005 mmol) was added. The reaction mixture was stirred for 18 h at 25 °C. Water (15 mL) was added followed by EtOAc (15 mL) and the layers were separated. The aqueous portion was extracted with EtOAc (2 × 15 mL). The organic

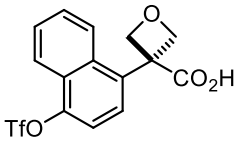
extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude was dissolved in 5 mL of Et_2O and transferred in a separating funnel. Pentane (20 mL) was added and the organic layer was extracted with sat. aq. $NaHCO_3$ (4 × 30 mL). The aqueous extracts were combined and acidified to pH ~ 1 with aq. HCl (1 M, ~100 mL). The aqueous portion was extracted with EtOAc (3 × 80 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure affording carboxylic acid **370** (294 mg, 90%) as a white solid. R_f = 0.27 (30% EtOAc/hexane + 0.5% AcOH); mp = 110–112 °C, IR (film)/cm^{-1} 2967 (br. COOH), 2892, 1707 (C=O), 1498, 1416, 1297, 1252, 1203, 1133, 883, 842, 782; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.19 (br s, 1 H, CO_2H), 7.41–7.29 (m, 4 H, 4 × Ar-CH), 5.29 (d, *J* = 6.4 Hz, 2 H, C*H*HOC*H*H), 5.03 (d, *J* = 6.4 Hz, 2 H, CH*H*OCH*H*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.8 (CO_2H), 149.0 (Ar-C_q-OTf), 139.1 (Ar-C_q-C_q), 128.3 (2 × Ar-CH), 121.9 (2 × Ar-CH), 118.7 (q, $^1J_{C\text{-}F}$ = 320.8 Hz, CF_3), 79.1 (CH_2OCH_2), 52.6 (C_q); ^{19}F{^{1}H} NMR (377 MHz, $CDCl_3$) δ –72.8; HRMS (–ESI) *m*/*z* calcd for $C_{11}H_8O_6SF_3$ [M–H]: 324.9994, Found: 324.9983.



3-(3-Methyl-4-(((trifluoromethyl)sulfonyl)oxy)phenyl)oxetane-3-carboxylic acid (371)

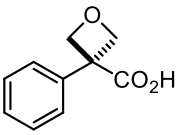
$NaIO_4$ (3.20 g, 15.1 mmol) was added to a solution of oxetane furan **338** (802 mg, 2.13 mmol) in heptane/EtOAc/H_2O (13.3 mL/13.3 mL/26.7 mL). The reaction mixture was stirred for 5 min and $RuCl_3$ (11.0 mg, 0.053 mmol) was added. The reaction mixture was stirred for 24 h at 25 °C. Water (50 mL) was added followed by EtOAc (50 mL) and the layers were separated. The aqueous portion was extracted with EtOAc (2 × 50 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude was dissolved in 10 mL of Et_2O and transferred in a separating funnel. Hexane (40 mL) was added and the organic layer was extracted with sat. aq. $NaHCO_3$ (3 × 30 mL). The aqueous extracts were combined and acidified to pH ~ 1 with aq. HCl (1 M, ~80 mL). The aqueous portion was extracted with Et_2O (4 × 20 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure affording carboxylic acid **371** (681 mg, 94%) as a light pink solid. R_f = 0.15 (30% EtOAc/hexane + 0.5% AcOH); mp = 83–85 °C, IR (film)/cm^{-1} 2967 (br. COOH), 2892, 1699 (C=O), 1494, 1401, 1248, 1207, 1140, 1095, 913, 864; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (br s, 1 H, CO_2H), 7.27 (d, *J* = 8.5 Hz, 1 H, Ar-CH), 7.20 (d, *J* = 2.4 Hz, 1 H, Ar-CH), 7.16 (dd, *J* = 8.5, 2.4 Hz, 1 H, Ar-CH), 5.28 (d, *J* = 6.3 Hz, 2 H, C*H*HOC*H*H), 5.02 (d, *J* = 6.3 Hz, 2 H, CH*H*OCH*H*), 2.41 (s, 3 H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.9 (CO_2H), 147.8 (Ar-C_q-OTf), 138.8 (Ar-C_q-C_q), 131.7 (Ar-C_q-CH_3), 130.1 (Ar-CH), 125.6 (Ar-CH), 121.8 (Ar-CH), 118.6 (q, $^1J_{C\text{-}F}$ = 320.1 Hz, CF_3),

79.1 (CH_2OCH_2), 52.6 (C_q), 16.5 (CH_3); $^{19}F\{^1H\}$ NMR (377 MHz, $CDCl_3$) δ –73.7; HRMS (–ESI) *m*/*z* calcd for $C_{12}H_{10}O_6SF_3$ [M–H]: 339.0150, Found: 339.0155.



3-(4-(((Trifluoromethyl)sulfonyl)oxy)naphthalen-1-yl)oxetane-3-carboxylic acid (372)

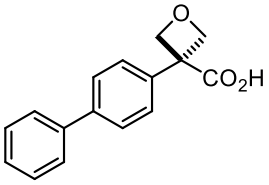
$NaIO_4$ (843 mg, 3.94 mmol) was added to a solution of oxetane furan **339** (231 mg, 0.56 mmol) in heptane/EtOAc/H_2O (3.50 mL/3.50 mL/7.00 mL). The reaction mixture was stirred for 5 min and $RuCl_3$ (2.90 mg, 0.014 mmol) was added. The reaction mixture was stirred for 18 h at 25 °C. Water (15 mL) was added followed by EtOAc (15 mL) and the layers were separated. The aqueous portion was extracted with EtOAc (2 × 15 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude was dissolved in 5 mL of Et_2O and transferred in a separating funnel. Pentane (10 mL) was added and the organic layer was extracted with aq. K_2CO_3 (1 M, 3 × 15 mL). The aqueous extracts were combined and acidified to pH ~ 1 with aq. HCl (1 M, ~50 mL). The aqueous portion was extracted with EtOAc (3 × 50 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure affording carboxylic acid **372** (165 mg, 78%) as a shiny grey solid. R_f = 0.42 (50% EtOAc/hexane + 0.5% AcOH); mp = 66–70 °C, IR (film)/cm^{-1} 2959 (br. COOH), 1707 (C=O), 1420, 1207, 1133, 1013, 976, 920, 857, 820, 766, 730; ^1H NMR (400 MHz, $CDCl_3$) δ 8.14 (d, *J* = 7.9 Hz, 1 H, Ar-CH), 7.67 (ddd, *J* = 8.3, 6.9, 1.2 Hz, 1 H, Ar-CH), 7.60 (ddd, *J* = 8.3, 6.9, 1.4 Hz, 1 H, Ar-CH), 7.49 (d, *J* = 8.0 Hz, 1 H, Ar-CH), 7.40 (d, *J* = 8.3 Hz, 1 H, Ar-CH), 7.34 (d, *J* = 8.1 Hz, 1 H, Ar-CH), 5.45 (d, *J* = 6.2 Hz, 2 H, C*H*HOC*H*H), 5.25 (d, *J* = 6.2 Hz, 2 H, CH*H*OCH*H*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.9 (CO_2H), 145.5 (Ar-C_q-OTf), 135.8 (Ar-C_q-C_q), 131.8 (Ar-C_q-C_q), 128.3 (Ar-CH), 128.0 (Ar-CH), 126.8 (Ar-C_q-C_q), 124.9 (Ar-CH), 124.2 (Ar-CH), 122.0 (Ar-CH), 118.7 (q, $^1J_{C\text{-}F}$ = 320.9 Hz, CF_3), 117.2 (Ar-CH), 78.8 (CH_2OCH_2), 53.1 (C_q); $^{19}F\{^1H\}$ NMR (377 MHz, $CDCl_3$) δ –73.2; HRMS (–ESI) *m*/*z* calcd for $C_{15}H_{10}O_6SF_3$ [M–H]: 375.0150, Found: 375.0157.



3-Phenyloxetane-3-carboxylic acid (373)

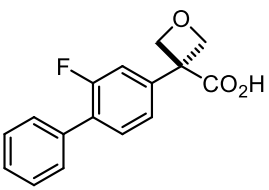
$NaIO_4$ (2.20 g, 10.3 mmol) was added to a solution of oxetane furan **340** (316 mg, 1.47 mmol) in heptane/EtOAc/H_2O (9.20 mL/9.20 mL/18.4 mL). The reaction mixture was stirred for 5 min and $RuCl_3$ (1.5 mg, 0.0072 mmol) was added. The reaction mixture was stirred for 18 h at 25 °C. Water (20 mL) was added followed by EtOAc (20 mL) and the layers were separated. The aqueous portion was extracted with EtOAc (2 × 40 mL). The organic extracts were combined, dried over Na_2SO_4, filtered through celite® and concentrated under reduced pressure to afford carboxylic acid **373** (252 mg, 96%) as

colourless needle crystals. R_f = 0.15 (30% EtOAc/hexane + 0.5% AcOH); mp = 116–117 °C; IR (film)/cm^{-1} 3000 (br. COOH), 2963, 2899, 1722 (C=O), 1244, 1174, 950, 734, 700; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.40 (br s, 1 H, CO_2H), 7.44–7.31 (m, 3 H, 3 × Ar-CH), 7.30–7.22 (m, 2 H, 2 × Ar-CH), 5.28 (d, *J* = 6.3 Hz, 2 H, C*H*HOC*H*H), 5.06 (d, *J* = 6.3 Hz, 2 H, CH*H*OCH*H*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.9 (CO_2H), 138.7 (Ar-C_q-C_q), 128.9 (2 × Ar-CH), 127.9 (Ar-CH), 126.1 (2 × Ar-CH), 79.4 (CH_2OCH_2), 53.0 (C_q); HRMS (–ESI) *m*/*z* calcd for $C_{10}H_9O_3$ [M–H]: 177.0552, Found: 177.0560. Compound previously reported without characterisation data.[257]



3-([1,1'-Biphenyl]-4-yl)oxetane-3-carboxylic acid (375)

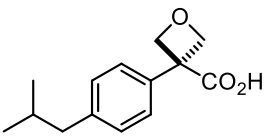
$NaIO_4$ (824 mg, 3.85 mmol) was added to a solution of oxetane furan **342** (158 mg, 0.55 mmol) in heptane/EtOAc/H_2O (3.50 mL/3.50 mL/6.80 mL). The reaction mixture was stirred for 5 min and a solution of $RuCl_3$ (0.05 M in water, 55 µL, 0.00275 mmol) was added. The reaction mixture was stirred for 18 h at 25 °C. Water (15 mL) was added followed by EtOAc (15 mL) and the layers were separated. The aqueous portion was extracted with EtOAc (2 × 15 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude was dissolved in 5 mL of Et_2O and transferred to a separating funnel. Pentane (15 mL) was added and the organic layer was extracted with sat. aq. $NaHCO_3$ (4 × 15 mL). The aqueous extracts were combined and acidified to pH ~ 1 with aq. HCl (1 M, ~100 mL). The aqueous portion was extracted with EtOAc (3 × 80 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure affording carboxylic acid **375** (127 mg, 91%) as a white solid. R_f = 0.47 (50% EtOAc/hexane + 0.5% AcOH); mp = 207–208 °C, IR (film)/cm^{-1} 2922 (br. COOH), 1722 (C=O), 1259, 965, 935, 842, 760; ^{1}H NMR (400 MHz, acetone-d_6) δ 11.41 (br s, 1 H, CO_2H), 7.76–7.63 (m, 4 H, 4 × Ar-CH), 7.52–7.42 (m, 4 H, 4 × Ar-CH), 7.41–7.34 (m, 1 H, Ar-CH), 5.22 (d, *J* = 6.2 Hz, 2 H, C*H*HOC*H*H), 5.00 (d, *J* = 6.2 Hz, 2 H, CH*H*OCH*H*); ^{13}C NMR (101 MHz, acetone-d_6) δ 174.7 (CO_2H), 141.2 (Ar-C_q-C_q), 141.0 (Ar-C_q-C_q), 140.2 (Ar-C_q-C_q), 129.8 (2 × Ar-CH), 128.3 (Ar-CH), 128.0 (2 × Ar-CH), 127.7 (2 × Ar-CH), 127.6 (2 × Ar-CH), 79.9 (CH_2OCH_2), 53.7 (C_q); HRMS (–ESI) *m*/*z* calcd for $C_{16}H_{13}O_3$ [M–H]: 253.0865, Found: 253.0874.



3-(2-Fluoro-[1,1'-biphenyl]-4-yl)oxetane-3-carboxylic acid (376)

$NaIO_4$ (573 mg, 2.68 mmol) was added to a solution of oxetane furan **343** (118 mg, 0.38 mmol) in heptane/EtOAc/H_2O (2.40 mL/2.40 mL/4.80 mL). The reaction mixture was stirred for 5 min and a solution of $RuCl_3$ (0.05 M in water, 38.3 µL, 0.0019 mmol) was added. The reaction mixture was stirred for 18 h at 25 °C. Water (10 mL) was added followed by EtOAc (10 mL)

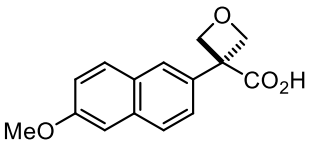
and the layers were separated. The aqueous portion was extracted with EtOAc (2 × 10 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude was dissolved in 5 mL of Et_2O and transferred to a separating funnel. Hexane (10 mL) was added and the organic layer was extracted with aq. NaOH (1 M, 3 × 10 mL). The aqueous extracts were combined and acidified to pH ~ 1 with aq. HCl (1 M, ~30 mL). The aqueous portion was extracted with Et_2O (3 × 15 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure affording carboxylic acid **376** (94.5 mg, 91%) as a white solid. R_f = 0.10 (30% EtOAc/hexane + 0.5% AcOH); mp = 175–178 °C; IR (film)/cm^{-1} 2959, 2922, 2881, 1725 (C=O), 1433, 1408, 1252, 1189, 1133, 946, 902, 864, 831, 767, 738; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58–7.52 (m, 2 H, 2 × Ar-CH), 7.52–7.43 (m, 3 H, 3 × Ar-CH), 7.42–7.37 (m, 1 H, Ar-CH), 7.17–7.07 (m, 2 H, 2 × Ar-CH), 5.31 (d, *J* = 6.4 Hz, 2 H, C*H*HOC*H*H), 5.07 (d, *J* = 6.4 Hz, 2 H, CH*H*OCH*H*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.9 (CO_2H), 159.7 (d, $^1J_{C\text{-}F}$ = 249.4 Hz, Ar-C_q-F), 139.8 (d, $^2J_{C\text{-}F}$ = 7.4 Hz, Ar-C_q-C_q), 135.0 (Ar-C_q-C_q), 131.2 (d, $^3J_{C\text{-}F}$ = 4.0 Hz, Ar-CH), 128.9 (d, $^4J_{C\text{-}F}$ = 3.2 Hz, 2 × Ar-CH), 128.8 (Ar-C_q-C_q), 128.5 (2 × Ar-CH), 128.0 (Ar-CH), 122.2 (d, $^4J_{C\text{-}F}$ = 3.6 Hz, Ar-CH), 114.3 (d, $^2J_{C\text{-}F}$ = 24.3 Hz, Ar-CH), 79.2 (CH_2OCH_2), 52.7 (C_q); ^{19}F NMR (377 MHz, $CDCl_3$) δ –116.4 (dd, *J* = 10.4, 8.1 Hz); HRMS (–ESI) *m*/*z* calcd for $C_{16}H_{12}O_3F$ [M–H]: 271.0770, Found: 271.0775.



3-(4-Isobutylphenyl)oxetane-3-carboxylic acid (377)

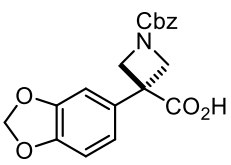
$NaIO_4$ (719 mg, 3.36 mmol) was added to a solution of oxetane furan **341** (129 mg, 0.48 mmol) in heptane/EtOAc/H_2O (3.00 mL/3.00 mL/6.00 mL). The reaction mixture was stirred for 5 min and a solution of $RuCl_3$ (0.05 M in water, 48 µL, 0.00275 mmol) was added. The reaction mixture was stirred for 18 h at 25 °C. Water (15 mL) was added followed by EtOAc (15 mL) and the layers were separated. The aqueous portion was extracted with EtOAc (2 × 15 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude was dissolved in 5 mL of Et_2O and transferred to a separating funnel. Pentane (20 mL) was added and the organic layer was extracted with aq. NaOH (1 M, 4 × 20 mL). The aqueous extracts were combined and acidified to pH ~ 1 with aq. HCl (1 M, ~100 mL). The aqueous portion was extracted with EtOAc (3 × 60 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure affording carboxylic acid **377** (71.9 mg, 64%) as a white solid. R_f = 0.34 (30% EtOAc/hexane + 0.5% AcOH); mp = 90–93 °C, IR (film)/cm^{-1} 2955 (br. COOH), 2922, 1733 (C=O), 1464, 1244, 1162, 1125, 984, 935, 842, 790, 730, 697; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 (s, 4 H, 4 × Ar-CH), 5.27 (d, *J* = 6.2 Hz, 2 H, C*H*HOC*H*H), 5.05 (d, *J* = 6.2 Hz, 2 H, CH*H*OCH*H*), 2.48 (d, *J* = 7.2 Hz, 2 H, Ar-C_q-CH_2), 1.86 (dh, *J* = 7.2, 6.7 Hz, 1 H, C*H*(CH_3)$_2$), 0.92 (d, *J* = 6.7 Hz, 6 H, CH(CH_3)$_2$); ^{13}C NMR (101 MHz,

$CDCl_3$) δ 179.1 (CO_2H), 141.5 (Ar-C_q-CH_2), 135.9 (Ar-C_q-C_q), 129.6 (2 × Ar-CH), 125.8 (2 × Ar-CH), 79.5 (CH_2OCH_2), 52.7 (C_q), 45.0 (Ar-CH_2), 30.2 ($CH(CH_3)_2$), 22.4 ($CH(CH_3)_2$); HRMS (–ESI) *m*/*z* calcd for $C_{14}H_{17}O_3$ [M–H]: 233.1178, Found: 233.1184.



3-(6-Methoxynaphthalen-2-yl)oxetane-3-carboxylic acid (378)

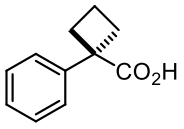
$NaIO_4$ (794 mg, 3.70 mmol) was added to a solution of oxetane furan **329** (157 mg, 0.53 mmol) in heptane/EtOAc/H_2O (1.67 mL/5.00 mL/6.60 mL). The reaction mixture was stirred for 5 min and a solution of $RuCl_3$ (0.05 M in water, 53 µL, 0.00267 mmol) was added. The reaction mixture was stirred for 24 h at 25 °C. Water (15 mL) was added followed by EtOAc (15 mL) and the layers were separated. The aqueous portion was extracted with EtOAc (2 × 15 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude was dissolved in 5 mL of Et_2O and transferred to a separating funnel. Pentane (20 mL) was added and the organic layer was extracted with aq. NaOH (1 M, 4 × 20 mL). The aqueous extracts were combined and acidified to pH ~ 1 with aq. HCl (1 M, ~100 mL). The aqueous portion was extracted with EtOAc (3 × 60 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography (10 to 20% EtOAc/CH_2Cl_2 + 0.5% AcOH) afforded oxetane **378** (24.7 mg, 18%) as a yellow solid. R_f = 0.34 (30% EtOAc/ CH_2Cl_2 + 0.5% AcOH); mp = 172–178 °C, IR (film)/cm^{-1} 2967 (br. COOH), 2982, 1729 (C=O), 1606, 1487, 1394, 1267, 1203, 1166, 1054, 991, 909, 808; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.6 Hz, 1 H, Ar-CH), 7.72 (d, *J* = 9.0 Hz, 1 H, Ar-CH), 7.62 (d, *J* = 6.3 Hz, 1 H, Ar-CH), 7.32 (dd, *J* = 8.5, 2.0 Hz, 1 H, Ar-CH), 7.18 (dd, *J* = 8.9, 2.6 Hz, 1 H, Ar-CH), 7.13 (d, *J* = 2.6 Hz, 1 H, Ar-CH), 5.34 (d, *J* = 6.3 Hz, 2 H, C*H*HOC*H*H), 5.14 (d, *J* = 6.3 Hz, 2 H, CH*H*OCH*H*), 3.93 (s, 3 H, OCH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.8 (CO_2H), 158.1 (Ar-C_q-OCH_3), 133.9 (Ar-C_q-C_q), 133.6 (Ar-C_q-C_q), 129.4 (Ar-CH), 128.5 (Ar-C_q-C_q), 127.7 (Ar-CH), 125.0 (Ar-CH), 124.3 (Ar-CH), 119.5 (Ar-CH), 105.6 (Ar-CH), 79.4 (CH_2OCH_2), 55.3 (OCH_3), 53.0 (C_q); HRMS (–ESI) *m*/*z* calcd for $C_{15}H_{13}O_4$ [M–H]: 257.0814, Found: 257.0819.



3-(Benzo[d][1,3]dioxol-5-yl)-1-((benzyloxy)carbonyl)azetidine-3-carboxylic acid (382)

$NaIO_4$ (285 mg, 1.33 mmol) was added to a solution of azetidine furan **348** (74.9 mg, 0.19 mmol) in heptane/EtOAc/H_2O (1.20 mL/ 1.20 mL/ 2.35 mL). The reaction mixture was stirred for 5 min and $RuCl_3$ (1.00 mg, 0.00475 mmol) was added. The reaction mixture was stirred for 24 h at 25 °C. Water (15 mL) was added followed by EtOAc (15 mL) and the layers were separated. The aqueous portion was extracted with EtOAc (2 × 15 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and

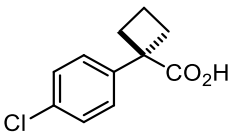
concentrated under reduced pressure. Purification by flash column chromatography (50% Et_2O/pentane followed by 50% Et_2O/pentane + 0.5% AcOH) afforded azetidine **382** (36.5 mg, 54%) as a yellow solid. R_f = 0.19 (50% Et_2O/pentane + 0.5% AcOH); mp = 146–148 °C, IR (film)/cm^{-1} 2959 (br. COOH), 2892, 1707 (C=O), 1490, 1438, 1456, 1222, 1155, 1095, 1036, 931, 905, 812, 764, 730, 700; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40–7.29 (m, 5 H, 5 × Ar-CH), 6.79 (d, *J* = 8.0 Hz, 1 H, Ar-CH), 6.77–6.70 (m, 2 H, 2 × Ar-CH), 5.96 (s, 2 H, OCH_2O), 5.58 (s, br, 1 H, CO_2H), 5.10 (s, 2 H, OCH_2Ph), 4.65 (d, *J* = 8.8 Hz, 2 H, C*H*HNC*H*H), 4.33 (d, *J* = 8.8 Hz, 2 H, CH*H*NCH*H*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.6 (CO_2H), 156.3 ($C{=}O_{(carbamate)}$), 148.1 (Ar-C_q-OCH_2), 147.4 (Ar-C_q-OCH_2), 136.2 (Ar-C_q-CH_2), 132.4 (Ar-C_q-C_q), 128.5 (2 × Ar-CH), 128.1 (Ar-CH), 128.0 (2 × Ar-CH), 119.8 (Ar-CH), 108.4 (Ar-CH), 107.1 (Ar-CH), 101.4 (OCH_2O), 67.1 (OCH_2Ph), 58.4 (br, CH_2NCH_2), 47.4 (C_q); HRMS (+APCI) *m*/*z* calcd for $C_{19}H_{18}O_6^+$ $[M+H]^+$: 356.1129, Found: 356.1123.



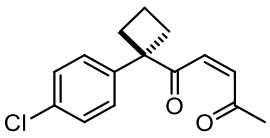
1-Phenylcyclobutane-1-carboxylic acid (383)

$NaIO_4$ (1.77 g, 8.26 mmol) was added to a solution of cyclobutane furan **349** (252 mg, 1.18 mmol) in heptane/EtOAc/H_2O (7.40 mL/ 7.40 mL/ 14.7 mL). The reaction mixture was stirred for 5 min and $RuCl_3$ (6.1 mg, 0.0295 mmol) was added. The reaction mixture was stirred for 18 h at 25 °C. Water (15 mL) was added followed by EtOAc (15 mL) and the layers were separated. The aqueous portion was extracted with EtOAc (2 × 15 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude was dissolved in 5 mL of Et_2O, filtrated through a pad of silica and concentrated under reduced pressure to afford cyclobutane **383** (217 mg, 100%) as a grey solid. R_f = 0.30 (20% Et_2O/pentane); mp = 77–83 °C [lit. 104–105 °C][221], IR (film)/cm^{-1} 2955 (br. COOH), 2989, 1695 (C=O), 1297, 730, 697; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41–7.27 (m, 4 H, 4 × Ar-CH), 7.30–7.21 (m, 1 H, Ar-CH), 2.92–2.79 (m, 2 H, CH_2), 2.61–2.47 (m, 2 H, CH_2), 2.17–2.02 (m, 1 H, C*H*H), 1.96–1.80 (m, 1 H, CH*H*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 181.6 (CO_2H), 143.1 (Ar-C_q-C_q), 128.3 (2 × Ar-CH), 126.8 (Ar-CH), 126.4 (2 × Ar-CH), 52.1 (C_q), 32.3 ($CH_2CH_2CH_2$), 16.6 ($CH_2CH_2CH_2$). The observed characterisation data (^{1}H, ^{13}C NMR) was consistent with that previously reported.[221]

1-(4-Chlorophenyl)cyclobutane-1-carboxylic acid (384) and **(*Z*)-1-(1-(4-chlorophenyl)cyclobutyl)pent-2-ene-1,4-dione (*(Z)*-385)**



384



***(Z)*-385**

$NaIO_4$ (1.75 g, 8.16 mmol) was added to a solution of cyclobutane furan **350** (288 mg, 1.17 mmol) in heptane/EtOAc/H_2O (7.30 mL/ 7.30 mL/ 14.7 mL). The reaction mixture was stirred for 5 min and $RuCl_3$ (6.1 mg, 0.0295 mmol) was added. The reaction mixture was stirred for 18 h at 25 °C. Water (15 mL) was added followed by EtOAc (15 mL) and the layers were separated. The aqueous portion was extracted with EtOAc (2 × 15 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude was dissolved in 5 mL of Et_2O and transferred in a separating funnel. Hexane (10 mL) was added and the organic layer was extracted with aq. NaOH (1 M, 4 × 10 mL). The remaining organic layer was dried over Na_2SO_4, and concentrated under reduced pressure. Purification by flash column chromatography (20% Et_2O/pentane) afforded alkene **(*Z*)-385** (45.1 mg, 15%) as a colourless oil.

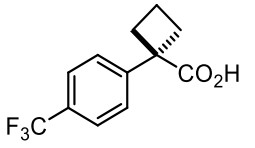
The aqueous extracts were combined and acidified to pH ~ 1 with aq. HCl (1 M, ~50 mL). The aqueous portion was extracted with Et_2O (3 × 20 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford cyclobutane acid **384** (183 mg, 74 %) as a grey solid.

***(Z)*-385**: R_f = 0.24 (20% Et_2O/pentane); IR (film)/cm^{-1} 2984, 2948, 1688 (C=O), 1610 (C=O), 1490, 1386, 1353, 1162, 1092, 1013, 834; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36–7.31 (m, 2 H, 2 × Ar-CH), 7.21–7.15 (m, 2 H, 2 × Ar-CH), 6.24 (d, *J* = 12.0 Hz, 1 H, CH=C*H*), 6.17 (d, *J* = 12.0 Hz, 1 H, C*H*=CH), 2.86–2.74 (m, 2 H, CH_2), 2.49–2.35 (m, 2 H, CH_2), 2.28 (s, 3 H, CH_3), 2.09–1.83 (m, 2 H, CH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 202.2 (C=O), 199.8 (C=O), 140.6 (*C*H=CH), 133.0 (Ar-C_q-C_q), 129.3 (Ar-C_q-Cl), 129.1 (CH=*C*H), 129.0 (2 × Ar-CH), 127.9 (2 × Ar-CH), 57.3 (C_q), 30.4 ($CH_2CH_2CH_2$), 29.4 (CH_3), 15.9 ($CH_2CH_2CH_2$). HRMS (–APCI) *m*/*z* calcd for $C_{15}H_{15}O_2{}^{35}Cl^{\bullet-}$ $[M]^{\bullet-}$: 262.0766, Found: 262.0764.

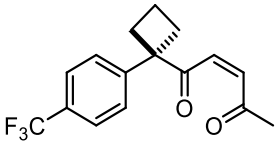
384: R_f = 0.23 (20% Et_2O/pentane); mp = 79–83 °C [lit. 89–90 °C][252], IR (film)/cm^{-1} 2989 (br. COOH), 1692 (C=O), 1490, 1401, 1293, 1092, 1013, 823; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33–7.28 (m, 2 H, 2 × Ar-CH), 7.26–7.22 (m, 2 × Ar-CH), 2.91–2.79 (m, 2 H, CH_2), 2.56–2.43 (m, 2 H, CH_2), 2.19–2.02 (m, 1 H, C*H*H), 1.94–1.82 (m, 1 H, CH*H*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 181.7 (CO_2H), 141.6 (Ar-C_q-C_q), 132.8 (Ar-C_q-Cl), 128.4 (2 × Ar-CH), 127.9 (2 × Ar-CH), 51.7

(C_q), 32.2 ($CH_2CH_2CH_2$), 16.5 ($CH_2CH_2CH_2$). HRMS (–APCI) *m*/*z* calcd for $C_{11}H_{10}O_2Cl^-$ $[M–H]^-$: 209.0375, Found: 209.0368. Compound previously reported without characterisation data.[252]

1-(4-(Trifluoromethyl)phenyl)cyclobutane-1-carboxylic acid (386) and **(*Z*)-1-(1-(4-(trifluoromethyl)phenyl)cyclobutyl)pent-2-ene-1,4-dione (*(Z)*-387)**



386



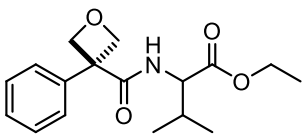
***(Z)*-387**

$NaIO_4$ (460 mg, 2.15 mmol) was added to a solution of cyclobutane furan **351** (86.1 mg, 0.31 mmol) in heptane/EtOAc/H_2O (1.90 mL/ 1.90 mL/ 3.90 mL). The reaction mixture was stirred for 5 min and $RuCl_3$ (1.6 mg, 0.00768 mmol) was added. The reaction mixture was stirred for 18 h at 25 °C. Water (15 mL) was added followed by EtOAc (15 mL) and the layers were separated. The aqueous portion was extracted with EtOAc (2 × 15 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude was dissolved in 5 mL of Et_2O and transferred to a separating funnel. Hexane (5 mL) was added and the organic layer was extracted with aq. NaOH (1 M, 4 × 5 mL). The remaining organic layer was dried over Na_2SO_4, and concentrated under reduced pressure. Purification by flash column chromatography (20% Et_2O/pentane) afforded alkene ***(Z)*-387** (17.3 mg, 19%) as a colourless oil.

The aqueous extracts were combined and acidify to pH ~ 1 with aq. HCl (1 M, ~30 mL). The aqueous portion was extracted with Et_2O (4 × 10 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford cyclobutane acid **386** (41.3 mg, 55 %) as a yellow solid.

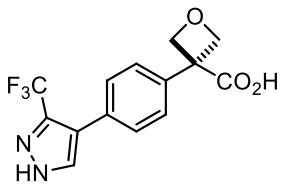
***(Z)*-387**: R_f = 0.23 (20% Et_2O/pentane); IR (film)/cm^{-1} 2948, 1692 (C=O), 1613 (C=O), 1408, 1326, 1162, 1118, 1069, 1017, 846; ^1H NMR (400 MHz, $CDCl_3$) δ 7.65–7.59 (m, 2 H, 2 × Ar-CH), 7.40–7.33 (m, 2 H, 2 × Ar-CH), 6.26 (d, *J* = 12.0 Hz, 1 H, CH=C*H*), 6.17 (d, *J* = 12.0 Hz, 1 H, C*H*=CH), 2.91–2.79 (m, 2 H, CH_2), 2.54–2.41 (m, 2 H, CH_2), 2.28 (s, 3 H, CH_3), 2.12–2.00 (m, 1 H, C*H*H), 2.00–1.85 (m, 1 H, CH*H*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 201.9 (C=O), 199.6 (C=O), 146.2 (Ar-C_q-C_q), 140.7 (*C*H=CH), 129.3 (q, $^2J_{C\text{-}F}$ = 33.6 Hz, Ar-C_q-CF_3), 129.1 (CH=*C*H), 126.9 (2 × Ar-CH), 125.7 (q, $^3J_{C\text{-}F}$ = 4.0 Hz, 2 × Ar-CH), 124.0 (q, $^1J_{C\text{-}F}$ = 272.0 Hz, CF_3), 57.8 (C_q), 30.5 ($CH_2CH_2CH_2$), 29.4 (CH_3), 16.0 ($CH_2CH_2CH_2$); $^{19}F\{^1H\}$ NMR (377 MHz, $CDCl_3$) δ –62.5; HRMS (+APCI) *m*/*z* calcd for $C_{16}H_{16}F_3O_2^+$ $[M+H]^+$: 297.1097, Found: 297.1104.

386: R_f = 0.22 (20% Et_2O/pentane); mp = 75–79 °C, IR (film)/cm^{-1} 2989 (br. COOH), 2852, 1699 (C=O), 1408, 1323, 1162, 1118, 1069, 1017, 834, 719; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63–7.57 (m, 2 H, 2 × Ar-CH), 7.46–7.39 (m, 2 × Ar-CH), 2.94–2.83 (m, 2 H, CH_2), 2.62–2.48 (m, 2 H, CH_2), 2.21–2.07 (m, 1 H, C*H*H), 1.97–1.83 (m, 1 H, CH*H*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 180.8 (CO_2H), 147.1 (Ar-C_q-C_q), 129.3 (q, $^2J_{C\text{-}F}$ = 32.3 Hz, Ar-C_q-CF_3), 126.9 (2 × Ar-CH), 125.3 (q, $^3J_{C\text{-}F}$ = 3.6 Hz, 2 × Ar-CH), 124.3 (q, $^1J_{C\text{-}F}$ = 292 Hz, CF_3), 52.1 (C_q), 32.3 ($CH_2CH_2CH_2$), 16.7 ($CH_2CH_2CH_2$); ^{19}F{^{1}H} NMR (377 MHz, $CDCl_3$) δ –62.5; HRMS (–APCI) *m*/*z* calcd for $C_{12}H_{10}F_3O_2^-$ [M–H]$^-$: 243.0638, Found: 243.0638. The observed characterisation data (^{1}H NMR) was consistent with that previously reported.[258]



Ethyl (3-phenyloxetane-3-carbonyl)valinate (388)

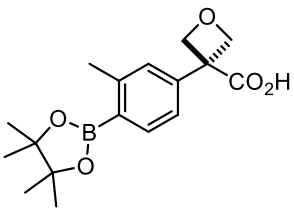
DIPEA (55.7 µL, 0.32 mmol) was added to a solution of racemic valine ethyl ester hydrochloride (21.8 mg, 0.12 mmol), oxetane acid **373** (17.8 mg, 0.10 mmol) and HATU (45.6 mg, 0.12 mmol) in CH_2Cl_2 (1.0 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h and then 20 °C for 23 h. Water (10 mL) was then added followed by CH_2Cl_2 (10 mL) and the layers were separated. The aqueous portion was extracted with CH_2Cl_2 (2 × 10 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography (40% Et_2O/hexane) afforded oxetane amide **388** (28.9 mg, 95%) as a white solid. R_f = 0.19 (50% Et_2O/hexane); mp = 80–82 °C, IR (film)/cm^{-1} 3317 (br, NH), 2963, 2877, 1736 (C=O, ester), 1654 (C=O, amide), 1524, 1464, 1371, 1312, 1255, 1196, 1151, 1025, 997, 943, 760, 700; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50–7.42 (m, 2 H, 2 × Ar-CH), 7.41–7.34 (m, 1 H, Ar-CH), 7.30–7.22 (m, 2 H, 2 × Ar-CH), 5.66 (d, *J* = 8.7 Hz, 1 H, NH), 5.34 (d, *J* = 5.7 Hz, 1 H, C*H*HOCHH), 5.26 (d, *J* = 5.7 Hz, 1 H, CH*H*OCHH), 5.05 (d, *J* = 5.7 Hz, 1 H, CHHOC*H*H), 5.00 (d, *J* = 5.7 Hz, 1 H, CHHOCH*H*), 4.52 (dd, *J* = 8.7, 4.5 Hz, 1 H, NCHC=O), 4.22–4.05 (m, 2 H, C*H*$_2$CH$_3$), 2.09 (hd, *J* = 6.9, 4.5 Hz, 1 H,CH_3CHCH_3), 1.24 (t, *J* = 7.1 Hz, 3 H, CH_2CH_3), 0.80 (d, *J* = 6.9 Hz, 3 H, C*H*$_3$CHCH$_3$), 0.68 (d, *J* = 6.9 Hz, 3 H, CH_3CHCH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.6 (C=O), 171.5 (C=O), 140.1 (Ar-C_q-C_q), 129.3 (2 × Ar-CH), 128.0 (Ar-CH), 126.2 (2 × Ar-CH), 79.5 (CH_2OCH_2), 79.2 (CH_2OCH_2), 61.3 (CH_2CH_3), 57.1 (N*C*HC=O), 53.5 (C_q), 31.1 (CH_3CHCH_3), 18.8 (CH_3CHCH_3), 17.3 (CH_3CHCH_3), 14.1 (CH_2CH_3); HRMS (+ESI) *m*/*z* calcd for $C_{17}H_{24}NO_4$ [M+H]: 306.1705, Found: 306.1700.



3-(4-(3-(Trifluoromethyl)-1*H*-pyrazol-4-yl)phenyl)oxetane-3-carboxylic acid (389)

Triflate acid **370** (32.6 mg, 0.10 mmol), 4-(pinacol ester)phenyl)-3-(trifluoromethyl)-1*H*-pyrazole (34.1 mg, 0.13 mmol), $Pd(PPh_3)_4$

(5.8 mg, 0.005 mmol), and K_2CO_3 (55.3 mg, 0.40 mmol) were added to a reaction vial. The reaction vial was evacuated and then refilled with nitrogen three times. DME/water (8:1, 1.0 mL) was added via syringe. The reaction mixture was stirred at 90 °C for 18 h then cooled to rt. Et_2O (20 mL) was added followed by aq. HCl (1 M, 10 mL) and the phases were separated. The aqueous portion was extracted with EtOAc (2 × 10 mL). The organic extracts were combined, dried over Na_2SO_4, filtered through celite® and concentrated under reduced pressure. Purification by flash column chromatography (20 to 50% acetone/pentane + 1% AcOH) afforded oxetane acid **389** (14.7 mg, 45%, contains 5% of triflate **370**) as a yellow solid. R_f = 0.23 (30% acetone/pentane + 1% AcOH); mp = 209–210 °C; IR (film)/cm^{-1} 3179 (br, NH), 2892 (br, CO_2H), 1703 (C=O), 1476, 1258, 1256, 1200, 1155, 1118, 980, 939, 823; ^{1}H NMR (400 MHz, acetone-d_6) δ 8.13 (d, J = 1.1 Hz, 1 H, N-Ar-CH), 7.54–7.49 (m, 2 H, 2 × Ar-CH), 7.45–7.40 (m, 2 H, 2 × Ar-CH), 5.21 (d, J = 6.2 Hz, 2 H, C*H*HOC*H*H), 4.98 (d, J = 6.2 Hz, 2 H, CH*H*OCH*H*); ^{13}C NMR (101 MHz, acetone-d_6) δ 174.7 (CO_2H), 140.5 (Ar-C_q-C_q), 131.2 (Ar-C_q-$C_{q(pyrazole)}$), 131.0 (N-Ar-CH), 129.6 (2 × Ar-CH), 128.3 (q, $^2J_{C\text{-}F}$ = 33.6 Hz, C_q-CF_3), 127.3 (2 × Ar-CH), 123.2 (q, $^1J_{C\text{-}F}$ = 268.9 Hz, CF_3), 121.4 (Ar-C_q-$C_{q(pyrazole)}$), 79.9 (CH_2OCH_2), 53.7 (C_q); ^{19}F{^{1}H} NMR (377 MHz, $CDCl_3$) δ –59.5; HRMS (–ESI) m/z calcd for $C_{14}H_{10}N_2O_3F_3$ [M–H]: 311.0644, Found: 311.0638.

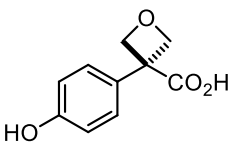


3-(3-Methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)oxetane-3-carboxylic acid (390)

Triflate acid **371** (34.0 mg, 0.10 mmol), Bis(pinacolato)diboron (27.9 mg, 0.11 mmol), Pd(dppf)Cl_2 (7.3 mg, 0.01 mmol), and KOAc (39.3 mg, 0.40 mmol) were added to a reaction vial. The reaction vial was evacuated and then refilled with nitrogen three times. Dioxane (500 µL) was added via syringe. The reaction mixture was stirred at 90 °C for 22 h then cooled to rt. Aq. HCl (1 M, 10 mL) was then added. The aqueous portion was extracted with EtOAc (3 × 10 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography (30% EtOAc/pentane + 0.5% AcOH) afforded oxetane acid **390** (29.0 mg, 91%) as a white solid. R_f = 0.19 (30% EtOAc/pentane + 0.5% AcOH); mp = 182–184 °C; IR (film)/cm^{-1} 2974 (br, CO_2H), 1736 (C=O), 1610, 1375, 1349, 1315, 1271, 1140, 1088, 905, 857, 827, 730, 663; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82–7.75 (m, 1 H, Ar-CH), 7.08–7.01 (m, 2 H, 2 × Ar-CH), 5.26 (d, J = 6.2 Hz, 2 H, C*H*HOC*H*H), 5.04 (d, J = 6.2 Hz, 2 H, CH*H*OCH*H*), 2.55 (s, 3 H, CH_3), 1.34 (s, 12 H, 4 × CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.3 (CO_2H), 145.7 (Ar-C_q-CH_3), 141.1 (Ar-C_q-C_q), 136.4 (Ar-CH), 127.4 (Ar-CH), 122.4 (Ar-CH), 83.6 (2 × OC_q(CH_3)$_2$), 79.3 (CH_2OCH_2), 53.0 (C_q), 24.8 (4 × CH_3), 22.3 (Ar-C_q-

CH_3)*; $^{11}B\{^1H\}$ NMR (128 MHz, $CDCl_3$) δ –31.1; HRMS (–ESI) *m*/*z* calcd for $C_{17}H_{22}O_5{}^{11}B$ [M–H]: 317.1560, Found: 317.1571.

*The quaternary carbon adjacent to boron was not observed.



3-(4-Hydroxyphenyl)oxetane-3-carboxylic acid (391)

A solution of TBAF (1 M in THF, 210 µL, 0.21 mmol) was added dropwise to a solution of **361** (37.1 mg, 0.11 mmol) in THF (1.0 mL) at 0 °C. The reaction mixture was stirred for 10 min at 0 °C and then 6 h at 25 °C. Water (3 mL) and aq. HCl (1 M, 3 mL) were added followed by Et_2O (10 mL). The layers were separated and the aqueous portion was extracted with Et_2O (3 × 10 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude was dissolved in 2 mL of EtOAc and transferred to a separating funnel. Et_2O (5 mL) was added and the organic layer was extracted with aq. NaOH (1 M, 4 × 5 mL). The aqueous extracts were combined and acidified to pH ~ 1 with aq. HCl (1 M, ~30 mL). The aqueous portion was extracted with EtOAc (3 × 15 mL). The organic extracts were combined, dried over Na_2SO_4, and concentrated under reduced pressure to give carboxylic acid **391** (13.5 mg, 70%) as a yellow solid. R_f = 0.20 (20% Acetone/hexane + 1% AcOH); mp = 137–138 °C; IR (film)/cm^{-1} 3250 (br, OH), 2959 (br. COOH), 1703 (C=O), 1591, 1513, 1438, 1364, 1259, 1215, 1162, 1129, 1066, 961, 939, 797, 729; ^1H NMR (400 MHz, acetone-d_6) δ 8.44 (s, br, OH), 7.21–7.13 (s, 2 H, 2 × Ar-CH), 6.89–6.83 (s, 2 H, 2 × Ar-CH), 5.13 (d, *J* = 6.1 Hz, 2 H, C*H*HOC*H*H), 4.89 (d, *J* = 6.1 Hz, 2 H, CH*H*OCH*H*); ^{13}C NMR (101 MHz, acetone-d_6) δ 175.1 (CO_2H), 157.5 (Ar-C_q-OH), 131.9 (Ar-C_q-C_q), 128.2 (2 × Ar-CH), 116.2 (2 × Ar-CH), 80.0 (CH_2OCH_2), 53.2 (C_q); HRMS (–APCI) *m*/*z* calcd for $C_{10}H_9O_4^-$ $[M–H]^-$: 193.0506, Found: 193.0499.

8.2.7 Synthesis of 3-Aryl-3-Alkyl Oxetanes and Azetidines (Part 6.4)

Photoredox apparatus: Photoredox reactions were performed in oven-dried 4 mL vials (product code: 854190, Sigma-Aldrich) which were sealed with screwcaps with PTFE/silicon septa (product code: SU860078, Sigma-Aldrich). Reactions were run in batches of two (Figure 8.1) or four. The vials were attached together using two elastic bands positioned over the screw-caps. Irradiation was provided by two 40 W Kessil PR160 LED lamps with intensity dials set to maximum, and placed at 4 cm away from the centre of the vials. When a fan (Honeywell HT900E) was used, setting III was employed, and the fan was placed at 14 cm away on the front of the vials. The reactions were stirred at 1000 rpm.

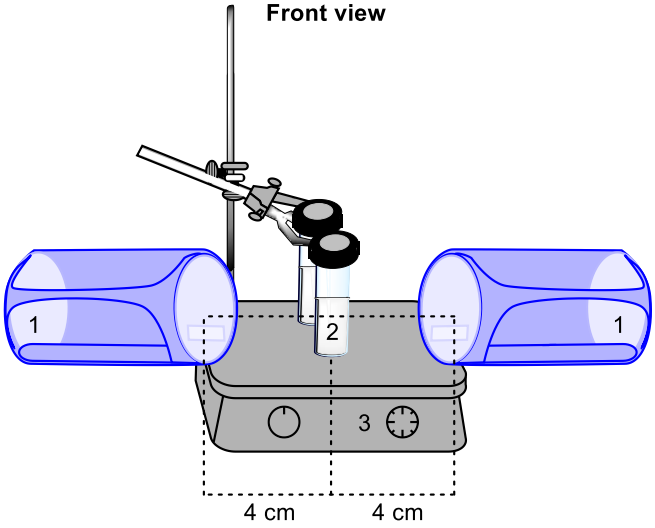
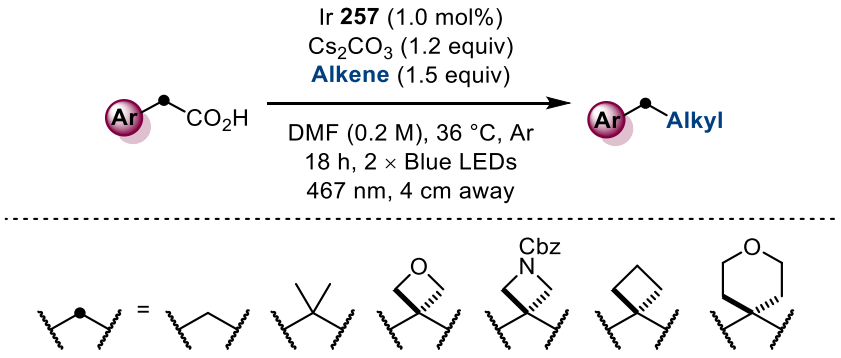


Figure 8.1: Two-vials photoredox set up. 1 = Kessil lamps. 2 = vial. 3 = hot plate. The vials are attached together using two elastic bands positioned over the screw-caps.

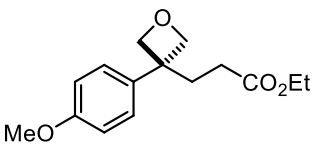
General procedures for photoredox-catalysed reaction:



General procedure 1A: An oven-dried 4 mL vial was charged with: carboxylic acid (0.20 mmol, 1.0 equiv), oven-dried Cs_2CO_3 (78.2 mg, 0.24 mmol, 1.2 equiv), and Ir **257** (2.2 mg, 0.002 mmol, 1.0 mol%). The vial was then sealed with a screwcap equipped with a PTFE/silicon septum. DMF (1.0 mL) was added *via* syringe. Argon was then bubbled through the mixture for 10 min. Liquid alkene (0.30 mmol, 1.5 equiv) was then added *via* syringe under

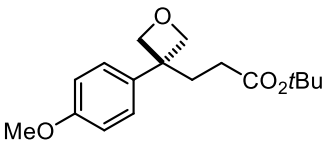
argon. The cap was then sealed with parafilm on top. The reaction mixture was then stirred at 1000 rpm using the set-up shown in Figure 8.1 and irradiated with two 467 nm Kessel lamps at 36 °C (heat generated by the lamps), for 18 h. The lights were then switched off and the reaction mixture was transferred into a separating funnel. Water (10 mL) and Et_2O or EtOAc (10 mL) were added and the layers were separated. The aqueous portion was extracted with Et_2O or EtOAc (2 × 10 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography.

General procedure 1B: An oven-dried 4 mL vial was charged with: carboxylic acid (0.20 mmol, 1.0 equiv), oven-dried Cs_2CO_3 (78.2 mg, 0.24 mmol, 1.2 equiv), Ir **257** (2.2 mg, 0.002 mmol, 1.0 mol%) and solid alkene (0.30 mmol, 1.5 equiv). The vial was then sealed with a screwcap equipped with a PTFE/silicon septum. DMF (1.0 mL) was added *via* syringe. Argon was then bubbled through the mixture for 10 min. The cap was then sealed with parafilm on top. The reaction mixture was then stirred at 1000 rpm using the set-up shown in Figure 8.1, irradiated with two 467 nm Kessel lamps at 36 °C (heat generated by the lamps), for 18 h. The lights were then switched off and the reaction mixture was transferred into a separating funnel. Water (10 mL) and Et_2O or EtOAc (10 mL) were added and the layers were separated. The aqueous portion was extracted with Et_2O or EtOAc (2 × 10 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography.



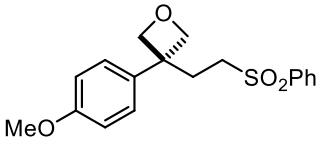
Ethyl 3-(3-(4-methoxyphenyl)oxetan-3-yl)propanoate (396)

Following general procedure **1A**, oxetane acid **314** (41.6 mg, 0.20 mmol) and ethyl acrylate (33 µL, 0.30 mmol) were used. Purification by basic alumina (IV) column chromatography (20% Et_2O/pentane) afforded oxetane **396** (29.9 mg, 57%) as a colourless oil. R_f = 0.33 (30% Et_2O/pentane); IR (film)/cm^{-1} 2935, 2869, 1728 (C=O), 1612, 1580, 1514, 1445, 1375, 1294, 1245, 1178, 1115, 1030, 981, 830, 616, 556; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.99–6.92 (m, 2 H, 2 × Ar-CH), 6.92–6.85 (m, 2 H, 2 × Ar-CH), 4.95 (d, *J* = 5.7 Hz, 2 H, C*H*HOC*H*H), 4.64 (d, *J* = 5.7 Hz, 2 H, CH*H*OCH*H*), 4.06 (q, *J* = 7.1 Hz, 2 H, C*H*$_2$CH$_3$), 3.81 (s, 3 H, OCH$_3$), 2.45–2.35 (m, 2 H, C*H*$_2$CH$_2$), 2.17–2.07 (m, 2 H, CH$_2$C*H*$_2$), 1.22 (t, *J* = 7.1 Hz, 3 H, CH$_2$C*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.1 (C=O), 158.1 (Ar-*C*$_q$-OCH$_3$), 135.9 (Ar-*C*$_q$-C$_q$), 126.8 (2 × Ar-CH), 114.0 (2 × Ar-CH), 81.5 (*C*H$_2$O*C*H$_2$), 60.4 (*C*H$_2$CH$_3$), 55.3 (OCH$_3$), 46.3 (C$_q$), 35.9 (*C*H$_2$CH$_2$), 29.9 (CH$_2$*C*H$_2$), 14.1 (CH$_2$*C*H$_3$); HRMS (+ESI) *m*/*z* calcd for $C_{15}H_{21}O_4^+$ [M+H]$^+$: 265.1434, Found: 265.1434.



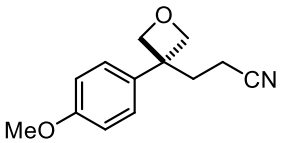
tert-Butyl 3-(3-(4-methoxyphenyl)oxetan-3-yl)propanoate (399)

Following general procedure **1A**, oxetane acid **314** (41.6 mg, 0.20 mmol) and *t*Bu-acrylate (45 µL, 0.30 mmol) were used. Purification by basic alumina (IV) column chromatography (20% Et_2O/pentane) afforded oxetane **399** (31.9 mg, 55%) as a white solid. R_f = 0.35 (30% Et_2O/pentane); mp = 90–91 °C; IR (film)/cm^{-1} 2963, 2933, 2870, 1722 (C=O), 1613, 1513, 1364, 1289, 1244, 1148, 1032, 980, 842, 816; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.98–6.92 (m, 2 H, 2 × Ar-CH), 6.92–6.86 (m, 2 H, 2 × Ar-CH), 4.94 (d, *J* = 5.7 Hz, 2 H, C*H*HOC*H*H), 4.65 (d, *J* = 5.7 Hz, 2 H, CH*H*OCH*H*), 3.81 (s, 3 H, OCH_3), 2.40–2.31 (m, 2 H, CH_2CH$_2$), 2.09–1.99 (m, 2 H, CH$_2$CH_2), 1.41 (s, 9 H, 3 × CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.4 (C=O), 158.1 (Ar-C_q-OCH_3), 136.1 (Ar-C_q-C_q), 126.8 (2 × Ar-CH), 113.9 (2 × Ar-CH), 81.6 (*C*H$_2$O*C*H$_2$), 80.4 (C_q(CH_3)$_3$), 55.3 (OCH_3), 46.2 (C_q), 36.0 (*C*H$_2$CH$_2$), 31.0 (CH$_2$*C*H$_2$), 28.0 (C_q(*C*H$_3$)$_3$); HRMS (+APCI) *m*/*z* calcd for $C_{17}H_{24}NaO_4^+$ [M+Na]$^+$: 315.1567, Found: 315.1553.



3-(4-Methoxyphenyl)-3-(2-(phenylsulfonyl)ethyl)oxetane (400)

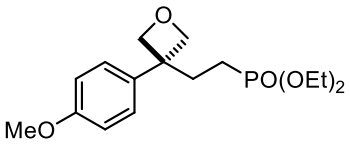
Following general procedure **1B**, oxetane acid **314** (41.6 mg, 0.20 mmol) and phenyl vinyl sulfone (50.5 mg, 0.30 mmol) were used. Purification by basic alumina (IV) column chromatography (2% Et_2O/CH_2Cl_2) afforded oxetane **400** (17.9 mg, 27%) as a colourless oil. R_f = 0.31 (4% Et_2O/CH_2Cl_2); IR (film)/cm^{-1} 2937, 2870, 1610, 1513, 1446, 1304 and 1248 (O=S=O), 1181, 1144, 1088, 1028, 980, 831, 745, 689; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90–7.83 (m, 2 H, 2 × Ar-CH), 7.71–7.63 (m, 1 H, Ar-CH), 7.61–7.54 (m, 2 H, 2 × Ar-CH), 6.87 (s, 4 H, 4 × Ar-CH), 4.92 (d, *J* = 5.9 Hz, 2 H, C*H*HOC*H*H), 4.54 (d, *J* = 5.9 Hz, 2 H, CH*H*OCH*H*), 3.81 (s, 3 H, OCH_3), 2.95–2.84 (m, 2 H, CH_2CH$_2$), 2.50–2.49 (m, 2 H, CH$_2$CH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.4 (Ar-C_q-OCH_3), 134.5 (Ar-C_q-C_q), 133.8 (Ar-CH), 129.4 (2 × Ar-CH), 128.4 (Ar-C_q-SO_2), 128.0 (2 × Ar-CH), 126.6 (2 × Ar-CH), 114.3 (2 × Ar-CH), 81.0 (*C*H$_2$O*C*H$_2$), 55.3 (OCH_3), 52.2 (CH$_2$*C*H$_2$SO$_2$), 45.7 (C_q), 33.3 (*C*H$_2$CH$_2$SO$_2$); HRMS (+ESI) *m*/*z* calcd for $C_{18}H_{21}O_4S$ [M+H]: 333.1161, Found: 333.1162.



3-(3-(4-Methoxyphenyl)oxetan-3-yl)propanenitrile (401)

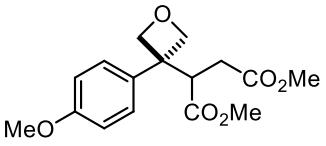
Following general procedure **1A**, oxetane acid **314** (41.6 mg, 0.20 mmol) and acrylonitrile (20 µL, 0.30 mmol) were used. Purification by basic alumina (IV) column chromatography (30% Et_2O/pentane) afforded oxetane **401** (4.8 mg, containing 6% of BHT, 11%) as a colourless oil. R_f = 0.17 (50% Et_2O/pentane); IR (film)/cm^{-1} 2937, 2870, 2233 (CN), 1610, 1513, 1297, 1248, 1181, 1028, 984, 831, 834; ^{1}H NMR

(400 MHz, $CDCl_3$) δ 7.00–6.95 (m, 2 H, 2 × Ar-CH), 6.95–6.90 (m, 2 H, 2 × Ar-CH), 5.00 (d, *J* = 5.9 Hz, 2 H, C*H*HOC*H*H), 4.72 (d, *J* = 5.9 Hz, 2 H, CH*H*OCH*H*), 3.83 (s, 3 H, OCH_3), 2.51–2.39 (m, 2 H, C$H_2$$CH_2$), 2.15–2.05 (m, 2 H, CH_2CH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.6 (Ar-C_q-OCH_3), 134.2 (Ar-C_q-C_q), 126.7 (2 × Ar-CH), 119.1 (CN), 114.4 (2 × Ar-CH), 81.1 (CH_2OCH_2), 55.3 (OCH_3), 46.4 (C_q), 36.2 (CH_2CH_2), 13.0 (CH_2CH_2); HRMS (+EI) *m*/*z* calcd for $C_{13}H_5NO_2^{\bullet+}$ $[M]^{\bullet+}$: 217.1097, Found: 217.1106.



Diethyl (2-(3-(4-methoxyphenyl)oxetan-3-yl)ethyl)phosphonate (402)

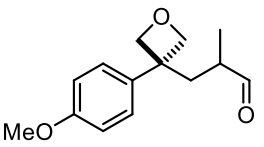
Following general procedure **1A**, oxetane acid **314** (41.6 mg, 0.20 mmol) and diethyl vinylphosphonate (46 µL, 0.30 mmol) were used. Purification by basic alumina (IV) column chromatography (100% EtOAc) afforded oxetane **402** (10.8 mg, 16%) as a colourless oil. R_f = 0.12 (100% EtOAc); IR (film)/cm^{-1} 2981, 2933, 2870, 1613, 1513, 1244 (P=O), 1028, 965, 827; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.96–6.91 (m, 2 H, 2 × Ar-CH), 6.91–6.86 (m, 2 H, 2 × Ar-CH), 4.94 (d, *J* = 5.7 Hz, 2 H, C*H*HOC*H*H), 4.61 (d, *J* = 5.7 Hz, 2 H, CH*H*OCH*H*), 4.11–3.99 (m, 4 H, 2 × C$H_2$$CH_3$), 3.81 (s, 3 H, OCH_3), 2.40–2.26 (m, 2 H, C$H_2$$CH_2$), 1.60–1.45 (m, 2 H, CH_2CH_2), 1.29 (t, *J* = 7.1 Hz, 6 H, 2 × CH_2CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.2 (Ar-C_q-OCH_3), 135.5 (Ar-C_q-C_q), 126.8 (2 × Ar-CH), 114.0 (2 × Ar-CH), 81.2 (CH_2OCH_2), 61.6 (d, $^2J_{C-P}$ = 6.4 Hz, 2 × CH_2CH_3), 55.3 (OCH_3), 46.7 (d, $^3J_{C-P}$ = 18.4 Hz, C_q), 33.6 (d, $^2J_{C-P}$ = 4.0 Hz, CH_2CH_2P), 21.1 (d, $^1J_{C-P}$ = 142.6 Hz, CH_2CH_2P), 16.4 (d, $^3J_{C-P}$ = 5.7 Hz, 2 × CH_2CH_3); ^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$) δ 31.7; HRMS (+ESI) *m*/*z* calcd for $C_{16}H_{26}O_5P$ [M+H]: 329.1518, Found: 329.1523.



Dimethyl 2-(3-(4-methoxyphenyl)oxetan-3-yl)succinate (403)

Following general procedure **1B**, oxetane acid **314** (41.6 mg, 0.20 mmol) and dimethyl fumarate (43.2 mg, 0.30 mmol) were used. Purification by basic alumina (IV) column chromatography (30% Et_2O/pentane) afforded oxetane **403** (33.6 mg, 54%) as a colourless oil. R_f = 0.10 (30% Et_2O/pentane); IR (film)/cm^{-1} 2952, 1733 (C=O), 1613, 1513, 1438, 1248, 1166, 1028, 987, 838; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.92–6.83 (m, 4 H, 4 × Ar-CH), 5.12 (d, *J* = 6.2 Hz, 1 H, C*H*HOCHH), 4.98 (d, *J* = 6.2 Hz, 2 H, CH*H*OCHH), 4.94 (d, *J* = 6.1 Hz, 1 H, CHHOC*H*H), 4.84 (d, *J* = 6.1 Hz, 1 H, CHHOCH*H*), 3.80 (s, 3 H, OCH_3), 3.66 (s, 3 H, CO_2CH_3), 3.65 (s, 3 H, CO_2CH_3), 3.63 (dd, *J* = 11.4, 3.3 Hz, 1 H, C*H*CO_2CH_3), 2.64 (dd, *J* = 16.9, 11.4 Hz, 1 H, CHC*H*H), 2.35 (dd, *J* = 16.9, 3.3 Hz, 1 H, CHCH*H*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.5 (C=O), 172.2 (C=O), 158.5 (Ar-C_q-OCH_3), 133.7 (Ar-C_q-C_q), 127.4 (2 × Ar-CH), 113.9 (2 × Ar-CH),

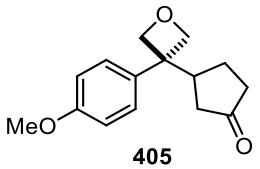
80.4 (CH_2OCH_2), 80.3 (CH_2OCH_2), 55.2 (OCH_3), 51.9 (2 × CO_2CH_3), 49.0 (CH), 48.6 (C_q), 31.9 (CH_2); HRMS (+ESI) *m*/*z* calcd for $C_{16}H_{21}O_6$ [M+H]: 309.1338, Found: 309.1310.



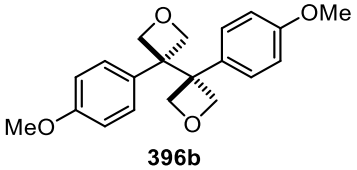
3-(3-(4-Methoxyphenyl)oxetan-3-yl)-2-methylpropanal (404)

Following general procedure **1A**, oxetane acid **314** (41.6 mg, 0.20 mmol) and methacrolein (25 µL, 0.30 mmol) were used. Purification by basic alumina (IV) column chromatography (30% to 70% Et_2O/pentane) afforded oxetane **404** (15.1 mg, 32%) as a colourless oil. R_f = 0.15 (30% Et_2O/pentane); IR (film)/cm^{-1} 2933, 2870, 1722 (C=O), 1610, 1513, 1461, 1297, 1248, 1181, 1028, 984, 834; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.30 (d, *J* = 2.0 Hz, 1 H, HC=O), 7.01–6.95 (m, 2 H, 2 × Ar-CH), 6.92–6.87 (m, 2 H, 2 × Ar-CH), 5.01 (dd, *J* = 5.7, 0.8 Hz, 1 H, C*H*HOCHH), 4.93 (d, *J* = 5.7 Hz, 2 H, CH*H*OCHH), 4.68 (d, *J* = 5.9 Hz, 2 H, CHHOC*H*$_2$), 3.81 (s, 3 H, OCH_3), 2.64–2.53 (m, 1 H, CH_3CH), 2.18–2.06 (m, 2 H, C*H*$_2$CH), 1.03–0.97 (m, 3 H, C*H*$_3$CH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.7 (C=O), 158.3 (Ar-*C*$_q$-OCH_3), 135.8 (Ar-*C*$_q$-C_q), 126.9 (2 × Ar-CH), 114.1 (2 × Ar-CH), 82.6 (*C*H_2OCH_2), 81.7 (CH_2OCH_2), 55.2 (OCH_3), 46.4 (C_q), 43.5 (CH), 42.0 (CH_2), 14.8 (CH_3); HRMS (+ESI) *m*/*z* calcd for $C_{14}H_{19}O_3$ [M+H]: 235.1334, Found: 235.1327.

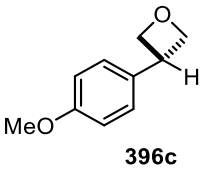
3-(3-(4-Methoxyphenyl)oxetan-3-yl)cyclopentan-1-one (405), 3,3'-bis(4-methoxyphenyl)-3,3'-bioxetane (396b) and **3-(4-methoxyphenyl)oxetane (396c).**



405



396b



396c

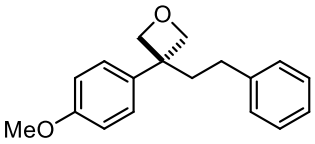
Following general procedure **1A**, oxetane acid **314** (41.6 mg, 0.20 mmol) and 2-cyclopenten-1-one (25 µL, 0.30 mmol) were used. Purification by basic alumina (IV) column chromatography (40% to 60% Et_2O/pentane) afforded oxetane **396c** (2.5 mg, impure, 7%) as a colourless oil, followed by dimer **396b** (3.7 mg, containing 7% BHT, 11%) as a white film, and oxetane **405** (12.4 mg, 25%) as a white solid.

Oxetane **396c**: R_f = 0.53 (40% Et_2O/pentane); IR (film)/cm^{-1} 2933, 2870, 1722 (C=O), 1610, 1513, 1461, 1297, 1248, 1181, 1028, 984, 834; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37–7.31 (m, 2 H, 2 × Ar-CH), 6.95–6.88 (m, 2 H, 2 × Ar-CH), 5.10–5.02 (m, 2 H, C*H*HOC*H*H), 4.80–4.71 (m, 2 H, CH*H*OCH*H*), 4.26–4.13 (m, 1 H, CH), 3.82 (s, 3 H, OCH_3).[x] The observed characterisation data (^{1}H NMR) was consistent with that previously reported.[259]

[x] Signals in ^{13}C NMR are too low due to the small amount of product in the sample.

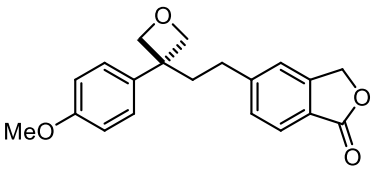
Dimer **396b:** R_f = 0.47 (60% Et_2O/pentane); IR (film)/cm^{-1} 2948, 2881, 1613, 1513, 1297, 1248, 1181, 1032, 991, 831; ^1H NMR (400 MHz, $CDCl_3$) δ 6.68 (d, *J* = 8.0 Hz, 4 H, 4 × Ar-CH), 6.38 (d, *J* = 8.0 Hz, 4 H, 4 × Ar-CH), 5.30 (d, *J* = 6.3 Hz, 4 H, 2 × C*H*HOC*H*H), 5.07 (d, *J* = 6.3 Hz, 4 H, 2 × CH*H*OCH*H*), 3.78 (s, 6 H, 2 × OCH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.1 (2 × Ar-C_q-OCH_3), 134.9 (2 × Ar-C_q-C_q), 128.3 (4 × Ar-CH), 112.9 (4 × Ar-CH), 79.6 (2 × CH_2OCH_2), 55.2 (2 × OCH_3), 50.9 (2 × C_q); HRMS (+APCI) *m*/*z* calcd for $C_{20}H_{23}O_4^+$ $[M+H]^+$: 327.1591, Found: 327.1603.

Oxetane **405**: R_f = 0.20 (60% Et_2O/pentane); IR (film)/cm^{-1} 2955, 2873, 1740 (C=O), 1616, 1513, 1297, 1248, 1181, 1028, 984, 834; ^1H NMR (400 MHz, $CDCl_3$) δ 6.94–6.81 (m, 4 H, 4 × Ar-CH), 5.01 (ddd, *J* = 8.6, 6.1, 1.5 Hz, 1 H, C*H*HOC*H*H), 4.73 (dd, *J* = 12.5, 6.1 Hz, 2 H, CH*H*OCH*H*), 3.82 (s, 3 H, OCH_3), 2.91 (tt, *J* = 11.3, 6.3 Hz, 1 H, CH), 2.37 (dd, *J* = 18.2, 7.4 Hz, 1 H, CHC*H*HCO), 2.29–1.96 (m, 4 H, C*H*HCH$_2$CO, CH$_2$C*H*$_2$CO, CHCH*H*CO), 1.70–1.53 (m, 1 H, CH*H*CH$_2$CO); ^{13}C NMR (101 MHz, $CDCl_3$) δ 217.7 (C=O), 158.3 (Ar-C_q-OCH_3), 134.8 (Ar-C_q-C_q), 127.5 (2 × Ar-CH), 113.8 (2 × Ar-CH), 80.4 (CH_2OCH_2), 80.0 (CH_2OCH_2), 55.3 (OCH_3), 48.6 (C_q), 45.4 (CH), 40.4 (CHCH_2CO), 38.4 (CH_2CH_2CO), 24.2 (CH_2CH_2CO); HRMS (+APCI) *m*/*z* calcd for $C_{15}H_{19}O_3^+$ $[M+H]^+$: 247.1329, Found: 247.1329.



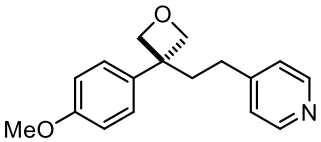
3-(4-Methoxyphenyl)-3-phenethyloxetane (406)

Following general procedure **1A**, oxetane acid **314** (41.6 mg, 0.20 mmol) and styrene (35 µL, 0.30 mmol) were used. Purification by basic alumina (IV) column chromatography (10% to 70% Et_2O/pentane) afforded oxetane **406** (18.6 mg, 35%, containing 9% of **396c**) as a colourless oil. R_f = 0.21 (10% Et_2O/pentane); IR (film)/cm^{-1} 2931, 2866, 1611, 1513, 1453, 1295, 1244, 1178, 1031, 980, 829, 748, 699, 640; ^1H NMR (400 MHz, $CDCl_3$) δ 7.31–7.23 (m, 2 H, 2 × Ar-CH), 7.21–7.15 (m, 1 H, Ar-CH), 7.15–7.10 (m, 2 H, 2 × Ar-CH), 7.07–7.01 (m, 2 H, 2 × Ar-CH), 6.96–6.90 (m, 2 H, 2 × Ar-CH), 4.98 (d, *J* = 5.5 Hz, 2 H, C*H*HOC*H*H), 4.68 (d, *J* = 5.5 Hz, 2 H, CH*H*OCH*H*), 3.85 (s, 3 H, OCH_3), 2.47–2.34 (m, 4 H, 2 × CH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.0 (Ar-C_q-OCH_3), 141.9 (Ar-C_q-CH_2), 136.7 (Ar-C_q-C_q), 128.4 (2 × Ar-CH), 128.3 (2 × Ar-CH), 126.8 (2 × Ar-CH), 125.9 (Ar-CH), 113.9 (2 × Ar-CH), 81.9 (CH_2OCH_2), 55.3 (OCH_3), 46.9 (C_q), 43.1 (CH_2), 30.9 (CH_2); HRMS (+APCI) *m*/*z* calcd for $C_{17}H_{18}O^{\bullet+}$ $[M-OCH_3+H]^{\bullet+}$: 238.1352, Found: 238.1358.



5-(2-(3-(4-methoxyphenyl)oxetan-3-yl)ethyl)isobenzofuran-1(3*H*)-one (407)

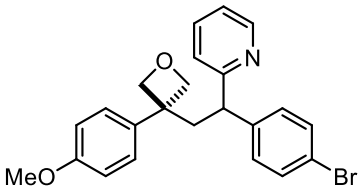
Following general procedure **1B**, oxetane acid **314** (41.6 mg, 0.20 mmol) and 5-vinylisobenzofuran-1(3*H*)-one[y] (48.1 mg, 0.30 mmol) were used. Purification by basic alumina (IV) column chromatography (20% to 70% Et_2O/pentane) afforded oxetane **407** (39.1 mg, 60%) as a white solid. R_f = 0.14 (70% Et_2O/pentane); mp = 148–149 °C; IR (film)/cm^{-1} 2922, 2855, 1751 (C=O), 1613, 1513, 1453, 1356, 1293, 1244, 1181, 1118, 1036, 1002, 831, 775, 730; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (dd, *J* = 7.9, 0.7 Hz, 1 H, Ar-CH), 7.31–7.24 (m, 1 H, Ar-CH), 7.22 (dd, *J* = 1.6, 0.7 Hz, 1 H, Ar-CH), 7.04–6.98 (m, 2 H, 2 × Ar-CH), 6.96–6.90 (m, 2 H, 2 × Ar-CH), 5.26 (s, 2 H, C*H*$_2$OCO), 5.00 (d, *J* = 5.7 Hz, 2 H, C*H*HOC*H*H), 4.67 (d, *J* = 5.7 Hz, 2 H, CH*H*OCH*H*), 3.84 (s, 3 H, OCH_3), 2.60–2.50 (m, 2 H, C*H*$_2$CH$_2$), 2.45–2.36 (m, 2 H, CH$_2$C*H*$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.0 (C=O), 158.2 (Ar-*C*$_q$-OCH_3), 149.1 (Ar-*C*$_q$-CO), 147.1 (Ar-*C*$_q$-CH_2O), 136.1 (Ar-*C*$_q$-C_q), 129.5 (Ar-CH), 126.7 (2 × Ar-CH), 125.7 (Ar-CH), 123.7 (Ar-*C*$_q$-CH_2), 121.7 (Ar-CH), 114.0 (2 × Ar-CH), 81.6 (*C*H$_2$O*C*H$_2$), 55.3 (OCH_3), 46.9 (C_q), 43.0 (CH_2), 31.4 (CH_2); HRMS (+ESI) *m*/*z* calcd for $C_{22}H_{24}NO_4$ [M+MeCN+H]: 366.1705, Found: 366.1710.



4-(2-(3-(4-Methoxyphenyl)oxetan-3-yl)ethyl)pyridine (408)

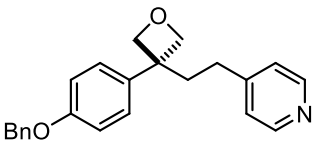
Following general procedure **1A**, oxetane acid **314** (41.6 mg, 0.20 mmol) and 4-vinylpyridine (35 µL, 0.30 mmol) were used. Purification by basic alumina (IV) column chromatography (60% Et_2O/pentane) afforded oxetane **408** (29.5 mg, 55%) as a yellow oil. R_f = 0.03 (60% Et_2O/pentane); IR (film)/cm^{-1} 2869, 1601, 1513, 1462, 1416, 1297, 1245, 1179, 1029, 979, 829; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50–8.42 (m, 2 H, 2 × Ar$_{(pyridine)}$-CH), 7.07–7.03 (m, 2 H, 2 × Ar$_{(pyridine)}$-CH), 7.03–6.98 (m, 2 H, 2 × Ar-CH), 6.96–6.90 (m, 2 H, 2 × Ar-CH), 5.00 (d, *J* = 5.7 Hz, 2 H, C*H*HOC*H*H), 4.67 (d, *J* = 5.7 Hz, 2 H, CH*H*OCH*H*), 3.84 (s, 3 H, OCH_3), 2.46–2.32 (m, 4 H, 2 × CH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.2 (Ar-*C*$_q$-OCH_3), 150.8 (Ar$_{(pyridine)}$-*C*$_q$-CH_2), 149.6 (2 × Ar$_{(pyridine)}$-CH), 136.0 (Ar-*C*$_q$-C_q), 126.7 (2 × Ar-CH), 123.7 (2 × Ar$_{(pyridine)}$-CH), 114.0 (2 × Ar-CH), 81.6 (*C*H$_2$O*C*H$_2$), 55.3 (OCH_3), 46.8 (C_q), 41.8 (CH_2), 30.3 (CH_2); HRMS (+ESI) *m*/*z* calcd for $C_{17}H_{20}NO_2^+$ [M+H]$^+$: 270.1489, Found: 270.1486.

[y] Provided by Pfizer



2-(1-(4-Bromophenyl)-2-(3-(4-methoxyphenyl)oxetan-3-yl)ethyl)pyridine (409)

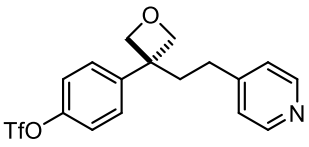
Following general procedure **1B**, oxetane acid **314** (41.6 mg, 0.20 mmol) and 2-(1-(4-bromophenyl)vinyl)pyridine[z] (78.0 mg, 0.30 mmol) were used. Purification by basic alumina (IV) column chromatography (60% Et_2O/pentane) afforded oxetane **409** (44.3 mg, 53%) as a colourless paste. R_f = 0.03 (70% Et_2O/pentane); IR (film)/cm^{-1} 2933, 2870, 1610, 1513, 1487, 1248, 1181, 1073, 1028, 984, 831, 723; ^1H NMR (400 MHz, $CDCl_3$) δ 8.42 (dd, *J* = 4.8, 1.6 Hz, 1 H, $Ar_{(pyridine)}$-CH), 8.36 (d, *J* = 2.2 Hz, 1 H, $Ar_{(pyridine)}$-CH), 7.49–7.41 (m, 1 H, $Ar_{(pyridine)}$-CH), 7.41–7.36 (m, 2 H, 2 × $Ar_{(p\text{-}Br)}$-CH), 7.17 (ddd, *J* = 7.9, 4.8, 0.8 Hz, 1 H, $Ar_{(pyridine)}$-CH), 7.07–6.99 (m, 2 H, 2 × $Ar_{(p\text{-}Br)}$-CH), 6.99–6.94 (m, 2 H, 2 × Ar-CH), 6.94–6.88 (m, 2 H, 2 × Ar-CH), 4.72 (dd, *J* = 5.9, 4.1 Hz, 2 H, C*H*HOC*H*H), 4.38 (dd, *J* = 5.9, 1.8 Hz, 2 H, CH*H*OCH*H*), 3.84 (s, 3 H, OCH_3), 3.60 (dd, *J* = 7.5, 7.0 Hz, 1 H, CH), 2.95 (dd, *J* = 13.9, 7.5 Hz, 1 H, C*H*H), 2.86 (dd, *J* = 13.9, 7.0 Hz, 1 H, CH*H*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.2 (Ar-C_q-OCH_3), 149.4 ($Ar_{(pyridine)}$-CH), 148.0 ($Ar_{(pyridine)}$-CH), 142.3 ($Ar_{(pyridine)}$-C_q-CH), 139.3 ($Ar_{(p\text{-}Br)}$-C_q-CH), 135.7 (Ar-C_q-C_q), 134.9 ($Ar_{(pyridine)}$-CH), 131.8 (2 × $Ar_{(p\text{-}Br)}$-CH), 129.5 (2 × $Ar_{(p\text{-}Br)}$-CH), 127.0 (2 × Ar-CH), 123.5 ($Ar_{(pyridine)}$-CH), 120.6 (Ar-C_q-Br), 114.2 (2 × Ar-CH), 81.9 (CH_2OCH_2), 81.5 (CH_2OCH_2), 55.3 (OCH_3), 47.0 (C_q), 45.8 (CH_2), 44.9 (CH); HRMS (+ESI) *m*/*z* calcd for $C_{23}H_{23}NO_2{}^{79}Br$ [M+H]: 424.0912, Found: 424.0904.



4-(2-(3-(4-(Benzyloxy)phenyl)oxetan-3-yl)ethyl)pyridine (410)

Following general procedure **1A**, oxetane acid **362** (56.9 mg, 0.20 mmol) and 4-vinylpyridine (35 µL, 0.30 mmol) were used. Purification by basic alumina (IV) column chromatography (50% Et_2O/pentane) afforded oxetane **410** (42.5 mg, 62%) as a yellow solid. R_f = 0.10 (70% Et_2O/pentane); mp = 106–108 °C; IR (film)/cm^{-1} 2929, 2858, 1595, 1513, 1453, 1412, 1244, 1185, 1118, 1021, 980, 820, 797, 741; ^1H NMR (400 MHz, $CDCl_3$) δ 8.52–8.40 (m, 2 H, 2 × $Ar_{(pyridine)}$-CH), 7.51–7.32 (m, 5 H, 5 × Ph-CH), 7.09–7.03 (m, 2 H, 2 × $Ar_{(pyridine)}$-CH), 7.01 (s, 4 H, 4 × Ar-CH), 5.09 (s, 2 H, CH_2Ph), 4.99 (d, *J* = 5.7 Hz, 2 H, C*H*HOC*H*H), 4.67 (d, *J* = 5.7 Hz, 2 H, CH*H*OCH*H*), 2.47–2.34 (m, 4 H, 2 × CH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.4 (Ar-C_q-OBn), 150.6 ($Ar_{(pyridine)}$-C_q-CH_2), 149.8 (2 × $Ar_{(pyridine)}$-CH), 136.9 (Ar-C_q-CH_2), 136.4 (Ar-C_q-C_q), 128.6 (2 × Ph-CH), 128.0 (Ph-CH), 127.5 (2 × Ph-CH), 126.8 (2 × Ar-CH), 123.7 (2 × $Ar_{(pyridine)}$-CH), 115.0 (2 × Ar-CH), 81.6 (CH_2OCH_2), 70.1 (CH_2Ph), 46.9 (C_q), 41.8 (CH_2), 30.3 (CH_2); HRMS (+ESI) *m*/*z* calcd for $C_{23}H_{24}NO_2$ [M+H]: 346.1807, Found: 346.1813.

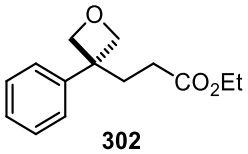
[z] Provided by Pfizer



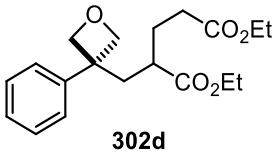
4-(3-(2-(pyridin-4-yl)ethyl)oxetan-3-yl)phenyl trifluoromethanesulfonate (411)

Following general procedure **1A**, oxetane acid **370** (65.2 mg, 0.20 mmol) and 4-vinylpyridine (35 µL, 0.30 mmol) were used. Purification by basic alumina (IV) column chromatography (50% Et_2O/pentane) afforded oxetane **411** (6.6 mg, 70% pure, 9%) as a colourless oil. R_f = 0.08 (100% Et_2O); IR (film)/cm^{-1} 2944, 2873, 1602, 1505, 1423, 1215, 1140, 890; ^1H NMR (400 MHz, $CDCl_3$) δ 8.50–8.47 (m, 2 H, 2 × $Ar_{(pyridine)}$-CH), 7.35–7.29 (m, 2 H, 2 × Ar-CH), 7.20–7.15 (m, 2 H, 2 × Ar-CH), 7.07–7.03 (m, 2 H, 2 × $Ar_{(pyridine)}$-CH), 4.99 (d, *J* = 5.9 Hz, 2 H, C*H*HOC*H*H), 4.72 (d, *J* = 5.9 Hz, 2 H, CH*H*OCH*H*), 2.45–2.40 (m, 4 H, 2 × CH_2); ^{13}C NMR (101 MHz, $CDCl_3$)[aa] δ 149.94 ($Ar_{(pyridine)}$-C_q-CH_2), 149.86 (2 × $Ar_{(pyridine)}$-CH), 148.1 (Ar-C_q-OTf), 144.7 (Ar-C_q-C_q), 127.6 (2 × Ar-CH), 123.6 (2 × $Ar_{(pyridine)}$-CH), 121.7 (2 × Ar-CH), 81.1 (CH_2OCH_2), 47.3 (C_q), 41.5 (CH_2), 30.2 (CH_2); $^{19}F\{^1H\}$ NMR (377 MHz, $CDCl_3$) δ –72.8; HRMS (+APCI) *m*/*z* calcd for $C_{17}H_{17}NO_4SF_3^+$ $[M+H]^+$: 388.0825, Found: 388.0818.

Ethyl 3-(3-phenyloxetan-3-yl)propanoate (302) and **diethyl 2-((3-phenyloxetan-3-yl)methyl)pentanedioate (302d)**



302



302d

Following general procedure **1A**, oxetane acid **373** (35.6 mg, 0.20 mmol) and ethyl acrylate (33 µL, 0.30 mmol) were used. Purification by basic alumina (IV) column chromatography (20% Et_2O/pentane) afforded oxetane **302** (17.2 mg, 37%) as a colourless oil, followed by oxetane **302d** (5.3 mg, 8%) as a colourless oil.

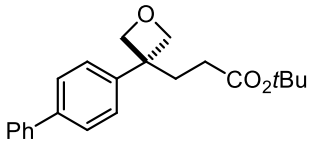
Oxetane **302**: R_f = 0.38 (30% Et_2O/pentane); IR (film)/cm^{-1} 2937, 2870, 1729 (C=O), 1446, 1293, 1177, 1073, 1028, 980, 920, 760, 700; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40–7.32 (m, 2 H, 2 × Ar-CH), 7.29–7.22 (m, 1 H, Ar-CH), 7.05–7.00 (m, 2 H, 2 × Ar-CH), 5.00 (d, *J* = 5.7 Hz, 2 H, C*H*HOC*H*H), 4.67 (d, *J* = 5.7 Hz, 2 H, CH*H*OCH*H*), 4.06 (q, *J* = 7.1 Hz, 2 H, C*H*$_2$CH$_3$), 2.49–2.38 (m, 2 H, C*H*$_2$CH$_2$), 2.19–2.09 (m, 2 H, CH$_2$C*H*$_2$), 1.22 (t, *J* = 7.1 Hz, 3 H, CH$_2$C*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.0 (C=O), 143.8 (Ar-C_q-C_q), 128.6 (2 × Ar-CH), 126.6 (Ar-CH), 125.7 (2 × Ar-CH), 81.4 (CH_2OCH_2), 60.5 (CH_2CH_3), 46.8 (C_q), 35.9 (CH_2CH_2), 29.8

[aa] CF_3 signal not observed

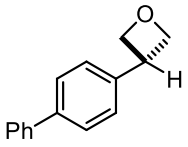
(CH_2CH_2), 14.1 (CH_2CH_3); HRMS (+ESI) *m*/*z* calcd for $C_{14}H_{19}O_3$ [M+H]: 235.1334, Found: 235.1340.

Oxetane **302d**: R_f = 0.24 (30% Et_2O/pentane); IR (film)/cm^{-1} 2978, 2937, 2870, 1729 (C=O), 1446, 1379, 1252, 1159, 1028, 984, 764, 704; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39–7.31 (m, 2 H, 2 × Ar-CH), 7.27–7.22 (m, 1 H, Ar-CH), 7.09–7.02 (m, 2 H, 2 × Ar-CH), 5.00 (d, *J* = 5.5 Hz, 1 H, C*H*HOCHH), 4.93 (d, *J* = 5.7 Hz, 1 H, CHHOC*H*H), 4.93 (m, 2 H, CH*H*OCH*H*), 4.08 (q, *J* = 7.2 Hz, 2 H, CH_2CH$_3$), 3.96–3.77 (m, 2 H, CH_2CH$_3$), 2.66 (dd, *J* = 14.6, 10.3 Hz, 1 H, C_qC*H*HCH), 2.25–2.09 (m, 4 H, C_qCH*H*CH, CH, CHCH_2CH$_2$), 1.92–1.78 (m, 1 H, CH_2C*H*HCO$_2$), 1.75–1.63 (m, 1 H, CH_2CH*H*CO$_2$), 1.21 (t, *J* = 7.2 Hz, 3 H, CH_2CH_3), 1.17 (t, *J* = 7.2 Hz, 3 H, CH_2CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.0 (C=O), 172.6 (C=O), 143.7 (Ar-C_q-C_q), 128.4 (2 × Ar-CH), 126.6 (Ar-CH), 126.0 (2 × Ar-CH), 82.0 (*C*H_2OCH$_2$), 81.6 (CH_2O*C*H$_2$), 60.5 (*C*H_2CH$_3$), 60.4 (*C*H_2CH$_3$), 47.1 (C_q), 43.2 (C_q*C*H_2CH), 41.3 (CH), 31.6 (CH*C*H_2CH$_2$), 28.7 (CH_2*C*H_2CO$_2$), 14.2 (CH_2*C*H$_3$), 14.0 (CH_2*C*H$_3$); HRMS (+APCI) *m*/*z* calcd for $C_{19}H_{27}O_5^+$ $[M+H]^+$: 335.1853, Found: 335.1846.

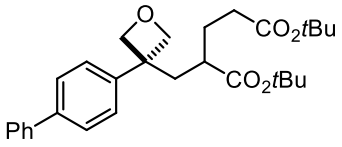
***tert*-Butyl 3-(3-([1,1'-biphenyl]-4-yl)oxetan-3-yl)propanoate (412), 3-([1,1'-biphenyl]-4-yl)oxetane (412c)** and **di-*tert*-butyl 2-((3-([1,1'-biphenyl]-4-yl)oxetan-3-yl)methyl)pentanedioate (412d)**



412



412c



412d

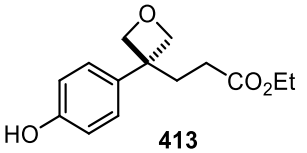
Following general procedure **1A**, oxetane acid **375** (50.9 mg, 0.20 mmol) and *t*Bu-acrylate (45 µL, 0.30 mmol) were used. Purification by basic alumina (IV) column chromatography (10% to 20% Et_2O/pentane) afforded oxetane **412c** (13.5 mg, 32%) as a white solid, followed by oxetane **412** (16.5 mg, 24%) as a white solid and oxetane **412d** (4.2 mg, 5%) as a colourless oil.

Oxetane **412c**: R_f = 0.41 (20% Et_2O/pentane); mp = 65–67 °C; IR (film)/cm^{-1} 2952, 2870, 1487, 1006, 976, 913, 838, 767, 726, 693; ^1H NMR (400 MHz, $CDCl_3$) δ 7.68–7.57 (m, 4 H, 4 × Ar-CH), 7.54–7.42 (m, 4 H, 4 × Ar-CH), 7.42–7.33 (m, 1 H, Ar-CH), 5.13 (dd, *J* = 8.5, 6.0 Hz, 2 H, C*H*HOC*H*H), 4.84 (dd, *J* = 6.8, 6.0 Hz, 2 H, CH*H*OCH*H*), 4.30 (tt, *J* = 8.5, 6.8, 1 H, CH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.7 (Ar-C_q), 140.5 (Ar-C_q), 140.0 (Ar-C_q), 128.8 (2 × Ar-CH), 127.4 (2 × Ar-CH), 127.3 (Ar-CH), 127.2 (2 × Ar-CH), 127.0 (2 × Ar-CH), 78.9 (*C*H_2O*C*H$_2$), 40.0 (CH). The observed characterisation data (^1H, ^{13}C NMR) was consistent with that previously reported.[260]

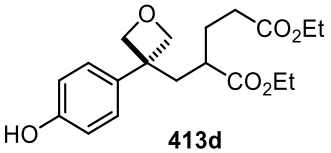
Oxetane **412**: R_f = 0.28 (20% Et_2O/pentane); mp = 97–98 °C; IR (film)/cm^{-1} 2933, 2870, 1725 (C=O), 1487, 1367, 1151, 984, 842, 767, 734, 700; ^1H NMR (400 MHz, $CDCl_3$) δ 7.65–7.54 (m, 4 H, 4 × Ar-CH), 7.50–7.41 (m, 2 H, 2 × Ar-CH), 7.40–7.33 (m, 1 H, Ar-CH), 7.15–7.08 (m, 2 H, 2 × Ar-CH), 5.02 (d, *J* = 5.7 Hz, 2 H, C*H*HOC*H*H), 4.71 (d, *J* = 5.7 Hz, 2 H, CH*H*OCH*H*), 2.49–2.37 (m, 2 H, C$H_2$$CH_2$), 2.17–2.05 (m, 2 H, CH_2CH_2), 1.41 (s, 9 H, 3 × CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.4 (C=O), 143.0 (Ar-C_q), 140.6 (Ar-C_q), 139.5 (Ar-C_q), 128.8 (2 × Ar-CH), 127.31 (Ar-CH), 127.28 (2 × Ar-CH), 127.0 (2 × Ar-CH), 126.2 (2 × Ar-CH), 81.5 (CH_2OCH_2), 80.5 ($C_q(CH_3)_3$), 46.7 (C_q), 35.9 (CH_2CH_2), 31.0 (CH_2CH_2), 28.0 ($C_q(CH_3)_3$); HRMS (+ESI) *m*/*z* calcd for $C_{24}H_{29}NO_3Na^+$ $[M+MeCN+Na]^+$: 402.2045, Found: 402.2024.

Oxetane **412d**: R_f = 0.19 (20% Et_2O/pentane); IR (film)/cm^{-1} 2974, 2933, 2870, 1725 (C=O), 1367, 1256, 1148, 987, 842, 767, 700; ^1H NMR (400 MHz, $CDCl_3$) δ 7.63–7.54 (m, 4 H, 4 × Ar-CH), 7.50–7.41 (m, 2 H, 2 × Ar-CH), 7.40–7.32 (m, 1 H, Ar-CH), 7.21–7.12 (m, 2 H, 2 × Ar-CH), 4.99 (dd, *J* = 5.7, 1.9 Hz, 2 H, C*H*HOC*H*H), 4.75 (d, *J* = 5.7 Hz, 1 H, CH*H*OCHH), 4.71 (d, *J* = 5.7 Hz, 1 H, CHHOCH*H*), 2.70 (dd, *J* = 14.5, 10.1 Hz, 1 H, C_qC*H*HCH), 2.22–1.99 (m, 4 H, C_qCH*H*CH, CH, CHC$H_2$$CH_2$), 1.88–1.75 (m, 1 H, CH_2C*H*HCO_2), 1.69–1.61 (m, 1 H, CH_2CH*H*CO_2), 1.38 (s, 9 H, 3 × CH_3), 1.36 (s, 9 H, 3 × CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.6 (C=O), 172.0 (C=O), 143.2 (Ar-C_q), 140.7 (Ar-C_q), 139.5 (Ar-C_q), 128.8 (2 × Ar-CH), 127.3 (4 × Ar-CH), 127.0 (Ar-CH), 126.5 (2 × Ar-CH), 82.6 (CH_2OCH_2), 81.4 (CH_2OCH_2), 80.7 ($C_q(CH_3)_3$), 80.3 ($C_q(CH_3)_3$), 47.0 (C_q), 43.2 (C_qCH_2CH), 42.1 (CH), 32.9 ($CHCH_2CH_2$), 29.4 ($CH_2CH_2CO_2$), 28.0 ($C_q(CH_3)_3$), 27.9 ($C_q(CH_3)_3$); HRMS (+ESI) *m*/*z* calcd for $C_{29}H_{38}O_5Na$ [M+Na]: 489.2617, Found: 489.2618.

Ethyl 3-(3-(4-hydroxyphenyl)oxetan-3-yl)propanoate (413) and **diethyl 2-((3-(4-hydroxyphenyl)oxetan-3-yl)methyl)pentanedioate (413d)**



413



413d

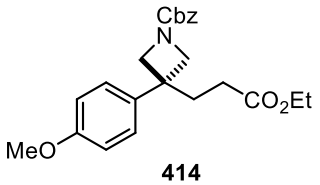
Following general procedure **1A**, TIPS-protected-oxetane acid **361** (70.1 mg, 0.20 mmol) and ethyl acrylate (33 µL, 0.30 mmol) were used. Purification by basic alumina (IV) column chromatography (30% to 50% Et_2O/pentane) afforded oxetane **413** (11.1 mg, 22%) as a colourless oil, followed by oxetane **413d** (3.6 mg, 5%) as a colourless oil.

Oxetane **413**: R_f = 0.29 (50% Et_2O/pentane); IR (film)/cm^{-1} 3306 (br, OH), 2959, 2877, 1729 (C=O), 1613, 1517, 1446, 1375, 1267, 1226, 1177, 980, 834; ^1H NMR (400 MHz, $CDCl_3$) δ 6.91–6.84 (m, 2 H, 2 × Ar-CH), 6.83–6.76 (m, 2 H, 2 × Ar-CH), 5.75 (s, 1 H, OH), 4.96 (d,

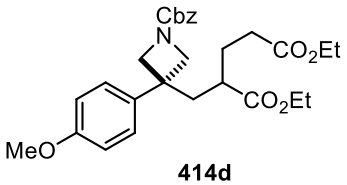
J = 5.7 Hz, 2 H, C*H*HOC*H*H), 4.66 (d, *J* = 5.7 Hz, 2 H, CH*H*OCH*H*), 4.07 (q, *J* = 7.2 Hz, 2 H, C*H*$_2$CH$_3$), 2.45–2.35 (m, 2 H, C*H*$_2$CH$_2$), 2.19–2.08 (m, 2 H, CH$_2$C*H*$_2$), 1.22 (t, *J* = 7.2 Hz, 3 H, CH$_2$C*H*$_3$); ^{13}C NMR (101 MHz, CDCl$_3$) δ 173.3 (C=O), 154.4 (Ar-C$_q$-OH), 135.5 (Ar-*C*$_q$-C$_q$), 127.0 (2 × Ar-CH), 115.4 (2 × Ar-CH), 81.7 (*C*H$_2$O*C*H$_2$), 60.6 (*C*H$_2$CH$_3$), 46.2 (C$_q$), 35.9 (*C*H$_2$CH$_2$), 29.9 (CH$_2$*C*H$_2$), 14.1 (CH$_2$*C*H$_3$); HRMS (+APCI) *m*/*z* calcd for C$_{14}$H$_{19}$O$_6^+$ [M+H]$^+$: 251.1278, Found: 251.1281.

Oxetane **413d**: R$_f$ = 0.18 (50% Et$_2$O/pentane); IR (film)/cm^{-1} 3377 (br, OH), 2959, 2873, 1729 (C=O), 1520, 1267, 1222, 1177, 834; ^{1}H NMR (400 MHz, CDCl$_3$) δ 6.95–6.77 (m, 2 H, 2 × Ar-CH), 6.82–6.77 (m, 2 H, 2 × Ar-CH), 5.10 (s, 1 H, OH), 4.95 (d, *J* = 5.7 Hz, 1 H, C*H*HOCHH), 4.88 (d, *J* = 5.7 Hz, 1 H, CH*H*OCHH), 4.63 (d, *J* = 5.7 Hz, 2 H, CHHOC*H*$_2$), 4.09 (q, *J* = 7.2 Hz, 2 H, C*H*$_2$CH$_3$), 3.98–3.81 (m, 2 H, C*H*$_2$CH$_3$), 2.62 (dd, *J* = 14.2, 10.3 Hz, 1 H, C$_q$C*H*HCH), 2.26–2.07 (m, 4 H, C$_q$CH*H*CH, CH, CHC*H*$_2$CH$_2$), 1.92–1.78 (m, 1 H, CH$_2$C*H*HCO$_2$), 1.77–1.65 (m, 1 H, CH$_2$CH*H*CO$_2$), 1.22 (t, *J* = 7.2 Hz, 3 H, CH$_2$C*H*$_3$), 1.19 (t, *J* = 7.2 Hz, 3 H, CH$_2$C*H*$_3$); ^{13}C NMR (101 MHz, CDCl$_3$) δ 175.0 (C=O), 172.7 (C=O), 154.2 (Ar-C$_q$-OH), 135.8 (Ar-*C*$_q$-C$_q$), 127.3 (2 × Ar-CH), 115.3 (2 × Ar-CH), 82.1 (*C*H$_2$OCH$_2$), 81.8 (CH$_2$O*C*H$_2$), 60.54 (*C*H$_2$CH$_3$), 60.48 (*C*H$_2$CH$_3$), 46.5 (C$_q$), 43.3 (C$_q$*C*H$_2$CH), 41.4 (CH), 31.7 (CH*C*H$_2$CH$_2$), 28.7 (CH$_2$*C*H$_2$CO$_2$), 14.1 (CH$_2$*C*H$_3$), 14.0 (CH$_2$*C*H$_3$); HRMS (+APCI) *m*/*z* calcd. for C$_{19}$H$_{27}$O$_6^+$ [M+H]$^+$: 351.1802, Found: 351.1802.

Benzyl 3-(3-ethoxy-3-oxopropyl)-3-(4-methoxyphenyl)azetidine-1-carboxylate (414) and **diethyl 2-((1-((benzyloxy)carbonyl)-3-(4-methoxyphenyl)azetidin-3-yl)methyl)pentanedioate (414d)**



414



414d

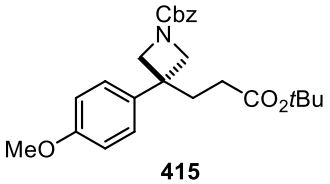
Following general procedure **1A**, azetidine acid **316** (68.3 mg, 0.20 mmol) and ethyl acrylate (33 μL, 0.30 mmol) were used. Purification by flash column chromatography (40% Et$_2$O/pentane) afforded azetidine **414** (42.5 mg, 53%) as a colourless oil, followed by azetidine **414d** (11.7 mg, 12%) as a colourless oil.

Azetidine **414**: R$_f$ = 0.50 (70% Et$_2$O/pentane); IR (film)/cm^{-1} 2954, 1704 (C=O), 1515, 1444, 1414, 1353, 1294, 1246, 1178, 1146, 1115, 1029, 831, 765, 733, 698; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.33–7.20 (m, 5 H, 5 × Ar-CH), 6.96–6.88 (m, 2 H, 2 × Ar-CH), 6.84–6.76 (m, 2 H, 2 × Ar-CH), 5.02 (s, 2 H, CH$_2$Ph), 4.17 (d, *J* = 8.3 Hz, 2 H, C*H*HNC*H*H), 3.97 (q, *J* = 7.2 Hz,

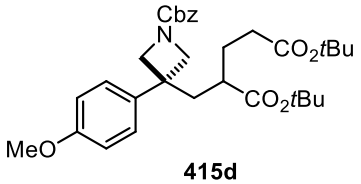
2 H, CH_2CH$_3$), 3.95 (d, *J* = 8.3 Hz, 2 H, CH*H*NCH*H*), 3.72 (s, 3 H, OCH$_3$), 2.23–2.13 (m, 2 H, CH_2CH$_2$), 2.06–1.96 (m, 2 H, CH$_2$CH_2), 1.13 (t, *J* = 7.2 Hz, 3 H, CH$_2$CH_3); ^{13}C NMR (101 MHz, CDCl$_3$) δ 172.8 (C=O$_{ester}$), 158.3 (Ar-C_q-OCH$_3$), 156.5 (C=O), 136.6 (Ar-C_q-CH$_2$), 135.5 (Ar-C_q-C$_q$), 128.4 (2 × Ar-CH), 128.0 (Ar-CH), 127.9 (2 × Ar-CH), 127.0 (2 × Ar-CH), 114.0 (2 × Ar-CH), 66.7 (CH$_2$Ph), 60.5 (*C*H$_2$CH$_3$), 59.7 (br, *C*H$_2$N*C*H$_2$), 55.3 (OCH$_3$), 41.3 (C$_q$), 36.9 (*C*H$_2$CH$_2$), 29.8 (CH$_2$*C*H$_2$), 14.1 (CH$_2$*C*H$_3$); HRMS (+ESI) *m*/*z* calcd for $C_{23}H_{28}NO_5^+$ [M+H]$^+$: 398.1962, Found: 398.1963.

Azetidine **414d**: R_f = 0.43 (70% Et$_2$O/pentane); IR (film)/cm^{-1} 2955, 1707 (C=O), 1513, 1416, 1356, 1248, 1177, 1118, 1032, 831; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.41–7.28 (m, 5 H, 5 × Ar-CH), 7.06–6.98 (m, 2 H, 2 × Ar-CH), 6.90–6.83 (m, 2 H, 2 × Ar-CH), 5.08 (s, 2 H, CH$_2$Ph), 4.28 (d, *J* = 8.3 Hz, 1 H, C*H*HNCHH), 4.20 (d, *J* = 8.3 Hz, 1 H, CH*H*NCHH), 4.08 (q, *J* = 7.1 Hz, 2 H, CH_2CH$_3$), 4.01 (d, *J* = 8.3 Hz, 2 H, CHHNCH_2), 3.95–3.82 (m, 2 H, CH_2CH$_3$), 3.80 (s, 3H, OCH$_3$), 2.50 (dd, *J* = 14.0, 9.6 Hz, 1 H, C$_q$C*H*HCH), 2.25–2.08 (m, 3 H, CH, CHCH_2CH$_2$), 1.97 (dd, *J* = 14.0, 3.1 Hz, 1 H, C$_q$CH*H*CH), 1.88–1.73 (m, 1 H, CH$_2$C*H*HCO$_2$), 1.72–1.65 (m, 1 H, CH$_2$CH*H*CO$_2$), 1.21 (t, *J* = 7.2 Hz, 3 H, CH$_2$CH_3), 1.17 (t, *J* = 7.1 Hz, 3 H, CH$_2$CH_3); ^{13}C NMR (101 MHz, CDCl$_3$) δ 174.9 (C=O$_{ester}$), 172.5 (C=O$_{ester}$), 158.2 (Ar-C_q-OCH$_3$), 156.4 (C=O), 136.5 (Ar-C_q-CH$_2$), 135.4 (Ar-C_q-C$_q$), 128.4 (2 × Ar-CH), 128.0 (Ar-CH), 127.95 (2 × Ar-CH), 127.4 (2 × Ar-CH), 113.8 (2 × Ar-CH), 66.7 (CH$_2$Ph), 60.5 (*C*H$_2$CH$_3$), 60.4 (*C*H$_2$CH$_3$), 59.5 (br, *C*H$_2$N*C*H$_2$), 55.3 (OCH$_3$), 44.2 (C$_q$), 41.5 (C$_q$*C*H$_2$CH), 41.3 (CH), 31.6 (CH*C*H$_2$CH$_2$), 28.8 (CH$_2$*C*H$_2$CO$_2$), 14.1 (CH$_2$*C*H$_3$), 14.0 (CH$_2$*C*H$_3$). The observed characterisation data (^{1}H, ^{13}C NMR) was consistent with that previously reported.[220]

Benzyl 3-(3-(tert-butoxy)-3-oxopropyl)-3-(4-methoxyphenyl)azetidine-1-carboxylate (415) and **di-*tert*-butyl 2-((1-((benzyloxy)carbonyl)-3-(4-methoxyphenyl)azetidin-3-yl)methyl)pentanedioate (415d)**



415

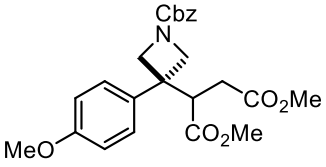


415d

Following general procedure **1A**, azetidine acid **316** (68.3 mg, 0.20 mmol) and *t*Bu-acrylate (45 µL, 0.30 mmol) were used. Purification by flash column chromatography (3% to 4% Et$_2$O/CH$_2$Cl$_2$) afforded azetidine **415** (41.3 mg, 49%) as a colourless oil, followed by azetidine **415d** (15.3 mg, 14%) as a pink oil.

Azetidine **415**: R_f = 0.39 (4% Et_2O/CH_2Cl_2); IR (film)/cm^{-1} 2955, 2885, 1707 (C=O), 1513, 1416, 1356, 1248, 1148, 1032, 767, 700; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32–7.20 (m, 5 H, 5 × Ar-CH), 6.97–6.88 (m, 2 H, 2 × Ar-CH), 6.84–6.76 (m, 2 H, 2 × Ar-CH), 5.02 (s, 2 H, CH_2Ph), 4.16 (d, *J* = 8.2 Hz, 2 H, C*H*HNC*H*H), 3.96 (d, *J* = 8.2 Hz, 2 H, CH*H*NCH*H*), 3.72 (s, 3 H, OCH_3), 2.18–2.06 (m, 2 H, CH_2CH_2), 2.01–1.87 (m, 2 H, CH_2CH_2), 1.31 (s, 9 H, 3 × CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.3 ($C{=}O_{ester}$), 158.2 (Ar-C_q-OCH_3), 156.5 (C=O), 136.5 (Ar-C_q-CH_2), 135.7 (Ar-C_q-C_q), 128.4 (2 × Ar-CH), 128.0 (Ar-CH), 127.9 (2 × Ar-CH), 127.0 (2 × Ar-CH), 113.9 (2 × Ar-CH), 80.5 ($C_q(CH_3)_3$), 66.7 (CH_2Ph), 60.2 and 59.3 (br, CH_2NCH_2), 55.3 (OCH_3), 41.3 (C_q), 36.9 (CH_2CH_2), 30.9 (CH_2CH_2), 28.0 ($C_q(CH_3)_3$); HRMS (+ESI) *m*/*z* calcd for $C_{25}H_{32}NO_5$ [M+H]: 426.2280, Found: 426.2284.

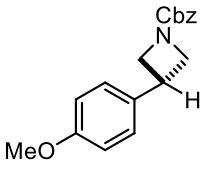
Azetidine **415d**: R_f = 0.23 (4% Et_2O/CH_2Cl_2); IR (film)/cm^{-1} 2974, 1714 (C=O), 1513, 1416, 1364, 1248, 1144, 1036, 831, 700; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40–7.26 (m, 5 H, 5 × Ar-CH), 7.07–7.00 (m, 2 H, 2 × Ar-CH), 6.90–6.83 (m, 2 H, 2 × Ar-CH), 5.08 (s, 2 H, CH_2Ph), 4.23 (dd, *J* = 8.3, 6.1 Hz, 2 H, C*H*HNC*H*H), 4.07 (d, *J* = 8.3 Hz, 1 H, CH*H*NCHH), 4.02 (d, *J* = 8.3 Hz, 1 H, CHHNCH*H*), 3.80 (s, 3 H, OCH_3), 2.47 (dd, *J* = 14.0, 9.4 Hz, 1 H, C_qC*H*HCH), 2.22–2.04 (m, 2 H, CHC$H_2$$CH_2$), 2.04–1.94 (m, 1 H, CH), 1.84 (dd, *J* = 14.0, 3.0 Hz, 1 H, C_qCH*H*CH), 1.80–1.68 (m, 1 H, CH_2CHHCO_2), 1.62–1.51 (m, 1 H, CH_2CHHCO_2), 1.38 (s, 9 H, 3 × CH_3), 1.37 (s, 9 H, 3 × CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.5 ($C{=}O_{ester}$), 171.9 ($C{=}O_{ester}$), 158.2 (Ar-C_q-OCH_3), 156.4 (C=O), 136.6 (Ar-C_q-CH_2), 135.9 (Ar-C_q-C_q), 128.4 (2 × Ar-CH), 128.0 (Ar-CH), 127.9 (2 × Ar-CH), 127.3 (2 × Ar-CH), 113.9 (2 × Ar-CH), 80.7 ($C_q(CH_3)_3$), 80.3 ($C_q(CH_3)_3$), 66.6 (CH_2Ph), 61.4 and 59.7 (br, CH_2NCH_2), 55.3 (OCH_3), 44.2 (C_qCH_2CH), 42.2 (CH), 41.6 (C_q), 32.9 ($CHCH_2CH_2$), 29.3 ($CH_2CH_2CO_2$), 28.0 ($C_q(CH_3)_3$), 27.9 ($C_q(CH_3)_3$); HRMS (+ESI) *m*/*z* calcd for $C_{32}H_{43}NO_7Na$ [M+Na]: 576.2937, Found: 576.2935.



Dimethyl 2-(1-((benzyloxy)carbonyl)-3-(4-methoxyphenyl)azetidin-3-yl)succinate (416)

Following general procedure **1B**, azetidine acid **316** (68.3 mg, 0.20 mmol) and dimethyl fumarate (43.2 mg, 0.30 mmol) were used. Purification by flash column chromatography (50% Et_2O/pentane) afforded azetidine **416** (43.2 mg, 49%) as a colourless oil. R_f = 0.14 (50% Et_2O/pentane); IR (film)/cm^{-1} 2952, 1733 (C=O), 1710 (C=O), 1513, 1416, 1356, 1252, 1166, 1118, 1028, 834, 752, 700; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40–7.28 (m, 5 H, 5 × Ar-CH), 6.98–6.92 (m, 2 H, 2 × Ar-CH), 6.89–6.83 (m, 2 H, 2 × Ar-CH), 5.09 (s, 2 H, CH_2Ph), 4.58 (d, *J* = 8.8 Hz, 1 H, C*H*HNCHH), 4.31 (d, *J* = 8.8 Hz, 1 H, CHHNC*H*H), 4.27 (s, 2 H, CH*H*NCH*H*), 3.80 (s, 3 H, OCH_3), 3.64 (s, 3 H, CO_2CH_3), 3.63 (s, 3 H, CO_2CH_3), 3.41 (dd, *J* = 11.5, 3.1 Hz, 1 H, C*H*CO_2CH_3), 2.61 (dd, *J* = 16.9, 11.5 Hz, 1 H, CHC*H*H), 2.32 (dd, *J* = 16.9, 3.1 Hz, 1 H, CHCH*H*); ^{13}C NMR (101 MHz,

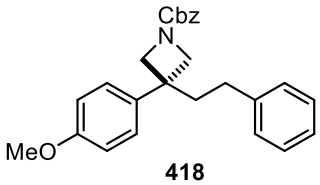
$CDCl_3$) δ 172.2 (C=O_{ester}), 172.0 (C=O_{ester}), 158.6 (Ar-C_q-OCH_3), 156.2 (C=O), 136.4 (Ar-C_q-CH_2), 133.4 (Ar-C_q-C_q), 128.5 (2 × Ar-CH), 128.1 (Ar-CH), 128.0 (2 × Ar-CH), 127.7 (2 × Ar-CH), 113.9 (2 × Ar-CH), 66.8 (CH_2Ph), 58.8 (br, CH_2NCH_2), 55.3 (OCH_3), 52.0 (CO_2CH_3), 51.9 (CO_2CH_3), 49.6 (CH), 43.3 (C_q), 32.0 (CH_2); HRMS (+ESI) *m*/*z* calcd for $C_{24}H_{28}NO_7$ [M+H]: 442.1866, Found: 442.1854.



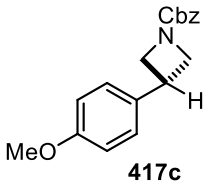
Benzyl 3-(4-methoxyphenyl)azetidine-1-carboxylate (417c)

Following general procedure **1A**, azetidine acid **316** (68.3 mg, 0.20 mmol) and 2-cyclopenten-1-one (25 µL, 0.30 mmol) were used. Purification by flash column chromatography (40% to 70% Et_2O/pentane) afforded azetidine **417c** (5.3 mg, 9%) as a yellow oil. R_f = 0.36 (40% Et_2O/pentane); IR (film)/cm^{-1} 2959, 2885, 1707 (C=O), 1513, 1412, 1353, 1289, 1248, 1177, 1125, 1032, 827; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45–7.29 (m, 5 H, 5 × Ar-CH), 7.26–7.20 (m, 2 H, 2 × Ar-CH), 6.93–6.86 (m, 2 H, 2 × Ar-CH), 5.14 (s, 2 H, CH_2Ph), 4.40 (t, *J* = 8.7 Hz, 2 H, C*H*HNC*H*H), 4.03 (dd, *J* = 8.7, 6.1 Hz, 2 H, CH*H*NCH*H*), 3.81 (s, 3 H, OCH_3), 3.75 (tt, *J* = 8.7, 6.1 Hz, 1 H, CH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.6 (Ar-C_q-OCH_3), 156.4 (C=O), 136.7 (Ar-C_q-CH_2), 133.9 (Ar-C_q-C_q), 128.5 (2 × Ar-CH), 128.02 (Ar-CH), 127.98 (2 × Ar-CH), 127.8 (2 × Ar-CH), 114.1 (2 × Ar-CH), 66.6 (CH_2Ph), 56.9 (br, CH_2NCH_2), 55.3 (OCH_3), 33.3 (CH). The observed characterisation data (^{1}H and ^{13}C NMR) was consistent with that previously reported.[220]

Benzyl 3-(4-methoxyphenyl)-3-phenethylazetidine-1-carboxylate (418) and **benzyl 3-(4-methoxyphenyl)azetidine-1-carboxylate (417c)**



418



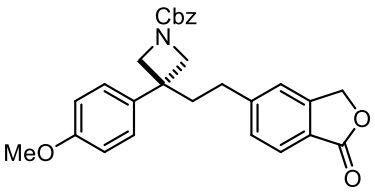
417c

Following general procedure **1A**, azetidine acid **316** (68.3 mg, 0.20 mmol) and styrene (35 µL, 0.30 mmol) were used. Purification by flash column chromatography (2% Et_2O/CH_2Cl_2) afforded azetidine **418** (27.2 mg, 34%) as a yellow oil, followed by azetidine **417c** (2.1 mg, 4%) as a colourless oil.

Azetidine **418**: R_f = 0.50 (2% Et_2O/CH_2Cl_2); IR (film)/cm^{-1} 2952, 1707 (C=O), 1513, 1416, 1356, 1248, 1181, 1118, 1032, 831; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43–7.29 (m, 5 H, 5 × Ar-CH), 7.26–7.22 (m, 2 H, 2 × Ar-CH), 7.20–7.14 (m, 1 H, Ar-CH), 7.13–7.03 (m, 4 H, 4 × Ar-CH), 6.97–6.90 (m, 2 H, 2 × Ar-CH), 5.11 (s, 2 H, CH_2Ph), 4.28 (d, *J* = 8.2 Hz, 2 H, C*H*HNC*H*H), 4.08 (d, *J* = 8.2 Hz, 2 H, CH*H*NCH*H*), 3.84 (s, 3 H, OCH_3), 2.45–2.32 (m, 2 H, CH_2), 2.27–2.15

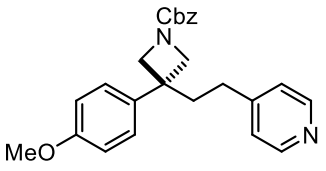
(m, 2 H, CH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.1 (Ar-C_q-OCH_3), 156.5 (C=O), 141.5 (Ar-C_q-CH_2CH_2), 136.6 (Ar-C_q-CH_2O), 136.3 (Ar-C_q-C_q), 128.5 (2 × Ar-CH), 128.4 (2 × Ar-CH), 128.2 (2 × Ar-CH), 128.02 (Ar-CH), 127.96 (2 × Ar-CH), 127.0 (2 × Ar-CH), 125.9 (Ar-CH), 113.9 (2 × Ar-CH), 66.7 (CH_2Ph), 59.6 (br, CH_2NCH_2), 55.3 (OCH_3), 44.2 (CH_2), 42.0 (C_q), 30.9 (CH_2). The observed characterisation data (^1H and ^{13}C NMR) was consistent with that previously reported.[220]

Azetidine **417c**: Identical spectroscopic data were obtained.



Benzyl 3-(4-methoxyphenyl)-3-(2-(1-oxo-1,3-dihydroisobenzofuran-5-yl)ethyl)azetidine-1-carboxylate (419)

Following general procedure **1B**, azetidine acid **316** (68.3 mg, 0.20 mmol) and 5-vinylisobenzofuran-1(3*H*)-one[bb] (48.1 mg, 0.30 mmol) were used. Purification by flash column chromatography (80% Et_2O/pentane) afforded azetidine **419** (51.3 mg, 56%) as a white solid. R_f = 0.19 (80% Et_2O/pentane); mp = 45–49 °C; IR (film)/cm^{-1} 2952, 1763 (C=O), 1707 (C=O), 1617, 1513, 1416, 1356, 1248, 1118, 1043, 834, 700; ^1H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, *J* = 7.8 Hz, 1 H, Ar-CH), 7.38–7.29 (m, 5 H, 5 × Ar-CH), 7.23 (dd, *J* = 7.8, 1.3 Hz, 1 H, Ar-CH), 7.18 (s, 1 H, Ar-CH), 7.10–7.03 (m, 2 H, 2 × Ar-CH), 6.96–6.89 (m, 2 H, 2 × Ar-CH), 5.24 (s, 2 H, CH_2OCO), 5.11 (s, 2 H, CH_2Ph), 4.31 (d, *J* = 8.3 Hz, 2 H, C*H*HNC*H*H), 4.07 (d, *J* = 8.3 Hz, 2 H, CH*H*NCH*H*), 3.83 (s, 3 H, OCH_3), 2.51 (dd, *J* = 11.1, 5.8 Hz, 2 H, C$H_2$$CH_2$), 2.24 (dd, *J* = 11.1, 6.2 Hz, 2 H, CH_2CH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.9 ($C=O_{ester}$), 158.3 (Ar-C_q-OCH_3), 156.6 (C=O), 148.7 (Ar-C_q-CO), 147.1 (Ar-C_q-CH_2O), 136.5 (Ar-C_q-$CH_{2(Cbz)}$), 135.8 (Ar-C_q-C_q), 129.5 (Ar-CH), 128.5 (2 × Ar-CH), 128.1 (Ar-CH), 128.0 (2 × Ar-CH), 127.0 (2 × Ar-CH), 125.8 (Ar-CH), 123.8 (Ar-C_q-CH_2CH_2), 121.6 (Ar-CH), 114.1 (2 × Ar-CH), 69.3 (CH_2OCO_{ester}), 66.8 (CH_2Ph), 60.3 (br, CH_2NCH_2), 55.3 (OCH_3), 44.0 (CH_2), 42.0 (C_q), 31.5 (CH_2); HRMS (+APCI) *m*/*z* calcd for $C_{28}H_{28}NO_5^+$ $[M+H]^+$: 458.1962, Found: 458.1959.

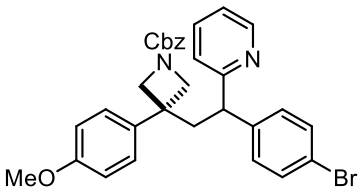


Benzyl 3-(4-methoxyphenyl)-3-(2-(pyridin-4-yl)ethyl)azetidine-1-carboxylate (420)

Following general procedure **1A**, azetidine acid **316** (68.3 mg, 0.20 mmol) and 4-vinylpyridine (35 µL, 0.30 mmol) were used. Purification by flash column chromatography (100% Et_2O) afforded azetidine **420** (62.5 mg, 78%) as a colourless oil. R_f = 0.13 (100% Et_2O); IR (film)/cm^{-1} 2952, 1707 (C=O), 1602, 1513,

[bb] Provided by Pfizer

1416, 1356, 1248, 1181, 1148, 1118, 1032, 831, 767, 700; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49–8.42 (m, 2 H, 2 × $Ar_{(pyridine)}$-CH), 7.40–7.28 (m, 5 H, 5 × Ar-CH), 7.10–7.03 (m, 2 H, 2 × Ar-CH), 7.03–6.99 (m, 2 H, 2 × $Ar_{(pyridine)}$-CH), 6.96–6.89 (m, 2 H, 2 × Ar-CH), 5.11 (s, 2 H, CH_2Ph), 4.30 (d, *J* = 8.2 Hz, 2 H, C*H*HNC*H*H), 4.07 (d, *J* = 8.2 Hz, 2 H, CH*H*NCH*H*), 3.83 (s, 3 H, OCH_3), 2.37 (dd, *J* = 10.8, 4.8 Hz, 2 H, C$H_2$$CH_2$), 2.21 (dd, *J* = 11.3, 6.3 Hz, 2 H, CH_2CH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.3 (Ar-C_q-OCH_3), 156.5 (C=O), 150.3 ($Ar_{(pyridine)}$-C_q), 149.7 (2 × $Ar_{(pyridine)}$-CH), 136.5 (Ar-C_q-CH_2), 135.8 (Ar-C_q-C_q), 128.5 (2 × Ar-CH), 128.1 (Ar-CH), 128.0 (2 × Ar-CH), 127.0 (2 × Ar-CH), 123.6 (2 × $Ar_{(pyridine)}$-CH), 114.0 (2 × Ar-CH), 66.7 (CH_2Ph), 59.4 (br, CH_2NCH_2), 55.3 (OCH_3), 42.9 (CH_2), 41.9 (C_q), 30.3 (CH_2); HRMS (+ESI) *m*/*z* calcd for $C_{25}H_{27}N_2O_3$ [M+H]: 403.2022, Found: 403.2028.

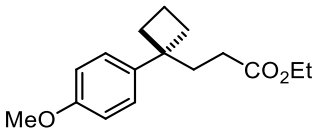


Benzyl 3-(2-(4-bromophenyl)-2-(pyridin-2-yl)ethyl)-3-(4-methoxyphenyl)azetidine-1-carboxylate (421)

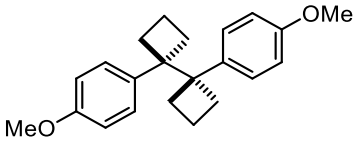
Following general procedure **1B**, azetidine acid **316** (68.3 mg, 0.20 mmol) and 2-(1-(4-bromophenyl)vinyl)pyridine[cc] (78.0 mg, 0.30 mmol) were used. Purification by flash column chromatography (100% Et_2O) afforded azetidine **421** (76.3 mg, 68%) as a bright yellow solid. R_f = 0.18 (100% Et_2O); mp = 51–55 °C; IR (film)/cm^{-1} 2955, 1707 (C=O), 1513, 1420, 1356, 1248, 1181, 1148, 1118, 1028, 831, 726; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (dd, *J* = 4.8, 1.6 Hz, 1 H, $Ar_{(pyridine)}$-CH), 8.32 (d, *J* = 2.3 Hz, 1 H, $Ar_{(pyridine)}$-CH), 7.46–7.28 (m, 8 H, 5 × Ph-CH, 2 × $Ar_{(p\text{-}Br)}$-CH, $Ar_{(pyridine)}$-CH), 7.15 (dd, *J* = 8.0, 4.8 Hz, 1 H, $Ar_{(pyridine)}$-CH), 7.06–6.94 (m, 4 H, 2 × $Ar_{(p\text{-}Br)}$-CH, 2 × Ar-CH), 6.93–6.83 (m, 2 H, 2 × Ar-CH), 5.05 (s, 2 H, CH_2Ph), 4.08 (dd, *J* = 8.5, 3.9 Hz, 2 H, C*H*HNC*H*H), 3.83 (s, 3 H, OCH_3), 3.83–3.73 (m, 2 H, CH*H*NCH*H*), 3.59 (dd, *J* = 7.6, 6.8 Hz, 1 H, CH), 2.80 (dd, *J* = 13.6, 7.6 Hz, 1 H, C*H*H), 2.72 (dd, *J* = 13.6, 6.8 Hz, 1 H, CH*H*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.2 (Ar-C_q-OCH_3), 156.4 (C=O), 149.3 ($Ar_{(pyridine)}$-CH), 148.0 ($Ar_{(pyridine)}$-CH), 142.2 ($Ar_{(p\text{-}Br)}$-C_q-CH), 139.3 ($Ar_{(pyridine)}$-C_q-CH), 136.5 (Ph-C_q-CH_2), 135.4 (Ar-C_q-C_q), 134.9 ($Ar_{(pyridine)}$-CH), 131.9 (2 × $Ar_{(p\text{-}Br)}$-CH), 129.4 (2 × $Ar_{(p\text{-}Br)}$-CH), 128.5 (2 × Ph-CH), 128.1 (Ph-CH), 128.0 (2 × Ph-CH), 127.3 (2 × Ar-CH), 123.5 ($Ar_{(pyridine)}$-CH), 120.7 (Ar-C_q-Br), 114.1 (2 × Ar-CH), 66.7 (CH_2Ph), 60.8 (br, CH_2NCH_2), 55.3 (OCH_3), 46.8 (CH_2), 45.0 (CH), 41.8 (C_q); HRMS (+ESI) *m*/*z* calcd for $C_{31}H_{30}N_2O_3{}^{79}Br$ [M+H]: 557.1440, Found: 557.1448.

[cc] Provided by Pfizer

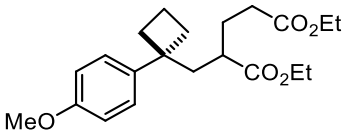
Ethyl 3-(1-(4-methoxyphenyl)cyclobutyl)propanoate (422), 1,1'-bis(4-methoxyphenyl)-1,1'-bi(cyclobutane) (422b), and **diethyl 2-((1-(4-methoxyphenyl)cyclobutyl)methyl)pentanedioate (422d)**



422



422b



422d

Following general procedure **1A**, cyclobutane acid **319** (41.3 mg, 0.20 mmol) and ethyl acrylate (33 µL, 0.30 mmol) were used. Purification by flash column chromatography (4% to 20% Et_2O/pentane) afforded dimer **422b** (1.9 mg, 6%) as a colourless oil, followed by cyclobutane **422** (19.0 mg, 36%) as a colourless oil and cyclobutane **422d** (5.3 mg, 7%) as a colourless oil.

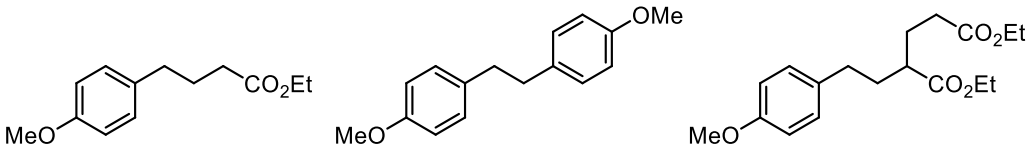
Dimer **422b:** R_f = 0.32 (4% Et_2O/pentane); IR (film)/cm^{-1} 2978, 2944, 1610, 1513, 1464, 1297, 1244, 1177, 1036, 827, 801; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.64 (s, 8 H, 8 × Ar-CH), 3.77 (s, 6 H, 2 × OCH_3), 2.70–2.55 (m, 4 H, 2 × CH_2), 2.25–2.13 (m, 4 H, 2 × CH_2), 1.82–1.65 (m, 4 H, 2 × CH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.1 (2 × Ar-C_q-OCH_3), 138.5 (2 × Ar-C_q-C_q), 128.9 (4 × Ar-CH), 112.0 (4 × Ar-CH), 55.2 (2 × OCH_3), 52.6 (2 × C_q), 29.9 (2 × $CH_2CH_2CH_2$), 15.1 (2 × $CH_2CH_2CH_2$); HRMS (+APCI) *m*/*z* calcd for $C_{22}H_{30}NO_2^+$ $[M+NH_4]^+$: 340.2271, Found: 340.2275.

Cyclobutane **422**: R_f = 0.14 (4% Et_2O/pentane); IR (film)/cm^{-1} 2978, 2933, 1733 (C=O), 1610, 1513, 1293, 1248, 1177, 1036, 831; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.07–7.00 (m, 2 H, 2 × Ar-CH), 6.88–6.81 (m, 2 H, 2 × Ar-CH), 4.04 (q, *J* = 7.2 Hz, 2 H, CH_2CH_3), 3.80 (s, 3 H, OCH_3), 2.40–2.25 (m, 2 H, CH_2CH_2), 2.15–2.06 (m, 5 H, CH_2CH_2, $CH_{2(cyclobutane)}$, $CHH_{(cyclobutane)}$), 2.06–1.98 (m, 2 H, $CH_{2(cyclobutane)}$), 1.89–1.78 (m, 1 H, $CHH_{(cyclobutane)}$), 1.21 (t, *J* = 7.2 Hz, 3 H, CH_2CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.0 (C=O), 157.4 (Ar-C_q-OCH_3), 141.1 (Ar-C_q-C_q), 126.7 (2 × Ar-CH), 113.4 (2 × Ar-CH), 60.2 (CH_2CH_3), 55.2 (OCH_3), 45.3 (C_q), 37.3 (CH_2CH_2), 32.5 (2 × $CH_2CH_2CH_2$), 30.1 (CH_2CH_2), 15.8 (2 × $CH_2CH_2CH_2$), 14.2 (CH_2CH_3); HRMS (+APCI) *m*/*z* calcd for $C_{16}H_{22}O_3Na^+$ $[M+Na]^+$: 285.1461, Found: 285.1465.

Cyclobutane **422d**: R_f = 0.29 (20% Et_2O/pentane); IR (film)/cm^{-1} 2978, 1733 (C=O), 1610, 1513, 1248, 1177, 1036, 831; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11–7.04 (m, 2 H, 2 × Ar-CH), 6.87–6.80 (m, 2 H, 2 × Ar-CH), 4.07 (q, *J* = 7.1 Hz, 2 H, CH_2CH_3), 3.92–3.81 (m, 2 H, CH_2CH_3), 3.80 (s, 3 H, OCH_3), 2.42–2.22 (m, 3 H, C_qCHHCH, 2 × $CH_{(cyclobutane)}$), 2.19–1.95 (m, 6 H, 3 × $CH_{(cyclobutane)}$, $CHCO_2$, $CHCH_2CH_2$), 1.86–1.71 (m, 3 H, CH_2CHHCO_2, C_qCHHCH, $CH_{(cyclobutane)}$), 1.69–1.61 (m, 1 H, CH_2CHHCO_2), 1.21 (t, *J* = 7.2 Hz, 3 H, CH_2CH_3), 1.17 (t, *J* = 7.2 Hz, 3 H, CH_2CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.8 (C=O), 172.8 (C=O), 157.4 (Ar-C_q-OCH_3), 140.6 (Ar-C_q-C_q), 127.1 (2 × Ar-CH), 113.3 (2 × Ar-CH), 60.3 (CH_2CH_3), 60.2

(CH_2CH_3), 55.2 (OCH_3), 45.7 (C_q), 44.9 (C_qCH_2CH), 41.5 (CH), 33.6 ($CH_{2(cyclobutane)}$), 33.0 ($CH_{2(cyclobutane)}$), 31.8 ($CHCH_2CH_2$), 29.9 ($CH_2CH_2CO_2$), 15.9 ($CH_{2(cyclobutane)}$), 14.1 (CH_2CH_3), 14.0 (CH_2CH_3); HRMS (+ESI) *m*/*z* calcd for $C_{21}H_{31}O_5$ [M+H]: 363.2171, Found: 363.2173.

Ethyl 4-(4-methoxyphenyl)butanoate (426), 1,2-bis(4-methoxyphenyl)ethane (426b), and **diethyl 2-(4-methoxyphenethyl)pentanedioate (426d)**



426 **426b** **426d**

Following general procedure **1A**, 4-methoxyphenylacetic acid **423** (33.2 mg, 0.20 mmol) and ethyl acrylate (33 µL, 0.30 mmol) were used. Purification by flash column chromatography (4% to 20% Et_2O/pentane) afforded dimer **426b** (2.6 mg, 11%) as a white film, followed by alkane **426** (16.7 mg, 38%) as a colourless oil and alkane **426d** (5.9 mg, 9%) as a colourless oil.

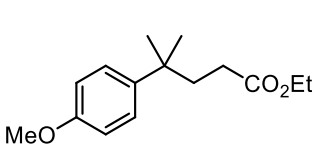
Dimer **426b:** R_f = 0.79 (20% Et_2O/pentane); IR (film)/cm^{-1} 2914, 1509, 1304, 1244, 1177, 1028, 679; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14–7.04 (m, 4 H, 4 × Ar-CH), 6.87–6.77 (m, 4 H, 4 × Ar-CH), 3.80 (s, 6 H, 2 × OCH_3), 2.83 (s, 4 H, 2 × CH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.0 (2 × Ar-C_q-OCH_3), 134.0 (2 × Ar-C_q-CH_2), 129.4 (4 × Ar-CH), 113.7 (4 × Ar-CH), 55.2 (2 × OCH_3), 37.3 (2 × CH_2). The observed characterisation data (^{1}H and ^{13}C NMR) was consistent with that previously reported.[261]

Alkane **426**: R_f = 0.61 (20% Et_2O/pentane); IR (film)/cm^{-1} 2937, 1729 (C=O), 1610, 1513, 1461, 1300, 1244, 1177, 1036, 812; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15–7.06 (m, 2 H, 2 × Ar-CH), 6.89–6.79 (m, 2 H, 2 × Ar-CH), 4.13 (q, *J* = 7.1 Hz, 2 H, C$H_2$$CH_3$), 3.80 (s, 3 H, OCH_3), 2.60 (t, *J* = 7.6 Hz, 2 H, C$H_2$$CH_2CH_2$), 2.31 (t, *J* = 7.5 Hz, 2 H, CH_2CH_2CH_2), 2.00–1.86 (m, 2 H, CH_2C$H_2$$CH_2$), 1.21 (t, *J* = 7.1 Hz, 3 H, CH_2CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.6 (C=O), 157.8 (Ar-C_q-OCH_3), 133.5 (Ar-C_q-CH_2), 129.4 (2 × Ar-CH), 113.7 (2 × Ar-CH), 60.2 (CH_2CH_3), 55.2 (OCH_3), 34.2 (CH_2), 33.6 (CH_2), 26.8 (CH_2), 14.2 (CH_2CH_3); The observed characterisation data (^{1}H NMR) was consistent with that previously reported.[262]

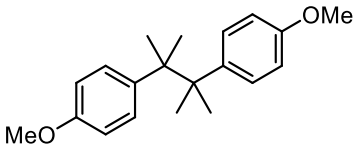
Alkane **426d**: R_f = 0.30 (20% Et_2O/pentane); IR (film)/cm^{-1} 2981, 2937, 1729 (C=O), 1610, 1513, 1453, 1379, 1244, 1177, 1036, 827; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13–7.05 (m, 2 H, 2 × Ar-CH), 6.87–6.79 (m, 2 H, 2 × Ar-CH), 4.21–4.08 (m, 4 H, 2 × C$H_2$$CH_3$), 3.79 (s, 3 H, OCH_3), 2.64–2.48 (m, 2 H, 2 × CH), 2.47–2.35 (m, 1 H, CH), 2.35–2.27 (m, 2 H, 2 × CH), 2.02–1.81 (m, 3 H, 3 × CH), 1.79–1.67 (m, 1 H, CH), 1.29 (t, *J* = 7.1 Hz, 3 H, CH_2CH_3), 1.25 (t, *J* = 7.2 Hz, 3 H, CH_2CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.4 (C=O), 173.0 (C=O), 157.8

(Ar-C_q-OCH_3), 133.5 (Ar-C_q-CH_2), 129.3 (2 × Ar-CH), 113.8 (2 × Ar-CH), 60.41 (CH_2CH_3), 60.36 (CH_2CH_3), 55.2 (OCH_3), 44.3 (CH), 34.2 (CH_2), 32.6 (CH_2), 32.0 (CH_2), 27.2 (CH_2), 14.3 (CH_2CH_3), 14.2 (CH_2CH_3); HRMS (+APCI) *m*/*z* calcd for $C_{18}H_{27}O_5^+$ $[M+H]^+$: 323.1853, Found: 323.1851.

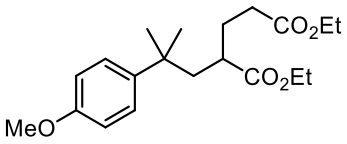
Ethyl 4-(4-methoxyphenyl)-4-methylpentanoate (427), 4,4'-(2,3-dimethylbutane-2,3-diyl)bis(methoxybenzene) (427b), and **diethyl 2-(2-(4-methoxyphenyl)-2-methylpropyl)pentanedioate (427d)**



427



427b



427d

Following general procedure **1A**, 2-(4-methoxyphenyl)-2-methylpropanoic acid **424** (38.8 mg, 0.20 mmol) and ethyl acrylate (33 µL, 0.30 mmol) were used. Purification by flash column chromatography (4% to 20% Et_2O/pentane) afforded dimer **427b** (11.3 mg, 38%) as a white solid, followed by alkane **427** (16.2 mg, 32%) as a colourless oil and alkane **427d** (7.0 mg, 10%) as a colourless oil.

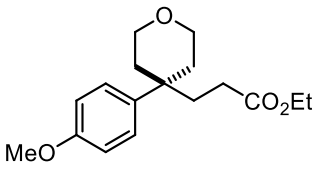
Dimer **427b:** R_f = 0.54 (4% Et_2O/pentane); mp = 185–188 °C [lit. 184 °C][263]; IR (film)/cm^{-1} 2985, 2832, 1610, 1513, 1293, 1244, 1185, 1036, 831; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.01–6.93 (m, 4 H, 4 × Ar-CH), 6.77–6.69 (m, 4 H, 4 × Ar-CH), 3.80 (s, 6 H, 2 × OCH_3), 1.28 (s, 12 H, 4 × CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.3 (2 × Ar-C_q-OCH_3), 139.1 (2 × Ar-C_q-C_q), 129.6 (4 × Ar-CH), 111.8 (4 × Ar-CH), 55.1 (2 × OCH_3), 43.1 (2 × C_q), 25.3 (4 × CH_3). The observed characterisation data (^{1}H and ^{13}C NMR) was consistent with that previously reported.[264]

gem-Dimethyl **427**: R_f = 0.23 (4% Et_2O/pentane); IR (film)/cm^{-1} 2959, 1729 (C=O), 1610, 1513, 1461, 1371, 1297, 1248, 1181, 1036, 831; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27–7.21 (m, 2 H, 2 × Ar-CH), 6.89–6.82 (m, 2 H, 2 × Ar-CH), 4.06 (q, *J* = 7.1 Hz, 2 H, CH_2CH_3), 3.80 (s, 3 H, OCH_3), 2.10–2.03 (m, 2 H, CH_2CH_2), 1.98–1.91 (m, 2 H, CH_2CH_2), 1.31 (s, 6 H, 2 × CH_3), 1.21 (t, *J* = 7.1 Hz, 3 H, CH_2CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.1 (C=O), 157.5 (Ar-C_q-OCH_3), 140.1 (Ar-C_q-C_q), 126.8 (2 × Ar-CH), 113.5 (2 × Ar-CH), 60.2 (CH_2CH_3), 55.2 (OCH_3), 39.0 (CH_2), 36.7 (C_q), 30.3 (CH_2), 28.9 (2 × CH_3), 14.2 (CH_2CH_3); HRMS (+ESI) *m*/*z* calcd for $C_{17}H_{26}NO_3$ [M+MeCN+H]: 292.1913, Found: 292.1919.

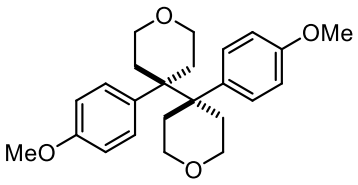
gem-Dimethyl **427d**: R_f = 0.34 (20% Et_2O/pentane); IR (film)/cm^{-1} 2959, 1729 (C=O), 1513, 1461, 1379, 1252, 1185, 1036, 831; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26–7.20 (m, 2 H, 2 × Ar-CH), 6.87–6.80 (m, 2 H, 2 × Ar-CH), 4.09 (q, *J* = 7.1 Hz, 2 H, CH_2CH_3), 3.98–3.81 (m, 2 H,

C*H*$_2$CH$_3$), 3.79 (s, 3 H, OCH$_3$), 2.29–2.14 (m, 4 H, C$_q$C*H*HCH, CH, CHC*H*$_2$CH$_2$), 1.83–1.62 (m, 3 H, C$_q$CH*H*CH, CH$_2$C*H*$_2$CO$_2$), 1.29 (s, 3 H, CH$_3$), 1.26 (s, 3 H, CH$_3$), 1.22 (t, *J* = 7.1 Hz, 3 H, CH$_2$C*H*$_3$), 1.16 (t, *J* = 7.2 Hz, 3 H, CH$_2$C*H*$_3$); ^{13}C NMR (101 MHz, CDCl$_3$) δ 176.1 (C=O), 172.8 (C=O), 157.5 (Ar-*C*$_q$-OCH$_3$), 140.1 (Ar-*C*$_q$-C$_q$), 127.0 (2 × Ar-CH), 113.3 (2 × Ar-CH), 60.4 (*C*H$_2$CH$_3$), 60.2 (*C*H$_2$CH$_3$), 55.2 (OCH$_3$), 46.6 (C$_q$*C*H$_2$CH), 41.5 (CH), 37.2 (C$_q$), 31.8 (CH*C*H$_2$CH$_2$), 29.6 (CH$_2$*C*H$_2$CO$_2$), 29.2 (CH$_3$), 28.7 (CH$_3$), 14.2 (CH$_2$*C*H$_3$), 14.0 (CH$_2$*C*H$_3$); HRMS (+ESI) *m*/*z* calcd for C$_{20}$H$_{31}$O$_5$ [M+H]: 351.2171, Found: 351.2167.

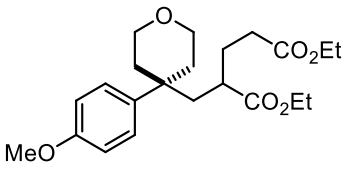
Ethyl 3-(4-(4-methoxyphenyl)tetrahydro-2H-pyran-4-yl)propanoate (428), 4,4'-bis(4-methoxyphenyl)octahydro-2H,2'H-4,4'-bipyran (428b), and **diethyl 2-((4-(4-methoxyphenyl)tetrahydro-2H-pyran-4-yl)methyl)pentanedioate (428d)**



428



428b



428d

Following general procedure **1A**, 4-(4-methoxyphenyl)tetrahydro-2H-pyran-4-carboxylic acid **425** (47.3 mg, 0.20 mmol) and ethyl acrylate (33 µL, 0.30 mmol) were used. Purification by flash column chromatography (8% to 60% Et$_2$O/pentane) afforded THP **428** (19.3 mg, 33%) as a colourless oil, followed by alkaneTHP **428d** (9.5 mg, 12%) as a colourless oil and dimer **428b** (8.7 mg, 23%) as a white solid.

THP **428**: R$_f$ = 0.31 (40% Et$_2$O/pentane); IR (film)/cm^{-1} 2937, 2855, 1729 (C =O), 1610, 1513, 1453, 1375, 1297, 1248, 1185, 1114, 1032, 827; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.22–7.12 (m, 2 H, 2 × Ar-CH), 6.94–6.83 (m, 2 H, 2 × Ar-CH), 4.02 (q, *J* = 7.1 Hz, 2 H, C*H*$_2$CH$_3$), 3.81 (s, 3 H, OCH$_3$), 3.81–3.74 (m, 2 H, C*H*HOC*H*H), 3.55 (ddd, *J* = 11.8, 9.3, 2.7 Hz, 2 H, CH*H*OCH*H*), 2.17–2.06 (m, 2 H, C*H*HC$_q$C*H*H), 2.00–1.88 (m, 4 H, C*H*$_2$C*H*$_2$CO$_2$), 1.81 (ddd, *J* = 13.6, 9.3, 3.7 Hz, 2 H, CH*H*C$_q$CH*H*), 1.19 (t, *J* = 7.1 Hz, 3 H, CH$_2$C*H*$_3$); ^{13}C NMR (101 MHz, CDCl$_3$) δ 173.7 (C=O), 157.7 (Ar-*C*$_q$-OCH$_3$), 135.9 (Ar-*C*$_q$-C$_q$), 127.8 (2 × Ar-CH), 113.9 (2 × Ar-CH), 64.2 (*C*H$_2$O*C*H$_2$), 60.3 (*C*H$_2$CH$_3$), 55.2 (OCH$_3$), 38.22 (C$_q$), 38.16 (CH$_2$), 36.2 (*C*H$_2$C$_q$*C*H$_2$), 28.8 (CH$_2$), 14.1 (CH$_2$*C*H$_3$); HRMS (+ESI) *m*/*z* calcd for C$_{17}$H$_{25}$O$_4$ [M+H]: 293.1753, Found: 293.1748.

THP **428d**: R$_f$ = 0.24 (40% Et$_2$O/pentane); IR (film)/cm^{-1} 2937, 2855, 1729 (C=O), 1610, 1513, 1453, 1379, 1252, 1185, 1118, 1032, 831; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.21–7.10 (m, 2 H, 2 × Ar-CH), 6.90–6.84 (m, 2 H, 2 × Ar-CH), 4.07 (q, *J* = 7.1 Hz, 2 H, C*H*$_2$CH$_3$), 3.94–3.81 (m, 2 H, C*H*$_2$CH$_3$), 3.81 (s, 3 H, OCH$_3$), 3.79–3.70 (m, 2 H, C*H*HOC*H*H), 3.51 (dddd, *J* = 14.4, 11.9,

9.5, 2.7 Hz, 2 H, CH*H*OCH*H*), 2.27 (dd, *J* = 14.0, 9.5 Hz, 1 H, C_qCHHCH), 2.19–2.05 (m, 4 H, CH, $CHHCH_2CO_2$, $CHHC_qCHH$), 2.05–1.91 (m, 1 H, $CHHCH_2CO_2$), 1.85–1.66 (m, 3 H, $CHHC_qCHH$, CH_2CHHCO_2), 1.64–1.55 (m, 1 H, CH_2CHHCO_2), 1.55 (dd, *J* = 14.0, 2.0 Hz, 1 H, C_qCHHCH), 1.21 (t, *J* = 7.1 Hz, 3 H, CH_2CH_3), 1.16 (t, *J* = 7.2 Hz, 3 H, CH_2CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.8 (C=O), 172.7 (C=O), 157.7 (Ar-C_q-OCH_3), 135.6 (Ar-C_q-C_q), 128.2 (2 × Ar-CH), 113.7 (2 × Ar-CH), 64.2 (CH_2OCH_2), 64.1 (CH_2OCH_2), 60.4 (CH_2CH_3), 60.3 (CH_2CH_3), 55.2 (OCH_3), 45.9 (C_qCH_2CH), 40.1 (CH), 38.7 (C_q), 36.8 ($CH_2C_qCH_2$), 36.0 ($CH_2C_qCH_2$), 31.6 ($CHCH_2CH_2$), 29.5 ($CH_2CH_2CO_2$), 14.1 (CH_2CH_3), 14.0 (CH_2CH_3); HRMS (+ESI) *m*/*z* calcd for $C_{22}H_{33}O_6$ [M+H]: 393.2277, Found: 393.2273.

Dimer **428b:** R_f = 0.06 (40% Et_2O/pentane); mp = 180–185 °C; IR (film)/cm^{-1} 2955, 2862, 1733, 1610, 1513, 1293, 1252, 1185, 1107, 1032, 849, 801; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.81–6.67 (m, 8 H, 8 × Ar-CH), 3.82 (s, 6 H, 2 × OCH_3), 3.72 (ddd, J = 11.7, 4.0, 2.1 Hz, 4 H, 2 × $CHHOCHH$), 3.26 (td, *J* = 11.7, 1.9 Hz, 4 H, 2 × CH*H*OCH*H*), 2.11–2.03 (m, 4 H, 2 × $CHHC_qCHH$), 1.99 (ddd, *J* = 13.6, 11.7, 4.2 Hz, 4 H, 2 × CH*H*C_qCH*H*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.7 (2 × Ar-C_q-OCH_3), 131.1 (4 × Ar-CH), 130.7 (2 × Ar-C_q-C_q), 112.6 (4 × Ar-CH), 64.5 (2 × CH_2OCH_2), 55.1 (2 × OCH_3), 46.9 (2 × C_q), 36.8 (2 × $CH_2C_qCH_2$); HRMS (+ESI) *m*/*z* calcd for $C_{26}H_{34}NO_4$ [M+MeCN+H]: 424.2488, Found: 424.2500.

9. References

1 Kola, I.; Landis, J. *Nat. Rev. Drug Discov.* **2004**, *3*, 711–716.

2 Leeson, P. D.; Springthorpe, B. *Nat. Rev. Drug Discov*. **2007**, *6*, 881–890.

3 Waring, M. J. *Expert Opin. Drug Discov.* **2010**, *5*, 235–248.

4 Yalkowky, S. H.; Valvani, S. C. *J. Pharm. Sci*. **1980**, *69*, 912–922.

5 Gleeson, M. P. *J. Med. Chem.* **2008**, *51*, 817–834.

6 Waring, M. J. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 2844–2851.

7 Nassar, A.-E. F.; Kamel, A. M.; Clarimont, C. *Drug Discov. Today* **2004**, *9*, 1020–1028.

8 Johnson, T. W.; Dress, K. R.; Edwards, M. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 5560–5564.

9 Lewis, D. F. V; Dickins, M. *Drug Metab. Rev.* **2003**, *35*, 1–18.

10 Borchard, U. *Clin. Physiol. Biochem*. **1980**, *8*, 28–34.

11 Waring, M. J.; Johnstone, C.; *Bioorg. Med. Chem. Lett*. **2007**, *17*, 1759–1764.

12 Ritchie, T. J.; Macdonald, S. J. F.; Young, R. J.; Pickett, S. D. *Drug Discov. Today* **2011**, *16*, 164–171.

13 Veber, D. F.; Johnson, S. R.; Cheng, H.; Smith, B. R.; Ward, K. W.; Kopple, K. D. *J. Med. Chem*. **2002**, *45*, 2615–2623.

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

15 Badertscher, M.; Bischofberger, K.; Munk, M. E.; Pretsch, E. *J. Chem. Inf. Comput. Sci.* **2001**, *41*, 889–893.

16 (a) Lipinski, C. A.; Lombardo, F.; Dominy, B. W.; Feeney, P. J. *Adv. Drug Deliv. Rev.* **1997**, 3–25. (b) Lipinski, C. A.; Lombardo, F.; Dominy, B. W.; Feeney, P. J. *Adv. Drug Deliv. Rev.* **2012**, *64*, 4–17.

17 Congreve, M.; Carr, R.; Murray, C.; Jhoti, H. *Drug Discovery Today* **2003**, *8*, 876−877.

18 Murray, C. W.; Rees, D. C. *Angew. Chem. Int. Ed.* **2016**, *55*, 488–492.

19 Nadin, A.; Hattotuwagama, C.; Churcher, I. *Angew. Chem. Int. Ed.* **2012**, *51*, 1114–1122.

20 Brown, D. G.; Boström, J. *J. Med. Chem.* **2016**, *59*, 4443–4458.

21 Blakemore, D. C.; Castro, L.; Churcher, I.; Rees, D. C.; Thomas, A. W.; Wilson, D. M.; Wood, A. *Nat. Chem.* **2018**, *10*, 383–394.

22 Vitaku, E.; Smith, D. T.; Njardarson, J. T. *J. Med. Chem.* **2014**, *57*, 10257–10274.

23 Delost, M. D.; Smith, D. T.; Anderson, B. J.; Njardarson, J. T. *J. Med. Chem.* **2018**, *61*, 10996–11020.

24 Brandi, A.; Cicchi, S.; Cordero, F. M. *Chem. Rev.* **2008**, *108*, 3988–4035.

25 Bott, T. M.; West, F. G. *Heterocycles* **2011**, *84*, 223–264.

26 Bull, J. A.; Croft, R. A.; Davis, O. A.; Doran, R.; Morgan, K. F. *Chem. Rev.* **2016**, *116*, 12150–12233.

27 Vil, V.; Terent'ev, A. O.; Al Quntar, A. A. A.; Gloriozova, T. A.; Savidov, N.; Dembitsky, V. M. *Appl. Microbiol. Biotechnol.* **2019**, *103*, 2449–2467.

28 Kutateladze, A. G.; Holt, T.; Reddy, D. S. *J. Org. Chem.* **2019**, *84*, 7575–7586.

29 (a) Wani, M. C.; Taylor, H. L.; Wall, M. E.; Coggon, P.; McPhail, A.T. *J. Am. Chem. Soc*. **1971**, *93*, 2325–2327. (b) Gueritte, F. *Curr. Pharm. Des*. **2001**, *7*, 1229−1249.

30 Shimada, N.; Hasegawa, S.; Harada, T.; Tomisawa, T.; Fujii, A.; Takita, T. *J. Antibiot.* **1986**, *39*, 1623–1625.

31 Omura, S.; Murata, M.; Imamura, N.; Iwai, Y.; Tanaka, H.; Furusaki, A.; Matsumoto, T. *J. Antibiot.* **1984**, *37*, 1324–1332.

32 Takemoto, T.; Nomoto, K.; Fushiya, S.; Ouchi, R.; Kusano, G.; Hikino, H.; Takagi, S.; Matsuura, Y.; Kakudo, M. *Proc. Jpn. Acad. Ser. B*. **1978**, *54*, 469–473.

33 Kobayashi, J.; Cheng, J.; Ishibashi, M.; Walchli, M. R.; Yamamura, S.; Ohizumi, Y. *J. Chem. Soc., Perkin Trans. I* **1991**, 1135–1137.

34 (a) Pell, A. S.; Pilcher, G. *Trans. Faraday Soc*. **1965**, *61*, 71−77. (b) Eigenmann, H. K.; Golden, D. M.; Benson, S. W. *J. Phys. Chem*. **1973**, *77*, 1687−1691. (c) Benson, S. W.;Cruickshank, F. R.; Golden, D. M.; Haugen, G. R.; O'Neal, H. E.; Rodgers, A. S.; Shaw, R.; Walsh, R. *Chem. Rev.* **1969**, *69*, 279–324. (d) Dudev, T.; Lim, C. *J. Am. Chem. Soc.* **1998**, *120*, 4450–4458.

35 (a) Chan, S. I.; Zinn, J.; Gwinn, W. D. *J. Chem. Phys*. **1961**, *34*, 1319−1329. (b) Luger, P.; Buschmann, J. *J. Am. Chem. Soc*. **1984**, *106*, 7118−7121. (c) Holan, G.; Kowala, C.; Wunderlich, J. A. *J. Chem. Soc., Chem. Commun*. **1973**, 34−34. (d) Moore, J. A.; Ayers, R. S. *Small Ring Heterocycles–Part 2: Azetidines, β-Lactams, Diazetidines, and Diaziridines*, Wiley, New York, **1983**.

36 Katritzky, A. R.; Ramsden, C. A.; Joule, J. A.; Zhdankin, V. V. *Handbook of Heterocyclic Chemistry*; Elsevier, Oxford, **2010**, 210–237.

37 Anet, F. L. A. *J. Am. Chem. Soc*. **1985**, *107*, 4335–4337.

38 Kölmel, C.; Ochsenfeld, C.; Ahlrichs, R. *Theor. Chim. Acta* **1991**, *82*, 271–284.

39 Anet, F. A. L.; Yavari, I. *J. Am. Chem. Soc*. **1977**, *99*, 2794–2796.

40 Stepan, A. F.; Karki, K.; McDonald, W. S.; Dorff, P. H.; Dutra, J. K.; DiRico, K. J.; Won, A.; Subramanyam, C.; Efremov, I. V.; O'Donnell, C. J.; Nolan, C. E.; Becker, S. L.; Pustilnik, L. R.; Sneed, B.; Sun, H.; Lu, Y.; Robshaw, A. E.; Riddell, D.; O'Sullivan, T. J.; Sibley, E.; Capetta, S.; Atchison, K.; Hallgren, A. J.; Miller, E.; Wood, A.; Obach, R. S. *J. Med. Chem.* **2011**, *54*, 7772–7783.

41 Di, L.; Whitney-Pickett, C.; Umland, J. P.; Zhang, H.; Zhang, X.; Gebhard, D. F.; Lai, Y.; Federico, J. J.; Davidson, R. E.; Smith, R.; Reyner, E. L.; Lee, C.; Feng, B.; Rotter, C.; Varma, M. V.; Kempshall, S.; Fenner, K.; El-kattan, A. F.; Liston, T. E.; Troutman, M. D. *J. Pharm. Sci.* **2011**, *100*, 4974–4985.

42 Kung, P. P.; Bingham, P.; Brooun, A.; Collins, M.; Deng, Y. L.; Dinh, D.; Fan, C.; Gajiwala, K. S.; Grantner, R.; Gukasyan, H. J.; Hu, W.; Huang, B.; Kania, R.; Kephart, S. E.; Krivacic, C.; Kumpf, R. A.; Khamphavong, P.; Kraus, M.; Liu, W.; Maegley, K. A.; Nguyen, L.; Ren, S.; Richter, D.; Rollins, R. A.; Sach, N.; Sharma, S.; Sherrill, J.; Spangler, J.; Stewart, A. E.; Sutton, S.; Uryu, S.; Verhelle, D.; Wang, H.; Wang, S.;

Wythes, M.; Xin, S.; Yamazaki, S.; Zhu, H.; Zhu, J.; Zehnder, L.; Edwards, M. *J. Med. Chem.* **2018**, *61*, 650–665.

43 Dowling, J. E.; Alimzhanov, M.; Bao, L.; Block, M. H.; Chuaqui, C.; Cooke, E. L.; Denz, C. R.; Hird, A.; Huang, S.; Larsen, N. A.; Peng, B.; Pontz, T. W.; Rivard-Costa, C.; Saeh, J. C.; Thakur, K.; Ye, Q.; Zhang, T.; Lyne, P. D. *ACS Med. Chem. Lett.* **2013**, *4*, 800–805.

44 Wuitschik, G.; Carreira, E. M.; Wagner, B.; Fischer, H.; Parrilla, I.; Schuler, F.; Rogers-Evans, M.; Müller, K. *J. Med. Chem.* **2010**, *53*, 3227–3246.

45 Wuitschik, G.; Rogers-Evans, M.; Müller, K.; Fischer, H.; Wagner, B.; Schuler, F.; Polonchuk, L.; Carreira, E. M. *Angew. Chem. Int. Ed.* **2006**, *45*, 7736–7739.

46 (a) Wuitschik, G.; Rogers-Evans, M.; Buckl, A.; Bernasconi, M.; Märki, M.; Godel, T.; Fischer, H.; Wagner, B.; Parrilla, I.; Schuler, F.; Schneider, J.; Alker, A.; Schweizer, W. B.; Müller, K.; Carreira, E. M. *Angew. Chem. Int. Ed.* **2008**, *47*, 4512–4515. (b) Burkhard, J. A.; Wuitschik, G.; Rogers-Evans, M.; Müller, K.; Carreira, E. M. *Angew. Chem. Int. Ed.* **2010**, *49*, 9052–9067.

47 Burkhard, J. A.; Wuitschik, G.; Plancher, J.-M.; Rogers-Evans, M.; Carreira, E. M. *Org. Lett.* **2013**, *15*, 4312–4315.

48 (a) Powell, N. H.; Clarkson, G. J.; Notman, R.; Raubo, P.; Martin, N. G.; Shipman, M. *Chem. Commun.* **2014**, *50*, 8797–8800. (b) Möller, G. P.; Müller, S.; Wolfstädter, B. T.; Wolfrum, S.; Schepmann, D.; Wünsch, B.; Carreira, E. M. *Org. Lett.* **2017**, *19*, 2510–2513.

49 Lassalas, P.; Oukoloff, K.; Makani, V.; James, M.; Tran, V.; Yao, Y.; Huang, L.; Vijayendran, K.; Monti, L.; Trojanowski, J. Q.; Lee, V. M.-Y.; Kozlowski, M. C.; Smith, A. B.; Brunden, K. R.; Ballatore, C. *ACS Med. Chem. Lett.* **2017**, *8*, 864–868.

50 Croft, R. A.; Mousseau, J. J.; Choi, C.; Bull, J. A. *Chem. Eur. J.* **2016**, *22*, 16271–16276.

51 Croft, R. A.; Mousseau, J. J.; Choi, C.; Bull, J. A. *Chem. Eur. J.* **2018**, *24*, 818–821.

52 Croft, R. A.; Mousseau, J. J.; Choi, C.; Bull, J. A. *Tetrahedron* **2018**, *74*, 5427–5435.

53 Zheng, Y.-J.; Tice, C. M. *Expert Opin. Drug Discov.* **2016**, *11*, 831–834.

54 Panchaud, P.; Surivet, J. P.; Diethelm, S.; Blumstein, A. C.; Gauvin, J. C.; Jacob, L.; Masse, F.; Mathieu, G.; Mirre, A.; Schmitt, C.; Enderlin-Paput, M.; Lange, R.; Gnerre, C.; Seeland, S.; Herrmann, C.; Locher, H. H.; Seiler, P.; Ritz, D.; Rueedi, G. *J. Med. Chem.* **2020**, *63*, 88–102.

55 Hansen, C. P.; Jensen, A. A.; Christensen, J. K.; Balle, T.; Liljefors, T.; Frølund, B. *J. Med. Chem.* **2008**, *51*, 7380–7395.

56 Lu, Y.; Gutgesell, L. M.; Xiong, R.; Zhao, J.; Li, Y.; Rosales, C. I.; Hollas, M.; Shen, Z.; Gordon-Blake, J.; Dye, K.; Wang, Y.; Lee, S.; Chen, H.; He, D.; Dubrovyskyii, O.; Zhao, H.; Huang, F.; Lasek, A. W.; Tonetti, D. A.; Thatcher, G. R. J. *J. Med. Chem.* **2019**, *62*, 11301–11323.

57 Burkhard, J. A.; Wagner, B.; Fischer, H.; Schuler, F.; Müller, K.; Carreira, E. M. *Angew. Chem. Int. Ed.* **2010**, *49*, 3524–3527.

58 Feskov, I. O.; Chernykh, A. V.; Kuchkovska, Y. O.; Daniliuc, C. G.; Kondratov, I. S.; Grygorenko, O. O. *J. Org. Chem.* **2019**, *84*, 1363–1371.

59 Nichols, D. E.; Frescas, S.; Marona-Lewicka, D.; Kurrasch-Orbaugh, D. M. *J. Med. Chem.* **2002**, *45*, 4344–4349.

60 (a) Searles, S.; Gortatowski, M. J. *J. Am. Chem. Soc.* **1953**, *75*, 3030–3031. (b) Searles, S.; Nickerson, R. G.; Witsiepe, W. K. *J. Org. Chem.* **1959**, *24*, 1839–1844.

61 De Kimpe, N.; Boeykens, M.; Tourwé, D. *Tetrahedron* **1998**, *54*, 2619–2630.

62 Enders, D.; Gries, J. *Synthesis* **2005**, 3508–3516.

63 (a) Nguyen, T. N. T.; Magueur, G.; Ourévitch, M.; Crousse, B.; Bégué, J. P.; Bonnet-Delpon, D. *J. Org. Chem.* **2005**, *70*, 699–702. (b) Kiss, L.; Mangelinckx, S.; Fülöp, F.; De Kimpe, N. *Org. Lett.* **2007**, *9*, 4399–4402.

64 (a) Nagai, M.; Kato, K.; Takita, T.; Nishiyama, S.; Yamamura, S. A *Tetrahedron Lett*. **1990**, *31*, 119−120. (b) Nagai, M.; Kato, K.; Takita, T.; Nishiyama, S.; Yamamura, *Tetrahedron* **1990**, *46*, 7703−7710.

65 (a) Homsi, F.; Rousseau, G. *J. Org. Chem.* **1999**, *64*, 81–85. (b) Robin, S.; Rousseau, G. *Eur. J. Org. Chem.* **2000**, 3007–3011.

66 Ehlinger, E.; Magnus, P. *J. Am. Chem. Soc.* **1980**, *102*, 5004–5011.

67 Franck, X.; Leleu, S.; Outurquin, F. *Tetrahedron Lett.* **2010**, *51*, 4437–4440.

68 Blythin, D. J.; Green, M. J.; Lauzon, M. J. R.; Shue, H.-J. *J. Org. Chem.* **1994**, *59*, 6098–6100.

69 Agami, C.; Couty, F.; Evano, G. *Tetrahedron Asymmetry* **2002**, *13*, 297–302.

70 (a) Morgan, K.; Doran, R.; Croft, R.; Hollingsworth, I.; Bull, J. *Synlett* **2016**, *27*, 106–110. (b) Morgan, K. F.; Hollingsworth, I. A.; Bull, J. A. *Chem. Commun.* **2014**, *50*, 5203–5205. (c) Davis, O. A.; Croft, R. A.; Bull, J. A. *Chem. Commun.* **2015**, *51*, 15446–15449. (d) Davis, O. A.; Bull, J. A. *Angew. Chem. Int. Ed.* **2014**, *53*, 14230–14234. (e) Boddy, A. J.; Affron, D. P.; Cordier, C. J.; Rivers, E. L.; Spivey, A. C.; Bull, J. A. *Angew. Chem. Int. Ed.* **2019**, *58*, 1458–1462.

71 D'Auria, M. *Photochem. Photobiol. Sci.* **2019**, *18*, 2297–2362.

72 Fréneau, M.; Hoffmann, N. *J. Photochem. Photobiol. C Photochem. Rev.* **2017**, *33*, 83–108.

73 (a) Xue, J.; Zhang, Y.; Wu, T.; Fun, H. K.; Xu, J. H. *J. Chem. Soc. Perkin Trans. 1.* **2001**, 183–191. (b) Matsumura, K.; Mori, T.; Inoue, Y. *J. Org. Chem.* **2010**, *75*, 5461–5469.

74 (a) Becker, M. R.; Richardson, A. D.; Schindler, C. S. *Nat. Commun.* **2019**, *10*, 5095, https://doi.org/10.1038/s41467-019-13072-x. (b) Becker, M. R.; Wearing, E. R.; Schindler, C. *Synthesis of azetidines via visible light-mediated intermolecular [2+2] photocycloaddition*, **2020**, https://doi.org/10.26434/chemrxiv.11832993.v1

75 Staudinger, H. *Justus Liebigs Ann. Chem*. **1907**, *356*, 51–123.

76 (a) Duncton, M. A. J.; Estiarte, M. A.; Tan, D.; Kaub, C.; O'Mahony, D. J. R.; Johnson, R. J.; Cox, M.; Edwards, W. T.; Wan, M.; Kincaid, J.; Kelly, M. G. *Org. Lett.* **2008**, *10*, 3259–3262. (b) González-Bobes, F.; Fu, G. C. *J. Am. Chem. Soc.* **2006**, *128*, 5360–5361. (c) Liu, Z.; Luan, N.; Shen, L.; Li, J.; Zou, D.; Wu, Y.; Wu, Y. *J. Org. Chem.* **2019**, *84*, 12358–12365. (d) Molander, G. A.; Traister, K. M.; O'Neill, B. T. *J. Org. Chem.* **2014**, *79*, 5771–5780. (e) Barré, B.; Gonnard, L.; Campagne, R.; Reymond, S.; Marin, J.;

Ciapetti, P.; Brellier, M.; Guérinot, A.; Cossy, J. *Org. Lett.* **2014**, *16*, 6160–6163. (f) Parmar, D.; Henkel, L.; Dib, J.; Rueping, M. *Chem. Commun.* **2015**, *51*, 2111–2113.

77 Wuitschik, G. *Oxetanes in Drug Discovery*; Ph.D. Thesis, ETH Zurich, **2008**.

78 (a) Heimann, A.; Dahmann, G.; Grundl, M.; Mueller, S. G.; Wellenzohn, B. *Piperazine derivatives and their use as positive allosteric modulators of MGLU5 receptors*. WO2013087805 A1, **2013**. (b) Blake, J. F.; Brandhuber, B. J.; Haas, J.; Newhouse, B.; Thomas, A. A.; Winski, S. L. *N-(Arylalkyl)-N'- pyrazoleurea, thiourea, guanidine and cyanoguanidine compounds as TrkA kinase inhibitors*. WO2014078331 A1, **2014**. (c) Alexander, R. P.; Calmiano, M. D.; Defays, S.; Durieu, V.; Deligny, M.; Heer, J. P.; Jackson, V. E.; Keyaerts, J.; Kroeplien, B., Maccoss, M.; Sabnis, Y. A.; Selby, M. D.; Swinnen, D. L. L.; Van Houtvin, N.; Zhu, Z. *Fused tricylic benzimidazoles derivatives as modulators of TNF activity*. WO2015086525 A1, **2015**

79 (a) Guérot, C.; Tchitchanov, B. H.; Knust, H.; Carreira, E. M. *Org. Lett.* **2011**, *13*, 780–783. (b) Li, D. B.; Rogers-Evans, M.; Carreira, E. M. *Org. Lett.* **2013**, *15*, 4766–4769.

80 (a) Funke, W. *Chem. Ber*. **1969**, *102*, 3148–3158. (b) Funke, W. *Angew. Chem. Int. Ed.* **1969**, *8*, 70–71.

81 (a) Hayashi, K.; Sato, C.; Hiki, S.; Kumagai, T.; Tamai, S.; Abe, T.; Nagao, Y. *Tetrahedron Lett.* **1999**, *40*, 3761–3764. (b) Ji, Y.; Wojtas, L.; Lopchuk, J. M. *Arkivoc* **2018**, *4*, 195–214.

82 Bartnik, R.; Cal, D.; Marchand, A. P.; Alihodzic, S.; Devasagayaraj, A. *Synth. Commun.* **1998**, *28*, 3949–3954.

83 (a) Marchand, A. P.; Rajagopal, D.; Bott, S. G.; Archibald, T. G. *J. Org. Chem.* **1994**, *59*, 1608–1612. (b) Gianatassio, R.; Kadish, D. *Org. Lett*. **2019**, *21*, 2060–2063.

84 Lopchuk, J. M.; Fjelbye, K.; Kawamata, Y.; Malins, L. R.; Pan, C.; Gianatassio, R.; Wang, J.; Prieto, L.; Bradow, J.; Brandt, T. A.; Collins, M. R.; Elleraas, J.; Ewanicki, J.; Farrell, W.; Fadeyi, O. O.; Gallego, G. M.; Mousseau, J. J.; Oliver, R.; Sach, N. W.; Smith, J. K.; Spangler, J. E.; Zhu, H.; Zhu, J.; Baran, P. S. *J. Am. Chem. Soc.* **2017**, *139*, 3209–3226.

85 Fawcett, A.; Murtaza, A.; Gregson, C. H. U.; Aggarwal, V. K. *J. Am. Chem. Soc.* **2019**, *141*, 4573–4578.

86 Dryzhakov, M.; Richmond, E.; Moran, J. *Synthesis* **2016**, *48*, 935–959.

87 Rueping, M.; Nachtsheim, B. J. *Beilstein J. Org. Chem.* **2010**, *6*, 1–24.

88 Croft, A. R. *Exploring Oxetane Isosteres for Drug Discovery through the Catalytic Generation of Oxetanyl Carbocations*. PhD. Thesis. Imperial College London, London, **2018**.

89 (a) Wu, S.-B.; Long, C.; Kennelly, E. J. *Nat. Prod. Rep*. **2014**, 31, 1158–1174. (b) Mondal, S.; Panda, G. *RSC. Adv*. **2014**, *4*, 28317–28358.

90 Preston, G. W.; Wilson, A. J. *Chem. Soc. Rev.* **2013**, *42*, 3289–3301.

91 Galardy, R. E.; Craig, L. C.; Jamieson, J. D.; Printz, M. P. *J. Biol. Chem.* **1974**, *249*, 3510–3518.

92 (a) Meanwell, N. A. *J. Med. Chem.* **2011**, *54*, 2529–2591. (b) Patani, G. A.; LaVoie, E. J. *Chem. Rev.* **1996**, *96*, 3147–3176.

93 Griffen, E.; Leach, A. G.; Robb, G. R.; Warner, D. J. *J. Med. Chem.* **2011**, *54*, 7739–7750.

94 Ding, Y. *3,3–Diaryloxetanes as Bioisosteres in Medicinal Chemistry: Study and Understanding of ADME Properties*. MRes Thesis. Imperial College London, London, **2017**.

95 Yan, J.; Ni, T.; Yan, F. *Tetrahedron Lett.* **2015**, *56*, 1096–1098.

96 Song, S.; Sun, X.; Li, X.; Yuan, Y.; Jiao, N. *Org. Lett.* **2015**, *17*, 2886–2889.

97 Perry, G. J. P.; Quibell, J. M.; Panigrahi, A.; Larrosa, I. *J. Am. Chem. Soc*. **2017**, *139*, 11527–11536.

98 Wolfe, J. P.; Tomori, H.; Sadigho, J. P.; Yin, J.; Buchwald, S. L. *J. Org. Chem.*, **2000**, *65*, 1158–1174.

99 Åhman, J.; Buchwald, S. L. *Tetrahedron Lett.* **1997**, *38*, 6363–6366.

100 Maiti, D.; Buchwald, S. L. *J. Org. Chem.* **2010**, *75*, 1791–1794.

101 Santoso, M.; Somphol, K.; Kumar, N.; Black, D. S. *Tetrahedron* **2009**, *65*, 5977–5983.

102 Iovel, I.; Mertins, K.; Kischel, J.; Zapf, A.; Beller, M. *Angew. Chem. Int. Ed*. **2005**, *44*, 3913–3917.

103 Niggemann, M.; Meel, M. J. *Angew. Chem. Int. Ed.* **2010**, *49*, 3684–3687.

104 (a) Lombardo, F.; Shalaeva, M. Y.; Tupper, K. A.; Gao, F.; Abraham, M. H. *J. Med. Chem.* **2000**, *43*, 2922–2928. (b) Lombardo, F.; Shalaeva, M. Y.; Tupper, K. A.; Gao, F. *J. Med. Chem.* **2001**, *44*, 2490–2497.

105 OECD 107 Method, 1995. OECD guideline for the testing of chemicals adopted by the Council on 27th July 1995 Partition Coefficient (*n*-octanol/water): Shake Flask Method.

106 Marquess, D.; Choi, S-K.; Chinn, J. P.; Fatheree, P. R.; Turner, D. *Sodium channel modulators*. US7183323B2, **2007**.

107 Pettit, G. R.; Toki, B.; Herald, D. L.; Verdier-Pinard, P.; Boyd, M. R.; Hamel, E.; Pettit, R. K. *J. Med. Chem.* **1998**, *41*, 1688–1695.

108 Getahun, Z.; Chu, P. S.; Lin, C. M.; Hamel, E.; Jurd, L. *J. Med. Chem.* **1992**, *35*, 1058–1067.

109 Lammel Lindemann, J.; Webb, P. *Expert Opin. Ther. Targets* **2016**, *20*, 145–149.

110 (a) Scanlan, T. S.;Chellini, G.; Apriletti, J.; Baxter, J. D.; Ribeiro, R. C. J. *Selective thyroid hormone analogs*. WO98/57919, **1998**. (b) Yoshihara, H. A. I.; Apriletti, J. W.; Baxter, J. D.; Scanlan, T. S. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2821–2825.

111 Denis, C.; Dubois, M. A. J.; Voisin-Chiret, A. S.; Bureau, R.; Choi, C.; Mousseau, J. J.; Bull, J. A. *Org. Lett.* **2019**, *21*, 300–304.

112 Dubois, M. A. J.; Lazaridou, A.; Choi, C.; Mousseau, J. J.; Bull, J. A. *J. Org. Chem.* **2019**, *84*, 5943–5956.

113 Denis, C. *Conception, synthèse et évaluation biologique d'inhibiteurs des protéines de la famille Bcl-2 à visée anticancéreuse – Applications aux cancers de l'ovaire chimiorésistants*. PhD thesis. Centres d'Etudes et de la Recherche sur le Médicament de Normandie, Université de Caen, Caen, **2018**.

114 Lazaridou, A. *Synthesis & Reaction of 3-Aryl-3-Sulfanyl Azetidines as Novel Structural Motifs for Medicinal Chemists*. MRes thesis. Imperial College London, London, **2018**.

115 (a) Woodhead, S. J.; Downham, R.; Hamlett, C.; Howard, S.; Sore, H. F.; Verdonk, M. L.; Walker, D. W.; Luke, R. W. A. *Aryl- alkylamines and heteroaryl-alkylamines as protein kinase inhibitors*. PCT Int. Appl. WO2006136830A1, Dec 26, **2006**. (b) Donald, D. K.; Jennings, A. S. R.; Ray, N. C.; Roussel, F.; Sutton, J. M.; Tisselli, P.; Wilson, M. *Cyclic amine derivatives having beta2 adrenergic receptor agonist and muscarinic receptor antagonist activity*. WO2011048409A1, Apr 28, **2011**. (c) Debenham, J. S.; Graham, T. H.; Verras, A.; Zhang, Y.; Clements, M. J.; Kuethe, J. T.; Madsen-Duggan, C.; Liu, W.; Bhatt, U. R.; Chen, D.; Chen, Q.; Garcia-Calvo, M.; Geissler, W. M.; He, H.; Li, X.; Lisnock, J.; Shen, Z.; Tong, X.; Tung, E. C.; Wiltsie, J.; Xu, S.; Hale, J. J.; Pinto, S.; Shen, D. M. *Bioorganic Med. Chem. Lett.* **2013**, *23*, 6228–6233.

116 Fröhlich, J.; Sauter, F.; Blasl, K. *Heterocycles* **1994**, *37*, 1879–1891.

117 Yaroshevsky, A. A. *Geochemistry Int.* **2006**, *44*, 48–55.

118 (a) Haubenreisser, S.; Niggemann, M. *Adv. Synth. Catal.* **2011**, *353*, 469–474. (b) Davies, J.; Leonori, D. *Chem. Commun.* **2014**, *50*, 15171–15174.

119 (a) Thaxton, A.; Izenwasser, S.; Wade, D.; Stevens, E. D.; Mobley, D. L.; Jaber, V.; Lomenzo, S. A.; Trudell, M. L. *Bioorganic Med. Chem. Lett.* **2013**, *23*, 4404–4407. (b) Bouix-Peter, C.; Suzuki, I.; Rodeville, N.; Mauvais, P.; Pascal, J.-C. *Oxoazetidine derivatives, process for the preparation thereof and use thereof in human medicine and in cosmetics*. WO2010136830A1, **2010**.

120 Krasovskiy, A.; Knochel, P. *Angew. Chem. Int. Ed.* **2004**, *43*, 3333–3336.

121 Varchi, G.; Kofink, C.; Lindsay, D. M.; Knochel, P.; München, L.; Haus, F.; Mangini, O. A. *Chem. Commun*. **2003**, 396–397.

122 Ren, H.; Krasovskiy, A.; Knochel, P. *Chem. Commun.* **2005**, 543–545.

123 Cacchi, S.; Ciattini, P. G.; Morera, E.; Ortar, G.*Tetrahedron Lett.* **1986**, *27*, 5541–5544.

124 Scott, K. A.; Njardarson, J. T. *Top. Curr. Chem.* **2018**, *376*, 1–34.

125 Devendar, P.; Yang, G. F. *Top. Curr. Chem*. **2017**, *375*, 1–44.

126 (a) Isakovic, L.; Saavedra, O. M.; Llewellyn, D. B.; Claridge, S.; Zhan, L.; Bernstein, N.; Vaisburg, A.; Elowe, N.; Petschner, A. J.; Rahil, J.; Beaulieu, N.; Gauthier, F.; MacLeod, A. R.; Delorme, D.; Besterman, J. M.; Wahhab, A. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 2742–2746. (b) Le Grand, D. M. *1,3-Disubstituted azetidine derivatives for use as CCR-3 receptor antagonists in the treatment of inflammatory and allergic diseases*. WO2005026113A1, March 24, **2005**. (c) Kasai, S.; Kaku, T.; Kamaura, M. *Heterocyclic compounds*. WO2009051244A1, April 23, **2009**. (d) Kim, B.-J.; Kim, J.-H.; Kong, J.-H.; Cho, H.; Choi, Y.-R.; Kim, C.-S. *2-Arylmethylazetidine cabapenem derivatives and preparation thereof*. WO2006025634A1, March 9, **2006**.

127 (a) Cheshire, D.; Luker, T.; Mete, A. *Novel phenylheteroazetidines, useful as nitric oxide synthase inhibitors*. WO02/12187A1, Feb 2, **2002**. (b) Cohen, F.; Konradi, A. W.; Choi, T. A. J.; Machajewski, T. D.; Kane, T. R.; Hildebrandt, D. J. *Antibacterial agents*. WO2017/223349A1, Dec 28, **2017**.

128 Stankovic, S.; Goossens, H.; Catak, S.; Tezcan, M.; Waroquier, M.; Van Speybroeck, V.; D'hooghe, M.; De Kimpe, N. *J. Org. Chem*. **2012**, *77*, 3181−3190.

129 Phelan, J. P.; Patel, E. J.; Ellman, J. A. *Angew. Chem. Int. Ed*. **2014**, *53*, 11329−11332.

130 (a) Guindon, Y.; Frenette, R.; Fortin, R.; Rokach, J. *J. Org. Chem.* **1983**, *48*, 1357–1359. (b) Inada, Y.; Nishibayashi, Y.; Hidai, M.; Uemura, S. *J. Am. Chem. Soc.* **2002**, *124*, 15172–15173. (c) Firouzabadi, H.; Iranpoor, N.; Jafarpour, M. *Tetrahedron Lett.* **2006**, *47*, 93–97. (d) Chatterjee, P. N.; Roy, S. *J. Org. Chem.* **2010**, *75*, 4413–4423.

131 Biswas, S.; Samec, J. S. M. *Chem. Asian J.* **2013**, *8*, 974–981.

132 Jung, M. E.; Lyster, M. A. *J. Chem. Soc., Chem. Commun*. **1978**, 315−316.

133 Colomer, I.; Chamberlain, A. E. R.; Haughey, M. B.; Donohoe, T. J. *Nat. Rev. Chem.* **2017**, *1*, 0088.

134 Vuluga, D.; Legros, J.; Crousse, B.; Slawin, A. M. Z.; Laurence, C.; Nicolet, P.; Bonnet-Delpon, D. *J. Org. Chem.* **2011**, *76*, 1126–1133.

135 Berkessel, A.; Adrio, J. A.; Hüttenhain, D.; Neudörfl, J. M. *J. Am. Chem. Soc.* **2006**, *128*, 8421–8426.

136 Berkessel, A.; Adrio, J. A. *Adv. Synth. Catal.* **2004**, *346*, 275–280.

137 Brenek, S. J.; Caron, S.; Chisowa, E.; Delude, M. P.; Drexler, M. T.; Ewing, M. D.; Handfield, R. E.; Ide, N. D.; Nadkarni, D. V.; Nelson, J. D.; Olivier, M.; Perfect, H. H.; Phillips, J. E.; Teixeira, J. J.; Weekly, R. M.; Zelina, J. P. *Org. Process Res. Dev.* **2012**, *16*, 1348–1359.

138 Trillo, P.; Baeza, A.; Nájera, C. *J. Org. Chem.* **2012**, *77*, 7344–7354.

139 Mo, X.; Yakiwchuk, J.; Dansereau, J.; Adam McCubbin, J.; Hall, D. G. *J. Am. Chem. Soc.* **2015**, *137*, 9694–9703.

140 Vuković, V. D.; Richmond, E.; Wolf, E.; Moran, J. *Angew. Chem. Int. Ed.* **2017**, *56*, 3085–3089.

141 Qi, C.; Gandon, V.; Lebœuf, D. *Angew. Chem. Int. Ed.* **2018**, *57*, 14245–14249.

142 Willot, M.; Chen, J.; Zhu, J. *Synlett* **2009**, 577–580.

143 McCubbin, J. A.; Krokhin, O. V. *Tetrahedron Lett.* **2010**, *51*, 2447–2449.

144 Brown, H. C.; Okamoto, Y. *J. Am. Chem. Soc.* **1958**, *80*, 4979–4987.

145 Jiang, M.; Feng, L.; Feng, J.; Jiao, P. *Org. Lett.* **2017**, *19*, 2210–2213.

146 (a) Huang, Y.; Walji, A. M.; Larsen, C. H.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 15051–15053. (b) Wang, Z. *Molecules* **2019**, *24*, 3412.

147 Huang, Z.-H.; Zou, J.-P.; Jiang, W.-Q. *Tetrahedron Lett.* **2006**, *47*, 7965–7968.

148 Hashmi, A. S. K.; Schwarz, L.; Choi, J.; Frost, T. M. *Angew. Chem. Int. Ed.* **2000**, *39*, 2285–2288.

149 Bandini, M.; Cozzi, P. G.; Giacomini, M.; Melchiorre, P.; Selva, S.; Umani-Ronchi, A. *J. Org. Chem.* **2002**, *67*, 3700–3704.

150 Liang, D.; Li, X.; Zhang, W.; Li, Y.; Zhang, M.; Cheng, P. *Tetrahedron Lett.* **2016**, *57*, 1027–1030.

151 Aguilar, R.; Benavides, A.; Tamariz, J. *Synth. Commun.* **2004**, *34*, 2719–2735.

152 Alam, M. M.; Varala, R.; Adapa, S. R. *Tetrahedron Lett.* **2003**, *44*, 5115–5119.

153 Li, W.; Werner, T. *Org. Lett.* **2017**, *19*, 2568–2571.

154 Zhang, H. B.; Liu, L.; Liu, Y. L.; Chen, Y. J.; Wang, J.; Wang, D. *Synth. Commun.* **2007**, *37*, 173–181.

155 Bhattacharya, A.; Shukla, P. M.; Maji, B. *R. Soc. Open Sci.* **2017**, *4*, 170748.

156 Scriabine, I. *Bull. Chem. Soc. Fr.* **1961**, *6*, 1194–1198.

157 Sun, Z.-M.; Zhang, J.; Manan, R. S.; Zhao, P. *J. Am. Chem. Soc.* **2010**, *132*, 6935–6937.

158 Walter, F. R.; Veszelka, S.; Pásztói, M.; Péterfi, Z. A.; Tóth, A.; Rákhely, G.; Cervenak, L.; Ábrahám, C. S.; Deli, M. A. *J. Neurochem.* **2015**, *134*, 1040–1054.

159 Keating, G. M.; Croom, K. F. *Drugs* **2007**, *67*, 121–153.

160 Ciamician, G. *Science*. **1912**, *36*, 385–394.

161 Prier, C. K.; Rankic, D. A.; Macmillan, D. W. C. *Chem. Rev*. **2013**, *113*, 5322–5363.

162 Cano-Yelo, H.; Deronzier, A. *J. Chem. Soc., Perkin Trans. 2*, **1984**, 1093–1098.

163 Nicewicz, D. A.; MacMillan. D. W. C. *Science*. **2008**, *322*, 77–80.

164 Ischay, M.A.; Anzovino, M. E.; Du, J.; Yoon, T. P. *J. Am. Chem. Soc.* **2008**, *130*, 12886–12887.

165 Arias-Rotondo, D. M.; McCusker, J. K. *Chem. Soc. Rev.* **2016**, *45*, 5803–5820.

166 Twilton, J.; Le, C. C.; Zhang, P.; Shaw, M. H.; Evans, R. W.; MacMillan, D. W. C. *Nat. Rev. Chem.* **2017**, *1*, 1–18.

167 Ahlgren, G. *J. Org. Chem*. **1973**, *38*, 1369–1374.

168 Chambers, R. D.; Grievson, B. *J. Chem. Soc., Perkin Trans*. *1*. **1985**, *1*, 2215–2218.

169 Hirano, K.; Sakaguchi, S.; Ishii, Y. *Tetrahedron Lett.* **2002**, *43*, 3617–3620.

170 Hashizume, S.; Oisaki, K.; Kanai, M. *Org. Lett.* **2011**, *13*, 4288–4291.

171 Ravelli, D.; Zoccolillo, M.; Mella, M.; Fagnoni, M. *Adv. Synth. Catal.* **2014**, *356*, 2781–2786.

172 Jin, J.; MacMillan, D. W. C. *Angew. Chem. Int. Ed.* **2015**, *54*, 1565–1569.

173 Shaw, M. H.; Shurtleff, V. W.; Terrett, J. A.; Cuthbertson, J. D.; MacMillan, D. W. C. *Science* **2016**, *352*, 1301–1304.

174 Le, C.; Liang, Y.; Evans, R. W.; Li, X.; MacMillan, D. W. C. *Nature* **2017**, *547*, 79–83.

175 Bosset, C.; Beucher, H.; Bretel, G.; Pasquier, E.; Queguiner, L.; Henry, C.; Vos, A.; Edwards, J. P.; Meerpoel, L.; Berthelot, D. *Org. Lett.* **2018**, *20*, 6003–6006.

176 McManus, J. B.; Onuska, N. P. R.; Nicewicz, D. A. *J. Am. Chem. Soc.* **2018**, *140*, 9056–9060.

177 Nuhant, P.; Oderinde, M. S.; Genovino, J.; Juneau, A.; Gagné, Y.; Allais, C.; Chinigo, G. M.; Choi, C.; Sach, N. W.; Bernier, L.; Fobian, Y. M.; Bundesmann, M. W.; Khunte, B.; Frenette, M.; Fadeyi, O. O. *Angew. Chem. Int. Ed.* **2017**, *56*, 15309–15313.

178 Li, Z.; Wang, X.; Xia, S.; Jin, J. *Org. Lett.* **2019**, *21*, 4259–4265.

179 Constantin, T.; Zanini, M.; Regni, A.; Sheikh, N. S.; Juliá, F.; Leonori, D. *Science.* **2020**, *367*, 1021–1026.

180 Genovino, J.; Lian, Y.; Zhang, Y.; Hope, T. O.; Juneau, A.; Gagné, Y.; Ingle, G.; Frenette, M. *Org. Lett.* **2018**, *20*, 3229–3232.

181 Green, S. A.; Vásquez-Céspedes, S.; Shenvi, R. A. *J. Am. Chem. Soc.* **2018**, *140*, 11317–11324.

182 Kolahdouzan, K.; Khalaf, R.; Grandner, J. M.; Chen, Y.; Terrett, J. A.; Huestis, M. P. *ACS Catal.* **2020**, *10*, 405–411.

183 Roslin, S.; Odell, L. R. *Eur. J. Org. Chem.* **2017**, 1993–2007.

184 Nguyen, J. D.; Amato, E. M. D.; Narayanam, J. M. R.; Stephenson, C. R. J. *Nat. Chem.* **2012**, *4*, 854–859.

185 Li, Y.; Ge, L.; Muhammad, M.; Bao, H. *Synthesis* **2017**, *49*, 5263–5284.

186 Zuo, Z.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2014**, *136*, 5257–5260.

187 Noble, A.; Mccarver, S. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2015**, *137*, 624–627.

188 Zuo, Z.; Ahneman, D. T.; Chu, L.; Terrett, J. A.; Doyle, A. G.; Macmillan, D. W. C. *Science.* **2014**, *345*, 437–440.

189 Okada, K.; Okamoto, K.; Morita, N.; Okubo, K.; Oda, M. *J. Am. Chem. Soc.* **1991**, *113*, 9401–9402.

190 Tellis, J. C.; Primer, D. N.; Molander, G. A. *Science.* **2014**, *345*, 433–436.

191 Primer, D. N.; Karakaya, I.; Tellis, J. C.; Molander, G. A. *J. Am. Chem. Soc.* **2015**, *137*, 2195–2198.

192 Yamashita, Y.; Tellis, J. C.; Molander, G. A. *Proc. Natl. Acad. Sci.* **2015**, *112*, 12026–12029.

193 Primer, D. N.; Molander, G. A. *J. Am. Chem. Soc.* **2017**, *139*, 9847–9850.

194 Corcé, V.; Chamoreau, L. M.; Derat, E.; Goddard, J. P.; Ollivier, C.; Fensterbank, L. *Angew. Chem. Int. Ed.* **2015**, *54*, 11414–11418.

195 Pedley, J. B.; Naylor, R. D.; Kirby, S. P. *In Thermochemical Data of Organic Compounds*, 2nd ed.; Chapman and Hall: New York, **1986**.

196 (a) Chenneberg, L.; Baralle, A.; Daniel, M.; Fensterbank, L.; Goddard, J. P.; Ollivier, C. *Adv. Synth. Catal.* **2014**, *356*, 2756–2762. (b) Vara, B. A.; Patel, N. R.; Molander, G. A. *ACS Catal.* **2017**, *7*, 3955–3959. (c) Wu, J.; Bär, R. M.; Guo, L.; Noble, A.; Aggarwal, V. K. *Angew. Chem. Int. Ed.* **2019**, *58*, 18830–18834.

197 Lackner, G. L.; Quasdorf, K. W.; Overman, L. E. *J. Am. Chem. Soc.* **2013**, *135*, 15342–15345.

198 Lackner, G. L.; Quasdorf, K. W.; Pratsch, G.; Overman, L. E. *J. Org. Chem.* **2015**, *80*, 6012–6024.

199 Nawrat, C. C.; Jamison, C. R.; Slutskyy, Y.; MacMillan, D. W. C.; Overman, L. E. *J. Am. Chem. Soc.* **2015**, *137*, 11270–11273.

200 Zhang, X.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2016**, *138*, 13862–13865.

201 Munyemana, F.; Frisque-Hesbain, A.-M.; Devos, A.; Ghosez, L. *Tetrahedron Lett*. **1989**, *30*, 3077–3080.

202 Dubois, M. A. J.; Smith, M. A.; White, A. J. P.; Lee Wei Jie, A.; Mousseau, J. J.; Choi, C.; Bull, J. A. *Org. Lett.* **2020**, *22*, 5279–5283.

203 Buckman, B. O.; Nicholas, J. B.; Emayan, K.; Seiwert, S. D. *Lysophosphatidic acid receptor antagonists*. WO2013025733A1, Feb 21, **2013**.

204 Cernak, T. A.; Balkovec, J. M.; Nargund, R. P.; Reiter, M.; Sperbeck, D. M.; Dykstra, K. D.; Yu, Y.; Dreher, S.; Maloney, K. M.; Wu, Z.; Devita, R. J.; Verras, A. *Spirocyclic compounds*. WO2012009217A1, July 8, **2011**.

205 Tellew, J. E.; Wang, X.; Wan, Y.; Xie, Y. F.; Pan, S.; Jiang, J.; Xie, Y.; Hunt, T. A.; Edwards, L.; Beattie, D.; Healy, M. P.; West, R.; Lister, A. S. *Compositions and methods for modulating LPA receptors*. WO2012138648A1, April 3, **2012**.

206 Amani, G.; Armani, E.; Black-Aby, W.; Van de Poël, H.; Baker-Glenn, C.; Trivedi, N. *Aminoester derivatives*. WO2016/177849A1, Nov 10, **2016**.

207 Rieu, J. P.; Boucherle, A.; Cousse, H.; Mouzin, G. *Tetrahedron*. **1986**, *42*, 4095–4131.

208 (a) Wolfe, M. M.; Lichtenstein, D. R.; Singh, G. N. *Engl. J. Med*. **1999**, *340*, 1888–1899. (b) Singh, G.; Ramey, D. R.; Morfeld, D.; Shi, H.; Hatoum, H. T.; Fries, J. F. *Arch. Int. Med*. **1996**, *156*, 1530–1536. (c) Fries. J. F. *J. Rheumatol*. **1991**, 6–10. (d) Bally, M.; Dendukuri, N.; Rich, B.; Nadeau, L.; Helin-Salmivaara, A.; Garbe, E.; Brophy, J. *BMJ*. **2017**, doi: 10.1136/bmj.j1909.

209 (a) Windsor, M. A.; Hermanson, D. J.; Kingsley, P. J.; Xu, S.; Crews, B. C.; Ho, W.; Keenan, C. M.; Banerjee, S.; Sharkey, K. A.; Marnett, L. J. *ACS Med. Chem. Lett.* **2012**, *3*, 759. (b) Marnett, L. J.; Patel, S.; Hermanson, D. J.; Windsor, M. *Compositions and methods for substrate-selective inhibition of endocannabinoid oxygenation*. WO2014/015341A2, Jan 23, **2014**.

210 Stock, N.; Munoz, B.; Wrigley, J. D. J.; Shearman, M. S.; Beher, D.; Peachey, J.; Williamson, T. L.; Bain, G.; Chen, W.; Jiang, X.; St-Jacques, R.; Prasit, P. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2219–2223.

211 House, H. O.; Phillips, W. V.; Sayer, T. S. B.; Yau, C. C. *J. Org. Chem.* **1978**, *43*, 700–710.

212 (*a*) Amari, G.; Armani, E.; Black-Aby, W.; Van De Poël, H.; Baker-Glenn, C.; Trivedi, N. *Aminoester derivatives*. WO2016177849A1, Nov 10, **2016**. (*b*) He, Z.-T.; Hartwig, J. F. *Nat. Commun.* **2019**, *10*, 4083.

213 Merino, P.; Tejero, T.; Ignacio, J.; Matute, R. *Current Org. Chem*. **2007**, *11*, 1076–1091.

214 Noji, M.; Sunahara, H.; Tsuchiya, K.; Mukai, T.; Komasaka, A.; Ishii, K. *Synthesis* **2008**, 3835–3845.

215 Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936–3938.

216 (a) Lee, D. G.; Engh, M. Van Den. *Can. J. Chem.* **1972**, *50*, 3129–3134. (b) Smith III, A. B.; Scarborough, R. M. *Synth. Commun.* **1980**, *10*, 205–211. (c) Yoshifuji, S.; Arakawa, Y.; Nitta, Y. *Chem. Pharm. Bull.* **1987**, *35*, 357–363. (d) Michiharu, K.; Haruo, K.; Akira, Y. *Chem. Lett*. **1985**, *14*, 1785–1788.

217 (a) Piancatelli, G.; D'Auria, M.; D'Onofrio, F. *Synthesis* **1994**, 867–889. (b) Lipshutz, B. H. *Chem. Rev.* **1986**, *86*, 795–819. (c) Gingerich, S. B.; Jennings, P. W. *J. Org. Chem.* **1984**, *49*, 1284–1286.

218 Williams, P. D.; LeGoff, E. *J. Org. Chem.* **1981**, *46*, 4143–4147.

219 Kobayashi, Y.; Katsuno, H.; Sato, F. *Chem. Lett*. **1983**, 1771–1774.

220 Smith, M. A. *Synthesis and photocatalytic reactions of 3-arylazetidine-3-carboxylic acids. Novel heterocyclic motifs for drug discovery*. MRes Thesis. Imperial College London, London, **2019**.

221 He, W.; Zhou, B.; Liu, W.; Zhang, M.; Shen, Z.; Han, Z.; Jiang, Q.; Yang, Q.; Song, C.; Wang, R.; Niu, T.; Han, S.; Zhang, L.; Wu, J.; Guo, F.; Zhao, R.; Yu, W.; Chai, J.; Chang, J. *J. Med. Chem.* **2015**, *58*, 7341–7348.

222 Croft, R. A.; Dubois, M. A. J.; Boddy, A. J.; Denis, C.; Lazaridou, A.; Voisin-Chiret, A. S.; Bureau, R.; Choi, C.; Mousseau, J. J.; Bull, J. A. *Eur. J. Org. Chem.* **2019**, 5385–5395.

223 (a) Wu, J. I. C.; von Ragué Schleyer, P. *Pure Appl. Chem.* **2013**, *85*, 921–940. (b) Olah, G. A.; Jeuell, C. L.; Kelly, D. P.; Porter, R. D. *J. Am. Chem. Soc.* **1972**, *94*, 146–156.

224 White, C.; McGowan, M. A.; Zhou, H.; Sciammetta, N.; Fradera, X.; Lim, J.; Joshi, E. M.; Andrews, C.; Nickbarg, E. B.; Cowley, P.; Trewick, S.; Augustin, M.; von Köenig, K.; Lesburg, C. A.; Otte, K.; Knemeyer, I.; Woo, H.; Yu, W.; Cheng, M.; Spacciapoli, P.; Geda, P.; Song, X.; Smotrov, N.; Curran, P.; Heo, M. R.; Abeywickrema, P.; Miller, J. R.; Bennett, D. J.; Han, Y. *ACS Med. Chem. Lett.* **2020**, *11*, 550–557.

225 Chu, L.; Ohta, C.; Zuo, Z.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2014**, *136*, 10886–10889.

226 For details and procedure see: (a) Buzzetti, L.; Crisenza, G. E. M.; Melchiorre, P. *Angew. Chem. Int. Ed.* **2019**, *58*, 3730–3747. (b) Cismesia, M. A.; Yoon, T. P. *Chem. Sci.* **2015**, *6*, 5426–5434.

227 a) Hughes, M.; Boultwood, T.; Zeppetelli, G.; Bull, J. A. *J. Org. Chem.* **2013**, *78*, 844–854. b) Chawner, S. J.; Cases-Thomas, M. J.; Bull, J. A. *Eur. J. Org. Chem.* **2017**, 5015–5024.

228 Bocchi, V.; Palla, G. *Synthesis*. **1982**, 1096–1097.

229 Pierce, L. T.; Cahill, M. M.; McCarthy, F. O. *Tetrahedron* **2010**, *66*, 9754–9761.

230 Song, J.; Li, X.; Liang, A.; Li, J.; Zou, D.; Wu, Y.; Wu, Y. *Tetrahedron Lett.* **2014**, *55*, 2369–2372.

231 Sole, D.; Serrano, O. *J. Org. Chem*. **2008**, *73*, 9372–9378.

232 Poppe, M.; Chen, C.; Liu, F.; Poppe, S.; Tschierske, C. *Chem. Eur. J*. **2017**, *23*, 7196–7200.

233 Jammula, S. R.; Anna, V. R.; Tatina, S.; Krishna, T.; Sreenivas, B. Y.; Pal, M. *Tetrahedron Lett*., **2016**, *57*, 3924–3928.

234 Leete, E. *J. Am. Chem. Soc.* **1959**, *81*, 6023–6026.

235 Beswick, P. J.; Harling, J. D.; Kleanthous, S.; Patel, V. K.; Simpson, J.; *Propionic acid derivatives and their use as HPPARS activators*. WO2004/000762 A3, **2003**.

236 Phadnis, A. P.; Nanda, B.; Patwardhan, S. A.; Gupta, A. S. *In. J. Chem*. **1984**, *23*, 1098–1102.

237 Khalafi-Nezhad, A.; Alamdari, R. F.; Zekri, N. *Tetrahedron*, **2000**, *56*, 7503–7506.

238 Chiellini, G.; Nguyen, N.; Yoshihara, H. A. I.; Scanlan, T. S. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2607–2611.

239 King, P.; Thompson III, L. A.; Shi, J.; Thangathirupathy, S.; Warrier, J. S.; Islam, I.; Macor, J. E. *Selective NR2B antagonists*. US20150191452 A1, Dec. 29. **2015**.

240 Lee, Y. J.; Ling, R.; Mariano, P. S.; Yoon, U. C.; Kim, D. U.; Oh, S. W. *J. Org. Chem.* **1996**, *61*, 3304–3314.

241 Zheng, H.; Ghanbari, S.; Nakamura, S.; Hall, D.G. *Angew. Chem. Int. Ed*., **2012**, *51*, 6187–6190.

242 Zhersh, S.; Buryanov, V. V.; Karpenko, O. V.; Grygorenko, O. O.; Tolmachev, A. A. *Synthesis* **2011**, *22*, 3669–3674.

243 Justo de Pomar, J. C.; Soderquist, J. A. *Tetrahedron Lett*. **1998**, *39*, 4409–4412.

244 Haradahira, T.; Maeda, J.; Okauchi, T.; Zhang, M. R.; Hojo, J.; Kida, T.; Arai, T.; Yamamoto, F.; Sasaki, S.; Maeda, M.; Suzuki, K.; Suhara, T. *Nucl. Med. Biol*. **2002**, *29*, 517−525.

245 Gauvin, J-C.; Surivet, J-P. *Antibacterial quinazoline-4(3H)-one derivatives*. WO2015173329A1, Nov 19. **2015**.

246 Armer, R.; Belfield, A.; Bingham, M.; Johnson, A.; Margathe, J-F.; Avery, C.; Hughes, S.; Morrison, A. *Compounds useful as CSF1 modulators*. WO2016051193A1, Apr 07. **2016**.

247 Lewis, F. D.; Turro, N. J. *J. Am. Chem. Soc.* **1970**, *92*, 311–320.

248 Wang, Z.; Chen, Z.; Sun, J. *Angew. Chem. Int. Ed.* **2013**, *52*, 6685–6688.

249 Barsanti, P.A.; Bence, N. F.; Gosling, J.; Saha, A.; Taherbhoy, A. M.; Zapf, C. W.; Boyle, K.; Cardozo, M.; Mihalic, J.; Lawrenz, M.; Gallop, M.; Bruffey, J.; Cummins, T.; Robbins, D.; Tanaka, H.; Wang, C.; Cohen, F.; Palmer, W.; Sands, A. T.; Shunatona, H. *Inhibitors of CBL-B and methods of use thereof*. WO2019148005A1, Aug 01. **2019**.

250 Jena, T. K.; Khan, F. A. *J. Org. Chem.* **2019**, *84*, 14270–14280.

251 McManus, J. B.; Nicewicz, D. A. *J. Am. Chem. Soc.* **2017**, *139*, 2880–2883.

252 Roberts, D. D. *J. Org. Chem.* **1974**, *39*, 1265–1269.

253 Liptak, V. P.; Wulff, W. D. *Tetrahedron*, **2000**, *56*, 10229–10247.

254 Weedon, A. C.; Zhang, B. *Synthesis* **1992**, 95–100.

255 Wilt, J. W.; Roberts, D. D. *J. Org. Chem*. **1962**, *27*, 3430–3434.

256 (a) Anderson, G. H.; Smith, A. *Can. J. Chem.* **1968**, *46*, 1561–1570. (b) Holland, H. L.; Kindermann, M.; Kumaresan, S.; Stefanac, T. *Tetrahedron: Asymm.* **1993**, *4*, 1353–1364.

257 Fiege, H.; Jautelat, M.; Arlt, D. *Process for the preparation of 2,2-bis-chloro-methylalkanecarboxylic acid chlorides*. US4871484, Oct 3, **1989**.

258 Shen, D., M.;Egbertson, M.; Berger, R.; Qian, X.; Harper, B.; Yang, M.; Qiang Guo, Z.; Z.; Rada, V. L.; Wang, D.; Cernak, T. A.; Sinz, C.; Wang, M.; Wilson, J. E.; Xu, S. *Pyrimidone carboxamide compounds as PDE2 inhibitors*. US2017015633A1, Jan 19, **2017**.

259 Allwood, D. M.; Blakemore, D. C.; Brown, A. D.; Ley, S. V. *J. Org. Chem.* **2014**, *79*, 328–338.

260 Yang, Y.; Zhou, Q.; Cai, J.; Xue, T.; Liu, Y.; Jiang, Y.; Su, Y.; Chung, L.; Vicic, D. A. *Chem. Sci.* **2019**, *10*, 5275–5282.

261 Su, X.; Fox, D. J.; Blackwell, D. T.; Tanaka, K.; Spring, D. R. *Chem. Commun.* **2006**, 3883–3885.

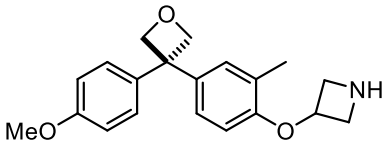
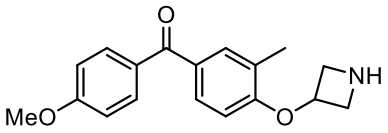
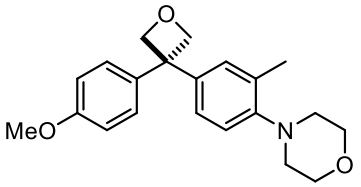
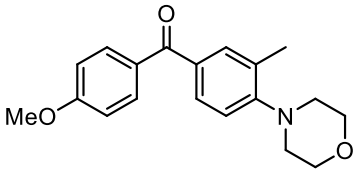
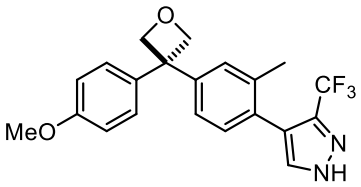
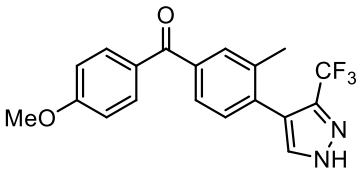
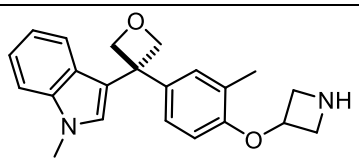
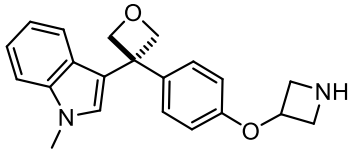
262 Kurono, N.; Sugita, K.; Takasugi, S.; Tokuda, M. *Tetrahedron* **1999**, *55*, 6097–6108.

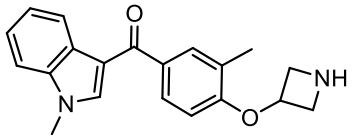
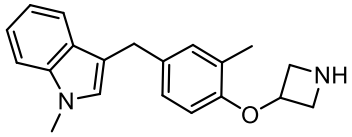
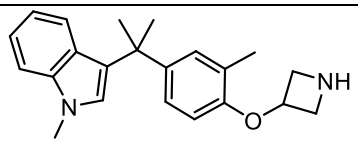
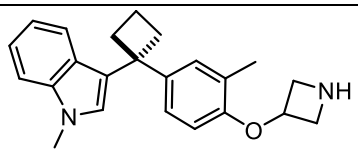
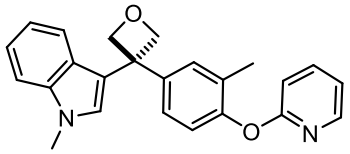
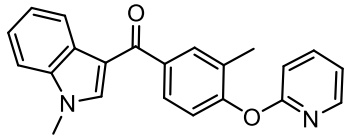
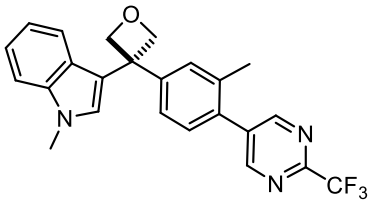
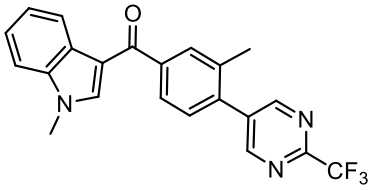
263 Hartmann, R. W.; Kranzfelder, G.; Von Angerer, E.; Schoenenberger, H. *J. Med. Chem.* **1980**, *23*, 841–848.

264 Resendiz, M. J. E.; Garcia-Garibay, M. A. *Org. Lett.* **2005**, *7*, 371–374.

10. Appendix

Table 10.1: Calculated physicochemical properties of compounds **8** to **15**, excluding phenols. [a] cLogD calculated for pH = 7.4. [b] cHLM in µL/min/mg. [c] cRRCK in 10^{-6} cm/s.

Compound	Nb	MW	clogP	clogD[a]	PSA	cHLM[b]	cRRCK[c]
	**8a**	325	2.88	1.76	39.7	50.1	7.02
	**8b**	297	3.50	1.44	47.6	43.1	9.91
	**9a**	339	2.83	3.40	30.9	40.1	23.3
	**9b**	311	3.49	3.46	38.8	61.7	22.7
	**10a**	388	4.33	4.52	47.1	67.6	2.04
	**10b**	360	4.89	4.26	55.0	73.7	2.65
	**12a**	348	3.42	2.13	35.4	30.1	3.38
	**13a**	334	2.92	1.89	35.4	13.8	4.04

	**12b**	320	4.03	2.12	43.3	34.0	3.38
	**12c**	306	4.67	2.26	26.2	37.7	1.7
	**12d**	334	5.47	2.27	26.2	41.1	1.35
	**12e**	347	5.66	2.87	26.2	42.3	0.48
	**14a**	370	4.51	4.13	36.3	59.8	2.03
	**14b**	342	4.92	3.99	44.1	35.9	2.59
	**15a**	423	3.93	4.19	39.9	32.9	2.91
	**15b**	395	4.43	3.78	47.8	24.0	2.51

Physicochemical Properties Measurement and Data

elogD. An automated reversed phase-HPLC method developed by Lombardo *et al*. was used for logD (pH 7.4) measurements. All the chromatographic runs were performed on a HP-1100 HPLC ChemStation at the ambient temperature. The HPLC columns used were Supelcosil LC-ABZ, 5 µm, 4.6 mm × 50 mm. A diode array detector was used to monitor signals at 210, 225, 245, and 310 nm. The mobile phase consisted of 15−75% of *A* and 85−25% of *B*.
Mobile phase A: methanol with addition of 0.25% 1-octanol.
Mobile phase B: 20 mM of MOPS (morpholine−propane−sulfonic acid) buffer prepared in octanol saturated water and 0.25% of n-decylamine.
Samples were prepared in 1:1 mixture of methanol/water at 100 µg/mL concentration.
The retention of each compound is obtained at three different concentrations of methanol in the mobile phase and extrapolated to 0% methanol (100% water).

slogD: Shake-flask logD experiment.

HLM Assay: The high throughput human microsomal stability assay was performed in a 384-well format. All liquid handling and incubation were conducted with a Biomek FX, equipped with one 3 position Mecour heat exchangers. Pooled human liver microsomes of 50 donors (Lot: HLM-103) were purchased from BioIVT. Each incubation contained test compound (1 µM), human liver microsomes (0.25 mM CYP protein equivalent to 0.806 mg/mL protein concentration), NADPH (1.3 mM), $MgCl_2$ (3.3 mM) and potassium phosphate buffer (100mM at pH 7.4). The final reaction volume was 45 mL containing 0.01% DMSO. The incubations were conducted at 37 °C at various time points (1, 4, 7, 12, 20, 25, 45, 60 min). Cold acetonitrile with mass spectrometry (MS) internal standard (IS, CP-628374) was then added to quench the reaction. The plates were centrifuged at 3000 rpm for 10 min at 4 ºC (Sorvall RC 3C Plus, Thermo Scientific, Waltham, MA). The water layer was transferred to the 384-well plate, sealed and subsequently analysed using LCeMS/MS. Control plates were prepared in the same manner without adding the NADPH cofactor to monitor any non-CYP catalysed decline. Propranolol (2D6, 1A2 and 2C19 substrate), quinidine (3A4), diclofenac (2C9), verapamil (3A4, 1A2, 2C), amitriptyline (2D6, 2C19) and naloxone (UGT2B7) were used as positive controls on each plate to monitor the activities of the various CYPs in the assay.

Solubility: Samples and controls were loaded onto an appropriate assay ready plated and centrifuged at 3000 rpm for 1 min. The samples were then diluted to 600 µM with the appropriate buffers (pH 3, 7.4, 10), shaken and incubated at 37 °C for 24 h. After this time the plates were again shaken, then centrifuged at 3000 rpm for 2 min. The supernatant was filtered through a 22 micron filter, diluted in MeCN and analysed by LCMS in presence of an internal standard.

Assay ready plated: Plate containing 6µL at 30 mM of test compounds in 96 deep well plate (volume = 600 µL). Or: containing 50 nL at 30 mM of test compound in 96 well plate (volume = 500 µL).

Aqueous buffer preparation: pH 3: 50µL of 1N hydrochloric acid was added to 500 mL of deionized water. The solution was titrated with 1N hydrochloric acid to pH 3, and back titrated with 1N sodium hydroxide. pH 7.4: 100 mM sodium phosphate buffer is made by adding 56.4 g of dibasic sodium phosphate and 10.3 g of monobasic sodium phosphate to 4 L of deionized water. 250 µL of 100 mM sodium phosphate buffer was diluted with 250 µL of deionized water. The solution was titrated with 1N hydrochloric acid to pH 7.4, and back titrated with 1N sodium hydroxide. pH 10: Fisher Scientific pH 10 buffer (SB116-500) containing potassium hydroxide, potassium carbonate, and potassium borate.

Chemical Stability Assay was performed in 384 well plate format (volume = 450 µL). Plates were prefilled with 70 µL of the appropriate buffer (pH 1.2, 7.4, 10) after which the wells were spiked with 5 µL of test compounds (1 mM). Samples were incubated for their timepoint of interest (1 h, 4 h, 24 h) at 37 °C after which the samples were diluted in MeCN (and pH 12.8 buffer for experiment at pH 1.2), mixed with an internal standard and analysed by LCMS.

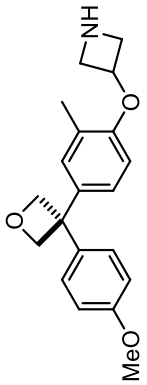
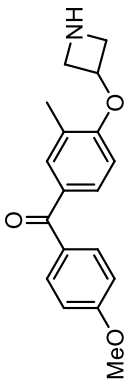
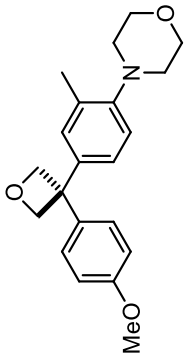
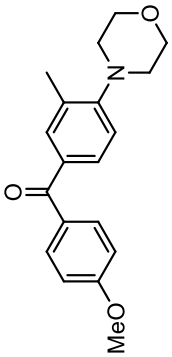
Aqueous buffer preparation: pH 3: 50 µL of 1N hydrochloric acid was added to 500 mL of deionized water. The solution was titrated with 1N hydrochloric acid to pH 3, and back titrated with 1N sodium hydroxide. pH 7.4: 100 mM sodium phosphate buffer is made by adding 56.4 g of dibasic sodium phosphate and 10.3 g of monobasic sodium phosphate to 4 L of deionized water. 250 µL of 100 mM sodium phosphate buffer was diluted with 250 µL of deionized water. The solution was titrated with 1N hydrochloric acid to pH 7.4, and back titrated with 1N sodium hydroxide. pH 10: Fisher Scientific pH 10 buffer (SB116-500) containing potassium hydroxide, potassium carbonate, and potassium borate. pH 12.8: 30 mL of 1N NaOH was added to 200 mL of deionized water. The solution was titrated with 1N sodium hydroxide to pH 12.8, and back titrated with 1N hydrochloric acid.

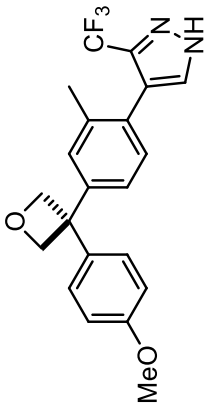
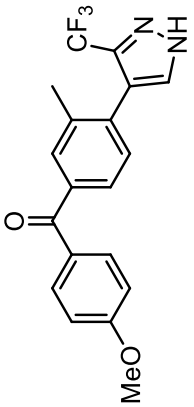
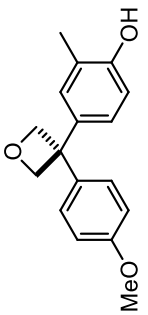
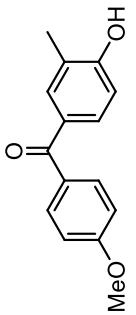
Permeability: Passive permeability assay were carried out using low-efflux MDCKII cells (Madin–Darby canine kidney cell line) developed by Troutman, also called Ralph Russ Canine Kidney cell (RRCK).[41] See paper for details.

Toxicity assay: [^{3}H] Dofetilide (DOF) binding assay was performed, studying the inhibition of [^{3}H] dofetilide binding to HERG transfected membranes by the test compounds. See methods previously used by Finlayson and Gintant. as an example.[1]

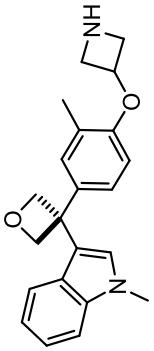
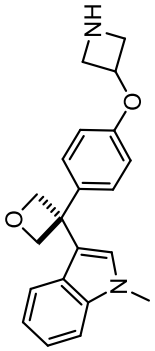
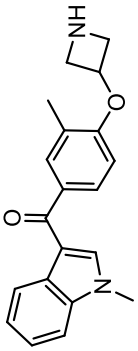
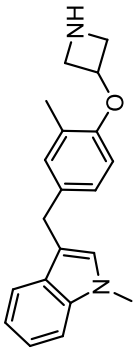
[1] (a) Finlayson, K. *et al*. *Eur. J. Pharmacol.* **2001**, *430*, 147–148. (b) Gintant, G. A. *J. Pharmacol. Toxicol. Methods* **2004**, *50*, 187–199.

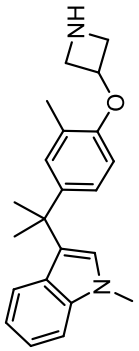
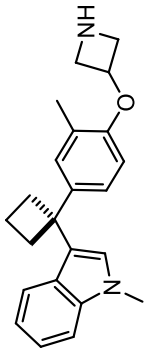
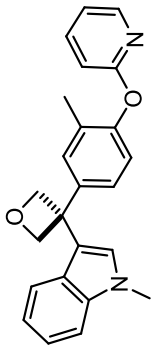
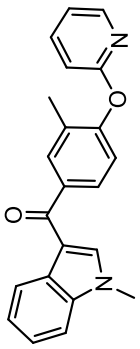
Table 10.2: Physicochemical properties collected are shown in the tables below. Where an experiment was repeated several times, the mean of the results was taken for the matched molecular pair comparison.

				
Properties	**8a**	**8b**	**9a**	**9b**
HLM (μL/min/mg)	7.0 8.0	7.0 8.0		
RRCK Permeability (10^{-6} cm/s)	10.6 8.35	11.0 7.45	25.2 23.4 20.6	32.1
elogD	2.10 1.60 1.43	1.90 1.70 1.63	3.50 3.66 3.67	3.90
slogD (pH 7.4)	1.06 1.14	1.17 1.24	3.47 3.45	3.06
DOF (IC_{50}, μM)	6.85	3.18	100	49.5
Solubility (μM), at pH: **3**	600	555.6	16.54/29.03	13.86/12.27
6.5	234.1 / 204.8	411.8/ 364.65	10.0/9.4	
7.4	411.7	423.55	0.1/0.26	1.01/1.21
10	249.9	371.55	0.31/0.49	2.59/17.0
%remaining at pH 1.2, time (h) **0**			100	100
1.2			84.6	88.6
4			49	105.8
24			68.3	73.7
%remaining at pH 7.4, time (h) **0**			100	100
1.2			74.0	84.7
4			73.5	78.1
24			69.8	60.8
%remaining at pH 10, time (h) **0**			100	100
1.2			66.6	90.9
4			65.4	69.9
24			60.7	76.5

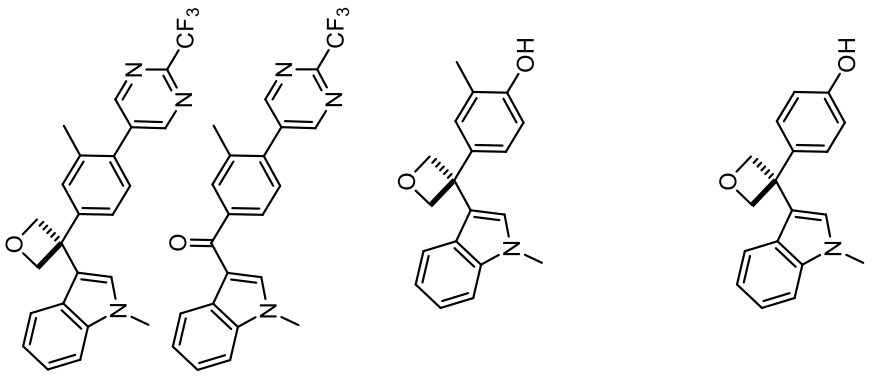
					

Properties		10a	10b	11a	11b
HLM (μL/min/mg)		50.6 56.8		78.8 78.8 82.3	72.9 81.9
RRCK Permeability (10^{-6} cm/s)		8.72	8.73	8.73 8.19 8.04	3.41
elogD		4.50	4.80	3.1 3.07	
slogD (pH 7.4)		4.62	4.74	3.22 3.21 3.25 3.22	3.49
DOF (IC_{50}, μM)		26.8	100	100	100
Solubility (μM), at pH:	**3**	0.27/0.75	0.49/0.44	335.87/377.9	4.78
	6.5	-	-	-	-
	7.4	0.30/0.67	0.10/2.38	284.88/358.88	5.23
	10	0.10/1.62	0.12/0.24	396.54 /440.08	544.5/561.85
%remaining at pH 1.2, time (h)	**0**	100	100	100	100
	1.2	102	86.7	51.4	87.0
	4	110.4	76.4	65.2	113.5
	24	85.5	46.3	72.3	92.3
%remaining at pH 7.4, time (h)	**0**	100	100	100	100
	1.2	101.5	96.6	99.3	109.1
	4	101	93.5	103.4	111.5
	24	89.5	50.9	103.2	106.7
%remaining at pH 10, time (h)	**0**	100	100	100	100
	1.2	102.2	102	108.5	99.9
	4	100.9	84.2	89.7	112.7
	24	105.7	65.3	98.5	111.1

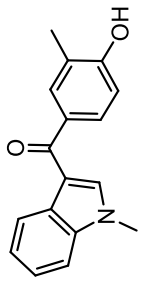
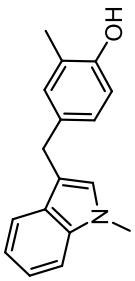
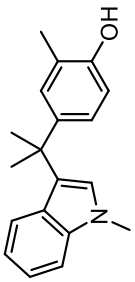
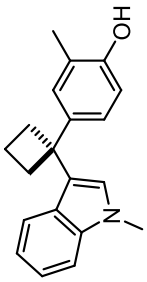
					
Properties		**12a**	**13a**	**12b**	**12c**
HLM (μL/min/mg)		7.0	7.0	7.0	7.0
RRCK Permeability (10^{-6} cm/s)				20.8	2.76
elogD		2.10	1.70		3.10
slogD (pH 7.4)		1.37	0.99	1.07	2.59 1.68
DOF (IC_{50}, μM)		10.5	13.6	0.09	6.14
Solubility (μM), at pH:	**3**	600	506.92	518.15	600
	6.5	-	-	-	-
	7.4	372.2	392.65	435.26	164.91
	10	343.88	284.43	258.21	32.2
%remaining at pH 1.2, time (h)	**0**	100	100	100	100
	1.2	108.5	96.4	83.1	123.2
	4	98.3	83.9	84.0	86.8
	24	130.1	49.2	117.3	130.6
%remaining at pH 7.4, time (h)	**0**	100	100	100	100
	1.2	95.7	95.9	106.4	98.2
	4	98.2	86.7	100.6	96.4
	24	100.9	99.9	101.3	91.9
%remaining at pH 10, time (h)	**0**	100	100	100	100
	1.2	106.5	103.1	105.7	104.6
	4	115.8	101.8	88.4	102.6
	24	113.5	93.7	94.8	90.1

Properties		12d	12e	14a	14b
HLM (μL/min/mg)		7.0 8.0	7.0 8.0		57.3
RRCK Permeability (10^{-6} cm/s)		2.76	1.21	9.59	
elogD		2.90	3.20	4.60	4.10
slogD (pH 7.4)		2.59	2.81	4.36	4.36 1.68
DOF (IC_{50}, μM)		6.07	5.78	100	100
Solubility (μM), at pH:	**3**	600	511.58	0.10	0.10
	6.5	-	-	-	-
	7.4	257.08	22.42	0.10	0.10/0.290
	10	9.21	2.53	0.10	0.18
%remaining at pH 1.2, time (h)	**0**	100	100		100
	1.2	56.1	140.3		139.8
	4	-	137.3		172.4
	24	-	119.7		160.4
%remaining at pH 7.4, time (h)	**0**	100	100		100
	1.2	107.2	109.9		82.8
	4	116.4	94.3		88.8
	24	104.8	101.0		74.7
%remaining at pH 10, time (h)	**0**	100	100		160.4
	1.2	95.4	98.2		92.9
	4	107.9	82.7		76.8
	24	108.7	81.3		76.4



Properties		15a	15b	16a	17a
HLM (μL/min/mg)		7.99 8.97	7.0	22.9 21.6 24.2	22.3 21.2 23.8
RRCK Permeability (10^{-6} cm/s)			16.1	12.4 13.1 9.27	21.5 27.7 26.5 22.0
elogD			4.33 4.30	3.80 3.73	3.30 3.28
slogD (pH 7.4)		5.10	4.21	3.64	3.25 3.27
DOF (IC_{50}, μM)		100	100	60.82/77.98	59.02
Solubility (μM), at pH:	**3**	0.10		0.45/0.34	7.28/13.02
	6.5	-		8.30	26.4/26.10
	7.4	0.10		0.24/0.20	8.04/12.02
	10	0.10		2.29/1.82	36.10/46.72
%remaining at pH 1.2, time (h)	**0**	100		100	100
	1.2	37.2		66.4	58.10
	4	15.7		66.4	69.2
	24	14.9		29.3	76.7
%remaining at pH 7.4, time (h)	**0**	100		100	100
	1.2	69.0		92.7	113.3
	4	49.0		63.0	97.3
	24	38.5		50.6	108.8
%remaining at pH 10, time (h)	**0**	100		100	100
	1.2	72.9		98.6	102.2
	4	59.6		61.8	102.5
	24	41.2		22.3	110.7

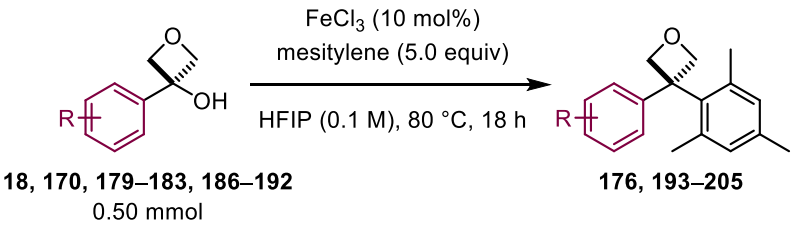





Properties		16b	16c	16d	16e
HLM (μL/min/mg)		17.97	10.8 12.1	27.1 25.6 28.8	13.63 15.3
RRCK Permeability (10^{-6} cm/s)		5.93			0.10
elogD		3.3	4.90 4.80 4.77	5.20 5.10 5.05	5.4
slogD (pH 7.4)		3.33	2.68 2.79	3.81 3.72	4.40
DOF (IC_{50}, μM)		100	100	55.15	100
Solubility (μM), at pH:	**3**	1.27	17.6/15.76	0.10	0.97
	6.5	-	180.4/154.3	48.10/43.65	-
	7.4	1.91	16.27/8.18	0.10	3.89
	10	262.9	10.40/11.76	0.10	0.58
%remaining at pH 1.2, time (h)	**0**	100	100	100	100
	1.2	97.5	89.2	47.10	82.0
	4	86.5	78.4	32.6	66.7
	24	23.1	48.4	32.5	21.10
%remaining at pH 7.4, time (h)	**0**	100	100	100	100
	1.2	93.6	97.8	71.3	92.8
	4	78.1	98.8	61.8	39.5
	24	28.2	86.6	57.6	28.4
%remaining at pH 10, time (h)	**0**	100	100	100	100
	1.2	99.5	101.5	84.3	98.5
	4	92.3	99.6	78.2	92.8
	24	101.9	86.0	84.8	47.2

Table 10.3: Solubility of 3,3-diaryloxetanes and diarylketones in different pH.

Compound			Solubility (μM)			
			pH = 3.0	pH = 6.5	pH = 7.4	pH = 10
		**16b**	1.27	n.d	1.91	262.9
		**16a**	0.40	8.30	0.22	2.06
		**17a (R = H)**	10.2	26.3	10.0	41.4
		**12b**	518.2	n.d	435.3	258.2
		**12a**	600	n.d	372.2	343.9
		**13a (R = H)**	506.9	n.d	393.7	284.4
		**11b**	4.78	n.d	5.23	553.2
		**11a**	356.9	n.d	321.9	418.3
		**8b**	555.6	388.2	423.6	371.6
		**8a**	600	219.4	411.7	249.9
		**9b**	13.1	n.d	1.11	9.79
		**9a**	22.8	9.70	0.18	0.80
		**10b**	0.47	n.d	1.24	0.18
		**10a**	0.51	n.d	0.49	0.86
		**14b**	0.10	n.d	0.20	0.18
		**14a**	0.10	n.d	0.10	0.10

Table 10.4: Electrophilic substituent constants σ_p^+ and σ_m^+ and yield of 3,3-diaryloxetanes for the reaction of oxetanols **18**, **170**, **179–183**, **186–192** with mesitylene.[144]



18, 170, 179–183, 186–192
0.50 mmol

176, 193–205

X (position)	σ+	Yield oxetane (%)
OMe (*p*)	-0.78	62
Me (*p*)	-0.311	81
F (*p*)	-0.073	81
H	0	73
OMe (*m*)	0.047	78
Cl (*p*)	0.114	80
I (*p*)	0.135	78
Br (*p*)	0.15	76
Br (*m*)	0.405	14
CF_3 (*m*)	0.52	3
CF_3 (*p*)	0.61	3

Figure 10.1: Assignment of a mixture of **195a** and **195b** by 2D NMR HMBC experiment.

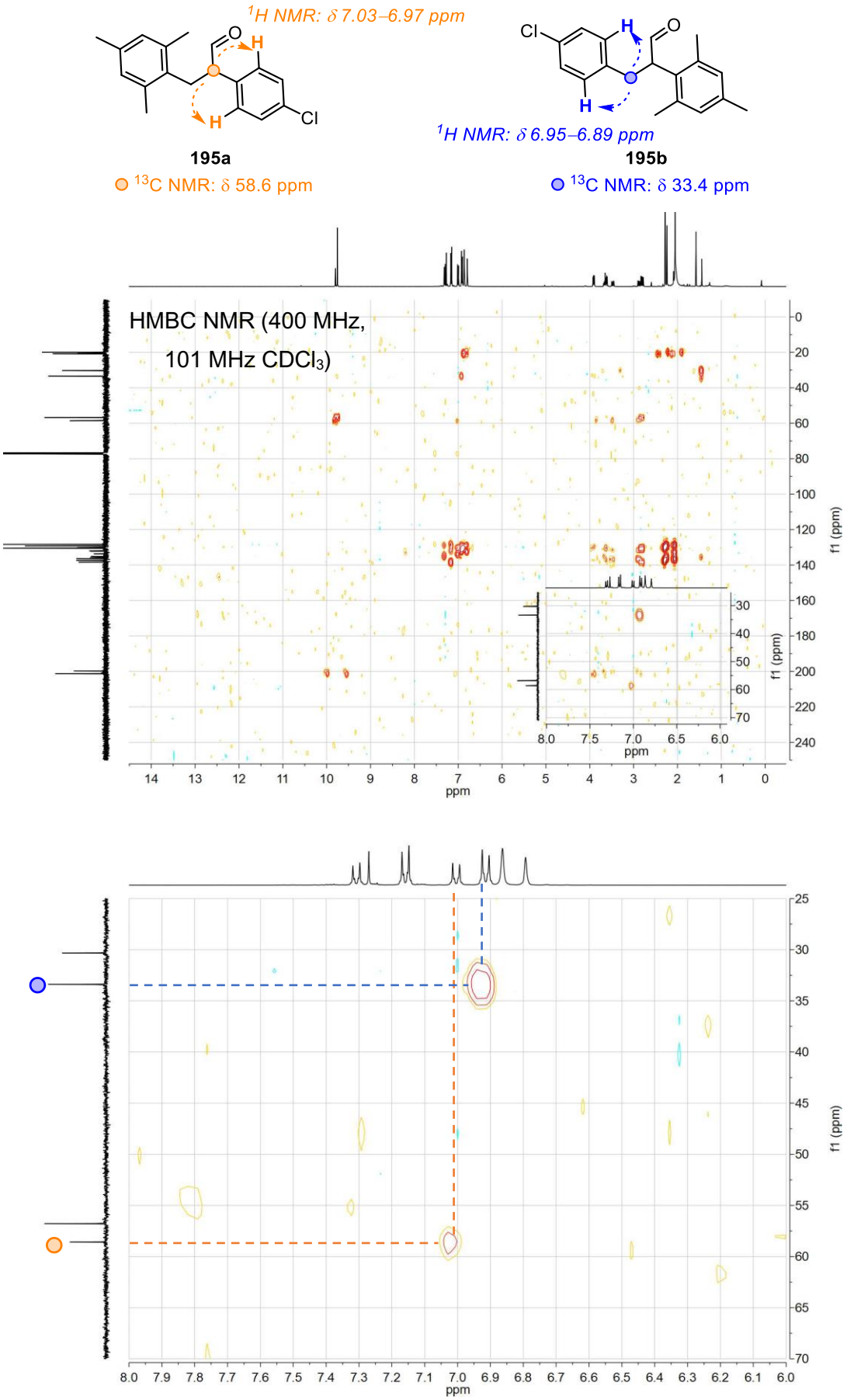
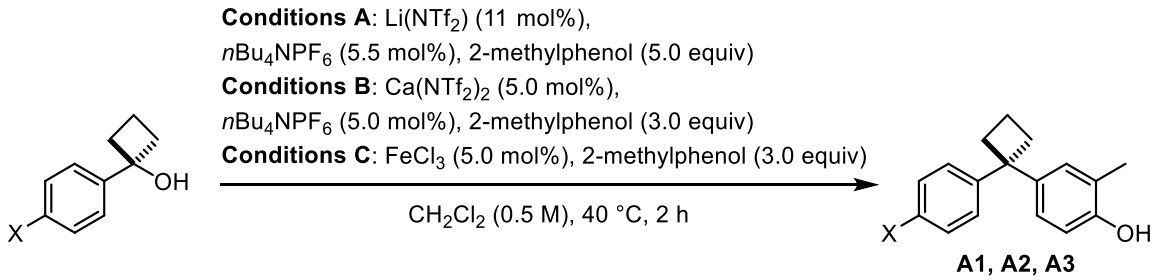


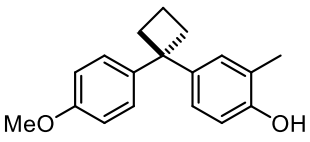
Table 10.5: Optimisation for the Friedel–Crafts alkylation of 2-methylphenol with cyclobutanol. Reactions were carried out on 0.25 mmol scale regarding the cyclobutanol.



A1, A2, A3

X =	Product N°	Yield 1,1-diarylcyclobutane (%)[a]		
		Conditions A (Li)	Conditions B (Ca)	Conditions C (Fe)
OMe	**A1**	10	89 (69)	46
H	**A2**	83	76	82 (86)
Cl	**A3**	82	85	81 (80)

[a] Yields calculated by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as the internal standard. Yields in bracket are isolated, with reaction performed on a 0.50 mmol scale.

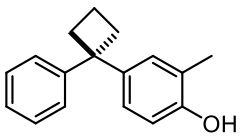


4-(1-(4-Methoxyphenyl)cyclobutyl)-2-methylphenol (A1)

Calcium(II) bis(trifluoromethanesulfonimide) (15.0 mg, 0.025 mmol) and tetrabutylammonium hexafluorophosphate (9.70 mg, 0.025 mmol) were added to a solution of cyclobutanol **317**[2] (89.0 mg, 0.50 mmol) and 2-methylphenol (155 µL, 1.50 mmol) in CH_2Cl_2 (1.0 mL). The reaction mixture was stirred at 40 °C for 2 h then sat. aq. $NaHCO_3$ (30 mL) was added followed by CH_2Cl_2 (30 mL). The layers were separated and the aqueous portion was extracted with CH_2Cl_2 (3 × 30 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash chromatography (5 to 10 % Et_2O/pentane) afforded cyclobutane **A1** (92 mg, 69%) as a white solid. R_f = 0.10 (5% Et_2O/pentane); mp = 89–92 °C; IR (film)/cm^{-1} 3345 (br, OH), 3205, 2937, 1612, 1505, 1461, 1410, 1360, 1237, 1176, 1125, 1019, 812; ^{1}H NMR (400 MHz, $CDCl_3$) 7.25–7.20 (m, 2 H, 2 × Ar-CH), 7.05–6.99 (m, 2 H, 2 × Ar-CH), 6.86–6.81 (m, 2 H, 2 × Ar-CH), 6.69 (d, J = 8.1 Hz, 1 H, Ar-CH), 4.62 (s, 1 H, OH), 3.79 (s, 3 H, OCH_3), 2.72–2.63 (m, 4 H, CH_2CH_2CH_2), 2.22 (s, 3 H, CH_3), 1.96 (tt, J = 8.7, 6.9 Hz, 2 H, $CH_2CH_2CH_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.2 (Ar-C_q-OCH_3), 151.4 (Ar-C_q-OH), 142.5 (Ar-C_q-CH_3), 142.4 (Ar-C_q-C_q), 128.8 (Ar-CH), 127.1 (2 × Ar-CH), 124.6 (Ar-CH), 123.3 (Ar-C_q-C_q), 114.5 (Ar-CH), 113.5 (2 × Ar-CH), 55.2 (OCH_3), 49.9

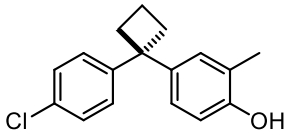
[2] Previously synthesised within the Bull group.

(C_q), 35.2 ($CH_2CH_2CH_2$), 16.5 (CH_3), 16.0 ($CH_2CH_2CH_2$); HRMS (+EI) *m*/*z* calcd for $C_{18}H_{20}O_2^{\bullet}$ $[M]^{\bullet}$: 268.1463; Found: 268.1458.



2-Methyl-4-(1-phenylcyclobutyl)phenol (A2)

Iron (III) chloride (4.0 mg, 0.025 mmol) was added to a solution of cyclobutanol **S11** (74.0 mg, 0.50 mmol) and 2-methylphenol (155 µL, 1.50 mmol) in CH_2Cl_2 (1.0 mL). The reaction mixture was stirred at 40 °C for 2 h then sat. aq. $NaHCO_3$ (30 mL) was added followed by CH_2Cl_2 (30 mL). The layers were separated and the aqueous portion was extracted with CH_2Cl_2 (3 × 30 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash chromatography (5% Et_2O/pentane) afforded cyclobutane **A2** (103 mg, 86%) as a colourless oil. R_f = 0.37 (10% Et_2O/pentane); IR (film)/cm^{-1} 3403 (br, OH), 2974, 2940, 1599, 1502, 1442, 1259, 1185, 1114, 1021, 812, 786, 749, 697; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36–7.25 (m, 4 H, 4 × Ar-CH), 7.17–7.13 (m, 1 H, Ar-CH), 7.09–7.02 (m, 2 H, 2 × Ar-CH), 6.70 (d, *J* = 8.2 Hz, 1 H, Ar-CH), 4.64 (s, 1 H, OH), 2.75–2.71 (m, 4 H, $CH_2CH_2CH_2$), 2.23 (s, 3 H, CH_3), 1.98 (pd, *J* = 7.3, 2.3 Hz, 2 H, $CH_2CH_2CH_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.5 (Ar-C_q-OH), 150.2 (Ar-C_q-CH_3), 142.0 (Ar-C_q-C_q), 128.9 (Ar-CH), 128.2 (2 × Ar-CH), 126.0 (2 × Ar-CH), 125.3 (Ar-CH), 124.7 (Ar-CH), 123.3 (Ar-C_q-C_q), 114.5 (Ar-CH), 50.5 (C_q), 35.1 ($CH_2CH_2CH_2$), 16.6 (CH_3), 16.0 ($CH_2CH_2CH_2$); HRMS (+EI) *m*/*z* calcd for $C_{17}H_{18}O^{\bullet}$ $[M]^{\bullet}$: 238.1358; Found: 238.1349.



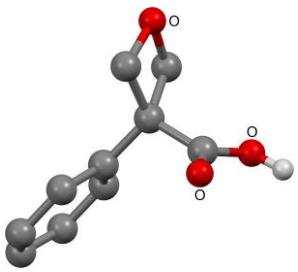
4-(1-(4-Chlorophenyl)cyclobutyl)-2-methylphenol (A3)

Iron (III) chloride (4.0 mg, 0.025 mmol) was added to a solution of 1-(4-chlorophenyl)cyclobutan-1-ol[3] (91.0 mg, 0.50 mmol) and 2-methylphenol (155 µL, 1.50 mmol) in CH_2Cl_2 (1.0 mL). The reaction mixture was stirred at 40 °C for 2 h then sat. aq. $NaHCO_3$ (30 mL) was added followed by CH_2Cl_2 (30 mL). The layers were separated and the aqueous portion was extracted with CH_2Cl_2 (3 × 30 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash chromatography (5% Et_2O/pentane) afforded cyclobutane **A3** (109 mg, 80%) as a colourless oil. R_f = 0.23 (5% Et_2O/pentane); IR (film)/cm^{-1} 3384 (br, OH), 2974, 2940, 1490, 1263, 1185, 1114, 1010, 816, 756; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26–7.19 (m, 4 H, 4 × Ar-CH), 7.02–6.99 (m, 2 H, 2 × Ar-CH), 6.70 (d, *J* = 8.0 Hz, 1 H, Ar-CH), 4.60 (s, 1 H, OH), 2.76–2.59 (m, 4 H, $CH_2CH_2CH_2$), 2.22 (s, 3 H, CH_3), 1.96 (dddd, *J* = 15.2, 8.2, 6.9, 4.1 Hz, 2 H, $CH_2CH_2CH_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.6 (Ar-C_q-OH), 148.8 (Ar-C_q-CH_3), 141.4 (Ar-C_q-C_q), 131.0 (Ar-C_q-Cl), 128.8 (Ar-CH), 128.3 (2 × Ar-CH), 127.5 (2 × Ar-CH), 124.6 (Ar-CH), 123.5 (Ar-C_q-C_q), 114.6 (Ar-CH),

[3] Previously synthesised within the Bull group.

50.1 (C_q), 35.0 ($CH_2CH_2CH_2$), 16.5 (CH_3), 16.0 ($CH_2CH_2CH_2$); HRMS (–ESI) *m*/*z* calcd for $C_{34}H_{31}O_2{}^{35}Cl_2{}^{3-}$ $[2M–3H]^{3-}$: 541.1718; Found: 541.1710.

Figure 10.2: Analysis of the X-ray crystal structure of 3-phenyl-3-oxetan carboxylic acid **373**.
A) Comparison of angles and bond length between unsubstituted oxetane and **373**.
B) Comparison of the ring puckering between unsubstituted oxetane and **373**.



373

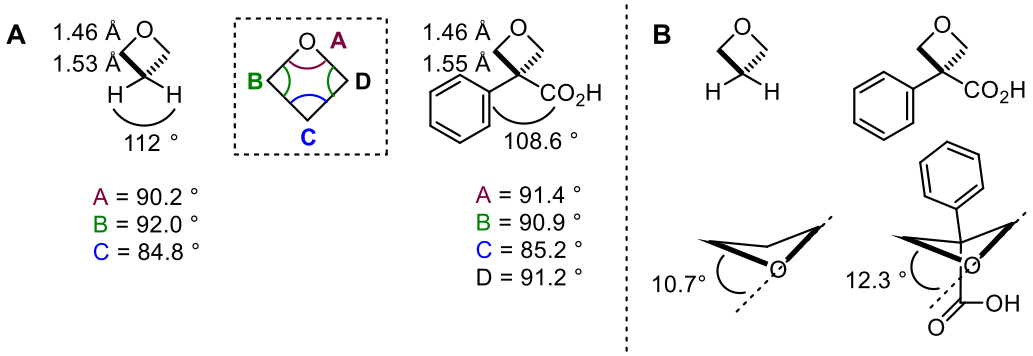
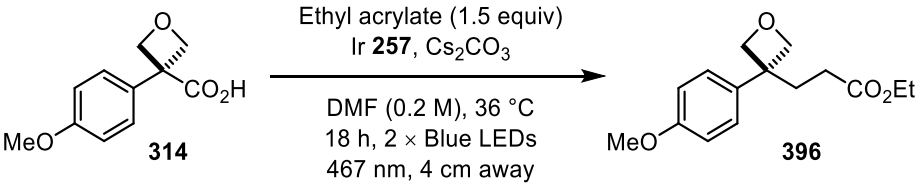


Table 10.6: Effect of the relaxation delay on the calculated crude ^{1}H NMR yield of oxetane **396**.



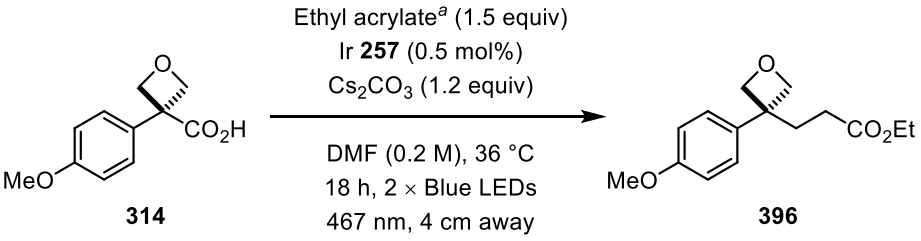
Entry	Experiment	Yield 396 (%)[a]	
		1 s delay	25 s delay
1	Internal standard calibration	115	100
2	Table 6.9, entry 2	81	70
3	Table 6.9, entry 3	73	62
4	Table 6.6, entry 3	65	60
5	Table 6.10, entry 4	74	64 (42)
6	Table 6.10, entry 2	78	67 (58)

[a] Yields calculated by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as the internal standard. Yields in bracket are isolated.

A NMR sample containing a known amount of product **396** and 1,3,5-trimethoxybenzene as the internal standard was first prepared. When a standard 1 s relaxation delay ^{1}H NMR spectroscopy was run, the calculated yield for oxetane **396** was 115% instead of expected 100% (entry 1, Table 10.6). The oxetane's CH_2, as well as the two alkane's CH_2 were found to be the slowest relaxing signals in product **396** and compared to the internal standard.[4] Increasing the relaxing time to 25 s improved the NMR spectrum yields accuracy and 100% yield of **396** was calculated. This disparity was found consistent throughout the previous experiments carried out (entry 2–6). Overall, 5% to 15% difference in yield of **396** was obtained when ^{1}H NMR spectroscopy was run with 25 s relaxation delay.

[4] T_1 measured by NMR spectroscopist Pete Haycock. T_1 for oxetane's CH_2 is 5 seconds.

Table 10.7: Comparison of the effect of different work up procedures and stationary phases on the yield of **396**.



314 **396**

Entry	Work up procedure and stationary phase	Yield 396 (%)[b]
1	Previous result from table 6.10, entry 3	(88)[c]
2	Aqueous work up	(64)[c] 57
3	Filtration through Celite	57
4[d]	Control in solvent	55
5	Silica gel	54
6	Silica + 1%NEt_3	56
7	Basic alumina (IV)	57
8	Florisil	50
9[e]	Repeat of entry 2	(70)[c] 57

[a] Alkene distilled on drying agent and under argon, and kept in the dark under argon at –20 °C. [b] Yields calculated by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as the internal standard, and 25 s delay. [c] 1 s Delay for the ^{1}H NMR spectroscopy. [d] Product **396** was dissolved and stirred in 30% Et_2O/pentane for 30 min. [e] The reaction was repeated with aqueous work up.

Oxetane **396** was previously obtained in 88% yield when 0.5 mol% of photocatalyst was used (see Table 6.10, entry 3). This result was obtained after removal of the solvent from the reaction mixture under reduced pressure and addition of the internal standard (entry 1, Table 10.7). The reaction was then repeated under the same conditions but a standard work up procedure was carried out prior to ^{1}H NMR spectroscopy measurement (entry 2). This resulted in 64% yield of oxetane **396**, calculated with 1s-relaxing delay, and 57% yield with longer relaxation delay. It was proposed that an impurity present in the crude product may affect the signals of **396** in the ^{1}H NMR spectrum leading to less accurate calculated yield. Filtration through Celite gave similar result as an aqueous work up and aided eliminating

impurities (entry 3). The crude mixture from entry 3 was then divided in five samples. The first sample was dissolved and stirred in 30% Et_2O/pentane (previous column solvent) for 30 min (entry 4). After removal of the solvent under reduced pressure, the calculated NMR yield remained unchanged compared to entry 3 and oxetane **396** proved to be stable in solution. The four remaining samples were then dissolved in 30% Et_2O/pentane and stirred in presence of silica (entry 5), basified silica (entry 6), basic alumina IV (entry 7) or Florasil (entry 8) for 30 min before filtration through Celite and removal of the solvent. The yield was not affected by the stationary phases which shows the stability of oxetane **396**.