University of HUDDERSFIELD

# HARD TO MAKE SPACE: IMPROVING ACCESS TO PRIVILEGED PHARMACOPHORES

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## ABSTRACT

Limited examples of the successful ring expansion of aziridines with sulfonium ylides to generate azetidines are known, but typically result in functional groups on azetidine that are not broadly useful for downstream chemistry. Described here is an investigation into the scope of this reaction including the discovery that *N*-activated 2-methoxy ester functionalised aziridines are not compatible with this protocol. Advances have also been made in understanding the reactivity of azirines with rhodium carbenoids to generate azetines from successful ring expansion, or *N*-vinylimine from ring opening.

An alternative route to azetidines from the 1,3-cleavage of azabicyclo[1.1.0]butanes is described, along with a proposed route to highly functionalised azetidines with control over the absolute configuration at each step. Early success reacting a range of reagents with an azabicyclo[1.1.0]butane of moderate steric bulk has been shown, as well as early steps towards a novel azetidine 3-sulfonamide synthesis.

Difluorocyclopropanation of alkenes using fluorinated acetate salts is often a slow, inefficient and energy-intensive process. Reported here is a modified protocol enabling the preparation of 1,1-difluorocyclopropanes in less than five minutes, using microwave irradiation. The new procedure is considerably faster than previously reported methods, employs easily removed, low-boiling point solvents and avoids the use of highly toxic or ozone-depleting substances. The method has been exemplified in a high-yielding synthesis of a difluoro analogue of a clinically used drug substance, and has also shown some utility in preparing 1,1-difluorocyclopropenes and as a novel procedure for the synthesis of halogenated alkyl ether esters from cyclic ethers.

Other investigations into the generation and reactivity of difluorocarbene reported here include successful proof of concept experiments showing the sensitivity of allyl functionalised difluoromethylene containing compounds to palladium species to generate difluorocarbene, as well as exploratory reactions to build on methods to generate 2,2-difluoroaziridines by addition of difluorocarbene to imines.

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Finally, I would like to thank my family for their support and encouragement throughout my studies that have brought me to this culmination of my life as a chemistry student thus far.

ABBREVIATIONS

| Abbreviation | Meaning |
|---|---|
| **α4β2-*nAChR*** | nicotinic acetylcholine receptor antagonist |
| **ABB** | azabicyclo[1.1.0]butane |
| **Ac** | acetyl |
| **Asn** | asparagine |
| **Boc** | *tert*-butoxycarbonyl |
| **bp** | boiling point |
| **Bz** | benzoyl |
| **Cbz** | benzyloxycarbonyl |
| **d** | doublet |
| **DABCO** | diazabicyclo[2.2.2]octane |
| **DAIB** | diacetoxyiodobenzene |
| **dba** | dibenzylideneacetone |
| **DBU** | 1,8-diazabicyclo[5.4.0]undec-7-ene |
| **DCM** | dichloromethane |
| **DMF** | dimethylformamide |
| **DMSO** | dimethyl sulfoxide |
| **Dpp** | diphenylphosphinyl |
| **EI** | electron impact ionisation |
| **ESI** | electrospray ionisation |
| **FDA** | Food and Drug Administration |
| **Fmoc** | fluorenylmethoxycarbonyl |
| **FTIR** | Fourier transform infrared |
| **Hal** | halogen |
| **IR** | infrared |
| **LDA** | lithium diisopropylamide |
| **m** | multiplet |
| **MAOS** | microwave assisted organic synthesis |
| **mp** | melting point |
| **Mes** | mesitylenesulfonyl |
| **NBS** | *N*-bromosuccinimide |
| **NMR** | nuclear magnetic resonance |
| **Ns** | 4-nitrobenzenesulfonyl |
| **ODS** | ozone depleting substance |
| **Ph** | phenyl |
| **PhI=NTs** | (*N*-(4-tolylsulfonyl)imino)phenyliodinane |
| **ppm** | parts per million |
| **Py** | pyridine |
| **rt** | room temperature |

| | |
|---|---|
| **s** | singlet |
| **SEGPHOS** | 5,5′-bis(diphenylphosphino)-4,4′-bi-1,3-benzodioxole |
| **STAB** | sodium triacetoxyborohydride |
| **t** | triplet |
| **TCCA** | trichloroisocyanuric acid |
| **Tf** | trifluoromethanesulfonyl |
| **TFDA** | trimethylsilyl 2,2-difluoro-2-(fluorosulfonyl)acetate |
| **THF** | tetrahydrofuran |
| **TLC** | thin layer chromatography |
| **Ts** | 4-toluenesulfonyl |

## CHAPTER 1: IMPROVING THE MAP OF AZETIDINE CHEMICAL SPACE

### 1.1 Introduction

The number of products available in the modern pharmaceutical market place is continually increasing, and although the importance and application of biomolecules for the treatment of medical conditions is starting to be realised more and more,[1] small-molecule drug products still dominate all aspects of disease prevention and cure. The number of products containing these small-molecule treatments is vast, and although the range and structural complexity of these compounds is broad, the volume of 'chemical space' mapped and exploited by them is relatively limited.

Chemical space can be described as the theoretical 3-dimensional space occupied by the total atomic coordinate set for any given design of organic molecule. An analogy to the complexity of chemical space can be drawn with the locations occupied in the universe by planets, stars and galaxies.[2] It is estimated[3] that the number of chemically feasible molecules (up to approximately 500 Daltons)[4] could be in the order of $10^{60}$ – $10^{100}$. Currently, the synthetic toolbox only allows chemists to create molecules that fill a small percentage of the total available chemical space. The areas that are currently difficult or impossible to access are typically filled by structural motifs of increasing complexity and contain asymmetric centres.

As an area of chemical space is populated more densely, it will be occupied by structurally analagous compounds (benzene rings and derivatives thereof, amino acids and derivatives thereof etc.). The arrangement of functional groups in any given isomer of a compound can be further described as the chemical environment of that molecule. This can describe simple variations of the chemical environment (*ortho*-, *meta*- or *para*- substituents on an aromatic ring) through to highly complex molecules with many asymmetric centres and diastereomers. Different molecules with comparable chemical environments will have different physical and reactive properties. In the examples shown, one might expect the preferred site of aromatic electrophilic substitution in methyl substituted phenols to occur where indicated by the arrows based on the combined ring activating effects of the two substituents (Figure 1).

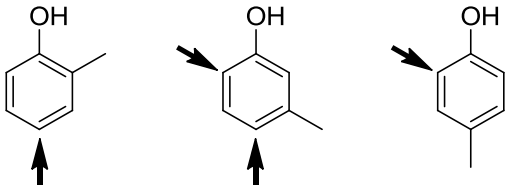



***Figure 1***: *Different chemical environments around methyl-functionalised phenols.*

The fundamental theory underpinning drug design is that a drug molecule and target in the body interact in a 'ligand-receptor' fashion. This concept was pioneered by Clark at the start of the 20$^{th}$ century with early research also demonstrating that the binding of a drug to a target receptor was an equilibrium process.[5] The strongest response to a drug is achieved when the greatest number of receptor sites are occupied by drug molecules.[6]

When designing a new drug, the chemical environment (including conformation and functionalisation) of the molecule is engineered to facilitate the strongest possible interaction with the target receptor. Many computational methods exist to predict the strength of an interaction between a drug 'ligand' and biological 'receptor'. This can be done using knowledge of the shape (obtained by x-ray crystal structure analysis of the target protein), molecular surface characteristics (calculated through computational simulation)[7] or by comparison of a drug candidate to other related biologically active ligands.

It is not sufficient for a drug molecule to simply match the receptor site in conformation and stereoelectronic shape to trigger a strong physiological response; it must also survive transit through the various tissues to reach its target. For an orally administered drug, the active ingredient must be sufficiently stable to highly acidic conditions, be of the correct lipophilicity to move across phospholipid bilayers and through cells, and be sufficiently metabolically resistant to survive in the body to reach the target receptor.

As a guideline, 'Lipinski's rule of 5' is followed when designing a new drug molecule. These guidelines state that for a molecule to be an attractive drug candidate with desirable physciochemical properties, it should contain no more than 5 *H*-bond donors, no more than 10 *H*-bond acceptors, have a molecular weight of no more than 500 Daltons and a LogP value no higher than 5.[8]

A modern approach of designing drugs that are more natural product-like has the potential to create more bioactive compounds. Such molecules are typically complex, containing more asymmetric centres, *gem*-coupled groups and a greater degree of saturation. This approach has been coined as the "escape from Flatland"[9] and refers to the recognition that candidates that contain more $sp^3$ centres are more likely to make it through clinical trials to become marketed drug products.

New molecules will always be required to satisfy unmet medical needs. When the volume of chemical space that is unmapped is considered alongside the currently inaccessible yet potentially efficacious range of drug-like molecules, it is clear to see the importance of gaining access to this 'hard to make' chemical space.

### 1.1.1 Azetidines

Incorporation of small rings into molecules is a strategy that can be used to increase the molecular rigidity of a compound by ensuring any group on the cycle is held in a specific area of the chemical environment (Figure 2).[10] One such ring is azetidine: a saturated four-membered heterocycle containing one nitrogen and three carbon atoms.[11] It, like other small heterocycles, is a versatile building block in organic chemistry.

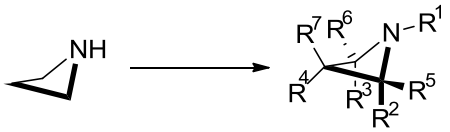



***Figure 2:*** *Possible diversity in the chemical environment of azetidines.*

The scope of azetidine containing drugs and their target biological receptors is broad (Figure 3),[12] yet in many examples the chemical environment around the heterocycle typically contains minimal functionalisation.

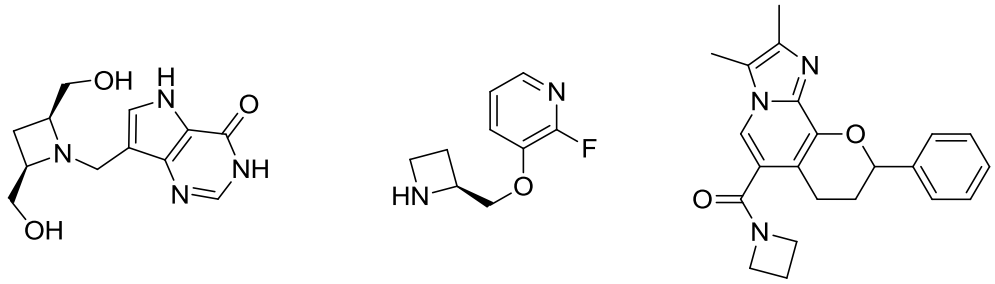



***Figure 3:*** *(left): N-ribosyl hydrolase inhibitor;* [12h] *(centre): nicotinic acetylcholine receptor (α4β2-nAChR) antagonist;*[12f] *(right): potassium-competitive acid blocker.*[12j]

A variety of procedures have been reported for the synthesis of azetidines (Figure 4). All facilitate varying degrees of substitution around the heterocyclic backbone, but there is no omnipotent method for the generation of complex azetidines.[13] The three procedures most widely employed are the cyclisation of 1,3-aminoalcohols or 1,3-aminohalides, the cyclisation of 1,3-dihalides or 1,3-diamines and the reduction of azetidin-2-ones (themselves an important motif in penicillin derived antibiotics).[14]

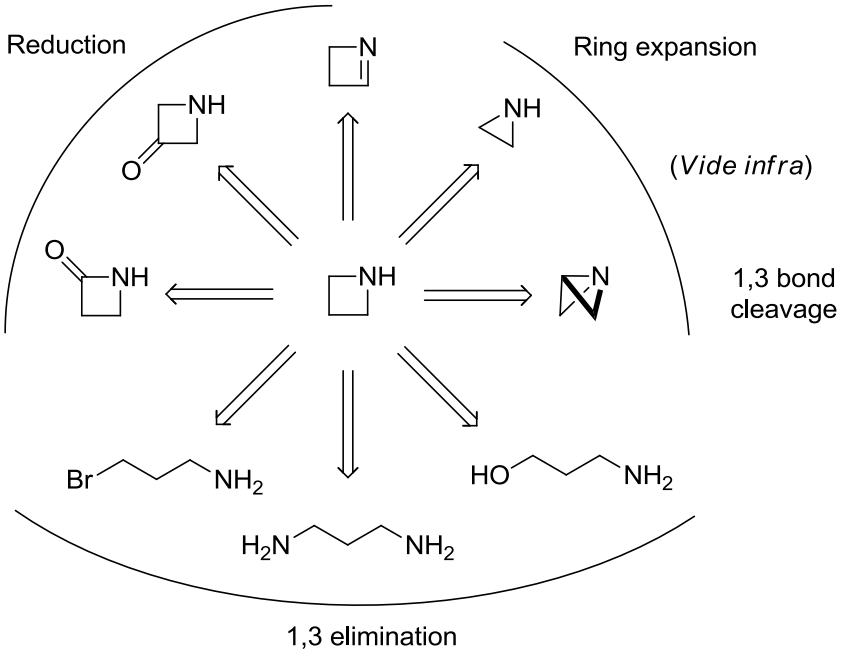
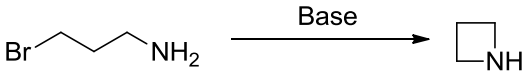



***Figure 4:*** *Retrosynthetic analysis of azetidine.*

The first of these methods demonstrated the synthesis of azetidines *via* the cyclisation of 1,3-aminohalides when, as a minor product of the reaction between 3-bromopropylamine and base, azetidine was isolated (Scheme 1).[15] Generally, this type of procedure suffers from low yields when substitution around the alkane backbone increases from the simplest hydrocarbon template. Most methods also favour secondary over primary amines to improve the rate of cyclisation.[16] Nonetheless, this method is still popular and used by many investigators.[17]

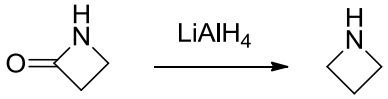



***Scheme 1:*** *Cyclisation of 1,3-aminohalide under alkali conditions.*[15]

The cyclisation of diamines and dihalides was also discovered around the same time (Scheme 2).[18] Again, the main drawback of these two procedures is the low yields as the substitution within the starting material increases.


***Scheme 2:*** *The cyclisation of diamines*[18a] *and dihalides*[18b].

The third method, the reduction of azetidin-2-ones, can theoretically be applied to any substituted heterocycle that does not contain other functional groups that would be sensitive to reducing conditions ($LiAlH_4$, $NaBH_4$ etc.) (Scheme 3).[19] With azetidine-2-ones the heterocyclic nitrogen must exist in its *N*-H form if *C-N* bond fission to furnish amino-3-alcohols is to be avoided.




***Scheme 3:*** *Reduction of azetidine-2-ones.*[19]

The first two examples mentioned above proceed *via* intramolecular $S_N2$ reactions. Suitable leaving groups must therefore be present to make ring closure facile. The lowest Baeyer (ring/angle) and Pitzer (eclipsing/torsional) strain energies within a saturated cyclic system are associated with six-membered rings. As ring size is reduced the two forms of ring strain increase. Examination of the strain energies of azacycles as ring number reduces from six to three indicates that for the four-membered azetidine heterocycle, the ring strain is higher than would be expected (Table 1).[20]

***Table 1:*** *Ring strain for carbocycles and heterocycles.*[20]

| Size | Ring | Strain[a] | Ring | Strain[a] | Ring | Strain[a] |
|---|---|---|---|---|---|---|
| **3** | cyclopropane | 27.5 | aziridine | 26.7 | cyclopropene | 55.5 |
| **4** | cyclobutane | 26.5 | azetidine | 24.7 | cyclobutene | 28.7 |
| **5** | cyclopentane | 6.2 | pyrrolidine | 5.8 | cyclopentene | 4.4 |
| **6** | cyclohexane | 0 | piperidine | 0 | cyclohexene | 0 |

*a: kcal mol*$^{-1}$*.*

Compared to aziridine and pyrrolidine, the Baeyer strain is higher than expected in azetidine and not simply half way between that of its neighbouring homologues. This is the result of the increased Pitzer strain caused by the substituents around the ring. Although azetidine (and cyclobutane) typically adopts a slightly puckered shape to reduce the energy of the ring by a small amount, it cannot distort from a planar arrangement sufficiently to minimise the energy any further. Cyclobutene, by definition, has a fully planar

arrangement of carbon atoms due to the presence of the double bond. The comparable ring strain energies between the unsaturated and saturated four-membered cycles further demonstrates azetidine is unable to sufficiently distort from a planar arrangement to significantly minimise the inherent ring strain.

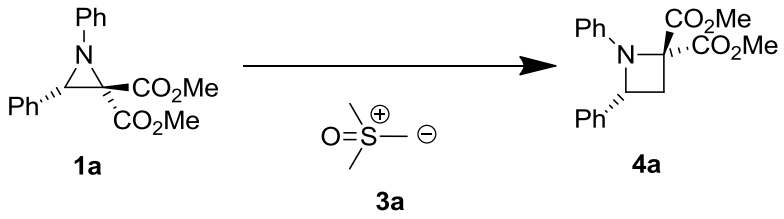
Whereas aziridine has an entropic aid to ring closure as all three ring atoms lie in the plane, azetidine ring closure has no such aid. This presents a larger energy barrier to overcome. The increased entropic penalty to form the new bond ultimately alters the kinetics of the reaction by slowing the rate of ring closure. Due to the increased effect of Pitzer strain on four-membered saturated heterocycles, as the chemical environment occupied by groups in the open-chain azetidine precursor expands, it becomes increasingly difficult to force bulky substituents to occupy adjacent areas of chemical space to facilitate ring closure. Furthermore, to relieve ring strain, azetidine will undergo ring opening reactions.[21]

Much research has been carried out into the three previously mentioned protocols, as well as multiple lesser used procedures, all of which are covered in detail in several review publications.[13, 14, 22] Access to the starting materials required to form complex azetidines can also be non-trivial, complicated further when stereogenic centres are introduced. New and improved asymmetric syntheses of azetidines are therefore desirable to enhance the map of the chemical space occupied by these potent pharmacophores.

### 1.1.2 Azetidines from aziridines

In the 1970s, a method for the synthesis of azetidines from aziridines was reported by Carrié *et al*.[23] This was the first reported example of the ring expansion of aziridines with achiral sulfonium and oxosulfonium ylides. In the 1980s, Nadir *et al.* also conducted research into the use of sulfonium and oxosulfonium ylides to expand the aziridine heterocycle.[24] There are three fundamental differences in the work reported by the two groups: the choice of aziridines, the choice of sulfonium ylides and the proposed reaction mechanisms based on the experimental outcomes.

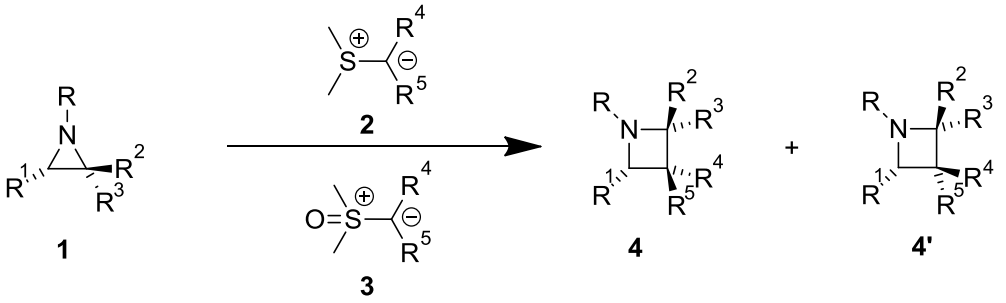
Carrié *et al*. employed *N*-phenyl aziridines (**1**) that were further functionalised with phenyl or ester groups at the C2 and C3 positions. These were each combined with sulfonium (**2**) and oxosulfonium (**3**) ylides, usually in THF: DMSO at room temperature (Table 2).[25] **3** is more stable to spontaneous decomposition, but also an altogether less reactive species.[26] Reliable ring expansion to generate azetidines (**4**) was observed only with dimethyl 1,3-diphenylaziridine 2,2-dicarboxylate (**1a**) (Scheme 4). **4** was usually obtained as a mixture of diastereoisomers (**4** and **4'**) with the additional carbon centre at the 3- position of the new heterocycle. In one isolated example ring expansion with trimethyl 1-phenylaziridine 2,2,3-tricarboxylate (**1b**) and dimethylsulfonium phenacylide (**2b**) was also successful. Methyl 1,3-diphenylaziridine 2-carboxylate (**1c**) was not reactive to the conditions investigated.




***Scheme 4:*** *The first reported aziridine ring expansion reaction.*[23]

It was suggested that these reactions proceed *via* a [3+1] cycloaddition between an intermediate azomethine ylide and the sulfonium ylide. When attempting to promote this equilibrium between **1c** and the corresponding azomethine ylide in boiling benzene (this type of thermal equilibrium has been reported by Huber *et al.*),[27] only decomposition and isomerisation products were observed.

***Table 2:*** *Scope of the investigations reported by Carrié et al.*[23, 25]



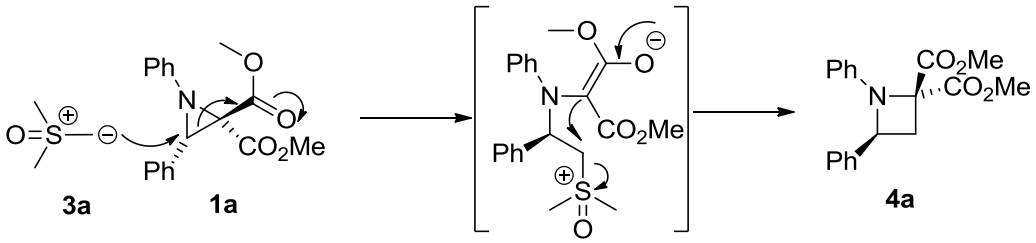

| Aziridine | R | $R^1$ | $R^2$ | $R^3$ | Ylide | $R^4$ | $R^5$ | Ratio 4:4' | Yield (NMR %) |
|---|---|---|---|---|---|---|---|---|---|
| **1a** | Ph | Ph | $CO_2Me$ | $CO_2Me$ | 2a | H | H | - | - |
| | | | | | 3a | H | H | - | 100 |
| | | | | | 2b | H | C(O)Ph | 79:21 | 100 |
| | | | | | 3b | H | C(O)Ph | - | - |
| | | | | | 2 | H | $CO_2Me$ | 95:5 | 100 |
| | | | | | 2 | H | $CO_2Et$ | 95:5 | 100 |
| | | | | | 2[a] | $C_{13}H_{15}$ | $C_{13}H_{15}$ | - | 100 |
| | | | | | 2 | Cl | $CO_2Et$ | 87:13 | 100 |
| | | | | | 2 | Br | $CO_2Et$ | 100:0 | 85 |
| **1b** | Ph | $CO_2Me$ | $CO_2Me$ | $CO_2Me$ | 2b | H | C(O)Ph | 48:52 | 100 |
| **1c** | Ph | Ph | $CO_2Me$ | H | 2a | H | H | - | - |

a: $C_{13}H_{15}$ = fluorenylidene.

Although Carrié *et al*. proposed the existence of an azomethine ylide intermediate in each reaction, the experiments synthesising **4** and **4'** were all performed at room temperature or below. Since azomethine ylides usually require elevated temperatures for generation, the involvement of a thermally generated azomethine ylide may not be correct.

An alternative mechanism would see an $S_N2$ attack by the ylide at aziridine C3 followed by a 1,4-elimination pathway involving an enolate intermediate (Scheme 5). With the lack of an *N*-activating

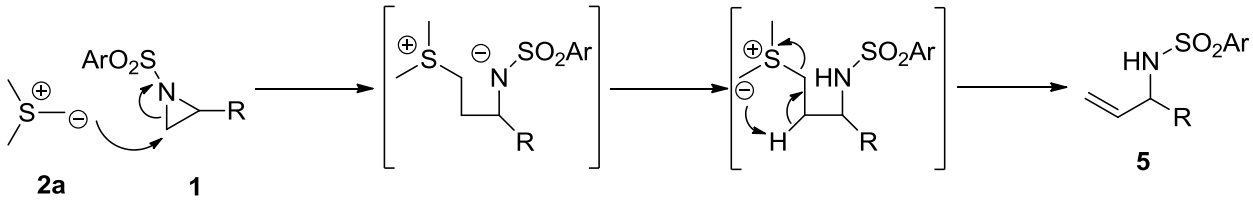
group and the presence of methyl esters at C2, the aziridine *C-C* bond was most facile bond to cleavage to give the azetidines described. This idea is discussed further below.



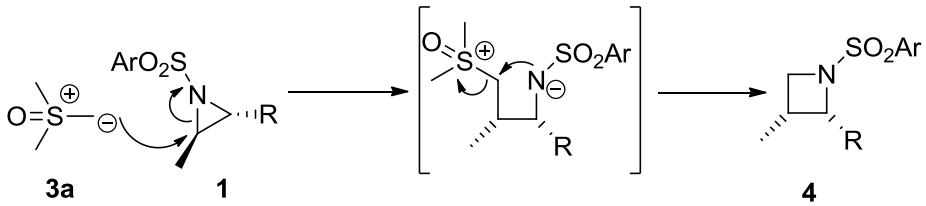

***Scheme 5:*** *Proposed $S_N2$ then 1,4-elimination mechanism in the reaction between* ***1a*** *and* ***3a****.*[23]

In contrast to the work of Carrié *et al.*, Nadir *et al.* reacted a larger selection of aziridines with only dimethylsulfonium methylide (**2a**) or dimethyloxosulfonium methylide (**3a**). The aziridines they employed shared the common functionalities of an *N*-$SO_2$Ar group and alkyl or aryl groups at the aziridine C2 and C3 positions. The solvents, temperatures and reaction times used by the two groups remained similar.

The results obtained by Nadir *et al*. can be categorized by sulfonium ylide choice. The use of ylide **2a** resulted in ring-opened 3-aminoalk-1-enes (**5**) (Scheme 6). It was proposed that the aziridine is first ring opened by the ylide in an $S_N2$ reaction at carbon, followed by proton transfer and expulsion of dimethylsulfide. Ylide **3a** converted aziridines to azetidines, with the new carbon centre present at the azetidine C4 position (Scheme 7, **Table 3**). The reaction is said to proceed *via* an $S_N2$ mechanism at carbon then 1,4-elimination of dimethylsulfoxide by nitrogen. When a single isomer of aziridine was charged to the reaction vessel, a single isomer of azetidine was isolated. For these reasons, they also discredited the intermediary of an azomethine ylide (cf. Carrié *et al.*).

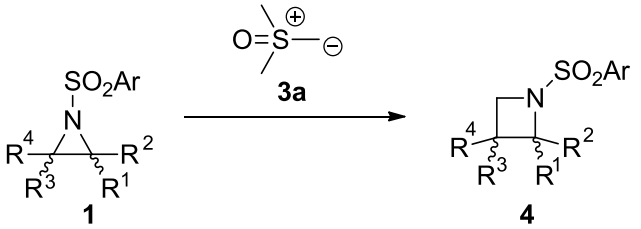



***Scheme 6:*** *Olefin formation via proposed proton transfer within the sulfonium ylide ring opened intermediate*.[24a]



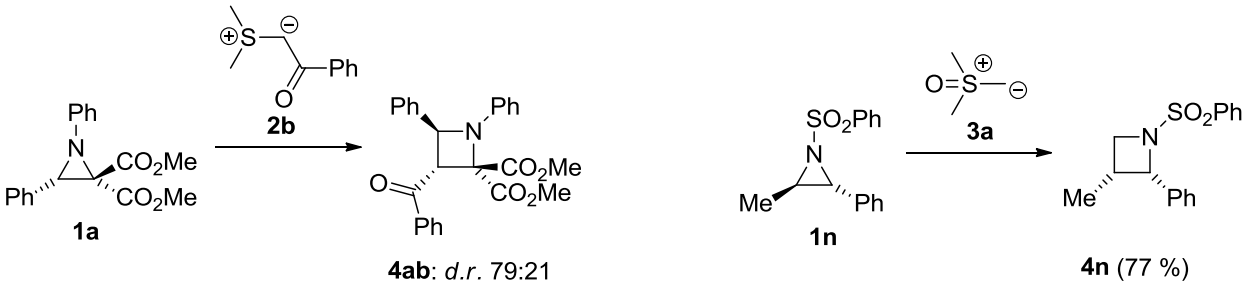

***Scheme 7:*** *Proposed $S_N2$ then 1,4-elimination mechanism.*[24a]

***Table 3:*** *Scope of aziridine ring opening according to Nadir et al.*[24a]




| Entry | Ar | $R^1$ | $R^2$ | $R^3$ | $R^4$ | Azetidine (yield %) |
|---|---|---|---|---|---|---|
| **1** | Ph | Ph | H | H | H | 51 |
| **2** | 4-MePh | Ph | H | H | H | 52 |
| **3** | 4-ClPh | Ph | H | H | H | 72 |
| **4** | 4-MePh | Me | H | H | H | 50 |
| **5** | Ph | 4-MePh | H | H | H | 20 |
| **6** | Ph | 3-MePh | H | H | H | 29 |
| **7** | Ph | 4-ClPh | H | H | H | 18 |
| **8** | Ph | 3-ClPh | H | H | H | 30 |
| **9** | Ph | 3-$NO_2$Ph | H | H | H | 5 |
| **10** | Ph | Bn | H | H | H | 34 |
| **11** | Ph | Ph | H | H | Me | 77 |
| **12** | Ph | Et | H | Me | H | 65 |

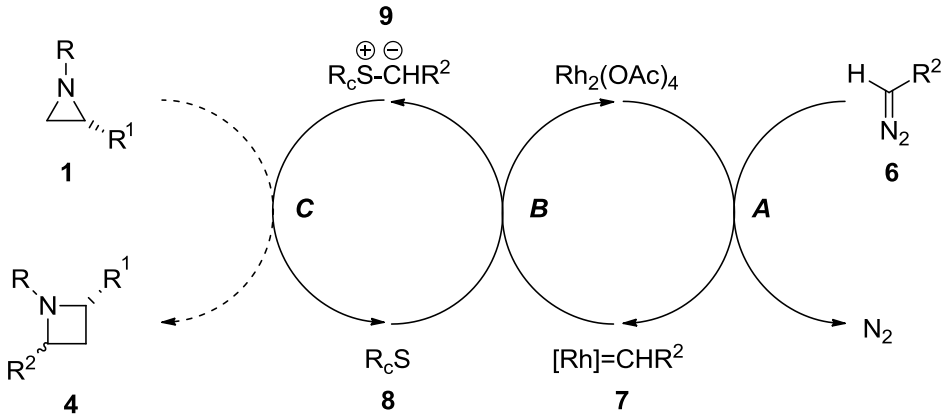
Although the two investigators utilized similar procedures, the results from each group were quite different. In the results published by Carrié *et al.*, most conversions of **1** to **4** were attained with sulfonium ylides **2**. By contrast, Nadir *et al.* found only oxosulfonium ylide **3a** was able to convert **1** to **4**. It seems that it is the choice of *C*- or *N*- activation that primarily dictates the pathway of the reaction (Scheme 8). The concept of *C*- or *N*- activation is discussed in more detail below.




***Scheme 8:*** *Summary representation of the Carrié et al. (left) and Nadir et al. (right) aziridine ring expansion investigations.*

Based on this research, a novel procedure for the asymmetric synthesis of azetidines from aziridines exploiting the *in situ* generation of chiral sulfonium ylides was proposed. The postulated ring expansion reaction demands a stoichiometric loading of a diazo functionalised precursor (**6**) in the presence of a substoichiometric loading of transition-metal catalyst and sulfide. After generating the carbenoid species (**7**) from the diazo and metal catalyst, this would react with the chiral sulfide (**8**) to generate the chiral

sulfonium ylide (**9**) and return the metal catalyst to the catalytic cyle. Following a successful reaction with the aziridine, **8** would then also be returned to the catalytic cycle. This strategy for the generation of chiral sulfonium ylides is a well-documented process reported by Aggarwal *et al.* (Scheme 9), and the linked cycles in the proposed mechanism are discussed below.[28]




***Scheme 9:*** *The catalytic generation of sulfonium ylides and their applicability to the azetidination of aziridines.*

Reaction A: Certain transition-metal complexes will react with diazo compounds to generate metal-carbene complexes.[29] These 'Fischer-type' carbene complexes (between carbon and a low oxidation state late transition-metal centre) are considered to react as electrophiles at the carbon centre.[30] Rhodium acetate dimer is a popular choice for forming such metal-carbenoid species and the driving force for the reaction is the generation of dinitrogen gas.[31]

Reaction B: The neutral nucleophilic chiral sulfide reacts with the electrophilic carbon of the metal-carbene complex. This reaction releases the metal complex back into solution, returning it to the catalytic cycle. The chiral sulfide now exists as part of a chiral sulfonium ylide; the reactive species for the postulated ring expansion of **1** to **4**. Many chiral sulfides are known and their uses have been developed over the years by various groups (Figure 5).[32] These procedures are dominated by asymmetric epoxidation procedures but chiral sulfides have also seen use as chiral ligands for transition-metal catalysed reactions.[33] The sulfides used as the precursors to the relevant sulfonium ylides are often easily recovered, making them ideal candidates for catalytic processes.

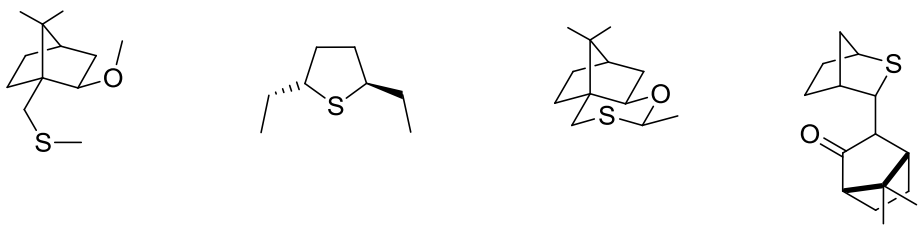



***Figure 5:*** *Examples of chiral sulfides*.[32]

Reaction C: In the final reaction of the proposed catalytic process, the chiral sulfonium ylide **9** reacts with the aziridine. A successful reaction would proceed *via* one of the two pathways discussed previously, thereby returning the chiral sulfide to the catalytic cycle following 1,4-elimination to form azetidine. One

important mechanistic detail to consider here will be the nature of the chiral sulfonium ylide addition to the aziridine. The matched or mismatched interaction between chiral ylide and chiral aziridine would be expected to guide the reaction along a single pathway to yield a high diasterioisomeric excess of product. The outcome of the reaction would imply which effects are controlling the ring opening process, as well as any stereoselectivity arising from substrate or reagent control of the mechanism.

The precedent has already been set for the use of achiral sulfonium ylides in the synthesis of aziridines from imines, and azetidines from aziridines.[34] The asymmetric synthesis of aziridines from imines using chiral sulfonium ylides has also been reported.[35] There is therefore scope for finding suitable chiral sulfonium ylides to use in studies for the proposed asymmetric reaction to form azetidines from aziridines.

In the discussed mechanisms, the 1,4-elimination step to displace sulfide would mechanistically resemble the established 1,4-elimination routes to azetidine. It may therefore suffer from slow rates of ring closure for reasons mentioned previously. The displacement of the chiral sulfide as a neutral leaving group is anticipated to be a strong driving force for this reaction. In addition to providing a new route to the desirable azetidine motif, it should also help to further understand the scope and mechanism of the reaction between aziridines and sulfonium ylides and improve access to the hard to make chemical environment around azetidine.

To allow a complete understanding of the results from any successful reaction between an aziridine and chiral sulfonium ylide, it will be necessary to charge the reaction vessel with a single enantiomer/diastereoisomer of aziridine. This should allow simple conclusions to be drawn about the diastereoselectivity and regioselectivity of the reaction. Aziridine synthesis has received much attention in recent decades; several strategies for aziridine syntheses exist and have been extensively reviewed elsewhere.[36] Popular racemic aziridine synthesis usually takes the form of carbene addition to imine, or nitrene addition to alkene. Routes to single enantiomers of aziridines include the use of amino-acid precursors or the stereospecific ring opening of epoxides prior by amines prior to 1,3-elimination from the resulting 1,2-amino alcohol (Figure 6). Judicious choice of procedure would be required when synthesising starting materials for this investigation; this is discussed below.

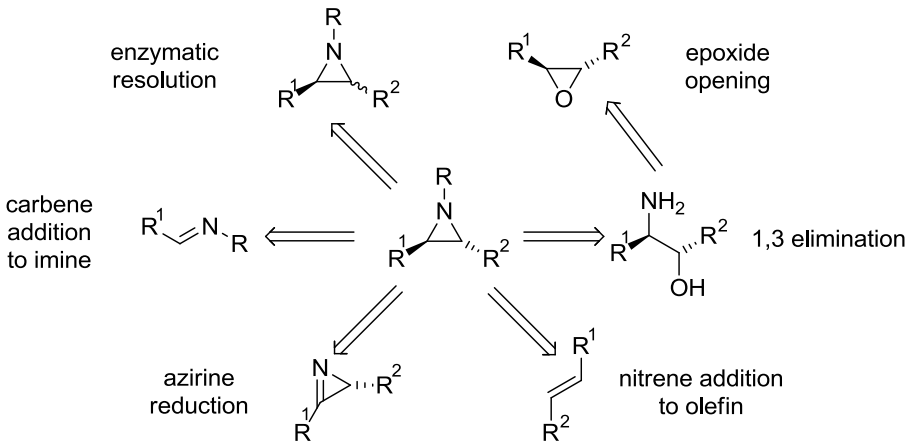
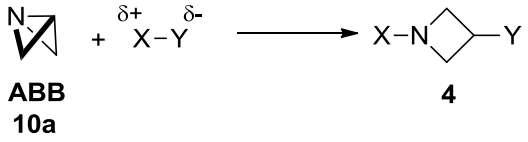



***Figure 6:*** *Retrosynthetic analysis of asymmetric aziridines*.[36]

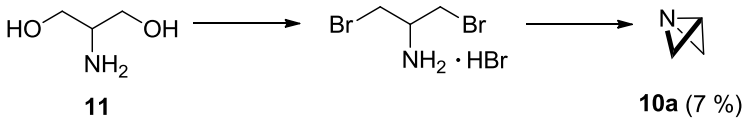
### 1.1.3 Azetidines from azabicyclo[1.1.0]butanes

An alternative route to azetidine lies in the ring opening of strained but stable azabicyclo[1.1.0]butane (ABB) molecules (Scheme 10).[37] Both the synthesis of the unfunctionalised parent compound azabicyclo[1.1.0]butane (**10a**) and the subsequent 1,3-bond cleavage reactions were pioneered in the 1960s by Funke.[37a] This was followed by further investigations by others (*vide infra*) into higher yielding methods to produce **10a**. These procedures have similarities with early and popular aziridine and azetidine synthesis methods. The rates and scope of ABB ring opening reactions also received further attention.

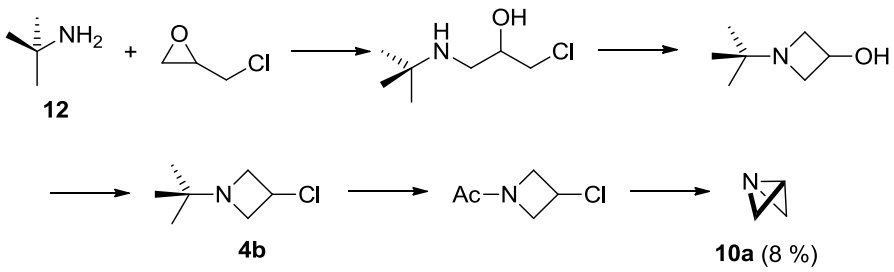



***Scheme 10:*** *General reaction scheme for the 1,3-bond cleavage of* ***10a****.*

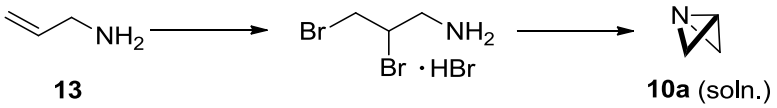
In the report by Funke, a method for the synthesis of **10a** in two steps from 2-amino-1,3-propanediol (**11**) but suffered from low yield (7 %) (Scheme 11).[37b] In an improved method to generate **10a**, the yield of the ABB from its precursor was reported to be 50 %, as determined by the product analysis of the reaction of **10a** with ethyl chloroformate.[37c] The number of steps to **10a** from the *tert*-butylamine starting material[38] (**12**) *via N*-tert-butyl-3-chloroazetidine[39] (**4b**) had, however, increased to five with an overall yield of 8 % from **12** (Scheme 12). In this synthesis, **4b** required conversion to the *N*-acyl azetidine with acetic anhydride and $BF_3$•$Et_2O$. This allowed the selective 1,3-elimination to occur to give **10a**. Azetidine **4b** is reported to undergo isomerisation to give aziridine products *via* an azabicyclo[1.1.0]butane intermediate, and so was not suitable for synthesising **10a**. The most recent procedure[37g] for the synthesis of **10a** offered optimized conditions based on those reported by other investigators.[40] This resulted in the highest yielding route to **10a** in the fewest steps from commercially available starting materials (allylamine **13**) (Scheme 13). Due to the similar boiling points of **10a** (52 °C) and the tetrahydrofuran (THF) solvent (66 °C) used in the reaction, **10a** synthesised using this method is obtained and used as a THF solution.




***Scheme 11:*** *Synthesis of* ***10a*** *according to Funke.*[37b]




***Scheme 12:*** *Synthesis of* ***10a*** *according to Paritosh*.[37c]

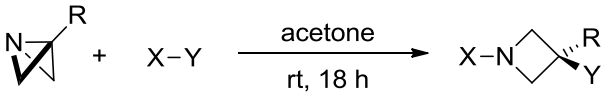



**13** **10a** (soln.)

***Scheme 13:*** *Synthesis of **10a** according to Nagao.*[37g]

Early experiments to probe the reactivity of **10a** and its 3-methyl (**10b**) and 3-ethyl (**10c**) analogues focused on the ring opening reaction by 1,3-bond cleavage of the heterocycle with a limited selection of thiols, chlorides and amines to yield the corresponding azetidines (**4**) (Table 4).[37a] Studies into the rate of hydrolysis of 3-phenylazabicyclo[1.1.0]butane (**10d**) in dilute aqueous buffers at a range of pHs (6.93 -9.18) were also performed.[41]

***Table 4:*** *Scope of ABB 1,3-bond cleavage according to Funke*.[37a]

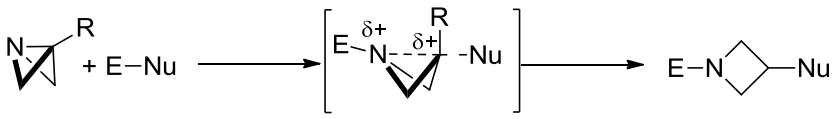



**10a-c** **4**

| ABB | R | X | Y | Azetidine yield (%) |
|---|---|---|---|---|
| **10a** | H | Ts | Cl | 72 |
| **10a** | H | H | SPh | 64 |
| **10b** | Me | Ts | Cl | 62 |
| **10b** | Me | H | SPh | 79 |
| **10b** | Me | H | $NC_5H_{10}$ | 36 |
| **10b** | Me | MeC(O) | Cl | 70 |
| **10c** | Et | Ts | Cl | 85 |

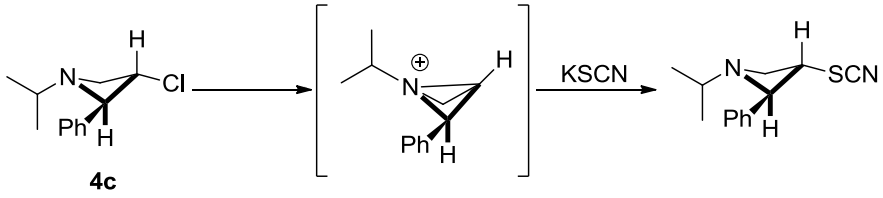
Funke proposed a mechanism involving initial formation of an intermediate quaternary nitrogen species, followed by nucleophilic attack at C3 to yield the corresponding azetidine (Scheme 14).[37a] Kurz *et al.*, when discussing the solvolytic cleavage of **10d** and the observed reverse reaction also proposed that an equilibrium ammonium intermediate might be forming.[37e] They also proposed in the same report that a transient species containing a C3 carbonium centre cannot be precluded. This was justified by the C3-phenyl aiding stabilisation of a positive charge on the benzylic carbon. A report by Touhami *et al.* also proposed the formation of an intermediate species containing a C3 carbonium centre (Scheme 15).[42]


***Scheme 14:*** *Intermediate ammonium species proposed by Funke*.[37a]



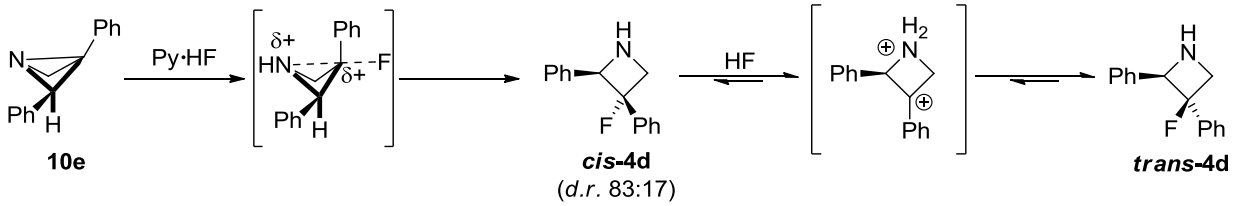

***Scheme 15:*** *Transient carbocation formation during 1,3-bond cleavage of ABB proposed by Kurz et al. and Touhami et al.*[37e, 42]

A more recent report about the reactivity of *trans*-2-aryl-3-chloroazetidines (**4c**) has also described a quaternary nitrogen centre within an intermediate ABB molecule (Scheme 16).[43] In order for ring opening to occur, these studies would infer that the nitrogen centre must first be quaternised such that cleavage of the N1-C3 bond becomes facile.




***Scheme 16:*** *Transient ammonium species according to De Kimpe et al.*[43]

Investigators also observed in the reaction of 2,3-diphenylazabicyclo[1.1.0]butane (**10e**) with Py•HF that the *cis*- product (2*R*,3*S*)-3-fluoro-2,3-diphenylazetidine (***cis*-4d**) would form preferentially (66 % d.e). Furthermore, when the ***cis*-4d** was stirred with HF, the compound would slowly isomerise to ***trans*-4d** *via* a proposed benzylic cation intermediate (Scheme 17).




***Scheme 17:*** *Isomerisation in azetidines from ABBs.*[42]

The routes to ABBs discussed above all exploit intramolecular cyclisation reactions involving 1,3- or 1,4-elimination of suitable leaving groups by nitrogen. An intermolecular process that can be employed is the addition of sulfonium ylides to the *C*=*N* bond of 2*H*-azirines. It is by this route that the first ABB compound 2,2-dimethyl-3-phenyl-1-azabicyclo[1.1.0]butane (**10f**) was synthesised.[44] Most studies into the reactivity of ABBs used the unfunctionalised parent compound **10a**. Where functionalisation was present, it was minimal and usually at C3. When the scope of possible reactions between azirines and sulfonium ylides is considered, there appears to be an underexploited route to ABB derived compounds with substituents also at C2 and C4. No such protocols have been reported to date.

Several routes to 2*H*-azirines (**14**) exist that would provide starting materials for the synthesis of substituted ABBs; several reviews describe this area of chemistry in detail (Figure 7).[45,46] The first synthesis was reported by Neber and involved the treatment of $\alpha$-unsaturated ketoxime tosylates with base to form the 2*H*-azirine.[47] Since its discovery, variations of the Neber reaction have been developed. These include the use of ketoxime mesylates[48] and ketone trimethylhydrazone halides.[49] Asymmetric examples are also known.[50] Another attractive, albeit more hazardous, route to azirines is *via* the thermal decomposition of vinyl azides.[51] The obvious hazards of azide toxicity and the potential for explosions, coupled with the high reactivity of the nitrene intermediate makes this protocol less common.

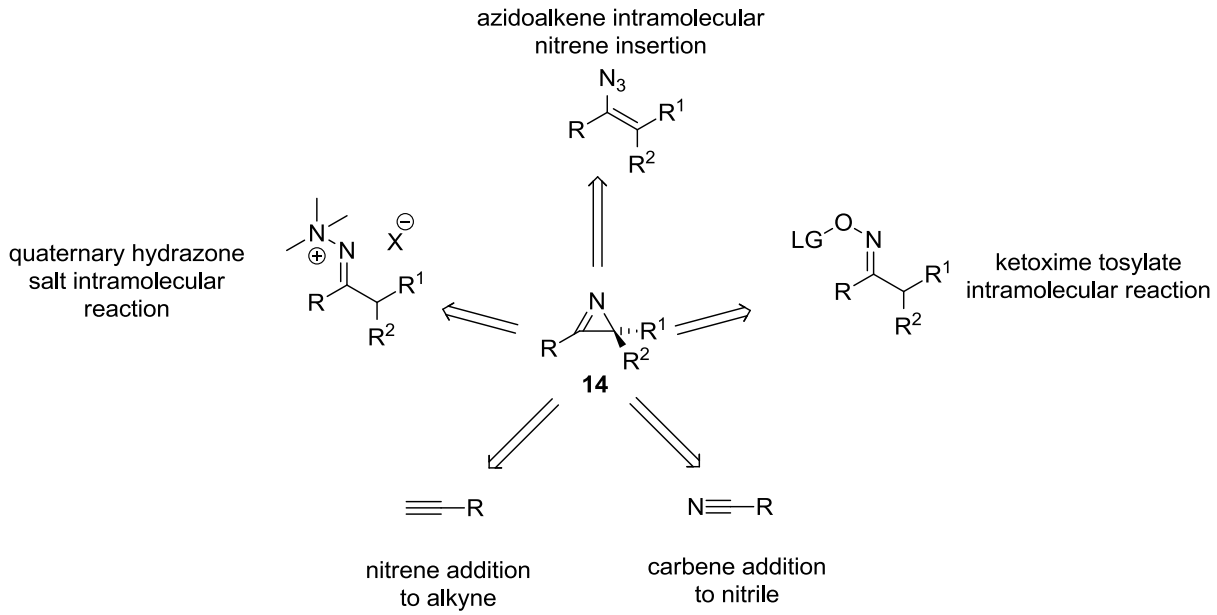
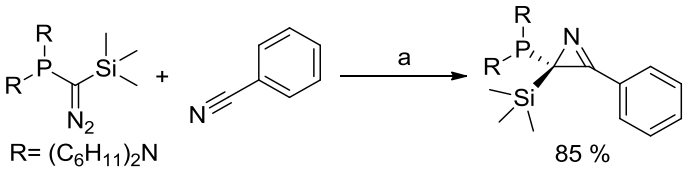



***Figure 7:*** *Azirine retrosynthetic analysis*.[45]

Two lesser reported methods also exist: the first is the [2+1] cycloaddition of nitrile and phosphinocarbene; only one example of this reaction is known (Scheme 18).[52] The second is the addition of nitrene to alkyne, followed by tautomerisation from the 1*H*-azirine to the more stable 2*H*-azirine. In the few examples of this intermolecular reaction, azide is typically decomposed to give the reactive nitrene intermediate and so has the same inherent risks mentioned for working with vinyl azides.[53]




***Scheme 18:*** *Addition of phosphinocarbene to nitrile.*[52] *Conditions* ***a****: toluene, rt, 18 h.*

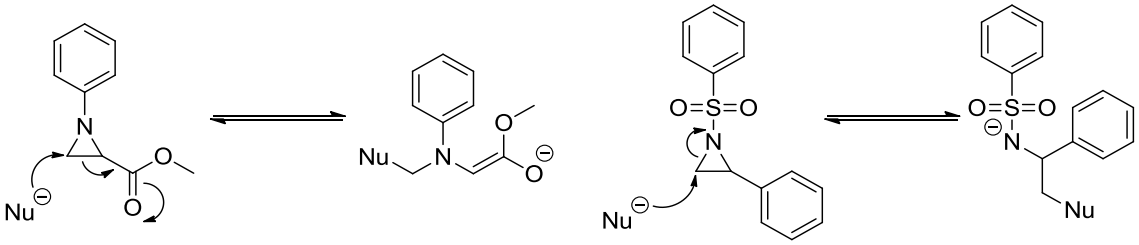
## 1.2 Results and discussion

### 1.2.1 Aziridine ring expansion

As mentioned above, successful aziridine ring expansion to azetidine with sulfonium ylides appears to rely on the functionalisation around the aziridine ring. The research conducted by Carrié *et al.* employed aziridine functionalized with an *N*-phenyl group, C3-phenyl group and two C2 methoxycarbonyl groups. Nadir *et al.* employed aziridines functionalized with *N*-arylsulfonyl groups combined with alkyl, phenyl or no functionality at C2 and C3. The Carrié aziridines could be said to be *C*-activated and the Nadir aziridines *N*-activated. To incorporate scope for downstream chemistry and further the understanding of this ring expansion, the inclusion of substituents that would install a pattern of functionalisation on azetidine that didn't match previously reported research was important: *N*-activated aziridines with C2 ester functionalities were desirable.

While aziridines are known electrophilic building blocks, suitable ring-activating groups are necessary to enable the heterocycle to be sufficiently reactive towards sulfonium ylides. Nucleophilic attack is facilitated by an electron withdrawing group at either carbon or nitrogen. Electron withdrawing groups include $–SO_2R$, $-CO_2R$ and $–P(O)R_2$. An *N*-activated aziridine (cf. Nadir) will display these functionalities on the nitrogen; a *C*-activated aziridine (cf. Carrié) will display these functionalities on the carbon. The unactivated aziridine positions will be functionalised with groups that do not exhibit significant electronic effects, such as -H, -alkyl or –aryl.

The nature of the activating group will facilitate nucleophilic attack by inductive (in the case of sulfonyl or phosphinyl) or resonance (in the case of carbonyl) electron withdrawing effects, enabling the aziridine to react with suitable nucleophiles in a ring opening fashion. Delocalising electron density away from the nitrogen should facilitate aziridine *C-N* bond cleavage. Where no *N*-activating group is present and instead a C2 ester functionality is present, delocalisation of electron density away from the aziridine into the carbonyl bond should favour *C-C* bond fission (Scheme 19).




***Scheme 19:*** *Resonance effects (left) or inductive effects (right) driving bond fission.*

With both an *N*-activating group and a C2 ester, the more labile of the *C-C* or *C-N* bonds should dictate whether a newly installed carbocentre exists in the azetidine C3 or C4 position. This should become clear through successful experimentation. In the case of a ring-opening ring-closing mechanism in which the *C-N* bond is cleaved, an electron withdrawing *N*-activating group could slow the rate of ring closure. Different *N*-activating groups may also tune the electronics of the aziridine to such an extent that *C-N* or *C-C* bond fission can be favoured in the presence of a neighbouring ester functionality (Figure 8).

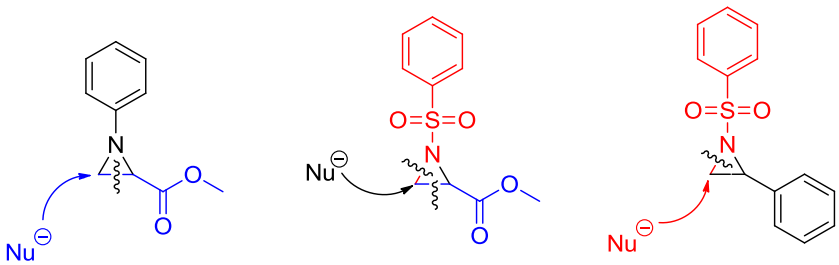
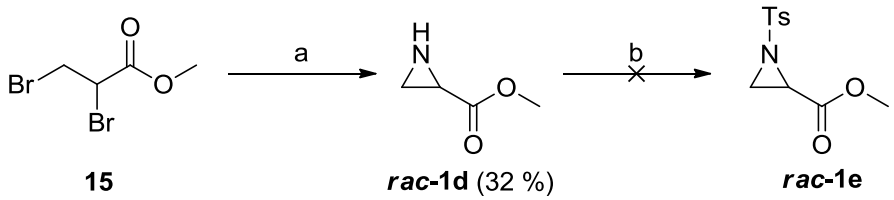



***Figure 8*** : *The combination of C- and N- activation in the same aziridine (centre) may highlight the more labile bond in an activated aziridine.*

From methyl 2,3-dibromopropionate (**15**) and ammonia, racemic methyl aziridine-2-carboxylate (***rac*-1d**) was synthesised to provide a suitably substituted aziridine to start investigations with.[54] Functionalisation

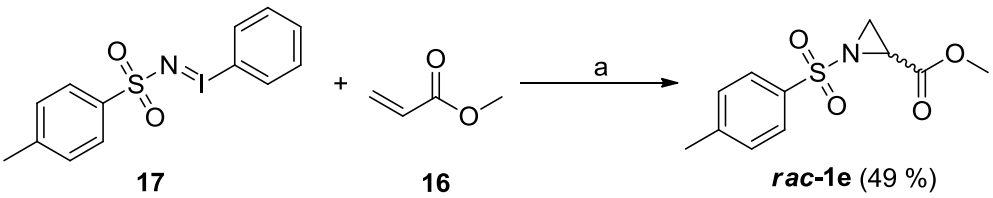
of nitrogen with 4-toluenesulfonyl chloride was attempted (Scheme 20). This protecting group would ensure the aziridine was activated with a pattern of functionalisation novel to this protocol. Although several methods exist to synthesize methyl 1-tosylaziridine-2-carboxylate (***rac*-1e**) in a single step, this route had the advantage of providing access to ***rac*-1e** *via* an isolated unfunctionalised *N*-H aziridine. This would allow a range of *N*-activating groups to be appended as investigations progressed.




***Scheme 20:**. Conditions[54] **a**: $NH_3$, MeCN, -20 °C. **b**: TsCl, $NEt_3$, DCM, rt, 16 h.*

The aziridination of **15** with ammonia displayed a lack of robustness with a broad range of crude yields recorded, from 0 to 81 %. This reaction was also unselective: multiple additional products were detected by TLC analysis of the crude product. IR analysis suggested there was potentially a mixture of ***rac*-1d** and an amide derivative, with two carbonyl stretches observed in the IR spectrum at 1729 and 1669 $cm^{-1}$. Indeed, the ammonolysis of esters to yield such amide products has been reported.[55] Scale or equipment choice did not appear to offer any improvement in the performance of the reaction. The expected volatility and chemical instability of isolated ***rac*-1d** also proved to be responsible for the wide range of yields.

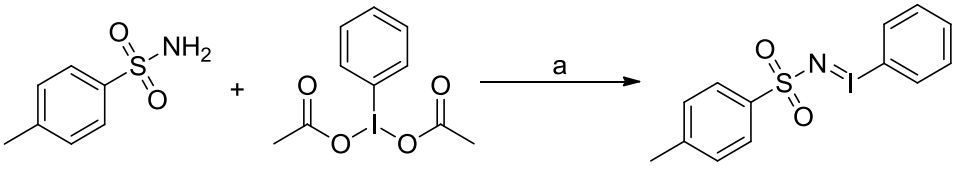
The reaction to install the *N*-tosyl group on ***rac*-1d** was unsuccessful; ***rac*-1e** could not be detected in the complex crude reaction mixture by $^1$H NMR even after total consumption of the starting material. The two-step method was abandoned in favour of the pioneering aziridination procedure of Evans *et al*.[56] Methyl acrylate (**16**) and (*N*-(4-tolylsulfonyl)imino)phenyliodinane[57] (**17**) were combined in a copper catalysed nitrene olefin insertion reaction (Scheme 21). The mechanism of this reaction has been discussed in the literature and it is believed that these copper catalysed aziridinations using iodinane reagents proceed *via* a copper-nitrene complex rather than an ylide type mechanism.[58] Although this method did not provide access to an unfunctionalised *N*-H aziridine, it did provide a single operationally straightforward step to the target aziridine ***rac*-1e**.




***Scheme 21:** Synthesis of **rac-1e**.[56] Optimised conditions **a**: 10 mol. % $Cu(OTf)_2$, MeCN, 25 °C.*

The stable hypervalent iodine compound **17** serving as the nitrene source was easily synthesised on multi-gram scale from equimolar quantities of 4-toluenesulfonamide (**18**) and diacetoxyiodobenzene (DAIB, **19**) under basic conditions (Scheme 22).[59] The catalyst selected for the reaction was copper$^{(II)}$

triflate, although catalysts based on other transition-metals (iron, rhodium, cobalt and manganese) have also been reported to work with varying degrees of success.[60] Generally, copper$^{(II)}$ catalysts have the advantage of being cheap, commercially available and air stable. $Cu(OTf)_2$ provided one of the best reported yields of ***rac*-1e** in this procedure as well as being easy to handle when the reaction is performed in acetonitrile.




**18** **19** **17** (36 %)

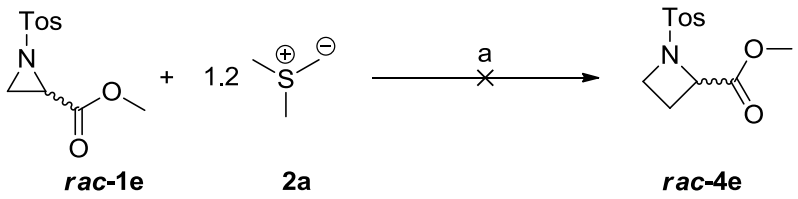
***Scheme 22:*** *Synthesis of a hypervalent iodinane reagent.[59] Conditions* ***a****: KOH, MeOH, rt, 3 h.*

During method development, Evans *et al.* described the observation that **17** was not soluble in the reaction medium. As the reaction proceeded, the solid iodinane was slowly taken into solution. The reaction was therefore easy to follow; the total disappearance of **17** as it was drawn into solution was indicative of a suitable time to halt the experiment. The duration of the experiment could be reduced by grinding the iodinane to a powder before charging to the flask.

The isolated yield of ***rac*-1e** was poor at only 25 % even when adhering to anhydrous reaction conditions. After scrupulous drying of solvent and glassware, use of fresh samples of all reagents and careful thermostatting of the reaction, poor catalyst quality was suspected to be the cause of the low yield in early reactions. $Cu(OTf)_2$, while being air stable, is also hygroscopic. Any decomposition of the catalyst over time through reaction with atmospheric moisture will have had the effect of reducing the effective catalyst loading in the reaction as well as introducing a source of $H_2O$ to the system. Use of different batches of catalyst at different reactions scales did not increase this yield however.

Throughout their report, Evans *et al.* discussed using 5 – 10 mol. % of catalyst, however in the reported methods only 5 mol. % catalyst loading was used. Modification of the procedure to increase the catalyst loading to 10 mol. % caused an immediate increace in the yield of ***rac*-1e** to 49 %. Useful quantities of a suitable aziridine to expose to sulfonium ylide ring expansion conditions were now available.

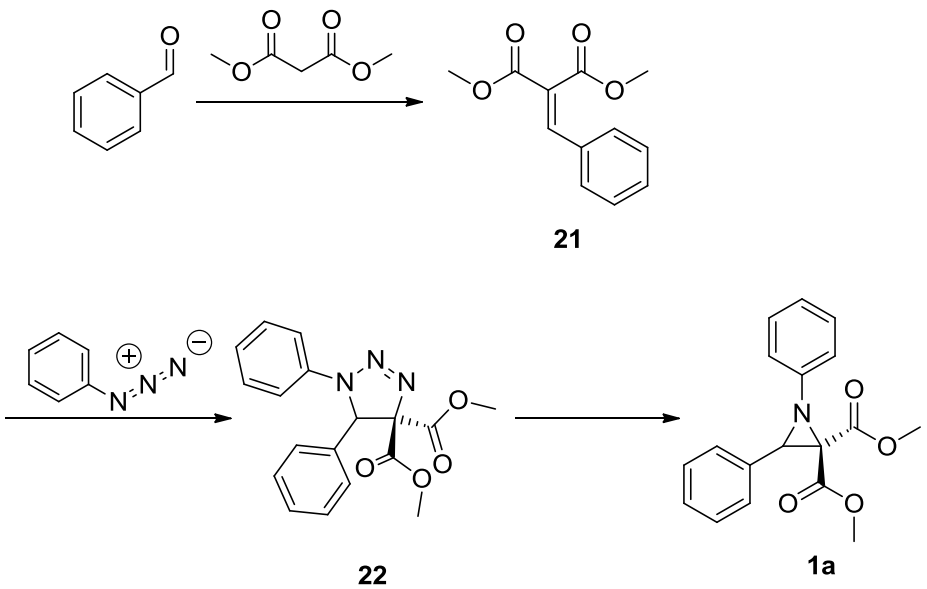
Taking conditions from the work of Carrié *et al.*, ***rac*-1e** was combined with sulfonium ylide **2a**. The ylide employed in these studies is not stable for extended periods of time, with an estimated lifetime in solution of a few minutes once warmed above 0 °C.[26] Ylide **2a** was generated *in situ* by deprotonation of trimethylsulfonium iodide (**20**) with *n*-butyllithium[61] followed by its immediate addition to a solution of ***rac*-1e** (Scheme 23). Analysis of all mother liquors and separated solids did not show the presence of any new material having been formed in the reaction. The target azetidine methyl 1-tosylazetidine-2-carboxylate (***rac*-4e**) could not be detected by $^1$H NMR and only the aziridine starting material was recovered.




***Scheme 23:*** *Reaction based on the conditions of Carrié et al.*[23] *Conditions* ***a****: THF:DMSO, 0 °C – rt, 8 h.*

The reason for the lack of reaction was not immediately clear. As only ***rac*-1e** was recovered, it was suspected that the relatively high reaction temperature range (0 °C – rt) and small excess of **20** (and therefore ylide **2a**) may have allowed the reactive species to be consumed before it had to time react with ***rac*-1e**. This observation was in contrast to the comments by Carrié *et al.* that aziridine **1a** was not stable in the presence of ylide **2a.** To validate the procedure being employed, replication of the method reported by Carrié *et al.* was attempted.[23]

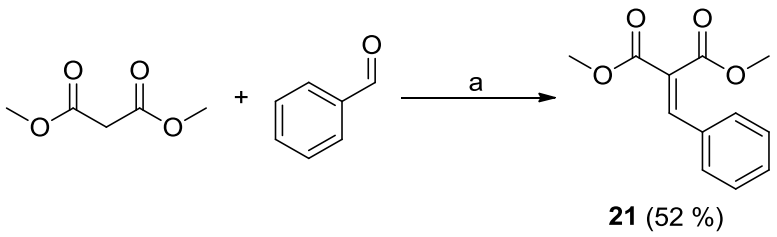
Carrié *et al.* reported the synthesis of **1a** from dimethyl 2-benzylidenemalonate (**21**), *via* thermolysis of the corresponding triazoline compound (**22**) (Scheme 24). Although this process was reported to take longer than one month to yield the aziridine, with the longest step being the Click reaction between **21** and azidobenzene, no alternative methods to synthesise **1a** have been published. Two alternative protocols to synthesise **1a** were also selected for evaluation, based on the addition of hydroxylamine derivatives to **21**, and the aza-Darzens reaction between dimethyl 2-bromomalonate and *N*-benzylideneaniline. These three approaches are discussed in detail below.




***Scheme 24:*** *The procedure reported by Carrié et al. towards the synthesis of* ***1a****.*

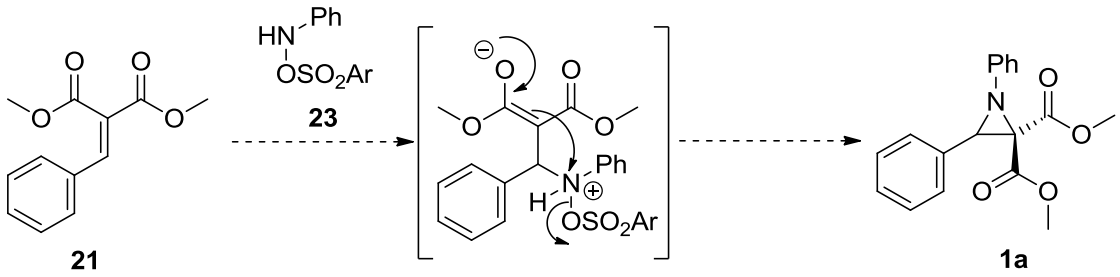
The Knoevenagel condensation between benzaldehyde and dimethylmalonate provided **21** in acceptable yield (Scheme 25).[62] **21** was then taken neat with an equimolar quantity of azidobenzene. The reported procedure stirred the two together for one month, followed by heating at 160 °C for 15 minutes to decompose the triazoline. This procedure was not successful. Weekly TLC analysis did not show any

reaction between **21** and azidobenzene, and **1a** was not detected in the reaction mixture following final heating and thermolysis. Two alternative routes to **1a** were now investigated.




***Scheme 25:*** *Knoevenagel condensation between benzaldehyde and dimethylmalonate.*[62]
*Conditions* ***a****: 10 mol. % piperidine, benzene, reflux (Dean Stark), 18 h.*

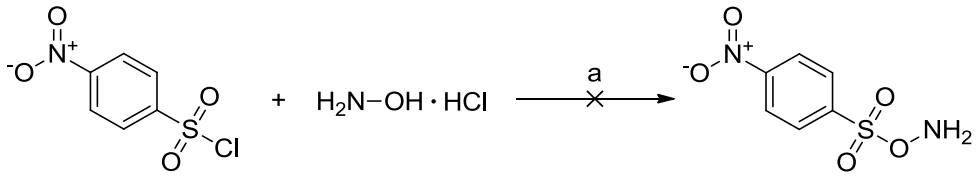
It was postulated that the unreported reaction of **21** with arylsulfonyl hydroxylamines (**23**) could allow access to **1a** *via* a conjugate addition process (Scheme 26). Examples of hydroxylamine addition to α,β-unsaturated carbonyls in an aza-Michael reaction are well-known.[63] *O*-(4-Nitrophenylsulfonyl)hydroxylamine (**23a**) belongs to a group of *O*-sulfonyl hydroxylamines, including *O*-(4-tosylsulfonyl)hydroxylamine (**23b**) and *O*-(mesitylenesulfonyl)hydroxylamine (**23c**). The *O*-4-nitrophenylsulfonyl leaving group is the most reactive in the series on account of the stabilizing electron withdrawing nature of the *p*-$NO_2$ functionality. The sulfonyl groups in each were expected to be increasingly better leaving groups in the order Mes<Ts<Ns. Hydroxylamines **23a** and **23c** are reported to be stable, whereas **23b** is reported to spontaneously decompose after only a few minutes when dried.[64, 65]




***Scheme 26:*** *Postulated aziridination of* ***21*** *with hydroxylamines.*

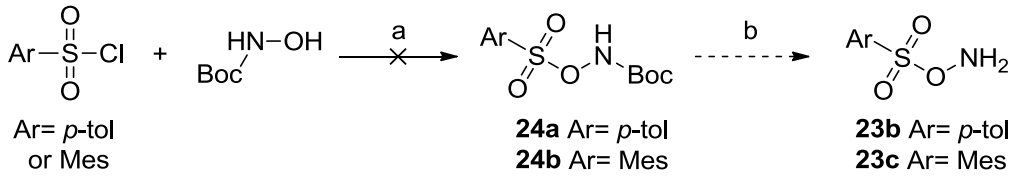
To obtain **1a** in a single step using this protocol an *N*-phenyl hydroxylamine reagent would be required. It was expected, however, that *N*-phenyl-*O*-(4-nitrophenylsulfonyl)hydroxylamine may not be sufficiently reactive towards **21**. Conjugation of the nitrogen lone pair into the phenyl ring and the increased steric bulk around the nitrogen centre could reduce the nucleophilicity of the hydroxylamine. The procedure would therefore be attempted with an *N*-unfunctionalised hydroxylamine first, with *N*-functionalisation in a subsequent step.

Hydroxylamines **23a**-**c** are not commercially available and few procedures exist for their synthesis. The reaction between hydroxylamine hydrochloride and 4-nitrobenzenesulfonyl chloride to give **23a** was not successful in our hands, returning only the unreacted starting materials (Scheme 27).[65]



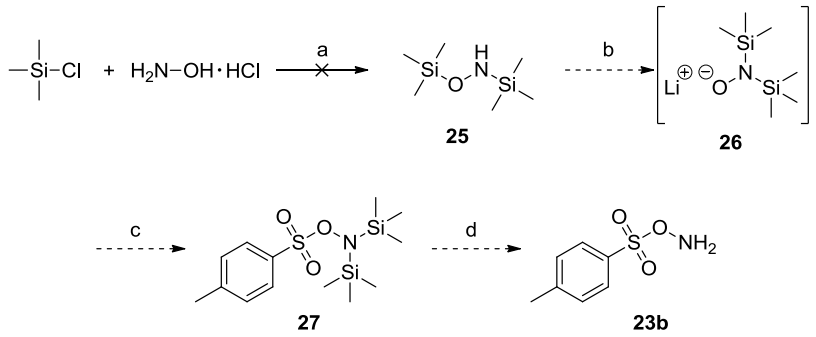
***Scheme 27:*** *Attempted synthesis of **22a** according to Fioravanti et al.*[65]
*Conditions **a**: 10 M $NaHCO_3$, THF, -10 °C,2 h.*

A second procedure describing the Boc-deprotection of *O*-acylhydroxylamine *N*-carbamates to access *O*-acylhydroxylamines was attempted:[64] In the reported two step method from commercially available materials, *N-tert*-butoxycarbonyl hydroxylamine was combined with 4-toluenesulfonyl chloride[66] or mesitylenesulfonyl chloride[64] to give the *N*-Boc *O*-acylhydroxylamines (Ts- **24a**, Ms- **24b**); the carbamate group was then removed with strong acid. The procedure was not able to provide us with **24a** or **24b** as the material could not be successfully isolated by recrystallisation from the crude products. Subsequent deprotection to expose the hydroxylamine was therefore not possible (Scheme 28).



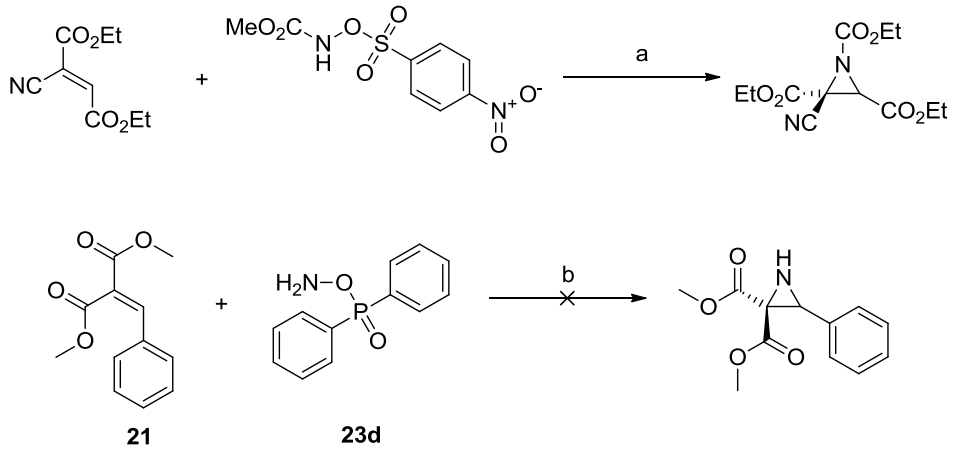

***Scheme 28:*** *Attempted synthesis of **23b** and **23c**, via carbamate **24a** and **24b,** according to Carpino.*[64, 66]
*Conditions **a**: $NEt_3$, DMF, 0°C, 30 min; **b**: 48 % HF, 0 °C, 8 min.*

The final procedure referred to exploited the rearrangement of *N*,*O*-bis(trimethylsilyl)hydroxylamine (**25**) followed by reaction with 4-toluenesulfonyl chloride and finally desilylation to yield **23b**.[67] Hydroxylamine **25** first had to be synthesised by addition of trimethylsilyl chloride to hydroxylamine. On exposure to *n*BuLi, **25** should rearrange to give the *O*-lithiated intermediate **26** which can react with 4-toluenesulfonyl chloride to give trimethylsilyl protected hydroxylamine **27**. Cleavage of the silyl groups with chloride would finally yield **23b** (Scheme 29). Although the reaction proceeded in agreement with literature observations, it was not possible to isolate **25** by distillation; instead only complex mixtures of unidentified compounds were observed.



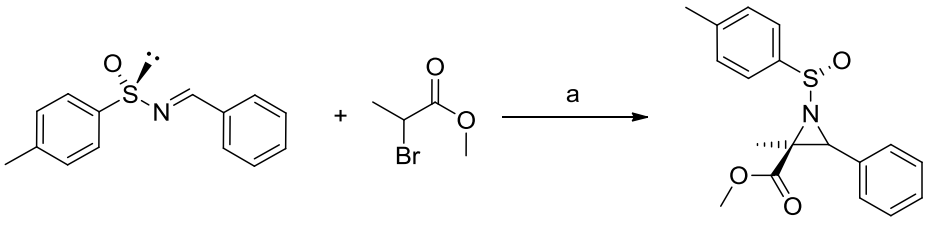

***Scheme 29:*** *Attempted synthesis of **23b**, via trimethylsilylhydroxylamine **27**, according to King and Walton.*[67]
*Conditions **a**: $NEt_3$, $ClSiMe_3$, THF:petroleum ether 40 – 60 fraction, reflux, 2 h; **b**: nBuLi, $Et_2O$, rt, 30 min; **c**: TsCl, -50 °C – rt, 2 h; **d**: 2M HCl, MeOH, 0 °C, 5 min.*

With **23a**-**c** unavailable for the investigation, the commercially available *O*-diphenylphosphinylhydroxylamine (**23d**) was selected. A procedure based on the reported conditions for the successful reaction of **23d** with diethyl-2-cyanofumerate to give the corresponding *N*-methoxycarbonyl aziridine was not successful: only starting materials **21** and **23d** were recovered (Scheme 30).[68]

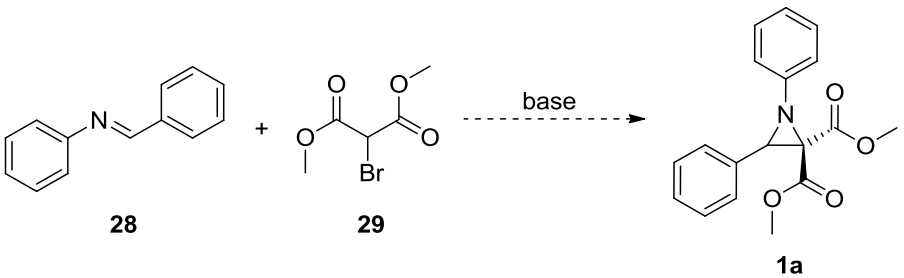



***Scheme 30:*** *Attempted aziridination of* ***21*** *with* **23d**. *Conditions* ***a*** *(Fioravanti et al.): 2 mol. eq. CaO, DCM, rt, 2 h.* ***b*** *(this study): 2 mol. eq. $NEt_3$, DCM, rt, 3 h.*

The second alternative approach to synthesize **1a** was an aza-Darzens reaction. An analogous procedure to the Darzens reaction, the aza-Darzens reaction exploits nucleophilic attack upon an imine by an anion bearing a suitable $\alpha$-leaving group,[69] of which the procedure of Davis *et al.* is representative (Scheme 31).[70] Aziridine **1a** could potentially be accessed in a single step from *N*-benzylideneaniline (**28**) and dimethyl 2-bromomalonate (**29**) (Scheme 32).



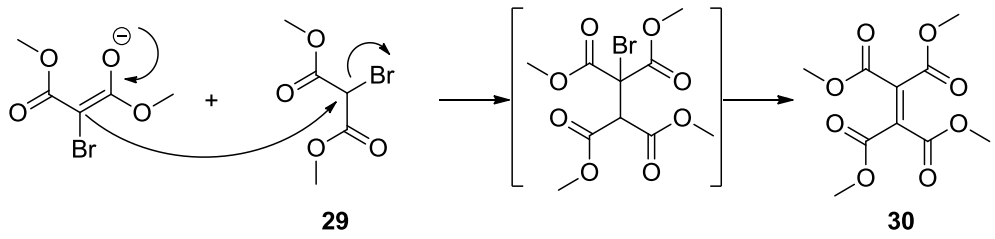

***Scheme 31:*** *The aza-Darzens reaction towards aziridine synthesis according to Davis et al.*[70] *Conditions* ***a****: LiHMDS, THF, rt, 2.5 h.*




***Scheme 32:*** *Proposed aza-Darzens aziridine synthesis.*

In contrast to the work of Davis *et al.* this investigation would attempt to synthesise **1a** in an aza-Darzens reaction using *N*-phenylimine rather than *N*-sulfinimine. The reaction was anticipated to proceed in a similar fashion to the Davis procedure none the less. Following deprotonation of **29**, the enolate would react with **28** at the N=C carbon, followed by 1,3-elimination to displace bromide.

In a first-pass reaction, **28**, **29** and $NEt_3$ were taken in a 1:2:2 stoichiometry. No reaction was observed by TLC at -78 °C, and at room temperature a colourless precipitate was seen to rapidly form. The crude material contained unreacted **28** and the HBr elimination product from the coupling of two equivalents of **29** (Scheme 33). Although this product was not isolated, tetramethyl ethene-1,1,2,2-tetracarboxylate (**30**) was tentatively identified by the 12 H singlet in the $^1$H NMR ($\delta$= 3.85 ppm).[71] One proposed mechanism to explain this side reaction is the reaction of the enolate form of **29** with an un-enolised second equivalent of the material. It is not obvious that $NEt_3$ would fully deprotonate **29** as proposed in Scheme 33 as the two are expected to have similar pKa values.[87] It is also possible that a bromonium derived intermediate could be involved in this side reaction.




***Scheme 33:*** *The base induced coupling of dimethyl 2-bromomalonate.*

The sterically hindered non-nucleophilic base 1,2-diazabicyclo[5.4.0]undec-7-ene (DBU) was substituted for $NEt_3$. At -78 °C precipitate formation was instantaneous and the crude product was seen to contain only unreacted **28** and **30**. NaOMe was substituted for DBU in a third set of reactions. No reaction was observed by TLC at -78 °C; at room temperature the crude product again only contained unreacted **28** and **30**.

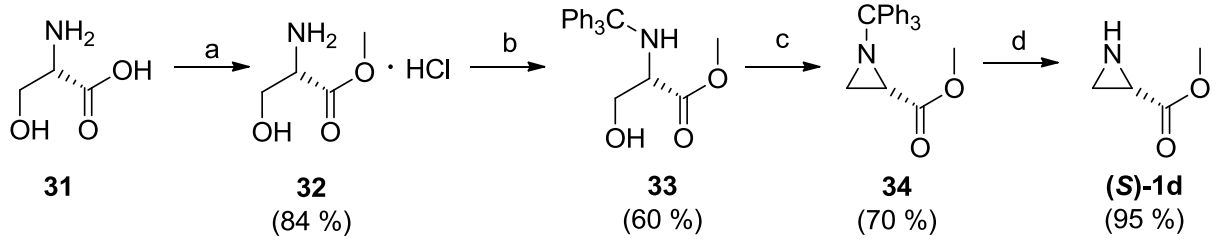
The final modifications of this aza-Darzens reaction were performed with an equimolar stoichiometry of **28**, **29** and NaOMe charged to a flask at -78 °C: no reaction was observed by TLC and no precipitate formed. At room temperature no reaction was observed. After refluxing in THF for 16 hours only starting material **28** and side product **30** were observed.

Tentative conclusions can be drawn to explain the lack of reactivity between the *N*-phenylimine and **29** and the successful reaction reported between *N*-sulfinimine and methyl 2-bromopropionate. Of the two reactive enolate species, the more stabilised malonate could be expected to be less reactive than the less stabilised propionate enolate. The electronic nature of the imine *N*-substituent would also be expected to have an effect on the electrophilicity of the *C=N* carbon. Whether resonance of the nitrogen lone pair into the *N*-phenyl aromatic ring or the inductive effects of the *N*-sulfoxide group has a stronger electron withdrawing effect on the *C=N* bond would have to be determined through experimentation.

Under all conditions investigated, generation of **30** was favoured exclusively over reaction at the imine. The failure of the aza-Darzens reaction between **27** and **28** may be indicative of the reduced nucleophilicity of the enolate rather than poor imine electrophilicity. Without experimental data from all the four possible experiments between methyl 2-bromopropionate or **29** and the *N*-sulfinimine or *N*-phenylimine, no single conclusion can be made about the outcome of this reaction, only the logical reasoning given above.

It had not been possible to replicate the procedure reported by Carrié *et al.* as it had not been possible to synthesise aziridine **1a** by the originally reported procedure, or alternative proposed routes. Moving forward, the application of the more forcing conditions reported by Nadir *et al*. to a broader range of *N*,*C*-activated aziridines was investigated. Aziridine **1e** was now synthesised in a stereocontrolled manner from an amino acid precursor. The route to **(*S*)-1e** proceeds *via* the isolated intermediate *N*-H aziridine **(*S*)-1d**, and therefore allowed functionalisation of the aziridine with other *N*-activating groups as required.

There are many routes that can be followed to access **(*S*)-1d** from (*S*)-serine (**31**).[72] (*S*)-Serine was chosen as a cheap enantiopure starting material with the necessary methyl alcohol side chain. The methyl ester functionality was first installed to give (*S*)-methyl 2-amino-3-hydroxypropanoate hydrochloride (**32**).[73] The nitrogen was then protected with a trityl group giving (*S*)-methyl 3-hydroxy-2-(tritylamino)propionate (**33**). In a two-step one-pot reaction, the alcohol was activated with methanesulfonyl chloride then displaced through intramolecular $S_N2$ reaction to yield (*S*)-methyl 1-tritylaziridine-2-carboxylate (**34**). The final step deprotected the nitrogen to produce **(*S*)-1d** in acceptable yields over 5 steps (Scheme 34).



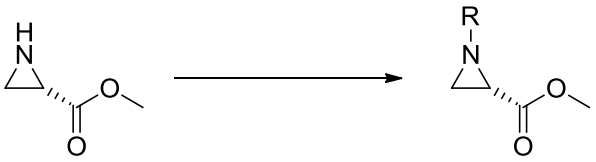

***Scheme 34:*** *Synthesis of aziridine* ***(S)-1d*** *from (S)-serine. Conditions* ***a****: 2.7 mol. eq. AcCl, MeOH, reflux 3.5 h.* ***b****: 1 mol. eq. $Ph_3CCl$, 2 mol. eq. $NEt_3$, DCM, 0 °C, 12 h.* ***c****: 1.01 mol. eq. $CH_3SO_2Cl$, 2.2 mol .eq. $NEt_3$, THF, reflux, 46 h.* ***d****: MeOH, $CF_3CO_2H$, $CHCl_3$, 5 °C, 2 h.*

Two methods were assessed for attachment of the trityl group to nitrogen. The first procedure was performed at room temperature for 1 hour with the liquid crude product being purified by column chromatography, providing **33** in 70 % yield.[74] The alternative procedure was performed at 0 °C overnight with the solid crude product purified by recrystallisation, providing **33** in 60 % yield.[72] By virtue of ease of purification the latter procedure was selected.

Conditions for the detritylation of **34** required extensive optimisation, with the final method based on those reported by many previous investigators.[72,75,76,77] The reaction was successful and consistently generated

**(*S*)-1d** in yields greater than 90 %. The route to **(*S*)-1d** provided a final yield of 35 % over 4 steps from (*S*)-serine. The volatile nature of **(*S*)-1d** was again apparent, but losses were minimised by removing residual solvent from the product at 0 °C.

Aziridine **(*S*)-1d** was functionalized with a selection of *N*-functional groups: *N*-Ts (**(*S*)-1e**),[54] *N*-Boc ((*S*)-1-*tert*-butoxycarbonyl 2-methoxycarbonyl aziridine, **(*S*)-1f**),[78] *N*-Cbz ((*S*)-1-benzyloxycarbonyl-2-methoxycarbonyl aziridine, **(*S*)-1g**)[76] and *N*-Dpp ((*S*)-methyl 1-(diphenylphosphoryl)aziridine-2-carboxylate, **(*S*)-1h**)[79] aziridines were all obtained (Scheme 35). As expected, the yields of aziridines **(*S*)-1e** – **h** were sensitive to the age of the batch of **(*S*)-1d**. Reducing the rate of decomposition of **(*S*)-1d** was not possible even when stored under nitrogen in the freezer; after 17 days **(*S*)-1d** was no longer detectable by $^1$H NMR in the bulk material. **(*S*)-1d** was therefore generated from **34** as required and used immediately. This strategy allowed the four aziridines derived from **(*S*)-1d** to be obtained in useful amounts. Furthermore, the yield of **(*S*)-1e** was increased to 68 % (literature cf. 22 %) by allowing the reaction to proceed for longer.



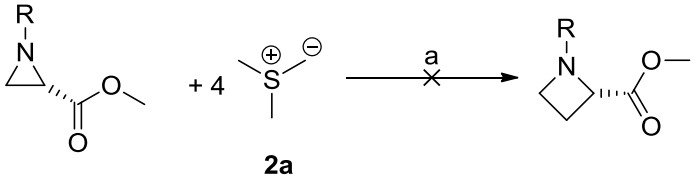

**(*S*)-1d**

| Conditions | R | Product | Yield % |
|---|---|---|---|
| a | Ts | **(S)-1e** | 68 |
| b | Boc | **(S)-1f** | 41 |
| c | Cbz | **(S)-1g** | 48 |
| d | Dpp | **(S)-1h** | 23 |

***Scheme 35:*** *Functionalisation of **(S)-1e**. Conditions **a**:[54] 2.5 mol .eq. $NEt_3$, 1 mol. eq. TsCl, $CHCl_3$, -10 °C, 16 h **b**:[78] 5 mol. eq. $NEt_3$, 1.1 mol. eq. $Boc_2O$, MeCN, 0 °C, 6 h **c**:[76] 2.5 mol. eq. $NEt_3$, 1.25 mol. eq. CbzCl, DCM, overnight **d**:[79] 2 mol. eq. $NEt_3$, 1.1 mol. eq. DppCl, DCM, 0 °C, overnight.*

Aziridines **(*S*)-1e**-**h** were combined with sulfonium ylide **2a** using the conditions of Nadir *et al.* (Scheme 36).[24] The corresponding azetidines or unreacted starting materials were not detected in the crude products. Only crude reaction mixtures that were intractable by column chromatography resulted, giving rise to complex $^1$H NMR spectra. Aziridines **(*S*)-1e**-**h** were also combined with oxosulfonium ylide **3a** (Scheme 37). The same outcome was observed for these reactions. The method of Nadir *et al.* clearly provided sufficiently reactive conditions compared to those of Carrié *et al.*, but the pathway taken in each reaction was not immediately obvious. The reactions between **(*S*)-1e** and **(*S*)-1f** and ylide **3a** were repeated in deuterated solvent with monitoring by $^1$H NMR at regular intervals *via* extraction and dilution of an aliquot of reaction mixture.

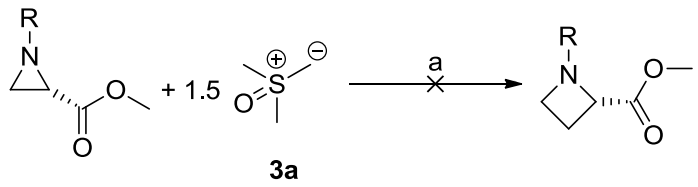
| Aziridine | R |
|---|---|
| **(S)-1e** | Ts |
| **(S)-1f** | Boc |
| **(S)-1g** | Cbz |
| **(S)-1h** | Dpp |




**2a**

***Scheme 36:*** *Reaction of aziridine **(S)-1e**-**h** with sulfonium ylide **2a**.[24] Conditions **a**: THF:DMSO, 0 °C – rt, 8 h.*

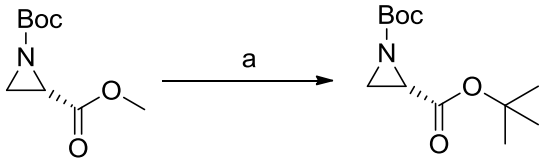
| Aziridine | R |
|---|---|
| **(S)-1e** | Ts |
| **(S)-1f** | Boc |
| **(S)-1g** | Cbz |
| **(S)-1h** | Dpp |




**3a**

***Scheme 37:*** *Reaction of* aziridine ***(S)-1e-h*** *with oxosulfonium ylide* ***3a****.*[24] *Conditions* ***a****: THF:DMSO, 0 °C – rt, 20 h.*

Monitoring showed an apparent reduction in the $^1$H NMR peak of the ester -$CH_3$ after less than 30 minutes, followed by the decomposition of the starting material. With this tentative indication of preferential reaction at the ester functionality, (*S*)-1,2-di-*tert*-butoxycarbonyl aziridine (**(*S*)-1i**) was prepared from **(*S*)-1f** (Scheme 38).[78] The increased steric bulk of the *tert*-butoxy ester did not prevent the same indiscriminate decomposition of the azetidine by the oxosulfonium ylide. It was clear that *N*-activated 2-alkoxycarbonyl aziridines were not compatible with the sulfonium ylide mediated ring expansion to azetidines and this aspect of the investigation was halted.



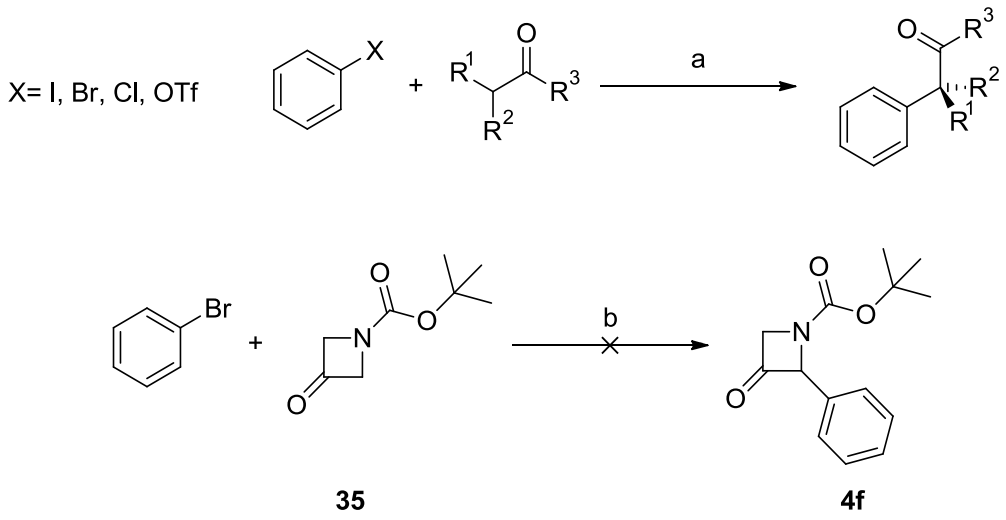

**(*S*)-1f** **(*S*)-1i** (32 %)

***Scheme 38:*** *Trans-esterification of aziridine* ***(S)-1f****.*[78] *Conditions* ***a****: 1.5 mol. eq. LiO$^t$Bu, THF, -20 °C, 2 h.*

### 1.2.2 Direct α-arylation of azetidine-3-one

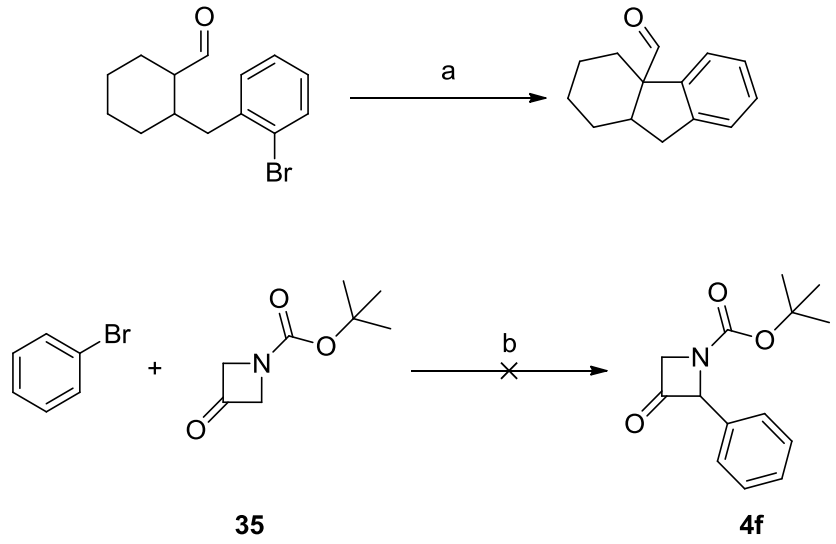
As an alternative route to functionalised azetidines, the direct arylation of the heterocycle was attempted. Many procedures have been reported for the α-arylation of carbonyl compounds; attempts to apply a selection of these to the commercially available compound *N-tert*-butoxycarbonyl 3-oxoazetidine (**35**) are described below.

Experiments to couple **35** with bromobenzene or phenyl trifluoromethanesulfonate in the presence of tris(dibenzylideneacetone)dipalladium$^{(0)}$ ($Pd(dba)_2$) and (*R*)-(+)-5,5′-bis(diphenylphosphino)-4,4′-bi-1,3-benzodioxole ((*R*)-SEGPHOS) to furnish *tert*-butyl 3-oxo-2-phenylazetidine-1-carboxylate (**4f**) based on the work of Hartwig *et al.* were unsuccessful (Scheme 39).[80] $^1$H NMR analysis of the crude product and of the fraction that could be isolated by column chromatography showed the complete consumption of **35**, the persistence of the *tert*-butyl group and new aromatic signals. The lack of azetidinyl methylene proton signals led us to believe that the heterocycle had been opened in the course of the reaction. The crude reaction mixture was not able to be purified sufficiently to confirm this observation however.




***Scheme 39:*** *α-arylation of **35** (bottom) based on conditions of Hartwig et al. (top).[80] Conditions **a**: 10 mol. % $Pd(dba)_2$, 12 mol. % (R)-SEGPHOS, 2 mol. eq. $NaO^tBu$, toluene, 80 °C. **b**: 10 mol. % $Pd(dba)_2$, 12 mol. % (R)-SEGPHOS, 2 mol. eq. $NaO^tBu$, toluene, 80 °C, 48 h.*

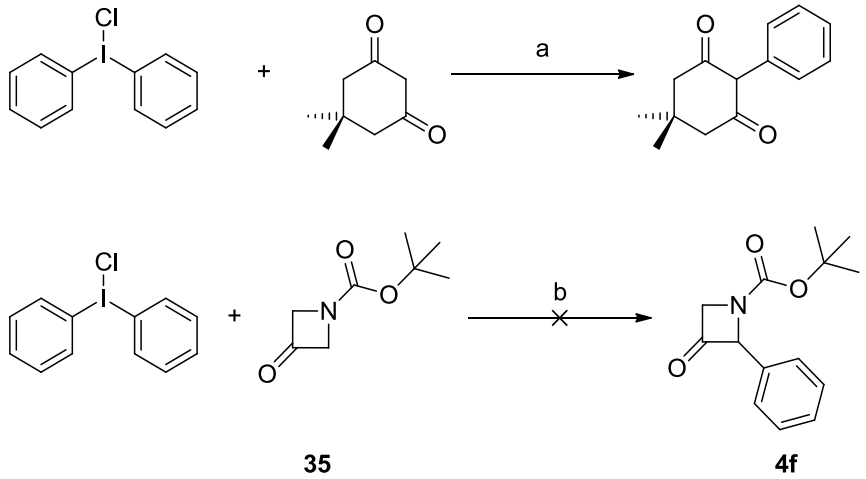
The same outcome was observed when (*R*)-SEGPHOS was omitted from the reaction mixture and when reaction time and temperature were altered. The attempted synthesis of **4f** following the alternative procedure of Muratake and Nakai was also not successful; a similar outcome was observed again by $^1$H NMR (Scheme 40).[81]




***Scheme 40:*** *α-arylation of **35** (bottom) based on conditions of Muratake and Nakai (top).[81] Conditions **a**: 10 mol. % $Pd(PPh_3)_2Cl_2$, 3 mol. eq. $Cs_2CO_3$, THF, 100 °C, 3 h. **b**: 1 mol. eq. BrPh, 10 mol. % $Pd(PPh_3)Cl_2$, 3 mol. eq. $Cs_2CO_3$, THF, 66 °C, 16 h.*

With heterocycle cleavage suspected during the metal catalysed reactions, a transition-metal free procedure was sought. The use of diphenyliodonium chloride as the arylating agent in the presence of a strong base was assessed (Scheme 41).[82] The pKa of cyclobutanone has been estimated to be 20.[83] The pKa of **35** was anticipated to be similar, making its deprotonation by $NaO^tBu$ in this procedure logical.

Using metal-catalyst free conditions to synthesise **4f**, $^{1}$H NMR analysis of the reaction showed once again that the heterocycle appeared to have been opened. Reducing the reaction time or substitution of diphenyliodonium triflate for diphenyliodonium chloride did not change outcome of the reaction.

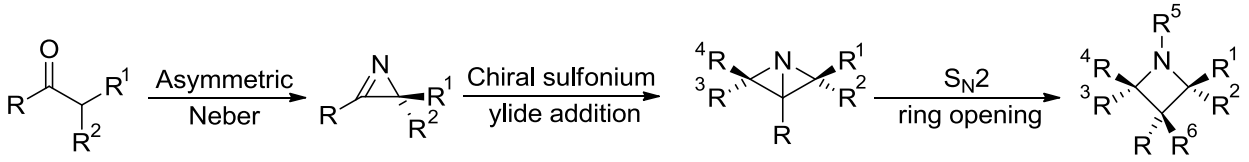



***Scheme 41:*** *$\alpha$-arylation of **35** (bottom) based on conditions of Yudis et al. (top).[82] Conditions **a**: 1 mol. eq. NaO$^{t}$Bu, $^{t}$BuOH, reflux, 4 h. **b**: 1 mol. eq. Ph$_2$ICl, 1 mol. eq. NaO$^{t}$Bu, $^{t}$BuOH, reflux, 3 h.*

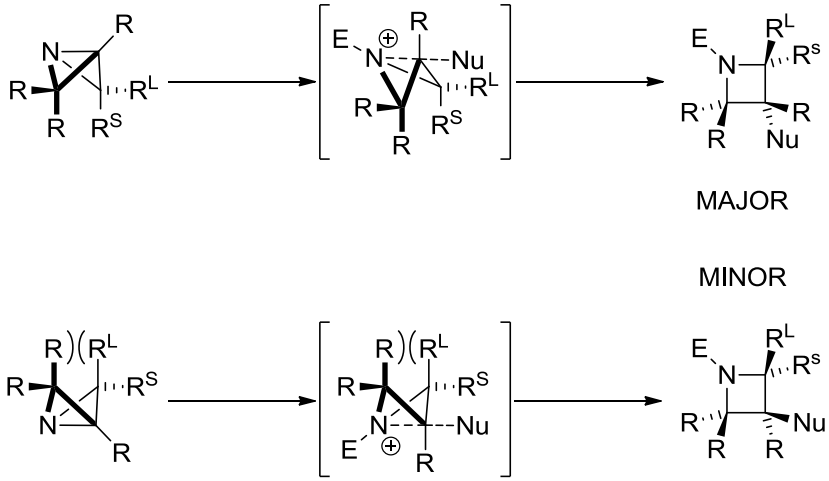
### 1.2.3 Azabicyclo[1.1.0]butane ring-opening

The second route to highly functionalised azetidines investigated was *via* 1,3-bond cleavage of azabicyclo[1.1.0]butanes. As discussed above, research in this area has already been carried out using the unfunctionalised parent compound **10a**. There are few accounts of the reaction using more substituted analogues, even though routes to more complex ABBs are reported.[44] Ring opening of **10a** would not give us access to highly functionalised azetidines. A synthetic route with the potential to produce highly functionalised azetidines, with asymmetric centres stereoselectively installed at C2, C3 and C4 was envisaged.

A new synthetic route was proposed (Scheme 42): from ketone starting materials, an asymmetric Neber reaction would install chirality at the product azirine C2; reaction of a chiral sulfonium ylide with an enantiomerically pure azirine should stereoselectively install the second asymmetric centre at the product ABB C3 and C4, influenced by matched or mismatched reagent control effects. The ABB 1,3-bond cleavage is expected to proceed *via* an $S_N2$ mechanism. The steric bulk of the complex ABB should provide a sufficiently high energy barrier to rotameric inversion between conformations, therefore the conformation that minimises 1,3-diaxial interactions is expected to dominate. In the final step, $S_N2$ bond cleavage will give a single stereoisomer at the product azetidine C3 (Scheme 43). The stepwise introduction of each new asymmetric centre to a pre-formed small ring should overcome the energy barrier associated with ring closing a complex hindered 1,3-aminoalcohol (or analogous) based intermediate. Choice of ABB C3 group will also be important if a C3 carbocationic centre is to be avoided. If this happens, an $S_N1$ type bond cleavage could occur, giving rise to two azetidine regioisomers that are epimeric at C3.

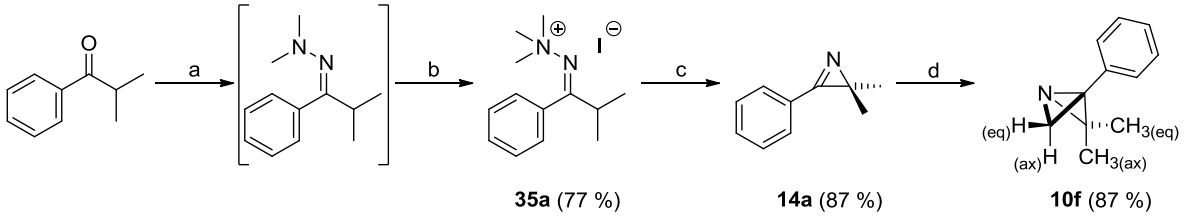



***Scheme 42:*** *Proposed route to highly functionalised azetidines.*



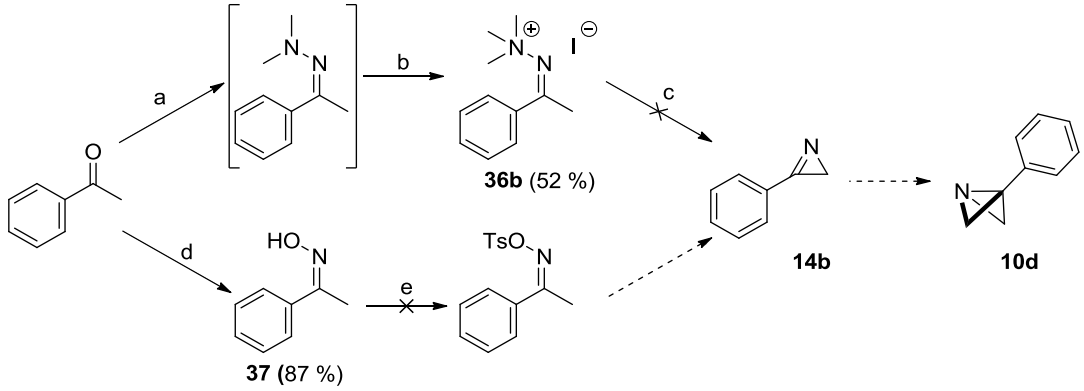

***Scheme 43:*** *Rationalisation for a stereoselective ABB ring opening reaction.*

Extensive studies have already been carried out into the ring opening of **10a** and related analogues with simple substitution at C3 (**10b**-**d**) (page 18 – 19). To begin assessing the feasibility of this route as well as supplement existing data and methods for ABB ring opening, the hydrazone route to the substituted ABB **10f**, *via* its azirine intermediate was followed. From isobutyrophenone, 1,1,1-trimethyl-2-(2-methyl-1-phenylpropylidene)hydrazin-1-ium iodide (**36a**) was synthesised in gram quantities over two steps. Iodide **36a** was then cleanly converted into 2,2-dimethyl-3-phenyl-2*H*-azirine (**14a**) with sodium *tert*-butoxide.[84] Following the pioneering work of Hortmann and Robertson, sulfonium ylide **2a** was combined with **14a** providing **10f** in good yield (Scheme 44).[44] Evidence from nOe experiments also showed that the substitution around the ABB core of **10f** was sufficient to prevent rotameric inversion about the 1,3-bond on the NMR timescale, causing the methylene and *gem*-dimethyl groups to occupy pseudo-axial and equatorial positions.




***Scheme 44:*** *The synthesis of ABB **10f** from isobutyrophenone.[84, 44] Conditions **a**: 2 mol. eq. $(Me_2N)NH_2$, reflux, 72 h. **b**: 3.5 mol. eq. $ICH_3$, EtOH, 45 °C, 5.5 h. **c**: 1.5 mol. eq. $NaO^tBu$, $^tBuOH$, 40 °C, 5 h. **d**: 5 mol. eq. ylide **2a**, THF, -10 °C, 1 h.*

Access to **10d**, the less functionalised analogue of **10f** was also desirable. By performing parallel reactions, it should have been straightforward to assess if the modest increase in steric bulk from the *gem*-dimethyl group in **10f** had any effect on the reactivity of this molecule. Acetophenone can be envisaged to be converted to azirine **14b**, which can be taken on to generate **10d**. Synthesis of **10d** *via* acetophenone oxime **37**[85] or 1,1,1-trimethyl-2-(1-phenylethylidene)hydrazin-1-ium iodide **36b**[86] were both unsuccessful (Scheme 45).



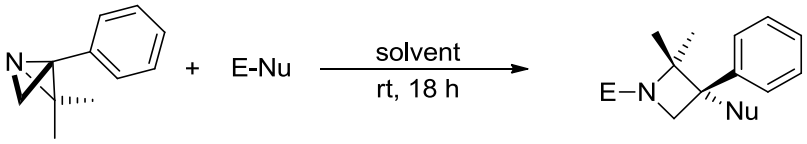

***Scheme 45:*** *The attempted synthesis of ABB **10d** from acetophenone via oxime[85] and hydrazinium iodide[86] routes. Conditions **a**: 1.2 mol. eq. $(Me_2N)NH_2$, reflux, 24 h. **b**: 3.5 mol. eq. $ICH_3$, EtOH, 43 °C, 4 h. **c**: 1.5 mol. eq. NaOMe, MeOH, 40 °C, 5 h. **d**: 1.5 mol. eq. $HONH_2{\cdot}HCl$, KOH, $MeCN:H_2O$, rt, 18 h. **e**: 1.3 mol. eq. TsCl, 1.3 mol. eq. py, DCM, rt, 3 h.*

The tosylated oxime could not be isolated from the crude reaction mixture. Attempts at displacing trimethylamine from **36b** all resulted in intractable mixtures of complex unidentified products. Although **10d** was unavailable at this time, not being able to perform parallel experiments with the two ABBs was not critical to or prohibitive to the progression of investigations.

With a suitably populated chemical environment around the ABB core of **10f**, the reactivity of this reasonably sterically crowded molecule with a range of reagents was assessed. The reactions performed were analogous to those reported by Funke[37a]: Azabicyclo[1.1.0]butane **10f** underwent 1,3-bond cleavage to give isolated azetidines.The yields of azetidines were universally lower than those generally observed when **10a** underwent similar 1,3-bond cleavage reactions.

The reaction with 4-toluenesulfonyl chloride (Table 5, entry 1) gave us a direct comparison of the relative reactivities of **10a** and **10f**. The lower yield of **4g** (40 %) when compared to the azetidine generated in the reaction between TsCl and **10a** (72 %) was rationalised by the increased steric bulk around the ABB, specifically the C3 aromatic ring, hindering nucleophilic attack. As optimisation of this reaction was not a priority at the time, it was expected that the yield could be improved as the investigation progressed. The use of thiobenzoic acid (Table 5, entry 2) allowed us to assess the reactivity of an organic acid with **10f**, as well as provide an azetidine with an important functional group for use in later studies (discussed below).

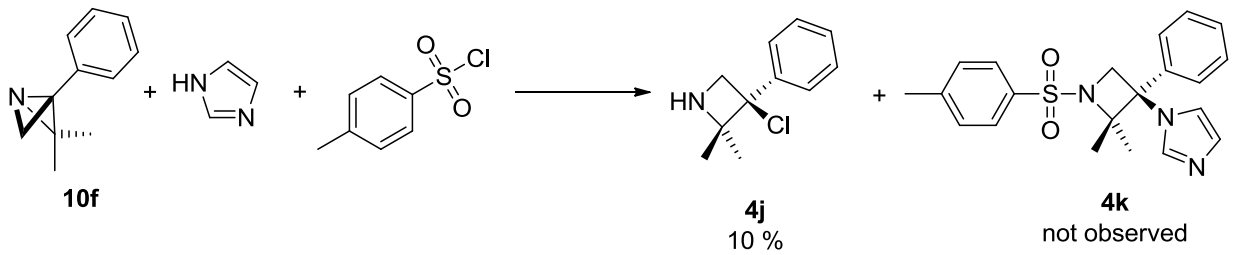
***Table 5:*** *1,3-bond cleavage of* ***10f****.*




| Entry | E | Nu | Solvent | Azetidine | Yield (%) |
|---|---|---|---|---|---|
| **1** | Ts | Cl | Acetone | **4g** | 40 |
| **2** | H | SC(O)Ph | THF | **4h** | 45 |
| **3** | H | Imidazole | Acetone | **4i** | 3 |
| **4** | H | pyrazole | Acetone | - | 0 |
| **5** | H | Cl | Acetone | **4j** | 10 |

The reactions with imidazole and pyrazole (Table 5, entry 3 and 4) were intended to probe the reactivity of **10f** with an aromatic amine. The low yields observed in these two reactions were suspected to be symptomatic of the weakly basic nitrogen of the ABB (pKa ≈8) being incompatible with the only moderately acidic *N*-H environments of the heterocyclic bases (pKa ≈14).[87] Approach of the large electron-rich aromatic heterocycle to the benzylic ABB carbon may also have been hindered.

The ring opening of **10f** with HCl (Table 5, entry 5) was observed as an unexpected side product during a three component experiment involving the ABB, imidazole and 4-toluenesulfonyl chloride (Scheme 46). The reaction to synthesise **4g** was experimentally observed to be rapid, with an isolated yield of 26 % obtained in one reaction where workup was performed immediately after addition of 4-toluenesulfonyl chloride to **10f** was complete. The reaction between **10f** and imidazole is comparatively slow. The purpose of this experiment was to discover if it was possible to have one reagent activate the ABB and another effect the 1,3-bond cleavage (thus generating 1-(2,2-dimethyl-3-phenyl-1-tosylazetidin-3-yl)-1*H*-imidazole **4k**), or if a mixture of **4g** and **4i** would result from two competing reaction processes. The reaction between imidazole and 4-tolunenesulfonyl chloride under Schotten-Baumann conditions is also known to form the commercially available *N*-4-toluenesulfonylimidazole.[88, 89]

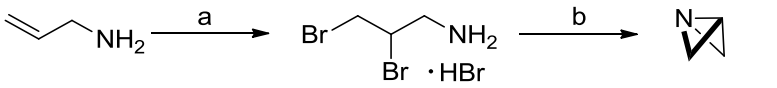



***Scheme 46:*** *Competition reaction between* ***10f****, imidazole and 4-toluenesulfonyl chloride.*

In this experiment, generation of *N*-4-toluenesulfonylimidazole was the favoured reaction: **10f** reacted as a base with the HCl generated *in situ* to give 3-chloro-2,2-dimethyl-3-phenylazetidine (**4j**). The order of charging reagents to the reaction vessel (**10f**, imidazole and 4-toluenesulfonyl chloride in 1:1:1 stoichiometry) as well as reaction times and temperatures were all altered, but the same outcome was

observed in each experiment; each time a colourless precipitate (*N*-4-toluenesulfonylimidazole)[90] formed upon mixing of imidazole and 4-toluenesulfonyl chloride, with **4j** identified in the crude reaction products.

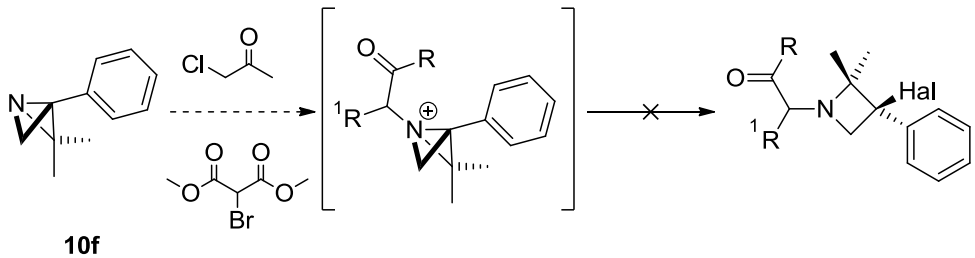
Confident that **10f** would react in the expected manner, it was also of interest to expand on the types of reactions that can be performed to ring open ABB, and to synthesise azetidines with interesting functional groups that would be useful to downstream reactions. There are currently no reports of carbon nucleophiles being used to effect the ring opening of ABBs. As well as using **10f**, it was desirable to perform any experiments with carbon nucleophiles with the unfunctionalised compound **10a** to highlight any effects the methyl or phenyl substituents may have on the reaction. It was possible to obtain a THF solution of **10a** from 2,3-dibromopropan-1-amine hydrobromide (**38**) (Scheme 47), but the unacceptable impurity profile observed in the $^1$H NMR of the **10a** solution made it unsuitable for use in the investigation at the time.




**13** **38** (94 %) **10a** (soln.)

***Scheme 47:*** *Synthesis of **10a**.[37g] Conditions **a**: 2 mol. eq. $Br_2$, EtOH, rt, 16 h. **b**: 3 mol. eq. nBuLi, THF, -78 °C, 1 h.*

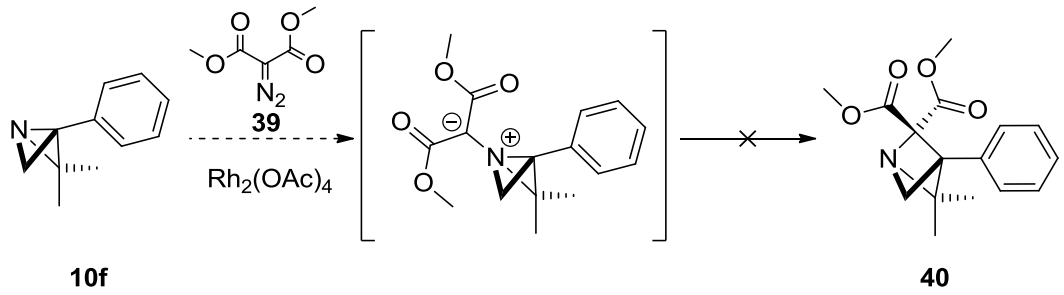
Addition of chloroacetone to **10f** (targeting the 1-(3-chloroazetidin-1-yl)-propanone) returned only starting material (Scheme 48). When repeated with the addition of 1 mol. eq. of NaO$^t$Bu, an azetidine was tentatively identified in the crude $^1$H NMR from the diagnostic methylene hydrogen signals at $\delta$= 4.46 and 3.83 ppm. Such a compound could not be isolated from this mixture however, preventing any conclusions of the reactivity of **10f** under basic conditions to be drawn. Similar reactions with dimethyl 2-bromomalonate returned only starting material in both experiments. Reaction of **10f** with the rhodium carbenoid derived from dimethyl 2-diazomalonate (**39**) was predicted to lead to an azabicyclo[1.1.1]pentane (**40**) (Scheme 49); only starting materials were recovered however.




**10f**

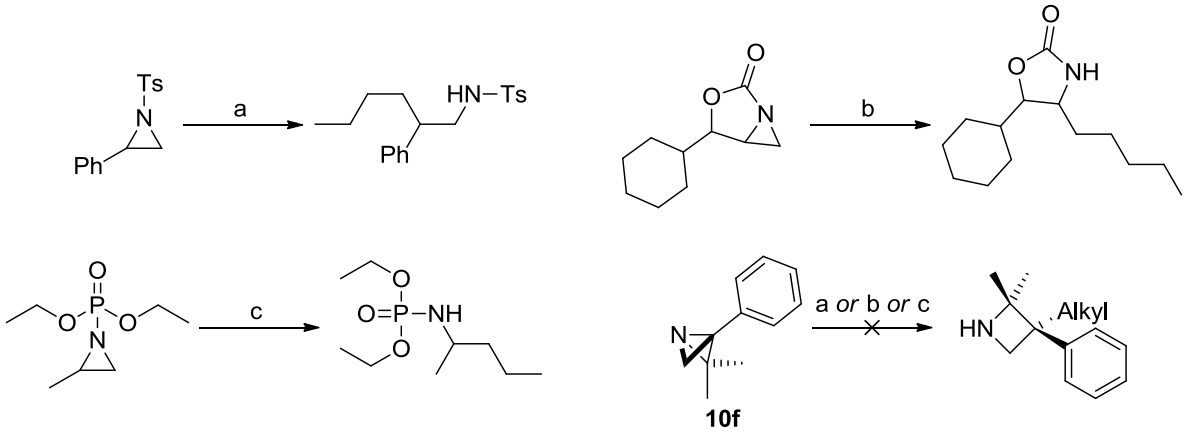
| R | $R^1$ | Hal |
|---|---|---|
| Me | H | Cl |
| OMe | $CO_2$Me | Br |

***Scheme 48:*** *Attempted reaction between **10f** and α-halo carbonyl compounds.*




***Scheme 49:*** *Attempted reaction between* ***10f*** *and rhodium carbenoid of* ***39****.*

Owing to similar bond cleavage patterns between the two heterocycles, procedures for the ring opening of aziridines by carbon nucleophiles were predicted to be applicable to azabicyclo[1.1.0]butanes (Scheme 50). **10f** was combined with butylzinc bromide (reported to ring open aziridines in the presence of $NiCl_2$),[91] di-*n*-butylcopper lithium (for the nucleophilic ring opening of aziridines)[92] and ethylmagnesium bromide.[93] No reaction was observed in all three experiments and only starting materials were recovered. In two deviations from literature methodologies, dimethylcopper lithium[94] was substituted for di-*n*-butylcopper lithium but again no reaction was observed. When methylmagnesium bromide was substituted for ethylmagnesium bromide analysis of the crude product did show approximately 25 % conversion to what appeared to be the expected compound 2,2,3-trimethyl-3-phenylazetidine (**4l**).




***Scheme 50:*** *Reported ring opening of aziridines by nucleophilic carbon. Conditions* ***a****:*[91] *3 mol. eq. nBuZnBr, 10 mol. % dimethyl fumarate, 5 mol. % $NiCl_2$·glyme, dioxane, rt, 6 h.* ***b****:*[92] *2 mol. eq. $nBu_2CuLi$, THF, rt, 4 h.* ***c****:*[93] *3 mol. eq. EtMgBr, 5 mol. % CuI, THF, 0 °C, 2 h.*

In all successful reactions discussed here in which **10f** was converted to the corresponding azetidine, conversion was easy to detect and quantify owing to the diagnostic peaks in the $^1$H NMR relating to the C4 methylene group (Figure 9). Substitution of methylmagnesium chloride (**41**) for bromide gave a slight increase in conversion. All other method optimisation steps (concentration, stoichiometry, temperature and time) failed to improve the conversion of **10f** to **4l**. The reaction appeared to proceed cleanly each time, yet purification was challenging. Using optimised conditions, the compound that was originally identified as **4l** was isolated in 8 % yield from a crude reaction mixture containing 26 % yield of azetidine by $^1$H NMR integration.

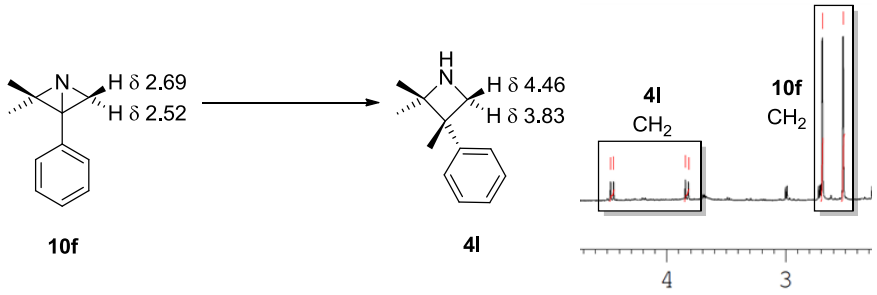



***Figure 9:*** *NMR shift of methylene hydrogens in* ***10f*** *and* ***4l*** *as typically observed during ABB ring opening experiments.*

Based on proposals in the literature for the mechanism of azabicyclo[1.1.0]butane ring opening,[37a,37e,42,43] addition of a Lewis acidic component to the reaction mixture was predicted to promote the reaction between **41** and **10f** by complexation with nitrogen.[95] Addition of one equivalent of magnesium bromide dietherate (**42**) moderately increased the conversion of **10f** to **4l**. Improved conversion was most noticeable when **10f** and **42** were premixed at room temperature for 30 minutes before addition of **41**. The effect of Lewis acid on the reactivity of **10f** was further demonstrated: when repeating the reaction between **10f** and dimethylcopper lithium in the presence of **42** a reaction was observed by $^{1}$H NMR, although no azetidine was identified or isolated. After further method optimisation, a conversion of **10f** to **4l** of 50 % was possible. The use of alternative Lewis acids ($ZnI_2$, $BF_3{\cdot}Et_2O$, CuCl) did not improve the yield, and the procedure was seen to lack robustness.

Early experiments from this investigation were repeated to try and identify the reason for the lack of reproducibility of the method. It was found during repeat experiments that **4l** was still present in crude products. The conversion rates were generally reduced by comparison with first pass reactions however, with a broad range observed (10 – 50 % across all experiments with Lewis acid **42**), and it was becoming increasingly difficult to isolate the azetidine from each reaction mixture.

The cause of the lack of repeatability of these results remained elusive even after multiple experiments with different batches of **10f**, **41**, **42** and solvent, although ring opening of the ABB to give the azetidine did appear to be occurring in every experiment. A high purity sample of **4l** was never able to be obtained due to isolation difficulties but $^{1}$H NMR data was consistent with what would be expected for compound **4l**. Chemical shifts, integrals, and comparison with other azetidines made using this ring opening protocol (**4g** – **j**) were in good agreement. IR spectra contained the expected absorption peaks (*N*-H at 3471 $cm^{-1}$, methylene at 2924 $cm^{-1}$) and MS identified a dimerised product peak (m/z for $2M+H^+$ = 349.2).

When reviewing ABB ring opening with sulfur nucleophiles, the possibility of developing a novel and potentially straightforward azetidine sulfonamide synthesis was addressed. Cyclic amine (including azetidine) sulfonamides are known where the azacycle nitrogen provides the ‘amide’ component of the sulfonamide.[96] There are no reports where the sulfonamide motif is bound to one of the azetidine carbons. Sulfonamides are privileged structures in drug design and are prevalent in such physiologically

active compounds as antibiotics (Mafenide,[97] Succinylsulfathiazole[98]), COX-2 inhibitors (Celecoxib[99]) and diuretics (Metolazone[100]) (Figure 10).

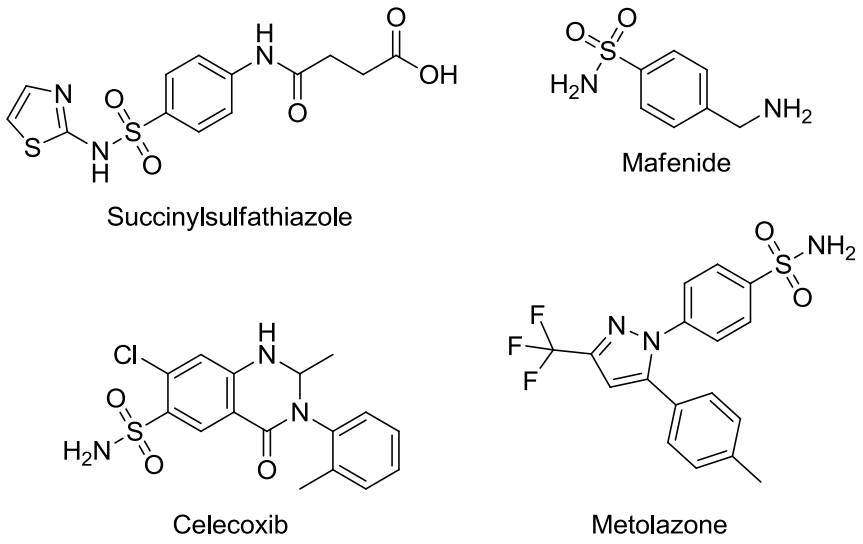
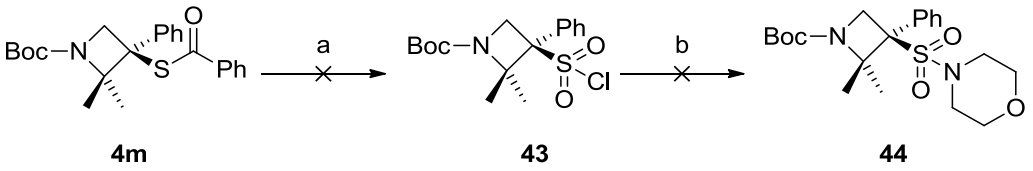



***Figure 10:*** *Sulfonamide containing drug molecules.*

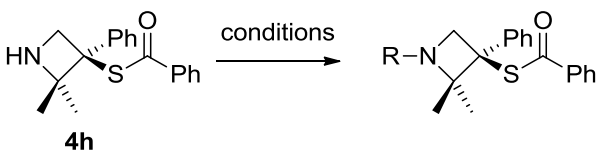
Early in the investigation using ABBs, (2,2-dimethyl-3-phenylazetidin-3-yl) benzothioate (**4h**) was synthesised (Table 5, entry 2) but was observed to be unstable, decomposing entirely within hours of synthesis. The *N*-Boc derivative (**4m**) was synthesised from crude **4h** immediately following work-up, and is a stable crystalline solid. With **4m** in hand, the procedure of Ho *et al.* for the two step, one pot conversion of aryl thioesters first into sulfonyl chlorides and then to sulfonamides was applied.[101] Using trichloroisocyanuric acid (TCCA) as the chlorine source in an oxidative chlorination of thioester **4m**, the sulfonyl chloride (**43**) could then be isolated (if stable) or the reagents for the second step added to the reaction vessel to generate the sulfonamide (**44**) (Scheme 51).




***Scheme 51:*** *Attempted sulfonamide synthesis via the oxidative chlorination of thioester* ***4m****.*[101] *Conditions* ***a****: 1.2 mol. eq. TCCA, 3.4 mol. eq.* $BnBu_3NCl$*, 1 mol. eq.* $NaHCO_3$*, MeCN, 0 °C, 20 min.* ***b****: 1.2 mol. eq. Morpholine, 5 mol. eq.* $NEt_3$*, MeCN, rt, 6 h.*

Sulfonyl chloride **43** or sulfonamide **44** could not be synthesised with this procedure. No peaks were observed in the $^1$H NMR spectrum of the isolated crude **43** indicating the presence of the *tert*-butoxycarbonyl group. The same observation was made of the isolated crude product of **44**. The reported conditions employed in this study were proposed to be sufficiently mild to accommodate acid sensitive groups.[101] The absence of peaks in the $^1$H NMR spectra associated with the *N*-Boc group would indicate that the conditions were sufficiently acidic enough (approximately pH 6-5)[101] to cleave the carbamate group, allowing the consequential decomposition of the azetidine.

Attempts to synthesise analogues of **4h** with acid-stable *N*- protecting groups were unsuccessful. The *N*-Ts compound (2,2-dimethyl-3-phenyl-1-tosylazetidin-3-yl) benzothioate (**4n**) was found to decompose as rapidly as **4h**. The *N*-Fmoc (**4o**) and *N*-Acyl[54] (**4p**) analogues were only tentatively identified in the respective crude products and were unable to be isolated by column chromatography (Scheme 52). This investigation was therefore halted.



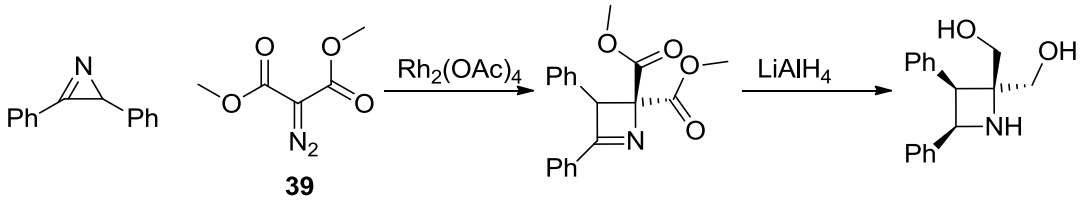

**4h**

| Conditions | R | Azetidine | Yield % |
|---|---|---|---|
| a | Boc | **4m** | 30 |
| b | Ts | **4n** | 23 |
| c | Fmoc | **4o** | - |
| d | Ac | **4p** | - |

***Scheme 52:*** *Attempted synthesis of acid stable N-protected derivatives of **4h**. Conditions **a**:[78] 1.1 mol. eq. $Boc_2O$, 5 mol. eq. $NEt_3$, MeCN, 0 °C, 6 h. **b**:[54] 1.1 mol. eq. TsCl, 1.6 mol. eq. $NEt_3$, $CHCl_3$, rt, 16 h. **c**:[102] 1 mol. eq. FMocCl, 1 mol. eq. LiHMDS, THF, rt, 1 h. d:[54] 1.1 mol. eq. AcCl, 1 mol. eq. $NEt_3$, $CHCl_3$, 0 °C, 2 h.*

### 1.2.4 Ring expansion of azirines.

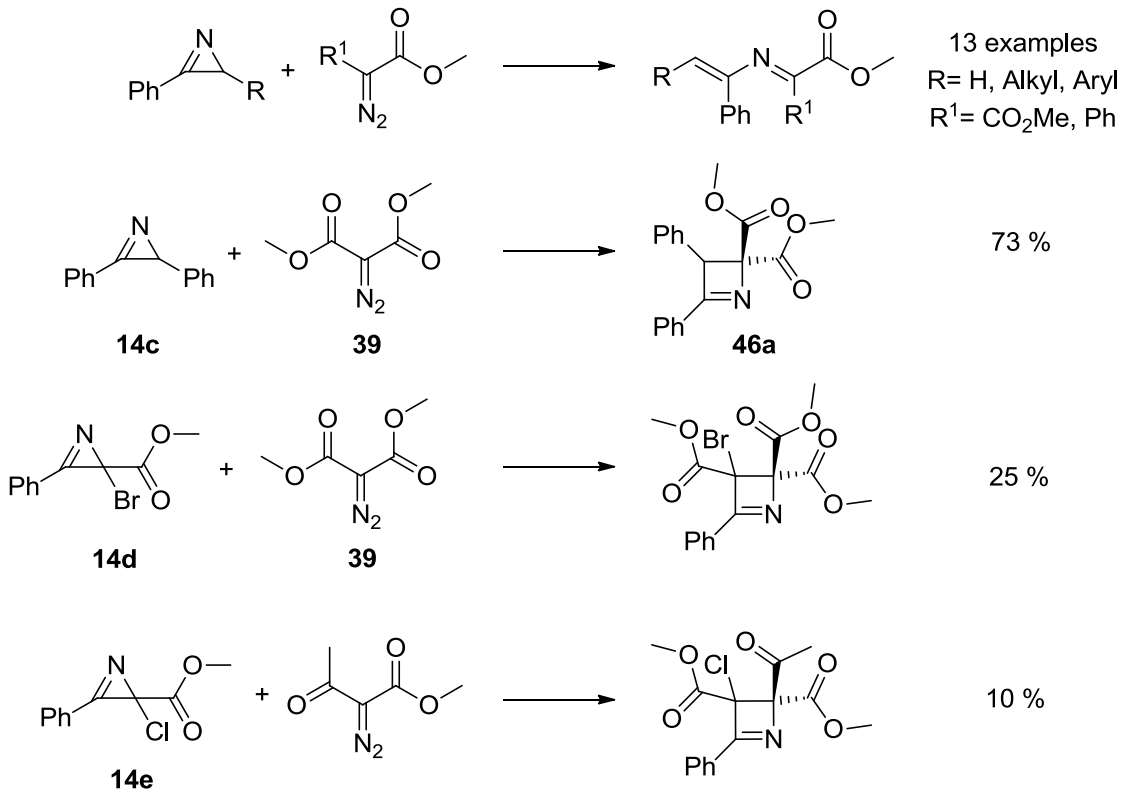
During investigations into the ring opening of **10f** with metal-carbenoids, publications from Khlebnikov *et al.* describing the reaction between an azirine and rhodium carbenoid that resulted in the formation of an azetine came to our attention.[103] The azetine was then reduced to give an azetidine (Scheme 53).[104] Were this protocol to prove general and reliable, it would provide an interesting and underexploited route to complex azetidines. Both azirine ring expansion and ABB ring opening routes to azetidine could facilitate different procedures being applied to a common (asymmetric) azirine starting material, thus increasing the potential number of routes to complex azetidines.




**39**

***Scheme 53:*** *Aziridine synthesis from azirine according to Khlebnikov et al.[104]*

When reacting azirines with single equivalents of the rhodium carbenoids of **39** or methyl 2-diazo-2-phenylacetate (**45**), the general trend towards *N*-vinylimine generation was observed, irrespective of the functionality present in the azirine. It was reported that when 2,3-diphenyl-2*H*-azirine (**14c**) and the rhodium carbenoid of **39** were combined, the uncommon product dimethyl 3,4-diphenylazete-2,2(3*H*)-dicarboxylate (**46a**) was isolated in good yield. Isolation of small quantities of azetines from the major *N*-vinylimine products when methyl 2-bromo-3-phenyl-2*H*-azirine-2-carboxylate (**14d**) or 2-chloro-3-phenyl-2*H*-azirine-2-carboxylate (**14e**) were employed was also reported (Scheme 54).

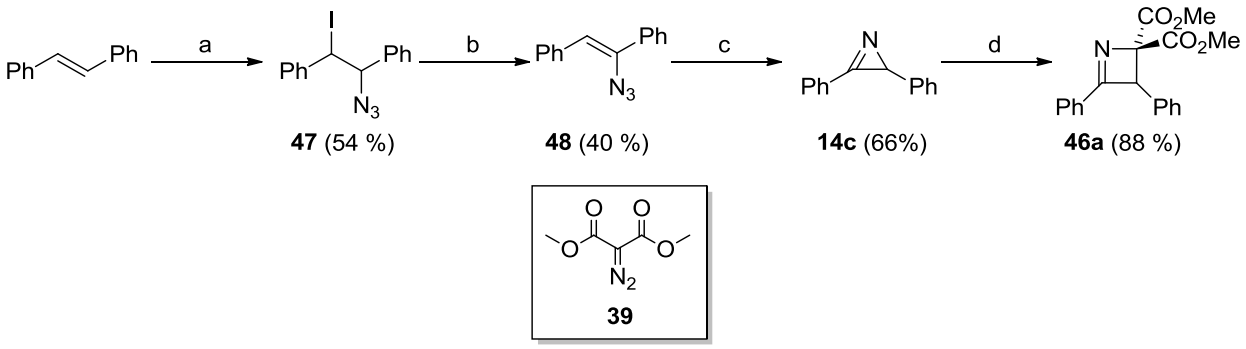



***Scheme 54:*** *Reactions of azirines with diazo derived metal-carbenoids to form enamines or azetines according to Khlebnikov et al.*[103]

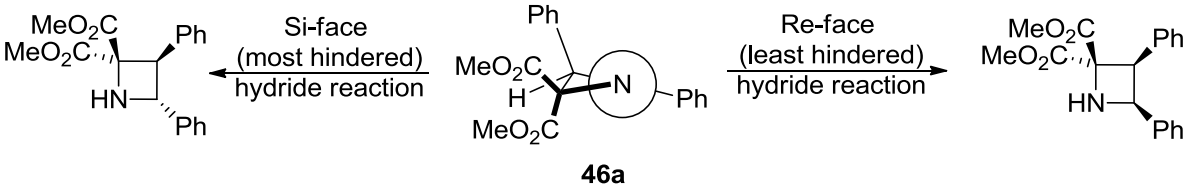
It was apparent that small advances in the understanding of this ring expansion had been made, but further work should be done to improve the scope and understanding of the reaction. Validation of the results was the primary goal as there appeared to be inconsistencies in some of the reports across different publications. One concise mechanism by which these ring expansion reactions proceed also did not appear to be immediately apparent.

From the reaction of ICl and $NaN_3$ with *trans*-stilbene to give (1-azido-2-iodoethane-1,2-diyl)dibenzene (**47**), this intermediate was converted to the required azide intermediate (1-azidoethene-1,2-diyl)dibenzene (**48**) with $KO^tBu$ and thence thermolysed to generate **14c**.[51] The rhodium carbenoid procedure with **39** was applied to **14c** and **46a** was isolated in good yield (Scheme 55).

Following the reported $LiAlH_4$ reduction procedure for **46a** resulted in total decomposition of the azetine. Substitution of sodium triacetoxyborohydride (STAB) for $LiAlH_4$ under a range of mild to forcing conditions caused either no reaction or the total decomposition of **46a**. Further experimentation to effect this reduction is required. When using $LiAlH_4$, this reaction is reported occur selectively at one diastereotopic face to give a diastereomerically enriched azetidine product (Scheme 56).

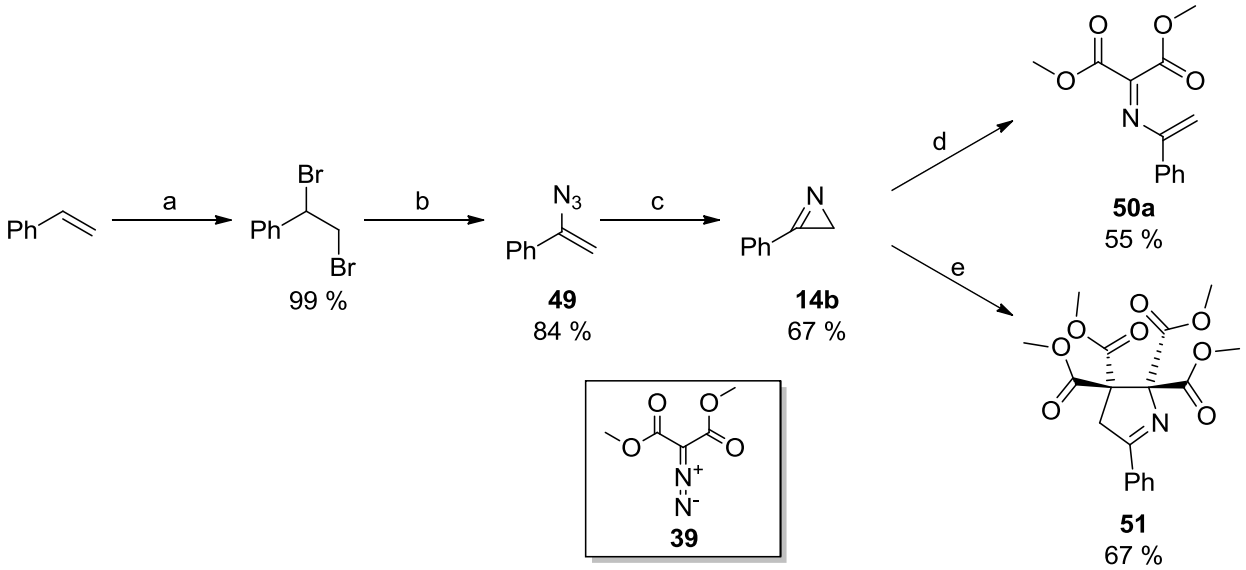



***Scheme 55:*** *Synthesis of azirine **14c**[51] and its ring expansion to azetine **46a**[104]. Conditions **a**: 2.5 mol. eq. $NaN_3$, 1.1 mol. eq. ICl, MeCN, rt, 19.5 h. **b**: 1.2 mol. eq. $KO^tBu$, $Et_2O$, 0 °C, 16 h. **c**: hexane, reflux, 2.75 h. **d**: 1.2 mol. eq. **39**, 4 mol. % $Rh_2(OAc)_4$, $CHCl_3$, reflux, 16 h.*



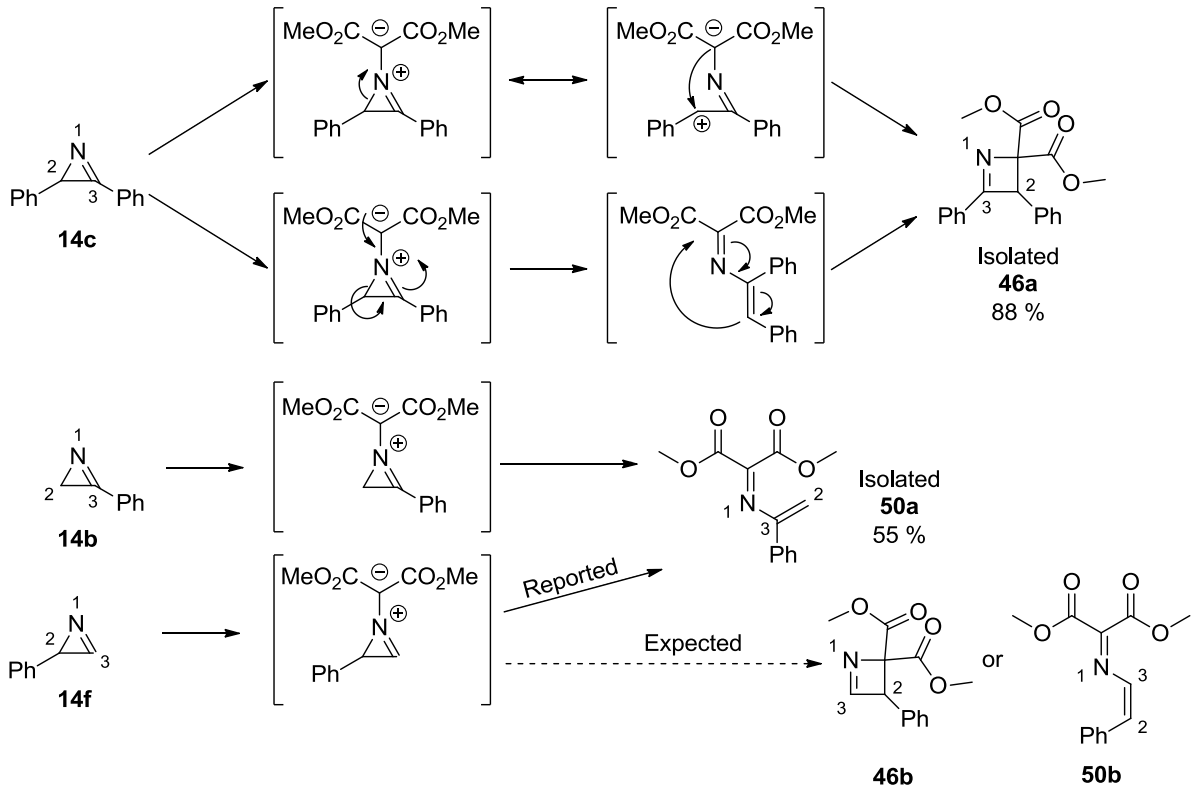

***Scheme 56:*** *Face-selective reduction of azetine.*

3-Phenyl-2*H*-azirine (**14b**) was obtained by thermolysis of (1-azidovinyl)benzene **49**)[105] and converted in the presence of $Rh_2(OAc_4)$ with one equivalent of **39** to dimethyl 2-((1-phenylvinyl)imino)malonate (**50a**), and with two equivalents of **39** to tetramethyl 5-phenyl-2*H*-pyrrole-2,2,3,3(4*H*)tetracarboxylate (**51**) in agreement with literature results (Scheme 57).



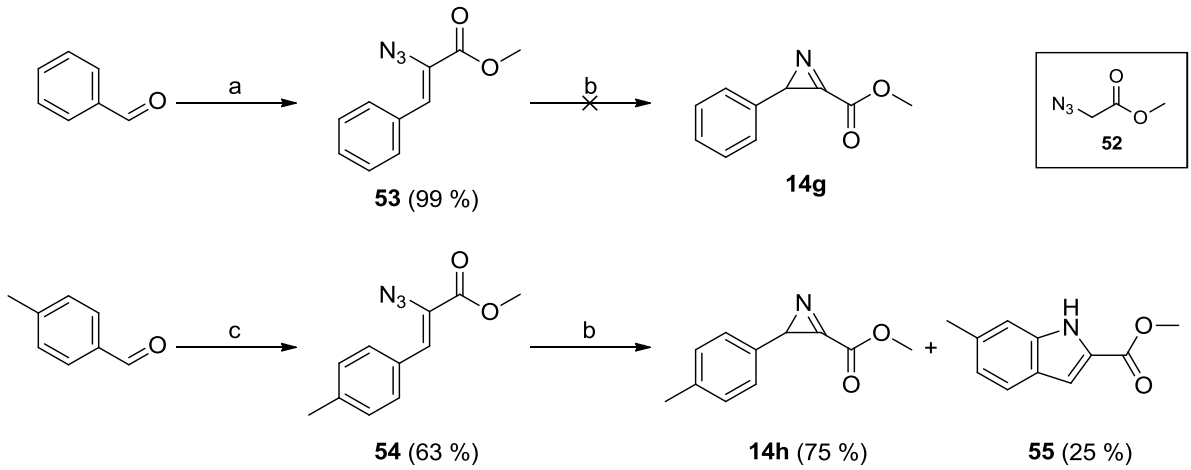

***Scheme 57:*** *Synthesis of azirine **14b**[105] and its reactions with the rhodium carbenoid of **39**.Conditions **a**.1 mol. eq. $Br_2$, $CHCl_3$, 0 °C, 2.5 h. **b**: 1 mol. eq. $NaN_3$, DMF, rt, 17 h then 1.5 mol. eq. $KO^tBu$, benzene, rt, 5 h. **c**: PhMe, reflux, 7 h. **d**: 1.2 mol. eq. **39**, 10 mol. % $Rh_2(OAc)_4$, $CHCl_3$, reflux, 17 h. **e**: 2.1 mol. eq. **39**, 10 mol. % $Rh_2(OAc)_4$, $CHCl_3$, reflux, 18 h.*

Having demonstrated the reproducibility of the reported results, the scope of this procedure was now investigated. There was one arrangement of functional groups around the azirine starting material that had not been discussed extensively by previous researchers. The two examples that yielded azetine from azirine had C2 substituents that could stabilise a proposed carbocation intermediate. It was reported, however, that both **14b** and 2-phenyl-2*H*-azirine (**14f**) both generated the identical ring opened enamine product **50a**.[104] Based on the proposed mechanisms, these reported outcomes are inconsistent: **14f** would be expected to give dimethyl 3-phenylazete-2,2(3*H*)-dicarboxylate (**46b**) or (Z)-dimethyl 2-(styrylimino)malonate (**50b**) (Scheme 58).



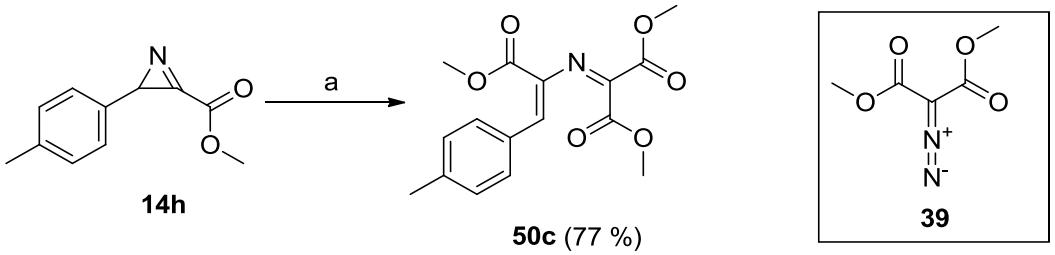

***Scheme 58:*** *Validation of reported procedures, including reported proposals for the reaction mechanism (Top, middle: this investigation and literature. Bottom: literature).*[104, 103]

Azetine **46a** and *N*-vinylimine **50a** could be generated in agreement with the literature, but azirine **14f** was not able to be synthesised[106] to validate the reported outcome of its reaction with the rhodium carbenoid from **39**. An alternative 2-aryl azirine was sought to test the hypothesis that 2-aryl azirines are required for successful ring expansion. Benzaldehyde was combined with methyl 2-azidoacetate (**52**) to generate methyl 2-azido-3-phenylacrylate (**53**).[107] Azide **53** was thermolysed according to literature procedures but failed to give methyl 2-phenyl-2*H*-azirine-3-carboxylate **14g**.[108] Following the same synthetic route, the tolyl analogues methyl 2-azido-3-(4-tolyl)acrylate (**54**) and its thermolysis product methyl 2-(4-tolyl)-2*H*-azirine-3-carboxylate (**14h**) were successfully synthesised. As was expected, and in agreement with reported results, the isomeric product methyl 6-methyl-1*H*-indole-2-carboxylate (**55**) (a result of the formal *C*-H nitrene insertion) was also generated (Scheme 59). A quantitative yield of **14h** and **55** was obtained in a 3:1 ratio based on $^{1}$H NMR integration.




***Scheme 59:*** *Synthesis of azirines **14g** and **14h**.[107], [108]Conditions **a**: 2.25 mol. eq. **52**, 2.25 mol. eq. NaOMe, MeOH, 0 °C, 16 h. **b**: cyclohexane, reflux, 17 h. **c**: 3 mol. eq. **52**, 1 mol. eq. NaOMe, MeOH, -10 °C, 4 h.*

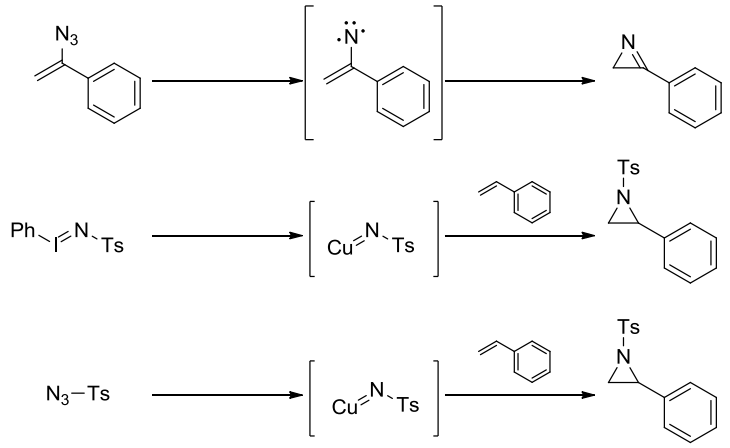
Reaction of **14h** with $Rh_2(OAc_4)$ and a slight excess of **39** yielded the ring opened product dimethyl 2-((3-methoxy-3-oxo-1-(4-tolyl)prop-1-en-2-yl)imino)malonate (**50c**) exclusively (Scheme 60). Although **14h** and **55** were found to be inseparable by column chromatography, **55** was shown experimentally to be unreactive towards the $Rh_2(OAc)_4$ and **39** reaction mixture conditions. Indole **55** was subsequently separated from **50c** in quantities consistent with those calculated based on a 3:1 ratio of **14h**:**55** charged to the reaction flask at the start of the reaction. Due to time constraints, this investigation was not pursued.




***Scheme 60:*** *Ring opening of **14h** with the rhodium carbenoid of **39**. Conditions **a**: 1.2 mol. eq. **39**, 10 mol. % $Rh_2(OAc)_4$, $CHCl_3$, reflux, 16 h.*

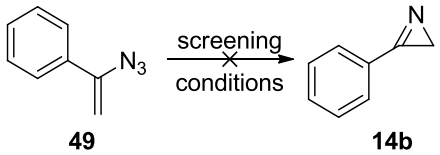
### 1.2.5 Transition-metal induced azide decomposition

In the thermal decomposition reactions of azides, the reactive intermediate is thought to be a nitrene species, generated by the loss of diatomic nitrogen gas from the $-N_3$ moiety.[105] Such reactive nitrene species are also known to be generated by formation of metal-nitrene complexes, as in the Evans aziridination method.[56] Copper is known to catalyse the decomposition of benzene sulfonyl azide *via* a proposed nitrene intermediate.[109] A small set of screening reactions were performed with previously synthesised azides to see if azirines could be generated *via* an alternative route using lower temperatures and shorter reaction times by exposure to transition-metal complexes (Scheme 61).



***Scheme 61:*** *Top: nitrene generation by azide thermolysis.[105] Middle: copper-nitrene complex formation from iodinane.[56] Bottom: copper-nitrene complex formation from azide.*[109]

Azidoalkene **49** was selected for the study: styrenyl azides such as **48** or **53** have prescident for indole formation when exposed to metal catalysis (i.e. **54** to **55** with $Rh_2(OAc)_4$).[110] Copper is known to form nitrene complexes, thus copper$^{(II)}$ triflate was selected for this screen.[109] A single reaction with $Rh_2(OAc)_4$ was also performed based on other reports having used such a metal to decompose azides.[110] All reactions were performed in anhydrous chloroform with a 10 mol. % catalyst loading at either room temperature or reflux for 6 or 24 hours. The target compound **14b** has a diagnostic $^1$H NMR singlet at $\delta$= 1.80 ppm: all experiments returned only starting material according to $^1$H NMR analysis. The reactions were repeated with the addition of 1 mol. eq. of diacetoxyiodobenzene (DAIB). Azidoalkene **49** was now consumed in every experiment but **14b** could not be identified by $^1$H NMR analysis of the crude products (Scheme 62).




**49** **14b**

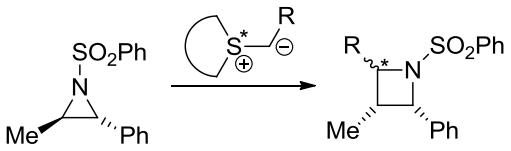
***Scheme 62:*** *Screening azide **49** for reactivity against copper or rhodium catalysts.*

## 1.3 Conclusions

Of the investigations into the synthesis of complex azetidines by the ring expansion of aziridines with sulfonium ylides, the ring opening of azabicyclo[1.1.0]butanes and the ring expansion of azirines with metal-carbenoids, the understanding of these processes within the group has been significantly improved. Progress has also been made in synthesising new complex azetidines, in particular using an azabicyclo[1.1.0]butane 1,3-bond cleavage method. Work covered herein should pave the way for continued investigations into these particular protocols in the near future.

Attempts to expand the scope of the ring expansion of aziridines with sulfonium ylides saw the synthesis of a number of 2-alkoxycarbonyl aziridines with different nitrogen activating groups. Neither dimethylsulfonium or dimethyl(oxo)sulfonium methylide species could effect the desired ring expansion as reported by Carrié *et al.*[25] and Nadir *et al.*[24] The presence of an *N*-activating group and C2 ester functionality made the aziridines too reactive towards both sulfonium ylides, leading to the total but non-selective consumption of the starting materials.

In going forward with this investigation, there are aziridines with alternative functional groups that could be combined with sulfonium ylides to explore this reaction further. This includes more or less electron withdrawing or sterically demanding groups than the ester and four *N*- groups used in these experiments. If it emerges that only aziridines such as those originally reported by Carrié *et al.*[25] and Nadir *et al.*[24] are able to undergo ring expansion with sulfonium ylides, the next step would be to attempt this ring expansion with chiral sulfonium ylides (Scheme 63). This would begin to address the questions of whether asymmetric aziridines can be ring expanded in a stereoselective manner, and therefore indicate if the postulated asymmetric synthesis is ultimately feasible. The ring expansion of aziridines with sulfonium ylides will continue to present an interesting challenge for future research in the group.




***Scheme 63:*** *Proposed stereoselectivity in the ring expansion of aziridines to azetidines using chiral sulfonium ylides.*

Ongoing investigations into the 1-3 ring opening of azabicyclo[1.1.0]butane molecules with a selection of nucleophiles has provided some early encouraging results. We have shown that an ABB with increased steric bulk incorporated into the heterocyclic core will still undergo 1,3-bond cleavage to generate azetidine. It has also been shown that such azetidines can be synthesised with the required thioester motif to take forward towards a novel azetidine sulfonamide synthesis.

In continuing this study, it would be desirable to pursue the synthesis of azetidine-3-sulfonamides by protecting 3-thioester azetidines with *N*-groups that allow the heterocycle to tolerate the oxidative chlorination and sulfonamide generation mentioned above. Should this not be possible, alternative routes for the conversion of thioesters to sulfonyl chlorides should be considered. Secondly, now that it has been established that azetidines with increased complexity can be synthesised as described above, expansion of the investigations to control the stereochemistry at each step of the proposed route should begin.

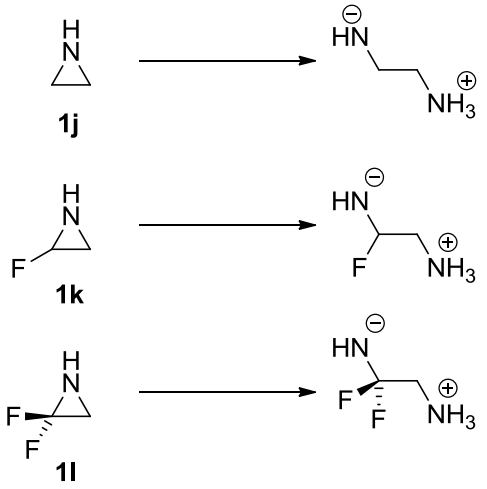
After a small number of experiments, it quickly became clear that a far more comprehensive investigation into the ring expansion of azirines with rhodium carbenoids would be required than time was available for during this course of work. Future experimentation with new examples in the future should aid in elucidating the mechanism, making this method a potentially powerful tool in the synthesis of complex azetidines.

## CHAPTER 2: GENERATION AND REACTIONS OF DIFLUOROCARBENE

### 2.1 Introduction

#### 2.1.1 Fluorine and its use in medicinal chemistry

Following the uniformly unsuccessful reactions between sulfonium ylides and *N*-activated 2-alkoxy aziridines, the use of halo-substituted aziridines in the investigation to broaden the scope of aziridine ring expansion to azetidine was pursued (see section 1.2.1). No examples of polyhaloaziridines being applied to the previously discussed ring expansion procedure are known and their use was desirable for two reasons. First, in contrast to the reactivity of oxiranes and thiiranes, the nitrogen of aziridine must typically be functionalised to activate the heterocycle carbons towards reactions with nucleophiles. Fluorinating the carbon positions of aziridine is an alternative way to activate the ring. The computationally calculated reactivity of aziridine (**1j**), 2-fluoroaziridine (**1k**) and 2,2-difluoroaziridine (**1l**) towards ring opening by ammonia illustrates this.[111] Aziridine **1k** was as reactive as non-fluorinated *N*-Ac aziridine; **1l** was more reactive than **1j** and **1k**. The increased Baeyer strain caused by the inclusion of fluorine(s) into aziridine was stated to be the cause of this trend (Figure 11).




| Aziridine | strain (kcal mol$^{-1}$) | Rate |
|---|---|---|
| **1j** | 27.3 | 1.00 |
| **1k** | 35.6 | 4.10 x $10^{11}$ |
| **1l** | 42.9 | 1.23 x $10^{13}$ |

***Figure 11:*** *Calculated ring opening rates and ring strain energies of some aziridines.*

Second, fluorine is not typically found in natural products but is frequently used by medicinal chemists when designing drug molecules.[112] Fluorinated species are interesting due to the ability of fluorine to alter the molecule's properties. Substituting a single fluorine group for another in a key site in a drug molecule can have a significant effect on the bioactivity and pharmacokinetic properties.

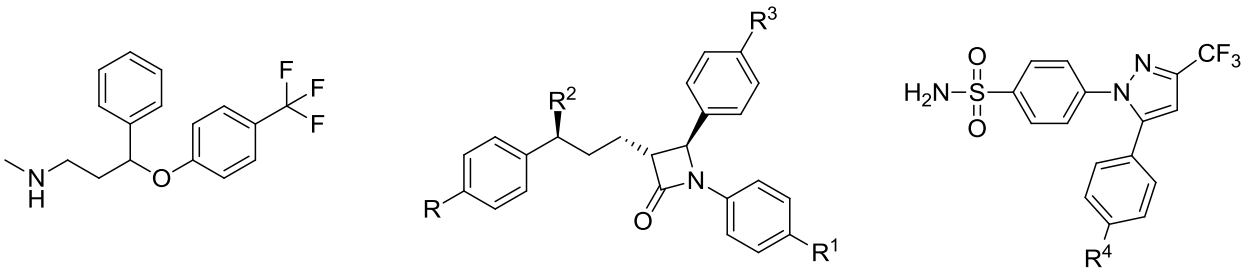
Fluorine incorporation can increase the acidity of an acid,[113] reduce the basicity of amines[114] or reverse the polarity of a double bond.[115] In turn, this can enhance diffusion characteristics across a membrane, enhance the metabolic stability of a molecule,[112] and alter the binding affinity of a molecule to its target receptor.[116] Modified receptor binding characteristics can be caused by non-specific lipophillic effects,

fluorophillic residues in receptor sites and effects on molecular conformation.[116] Since the first fluorine containing drug product was synthesised in 1957,[117] it is now estimated that almost 25 % of pharmaceutical pipeline drugs contain fluorine.[118] Prozac is one famous example of a trifluoromethyl substituted drug molecule that has achieved massive world-wide sales since its first approval for use by the FDA.[119]

Fluorine is a small atom, not much larger than hydrogen when covalently bound (1.47 and 1.20 Å van der Waals radii respectively)[120] and is smaller than a methyl group (2.0 Å).[121] It is the most electronegative of the elements (3.98 on the Pauling scale),[122] making it an excellent electron withdrawing group. In the vicinity of an acidic or basic group, electron density is significantly perturbed in the molecule; this can have a marked effect on the pKa: trifluoroacetic acid (pKa= - 0.25) is more than five orders of magnitude more acidic than acetic acid (pKa= 4.76).[87] The change in pKa can alter the membrane permeation of the molecule, thus altering its bioavailability.

Fluorine can affect the lipophilicity of a drug molecule, and is considered to be more lipophilic than hydrogen. A highly lipophilic molecule will often have excellent affinity for the binding site on the target receptor but will also have low aqueous solubility, reducing the bioavailability of the drug. The effect on lipophilicity when a single hydrogen was replaced with fluorine in nearly 300 molecules has been reported: the Gaussian distributions of log *D* for the non-fluorinated molecules had increased by +0.25 for the fluorinated examples.[112] The log *D*, or distribution coefficient, describes the ratio of molecules in each layer when partitioned between a pH 7 buffered aqueous and octanol system. The higher the value, the more lipophilic a molecule is.

P450 cytochromes in the liver are efficient at oxidising lipophilic molecules. If changing the polarity of a molecule is not an option to reduce its lipophilicity, another common strategy is to substitute fluorine for a metabolically active site. The small size of the fluorine atom does not usually alter the molecular conformation, and is therefore broadly considered to be a good hydrogen mimic in this respect. The enhanced stability of the *C*-F bond (116 kcal $mol^{-1}$) over the *C*-H bond (99 kcal $mol^{-1}$) is accepted as the reason for preventing metabolism at a given site in a molecule.[116] The drug Ezetimibe (**56**) is an excellent example of this stabilising effect, where inclusion of *para*-fluoro groups caused a reduction in $ED_{50}$ from 2.2 mg/Kg/day to 0.04 mg/Kg/day (Figure 12).[123, 124] Conversely, if a molecule in development has a very long half-life in the body, removal of a fluorine group can transform a previously metabolically inert site into a labile one: as seen with the COX II inhibitor Celecoxib (**57**) where the *para*-fluoro group was replaced with a methyl group.[99]

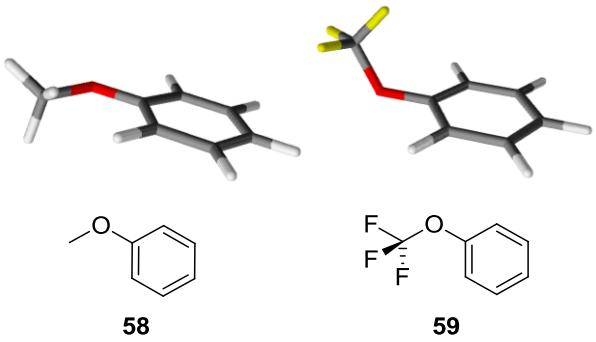


| | R | $R^1$ | $R^2$ | $R^3$ | $ED_{50}$ |
|---|---|---|---|---|---|
| | H | OMe | H | OMe | 2.2 |
| **56** | F | F | OH | OH | 0.04 |

| | $R^4$ | $t_{1/2}$ (h) |
|---|---|---|
| | F | 220 |
| **57** | Me | 3 |

***Figure 12:*** *Prozac (left), Ezetimibe (centre) and Celecoxib (right).*

Once the drug molecule arrives at a receptor site, the enhanced lipophilicity of fluorine causes it to have a slightly enhanced non-specific affinity for the binding site. As mentioned above, fluorine usually has a minimal effect on the shape of a molecule, but a small number of examples of fluorine effecting a conformational change in a molecule are known. Based on analysis of entries in the Cambridge Structural Database, a study comparing anisole moieties without *ortho*- substituents showed the -$OCH_3$ (**58**) group is found in the same plane as the phenyl ring. When perfluorinated, the -$OCF_3$ (**59**) group lies in an orthogonal conformation (Figure 13).[112]



**58** **59**

***Figure 13:*** *Conformations of fluorinated and non-fluorinated anisole.*[112]

Other investigators observed that tetrafluoroethoxyphenyl (**60**) had very similar structural and electronic properties to the metabolically unstable 2-phenylfuran (**61**) and was therefore an interesting substitution option for cholesterol ester transfer protein inhibitors (Figure 14).[125] This fluorination strategy has been exploited to replace metabolically labile oxygen atoms in phosphonate esters. In this example the difluoromethylene group was considered to be analogous both electronically and sterically to the C-O-P motif it replaced, giving C-$CF_2$-P in its place.[126]

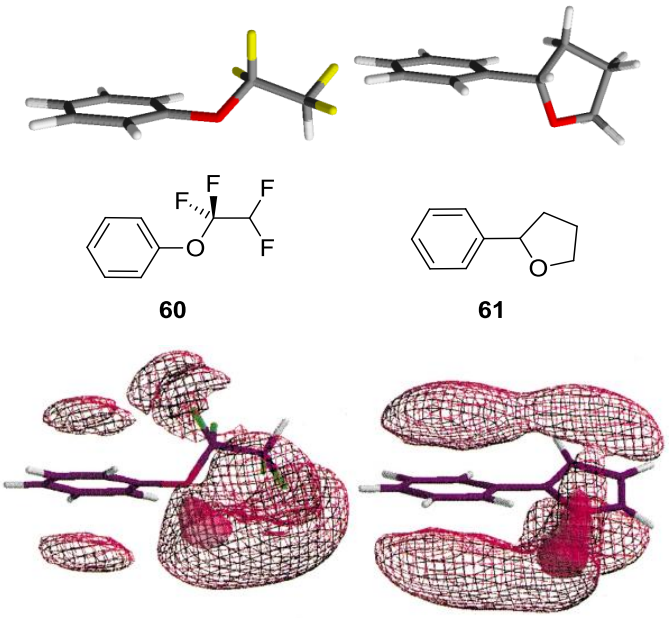
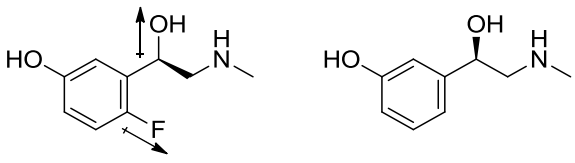



***Figure 14:*** *Comparison of tetrafluoroethoxyphenyl and 2-phenylfuran. Image taken from reference 125 showing the negative electrostatic potential of* ***60*** *and* ***61*** *in cholesteryl ester transferase protein.*

Numerous examples exist where a fluorinated species displays stronger binding to the target receptor than the non-fluorinated parent compound. The case of 6-fluorophenylephrine (**62**) showed that the fluorinated molecule displays an enhanced potency towards $\alpha_1$ and $\alpha_2$ adrenoreceptors but reduced interaction with $\beta$-adrenoreceptors, making it a specific $\alpha$-adrenergic agonist when compared to phenylephrine (**63**).[127] This activity was attributed to conformational changes induced in the molecule by repulsion of the benzylic hydroxyl group by the ring fluorine substituents (Figure 15). The non-fluorinated compound displayed no such selectivity. Studies have also shown that certain asparagine (Asn) environments display 'fluorophilic' characteristics, owing to the increased activity of selected fluorinated drugs when the fluorine site is in proximity to such Asn sites.[128] In the extreme, examples exist where the fluorine group is specifically susceptible to elimination. Loss of fluoride leaves a cationic species: this can cause irreversible inhibition of the enzyme through covalent bonding to the active site.[129]



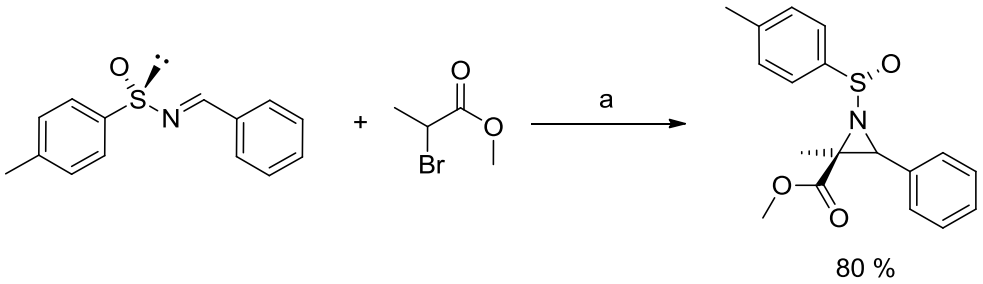

**62** **63**

***Figure 15:*** *Fluorinated and non-fluorinated phenylephrine, with the preferred conformation shown for* ***62****.*

### 2.1.2 Fluorinated aziridines and difluorocarbene.

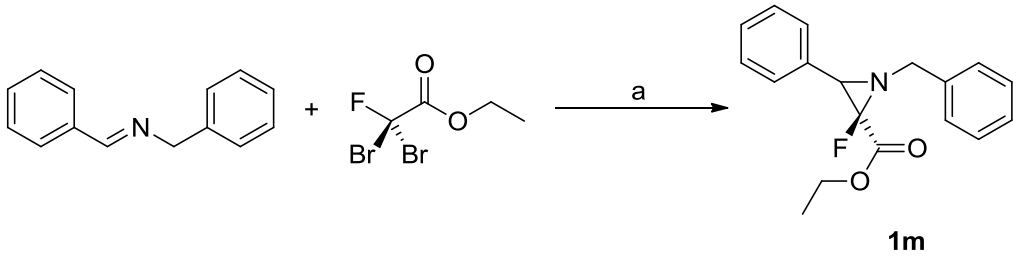
Addition of nitrenes to olefins is a popular route to aziridines.[36] Reactions at imine centres can also be used in the synthesis of aziridines as discussed previously (1.1.2 Azetidines from aziridines), including the addition of carbene equivalents to imines.[130] Such carbene equivalents often take the form of an $\alpha$-halo carbanion. These nucleophilic species react with the electrophilic imine carbon, forming an

intermediate with an anionic nitrogen that can then undergo 1,3-elimination to displace halide and form aziridine. This is analogous to the Darzens glycidic ester condensation, and is therefore referred to as an aza-Darzens reaction (Scheme 64).[69] Mono-fluorinated 2-alkoxycarbonyl aziridines (**1m**) have been synthesised by the Reformatsky type aza-Darzens reaction between ethyldibromofluoroacetate in the presence of zinc metal and aromatic imines (Scheme 65).[131]




80 %

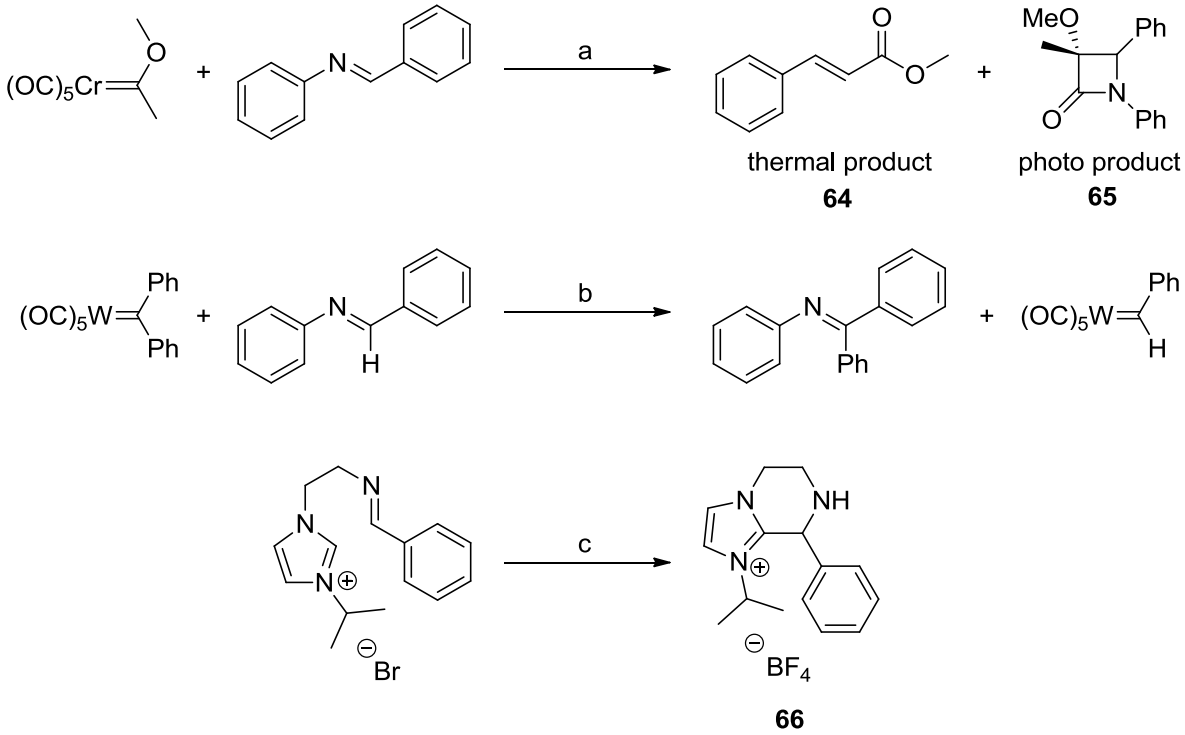
***Scheme 64:*** *Aza-Darzens aziridine synthesis a*ccording to Davis et al.[70] *Conditions* ***a****: LiHMDS, THF, rt, 2.5 h.*




**1m**

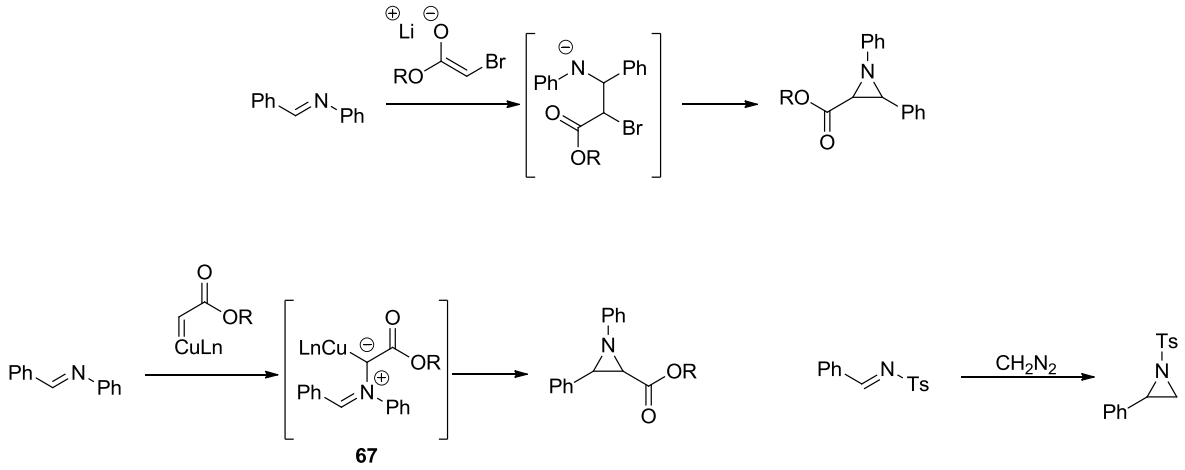
***Scheme 65:*** *Reformatsky type aza-Darzens reaction between ethyldibromofluoroacetate and aromatic imines.*[131] *Conditions* ***a****: 1 mol. eq. Zn, MeCN, -10 °C, 6 h.*

Carbene addition to imines is less prevalent in the literature. Hegedus reported the reaction of chromium carbene complexes (derived from chromium hexacarbonyl and $\alpha$-lithio species) in the presence of imines.[132] They suggested that one possible outcome from this reaction could be aziridine. Instead, they found that cinnamates (**64**) or β-lactams (**65**) resulted from reactions performed under thermal or photolytic conditions respectively (Scheme 66). Later reports showed imine metathesis type reactions with tungsten di-arylcarbene complexes were possible.[133] With the development of persistent *N*-heterocyclic carbene species, examples of their reaction with imines are also known. In an intramolecular process, a pendant NHC reacted at an imine centre to yield a piperazine (**66**), not an aziridine however.[134]



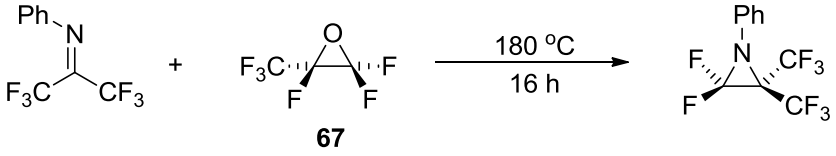

***Scheme 66:*** *Examples of carbene addition to imine. Conditions* ***a****:*[132] *50 °C, 2 h; or sunlight, $Et_2O$.* ***b****:*[133] *THF, 40 °C, 2 h.* ***c****:*[134] *NaH, THF, 25 °C, 16 h then $HBF_4{\cdot}OEt_2$, $Et_2O$, 0 °C, 35 min.*

Successful generation of aziridines from imine and carbene [2+1] cycloadditions are uncommon. One example of this reaction was reported for the copper catalysed addition of diazo esters to imines.[135] In comparison to the previously mentioned addition of carbene equivalents to imines, the addition of the copper carbenoid species is proposed to react first at the nitrogen of the imine, forming an iminium salt (**67**). This then undergoes cyclisation to generate aziridine (Scheme 67). A recent example of these rare reactions was reported whereby methylene is added to *N*-benzylidine toluenesulfonamide by exposing the imine to a single equivalent of diazomethane with no additional catalyst.[136]



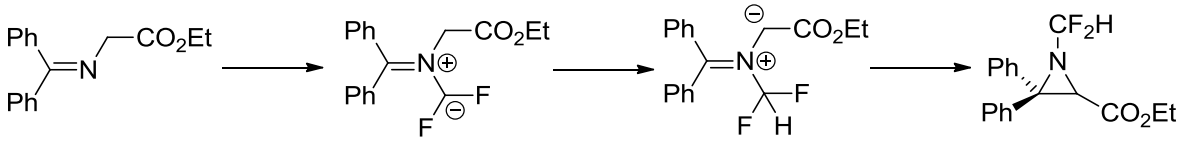

***Scheme 67:*** *Aziridines from imines. Top: addition of carbene equivalent.*[130] *Bottom: addition of copper carbenoid*[135] *or diazomethane to imines.*[136]

Few examples of difluorocarbene addition to an imine to generate aziridine exist; only one that yields a *gem*-difluoroaziridine where the new $CF_2$ group forms part of the aziridine ring has been reported. In this isolated example, the thermal generation of difluorocarbene from hexafluoropropene oxide (**67**) in the presence of *N*-alkyl or *N*-aryl bis-trifluoromethylimines to generate aziridines was shown (Scheme 68).[137] This provides an alternative route to 2,2-*gem*-difluoroaziridines; the usual route being *via* the 1,3-elimination of chloride from 2-chloro-2,2-difluoroethylamine derived compounds.[138] Monofluorocarbene has also been shown to react with aromatic imines, albeit in generally poor yields, to synthesise 2-fluoroaziridines. In this instance, the carbene is derived from the reduction of dibromofluoromethane in the presence of lead and tetrabutylammonium bromide in an ultrasonic bath.[139]




***Scheme 68:*** *Synthesis of gem-difluoroaziridine by the addition of difluorocarbene to imine.*

In another example of difluorocarbene reaction with imine, instead of occupying a position in the newly formed aziridine ring, a difluoromethyl moiety was appended to the resulting aziridine nitrogen.[140] This was proposed to have happened by attack of nitrogen on difluorocarbene, followed by a proton transfer and ring closing process within the rest of the Schiff base ester (Scheme 69). In all reports of aziridine synthesis by these protocols, carbenes and carbenoids are proposed to favour reaction at the nitrogen centre of imines to form azomethine ylides, while carbene equivalents will first react at the carbon centre of imines to form nitrogen anions, prior to cyclisation to generate the heterocycle.




***Scheme 69:*** *Aziridine with N-difluoromethyl functionality from difluorocarbene addition to imine.*[140]

Carbenes are divalent carbon species with two unbonded electrons and an overall neutral charge. This valency electron count of six makes carbenes inherently electron-poor. They can exist in the singlet or triplet state. The two states differ by the distribution of the two unbonded electrons in the two vacant orbitals on carbon. As well as the two filled bonding $\sigma$-orbitals, singlet carbenes have one wholly occupied s-orbital and one vacant p-orbital, and behave with both nucleophilic characteristics (cf. electron lone pair) and electrophilic characteristics (cf. vacant p-orbital). Triplet carbenes have a single electron in both unbonded orbitals and tend to react as diradicals. Whether the singlet or triplet state is considered the 'ground' state for a given carbene is influenced by the substituents on the carbene centre.[141]

Carbene substituents that are electron withdrawing stabilise the filled s-orbital. This increases the energy gap between the unbonded *s*- and *p*-orbitals, favouring the singlet state. In the case of dihalocarbenes,

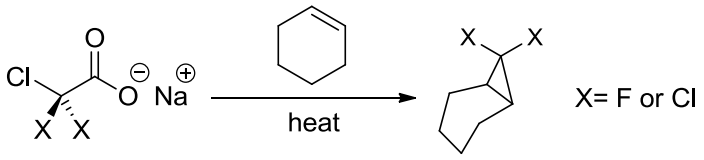
the electrons from the halogens also stabilise the carbene through π-electron back-donation to the carbene centre. These stabilising effects mean difluorocarbene is believed to have a long lifetime in solution in comparison to other non-stabilised carbenes, coupled with reduced nucleophilicity and increased electrophilicity.

Carbenes can exist in metal-carbene complexes as carbenoids or as the free carbene in solution.[31] Carbene complexes are normally referred to as Fischer or Schrock carbene complexes: both have contrasting properties (Table 6). Excluding persistent *N*-heterocyclic carbenes,[142] most uncomplexed carbenes have lifetimes of several nanoseconds to microseconds in solution, but due to their highly reactive nature will readily react with other components of the reaction mixture, themselves or even the solvent.[143, 144]

***Table 6:*** *Comparison of Fischer and Schrock carbenoids*

| | **Fischer** | **Schrock** |
|---|---|---|
| **Metal** | late transition-element | early transition-element |
| **Oxidation state** | low | high |
| **Metal ligands** | p-acceptors | not p-acceptors |
| **Carbene groups** | p-donors | not p-donors |
| **Carbene ground state** | single | triplet |
| **Example** | $(CO)_5Cr=C(OMe)(Me)$ | $(C_5H_5)_2MeTa=CH_2$ |

The generation and use of difluorocarbene has been known since the 1960s. The first reported experiment exploited the thermal decomposition of sodium chlorodifluoroacetate (**68**) in refluxing 1,2-dimethyoxyethane with cyclohexene to generate difluoronorcarane in 11 % yield (Scheme 70).[145] This work was the natural progression of investigations into dichlorocarbene generation from analagous halogenated acetate salts.[146] Although dibromo- and diiodocarbene are also known, there has been no report of their synthesis from the corresponding dibromo- or-diiodo chloroacetate salts. Dibromo- and diiodocarbene are synthesised by exposing the relevant haloform to strong base, causing deprotonating and subsequent loss of chloride to give the reactive dihalocarbene species.[147]




***Scheme 70:*** *Generation and trapping of dihalocarbene.*[145]

Subsequent to this, other methods have been introduced that can be broadly categorised by the era and mechanism by which they generate difluorocarbene. Most early difluorocarbene precursors are based on gaseous fluorinated hydrocarbons and ozone depleting substances (ODSs) such as tetrafluoroethene, hexafluorocyclopropane, chlorodifluoromethane. Other halogenated small molecules including hexafluoropropyleneoxide **67** and tetrachlorodifluoroacetone could be used, as well as highly reactive

species such as diazomethanes or difluorodiazirines. The next emergent class of precursors was based on heavy-metal containing complexes. These were superseded by less toxic compounds, but still relied on the use of ODSs. Modern difluorocarbene sources are environmentally benign and usually of low toxicity (Figure 16). As would be expected, the reaction conditions required when following older methods are considerably harsher than those used by modern difluorocarbene precursors. Common uses for difluorocarbene are the [2+1] cycloaddition with olefins to synthesise *gem*-difluorocyclopropanes or insertion into *O*-H, *S*-H or *N*–H bonds. The chemical behaviour of fluorocyclopropanated steroids is an early example of such experimentation.[148]

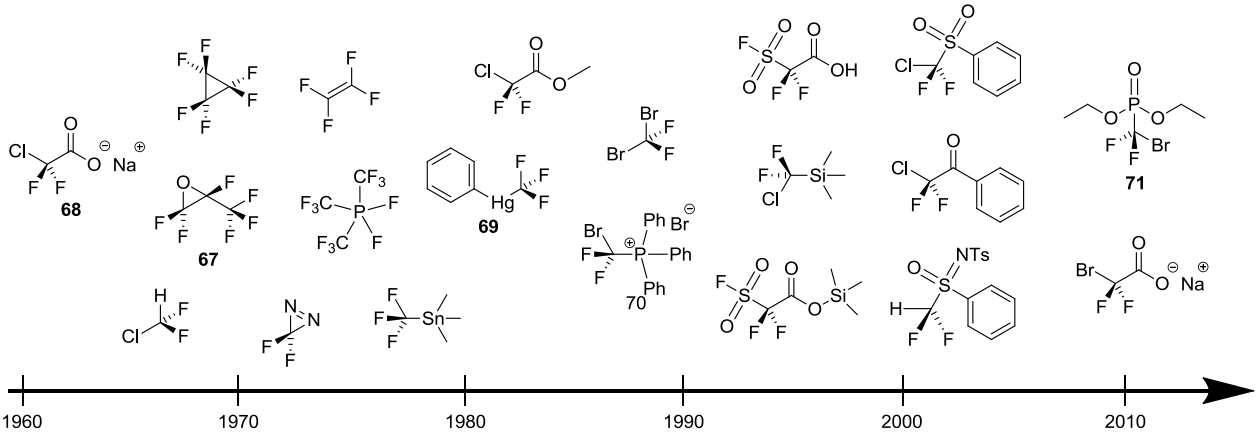
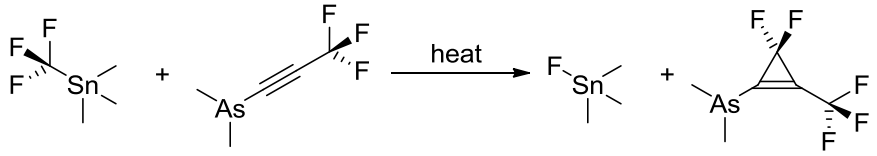



***Figure 16:*** *Evolution of difluorocarbene precursors.*

The first reported compounds, such as $(CF_3)_3PF_2$,[149] difluorodiazirine[150] and **67**[151], can all be used to synthesise cyclopropanes by thermolyis of the precursor to generate difluorocarbene in the presence of an olefin. These reactions all require high temperatures (between 100 – 200 °C), long reaction times and synthesise the cyclopropanes in the gas phase. Some precursors are gases at room temperature, and the volatile or gaseous products can be hard to isolate.

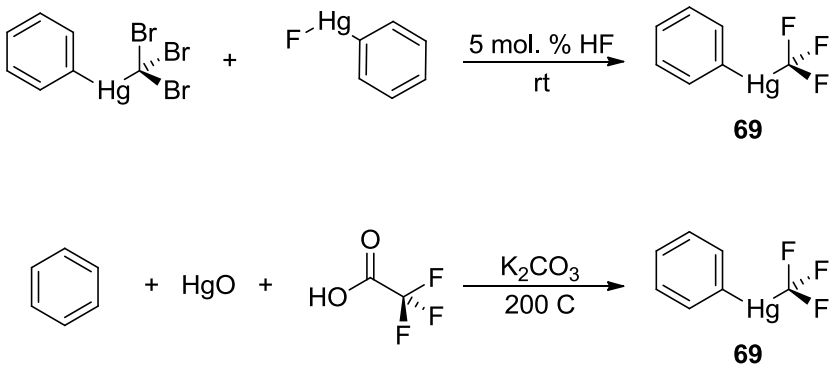
The observation that suitable heavy-metal compounds can liberate difluorocarbene upon thermolysis at 150 °C was reported as a side reaction during the elimination of trimethyltin fluoride from trifluoromethyl trimethyltin.[152] Perfluorocyclopropane generation was evidence of difluorocarbene evolution and trimerisation. Thermolysis of trifluoromethyl trimethyltin was also used to add difluorocarbene to a selection of heavy-metal alkyne complexes of the type $(CH_3)_nM(C{\equiv}CCF_3)_y$ where M = As, Ge or Si, giving *gem*-difluorocyclopropene containing complexes (Scheme 71).[153]




***Scheme 71:*** *Thermolysis of tin compounds to generate difluorocarbene.*[153]

In an evolution of this methodology, Seyferth *et al.* first demonstrated that trifluoromethyl trimethyltin could undergo iodide induced difluorocarbene transfer in refluxing toluene.[154] This was the first reported method for difluorocarbene generation that employed mild toluene reflux conditions compared to high temperature gas-phase thermolysis, as well as providing generally good yields of *gem*-difluorocyclopropanes from olefins.

Modification of another method for generating dichlorocarbene from phenyl(trichloromethyl)mercury allowed them to develop a straightforward synthesis of phenyl(trifluoromethyl)mercury (**69**) from non-gaseous reagents that did not involve the manipulation of metallic mercury.[155] Mercury compound **69** was easily obtained as a stable crystalline solid, and 'Seyferth reagent' is commercially available.[156] They speculated on the mechanism of its synthesis from phenyl(tribromomethyl)mercury, phenylmercuric fluoride and HF, but no conclusive proof was presented (Scheme 72). In the same way sodium iodide was employed to liberate difluorocarbene from trifluoromethyl trimethyltin, it was shown that iodide could aid decomposition of **69**. The synthesis of **69** has been improved upon, in which benzene, TFA and HgO can be combined in a single step reaction.[157]

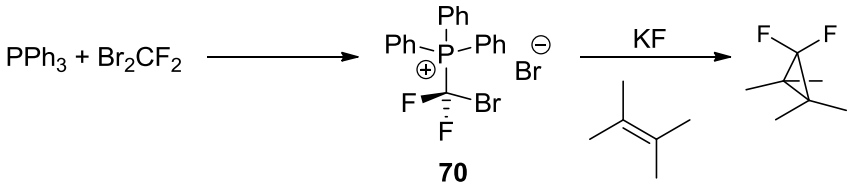



***Scheme 72:*** *Synthesis of phenyl(trifluoromethyl)mercury according to Seyferth et al (top) and Knunyants et al. (bottom).*[155]

The carbene precursor **69** is an easily synthesised and manipulated material that can be used in reflux systems to efficiently deliver *gem*-difluorocyclopropanes. It was one of the last heavy-metal based difluorocarbene sources to be reported as the toxic nature of these elements saw newer carbene precursors developed that posed fewer health risks for users. Although new chemical entities continued to be developed for the generation of difluorocarbene under mild conditions, none appeared to match the performance of Seyferth's reagent for several years, and ODSs were still commonly used when developing such compounds.

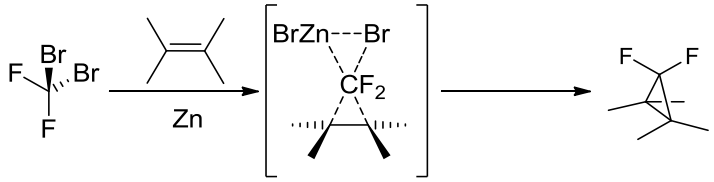
Examples of heavy-metal free, ODS derived precursors include triphenyl(bromodifluoromethyl)phosphonium bromide (**70**).[158] When combined with NaOMe, **70** will decompose to give difluorocarbene, which can be trapped with an olefin. The reported yields of cyclopropane were low. To overcome potential competition reactions between the carbene and alkoxide base, the phosphonium salt was instead synthesised *in situ* from $PPh_3$ and dibromodifluoromethane at

85 °C, with decomposition triggered by KF. The cyclopropane adduct was now obtained in good yield (Scheme 73).



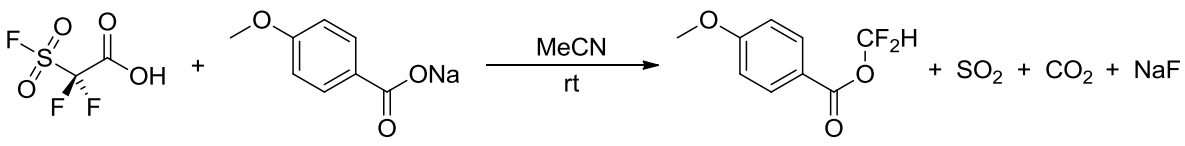

***Scheme 73:*** *In situ generation and decomposition of phosphonium difluorocarbene precursor.*[158]

Another heavy-metal free ODS was used as a difluoro modification of an existing dihalocarbene precursor. Chlorofluorocarbene can be generated from trichlorofluoromethane when exposed to reduced titanium, and the carbene trapped with olefins.[159] When $CF_2X_2$ (X= Cl, Br, I) was substituted for $CCl_3F$ the yields of the corresponding difluorocyclopropanes were low.[160] When $CBr_2F_2$ was exposed to zinc metal in the presence of substoichiometric iodine, near quantitative yields of difluorocyclopropanes were obtained. It was proposed that the mechanism of difluorocarbene delivery from $CBr_2F_2$ was analogous to a Simmons-Smith reaction (Scheme 74).[161]




***Scheme 74:*** *Simmons-Smith like addition of difluorocarbene to olefin from dibromodifluoromethane and zinc metal.*[160]

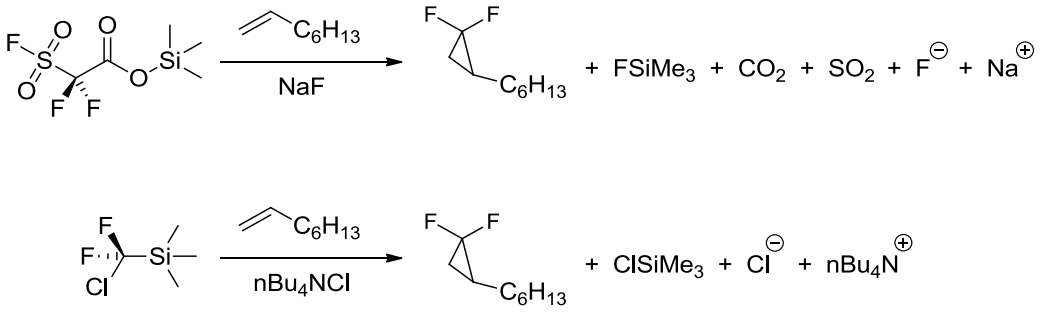
Modern sources of difluorocarbene have overcome the use of gases, heavy-metals and ODSs and are considered to be more environmentally friendly. Such precursors are designed to generate difluorocarbene with mild reagents and conditions. Exposure of fluorosulfonyl(difluoro)acetic acid to alkali metal alkanoates causes the acid to decompose to carbon dioxide, sulfur dioxide, difluorocarbene and metal fluoride. The isolation of difluoromethyl alkanoates from these experiments was proposed as the evidence of the generation of difluorocarbene (Scheme 75).[162]




***Scheme 75:*** *Decomposition of fluorosulfonyl(difluoro)acetic acid by alkyl metal alkanoates.*[162]

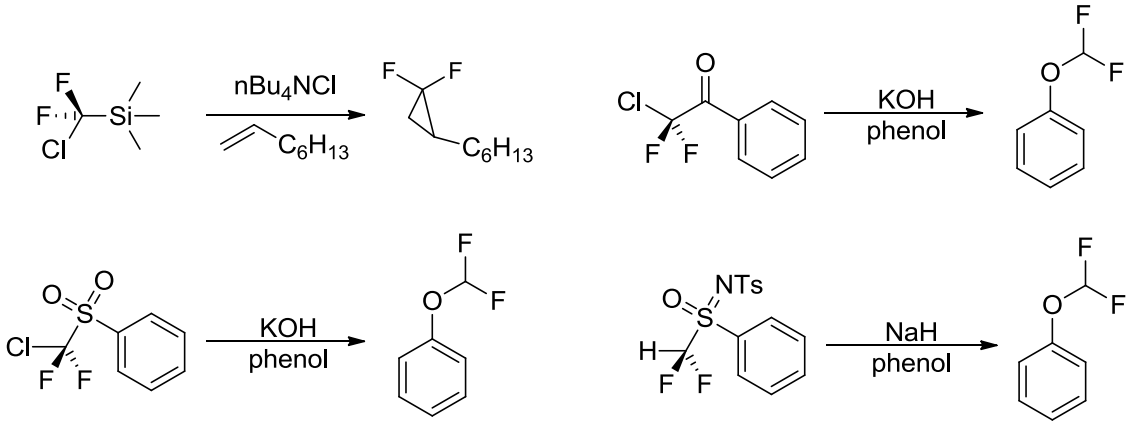
Using trimethylsilyl or triethylsilyl esters of fluorosulfonyl(difluoro)acetic acid (popularly abbreviated to TFDA and TEFDA respectively), it was shown that a sub-stoichiometric amount of fluoride could trigger the decomposition of the precursor and regenerate the fluoride ion.[163,164] Hu *et al.* reported trimethyl(chlorodifluoromethyl)silane will decompose to generate difluorocarbene when exposed to a

sub-stoichiometric source of chloride.[165] They proposed that through an $S_N2$ attack of chloride at silicon, a chlorodifluoro carbanion is liberated, which subsequently loses chloride to give difluorocarbene and regenerate the chloride ion (Scheme 76).




***Scheme 76:*** *Generation of difluorocarbene from halide sensitive precursors.*[163, 165]

They also report the use of 2-chloro-2,2-difluoroacetophenone,[166] chlorodifluoromethyl phenyl sulfone[167] and *N*-tosyl-(*S*)-difluoromethyl-(*S*)-phenylsulfoximine[168] to difluoromethylate heteroatomic nucleophiles under basic conditions (Scheme 77). A unique example of an efficient and non-toxic carbene source, diethyl(bromodifluoromethyl)phosphonate (**71**), is another reagent that undergoes decomposition under basic conditions to add difluorocarbene into *O*-H or *S*-H bonds in 20 minutes at temperatures as low as -78 °C.[169] It does, however, require an ODS for its synthesis.




***Scheme 77:*** *Novel difluorocarbene sources reported by Hu et al.*

By reviewing the difluorocarbene sources reported, it is clear that some have utility in adding difluorocarbene to unsaturated aliphatic systems, or to nucleophilic or anionic centres. For the addition of difluorocarbene to an olefin, research has shown that the carbene adds in a *cis*- manner across the double bond.[170] This outcome is indicative of a concerted [2+1] cycloaddition with the singlet carbene. A study of the kinetics of difluorocarbene addition to olefins has been reported where the results support the claims that difluorocarbene is electrophilic, less reactive than other dihalocarbenes and adds to olefinic double bonds in a concerted manner.[171]

## 2.2 Results and discussion

### 2.2.1 Addition of difluorocarbene to imines

Few reports of difluoromethylene incorporation into an aziridine are known. The priority of the investigation into the addition of difluorocarbene to imines was to synthesise novel aziridines to expose to the sulfonium methylide aziridine ring expansion reaction. It would also elaborate on the existing knowledge of this carbene's reaction with imines. Dichlorocarbene, generated from hexachloroacetone and NaOMe, will react with *N*-benzylidene aniline (**28**) at 0 °C in petroleum ether to generate 1,3-diphenyl-3,3-dichloroaziridine.[172] The reactivities of dichloro- and difluorocarbene are similar, with both being considered ambiphilic according to the Moss philicity scale (Figure 17).[144] If difluorocarbene can add to **28** in an analogous reaction, it would provide the *C*-activated aziridine 1,3-diphenyl-3,3-difluoroaziridine (**1n**) (cf. Carrié aziridines) for use in the sulfonium ylide aziridine ring expansion investigation. It was also of interest to discover if phosphonate **71** could facilitate the addition of difluorocarbene to imines: this would increase the number of applications **71** can be used for and allow aziridine synthesis under relatively benign conditions.[169]

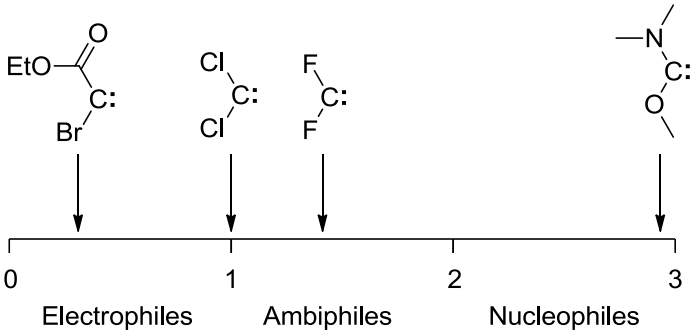
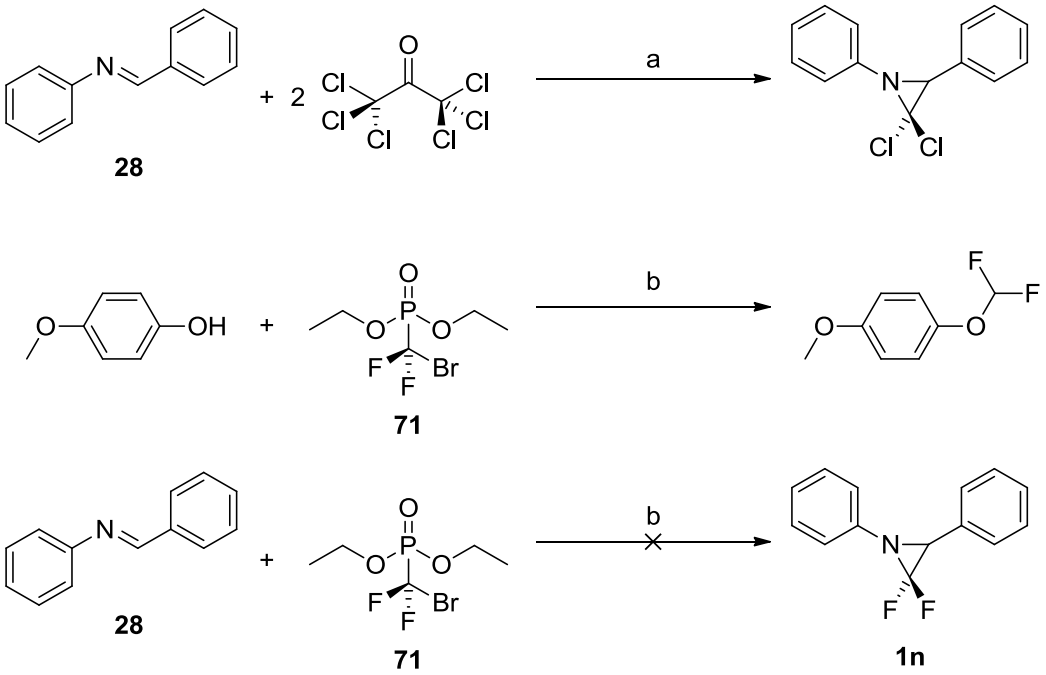



***Figure 17:*** *Moss carbene philicity scale.*[144]

In a first pass reaction, conditions were taken directly from the work of Zafrani *et al.* substituting **28** for the phenol derivatives (Scheme 78). The absence of signals in the $^{19}$F NMR spectrum of the crude product indicated that no new fluorinated molecules were synthesised in this reaction. $^{1}$H NMR analysis confirmed that only starting material **28** was recovered. The reaction was repeated for progressively longer times at room temperature. After 17 hours a reaction had occurred but column chromatography only isolated a single fraction that contained a complex mix of new fluorine environments as observed by $^{19}$F NMR.

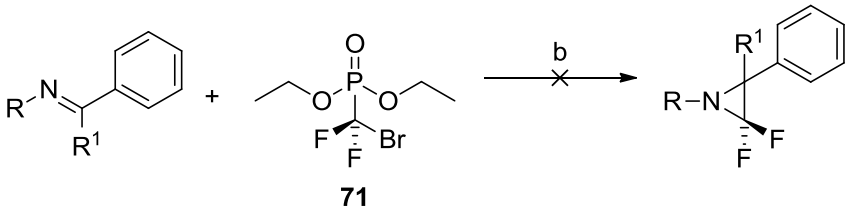



***Scheme 78:*** *Attempted synthesis of **1n**. Conditions **a** (Kadaba and Edwards):[172] 2 mol. eq. NaOMe, pet.ether, 0 °C, 5 h. **b** (Zafrani et al., this study):[169] 20 mol. eq. KOH, MeCN:$H_2O$, -78 °C – rt, 20 min.*

For every crude product, $^{19}F$ NMR spectra indicated no unreacted **71** remained. As the carbene source was water soluble however and therefore removed in the work-up, this was not a good indicator of precursor consumption or difluorocarbene generation. After validating the reaction conditions using 4-methoxy phenol, the result was consistent with that reported in the literature; the reproducibility of the method in our hands was confirmed.

Two more imines were substituted for **28** and the experiments were repeated. After 4 hours at room temperature the activated imine *N*-benzylidene-4-toluenesulfonamide (**72**) was totally consumed. No single product was obvious in the complex $^{1}H$ NMR spectra of the crude product. The only clearly identified change observed was the loss of the benzylic hydrogen signal and emergence of a broad singlet. The lack of any signals in the $^{19}F$ NMR spectra indicated no new fluorinated species had been synthesised and as such the outcome of the reaction was not investigated any further. No reaction was observed when the electron-rich diphenylmethyleneaniline (**73**) was used, only starting material was recovered after 15 hours at room temperature. Difluorocarbene generated from **71** under aqueous basic conditions was not compatible with imine **28**, **72** or **73** when trying to synthesise *gem*-difluorinated aziridines (Scheme 79).

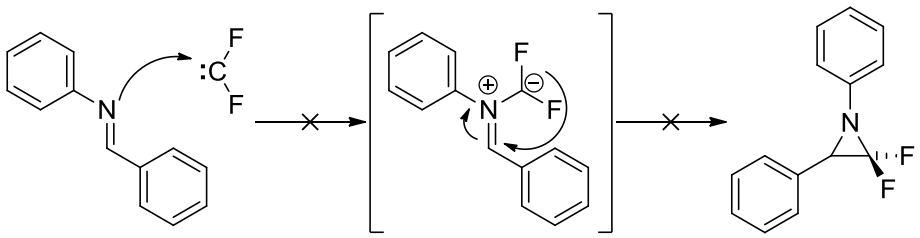
| Imine | R | $R^1$ |
|---|---|---|
| **28** | Ph | H |
| **72** | Ts | H |
| **73** | Ph | Ph |




***Scheme 79:*** *Attempted aziridination of imines with difluorocarbene derived from* ***71****.Conditions* ***a****: 20 mol. eq. KOH, MeCN:$H_2O$, -78 °C – rt, 20 min.*

Due to the electron-deficient property of difluorocarbene, it was expected that **28** and **73**, with their electron-rich phenyl substituents, would have been most reactive under these conditions. Imine **72** was expected to be the least reactive due the electron withdrawing *N*-tosyl group. These predictions were incorrect: only **28** and **72** were sensitive to the reaction conditions, and only the crude product from experiments with **28** showed any new fluorinated species having been synthesised. The reasons for this trend in reactivity were not immediately obvious. Three reasons for the failure of the experiment can be suggested nonetheless.

First, the addition of difluorocarbene to imine is not compatible with the aqueous conditions described for the use of **71**. In the proposed mechanism for the reaction between phenols and difluorocarbene, an anionic difluoromethyl ether intermediate is described and said to deprotonate a water molecule to give a difluoromethyl ether. Second, the conditions under which difluorocarbene is liberated from **71** are too mild to allow its reaction with anything other than moderately to highly-nucleophilic centres. In the reported procedure, the phenol substituents would have existed as potassium phenolate salts. Finally, the electronic nature of the carbene and imine may have been incompatible. Dichlorocarbene is more electrophilic than difluorocarbene. While dichlorocarbene added to **28** in the required way to generate aziridine, the only example of the analogous reaction of difluorocarbene used an imine with electron withdrawing trifluoromethyl groups. Imines **28**, **72** and **73** may have been too electron-rich at imine carbon to allow the required reaction path to be followed (Scheme 80).



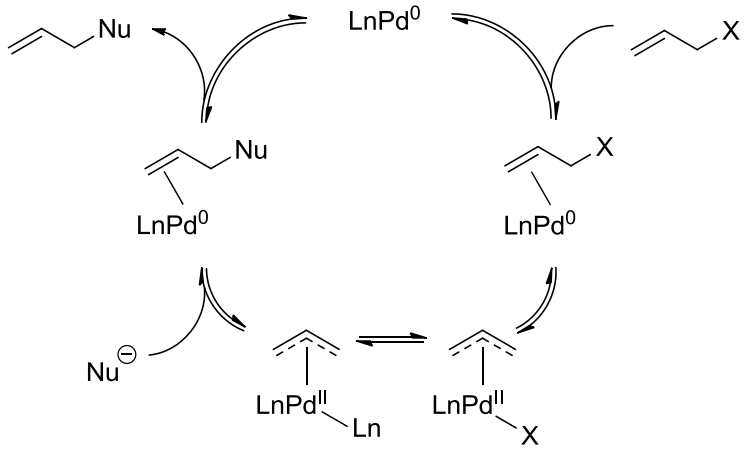

***Scheme 80:*** *Proposed mechanism for successful addition of carbene to imine.*

### 2.2.2 Development of new difluorocarbene precursors

Attention now turned to the development of a new class of carbene precursor. Many examples of difluorocarbene generation rely on the spontaneous thermal decomposition of the precursor to generate the reactive carbene species. The ability of the carbene to react with olefin traps in these examples is aided by the high temperatures used to trigger the initial decomposition. As difluorocarbene generation

protocols evolved the temperature of the reactions was able to be reduced. Some modern procedures exploit the action of catalytic halide on the carbene source to initiate decomposition and carbene liberation. In general, [2+1] cycloaddition of difluorocarbene to olefin requires reaction temperatures around 80 – 100 °C.[165] Difluorocarbene addition to phenolate or thoiphenolate has been shown to be possible at temperatures as low as -78 °C.[169]

There are no examples in the literature of the transition-metal catalysed decomposition of a carbene source to generate difluorocarbene, though many existing precursors have the potential to be modified to be used in such a way. Allyl groups display an affinity towards palladium coordination to give stable allylpalladium intermediates.[173] The Tsuji-Trost reaction is an excellent example with a broad scope for this process.[174] The catalytic $Pd^0$ species first coordinates to the olefin of the allyl group forming an $\eta^2$-species. Upon loss of a suitable leaving group an $\eta^3$-allylpalladium species then forms.[175] This intermediate complex is susceptible to nucleophilic attack, after which the newly formed allyl-nucleophile species is lost and the catalytic $Pd^0$ species is regenerated (Scheme 81).

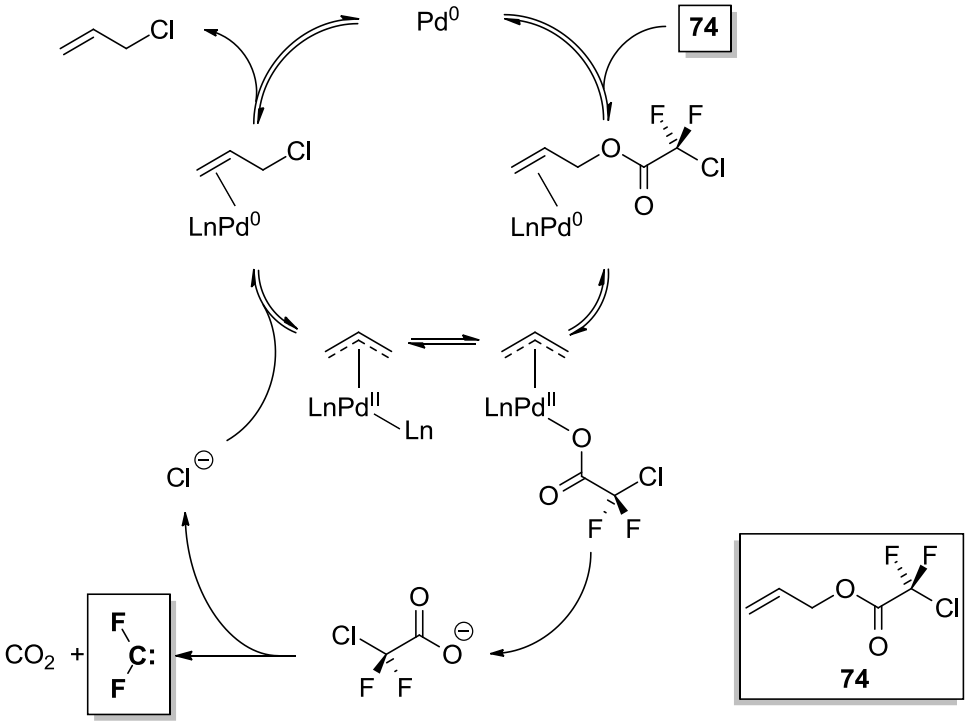



***Scheme 81:*** *Representative catalytic cycle in a Tsuji-Trost reaction.*[174]

In an analogous fashion to the decomposition of a trialkylsilyl ester functionalised precursor by substoichiometric halide to generate difluorocarbene (cf. TFDA),[164] this investigation aims to discover if the coordination of $Pd^0$ to an allyl functionalised precursor will trigger decomposition to liberate difluorocarbene. It is proposed that by modification of certain existing carbene precursors with allyl groups, following coordination of a $Pd^0$ species to the allyl group, the rest of the precursor will be lost as a leaving group from the allylpalladium intermediate. After this elimination, the leaving group would decompose in the usual way (cf. TFDA decomposing to $CO_2$, $SO_2$, $CF_2$ and $F^-$), liberating difluorocarbene in the process. A nucleophilic component will subsequently be released into solution; this will react with the allylpalladium complex to release the allyl group and return the $Pd^0$ to solution (Scheme 82).

Three existing difluorocarbene precursors were identified as candidates for this investigation. The allyl ester analogues of **68** (allyl chlorodifluoroacetate **74**), TFDA (allyl 2,2-difluoro-2-(fluorosulfonyl)acetate **75**) and **71** (diallyl(bromodifluoromethyl)phosphonate **76**) were all expected to be suitable compounds. As

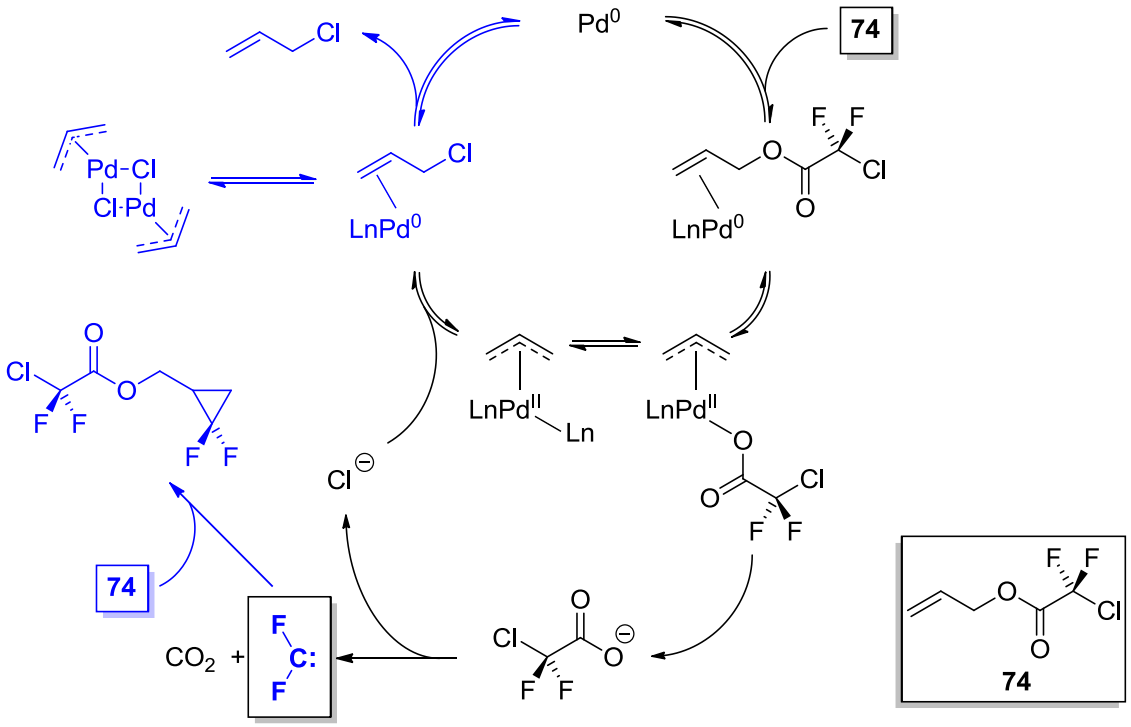
all are analogues of known difluorocarbene precursors, the allyl derivatives should surrender difluorocarbene in a similar fashion to the parent compounds if decomposition can be triggered.




***Scheme 82:*** *Proposed catalytic cycle for the palladium triggered decomposition of* ***74****.*

When planning this reaction, it was possible to identify potential side reactions. Difluorocarbene could react with the olefin of the allyl group on an uncomplexed precursor molecule. This would block the reactive allyl site and render the molecule inert to the catalytic process. Difluorocarbene reacts faster with electron-rich olefins: use of an electron-rich olefin as a trap should reduce carbene addition to the allyl group therefore.

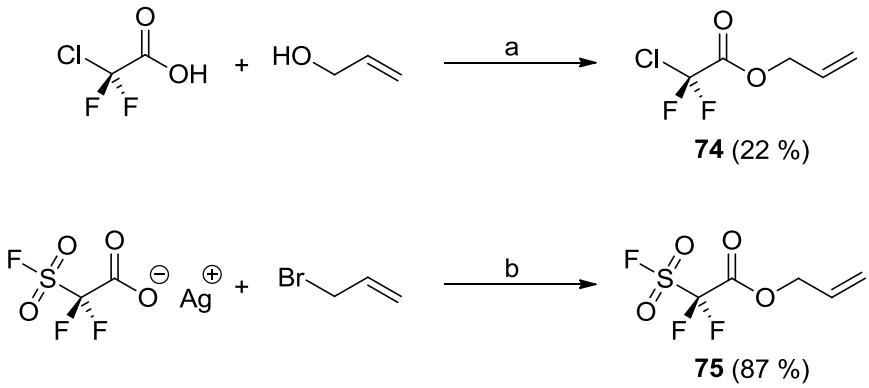
Just as addition of halide to allylpalladium complexes is known to yield allylhalides,[176] the same allylhalides would compete for the catalytic species.[177] This process would not prevent the desired reaction from proceeding, but the wrong position of the equilibrium in this step would reduce the rate of difluorocarbene generation. This concern was greatest for the proposed allyl chlorodifluoroacetate example **74**, where the stable allylpalladium$^{(II)}$ chloride dimer could form. This dimer can be employed as a source of palladium$^{(0)}$, however if it is sufficiently stable under these reaction conditions it will sequester most of the palladium from the reaction, causing it to reside off cycle. Formation of the stable allylpalladium chloride dimer *in situ* may therefore reduce the rate of turnover of the catalytic cycle. These processes are described below for the example of **74** (Scheme 83).




***Scheme 83:*** *Postulated catalytic cycle for* ***74*** *with anticipated detrimental side reactions highlighted.*

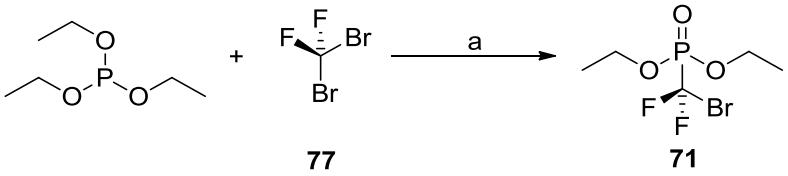
Allyl ester **74** can be used as an intermediate towards *gem*-difluoropyrolidines,[178] as a fluorinated mechanistic probe into valproic acid hepatotoxicity[179] and as an intermediate in trifluoroethyl compound synthesis.[180] Allyl ester **75** has previously been used by others as a novel fluorosulfonyl containing monomer/polymer.[181] Reports of the synthesis of **76** could not be found. For the three proposed precursors, literature precedent exists for the catalytic removal of allyl functionalities from carboxylates[182] and phosphonates.[183]

Allyl ester **74** was synthesised from chlorodifluoroacetic acid and allyl alcohol.[178] Allyl ester **75** was synthesised by reaction of allyl bromide with the silver salt of 2-(fluorosulfonyl)-2,2-difluoroacetic acid.[184] Both procedures yielded synthetically useful quantities of each compound.




***Scheme 84:*** *Synthesis of allyl esters* ***74*** *and* ***75****.Conditions* ***a****:*[178] *n-hexane, 70 °C, 9 h.* ***b****:*[184] *rt, 24 h.*

The synthesis of **76** was less trivial. The commercially available difluorocarbene precursor **71** can be synthesised *via* the Michaelis-Arbuzov reaction between triethyl phosphite and dibromodifluoromethane (**77**) (Scheme 85), and this is how the compound is typically synthesised according to literature precedent.[185] For safety reasons we opted to follow the more modern procedure of Savignac *et al.*; previous reports had described earlier procedures as being potentially explosive. Triallylphosphite was substituted for triethylphosphite in the reaction with **77** but phosphonate **76** was not detected in the crude reaction product. When validating the original method with triethylphosphite, **71** was recovered in less than 5 % yield. The reported procedure was performed on a 1 L scale; the attempted synthesis of **71** and **76** were performed on less than 100$^{th}$ of this scale. Halomethane **77** has a boiling point of approximately 22 °C: in a small scale reaction system at 60 °C, very little of this volatile reagent would remain in solution, even if used in excess with an efficient reflux condenser.

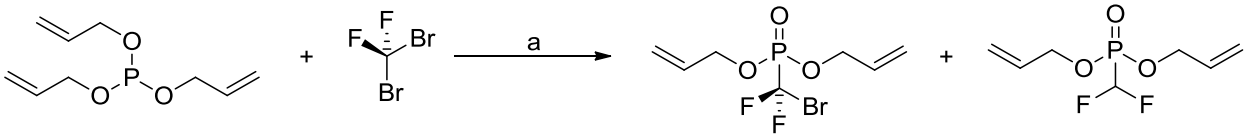



**77** **71**

***Scheme 85:*** *Synthesis of **71** via Michaelis-Arbuzov reaction. Conditions **a**:[185c] THF, 60 °C, 1.5 h.*

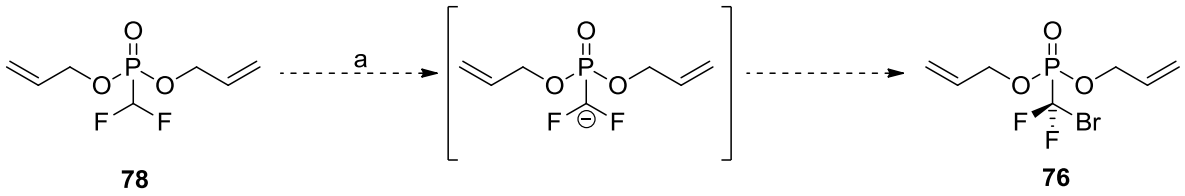
The method was modified; higher concentrations of the reagents were charged to screw-top reaction vials. With this set-up, the THF solution was heated to 100 °C for 6.5 hours to combine triallylphosphite and **77**, giving what was believed to be the target compound **76**. Purification of the phosphonate was done by column chromatography, but the reaction gave a wide range of isolated yields from 4 to 43 %. The phosphonate is not volatile, and samples kept in vials in a fridge for more than one year have shown no signs of decomposition. The cause for this wide range of yields was suspected to be due to the slow loss of **77** from the screw top reaction vials over the course of the experiment. With no other suitable vessels available at the time, and with useful quantities of phosphonate now synthesised, this procedure was not optimised any further.

After extensive two dimensional NMR and high resolution mass spectrometry analysis, what was initially thought to be the expected target compound **76** was in fact the debrominated analogue diallyl(difluoromethyl)phosphonate (**78**) (Scheme 86). If the Michaelis-Arbuzov reaction between triallylphosphite and **77** had proceeded as expected, **76** should have been obtained just as **71** was following method validation. While it is known that bromine is not present in the isolated product of this reaction, it was not clear at which point in the reaction it is lost. A compelling reason for the outcome of this reaction is not able to be made based on the evidence available.



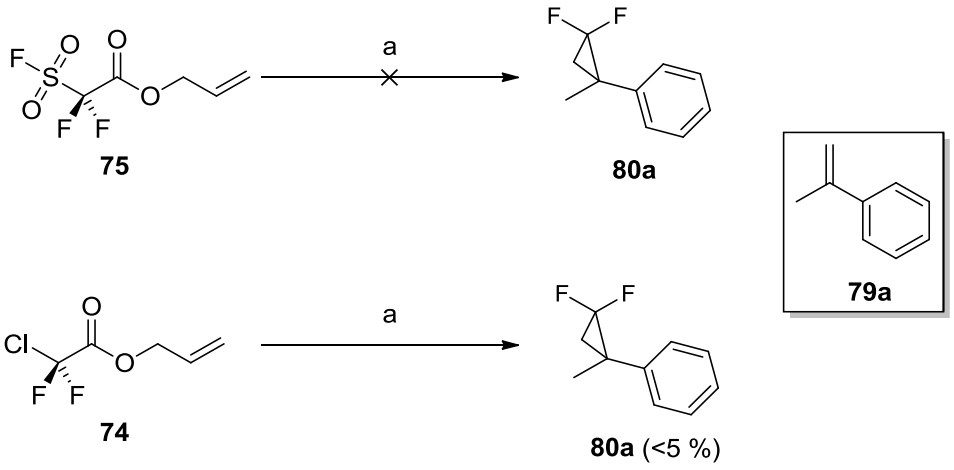

***Scheme 86:*** *Generation of debromo- product **78**. Conditions **a**: THF, sealed tube, 100 °C, 6 h.*

The anion of **78** is a known species and can be formed by the reaction of LDA with the protonated parent compound to give the lithiated methanion as a reactive intermediate *in situ*.[186] No reports of this species being quenched with electrophilic bromine exist in the literature. A procedure for the bromination of **78** can be proposed, for example employing *N*-bromosuccinimide (NBS) as a nucleophilic bromine source, but the literature precedent to use extremely toxic hexamethylphosphoramide made attempting any such procedure at this point in the investigation unappealing (Scheme 87).




***Scheme 87:*** *Proposed bromination of **78**.[186] Conditions **a**: 1 mol. eq. LDA, 1 mol. eq. HMPA, 0.5 mol. eq. NBS, THF, -78 °C, 15 min.*

Basing conditions on reports of deallylation of allyl esters, in first-pass reactions **74** and **75** were taken with substoichiometric tetrakis(triphenylphosphine)palladium$^{(0)}$ and triphenylphosphine in refluxing THF (Scheme 88).[182, 183] 2-Phenylpropene (**79a**) was selected as the carbene trap based on reports indicating this particular olefin couples well with difluorocarbene to give very good yields of the corresponding (2,2-difluoro-1-methylcyclopropyl)benzene (**80a**).




***Scheme 88:*** *Exposure of **74** and **75** to $Pd(PPh_3)_4$. Conditions **a**: 0.5 mol. eq. **79a**, 2 mol. % $Pd(PPh_3)_4$, 8 mol. % $PPh_3$, THF, reflux, 6 h.*

No reaction was observed for **75** and only the unreacted started materials were recovered. When exposed to $Pd(PPh_3)_4$, **74** had reacted in the desired manner. Analysis of the crude reaction product showed mostly starting material and reagent recovery, but crucially peaks in the $^{1}H$ and $^{19}F$ NMR spectra corresponding to **80a** could clearly be identified. Conversion was low, estimated to be less than 5 % by comparison of $^{1}H$ NMR integrations.

Repetition of the experiment with omission of the palladium species returned only unreacted starting materials. It was clear that the transition-metal complex had caused the expected decomposition of **74** to release difluorocarbene into the reaction mixture. Attempts to monitor reaction progress by conducting it in refluxing deuterated chloroform and extracting aliquots for analysis showed no reaction in this solvent. Performing the experiments with and without $Pd(PPh_3)_4$ at a higher temperature in refluxing 2-methyl THF gave the same results as in refluxing THF.

The close agreement of the estimated conversion of **79a** to **80a** and the catalyst loading implied this reaction may have a stoichiometric demand on the palladium species using these conditions. Repeating the experiment with a 20 mol. % $Pd(PPh_3)_4$ loading caused no conversion of **79a** to **80a** as evidenced by the lack of product peaks in the $^{19}F$ NMR. The reason for the loss of reactivity on increacing the metal complex loading was not obvious. The time to continue this investigation was not available and method optimisation was not able to be performed.

### 2.2.3 Microwave assisted synthesis of difluorocarbene adducts.

As an expansion of the investigation to develop new methods for the generation and reaction of difluorocarbene, time was taken to look at improving existing procedures for the use of known precursors. Many established carbene precursors can be categorised as being thermal sources of carbene; the systems in which they are used require relatively high temperatures to release the carbene species into the reaction mixture and to provide sufficient energy to allow it to react.

The development of a novel and potentially powerful methodology based on microwave heating of reactions was proposed for the next investigation. The use of microwave energy to rapidly and evenly heat reaction mixtures is a relatively new technique, and reports in recent decades have tried to define or discredit the existence of a non-thermal microwave effect on reactions.[187]

Microwave technology first saw use in inorganic chemistry labs around the 1970s and later in organic chemistry labs in the 1980s.[188] Since then, there have been many comprehensive and informative reviews of the technology. Early applications employed modified domestic appliances due to the lack of purpose built equipment. As such, these early systems made temperature and power a challenge to control. Obtaining consistent or predictable outcomes to reactions was difficult: modern equipment addresses this problem and the technology is discussed briefly below.

The key difference between microwave heating and conductive heating is the ability to rapidly and remotely provide energy to a reaction mixture. In conventional conductive heating systems, eg. a flask in an oil bath on a hot plate, the transfer of energy is slow and can result in significant temperature gradients within a reaction vessel. These temperature gradients can cause premature decomposition of compounds or incomplete reaction of starting materials. By comparison, microwave heating in an efficiently designed reactor provides instant, rapid and even heating of a reaction mixture remote from the heat source ie. the microwave generating magnetron. This provides a uniform temperature profile throughout a reaction mixture, resulting in a predictable and repeatable rate and outcome of reaction.

Microwave radiation occupies the part of the electromagnetic spectrum between infrared and radio waves. To avoid interference with commercial communication technologies that also rely on microwave radiation, most microwave heating appliances operate at a frequency of 2.45 GHz. As with all forms of electromagnetic radiation, the wave consists of an electronic and a magnetic component, both with equal frequency and amplitude oscillating in an orthogonal fashion. These two components cause the microwave heating mechanisms.

Just as IR and NMR spectroscopy exploit dipoles within a molecule to probe the types of chemical bond present, the magnetic field of the microwave radiation interacts with the overall molecular dipole to cause heating: this phenomenon is called 'dielectric heating'.[189] The larger the molecular dipole, the more a molecule will experience this heating effect. Consequently, non-polar molecules are said to be microwave transparent and bulk samples do not tend to heat when exposed to microwave radiation. A classic example to illustrate this is to compare the rise in temperature of the liquid when heating a sample of water (polar) and a sample of hexane (non-polar) in the same microwave field. The water sample will be at a higher temperature than the hexane sample after exposure to the microwave radiation for the same time.

As the magnetic field of the radiation oscillates, the molecules attempt to rotate to align with this field. If the frequency of oscillation is too low, each molecule has sufficient time to fully align with the magnetic field. If the frequency is too fast, the molecules do not have time to begin to move and will have no net rotation or energy gain. Microwave radiation is of the right frequency to allow molecules time to begin to rotate, but not to rotate sufficiently to become in phase with the radiation. As a molecule begins to align with the field of the microwave radiation, the field will have changed before it can become in phase with the radiation. As the molecule tries to change direction to move back into phase with the wave, energy is transferred to the system as molecular friction and collisions between rotating molecules. For this reason, gas samples with their widely spaced molecules cannot be heated using microwaves (Figure 18).

The dielectric constant, $\varepsilon'$, of a polar (solvent) molecule will affect its ability to couple with the microwave radiation, and is equal to the relative permittivity of the molecule at room temperature. The rate the solvent molecules lose energy to the medium is also important. This factor is called the loss tangent *tan* $\delta$. For two microwave active solvents with a similar dielectric constant, the one with the larger loss tangent

will transfer heat to the bulk faster. The loss tangent and dielectric constant can be used to calculate and compare the loss factor of a solvent ε''. ε'' can be used to compare which solvents will most efficiently convert stored microwave energy into thermal energy of the system. The equation relating them is $\tan\delta = \varepsilon''/\varepsilon'$.

The second heating effect associated with microwave energy is referred to as 'conductive heating' and is induced by the electric field of the radiation. Unlike in the traditional context, this conductive heating is not provided by the thermal energy of a heating mantle in contact with a reaction flask, but rather from solvated ions in the reaction mixture. As the electric field of the radiation oscillates, ions will move through solution to try and follow the phase of the wave. As they do this, they collide with other molecules and thus the kinetic energy of the migrating ions is converted into thermal energy within the system. Conductive heating is a stronger energy transfer mechanism than dielectric heating.

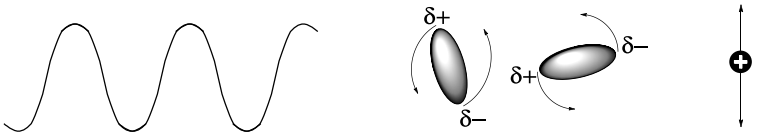



***Figure 18:*** *Schematic of microwave dielectric (left) and conductive (right) heating.*

The two modes of microwave heating mean that a solution can be heated in a rapid and homogeneous fashion; however these phenomena cannot be relied upon unless the radiation is applied to a system in a controlled way. Another property of oscillating waves is their ability to experience interference. In a domestic microwave oven, the microwave radiation field density is not uniform; after a short period of operation, a complex environment of standing waves with nodes and modes will develop within the microwave cavity. While this is sufficient for heating foodstuffs in a domestic setting, were two or more reaction vessels to be placed in this type of microwave environment, none of them would experience the same microwave heating effect. This is why no early scientific microwave methods could ever be classed as reliable.

There are two templates for microwave reactor design. In a single-mode reactor, microwave radiation is focussed onto a single point at the centre of the reactor cavity precisely where the reaction vessel is located (eg. CEM Discover® range).[190] The other type of reactor is closer in design to a domestic microwave appliance, but uses magnetrons equipped with radiation diffusers to ensure that a homogeneous microwave field free from standing waves is established (eg. Milestone MicroSYNTH® range).[191] These reactors have the advantage of being able to accommodate multiple reaction vessels of different sizes anywhere within the cavity, and will expose every vessel to the same radiation field every time.

Open (reflux) or sealed (high-pressure) vessels can usually be used in both reactor types. In both vessels, microwaves can superheat a solvent. Superheating can be described as raising the temperature of a liquid above its normal boiling point without the liquid changing phase to become a gas. This can

sometimes be achieved in conventionally heated systems, but microwave heating is able to consistently superheat a solvent as a side effect of the ways in which the radiation transfers energy to the system. For a pure solvent, the molecules are heated by the radiation faster than the bulk loses thermal energy but without the formation of boiling nuclei. As no boiling nuclei form, the solvent can be made to boil at 10 – 20 °C higher than expected. As ions and reagents are introduced to form a solution, boiling nuclei will be able to form and the super heating effect will become less pronounced.

In a sealed reaction vessel, this effect is more pronounced as the superheating caused by lack of boiling nuclei is greatly enhanced by the simple mathematical relationship described by the ideal gas law $PV = nRT$: as the temperature of the system increases, so too does the vapour pressure in the head space of the sealed vessel. The increase in vapour pressure prevents the liquid from boiling as there is no extra volume for the liquid to expand into as a gas. Modern vessels are able to withstand very high pressures (>100 atm),[191] allowing many solvents to be heated far in excess of their normal boiling point with any excess pressure being safely vented in a controlled manner. A reflux system is inherently safer as the risk of explosion is mitigated by running the reaction at atmospheric pressure.

The unique way in which microwaves transfer energy to a system was thought to be the reason why reactions can be seen to be influenced by a non-thermal microwave effect. In its simplest form, the rapid and uniform heating of a reaction in a microwave to temperatures in excess of those that can be achieved in traditional systems will have an effect on the kinetics of a reaction, increasing the rate of that reaction. This gives a simple explanation for why microwave reactions can be significantly faster than their conductively heated analogues. Alternatively, the unique microwave heating profile can give rise to unexpected results. Reports exist of reactions performed under microwave heating having a different outcome to when traditional conductive heating is employed, even when the final temperature of the two reactions is the same.[192]

For the monosulfonation of naphthalene (a classic demonstration of kinetic vs thermodynamic control of a reaction), the specific heating profiles obtained using microwave heating of a reaction in a sealed vessel allowed selective synthesis of the 1- or 2-naphthalenesulfonic acid. For a reaction time of only a few minutes, rapid heating using high microwave power gave predominantly the thermodynamic 2-naphthalenesulfonic acid product; slow heating using low microwave power gave predominantly the kinetic 1-naphthalenesulfonic acid. Very fast reactions are required to observe this effect. The slow heating rate gave results in agreement with conventional heating of the reaction using a hot plate. The close relationship between heating rate to a given temperature and relative rates of sulfonation/desulfonation at the 1- or 2- position of naphthalene is what gives rise to this observed difference in product ratio after reduced reaction times (Figure 19).

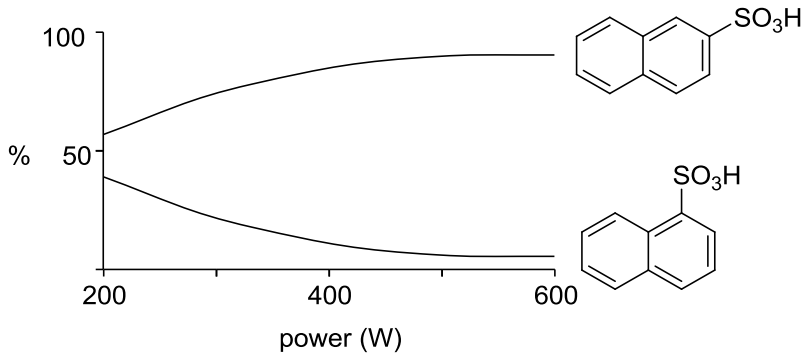



***Figure 19:*** *Ratios of 1- and 2-naphthalenesulfonic acid at different microwave powers.*[192]

For reaction mixtures that do not couple to microwave radiation and therefore will not heat rapidly, silicon carbide can be used as an energy transfer medium. Silicon carbide is a chemically inert ceramic material that couples strongly to microwave radiation. It can be added to a reaction mixture as a powder or doped into a Teflon disk or stirring bar to facilitate the transfer of microwave energy to a reaction mixture. Vessels made from sintered silicon carbide, or inserts for glass or polymer vessels are available. Such SiC vessels have been used to investigate the claims of non-thermal microwave effects:[193] microwave radiation will not penetrate a SiC vessel, but will be totally absorbed by it. The contents of the vessel will therefore be heated by traditional conductive methods. The use of SiC vessels allows the highly controlled delivery of microwave energy, but ensures only conductive heating of the contents occurs. In the report, identical reactions were performed in Pyrex and SiC vessels heated by microwave radiation. It was found that reactions heated directly by the microwave radiation gave exactly the same results as those heated by microwave energy delivered conductively *via* the SiC vessel. The identical results from both sets of reactions showed it was the rapid heating rate to high temperatures inside a microwave reactor that causes truncation in reaction times, not the microwave radiation specifically.

Another modern technology that has received much interest in recent years is continuous flow reactors. In its simplest form, a flow reactor allows a reaction mixture to be continually drawn from attached reservoirs and the solution pumped through a narrow bore tube to allow rapid heating, cooling or irradiation of the reaction mixture when it transits through the reactor cavity. The products will be contained in the solution as it exits the reactor and can be collected for processing (Figure 20).

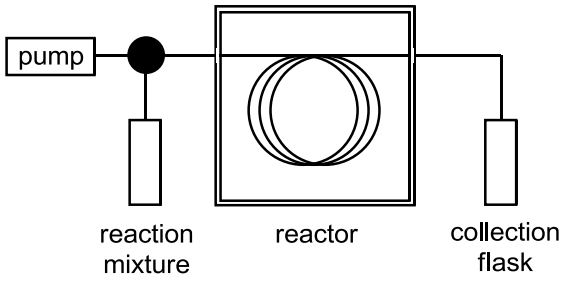



***Figure 20:*** *Flow reactor schematic.*

The use of high-pressure, small-bore reaction tubes allows a similar rapid heating profile and superheating of a solution to be achieved, like is possible with a microwave reactor, but in a purely conductive heating environment. In batch reactions, product output quantity is limited by the size of the reaction vessel. Reactions do not always perform on a large scale as they do in a small bench top experiment. This is due to establishment of thermal and concentration gradients in larger vessels. Inefficient stirring can cause areas of the reaction mixture to have different concentrations of reactants or products. Large externally heated vessels may be significantly cooler in the centre than the periphery.

In flow reactors, premixing of the chemicals and the small bore of the channel through the reactor means there is insufficient cross section for such gradients to be established. As long as chemicals continue to be fed into the flow reactor, product will continue to be generated and collected from the outlet, removing limitations imposed by absolute reactor volume. There is no requirement to halt the reaction to empty product from a vessel, recharge it with new material and start the reaction again.

In a batch context, the use of a large microwave cavity can allow several individual experiments to be run in parallel, often with reaction times approaching minutes or seconds compared to hours or days in conventionally heated systems, allowing the rapid screening of reactions. As demonstrated with the sulfonation of naphthalene, the use of microwaves can also give access to certain reaction pathways that would not normally occur with conventional heating methods.

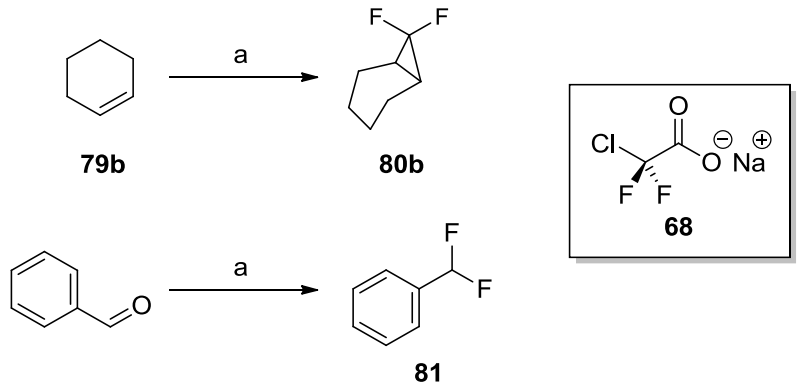
The advantages of rapid microwave heating and high-yielding flow applications are of particular importance and interest to the pharmaceutical industry where efficiency and productivity are critical to a company's success.[194] Microwave and flow reactor technology can be combined. Using this set up it is possible to exploit the highly controllable heating profile and power settings of a microwave and apply it to the continuous synthesis of large volumes of product.[195] This is considered by some to be the best available technology to allow highly controlled, high output chemistry to be conducted.

Several publications now exist that describe the application of microwave energy to heat a reaction, and as more is learned about the technology, the non-thermal microwave effect does appear to be a purely thermal phenomenon that is significantly more efficient than traditional heating methods. Although past claims of an unexplained, non-thermal microwave effect still have subscribers, it is generally believed that early unexplained results were caused by erroneous temperature monitoring of reactions or use of primitive microwave technology.[187]

With the enhancements in reaction performance that may be possible with microwave heating, the development of a new method for the generation of difluorocarbene from existing carbene sources was instigated. An easily handled precursor that is known to decompose to give difluorocarbene upon heating was chosen. Sodium chlorodifluoroacetate (**68**) and sodium bromodifluoroacetate both meet this requirement: **68** was chosen as it is relatively cheap and commercially available.

The common drawbacks associated with existing difluoromethylation procedures using halogenated acetate salts are that they are often slow, energy intensive processes requiring a large excess of the carbene precursor to obtain products in high yields. By exploiting the superior heating characteristics of microwave energy, a significant reduction in reaction time was sought, using fewer equivalents of the carbene source and low boiling-point solvents that will facilitate easier product processing. The use of high-pressure vessels and the superheating effect should facilitate the high temperatures required for these types of reactions. The choice of **68** as the carbene precursor would preclude toxic heavy-metals and ODSs from the method and produce only $CO_2$ and NaCl as benign side products.

In a test experiment based on the first reported reaction of difluorocarbene, **68** was heated in a THF solution using microwave irradiation with cyclohexene (**79b**) as the carbene trap.[145] THF was selected over the 1,2-dimethoxyethane used in the reported method as a solvent that would couple to the microwave radiation was required. Using moderate conditions of 500 W of power heating the system to 150 °C for 15 minutes, the expected product 7,7-difluorobicyclo[4.1.0]heptane (**80b**) was identified in the crude product by $^{1}H$ and $^{19}F$ NMR. The yield was estimated at 8 % based on NMR integration. This was in agreement with that reported for the synthesis of **80b** using conventional heating methods of 11 %. A second test reaction was performed with benzaldehyde as the carbene trap.[196] Using the same microwave conditions as before, (difluoromethyl)benzene (**81**) was identified in the crude reaction product by $^{19}F$ NMR. The yield was not estimated due to the complex nature $^{1}H$ NMR spectra. Satisfied by the qualitative evidence that difluorocarbene can be generated from **68** and effectively trapped when heated using microwave radiation, the method was now optimised (Scheme 89).




***Scheme 89:*** *Test reactions for the generation and trapping of difluorocarbene under microwave heating conditions. Conditions* ***a****: 0.16 mol. eq.* ***68****, THF, 500 W, 150 °C, 15 min.*

Both olefin and aldehyde were seen to be effective carbene traps. The clean conversion of **79b** to **80b** and the large number of examples of *gem*-difluorocyclopropane synthesis from difluorocarbene and olefin prompted their use during the early phase of this investigation. Results from these cyclopropanation reactions would allow the performance of this new method to be directly compared to those previously reported.

A new olefin was chosen to trap difluorocarbene generated using this emerging method. Yields of *gem*-difluorocyclopropane from the electron-rich compound 1,1,2,2-tetramethylethene (**79c**) using other procedures are all consistently high. Cyclohexene, by comparison, is only moderately electron-rich so is not the best alkene to use to trap an electron-deficient carbene.

Solvents were screened that solvated sodium chlorodifluoroacetate but not the sodium chloride by-product. By precipitating out the sodium chloride from the reaction mixture, the options of removing it by filtration or washing of the reaction mixture with water would be assessed. THF, MeCN, EtOAc, acetone and DMSO were identified as suitable solvents with respect to these criteria. With the exception of EtOAc, all can be removed by water during work up to leave the extracted product of the carbene [2+1] cycloaddition.

Using the microwave conditions detailed for the test reactions and a 3:1 stoichiometry of **68**:**79c** all but one of the selected solvents facilitated the carbene reaction to yield the target molecule (**80c**). DMSO should be avoided due to an explosive reaction occurring as soon as the microwave power was applied to the vessel. The highest conversion of **79c** to **80c** was qualitatively observed in THF by comparison of integrals in the $^{1}$H NMR spectra.

Two significant problems were identified with the procedure at this early stage. Although an efficient carbene trap, the volatility of **79c** and **80c** would make development of a work up procedure and accurate quantitation of the reaction challenging. The pressure limit on the CEM Discover microwave reactor in use at the time was also problematic. As a safety feature, if the pressure within the reaction vessel exceeds 300 psi the microwave will abort the experiment. Most experiments had to be repeated several times for this reason: sufficient quantities of $CO_2$ are generated in this procedure to just exceed this 300 psi limit.

To aid accurate quantitation, **79a** (Scheme 89, page 67) was substituted for **79c** as the carbene trap. This aromatic olefin is also reported to give high yields of cyclopropane when combined with difluorocarbene. Importantly, **79a** and **80a** have considerably higher boiling points than **79c** and **80c** making isolation and quantitation easier. A modern Milestone MicroSYNTH reactor was chosen to continue method development with. With an upper pressure limit of 1450 psi and an automatic pressure release mechanism that would not abort the run, $CO_2$ generation was no longer a problem. Optimised conditions were rapidly identified that were a compromise between the shortest possible reaction time and consideration to the longevity of the reactor parts.

Three equivalents of **68** were dissolved in the appropriate volume of a 0.5 mmol mL$^{-1}$ solution of olefin in THF. Fewer than 2.5 equivalents of **68** caused small but significant reduction in conversion of **79a** to **80a**; three equivalents ensured quantitative conversion of the olefin to cyclopropane. The reaction did not require the use of anhydrous reagents, an inert atmosphere or pre-drying of any of the reaction vessel parts, making execution of each experiment operationally straightforward.

A temperature of 170 °C provided a sufficient margin at which quantitative olefin conversion occurred in every experiment. It was established that 150 °C was the minimum temperature that could be tolerated by this reaction without any appreciable reduction in yield of the cyclopropane. At 130 °C cyclopropane was still generated but conversion was low at 33 % after 15 minutes.

The use of 300 W maximum energy was sufficient to rapidly heat the reaction mixture to the target temperature. As expected, higher power settings heated the reaction mixture to the target temperature faster, but in one example where a small volume of reaction mixture was being used, damage to the reactor vessel shield was observed at 700 W. Surplus microwave energy that could not be absorbed by the reaction mixture was absorbed by the reactor parts themselves; 300 W would not cause this damage irrespective of reaction volume but would still allow rapid heating to be achieved. Experiments using 200 W and 100 W showed that lower power settings were unable to heat the reaction mixture above the critical temperature of 150 °C that was previously identified.

Finally, five minutes reaction time was sufficient to allow the target temperature to be reached and held there for a short time (just over one minute in a typical reaction heating profile, Figure 21). This allowed quantitative conversion of **79a** to **80.** Shorter reaction times were acceptable, but five minutes ensured that the reaction should always go to completion. This still represents a significant truncation in time over previously reported procedures. During method development experiments and analysis of aborted runs, it was casually observed that, in most cases, once the vessel contents reached 150°C the reaction appeared to have finished with quantitative conversion of olefin to cyclopropane.

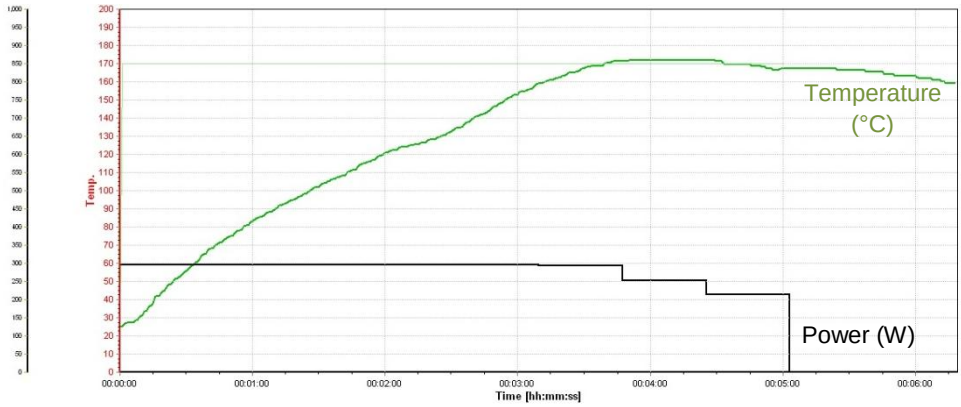
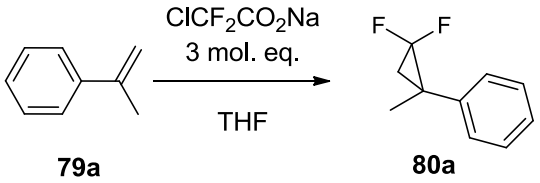



***Figure 21:*** *Typical heating and power profile.*

The optimised conditions for this method are 170 °C, 300 W, 5:00 minutes using a 0.5 mmol $mL^{-1}$ THF solution of olefin to solvate three molar equivalents of **68**. Under these conditions, quantitative conversion of **79a** to **80a** was always observed by $^{1}H$ NMR. Conditions in excess of those stated did not offer any real benefit or improvement to this reaction. Importantly, these conditions also provided sufficient margin of error, providing a robust method to take forward for further investigations. Method optimisation experiments are summarised below (Table 7).

***Table 7:*** *Microwave mediated difluorocyclopropanation: reaction conditions screen.*



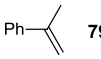
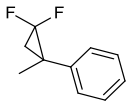
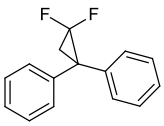
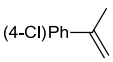
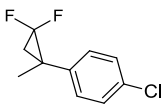
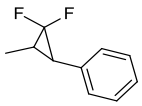
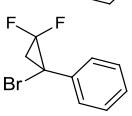

**79a** **80a**

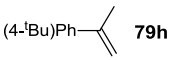
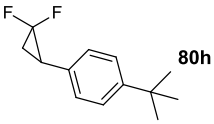
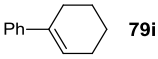
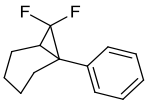
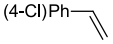
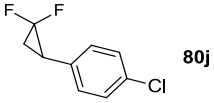
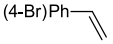
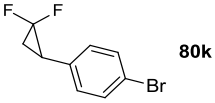
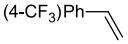
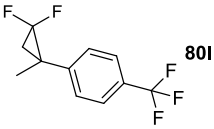
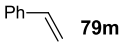
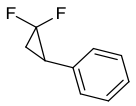
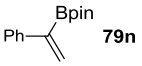
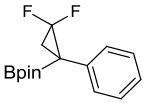
| Entry | Power (W) | Temperature (°C) | Time (minutes) | Conversion (%)[a] |
|---|---|---|---|---|
| **1** | 300 | 170 | 15 | 100 |
| **2** | 300 | 150 | 15 | 99 |
| **3** | 300 | 130 | 15 | 33 |
| **4** | 300 | 170 | 10 | 100 |
| **5** | 300 | 170 | 5 | 100 |
| **6** | 200 | 157[b] | 15 | 100 |
| **7** | 100 | 153[c] | 15 | 84 |
| **8** | 300 | 170 | 5 | 9[d] |
| **9** | 300 | 170 | 5 | 61[e] |

**a**: Conversion calculated by direct comparison of diagnostic starting material and product signals in $^{1}$H NMR of reaction mixture immediately after removal from microwave reactor. **b**: maximum temperature possible with 200 W. **c**: Maximum temperature possible with 100 W. **d**: Conversion with 1 mol. eq. of **68**. Maximum temperature possible was 140 °C **e**: Conversion with 2 mol. eq. of **68**. Maximum temperature possible was 161 °C.

Dilution of the cooled reaction mixture and extraction of the cyclopropane into diethyl ether is the preferred work-up for this method. Filtration-concentration or distillation of the cyclopropane was not as effective or straightforward. Concerns existed about the potentially volatile nature of some of the target cyclopropanes which caused problems during early method optimisation. High boiling-point aromatic olefins were chosen to facilitate efficient recovery of the cyclopropanes and to provide representative yields for this new method. In most instances the crude product was easily purified by column chromatography on silica gel with hexane. The scope of this method with aromatic alkenes is shown below (Table 8).

***Table 8:*** *Microwave mediated difluorocyclopropanation: scope.*

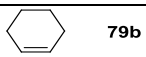
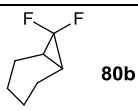
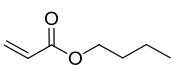
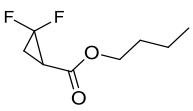
| Entry | Conditions | Olefin 79 | Cyclopropane 80 | Conversion[f] | Isolated yield (%) |
|---|---|---|---|---|---|
| 1 | a |  **79a** |  **80a** | 99 | 75 |
| 2 | a |  **79d** |  **80d** | 100 | 87 |
| 3 | a |  **79e** |  **80e** | 99 | 87 |
| 4 | a |  **79f** |  **80f** | 100 | 78 |
| 5 | a |  **79g** |  **80g** | 97 | 76 |

| | | | | | |
|---|---|---|---|---|---|
| 6 | a |  **79h** |  **80h** | 99 | 75 |
| 7 | a |  **79i** |  **80i** | 100 | 75 |
| 8 | a |  **79j** |  **80j** | 99 | 72 |
| 9 | a |  **79k** |  **80k** | 99 | 71 |
| 10 | a |  **79l** |  **80l** | 95 | 67 |
| 11 | a |  **79m** |  **80m** | 99 | 42 |
| 12‡ | a |  **79n** |  **80n** | 100 | 70 |

Conditions **a**: 6 mmol **68**, 0.5 mmol mL$^{-1}$ **79** in THF 4 mL, 300 W, 170 °C, 5 min. †: Conversion calculated using $^{1}$H NMR. ‡: Bpin = tetramethyldioxaborolane.

The only observed example of an aromatic olefin that was not compatible to the reaction conditions was 4-vinylaniline. This particularly electron-rich and reactive olefin reacted indiscriminately to give a charred black solid. As a means of quantifying any reactions that generated volatile *gem*-difluorocyclopropanes, reaction mixtures were routinely sampled immediately on opening the vessel for quantitative $^{19}$F NMR analysis. This should have facilitated assessment of the reaction success should the products be lost by a significant amount during workup and purification. The difluorocyclopropanation method was applied to a small number of aliphatic olefins, however complications during isolation and purification prevented accurate determination of yields (Table 9).

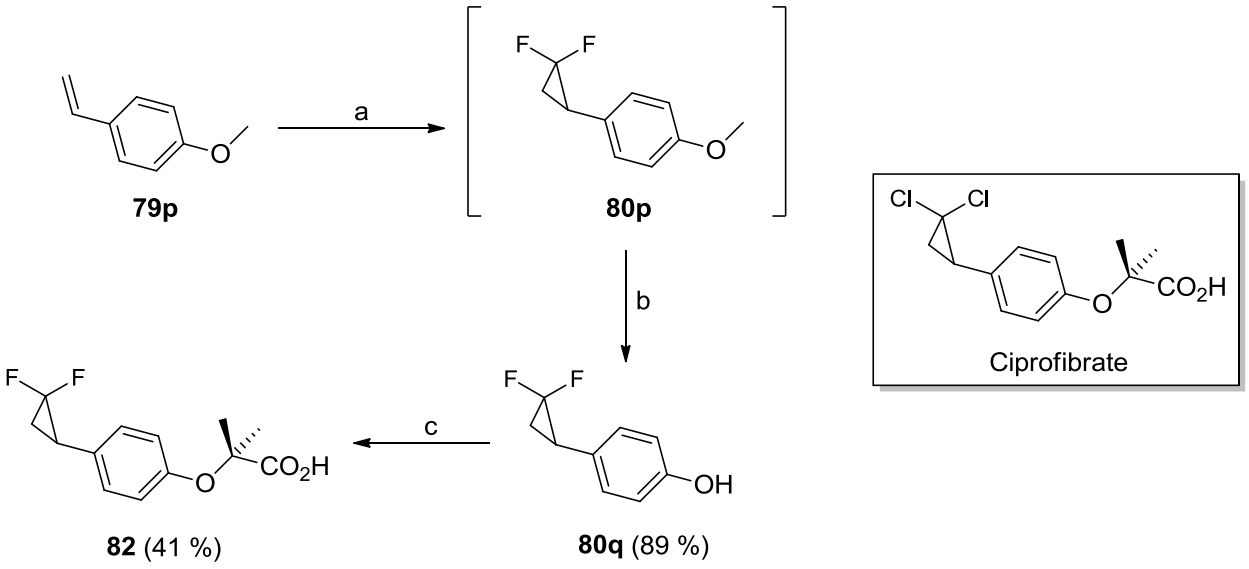
***Table 9:*** *Microwave mediated difluorocyclopropanation: aliphatic olefins*

| Entry | Conditions | Olefin 79 | Cyclopropane 80 | $^{1}$H NMR Conversion (%) | $^{19}$F NMR yield (%) |
|---|---|---|---|---|---|
| 1 | a |  **79b** |  **80b** | -† | 48 |
| 2 | a |  **79c** |  **80c** | 87 | 92 |
| 3 | a |  **79o** |  **80o** | 57 | 49 |

Conditions **a**: 6 mmol **68**, 0.5 mmol mL$^{-1}$ **79** in THF 4 mL, 300 W, 170 °C, 5 min. †: Solvent peak prevents accurate calculation of conversion.

Quantitative $^{19}F$ NMR studies were performed using the eretic calculation function in Topspin in comparison to an external 1,4-difluorobenzene standard. This fluorinated species was chosen specifically as its chemical shift did not fall on the characteristic bulge in the spectra base line associated with the fluorine signal inherent due to the NMR glassware. By comparison to the percentage conversion and isolated percentage yield results, it was apparent that the quantitative $^{19}F$ experiments were not consistent, even when every care had been taken to work with accurately prepared solutions. The figures given in Table 9 are therefore only able to be viewed as an illustration of the technique rather than as a reliable quantitation method, especially when synthesising volatile cyclopropanes that would not be possible to efficiently recover and quantify by conventional means.

The utility of this improved process was demonstrated with the delivery of a pharmacologically-relevant product; thus, an efficient synthesis of the difluoroanalogue[197] of the hyperlipidemia agent Ciprofibrate has been delivered. Difluorocylopropanation of 4-vinyl anisole (**79p**) under the established microwave conditions yields cyclopropane **80p**, which was directly converted to 4-(2,2-difluorocyclopropyl)phenol **80q** in an overall yield of 89%, and then to the *gem*-difluoro Ciprofibrate analogue (**82**) (Scheme 90).

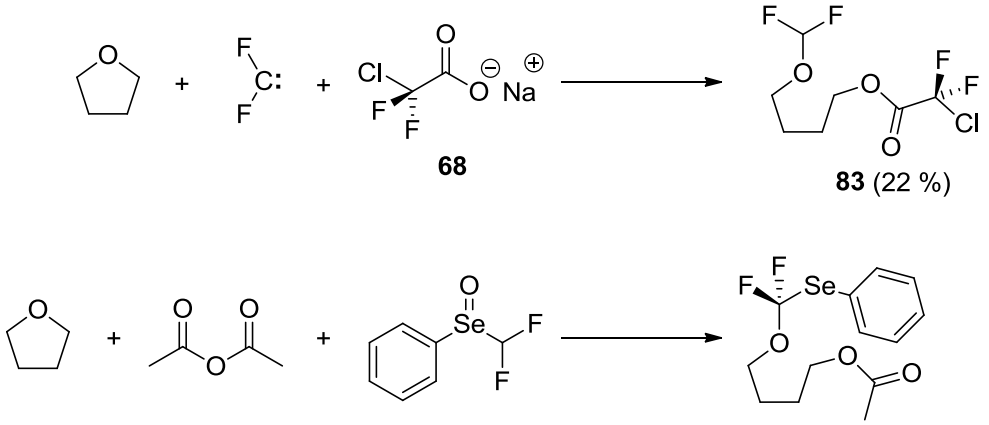



***Scheme 90:*** *Synthesis of Ciprofibrate analogue **82**. Conditions **a**: 3 mol. eq. $ClCF_2CO_2Na$, THF, 300 W, 170 °C, 5 minutes. **b**: $BBr_3$ DCM 89 %. **c**: NaOH, $CHCl_3$, acetone.*

Methods for the conversion of olefins to *gem*-difluorocyclopropanes can also convert alkynes to *gem*-difluorocyclopropenes.[198] The aromatic alkynes 4-ethynyltoluene, 1,2-diphenylacetylene and phenyl acetylene were screened against the established microwave conditions. The reactions with these alkynes did not proceed cleanly. The expected cyclopropenes were confirmed to be present by $^{19}F$ NMR analysis of the crude products but none were able to be isolated. It was not immediately obvious why the microwave-mediated difluorocyclopropenation did not proceed as efficiently, however at this time a second method optimisation process was not a priority.

An unexpected side reaction was identified that would not have been observed if a different solvent had be used for the microwave-mediated difluorocyclopropanation method. In every reaction mixture sample and isolated crude product a set of unidentified peaks were always seen to be present by $^{1}H$ and $^{19}F$ NMR. Initially, only a correlation between the $^{1}H$ triplet δ= 6.21 ppm (*J* 74.5 Hz) and the $^{19}F$ doublet δ= -84.36 ppm (*J* 74.5 Hz) could be made. During attempts to purify the product of the reaction between difluorocarbene and **79p**, the product that accounted for all of the unexpected peaks was isolated. After full characterisation of this compound it was apparent that the excess difluorocarbene and carbene precursor **68** present in the reaction mixture were reacting with THF. This competing reaction was opening the THF ring to yield 4-(difluoromethoxy)butyl 2-chloro-2,2-difluoroacetate (**83**) in 22 % after isolation.

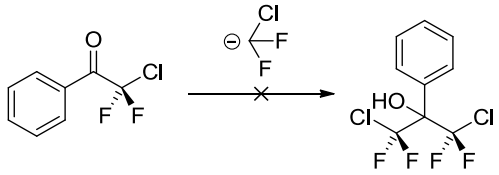
The isolation of the novel compound **83** highlighted a new process that would not be expected to happen with **68** under conventional atmospheric pressure heating conditions. The only other comparable synthesis of fluorinated compounds from THF used a selenoxide reagent and acetic anhydride to effect the ring opening (Scheme 91).[199] It also gave an insight into the mechanism of difluorocarbene generation and reaction in this microwave heated system.




***Scheme 91:*** *Fluorinated compounds from reactions with THF. Top: this investigation.*

Examples of concerted difluorocarbene release from a precursor molecule or *via* dechlorination of chloro(difluoro)methyl anion have both been proposed as the mechanism for the generation or delivery of the carbene species. For example, difluorocarbene generated from chlorodifluoromethane under strongly basic conditions is proposed to liberate difluorocarbene in a concerted manner.[200] Methyl chlorodifluoroacetate has been shown to liberate a chloro(difluoro)methyl anion into solution upon exposure to LiCl.[201] Trapping experiments have shown this to be the case. Sodium salt **68** has been shown to decompose by both pathways depending on the solvent. Kinetic studies in hydroxylic media implied a concerted decomposition to liberate difluorocarbene;[202] studies in non-hydroxylic media suggested that chloro(difluoro)methyl anion is first formed. The chloro(difluoro)methyl anion has also been shown to have a finite lifetime in solution.

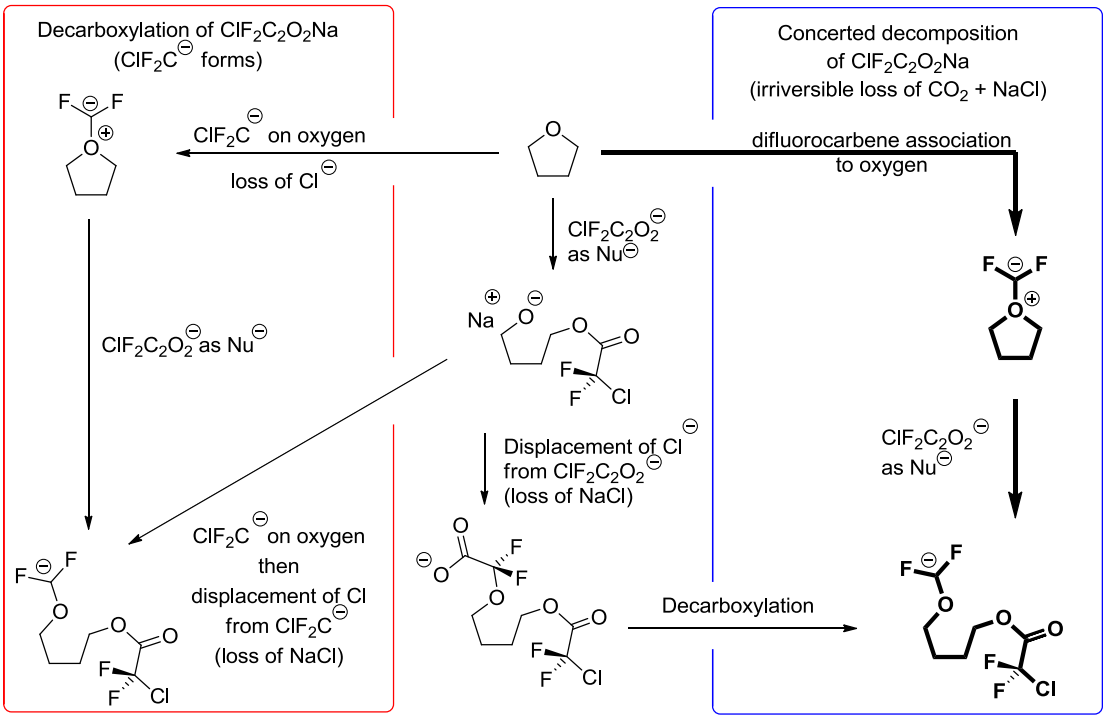
Attempts to identify any transient chloro(difluoro)methyl anion with a known trap for this species did not produce any evidence to support its presence:[201] no 1,3-dichloro-1,1,3,3-tetrafluoro-2-phenylpropan-2-ol was detected when **68** was decomposed under microwave heating conditions in the presence of chlorodifluoroacetophenone (Scheme 92).[203]



***Scheme 92:*** *Chloro(difluoro)methyl anion trapping experiment.*

The ring opening reaction to generate **83** would not be expected to take place in a conductively heated atmospheric pressure system as the temperature of the reaction would be limited to 66 °C. It may be possible to achieve the same reactivity using a sealed reaction tube or steel bomb, but the rapid heating that can be achieved with microwaves would not be possible for such a system, so would not give a direct comparison of the reaction conditions.

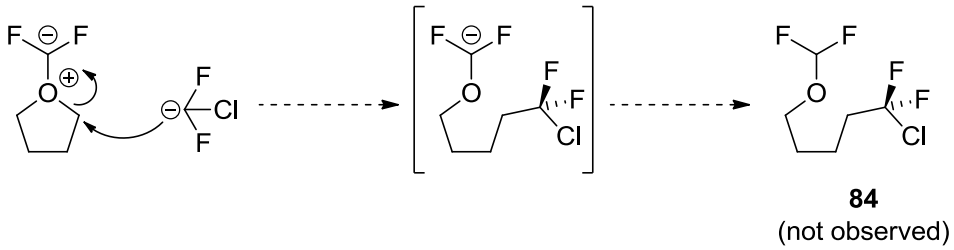
The structure of **83** implies that in the microwave induced decomposition of **68** in THF, difluorocarbene is generated in a concerted manner and the chloro(difluoro)methyl anion is not present in solution. The existence of difluorocarbene in solution is known as the expected *gem*-difluorocyclopropanes from a [2+1] cycloaddition process have been isolated. This proposal, a mechanism for the formation of **86**, and the reasons for chloro(difluoro)methyl anion not being involved are described below (Scheme 93).




***Scheme 93:*** *Possible mechanistic routes for the ring opening of THF by sodium chlorodifluoroacetate with microwave heating. Proposed mechanism is emphasised in bold in the blue box.*

Irrespective of the path to **83**, two molecules of **68** are required to ring open THF in this way. As described in bold in the blue box (Scheme 93), the first equivalent of **68** decomposes in a concerted manner to liberate carbon dioxide, difluorocarbene and chloride ion. The chloride ion is removed from the solution as a precipitate with sodium. The electron-poor difluorocarbene reacts with a lone pair of electrons on the oxygen of THF resulting in the formation of an oxonium ylide.

Reaction of the second equivalent of **68** through the carboxylate oxygen at the THF carbon adjacent to the oxonium ylide oxygen causes *C-O* bond cleavage, generating the difluoromethyl anion of **83**. The solvated sodium ion from the second equivalent of **68** provides the counterion for this species until it undergoes protonation to surrender the product **83**. If the chloro(difluoro)methyl anion was present in solution, it could also act as a nucleophile, attacking the THF carbon adjacent to the oxonium ylide. No evidence for the existence of 1-chloro-2,2-difluoro-5-(difluoromethoxy)pentane (**84**) in the reaction product was found (Scheme 94).




***Scheme 94:*** *Proposed mechanism towards **84**.*

If this pathway is correct, further proposals about the relative reaction rates of each step can be made; these are based on the observed quantitative conversion of olefin to cyclopropane, and the fact that **83** is the only detected side product. First, the rate of difluorocarbene liberation from the decomposition of **68** is slow enough that there is a concentration of carbene and **68** present in the reaction mixture at any given time during the reaction. If all **68** decomposed rapidly, no carboxylate would be present to provide the corresponding motif in **83**.

Second, the presence of carbene and carboxylate in solution would imply that oxonium formation is slower than carboxylate attack. If carboxylate attack was slow, it would be present in solution for long enough to decompose to give more carbene, and not react with the oxonium species, thus removing itself from the reaction medium as part of the stable product **83**. This also further implies the oxonium ylide is activated enough to allow the weakly nucleophilic carboxylate anion to be a good nucleophile.

Finally, the low yield of **83** compared to the quantitative conversion of olefin to cyclopropane would imply the reaction of carbene with olefin is faster than with THF, even though THF is in massive excess compared to all other reaction components.

The alternative routes shown in Scheme 93 are believed to be less probable. It is doubtful that difluorocarbene is delivered in the form of a carbene equivalent *via* chloro(difluoro)methyl anion (red box).

This would first require the decarboxylation of **68** to release chloro(difluoro)methyl anion into solution. The electronegative oxygen of THF would then have to react with this anionic species to displace chloride giving the oxonium intermediate.

Alternatively, and as could be observed if **68** was heated in THF under conventional reflux conditions, where the lack of sufficient thermal energy should not cause decomposition, the carboxylate would first have to react with THF to ring open the cyclic ether giving a sodium alkoxide-type intermediate. Two possible steps are now possible. The first, related to the chloro(difluoro)methyl anion pathway mentioned above, would require this anion to react with the alkoxide oxygen, displacing chloride from the chloro(difluoro)methyl anion to yield the **83** anion. The alternative is that the alkoxide reacts as a nucleophile, displacing chloride from the second equivalent of **68**. This di-acetate species with a terminal carboxyl group now undergoes decarboxylation to yield the **83** anion. This hypothesis could be tested by heating **68** in THF under atmospheric reflux conditions, once using conventional conductive heating and once using microwave heating to ensure that any differences due to the heating method are accounted for.

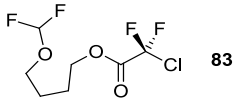
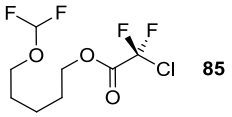
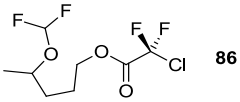
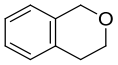
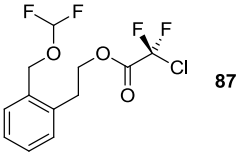
It is of course possible that upon formation, difluorocarbene could be dimerising or trimerising to give inert by-products. As tetrafluoroethene and perfluorocyclopropane are both gaseous species, they are unsurprisingly not observed in these reactions, and thus these side reactions cannot be proven with the results available to this investigation. Experiments to quench the postulated anion of **83** with an electrophile (allyl bromide) did not give rise to the allyl analogue of **83**, implying that the product anion is quenched rapidly *in situ* by adventitious protium.

Other cyclic ethers were also shown to undergo ring opening under conditions similar to those used when generating *gem*-difluorocyclopropanes. Similar 1.5 mmol $mL^{-1}$ solutions of **68** in THF, 2-methyl THF and tetrahydropyran were prepared. As **68** is not soluble in isochroman, a 0.5 mmol $L^{-1}$ of isochroman in EtOAc was used to solvate three equivalents of the precursor. EtOAc has been shown to be unreactive towards **68** under such microwave conditions. All four solutions were exposed to microwave radiation of up to 300 W at 160 °C for 5 minutes. The reduction in temperature from 170 to 160 °C was necessary so that all four reaction mixtures could be rapidly heated to a temperature that they could all be maintained at for the remainder of the experiment.

The ring-opened products were tentatively identified in the crude reaction products by $^{1}H$ and $^{19}F$ NMR (Table 10). For THF, tetrahydropyran and 2-methyl THF the products of ring opening (**83**, **85** and **86** respectively) were all isolated in low yield. 2-Methyl THF was seen to undergo ring-opening exclusively at the less hindered C5 carbon. None of the C2 ring opened isomer was detected or isolated. The ring-opened isochroman derivative **87** was not able to be isolated by column chromatography and was suspected to have decomposed soon after workup and purification attempts. **83**, **85** and **86** were also seen to be unstable, but decomposed over days when stored in the fridge as opposed to over minutes in the case of **87**. From analysis of the crude reaction product, it was not clear if isochroman had been ring-

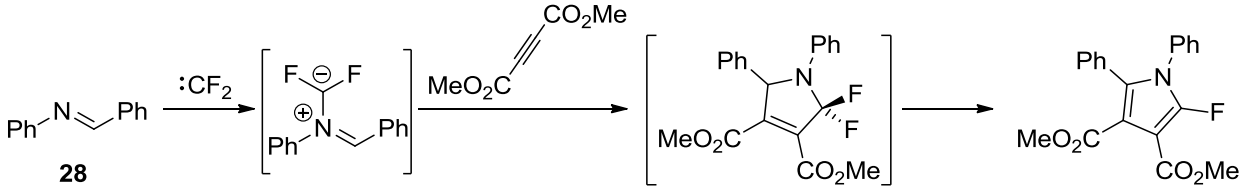
opened at C2 or C6. It was expected the slightly less hindered C6 position would be the site of ring-opening, although a mixture of isomers would not be surprising should they be isolated in future studies.

***Table 10:*** *Microwave mediated ring opening of cyclic ethers.*

| Entry | Conditions | Cyclic ether | Product | Yield % |
|---|---|---|---|---|
| 1 | a |  |  **83** | 22 |
| 2 | a |  |  **85** | 22 |
| 3 | a |  |  **86** | 20 |
| 4 | b |  |  **87** | - |

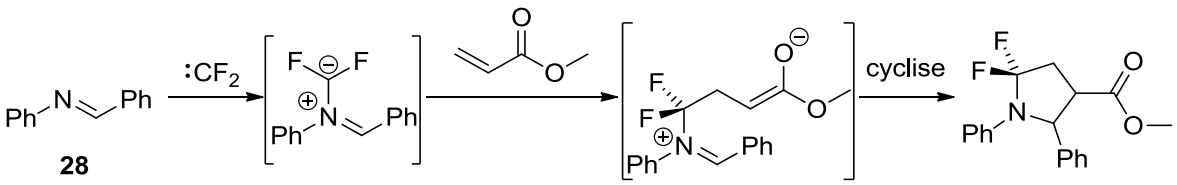
Conditions: **a**: 6 mmol **68**, 4 mL reagent, 300 W, 160 °C, 5 min. **b**: 6 mmol **68**, 2 mmol reagent, 4 mL EtOAc, 300 W, 160 °C, 5 min.

Drawing on aspects of two previously mentioned investigations, and based on the reported reaction between Schiff base **28**, difluorocarbene and dimethyl acetylenedicarboxylate (Scheme 95),[204] a one-pot three-component reaction between imine, olefin and difluorocarbene to generate a functionalised pyrollidine ring using a microwave mediated protocol was proposed (Scheme 96). The reactivity of difluorocarbene with olefins under microwave heating conditions has been clearly demonstrated. The reactivity of **28** was only tentatively shown with difluorocarbene generated from phosphonate precursor **71** under cold basic aqueous conditions (Scheme 79, page 62). In the proposed reaction, difluorocarbene was to be generated under comparatively forcing conditions from **68**, facilitating its reaction with **28**.



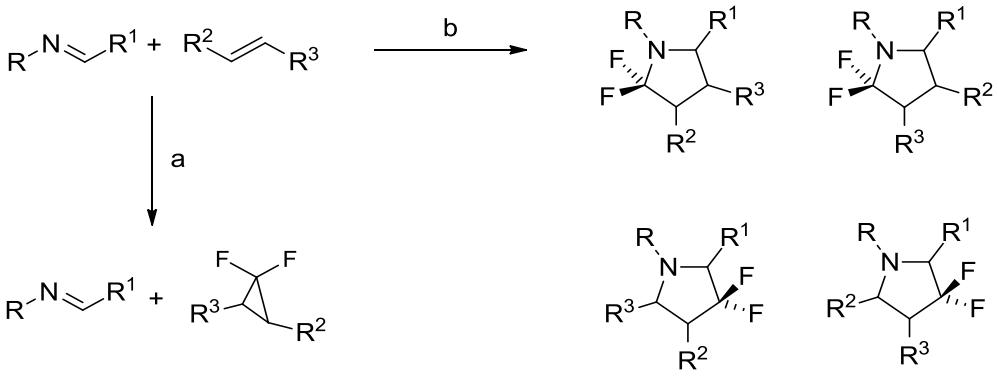

***Scheme 95:*** *Three-component reaction between imine, carbene and olefin, including proposed transition states.*[139]

Difluorocarbene is expected to react with the imine nitrogen lone pair first, forming an iminium ylide. In the presence of an olefin with an electron withdrawing group, such as methyl acrylate, this ylide would react at the δ+ end of the olefinic bond. The final step will require the enolate to cyclise onto the iminium *C=N*, closing the ring and neutralising the charge on nitrogen to generate a substituted pyrollidine (Scheme 96). Following a successful reaction, the *gem*-difluoro group may hydrolyse, leaving a carbonyl motif in its place.




***Scheme 96:*** *Proposed reaction between difluorocarbene, imine and olefin.*

The potential for a competing reaction pathway forming cyclopropane exclusively is a possibility with the reaction. More than one isomer of product may be generated depending on the electronic nature of the imine and olefin. Although doubtful based on observations from previous investigations, it would be unwise to exclude the possibility that difluorocarbene could be delivered *via* the chloro(difluoro)methyl anion. This species would be expected to attack at imine *C*, which gives rise to further isomers of product (Scheme 97).




***Scheme 97:*** *Proposed three component reaction between imine, difluorocarbene and olefin.**a**: competing reaction to generate cyclopropane exclusively **b**: potential isomers of product.*

*N*-benzylideneaniline was taken in THF solution with an equivalent of olefin and three equivalents of **68**. Reactions with methyl acrylate, butyl acrylate, styrene and 2-phenylpropene were heated to 160 °C for 5 minutes with 300 W. In every reaction only imine and the associated *gem*-difluorocyclopropane were detected in the crude products. Increasing the loading of imine did not change this outcome.

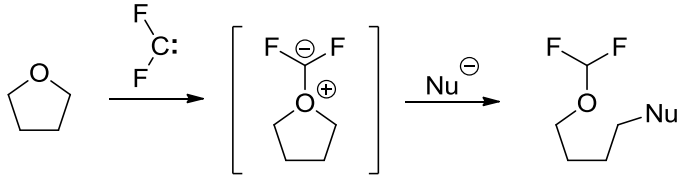
## 2.3 Conclusions

The investigation to increase the number of methods to synthesise *gem*-difluoroaziridines in one step by the reaction of difluorocarbene with imines was not successful. Difluorocarbene generated from diethyl(bromodifluoromethyl)phosphonate under basic aqueous conditions did not react with imines to give azetidines. Later investigations into three component reactions involving imine, olefin and difluorocarbene using the thermal decomposition reaction of sodium chlorodfluoroacetate to generate difluorocarbene in an organic solvent did not show any reaction occurring between carbene and imine. To progress this investigation, alternative imines could be used that have electron withdrawing groups at the imine carbon. This pattern of functionalisation on imine is what was used in the only reported example of difluorocarbene [2+1] cycloaddition to such systems.

In the investigation to develop a new class of transition-metal sensitive difluorocarbene precursor, two candidate molecules based on existing difluorocarbene precursors were synthesised. Allyl-2-(fluorosulfonyl)-2,2-difluoroacetate was not sensitive to substoichiometric $Pd(PPh_3)_4$. Allyl chlorodifluoroacetate was sensitive to substoichiometric $Pd(PPh_3)_4$, decomposing in the expected manner to generate difluorocarbene; this was trapped with an olefin giving the corresponding *gem*-difluorocyclopropane. No reaction was observed when the experiments were performed in the absence of the metal species. The next step in this investigation would require extensive method optimisation from the first pass reaction reported herein. The suspected dependency of the precursor on a stoichiometric loading of metal complex must be addressed also. If this is found to be the case, addition of a suitable compound that will convert the allylpalladium complex back into the catalytic species will be required.

Finally, the investigation with the goal of developing a new difluorocarbene-generating method using existing precursors has delivered an easily performed microwave-mediated procedure for the addition of difluorocarbene to olefins. This method offers greatly reduced reaction times, employs easily removed, low boiling-point solvents and uses a source of difluorocarbene that has comparatively low toxicity and is not an ozone depleting substance. The method was able to convert a broad range of aromatic and aliphatic olefins to the corresponding *gem*-difluorocyclopropanes, most of which were also able to be isolated and quantified. The synthetic use of this method was also exemplified by the successful synthesis of the fluorinated analogue of the hyperlipidemia agent Ciprofibrate.

The microwave assisted synthesis method was tentatively shown to add difluorocarbene to alkynes, yielding the expected *gem*-difluorocyclopropenes. Although the expected products were identified in the crude products, the conversions were not clean and the method will require further optimisation if it is to be used for this reaction. Furthermore, the discovery of the side reaction between difluorocarbene and carbene precursor **68** with the THF solvent of microwave mediated cyclopropanation procedure showed the novel ring-opening of cyclic ethers to generate unique polyhalogenated compounds. Although yields were low, the compounds were easily isolated. This reaction is believed to be unique to the microwave procedure described here. The ring-opening of cyclic ethers provides evidence to support the existence of free difluorocarbene in solution also. It would be of interest to perform these ring opening reactions in the presence of other nucleophiles to see if the corresponding fluorinated ethers can be generated (Scheme 98). The microwave method will again require optimisation if the scope and limitations of this reaction are to be fully explored.




***Scheme 98:*** *Proposed ring opening of cyclic oxonium by nucleophiles.*

## CHAPTER 3: EXPERIMENTAL

All chemicals were supplied by Sigma Aldrich, Alfa Aesar and Fisher Scientific and were used as received. Hexane, dimethylformamide (DMF), toluene, benzene and cyclohexane were purchased anhydrous. THF and $Et_2O$ were distilled from sodium benzophenone ketyl radical. MeCN and MeOH were distilled from calcium hydride. Dichloromethane (DCM), *tert*-butanol and chloroform were distilled from calcium sulfate.[205] All experiments were performed in oven-dry glassware under a protective atmosphere of nitrogen (dried by passage through anhydrous phosphorus pentoxide) as required.

All column chromatography was performed using Fisher silica gel, 60 Å pore size, 230-400 mesh, 40-63 µm. All thin layer chromatography (TLC) analysis was performed using silica gel on Merck aluminium TLC silica gel plates, 60 with 254 nm fluorescent indicator, with visualisation by fluorescence quenching using 254 nm light or staining with potassium permanganate solution.

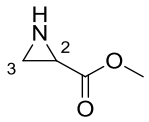
All melting points (Mp) were obtained using a Stuart SMP10 melting point instrument and are uncorrected.

Nuclear magnetic resonance (NMR) data were acquired using a Bruker Avance 400 or 500 MHz spectrometer with samples dissolved in an appropriate deuterated solvent. Chemical shifts ($\delta_H$) for hydrogen are expressed in parts per million (ppm) relative to tetramethylsilane (0.0 ppm). Chemical shifts for carbon ($\delta_C$) are reported in parts per million relative to the carbon resonances of the residual solvent peak. Chemical shifts for fluorine ($\delta_F$) are reported in parts per million relative to an external 1,1,1-trifluorotoluene reference. Chemical shifts for phosphorus ($\delta_P$) are reported in parts per million relative to an external $H_3PO_4$ reference. NMR results are reported as singlet (s), doublet (d), triplet (t), quartet (q) or combinations thereof, or multiplet (m). Coupling constants (J) are expressed in Hz and rounded to the nearest 0.1 Hz.

All Fourier transform infra-red (FTIR) data acquired as thin films using a Thermo Electron Corporation Nicolet 380 FTIR with Smart Orbit diamond window instrument with wavenumbers ($\nu_{max}$) being reported in $cm^{-1}$.

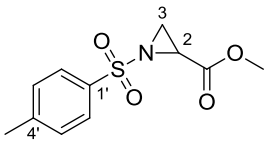
Mass spectrum (MS) data exploiting electron impact ionization in the positive mode ($EI^+$) was acquired using an Agilent Technologies 7890A GC System (Agilent Technologies 30 m × 0.250 mm, 0.25 µm film) with on-line Agilent Technologies 5975B inert XL EI/CI MSD. MS data exploiting electrospray ionisation in the positive mode ($ESI^+$) was acquired using a Bruker MicrOTOF-Q spectrometer or Thermo Scientific LTQ Orbitrap XL spectrometer with direct injection.

Methyl aziridine-2-carboxylate ***rac*-1d**:[54]



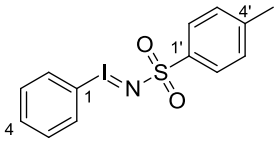

Ammonia gas was bubbled through a solution of methyl 2,3-dibromopropionate (1.18 g, 4.8 mmol) in MeCN (20 mL) at -20 °C with stirring for 6.5 hours. Excess ammonia was removed from the mixture *via* a stream of $N_2$ at room temperature for 1.25 hours. The mixture was filtered and the filtrate evaporated *in vacuo* to give a yellow oil (504 mg) which was purified by column chromatography (4:1 v/v DCM: $Et_2O$) to yield methyl aziridine-2-carboxylate as an unstable clear yellow volatile oil (158 mg, 32 %): $R_f$= 0.47 (4:1 v/v DCM:$Et_2O$); $^1$H NMR (400 MHz, $CDCl_3$) $\delta_H$ 3.70 (*s*, 3H, C-$\underline{H}_3$), 2.46 (*dd, J* 2.0, 4.0 Hz, 1H, 2-$\underline{H}$), 1.93 (*apparent s,* 1H, 3-$\underline{H}$), 1.80 (*d, J* 4.0 Hz, 1H, 3-$\underline{H}$); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta_C$ 172.4 ($\underline{C}$=O), 51.5 (O-$\underline{C}H_3$), 27.7 (2-$\underline{C}$H), 26.1 (3-$\underline{C}H_2$); $\nu_{max}$ (thin film, cm$^{-1}$) 3171, 2952, 2249, 1729 (C=O), 1669 (N-H), 1436, 1203, 1034 ($CO_2$Me), 732; *m/z* (EI$^+$) calculated for $C_4H_7NO_2$ [M$^+$]; 101.1, found 101.1.

Methyl 1-tosylaziridine-2-carboxylate ***rac*-1e**:[54]



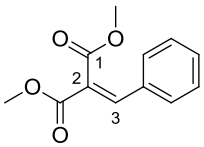

(*N*-(4-tolylsulfonyl)imino)phenyliodinane (410 mg, 1.10 mmol) was added to a stirred solution of $Cu(OTf)_2$ (39.0 mg, 0.10 mmol) and methyl acrylate (463 mg, 5.40 mmol) in MeCN (5 mL) at 25 °C and stirred until all solid was dissolved (ca. 1.5 h dependant on particle size). The mixture was eluted through a plug of silica gel with EtOAc (50 mL) and the solvent removed *in vacuo* to give a dark yellow solid (297 mg) which was purified by column chromatography (3:1 v/v hexane:EtOAc) to yield methyl 1-tosylaziridine-2-carboxylate as a clear yellow oil (133 mg, 49 %): $R_f$= 0.22 (3:1 v/v hexane:EtOAc); $^1$H NMR (400 MHz, $CDCl_3$) $\delta_H$ 7.84 (*d, J* 8.0 Hz, 2H, Ar-$\underline{H}$), 7.36 (*d, J* 8.0 Hz, 2H, Ar-$\underline{H}$), 3.73 (*s,* 3H, O$\underline{C}H_3$), 3.34 (*dd, J* 4.0, 8.0 Hz, 1H, 2-$\underline{H}$), 2.76 (*d, J* 8.0 Hz, 1H, 3-$\underline{H}_2$), 2.56 (*d, J* 4.0 Hz, 1H, 3-$\underline{H}_2$), 2.45 (*s,* 3H, Ar-C$\underline{H}_3$); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta_C$ 167.3 ($\underline{C}$=O), 145.3 (4'-$\underline{C}$), 133.9 (1'-$\underline{C}$), 129.9 (Ar $\underline{C}$H), 128.2 (Ar $\underline{C}$H), 52.9 (O$\underline{C}H_3$), 35.7 (2-$\underline{C}$H), 32.0 (3-$\underline{C}H_2$), 21.7 (4'C-$\underline{C}H_3$); $\nu_{max}$ (thin film, cm$^{-1}$) 1742 (C=O), 1596, 1536, 1494, 1439, 1393, 1328, 1291 (-$SO_2$N=), 1227, (-$SO_2$N=), 1091, 1034, 1018 ($CO_2$Me), 982, 949, 902 (Ar CH); *m/z* (ESI$^+$) calculated for $C_{11}H_{14}NO_4S$ [M+H$^+$]; 256.0638, found 256.0639 (error = 0.2662 ppm).

(*N*-(4-tolylsulfonyl)imino)phenyliodinane **17**:[57]




Diacetoxyiodobenzene (10.6 g, 33.0 mmol) was added *via* solid addition tube to an ice cold solution of 4-toluenesulfonamide (5.66 g, 33.0 mmol) and potassium hydroxide (4.67 g, 83.2 mmol) in MeOH (115 mL) at 0 °C with stirring at 0 °C for 0.5 hours then 3 hours at room temperature. Ice cold water (115 mL) was added and the mixture left to stand overnight. The precipitated crude yellow crystalline solid was collected by suction filtration, recrystallised from MeOH and left to stand at 8 °C for 24 hours. The solid was collected by suction filtration and washed thoroughly with the mother liquor to yield (*N*-(4-tolylsulfonyl)imino)phenyliodinane as a pale yellow crystalline solid (4.46 g, 36 %): Mp: 98 – 100 °C (lit. 102 – 104 °C); $^{1}$H NMR (400 MHz, $CD_3OD$) $\delta_H$ 8.03 (*d, J* 8.0 Hz, 2H, 2/6-H), 7.79 (*d, J* 8.0 Hz, 2H, Ts CH), 7.54 (*t, J* 8.0 Hz, 2H, 3/5-H), 7.35 (*d, J* 8.0 Hz, 2H, Ts CH), 7.14 (*t, J* 8.0 Hz, 1H, 4-H), 2.42 (*s,* 3H, Ts $CH_3$); $^{13}$C NMR (100 MHz, $CD_3OD$) $\delta_C$ 144.2 (1'-C), 144.1 (4'-C), 132.0 (1-C), 130.5 (2/6-CH), 129.9 (4-CH), 129.0 (Ts CH), 127.2 (3/5-CH), 125.7 (Ts CH), 21.4 ($CH_3$); $\nu_{max}$ (solid, cm$^{-1}$) 1592, 1493, 1468, 1444, 1265 (-$SO_2$N=), 1130 (-$SO_2$N=), 1078 (S=O), 988, 859 (Ar CH); *m/z* (ESI$^+$) calculated for $C_{13}H_{13}NO_2IS$ [M+H$^+$]; 373.9706, found 373.9703 (error = -0.8356 ppm).

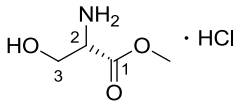
Dimethyl 2-benzylidenemalonate **21**:[62]




Benzaldehyde (6.32 g, 60.0 mmol), dimethyl malonate (6.59 g, 50.0 mmol) and piperidine (0.42 g, 5.00 mmol) were stirred at reflux in benzene (250 mL) with a Dean-Stark apparatus for 18 hours, then cooled to room temperature and added to well-stirred cold aqueous hydrochloric acid (5 % w/v, 50 mL) covered in $Et_2O$ (100 mL). The organic layer was removed and washed with water (100 mL), brine (100 mL), dried over anhydrous magnesium sulfate and concentrated *in vacuo* to give a yellow oil (11.3 g) which was purified by column chromatography (4:1 v/v petroleum ether 60-80:EtOAc) to yield dimethyl 2-benzylidenemalonate as a white crystalline solid (5.70 g, 52 %): $R_f$= 0.44 (4:1 v/v petroleum ether 60-80:EtOAc); Mp: 42-43 °C; $^{1}$H NMR (400 MHz, $CDCl_3$) $\delta_H$ 7.78 (*s,* 1H, 3-H), 7.44-7.38 (*m,* 5H, Ar CH), 3.85 (*s,* 6H, $OCH_3$); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta_C$ 167.1 (C=O), 164.5 (C=O), 143.0 (3-CH), 132.8 (2-C), 130.7 (Ar CH), 129.4 (Ar CH), 128.9 (Ar CH), 125.5 (Ar C), 52.7 ($OCH_3$); $\nu_{max}$ (thin film, cm$^{-1}$) 1722 (C=O), 1625, 1576, 1497, 1434, 1374, 1322, 1293 (C=C), 1257,

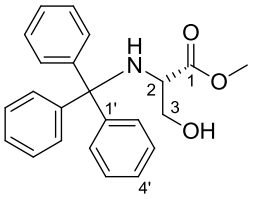
1214, 1198, 1105, 1081, 1060 ($CO_2Me$), 1001, 982, 938, 865, 830 (Ar CH); *m/z* ($ESI^+$) calculated for $C_{12}H_{12}O_4$ $[M+H^+]$; 221.08133, found 221.0808 (error = -0.0434 ppm).

(*S*)-methyl 2-amino-3-hydroxypropanoate hydrochloride **32**:[73]




Acetyl chloride (50.0 g, 635 mmol) was added gradually to MeOH (350 mL) at 0 °C with stirring, followed 10 minutes later by *L*-serine (24.5 g, 235 mmol) and the mixture heated at reflux for 3.5 hours. The solvent was removed *in vacuo* to give the crude product as a white solid (75.5 g) which was recrystallised from MeOH to yield (*S*)-methyl 2-amino-3-hydroxypropanoate hydrochloride as a white crystalline solid (30.7 g, 84 %): Mp: 176 – 177 °C (lit. 163 – 165 °C); $^1$H NMR (400 MHz, $CD_3OD$) $\delta_H$ 4.18 (*t, J* 4.0 Hz, 1H 2-H), 4.10-3.95 (*m,* 2H, 3-H), 3.87 (*s,* 3H, $OCH_3$); $^{13}$C NMR (100 MHz, $CD_3OD$) $\delta_C$ 168.0 (C=O), 59.3 (3-$CH_2$), 54.7 (2-CH), 52.3 ($OCH_3$); $\nu_{max}$ (solid, $cm^{-1}$) 3340.2 (N-H), 2919.4 (O-H), 2662.3, 2636.0, 2549.3, 2357.8, 1746.0 (C=O), 1590.6 (N-H), 1505.8, 1471.7, 1441.9, 1431.4, 1381.8, 1344.2, 1296.0, 1248.7, 1209.2 (OMe), 1156.9, 1124.9 (C-N), 1093.2 ($CO_2Me$), 1037.4, 899.8, 889.1, 843.9, 793.7, 740.6, 561.4, 516.6; *m/z* ($EI^+$) calculated for $C_4H_{10}NO_3$ $[M+H^+]$; 120.07, found 120.07.

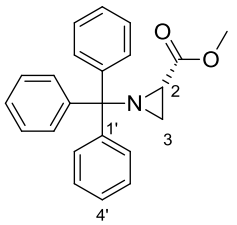
(*S*)-methyl 3-hydroxy-2-(tritylamino)propionate **33**:[72]




$NEt_3$ (40.5 g, 400 mmol) and a solution of trityl chloride (55.3 g, 200 mmol) in DCM (120 mL) were sequentially added dropwise to a suspension of (*S*)-methyl 2-amino-3-hydroxypropanoate hydrochloride (30.7 g, 198 mmol) in DCM (400 mL) at 0 °C stirred for 11 hours. The reaction mixture was filtered and the solvent removed *in vacuo* to yield an off-white powder which was dissolved in EtOAc (1.0 L). The solution was washed with sodium hydrogen carbonate (1.0 M aqueous solution, 200 mL), citric acid (10 % w/v aqueous solution, 200 mL) and water (200 mL), dried over anhydrous sodium sulfate and concentrated *in vacuo* to give a white powder (75.3 g) which was recrystallised from EtOAc:hexane (1:1 v/v) to yield (*S*)-methyl 3-hydroxy-2-(tritylamino)propionate as a white crystalline solid (43.3 g, 60 %): Mp: 155 – 156 °C (lit. 152 – 154 °C); $^1$H NMR (400 MHz, $CDCl_3$) $\delta_H$ 7.50-7.24 (*m*, 12H, 2'/3'/5'/6'-H), 7.19 (*tt*, *J* 1.0, 6.5 Hz, 3H, 4'-H), 3.73-3.68 (*m*, 1H, 2-H), 3.59-3.51

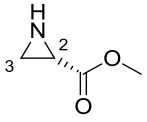
(*m,* 2H, 3-$\underline{H}_2$), 3.30 (*s,* 3H, O$\underline{CH}_3$); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta_C$ 173.9 ($\underline{C}$=O), 145.6 (1'-$\underline{C}$), 128.8 (Ar $\underline{C}$H), 128.0 (Ar $\underline{C}$H), 126.6 (4'-$\underline{C}$H), 71.0 ($\underline{C}Ph_3$), 65.0 (3-$\underline{C}H_2$), 57.8 (2-$\underline{C}$H), 52.0 (O$\underline{C}H_3$); $\nu_{max}$ (solid, $cm^{-1}$) 3453.6 (N-H), 3353.7 (O-H), 1701.1 (C=O), 1594.7, 1479.7, 1443.9, 1423.5, 1367.9, 1331.9, 1225.6, 1207.2, 1171.1, 1126.1, 1068.4 ($CO_2$Me), 1054.9 (C-OH), 1027.7, 1010.6, 963.8, 937.5, 916.8, 893.2, 859.8, 770.0, 753.4, 715.1, 697.1, 635.6, 610.8, 547.1, 497.6, 482.3, 462.2 (Ar CH); *m/z* (ESI$^+$) calculated for $C_{23}H_{23}NO_3Na$ [M+$Na^+$]; 384.1576, found 384.1570 (error = -0.0746 ppm).

(*S*)-methyl 1-tritylaziridine-2-carboxylate **34**:[77]



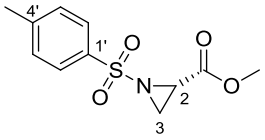

$NEt_3$ (2.23 g, 22.0 mmol) and methane sulfonyl chloride (1.15 g, 10.1 mmol) were added dropwise to a solution of (*S*)-methyl 3-hydroxy-2-(tritylamino)propionate (3.61 g, 10.0 mmol) in THF (50 mL) and the mixture stirred at room temperature for 0.5 hours then at reflux for 42 hours. The mixture was cooled to room temperature and the solvent removed *in vacuo* to yield a pale brown slurry which was dissolved in EtOAc (50 mL). The solution was washed with citric acid (10 % w/v aqueous solution, 3 x 10 mL), $NaHCO_3$ (saturated aqueous solution, 3 x 10 mL), dried over anhydrous magnesium sufate and concentrated *in vacuo* to give a pale yellow solid (2.98 g) which was recrystallised from MeOH (50 mL: 15 drops MeOH: $NEt_3$) to yield (*S*)-methyl 1-tritylaziridine-2-carboxylate as a white crystalline solid (2.41 g, 70 %): Mp: 135 – 136 °C (lit. 122 – 124 °C); $^1$H NMR (400 MHz, $CDCl_3$) $\delta_H$ 7.51-7.19 (*m*, 15H, Ar C$\underline{H}$), 3.76 (*s,* 3H, O$\underline{CH}_3$), 2.25 (*dd, J 2.0, 3.0 Hz,* 1H, 3C-$\underline{H}_2$), 1.89 (*dd, J 3.0, 6.0 Hz,* 1H, 2-$\underline{H}$), 1.41 (*dd, J* 2.0, 6.0 Hz, 1H, 3-$\underline{H}_2$); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta_C$ 172.0 ($\underline{C}$=O), 143.6 (1'-$\underline{C}$), 129.4 (Ar $\underline{C}$H), 127.7 (Ar $\underline{C}$H), 127.0 (Ar $\underline{C}$H), 74.4 ($\underline{C}Ph_3$), 52.2 (O$\underline{C}H_3$), 31.7 (2-$\underline{C}$H), 28.7 (3-$\underline{C}H_2$); $\nu_{max}$ (solid, $cm^{-1}$) 1745 (C=O), 1595, 1489, 1440, 1393, 1289, 1265, 1242, 1199, 1178 ($CO_2$Me), 1080 (C-N), 1034, 1014, 972, 926, 903, 840, 779, 733, 705, 630 (Ar CH); *m/z* (ESI$^+$) calculated for $C_{23}H_{21}NO_2Na$ [M+$Na^+$]; 366.1470, found 366.1465 (error = -0.0935 ppm).

(*S*)-methyl aziridine-2-carboxylate **(*S*)-1d**:[77]



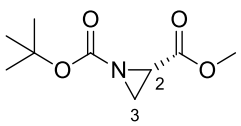
MeOH (25mL) and trifluoroacetic acid (74.5 g, 650 mmol) were added sequentially to (*S*)-methyl 1-tritylaziridine-2-carboxylate (10.3 g, 30.0 mmol) in chloroform (25 mL) at 5 °C and the mixture stirred for 2 hours, the solvent removed *in vacuo* and the residue partitioned between $H_2O$ (200 mL) and $Et_2O$ (200 mL). The ether layer was removed and the aqueous layer made basic by addition of solid $NaHCO_3$ (ca. pH 9). The aqueous layer was extracted with $Et_2O$ (10 x 100 mL), the combined organic extracts dried over anhydrous sodium sulfate and the solvent removed *in vacuo* at 0 °C to yield (*S*)-methyl aziridine-2-carboxylate as a volatile clear yellow oil (3.47 mg, 100 %) that did not require further purification: $^1$H NMR (400 MHz, $CDCl_3$) $\delta_H$ 3.76 (*s,* 3H*,* $OC\underline{H}_3$), 3.31 (*quin, J* 2.0 Hz, 1H, 2-H), 2.59 (*dd, J* 3.0, 6.0 Hz, 1H, 3-$\underline{H}_2$), 1.95 (*dd, J* 2.0, 3.0 Hz, 1H, 3-$\underline{H}_2$); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta_C$ 172.4 ($\underline{C}$=O), 51.5 ($O\underline{C}H_3$), 27.7 (2-CH), 26.1 (3-$\underline{C}H_2$); $\nu_{max}$ (thin film, $cm^{-1}$) 3291, 1725 (C=O), 1640 (N-H), 1446, 1395, 1232, 1018 ($CO_2Me$); *m/z* ($ESI^+$) calculated for $C_4H_8O_3$ [$M+H^+$]; 102.0550, found 102.0548 (error= -1.4254 ppm).

(*S*)-methyl 1-tosylaziridine-2-carboxylate **(*S*)-1e**:[54]



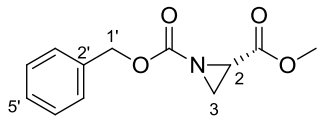

$NEt_3$ (2.98 g, 29.5 mmol) and 4-toluenesulfonyl chloride (2.25 g, 12.0 mmol) were added sequentially to (*S*)-methyl aziridine-2-carboxylate (1.19 g, 11.8 mmol) in chloroform (30 mL) and stirred at -10 °C for 16 hours. The mixture was washed with saturated aqueous $NaHCO_3$ (50 mL), $H_2O$ (50 mL), dried over anhydrous sodium sulfate and concentrated *in vacuo* to give a yellow oil (1.90 g) which was purified by column chromatography (7:3 v/v hexane:EtOAc) to yield (*S*)-methyl 1-tosylaziridine-2-carboxylate as a clear colourless oil (807 mg, 68 %): $R_f$= 0.42 (7:3 v/v hexane:EtOAc); $^1$H NMR (400 MHz, $CDCl_3$) $\delta_H$ 7.84 (*d, J* 8.0 Hz, 2H, Ar CH), 7.36 (*d, J* 8.0 Hz, 2H, Ar CH), 3.73 (*s,* 3H, $OC\underline{H}_3$), 3.34 (*dd, J* 4.0, 8.0 Hz, 1H, 2-H), 2.76 (*d, J* 8.0 Hz, 1H, 3-$\underline{H}_2$), 2.56 (*d, J* 4.0 Hz, 1H, 3-$\underline{H}_2$), 2.45 (*s,* 3H, Ts $C\underline{H}_3$); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta_C$ 167.3 ($\underline{C}$=O), 145.3 (4'-C), 133.9 (1'-C), 129.9 (Ar CH), 128.2 (Ar CH), 52.9 ($O\underline{C}H_3$), 35.7 (2-CH), 32.0 (3-$\underline{C}H_2$), 21.7 (Ts $\underline{C}H_3$); $\nu_{max}$ (thin film, $cm^{-1}$) 1743 (C=O), 1596, 1494, 1439, 1393, 1328, 1291 (-$SO_2$N=), 1228, 1158, 1091, 1035, 1018 ($CO_2Me$), 981, 903 (Ar CH); *m/z* ($ESI^+$) calculated for $C_{11}H_{13}O_4NSNa$ [$M+Na^+$]; 278.0457, found 278.0459 (error = 0.4257 ppm).

(*S*)-1-*tert*-butoxycarbonyl 2-methoxycarbonyl aziridine **1f**:[78]



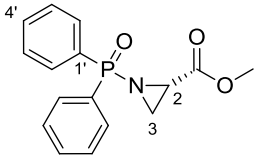
$NEt_3$ (1.02 g, 10.0 mmol) and a solution of *di-tert*-butyldicarbonate (490 mg, 2.30 mmol) in MeCN (1 mL) were added to (*S*)-methyl aziridine-2-carboxylate (206 mg, 2.0 mmol) in MeCN (6 mL) and the mixture stirred at room temperature for 6.5 hours. The solvent was removed *in vacuo* and the residue partitioned between EtOAc (20 mL) and $H_2O$ (10 mL). The aqueous layer was separated and extracted with EtOAc (3 x 20 mL), the combined organic layers washed with brine, dried over anhydrous sodium sulfate and the solvent removed *in vacuo* to give a yellow oil (269 mg) which was purified by column chromatography (7:3 v/v heptane:EtOAc) to yield (*S*)-1-*tert*-butoxycarbonyl 2-methoxycarbonyl aziridine as a clear yellow oil (83.0 mg, 41 %): $R_f$= 0.41 (7:3 v/v heptane:EtOAc); $^1$H NMR (400 MHz, $CDCl_3$) $\delta_H$ 3.78 (*s,* 3H, OC<u>H</u>$_3$), 3.04 (*dd, J* 2.5, 5.0 Hz, 1H, 2-<u>H</u>), 2.53 (*d, J* 2.5 Hz, 1H, 3-<u>H</u>$_2$), 2.41 (*d, J* 5.0 Hz, 1H, 3-<u>H</u>$_2$), 1.46 (*s,* 9H, $^t$Bu C<u>H</u>$_3$); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta_C$ 169.1 (<u>C</u>=O(OCH$_3$)), 159.3 (<u>C</u>=O(O$^t$Bu)), 81.4 (<u>C</u>(CH$_3$)$_3$), 52.6 (O<u>C</u>H$_3$), 34.8 (2-<u>C</u>H), 31.3 (3-<u>C</u>H$_2$), 27.9 ($^t$Bu <u>C</u>H$_3$); $\nu_{max}$ (thin film, cm$^{-1}$) 1724 (C=O), 1440, 1393 ($CMe_3$), 1369 ($CMe_3$), 1328, 1234, 1204, 1153, 1021 ($CO_2Me$), 852, 800; *m/z* (ESI$^+$) calculated for $C_9H_{15}NO_4Na$ [M+Na$^+$]; 224.09, found 224.09.

(*S*)-1-benzyloxycarbonyl-2-methoxycarbonyl aziridine **1g**:[76]



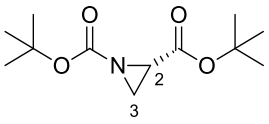

A solution of benzyloxychloroformate (852.0 mg, 5.0 mmol) in DCM (2 mL) was added dropwise with stirring to (*S*)-methyl aziridine-2-carboxylate (252 mg, 2.50 mmol) and $NEt_3$ (1.02 g, 10.1 mmol) in DCM (12 mL) at 0 °C and the resulting mixture left to stand at room temperature for 24 hours. The mixture was washed with $NaHSO_4$ (10 % w/v aqueous solution, 16 mL), $NaHCO_3$ (saturated aqueous solution, 16 mL), brine, dried over anhydrous magnesium sulfate and the solvent removed *in vacuo* to give a solid dispersion in a yellow oil (558 mg) which was purified by column chromatography (2:1 v/v hexane:EtOAc) to yield (*S*)-1-benzyl 2-methyl aziridine-1,2-dicarboxylate as a clear pale yellow oil (284 mg, 48 %): $R_f$= 0.39 (2:1 v/v hexane:EtOAc); $^1$H NMR (400 MHz, $CDCl_3$) $\delta_H$ 7.36-7.25 (*m,* 5H, Ar C<u>H</u>), 5.14 (*s,* 2H, 1'-<u>H</u>$_2$), 3.70 (*s,* 3H, OC<u>H</u>$_3$), 3.09 (*dd, J* 3.0, 5.5 Hz, 1H, 3-<u>H</u>$_2$), 2.59 (*dd, J* 1.0, 3.0 Hz, 1H, 3-<u>H</u>$_2$), 2.47 (*dd, J* 1.0, 5.5 Hz, 1H, 2-<u>H</u>); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta_C$ 168.7 (<u>C</u>=O(OCH$_3$), 160.8 (N-<u>C</u>=O), 140.9 (2'-<u>C</u>), 128.5 (4'/6'-<u>C</u>H), 127.7 (5'-<u>C</u>H), 127.0 (3'/7'-<u>C</u>H), 68.7 (1'-<u>C</u>H$_2$), 52.7 (O<u>C</u>H$_3$), 34.9 (2-<u>C</u>H), 31.4 (3-<u>C</u>H$_2$); $\nu_{max}$ (thin film, cm$^{-1}$) 3356, 1773 (C=O), 1496, 1453, 1396, 1323, 1192, 1080, 1020 ($CO_2Me$), 906 (Ar CH); *m/z* (ESI$^+$) calculated for $C_{12}H_{13}NO_4Na$ [M+Na$^+$]; 258.0737, found 258.0737 (error = 0.1991 ppm).

(*S*)-methyl 1-(diphenylphosphoryl)aziridine-2-carboxylate **1h**:[79]



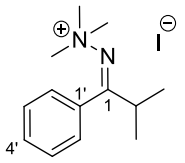

$K_2CO_3$ (2.79 g, 20.0 mmol) was added to (*S*)-methyl aziridine-2-carboxylate (405 mg, 4.0 mmol) in DCM (30 mL) *via* solid addition tube and the mixture stirred for 15 minutes. Diphenylphosphinic chloride (1.04 g, 4.40 mmol) and $NEt_3$ (800 mg g, 8.0 mmol) were added and the mixture stirred at 0 °C for 16 hours. The mixture was filtered and solvent removed *in vacuo* to give an orange gum (1.39 g) which was purified by column chromatography (100 % EtOAc) to yield (*S*)-methyl 1-(diphenylphosphoryl)aziridine-2-carboxylate as a yellow gum (271 mg, 23 %): $R_f$= 0.56 (100 % EtOAc); $^1$H NMR (400 MHz, $CDCl_3$) $\delta_H$ 7.96-7.91 (*m,* 4H, 2'/6'-H), 7.55-7.43 (*m,* 6H, 3'/4'/5'-H), 3.74 (*s,* 3H, $OCH_3$), 2.26 (*dd, J* 1.5, 3.0 Hz, 1H, 2-H), 1.88 (*dd, J 3*.0, 6.0 *Hz,* 1H, 3-$H_2$), 1.41 (*dd, J* 1.5, 6.0 Hz*,* 1H, 3-$H_2$); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta_C$ 169.7 (C=O), 132.2 (4'-CH), 131.6 (2'/6'-CH), 128.7 (3'/5'-CH), 52.6 ($OCH_3$), 32.3 (2-CH), 28.8 (3-$CH_2$); $\nu_{max}$ (thin film, $cm^{-1}$) 3448, 3059, 2954, 1745 (C=O), 1438 (P-$Ph_2$), 1395, 1290 (P=O), 1241, 1196, 1126, 1108, 1017 ($CO_2$Me), 1028, 986 (Ar CH); *m/z* ($ESI^+$) calculated for $C_{16}H_{16}NO_3PNa$ [M+$Na^+$]; 324.0765, found 324.0762 (error = -0.6212 ppm).

(*S*)-1,2-di-*tert*-butoxycarbonyl aziridine **1i**:[78]



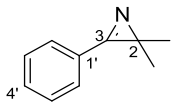

Li$O^t$Bu (1.0 M solution in THF, 3.30 mL, 3.30 mmol) was added dropwise to (*S*)-1-*tert*-butyl 2-methyl aziridine-1,2-dicarboxylate (397 mg, 2.20 mmol) in THF (4 mL) at -78 $^o$C and the mixture stirred for a further 2 hours at -20 °C. The reaction was quenched with saturated aqueous $NaHCO_3$ (30 mL), extracted with EtOAc (3 x 30 mL), the combined organic extracts washed with brine (10 mL), dried over anhydrous sodium sulfate and the solvent removed *in vacuo* to give a yellow oil (362 mg) which was purified by column chromatography (100 % DCM) to yield (*S*)-di-*tert*-butyl aziridine-1,2-dicarboxylate as a clear pale yellow oil (173 mg, 32 %): $R_f$= 0.63 (100 % DCM); $^1$H NMR (400 MHz, $CDCl_3$) $\delta_H$ 2.92 (*dd, J* 3.0, 5.0 Hz, 1H, 2-H), 2.47 (*dd, J* 1.5, 3.0 Hz, 1H, 3-$H_2$), 2.31 (*dd, J* 1.5, 5.0 Hz, 1H, 3-$H_2$), 1.50 (*s,* 9H, $^t$Bu $CH_3$), 1.46 (*s,* 9H, $^t$Bu $CH_3$); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta_C$ 167.5 (C=O), 159.8 (C=O), 82.5 ($C(CH_3)_3$), 81.85 ($C(CH_3)_3$), 35.8 (2-CH), 31.0 (3-$CH_2$), 28.0 ($^t$Bu $CH_3$), 27.9 ($^t$Bu $CH_3$); $\nu_{max}$ (thin film, $cm^{-1}$) 1722 (C=O), 1479, 1458, 1391 ($CMe_3$), 1367 ($CMe_3$), 1328, 1140, 1136 ($CO_2$Me); *m/z* ($ESI^+$) calculated for $C_{12}H_{21}NO_4Na$ [M+$Na^+$]; 266.1363, found 266.1364 (error = 0.6191 ppm).

1,1,1-trimethyl-2-(2-methyl-1-phenylpropylidene)hydrazin-1-ium iodide **36a**:[84]



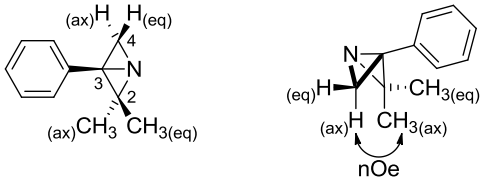

Isobutyrophenone (14.8 g, 100 mmol) and *N,N*-dimethylhydrazine (12.0 g, 200 mmol) were taken neat and stirred at reflux for 72 hours. The resulting aqueous layer was separated and extracted with $Et_2O$ (3 x 25 mL), the combined organic layers dried over anhydrous magnesium sulfate and the solvent removed *in vacuo* to furnish a yellow oil. The oil was taken in EtOH (5 mL), iodomethane (49.7 g, 350 mmol) was added and the solution stirred at a gentle reflux (45 °C) for 5.5 hours. The reaction mixture was poured slowly into vigorously stirred $Et_2O$ (300 mL) to give a yellow solid which was filtered and recrystallised from EtOH:EtOAc (1:1 v/v) to yield 1,1,1-trimethyl-2-(2-methyl-1-phenylpropylidene)hydrazin-1-ium iodide as a orange crystalline solid (25.7 g, 77 % ): Mp: 120-122 °C (lit. 138 – 140 °C); $^1$H NMR (500 MHz, $CDCl_3$) $\delta_H$ 7.57-7.54 (*m,* 3H, 3'/4'/5'-H), 7.27-7.25 (*m,* 2H, 2'/6'-H), 3.58 (*s,* 9H, N-$CH_3$), 2.88 (*heptet, J* 4.0 Hz, 1H, 2-H), 1.16 (*d, J* 4.0 Hz, 6H, 3-$CH_3$); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta_C$ 182.4 (C=N), 131.7 (1'-C), 130.6 (Ar CH), 129.3 (Ar CH), 126.6 (2'/6'-CH), 58.1 ($NCH_3$), 41.1 (2-CH), 19.6 (3-$CH_3$); $\nu_{max}$ (solid, cm$^{-1}$) 2969.6 ($NCH_3$), 1627.3 (C=N), 1483.6, 1464.4, 1442.7, 943.9, 823.7, 776.1, 711.0 (Ar CH); *m/z* (ESI$^+$) calculated for $C_{13}H_{21}N_2^+$ [$M^+$-I$^-$]; 205.1705, found 205.1699 (error = -0.24 ppm).

2,2-dimethyl-3-phenyl-2*H*-azirine **14a**:[84]



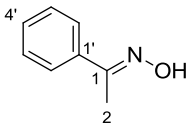

Sodium *tert*-butoxide (720 mg, 7.5 mmol) in *tert*-butyl alcohol (25 mL) at 40 °C was added dropwise (ca. 40 minutes) to 1,1,1-trimethyl-2-(2-methyl-1-phenylpropylidene)hydrazin-1-ium iodide (1.67 g, 5.0 mmol) in *tert*-butyl alcohol (9 mL) at 40 °C with stirring for a further 1.5 hours. The solvent was removed *in vacuo*, the residue taken in water (20 mL) and extracted with $Et_2O$ (3 x 20 mL). The combined organic extracts were dried over anhydrous sodium sulfate and concentrated *in vacuo* to yield 2,2-dimethyl-3-phenyl-2*H*-azirine as a clear yellow oil that did not require any further purification (633 mg, 87 %): $^1$H NMR (400 MHz, $CDCl_3$) $\delta_H$ 7.81 (*d, J* 8.0 Hz, 2H, 2'/6'-H), 7.54 (*t, J* 8.0 Hz, 3H, 3'/4'/5'-H), 1.42 (*s,* 6H, $CH_3$); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta_C$ 177.8 (C=N), 132.5 (Ar CH), 129.1 (Ar CH), 129.0 (2'/5'-CH), 125.9 (1'-C), 33.9 (2-C), 24.6 ($CH_3$); $\nu_{max}$ (thin film, cm$^{-1}$) 2971.0, 2923.4, 1728.0, 1683.0 (C=N), 1615.9, 1489.7, 1458.2, 1447.6 ($CMe_2$), 1372.3, 1256.9, 1198.3, 1169.8, 1133.0, 1070.7, 1085.5, 1020.0, 979.3, 954.5, 924.8, 873.9, 763.7 (Ar CH); *m/z* (ESI$^+$) calculated for $C_{10}H_{12}N$ [$M+H^+$]; 146.0964, found 146.0968 (error = 2.79 ppm).

2,2-dimethyl-3-phenyl-1-azabicyclo[1.1.0]butane **10f:**[44]




nBuLi (2.5 M in hexane, 0.76 mL, 1.99 mmol) was added dropwise to trimethylsulfonium iodide (444 mg, 2.00 mmol) in THF (8 mL) at 0 °C, with stirring for a further 5 minutes. The temperature was reduced to -10 °C and 2,2-dimethyl-3-phenyl-2*H*-azirine (62.7 mg, 0.40 mmol) was added dropwise and the solution stirred at -10 $^{o}$C to 0 $^{o}$C for 1 hour. Ice cold water (9 mL) was added, the organic layer separated and washed with water (10 mL). The combined aqueous layers were extracted with DCM (3 x 30 mL), the combined organic layers dried over anhydrous calcium sulfate and the solvent removed *in vacuo* to yield 2,2-dimethyl-3-phenyl-1-azabicyclo[1.1.0]butane as a clear yellow oil that did not require any further purification (56.5 mg, 87 %): $^{1}$H NMR (400 MHz, $CDCl_3$) $\delta_H$ 7.42-7.30 (*m,* 5H, Ar C<u>H</u>), 2.69 (*d, J* 1.5 Hz, 1H, 'eq' C<u>H</u>$_2$), 2.52 (*d, J* 1.5 Hz, 1H, 'ax' C<u>H</u>$_2$), 1.19 (*s,* 3H, 'ax' C<u>H</u>$_3$), 1.17 (*s,* 3H, 'eq' C<u>H</u>$_3$); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta_C$ 134.8 (Ar <u>C</u>), 128.5 (Ar <u>C</u>H), 128.3 (Ar <u>C</u>H), 127.8 (Ar <u>C</u>H), 68.2 (<u>C</u>-Ph), 54.1 (4-<u>C</u>H$_2$), 41.9 (2-<u>C</u>), 22.9 ('eq' <u>C</u>H$_3$), 12.8 ('ax' <u>C</u>H$_3$); $\nu_{max}$ (thin film, cm$^{-1}$) 1446.1 ($CMe_2$), 1373.5, 1301.2 1235.9, 1161.2, 1024.1, 874.5, 754.3 (Ar CH); *m/z* (ESI$^+$) calculated for $(C_{11}H_{13}N)_2H$ [2M+H$^+$]; 319.2169, found 319.2168 (error = -0.30 ppm).

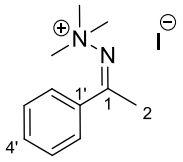
Acetophenone oxime **37**:[85]




Acetophenone (3.60 g, 30.0 mmol) and potassium hydroxide (5.64 g, 50.0 mmol) in water (11 mL) were added sequentially to a solution of hydroxylamine hydrochloride (3.11 g, 45.0 mmol) in MeOH (50 mL). The mixture was stirred at room temperature for 18 hours then diluted with ice cold water (40 mL) and extracted with $Et_2O$ (3 x 30 mL). The combined organic extracts were dried over anhydrous sodium sulfate and the solvent removed *in vacuo* to yield acetophenone oxime as a white crystalline solid that did not require further purification (3.53 g, 87 %): Mp: 64 – 66 °C (lit. 60 – 62 °C); $^{1}$H NMR (500 MHz, $CDCl_3$) $\delta_H$ 9.75 (*s,* 1H, O<u>H</u>), 7.63-7.61 (*m,* 2H, 2'/6'-<u>H</u>), 7.39-7.23 (*m,* 3H, 3'/4'/5'-<u>H</u>), 2.31 (*s,* 3H, 2-<u>H</u>$_3$); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta_C$ 156.0 (<u>C</u>=N), 136.5 (Ar <u>C</u>), 129.2 (2'-<u>C</u>H), 128.5 (Ar <u>C</u>H), 126.0 (Ar <u>C</u>H), 12.2 (2-<u>C</u>H$_3$); $\nu_{max}$ (solid, cm$^{-1}$) 3208.6 (OH), 2917.1, 1496.1

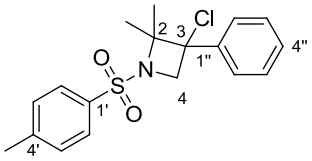
(C=N), 1444.8, 1365.1, 1301.5, 1079.5, 1001.2, 924.1, 758.9, 691.5 (Ar CH); *m/z* ($EI^+$) calculated for $C_8H_9NO$ [$M^+$]; 135.1, found 134.9.

1,1,1-trimethyl-2-(1-phenylethylidene)hydrazin-1-ium iodide **36b**:[84]




Acetophenone (1.20 g, 10.0 mmol) and *N,N*-dimethylhydrazine (0.79 g, 13.0 mmol) were taken neat and stirred at reflux for 24 hours. The resulting aqueous layer was separated and extracted in $Et_2O$ (3 x 5 mL), the combined organic layers dried over anhydrous potassium carbonate and the solvent removed *in vacuo* to furnish a yellow oil (1.28 g). The crude hydrazone was taken up immediately in EtOH (1 mL), iodomethane (5.00 g, 35.0 mmol) was added and the solution stirred at gentle reflux (45 °C) for 4 hours. The mixture was filtered and the solid washed with $Et_2O$. Further solid was obtained by dilution of the filtrate with copious quantities of $Et_2O$ followed by further filtration and washing of the solid. The solid was dried to constant mass to yield 1,1,1-trimethyl-2-(1-phenylethylidene)hydrazin-1-ium iodide as a pale yellow solid without the need for further purification (1.58 g, 52 % from acetophenone): Mp: 135-137 °C (lit. 147 °C); $^1$H NMR (500 MHz, $CDCl_3$) $\delta_H$ 7.75 (*d, J* 8.0 Hz, 2H, 2'/6'-H), 7.56 (*t, J* 8.0 Hz, 1H, 4'-H), 7.46 (*t, J* 8.0 Hz, 2H, 3'/5'-H), 3.99 (*s,* 9H, N-$CH_3$), 2.99 (*s,* 3H, $CH_3$); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta_C$ 173.1 (C=N), 136.1 (Ar C), 132.6 (4'-CH), 129.0 (3'/5'-CH), 127.5 (2'/6'-CH), 58.0 (N-$CH_3$), 21.0 ($CH_3$); $\nu_{max}$ (solid, $cm^{-1}$) 3003.5, 2947.3 ($NCH_3$), 1741.8, 1614.5 (C=N), 1593.8, 1573.4, 1467.2, 1447.9, 1411.5, 1366.1, 1295.9, 1239.2, 1186.4, 1169.1, 1134.4, 1087.0, 1024.5, 957.3, 945.9, 832.6, 780.8, 741.4, 701.8 (Ar CH); *m/z* ($ESI^+$) calculated for $C_{11}H_{17}N_2^+$ [$M^+$-I$^-$]; 177.1386, found: 177.1391.

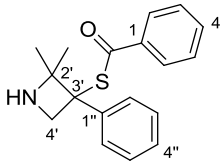
3-chloro-2,2-dimethyl-3-phenyl-1-tosylazetidine **4g**:[37a]




A solution of 2,2-dimethyl-3-phenyl-1-azabicyclo[1.1.0]butane (215 mg, 1.38 mmol) in acetone (1.6 mL) was added to a solution of 4-toluenesulfonyl chloride (229 mg, 1.20 mmol) in acetone (1.2 mL) at 0 °C with stirring at room temperature for a further 18 hours. The solvent was removed *in vacuo* to give an orange oil (437 mg) which was purified by column chromatography (9:1 v/v

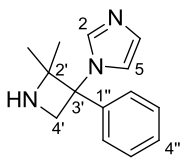
hexane:EtOAc) to yield 3-chloro-2,2-dimethyl-3-phenyl-1-tosylazetidine as a pale yellow solid (173 mg, 36 %): Mp: 114-116 °C; $R_f$= 0.22 (9:1 v/v hexane:EtOAc); $^1$H NMR (400 MHz, $CDCl_3$) $\delta_H$ 7.77 (*d, J* 6.5 Hz, 2H, Ts C<u>H</u>), 7.38-7.27 (*m,* 7H, Ph/Ts C<u>H</u>), 4.69 (*d, J* 6.5 Hz, 1H, 4-<u>H</u>$_2$), 4.00 (*d, J* 6.5 Hz, 1H 4-<u>H</u>$_2$), 2.44 (*s,* 3H*,* 4'C-C<u>H</u>$_3$), 1.79 (*s,* 3H, C<u>H</u>$_3$), 1.18 (*s,* 3H, C<u>H</u>$_3$); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta_C$ 143.8 (S-<u>C</u>), 138.8 (1''-<u>C</u>), 136.6 (4'-<u>C</u>), 129.7 (Ar <u>C</u>H), 128.5 (Ar <u>C</u>H), 128.5 (Ar <u>C</u>H), 127.7 (Ar <u>C</u>H), 126.7 (Ar <u>C</u>H), 79.3 (2-<u>C</u>), 72.1 (3-<u>C</u>), 59.4 (4-<u>C</u>H$_2$), 25.5 (2C-<u>C</u>H$_3$), 24.7 (2C-<u>C</u>H$_3$), 21.6 (4'C-<u>C</u>H$_3$); $\nu_{max}$ (solid, cm$^{-1}$) 2980.4, 1597.6 1494.5 1447.7 ($CMe_2$), 1340.9, 1322.3, 1304.0, 1262.4 (-$SO_2$N=), 1233.6, 1153.9, 1090.0, 1035.7, 1010.8, 815.2, 737.3 (C-Cl), 709.9, 691.2 (Ar CH); *m/z* (ESI$^+$) calculated for $C_{18}H_{20}NO_2SClNa$ [M+Na$^+$]; 372.0801, found 372.0795 (error = -0.45 ppm).

(2,2-dimethyl-3-phenylazetidin-3-yl)benzothioate **4h**:[37a]




A solution of 2,2-dimethyl-3-phenyl-1-azabicyclo[1.1.0]butane (80.3 mg, 0.50 mmol) in THF (0.5 mL) was added dropwise to a solution of thiobenzoic acid (69.1 mg, 0.50 mmol) in THF (0.5 mL) at 0 °C with stirring at room temperature for a further 16 hours. The solvent was removed *in vacuo* to give an orange foam (103 mg) which was purified by column chromatography (1:1 v/v hexane:EtOAc – 100 % EtOAc,) to yield (2,2-dimethyl-3-phenylazetidin-3-yl)benzothioate as an unstable clear pale yellow oil (66.9 g, 45 %): $^1$H NMR (400 MHz, $CDCl_3$) $\delta_H$ 7.85 (*dd, J* 1.0, 8.0 Hz*,* 2H, Ar C<u>H</u>), 7.52 (*dd, J* 1.0, 8.0 Hz, 1H, Ar C<u>H</u>), 7.43-7.30 (*m,* 7H, Ar C<u>H</u>), 4.79 (*d*, *J* 12.0 Hz, 1H, 4'-<u>H</u>$_2$), 3.94 (*d, J* 12.0 Hz, 1H, 4'-<u>H</u>$_2$), 1.67 (*s,* 3H, C<u>H</u>$_3$), 1.67 (*s,* 3H, C<u>H</u>$_3$); $\nu_{max}$ (thin film, cm$^{-1}$) 2975.6, 2931.2, 1663.5 (ArCOS), 1627.7, 1598.6, 1577.2, 1494.3, 1447.2 ($CMe_2$), 1417.5, 1205.6, 1175.2, 1162.3, 931.8, 907.0, 775.3, 648.2 (Ar CH).

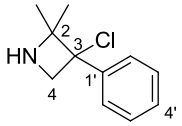
1-(2,2-dimethyl-3-phenylazetidin-3-yl)-1*H*-imidazole **4i**:[37a]




A solution of imidazole (32.1 mg, 0.47 mmol) in acetone (0.5 mL) was added to a solution of 2,2-dimethyl-3-phenyl-1-azabicyclo[1.1.0]butane (82.5 mg, 0.52 mmol) in acetone (0.5 mL) at 0 °C with stirring at room temperature for a further 16.5 hours. The solvent was removed *in vacuo* to give a yellow oil (107 mg). The oil was loaded onto a silica gel plug, eluted first with 9:1 v/v DCM:MeOH

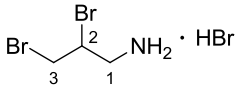
(20 mL) then the azetidine eluted with MeOH (20 mL) and the solvent removed *in vacuo* to yield 1-(2,2-dimethyl-3-phenylazetidin-3-yl)-1*H*-imidazole as a clear yellow oil (3.3 mg, 3 %): $^{1}$H NMR (400 MHz, $CDCl_3$) $\delta_H$ 7.54 (*apparent s,* 1H, 2-H), 7.40-7.32 (*m,* 3H, 3''/4''/5''-H), 7.21-7.18 (*m,* 2H, 2''/6''-H), 7.16 (*t, J* 1.0 Hz, 1H, imidazole CH), 7.05 (*apparent s, J* 1.0 Hz, 1H, imidazole CH), 4.31 (*d, J* 7.0 Hz, 1H, 4'-$H_2$), 4.12 (*d, J* 7.0 Hz, 1H, 4-$H_2$), 1.27 (*s,* 3H, $CH_3$), 1.18 (*s,* 3H, $CH_3$); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta_C$ 139.0 (1''-C), 137.0 (2-CH), 128.6 (3''/4''/5''-CH), 128.4 (2''/6''-CH), 128.2 (imidazole CH [7.05 ppm]), 127.2 (Ar CH [7.21-7.18 ppm]), 119.4 (imidazole CH [7.16 ppm]), 68.8 (3'-C), 68.2 (2'-C), 54.5 (4'-$CH_2$), 28.1 ($CH_3$), 25.9 ($CH_3$); $\nu_{max}$ (thin film, $cm^{-1}$) 1493.9 (NH), 1460.6, 1447.6 ($CMe_2$), 1326.1, 1233.3, 1084.4, 1063.5, 912.3, 817.9, 726.9, 703.1, 660.5 (Ar CH); *m/z* ($ESI^+$) calculated for $C_{14}H_{18}N_3$ [$M+H^+$]; 228.1501, found 228.1495 (error = -3.64 ppm).

3-chloro-2,2-dimethyl-3-phenylazetidine **4j**:[37a]



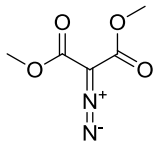

A solution of 4-toluenesulfonyl chloride (68.8 mg, 0.36 mmol) in acetone (0.5 mL) was added to a solution of 2,2-dimethyl-3-phenyl-1-azabicyclo[1.1.0]butane (56.2 mg, 0.35 mmol) and imidazole (24.5 mg, 0.36 mmol) in acetone (0.5 mL) at 0 °C with stirring at room temperature for a further 16 hours. The mixture was diluted with saturated aqueous sodium hydrogen carbonate (5 mL) and the aqueous solution extracted with $Et_2O$ (3 x 10 mL). The aqueous phase was made basic (pH 11) by addition of 2 M sodium hydroxide and extracted with $Et_2O$ (3 x 10 mL), the combined organic extracts dried over anhydrous sodium sulfate and the solvent removed *in vacuo* to yield 3-chloro-2,2-dimethyl-3-phenylazetidine as a clear pale yellow oil without the need for further purification (6.7 mg, 10 %): $^{1}$H NMR (400 MHz, $CDCl_3$) $\delta_H$ 7.43 (*d, J* 7.0 Hz, 2H, 2'/6'-H), 7.38 (*t, J* 7.0 Hz, 3H, 3'/4'/5'-H), 4.20 (*d, J* 9.0 Hz, 1H 4-$H_2$), 3.59 (*d, J* 9.0 Hz, 1H 4-$H_2$), 1.49 (*s,* 3H, $CH_3$), 0.88 (*s,* 3H, $CH_3$); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta_C$ 141.7 (1'-C), 128.9 (3'/5'-CH), 127.2 (4'-CH), 125.9 (2'/6'-CH), 79.8 (3-C), 68.2 (2-C), 54.3 (4-$CH_2$), 27.0 ($CH_3$), 24.0 ($CH_3$); $\nu_{max}$ (thin film, $cm^{-1}$) 2961.4, 2925.7, 1447.7 ($CMe_2$), 1374.2, 1260.3, 1232.9, 1152.0, 1071.0, 1022.2, 907.8, 802.4, 760.9, 729.7 (CCl), 699.3 (Ar CH); *m/z* ($ESI^+$) calculated for $C_{11}H_{14}NCl$ [$M^+$]; 160.1, found 160.1.

2,3-dibromopropan-1-amine hydrobromide **38**:[37g]



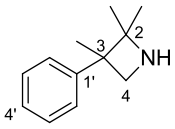
Bromine (16.9 g, 106 mmol) was added cautiously to EtOH (15 mL) at 0 °C with stirring. To this was added cautiously allylamine (2.85 g 49.9 mmol) and the mixture stirred at room temperature for 16 hours. The resulting precipitate was collected by filtration, washed with $Et_2O$ until no orange colour remained and allowed to dry to yield 2,3-dibromopropan-1-amine hydrobromide as a white crystalline solid without the need for further purification (14.0 g, 94 %): Mp: 170 – 172 °C (lit. 176 – 180 °C); $^1$H NMR (400 MHz, $CDCl_3$) $\delta_H$ 4.59-4.52 (*m,* 1H, 2-H), 4.03 (*dd, J* 11.0, 4.5 Hz, 1H, 1-$H_2$), 3.89 (*dd, J* 11.0, 8.5 Hz, 1H, 1-$H_2$), 3.73 (*dd, J* 14.0, 3.0 Hz, 1H, 3-$H_2$), 3.37 (*dd, J* 14.0, 9.5 Hz, 1H, 3-$H_2$); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta_C$ 46.6 (2-CH), 44.2 (3-$CH_2$), 32.7 (1-$CH_2$); $\nu_{max}$ (solid, $cm^{-1}$) 2998.8, 2943.9, 2859.4, 2786.6, 1588.4 ($NH_2$), 1470.9, 1441.1, 1427.0, 1393.4, 1324.3, 1223.4, 1168.2, 1091.3 (C-N), 1052.0, 1017.9, 960.5, 881.5, 823.7, 649.1, 570.2 (C-Br), 467.9; *m/z* ($ESI^+$) calculated for $C_3H_8Br_2N$ [$M+H^+$]; 217.8998, found 217.8998 (error = -0.22 ppm).

Dimethyl 2-diazomalonate **39**:[207]



A solution of sodium nitrite (523 mg, 7.58 mmol) and sulfuric acid (5 % aqueous, 1 mL) in water (4 mL) was added to a vigorously stirred solution of dimethyl 2-aminomalonate hydrochloride (1.10 g, 6.1 mmol) in DCM (30 mL) and water (35 mL) at room temperature and stirred for for 7 hours. The organic layer was separated, washed sequentially with saturated aqueous $NaHCO_3$ (100 mL), water (50 mL) and brine (30 mL), dried over anhydrous magnesium sulfate and the solvent removed *in vacuo* to give a bright yellow oil (302 mg) which was purified by column chromatography (1:1 v/v hexane:EtOAc) to yield dimethyl 2-diazomalonate as a clear yellow oil (98.5 mg, 10 %): $R_f$= 0.25 (1:1 v/v EtOAc:Hexane); $^1$H NMR (400 MHz, $CDCl_3$) $\delta_H$ 3.85 (*s,* 6H, $CH_3$); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta_C$ 161.5 (C=O), 52.6 ($CH_3$); $\nu_{max}$ (thin film, $cm^{-1}$) 2957.8, 2132.7 (CNN), 1758.2, 1734.1 ($CO_2$Me), 1686.4, 1435.1 (OMe), 1352.9, 1326.8, 1270.9, 1189.1($CO_2$Me), 1082.8, 970.9, 933.2, 819.3, 756.6, 668.9; *m/z* ($ESI^+$) calculated for $C_5H_6N_2O_4Na$ [$M+Na^+$]; 181.0226, found 181.0223 (error = -1.67 ppm).

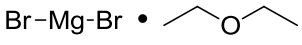
2,2,3-trimethyl-3-phenylazetidine **4l**:[37a]



Methylmagnesium chloride (3 M in THF, 0.33 mL, 1.00 mmol) was added dropwise to a solution of 2,2-dimethyl-3-phenyl-1-azabicyclo[1.1.0]butane (78.1 mg, 0.50 mmol) in THF (1 mL) at -78 °C and 100

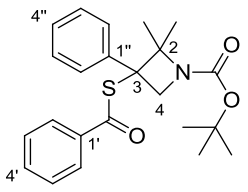
the mixture stirred for 1 hour, then at room temperature for a further 4 hours. The reaction mixture was poured on to vigorously stirred ice-cold saturated aqueous $NH_4Cl$, the aqueous solution extracted with $Et_2O$ (3 x 10 mL), the combined organic extracts dried over anhydrous magnesium sulfate and the solvent removed *in vacuo* to give a yellow oil (67.9 mg) which was purified by column chromatography (19:1 v/v DCM:MeOH) to yield 2,2,3-trimethyl-3-phenylazetidine as a clear yellow oil (6.8 mg g, 8 %): $R_f$= 0.13 (19:1 v/v DCM:MeOH); $^1$H NMR (400 MHz, $CDCl_3$) $\delta_H$ 7.46-7.38 (*m,* 3H, 3'/4'/5'-H), 7.32 (*d, J* 7.0 Hz, 2H, 2'/6'-H), 4.56 (*d, J* 11.0, 1H, 4-$H_2$), 4.08 (*d, J* 11.0 Hz, 1H, 4-$H_2$), 3.05 (*s,* 3H, 3C-C$H_3$), 1.76 (*s,* 3H, 2C-C$H_3$), 1.20 (*s,* 3H, 2C-C$H_3$); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta_C$ 135.0 (1'-C), 129.0 (3'/5'-CH), 129.0 (4'-CH), 126.9 (2'/6'-CH), 83.8 (3-C), 74.0 (2-C); 51.8 (3C $CH_3$), 46.4 ($CH_2$), 24.4 (2C $CH_3$), 21.1 (2C $CH_3$); $\nu_{max}$ (thin film, $cm^{-1}$) 2924.7, 1459.1, 1448.3 ($CMe_2$), 1378.6, 1151.9, 1090.9, 1003.8, 965.3, 764.0, 701.7 (Ar CH); *m/z* ($ESI^+$) calculated for $C_{12}H_{18}N$ [$M+H^+$]; 349.2, found 349.1.

Magnesium bromide dietherate **42**:[206]




Magnesium turnings (2.84 g, 117 mmol) in $Et_2O$ (50 mL) were taken in a 2 neck round bottom flask fitted with reflux condenser and pressure equalising dropping funnel. To this was added a solution of 1,2-dibromoethane (9.37 g, 49.9 mmol) in $Et_2O$ (50 mL) *via* dropping funnel over 7.5 hours and the solution stirred vigourously for a further 16 hours. The mixture was filtered and the biphasic filtrate cooled to below 0 °C. The resulting precipitate was collected and dried in a vacuum dessicator to yield magnesium bromide dietherate as a white crystalline solid (8.08 g, 25 %). The solid was used without further purification.

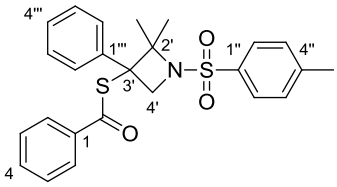
*tert*-butoxycarbonyl 3-(benzoylthio)-2,2-dimethyl-3-phenylazetidine **4m**:[78]




A solution of 2,2-dimethyl-3-phenyl-1-azabicyclo[1.1.0]butane (89.5 mg, 0.50 mmol) in THF (0.5 mL) was added dropwise to a solution of thiobenzoic acid (69.1 mg, 0.50 mmol) in THF (0.5 mL) at 0 °C with stirring at room temperature for a further 16 hours. The solvent was removed *in vacuo* to give an orange oil (174 mg). The oil was taken immediately in MeCN (3 mL) and cooled to 0 °C. Di-*tert*-butyl dicarbonate (120 mg, 0.55 mmol) and $NEt_3$ (250 mg, 2.50 mmol) were added sequentially and stirring

continued at room temperature for 6 hours. The solvent was removed *in vacuo* and the residue partitioned between EtOAc (30 mL) and water (30 mL). The aqueous layer was extracted with EtOAc (3 x 15 mL), the combined organic extracts dried over anhydrous sodium sulfate and the solvent removed *in vacuo* to give an orange oil (190 mg) which was purified by column chromatography (19:1 v/v hexane: EtOAc to 100 % EtOAc) to yield *tert*-butyl 3-(benzoylthio)-2,2-dimethyl-3-phenylazetidine-1-carboxylate as a white crystalline solid on standing (55.8 mg, 30 %): $R_f$= 0.28 (9:1 v/v hexane:EtOAc); Mp: 117 – 119 °C; $^1$H NMR (70 °C, 500 MHz, $d_6$-DMSO) $\delta_H$ 7.79 (*dd, J* 1.0, 7.5 Hz, 2H, Ar C<u>H</u>), 7.63 (*dt, J* 1.0, 7.5 Hz, 1H, Ar C<u>H</u>), 7.51-7.47 (*m,* 4H, Ar C<u>H</u>), 7.33 (*dt, J* 1.0, 7.5 Hz, 2H, Ar C<u>H</u>), 7.23 (*t, J* 7.5 Hz, 1H, Ar C<u>H</u>), 4.93 (*d, J* 10.0 Hz, 1H, 4-<u>$H_2$</u>), 4.02 (*d, J* 10.0 Hz, 1H, 4-<u>$H_2$</u>), 1.73 (*s,* 3H, 2C-C<u>$H_3$</u>), 1.40 (*s,* 9H, $^t$Bu C<u>$H_3$</u>), 0.95 (*s,* 3H, 2C-C<u>$H_3$</u>); $^{13}$C NMR (70 °C, 125 MHz, $d_6$-DMSO) $\delta_C$ 191.7 (S-<u>C</u>=O), 142.5 (1''-<u>C</u>), 139.2 (1'-<u>C</u>), 136.5 (Ar <u>C</u>H), 131.7 (Ar <u>C</u>H), 130.7 (Ar <u>C</u>H), 130.3 (Ar <u>C</u>H), 129.7 (Ar <u>C</u>H), 129.3 (Ar <u>C</u>H), 81.7 (<u>C</u>($CH_3$)$_3$), 74.3 (2-<u>C</u>), 61.3 (3-<u>C</u>), 58.2 (4-<u>C</u>$H_2$), 30.8 ($^t$Bu <u>C</u>$H_3$), 27.1 (C2-<u>C</u>$H_3$), 26.3 (C2-<u>C</u>$H_3$); $\nu_{max}$ (solid, cm$^{-1}$) 2975.9, 2929.9, 1696.4 (C=O), 1664.0 (ArCOS), 1446.8 ($CMe_2$), 1388.8 ($CMe_3$), 1364.3 ($CMe_3$), 1254.6 1205.1 1163.7 ($CO_2$Me), 1084.0, 907.0, 772.0, 731.4 (Ar CH), 688.1, 647.4; *m/z* (ESI$^+$) calculated for $C_{23}H_{27}NO_3SNa$ [M+Na$^+$]; 420.1610, found 420.1604 (error = -0.93 ppm).

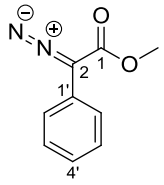
(2,2-dimethyl-3-phenyl-1-tosylazetidin-3-yl) benzothioate **4n**:[54]




A solution of 2,2-dimethyl-3-phenyl-1-azabicyclo[1.1.0]butane (89.4 mg, 0.50 mmol) in THF (0.5 mL) was added dropwise to a solution of thiobenzoic acid (69.1 mg, 0.50 mmol) in THF (0.5 mL) at 0 °C with stirring at room temperature for a further 16 hours. The solvent was removed *in vacuo* to give an orange oil (151 mg). The oil was taken immediately in chloroform (1 mL) and cooled to 0 °C. A solution of 4-toluenesulfonyl chloride (104 mg, 0.55 mmol) in chloroform (1 mL) and $NEt_3$ (81.0 mg, 0.80 mmol) was added and the solution stirred at room temperature for a further 6 hours. The reaction was diluted to 10 mL with chloroform, washed with saturated aqueous sodium hydrogen carbonate (10 mL), water (10 mL), dried over anhydrous sodium sulfate and the solvent removed *in vacuo* to give an orange oil (188 mg) which was purified by column chromatography (85:15 v/v hexane:EtOAc) to yield (2,2-dimethyl-3-phenyl-1-tosylazetidin-3-yl) benzothioate as an unstable pale orange solid (52.4 mg, 23 %): $R_f$= 0.08 (85:15 v/v hexane:EtOAc); $^1$H NMR (400 MHz, $CDCl_3$) $\delta_H$ 7.86 (*d, J* 8.0 Hz, 2H, Ar C<u>H</u>), 7.62 (*d, J* 7.0 Hz, 2H, Ar C<u>H</u>), 7.54 (*t, J* 8.0 Hz, 1H, Ar C<u>H</u>), 7.48-7.39 (*m,* 8H, Ar C<u>H</u>), 7.34 (*t, J* 8.0 Hz, 1H, Ar C<u>H</u>), 5.37 (*d, J* 10.5 Hz, 1H, 4'-<u>$H_2$</u>), 4.57 (*d, J* 10.5 Hz, 1H, 4'-<u>$H_2$</u>), 2.06 (*s,* 3H, 2'C-C<u>$H_3$</u>), 1.55 (*s,* 3H, 4''C-C<u>$H_3$</u>), 1.27 (*s,* 3H, 2'C-C<u>$H_3$</u>); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta_C$ 188.8 (<u>C</u>=O), 168.5 (1''-<u>C</u>), 138.6 (1-<u>C</u>), 135.8 (4''-<u>C</u>), 133.7 (1'''-<u>C</u>), 132.7 (Ar <u>C</u>H), 129.6 (Ar <u>C</u>H), 127.6

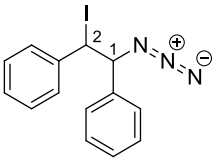
(Ar CH), 127.4 (Ar CH), 127.0 (Ar CH), 126.8 (Ar CH), 126.4 (Ar CH), 126.2 (Ar CH), 126.1 (Ar CH), 65.2 (3'-C), 59.1 (4'-$CH_2$), 58.1 (2'-C), 23.5 (2'C-$CH_3$), 22.9 (2'C-$CH_3$); $\nu_{max}$ (thin film, $cm^{-1}$) 1662.4 (ArCOS), 1633.6, 1577.1, 1447.2 ($CMe_2$), 1403.9, 1346.4, 1206.7 (-$SO_2N$=), 1143.4, 907.0, 729.8 (Ar CH), 689.0, 648.5, 533.7.

Methyl 2-diazo-2-phenylacetate **45**:[207]




A solution of sodium nitrite (428 mg, 6.2 mmol) and sulfuric acid (5 % aqueous, 1 mL) in water (4 mL) was added to a solution of phenylglycine methyl ester hydrochloride (1.00 g, 5.0 mmol) in DCM (30 mL) and water (35 mL) at room temperature and stirred for 7 hours. The organic layer was separated, washed with saturated aqueous sodium hydrogen carbonate (100 mL), water (50 mL), brine (30 mL), dried over anhydrous magnesium sulfate and the solvent removed *in vacuo* to give a bright yellow oil (652 mg) which was purified by column chromatography (9:1 v/v hexane:EtOAc) to yield methyl 2-diazo-2-phenylacetate as a clear bright yellow oil (88.3 mg, 7 %): $R_f$= 0.45 (9:1 v/v hexane:EtOAc); $^1$H NMR (400 MHz, $CDCl_3$) $\delta_H$ 7.48 (*d, J* 8.0 Hz, 2H, 2'/6'-CH), 7.39 (*t, J* 8.0 Hz, 2H, 3'/5'-CH), 7.18 (*t, J* 8.0 Hz, 1H, 4'-CH), 3.87 (*s,* 3H, $OCH_3$); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta_C$ 198.9 ($CN_2$), 165.7 (C=O), 129.0 (3'/5'-CH), 125.9 (4'-CH), 125.5 (1'-C), 124.0 (2'/6'-CH), 52.0 ($OCH_3$); $\nu_{max}$ (thin film, $cm^{-1}$) 2953.0, 2080.8 (CNN), 1698.7 (C=O), 1598.2, 1575.7, 1498.3, 1434.4 (OMe), 1351.6, 1286.3, 1246.7, 1191.6, 1152.5 ($CO_2Me$), 1050.9, 1025.3, 908.8, 754.1, 690.9, 668.6 (Ar CH); *m/z* ($ESI^+$) calculated for $C_9H_8N_2O_2Na$ [$M+Na^+$]; 199.0484, found 199.0478 (error = -4.39 ppm).

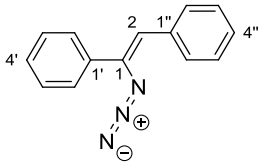
(1-azido-2-iodoethane-1,2-diyl)dibenzene **47**:[51]




Iodine monochloride (1.83 g, 11.3 mmol) was added gradually to a suspension of sodium azide (1.63 g, 25.0 mmol) in MeCN (10 mL) at -20 °C and the solution stirred for 20 minutes. *Trans*-stilbene (1.80 g, 10.0 mmol) was added in one portion *via* solid addition tube and the mixture stirred at room temperature for a further 19.5 hours. The reaction mixture was poured into 5 % aqueous $Na_2S_2O_3$ (20 mL) and the resulting colourless precipitate collected and dried in air. The crude product (3.35 g)

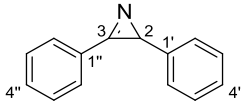
was recrystallised from MeOH to yield (1-azido-2-iodoethane-1,2-diyl)dibenzene as a pale yellow crystalline solid (1.87 g, 54 %): Mp: 119 – 121 °C (lit. 110 – 115 °C); $^{1}$H NMR (400 MHz, $CD_3OD$) $\delta_H$ 7.45 (*dd, J* 8.0, 1.5 Hz, 2H, *ortho* C<u>H</u>), 7.39 (*dt, J* 4.5, 1.5 Hz, 3H, *meta/ para* C<u>H</u>), 7.36-7.29 (*m,* 5H, Ar C<u>H</u>), 5.22 (*d, J* 9.5 Hz, 1H, 2-<u>H</u>), 5.10 (*d, J* 9.5 Hz, 1H, 1-<u>H</u>); $^{13}$C NMR (100 MHz, $CD_3OD$) $\delta_C$ 140.1 (1C Ar <u>C</u>), 137.7 (2C Ar <u>C</u>), 129.1 (Ar <u>C</u>H), 128.7 (Ar <u>C</u>H), 128.7 (Ar <u>C</u>H), 128.6 (Ar <u>C</u>H), 128.5 (Ar <u>C</u>H), 127.7 (Ar <u>C</u>H), 71.9 (1-<u>C</u>), 34.4 (2-<u>C</u>); $\nu_{max}$ (solid, $cm^{-1}$): 2092.3 (C-$N_3$), 1491.5, 1452.3, 1234.0, 1196.5, 1130.2, 1072.8, 833.2, 816.7, 755.6 (Ar CH), 644.5, 630.1, 609.1, 561.2, 506.3, 484.7; *m/z* ($ESI^+$) calculated for $C_{14}H_{12}IN_3Na$ [$M+Na^+$]; 371.9974, found 371.9968 (error = -0.76 ppm).

(1-azidoethene-1,2-diyl)dibenzene **48**:[51]



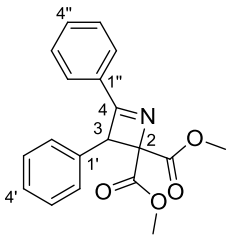

Potassium *tert*-butoxide (336.7 mg, 3.0 mmol) was added to (1-azido-2-iodoethane-1,2-diyl)dibenzene (905 mg, 2.5 mmol) in $Et_2O$ (7.5 mL) at 0 °C and stirred for 16 hours. The reaction was washed with water (2 x 15 mL), the combined aqueous washings extracted with $Et_2O$ (3 x 15 mL), the combined organic layers dried over anhydrous magnesium sulfate and the solvent removed *in vacuo* to give an orange oil (572 mg). The crude product was passed through an alumina plug with hexane (25 mL) and the solvent removed *in vacuo* to give a yellow oil that crystallised on standing (417 mg) which was recrystallised from hexane to yield (*Z*)-(1-azidoethene-1,2-diyl)dibenzene as a pale yellow crystalline solid (179 mg, 40 %): Mp: 65 – 67 °C (lit. 44 – 46 °C); $^{1}$H NMR (400 MHz, $CDCl_3$) $\delta_H$ 7.91 (*dt, J* 1.2, 6.6 Hz, 2H, Ar C<u>H</u>), 7.63-7.53 (*m,* 3H, Ar C<u>H</u>), 7.31-7.23 (*m,* 3H, Ar C<u>H</u>), 7.14 (*dt, J* 1.2, 6.6 Hz, 2H, Ar C<u>H</u>), 3.33 (*s,* 1H, 2-<u>H</u>); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta_C$ 163.5 (1-<u>C</u>), 140.9 (1'-<u>C</u>), 133.2 (Ar <u>C</u>H), 129.9 (Ar <u>C</u>H), 129.3 (Ar <u>C</u>H), 128.3 (Ar <u>C</u>H), 127.1 (Ar <u>C</u>H), 126.1 (Ar <u>C</u>H), 124.1 (1''-<u>C</u>), 34.5 (2-<u>C</u>); $\nu_{max}$ (solid, $cm^{-1}$) 3030.5 (CH), 2109.3 (C-$N_3$), 1740.9, 1596.8, 1494.1, 1488.6, 1450.0, 1325.0, 1308.3, 1272.1, 1075.6, 1023.7, 997.9, 981.8, 932.7, 910.7, 784.9, 768.3, 758.5 (Ar CH), 690.9, 662.3, 627.2, 572.8, 514.4, 427.3; *m/z* ($ESI^+$) calculated for $C_{14}H_{12}N$ [$M+H^+$]; 184.1, found 184.1.

2,3-diphenyl-2*H*-azirine **14c**:[51]



Potassium *tert*-butoxide (725.4 mg, 6.46 mmol) was added to (1-azido-2-iodoethane-1,2-diyl)dibenzene (1.87 g, 5.34 mmol) in $Et_2O$ (15 mL) at 0 °C and stirred for 17 hours. The reaction mixture was washed with water (2 x 30 mL), the combined aqueous washings extracted with $Et_2O$ (3 x 30 mL), the combined organic layers dried over anhydrous magnesium sulfate and the solvent removed *in vacuo* to give an orange oil (996 mg). The crude product was loaded onto an aluminium oxide column (3.4 g) and eluted with anhydrous hexane (40 mL). The resulting yellow solution was heated at reflux for 2.75 hours then the solvent was removed *in vacuo* to give a viscous yellow oil. The oil solidified on standing to yield 2,3-diphenyl-2*H*-azirine as a pale yellow crystalline solid that did not require further purification (680.0 mg, 66 %): Mp: 56 – 58 °C (lit. 60 – 62 °C); $^1$H NMR (400 MHz, $CDCl_3$) $\delta_H$ 7.91 (*dd, J* 1.5, 8.0 Hz, 2H, 2'/6'-H), 7.61-7.54 (*m,* 3H, 3'/4'/5'-H), 7.31-7.23 (*m,* 3H, 3''/4''/5''-H), 7.15 (*dd, J* 1.5, 8.0 Hz, 2H, 2''/6''-H), 3.33 (*s,* 1H, 2-H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta_C$ 163.5 (1'-C), 140.8 (1''-C), 133.2 (3'-CH), 129.9 (2'-CH), 129.3 (4'-CH), 128.3 (3''/5''-CH), 127.1 (4''-CH), 126.1 (2''/6''-CH), 124.1 (3-C), 34.5 (2-C); $\nu_{max}$ (solid, cm$^{-1}$) 1741.2, 1596.9 (C=N), 1494.4, 1488.7, 1450.2, 1324.8, 1307.9, 1260.0, 1075.6, 1022.5, 998.4, 932.7, 910.4, 862.4, 799.4, 785.6 ,691.6, 758.4 (Ar CH), 691.6, 662.9, 627.6, 573.3, 515.2; *m/z* (ESI$^+$) calculated for $C_{14}H_{11}NNa$ [M+Na$^+$]; 216.0789, found 216.0783 (error = 0.19 ppm).

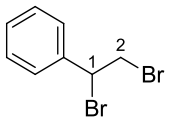
Dimethyl 3,4-diphenylazete-2,2(3*H*)-dicarboxylate **46a**:[104]




A solution of dimethyl 2-diazomalonate (95.0 mg, 0.60 mmol) in chloroform (1 mL) was added to 2,3-diphenyl-2*H*-azirine (94.5 mg, 0.49 mmol) and rhodium(II) acetate dimer (8.60 mg, 0.02 mmol) in chloroform (1 mL) and the solution heated at reflux for 17 hours. The reaction mixture was loaded onto a silica gel plug, eluted with EtOAc (10 mL) and the solvent was removed *in vacuo* to give a brown oil (223 mg) which was purified by column chromatography (6:1 v/v hexane:EtOAc) to yield dimethyl 3,4-diphenylazete-2,2(3*H*)-dicarboxylate as a clear brown oil (139 mg, 88 %): $R_f$= 0.05 (6:1 v/v hexane:EtOAc); $^1$H NMR (400 MHz, $CDCl_3$) $\delta_H$ 7.74 (*d, J* 7.5 Hz, 2H, 2''/6''-H), 7.52 (*t, J* 7.5 Hz, 1H, 4''-H), 7.41 (*t, J* 7.5 Hz, 2H, 3''/5''-H), 7.30-7.28 (*m,* 3H, 3'/4'/5'-H), 7.19 (*dd, J* 4.0, 7.5 Hz, 2H, 2'/6'-H), 5.43 (*s,* 1H, 3-H), 3.88 (*s,* 3H, $OCH_3$), 3.32 (*s,* 3H, $OCH_3$); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta_C$ 190.9 (C=N), 167.7 (C=O), 166.4 (C=O), 133.1 (1'-C), 132.8 (3''/5''-CH), 130.7 (1''-C), 128.7 (4''-CH), 128.6 (3C Ar CH), 126.6 (3C Ar CH), 128.2 (2'-CH), 126.9 (2''-CH), 77.0 (2-C), 55.4 (3-CH), 53.5 ($OCH_3$), 52.2 ($OCH_3$); $\nu_{max}$ (thin film, cm$^{-1}$) 2953.1, 1735.5 (C=O), 1603.5 (C=N), 1564.4, 1493.9, 1448.0, 1434.1 (OMe), 1360.4, 1256.9, 1196.4, 1151.0 ($CO_2Me$), 1102.8, 1061.3, 1022.5, 911.5,

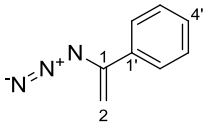
818.0, 792.5, 775.0, 761.7, 728.1 (Ar CH), 668.9, 647.3, 618.1, 536.0; *m/z* ($ESI^+$) calculated for $C_{19}H_{17}NO_4Na$ [$M+Na^+$]; 346.1056, found 346.1049 (error = -0.14 ppm).

(1,2-dibromoethyl)benzene:[208]




Bromine (6.40 g, 40.0 mmol) in chloroform (10.0 mL) was added drop-wise to a solution of styrene (4.18 g, 40.2 mmol) in chloroform (16 mL) at 0 °C and stirred for 2.5 hours. The solvent was removed *in vacuo* to give a brown crystalline solid which was recrystallised from EtOH to yield (1,2-dibromoethyl)benzene as an off-white crystalline solid (10.6 g, 99 %): Mp: 68-70 °C (lit. 73 – 75 °C); $^1$H NMR (400 MHz, $CDCl_3$) $\delta_H$ 7.42-7.35 (*m,* 5H, Ar C<u>H</u>), 5.15 (*dd, J* 5.0, 10.0 Hz, 1H, 1-<u>H</u>), 4.10-4.00 (*m,* 2H, 2-<u>$H_2$</u>); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta_C$ 138.6 (Ar <u>C</u>), 129.2 (Ar <u>C</u>H), 128.9 (Ar <u>C</u>H), 127.7 (Ar <u>C</u>H), 50.8 (1-<u>C</u>H), 35.0 (2-<u>C</u>$H_2$); $\nu_{max}$ (solid, $cm^{-1}$) 3064.8, 3031.4, 1495.7, 1455.2, 1431.6, 1361.6, 1310.7, 1291.6, 1230.7, 1198.2, 1155.1, 1133.3, 1077.0, 1051.2, 1023.4, 999.7, 907.1, 768.0 (Ar CH), 689.8, 661.8, 587.1 (C-Br), 553.3, 501.5, 482.5, 441.1, 425.0; *m/z* ($ESI^+$) calculated for $C_8H_8Br_2$ [$M^+$]; 261.9, found: 261.8: 263.9: 265.8 in a 1:2:1 ratio.

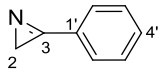
(1-azidovinyl)benzene **49**:[105]




A mixture of (1,2-Dibromoethyl)benzene (2.67 g, 10.1 mmol) and sodium azide (654 mg, 10.1 mmol) in DMF (15 mL) was stirred at room temperature for 17 hours. The reaction mixture was diluted with water (100 mL), extracted with hexane (3 x 100 mL), the combined organic extracts washed with water (2 x 100 mL), dried over anhydrous potassium carbonate and the solvent removed *in vacuo* to yield crude (1-azido-2-bromoethyl)benzene as a yellow oil (2.02 g). The oil was taken in benzene (10 mL) and added dropwise to a slurry of potassium *tert*-butoxide (1.68 g, 15.0 mmol) in benzene (15 mL) at 0 °C and the mixture stirred at room temperature for 5 hours. The reaction mixture was diluted with hexane (50 mL), washed with water (2 x 50 mL), dried over anhydrous potassium carbonate and the solvent removed *in vacuo* to yield (1-azidovinyl)benzene as a clear orange oil without the need for further purification (1.22 g, 84 %): $^1$H NMR (400 MHz, $CDCl_3$) $\delta_H$ 7.57-7.55 (*m,* 2H, 2'/6'-<u>H</u>), 7.36-7.35 (*m,* 3H, 3'/4'/5'-<u>H</u>), 5.43 (*d, J* 2.5 Hz, 1H, 2-<u>$H_2$</u>), 4.96 (*d, J* 2.5 Hz, 1H, 2-<u>$H_2$</u>); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta_C$ 145.02 (1-<u>C</u>), 134.3 (1'-<u>C</u>), 129.1 (Ar <u>C</u>H), 128.5 (Ar <u>C</u>H), 125.6 (2'/6'-<u>C</u>H),

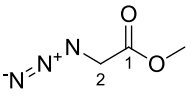
98.0 (2-$\underline{C}H_2$); $\nu_{max}$ (thin film, $cm^{-1}$) 3058.8 ($CH_2$), 2134.7 (C-$N_3$), 2100.3, 1610.0, 1276.5, 1493.7, 1445.4, 1406.8, 1289.0, 1220.7, 1183.9, 1070.5, 1027.2, 905.0, 837.5, 788.7, 766.2, 696.1 (Ar CH), 655.5, 538.5; *m/z* ($ESI^+$) calculated for $C_8H_7N_3$ [$M^+$]; 145.1, found 145.1.

3-phenyl-2*H*-azirine **14b**:[105]



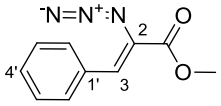

(1-Azidovinyl)benzene (1.22 g, 7.5 mmol) was loaded onto an aluminium oxide plug (6.0 g), eluted with hexane (30 mL) and the organic solution concentrated *in vacuo* to give a yellow oil (1.09 g). The oil was dissolved in toluene (25 mL) and heated at reflux for 7 hours, then concentrated *in vacuo* to yield 3-phenyl-2*H*-azirine as a clear orange oil without the need for further purification (584 mg, 67 %): $^1$H NMR (400 MHz, $CDCl_3$) $\delta_H$ 7.91 (*dd, J* 6.5, 7.5 Hz, 2H, 2'/6'-$\underline{H}$), 7.61-7.57 (*m,* 3H, 3'/4'/5'-$\underline{H}$), 1.80 (*s,* 2H, 2-$\underline{H}_2$); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta_C$ 165.8 (3-$\underline{C}$), 133.0 (3'/4'-$\underline{C}$H), 129.6 (2'/6'-$\underline{C}$H), 129.1 (3'/4'/5'-$\underline{C}$H), 127.3 (1'-$\underline{C}$), 19.2 (2-$\underline{C}H_2$); $\nu_{max}$ (thin film, $cm^{-1}$) 3060.3, 2094.2, 1667.4, 1606.1 (C=N), 1576.3, 1488.9, 1445.7 ($CH_2$), 1214.7, 1180.0, 1156.5, 1072.9, 1025.7, 1001.0, 888.2, 752.8 (Ar CH), 690.2, 628.0, 613.7, 547.1; *m/z* ($ESI^+$) calculated for $C_8H_8N$ [$M+H^+$]; 118.0657, found 118.0651 (error = -0.49 ppm).

Methyl 2-azidoacetate **52**: [107]



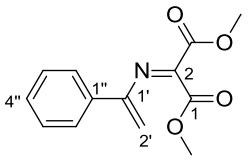

A solution of methyl bromoacetate (8.05 g, 52.6 mmol) in MeOH (4 mL) was combined in a single portion with a slurry of sodium azide (4.34 g, 66.8 mmol) in water (3 mL) and the mixture stirred at room temperature for 20 minutes then 80 °C for 2 hours. The mixture was cooled, the MeOH removed *in vacuo* and the residue dispersed in water (50 mL). The aqueous mixture was extracted with $Et_2O$ (3 x 80 mL), the combined organic extracts dried over anhydrous magnesium sulfate and the solvent removed *in vacuo* to yield methyl 2-azidoacetate as a clear pale yellow oil without the need for further purification (5.02 g, 82 %): $^1$H NMR (400 MHz, $CDCl_3$) $\delta_H$ 3.90 (*s,* 2H, 2-$\underline{H}_2$), 3.81 (*s,* 3H, O$\underline{C}H_3$); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta_C$ 168.8 ($\underline{C}$=O), 52.6 (2-$\underline{C}H_2$), 50.3 (O$\underline{C}H_3$); $\nu_{max}$ (thin film, $cm^{-1}$): 2101.0 (C-$N_3$), 1742.4 (C=O), 1438.2 (OMe), 1356.8, 1284.4, 1202.2, 1179.7 ($CO_2$Me), 997.8, 918.4, 842.7, 721.5, 648.7, 574.4, 554.1; *m/z* ($ESI^+$) calculated for $C_3H_5N_3O_2$ [$M^+$]; 115.0, found 115.0.

Methyl 2-azido-3-phenylacrylate **53**:[107]



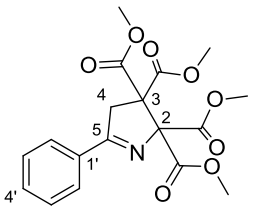
Sodium methoxide (540 mg, 10.0 mmol) in MeOH (5 mL) was added to methyl 2-azidoacetate (1.15 g, 10.0 mmol) and benzaldehyde (424 mg, 4.0 mmol) in MeOH (6 mL) at -20 °C and stirred for 1.5 hours. The reaction was warmed to 0 °C with stirring for a further 16 hours then poured into saturated aqueous $NH_4Cl$ (8 mL). The aqueous mixture was extracted with $Et_2O$ (3 x 15 mL), the combined organic extracts dried over anhydrous magnesium sulfate and the solvent removed *in vacuo* to yield (*Z*)-methyl 2-azido-3-phenylacrylate as an orange paste without the need for further purification (810 mg, 99 %): $^1$H NMR (400 MHz, $CDCl_3$) $\delta_H$ 7.82 (*d, J* 7.5 Hz, 2H, 2'/6'-C<u>H</u>), 7.41-7.34 (*m,* 3H, 3'/4'/5'-<u>H</u>), 6.92 (*s,* 1H, 3-<u>H</u>), 3.92 (*s,* 3H, OC<u>H</u>$_3$); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta_C$ 164.0 (<u>C</u>=O), 133.1 (1'-<u>C</u>), 130.6 (2'/6'-<u>C</u>H), 129.5 (Ar <u>C</u>H), 128.5 (Ar <u>C</u>H), 125.6 (3-<u>C</u>H), 125.3 (2-<u>C</u>N$_3$), 53.0 (O<u>C</u>H$_3$); $\nu_{max}$ (thin film, cm$^{-1}$) 2119.3 (C-N$_3$), 1715.8 (C=O), 1615.9, 1436.2 (OMe), 1448.0, 1378.5, 1260.0 ($CO_2$Me), 1087.0, 768.9, 669.0, 656.8; *m/z* (ESI$^+$) calculated for $(C_{10}H_9NO_2)_2$ $[(M-N_2)_2+H^+]$; 351.1345, found 351.1339 (error= -1.62 ppm).

Dimethyl 2-((1-phenylvinyl)imino)malonate **50a**:[104]



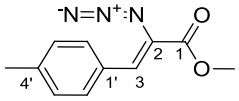
3-Phenyl-2*H*-azirine (106 mg, 0.55 mmol), rhodium acetate dimer (23.0 mg, 0.06 mmol) and dimethyl 2-diazomalonate (107 mg, 0.67 mmol) were dissolved in chloroform (2.5 mL) and stirred at reflux for 17 hours. The reaction mixture was loaded onto a silica gel plug, eluted with EtOAc (10.0 mL) and the solvent removed *in vacuo* to give a red-brown oil (200.9 mg) which was purified by column chromatography (40 g silica gel, 9:1 v/v petroleum ether 40 – 60 °C fraction:EtOAc) to yield dimethyl 2-((1-phenylvinyl)imino)malonate as a clear yellow oil (74.6 mg, 55 %): $R_f$= 0.13 (9:1 v/v petroleum ether 40 – 60 °C fraction:EtOAc); $^1$H NMR (400 MHz, $CDCl_3$) $\delta_H$ 7.47-7.45 (*m,* 2H, 2''/6''-C<u>H</u>), 7.37-7.35 (*m,* 3H, 3''/4''/5''-C<u>H</u>), 4.99 (*s,* 1H, 2'-C<u>H</u>$_2$), 4.61 (*s,* 1H, 2'-C<u>H</u>$_2$), 3.98 (*s,* 3H, OC<u>H</u>$_3$), 3.78 (*s,* 3H, OC<u>H</u>$_3$); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta_C$ 162.3 (<u>C</u>=O), 161.3 (<u>C</u>=O), 154.0 (<u>C</u>=N), 151.2 (<u>C</u>-N), 134.6 (1''-<u>C</u>), 129.0 (Ar <u>C</u>H), 128.5 (Ar <u>C</u>H), 125.8 (2''/6''-<u>C</u>H), 97.3 (2'-<u>C</u>H$_2$), 53.6 (O<u>C</u>H$_3$), 52.6 (O<u>C</u>H$_3$); $\nu_{max}$ (thin film, cm$^{-1}$) 2955.0 ($CH_2$), 1745.5 (C=O), 1653.1, 1608.5 (C=N), 1575.3, 1494.2, 1437.1 (OMe), 1325.5, 1248.7 ($CO_2$Me), 1191.7, 1075.3, 871.1, 774.9 (Ar CH), 693.6; *m/z* (ESI$^+$) calculated for $C_{13}H_{13}NO_4Na$ $[M+Na^+]$; 270.0743, found 270.0739 (error = -0.92 ppm).

Tetramethyl 5-phenyl-2*H*-pyrrole-2,2,3,3(4*H*) tetracarboxylate **51**:[104]



3-Phenyl-2*H*-azirine (59.1 mg, 0.31 mmol), rhodium acetate dimer (9.9 mg, 0.02 mmol) and dimethyl 2-diazomalonate (104 mg, 0.65 mmol) were dissolved in chloroform (2 mL) and stirred at reflux for 18 hours. The reaction mixture loaded onto a silica gel plug, eluted with EtOAc (10 mL) and the solvent removed *in vacuo* to give a brown oil (140 mg) which was purified by column chromatography (6:1 v/v to 1:1 v/v petroleum ether 40 – 60 °C fraction:EtOAc) to yield tetramethyl 5-phenyl-2*H*-pyrrole-2,2,3,3(4*H*) tetracarboxylate as an orange gum (80.6 mg, 67 %): $R_f$= 0.22 (6:1 v/v petroleum ether 40 – 60 °C fraction:EtOAc); $^1$H NMR (400 MHz, $CDCl_3$) $\delta_H$ 7.92 (*d, J* 8.0 Hz, 2H, 2'/6'-H), 7.51 (*t, J* 8.0 Hz, 1H, 4'-H), 7.44 (*t, J* 8.0 Hz, 2H, 3'/5'-H), 3.87 (*s,* 2H, 4-$H_2$), 3.83 (*s,* 6H, $OCH_3$), 3.76 (*s,* 6H, $OCH_3$); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta_C$ 175.1 (C=N), 169.8 (C=O), 168.2 (C=O), 168.1 (C=O) 166.0 (C=O), 132.5 (1'-C), 132.0 (4'-CH), 128.6 (3'-CH), 128.4 (2'-CH), 65.9 (2-C), 53.5-53.2 ($OCH_3$), 46.4 (4-$CH_2$), 40.8 (3-C); $\nu_{max}$ (thin film, $cm^{-1}$) 2955.7, 2925.3, 1736.1 (C=O), 1624.4 (C=N), 1434.7 (OMe), 1355.1, 1234.2 ($CO_2$Me), 1166.8, 1123.8, 1072.0, 1039.2, 962.8, 911.1, 871.8, 798.9, 782.6, 762.8, 729.5 (Ar CH), 648.2; *m/z* ($ESI^+$) calculated for $C_{18}H_{19}NO_8Na$ [M+$Na^+$]; 400.1009, found 400.1003 (error = -2.88 ppm).

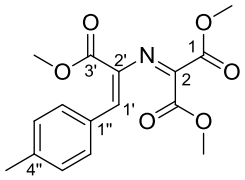
Methyl 2-azido-3-(4-tolyl)acrylate **54**:[108]



4-Tolualdehyde (396 mg, 3.3 mmol) and methyl 2-azidoacetate (1.15 g, 10.0 mmol) were added dropwise to a solution of sodium methoxide (195 mg, 3.6 mmol) in MeOH (1.10 mL) at -20 °C with stirring at -10 °C for a further 4 hours. The reaction mixture was partitioned between water (20 mL) and $Et_2O$ (20 mL), the aqueous layer separated and extracted with $Et_2O$ (2 x 20 mL), the combined organic extracts washed with water (2 x 20 mL), brine (20 mL), dried over anhydrous magnesium sulfate and the solvent removed *in vacuo* to give a yellow crystalline solid (862 mg) which was purified by column chromatography (19:1 v/v petroleum ether 40 – 60 °C fraction:EtOAc) to yield (*Z*)-methyl 2-azido-3-(4-tolyl)acrylate as a yellow crystalline solid (452 mg, 63 %): $R_f$= 0.27 (19:1 v/v petroleum ether 40 – 60 °C fraction:EtOAc); Mp: 57 – 59 °C (lit. 64 – 65 °C); $^1$H NMR (400 MHz, $CDCl_3$) $\delta_H$ 7.72 (*d, J* 8.0 Hz, 2H, Ar CH), 7.20 (*d, J* 8.0 Hz, 2H, Ar CH), 6.91 (*s,* 1H, 3-H), 3.91 (*s,* 3H, $OCH_3$), 2.38 (*s,* 3H, Ts $CH_3$); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta_C$ 164.2 (C=O), 139.9 (C-$N_3$), 130.6 (Ar CH), 130.4 (4'-C),

129.3 (Ar CH), 125.8 (3-CH), 124.4 (1'-C), 52.9 ($OCH_3$), 21.5 (4'C-$CH_3$); $\nu_{max}$ (solid, $cm^{-1}$) 2957.5, 2917.0, 2114.9 (C-$N_3$), 1708.0 (C=O), 1666.7, 1616.8, 1604.0, 1504.6, 1435.9 (OMe), 1414.2, 1378.5, 1321.8, 1295.0, 1247.6 ($CO_2Me$), 1208.4, 1180., 1126.9, 1114.0, 1077.3, 1016.3, 954.2, 887.5, 865.9, 844.6, 818.2, 755.0, 740.9 (Ar CH), 711.9, 650.2, 631.8, 553.2, 531.8, 465.0; *m/z* ($ESI^+$) calculated for $C_{11}H_{11}N_3O_2Na$ [$M+Na^+$]; 240.0749, found 240.0743 (error = -6.19 ppm).

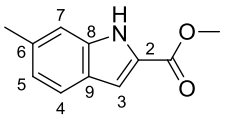
Dimethyl 2-((3-methoxy-3-oxo-1-(4-tolyl)prop-1-en-2-yl)imino)malonate **50c**:[104]




A solution of methyl 2-azido-3-(4-tolyl)acrylate (643 mg, 3.00 mmol) in cyclohexane (60 mL) was heated at reflux for 17 hours. The solvent was removed *in vacuo* to give an orange residue which solidified on standing (572 mg). The orange solid contained an inseperable mixture of methyl 2-(4-tolyl)-2*H*-azirine-3-carboxylate (**14h**) and methyl 6-methyl-1*H*-indole-2-carboxylate (**55**) in the ratio of 3:1.

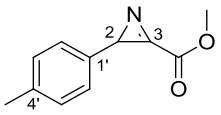
A solution of dimethyl 2-diazomalonate (96.8 mg, 0.61 mmol, 1.3 mol. eq. based on azirine loading) in chloroform (1 mL) was added to a solution of the crude methyl 2-(4-tolyl)-2*H*-azirine-3-carboxylate (**14h**, 114.6 mg, 0.60 mmol = 89.8 mg, 0.47 mmol azirine loading) and rhodium acetate dimer (9.1 mg, 0.02 mmol) in chloroform (1 mL) and the resulting mixture stirred at reflux for 16.5 hours. The reaction mixture was loaded onto a silica gel plug, eluted with EtOAc (15 mL) and the solvent removed *in vacuo* to give a dark yellow oil (211 mg) which was purified by column chromatography (9:1 v/v petroleum ether 40 – 60 °C fraction:EtOAc) to yield (*E*)-dimethyl 2-((3-methoxy-3-oxo-1-(4-tolyl)prop-1-en-2-yl)imino)malonate as a clear bright orange oil (87.7 mg, 77 %): $R_f$= 0.09 (9:1 v/v petroleum ether 40 – 60 °C fraction:EtOAc); $^1$H NMR (400 MHz, $CDCl_3$) $\delta_H$ 7.41 (*d, J* 8.0 Hz, 2H, 2''/6''-H), 7.28 (s, 1H, 1'-H), 7.18 (*d, J* 8.0 Hz, 2H, 3''/5''-H), 4.00 (*s,* 3H, 1C-$OCH_3$), 3.81 (*s,* 3H, 3'-$OCH_3$), 3.80 (*s,* 3H, 1C-$CH_3$), 2.36 (*s,* 3H, 4''C-$CH_3$); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta_C$ 162.9 (propenyl C=O), 162.5 (1C=O), 159.8 (2-C=O), 152.6 (C=N), 140.1 (1''-C), 133.3 (2'-C), 131.7 (2''/6''-CH), 130.8 (4''-C), 129.4 (3''/5''-CH), 128.3 (1'-CH); 53.5 (1C-$OCH_3$), 52.8 (1C-$OCH_3$), 52.6 (3'C-$OCH_3$), 21.5 (4''C-$CH_3$); $\nu_{max}$ (thin film, $cm^{-1}$) 2955.4, 1715.4 (C=O), 1604.2 (C=N), 1558.6, 1509.0, 1435.0 (OMe), 1317.8, 1242.2 ($CO_2Me$), 1202.0, 1183.6, 1099.6, 1072.8, 966.0, 814.7, 788.3, 757.1 (Ar CH), 649.9, 508.9; *m/z* ($ESI^+$) calculated for $C_{16}H_{17}NO_6Na$ [$M+Na^+$]; 342.0954, found: 342.0919.

The methyl 6-methyl-1*H*-indole-2-carboxylate (**55**)[108] impurity from the crude azirine product was isolated from crude dimethyl 2-((3-methoxy-3-oxo-1-(4-tolyl)prop-1-en-2-yl)imino)malonate (**50c**) as a colourless solid:



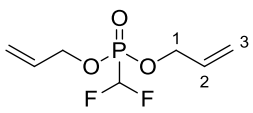

$R_f$= 0.26 (9:1 v/v petroleum ether 40 – 60 °C fraction:EtOAc); Mp: 120 – 122 °C (lit. 97 – 98 °C); $^1$H NMR (400 MHz, $CDCl_3$) $\delta_H$ 8.73 (*br-s,* 1H, N-H), 7.57 (*d, J* 8.0 Hz, 1H, 4-H), 7.20 (*s,* 1H, 7-H), 7.17 (*d, J* 1.5 Hz, 1H, 3-H), 6.99 (*d, J* 8.0 Hz, 1H, 5-H), 3.93 (*s,* 3H, $OCH_3$), 2.47 (*s,* 3H, 6-$CH_3$); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta_C$ 162.4 (C=O), 137.3 (9-C), 135.7 (8-C), 126.5 (6-C), 125.4 (2-C); 123.0 (5-CH); 122.2 (4-CH); 111.5 (7-CH); 108.8 (3-CH); 51.9 ($OCH_3$); 22.0 (6C-$CH_3$); $\nu_{max}$ (solid, $cm^{-1}$) 3326.8 (N-H), 2169.9, 1700.7 (C=O), 1527.1, 1438.6 (OMe), 1334.3, 1266.2 ($CO_2$Me), 1216.7, 832.0, 794.1, 743.2 (Ar CH), 669.0; *m/z* ($EI^+$) calculated for $C_{11}H_{11}NO_2$ [$M^+$]; 189.1, found: 189.1.

Subtraction of the peaks associated with methyl 6-methyl-1*H*-indole-2-carboxylate (**55**) from the crude spectra of methyl 2-(4-tolyl)-2*H*-azirine-3-carboxylate (**14h**)[108] allowed the $^1$H and $^{13}$C NMR characterisation to be assigned:




$^1$H NMR (400 MHz, $CDCl_3$) $\delta_H$ 7.14 (*d, J* 6.5 Hz, 2H, 2'/6'-H), 7.04 (*d, J* 6.5 Hz, 2H, 3'/5'-H), 4.02 (*s,* 3H, $OCH_3$), 3.46 (*s,* 1H, 2-H), 2.34 (*s,* 3H, 4'C-$CH_3$); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta_C$ 163.3 (C=O), 159.1 (C=N), 138.0 (4'-C), 135.2 (1'-C), 129.2 (2'/6'-CH), 126.4 (3'/5'-CH), 53.6 ($OCH_3$), 38.8 (2-CH), 21.2 (4'-$CH_3$).

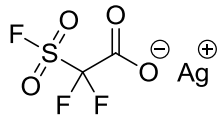
Diallyl (difluoromethyl) phosphonate **78**:[185c]




A solution of dibromodifluoromethane (681 mg, 3.25 mmol) and triallyl phosphite (606 mg, 3.0 mmol) in THF (0.9 mL) under an argon atmosphere in a screw-cap vial was stirred at 100 °C for 6.5 hours. The mixture was concentrated *in vacuo* to give a clear yellow oil (965 mg) which was purified by column chromatography (100 % DCM) to yield diallyl (difluoromethyl) phosphonate as a clear pale yellow oil (279 mg, 43 %): $R_f$= 0.08 (100 % $CH_2Cl_2$); **$^1$**H NMR (400 MHz, $CDCl_3$) $\delta_H$ 5.94 (*dt, $J_{HP}$* 27.7

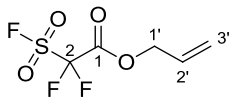
Hz, $J_{HF}$ 50.4 Hz, 1H, $CF_2$-H), 6.03-5.91 (*m,* 2H, 2-H), 5.44-5.31 (*m,* 4H, 3-$H_2$), 4.70 (*d, J* 6.0 Hz, 4H, 1-$H_2$); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta_C$ 131.8 (C-$F_2$H), 119.4 (3-$CH_2$), 111.3 (2-CH), 68.5 (*d, $J_{PC}$* 7.4 Hz, 1-$CH_2$); $^{19}$F NMR (400 MHz, $CDCl_3$) $\delta_F$ -134.86 (*dd, $J_{FH}$* 50.4 Hz, *$J_{FP}$* 93.0 Hz, 1F); $^{31}$P NMR (160 MHz, $CDCl_3$) $\delta_P$ 5.53 (*dtt, $J_{PC}$* 7.4 Hz, *$J_{PH}$* 27.7 Hz, *$J_{PF}$* 93.0 Hz, 1P); $\nu_{max}$ (thin film, $cm^{-1}$) 1458.3, 1425.9, 1265.2 (P=O), 1162.1, 1090.5, 1055.4 (C-F), 1009.5 (P-O-R), 986.1, 931.7, 863.9, 748.3, 648.4. 585.1. 520.9; *m/z* ($ESI^+$) calculated for $C_7H_{12}F_2O_3P$ [$M+H^+$]; 213.0487, found 213.0487 (error = -0.13 ppm).

Silver(I) 2,2-difluoro-2-(fluorosulfonyl)acetate:[184]



2,2-Difluoro-2-(fluorosulfonyl)actetic acid (6.55 g, 36.8 mmol) was added over 30 minutes to a suspension of silver(I) oxide (4.50 g, 19.4 mmol) in $Et_2O$ (25 mL) protected from light and stirred at room temperature for 16 hours. The mixture was filtered and the solvent removed *in vacuo*. The resulting off-white solid was dried under reduced pressure protected from light for 48 hours to yield silver(I) 2,2-difluoro-2-(fluorosulfonyl)acetate as an off-white solid (10.4 g, 99 %): Mp: 151 – 152 °C (lit. 158 – 160 °C); $^{13}$C NMR (100 MHz, $D_2O$) $\delta_C$ 159.8 (C=O), 114.3 (C-$F_2$); $^{19}$F NMR (400 MHz, $D_2O$) $\delta_F$ -37.2 (*s,* 1F, F-$SO_2$), -101.3 (2F, *d, J* 4.0 Hz, C-$F_2$); $\nu_{max}$ (solid, $cm^{-1}$) 3607, 3386, 1671 (C=O), 1427 (C=O), 1382 ($SO_2$), 1230, 1170 (C-F), 995, 831, 799 (S-F), 715, 647.

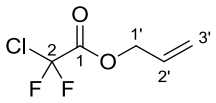
Allyl 2,2-difluoro-2-(fluorosulfonyl)acetate **75**:[184]



Allyl bromide (4.30 g, 35.5 mmol) was added to silver 2,2-difluoro-2-(fluorosulfonyl)acetate (9.17 g, 32.3 mmol) at -196 °C. The mixture was warmed to room temperature with stirring for a further 24 hours. The crude oil was distilled to give allyl 2,2-difluoro-2-(fluorosulfonyl)acetate as a clear colourless oil (6.10 g, 87 %): Bp: 45 – 47 °C at 25 mmHg (lit. 141 – 142 °C at 760 mmHg); $^1$H NMR (400 MHz, $CDCl_3$) $\delta_H$ 6.00-5.91 (*m,* 1H, 2'-H), 5.50-5.41 (*m,* 2H, 3'-$H_2$), 4.93 (*d, J* 6.0 Hz, 2H, 1'-$H_2$); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta_C$ 155.9 (C=O), 129.8 (2'-CH), 121.6 (3'-$CH_2$), 112.0 (C-$F_2$), 69.6 (1'-$CH_2$); $^{19}$F NMR (400 MHz, $CDCl_3$) $\delta_F$ 41.1 (*t, J* 4.0 Hz, 1F, F-$SO_2$), -103.5 (*d, J* 4.0 Hz, 2F, C-$F_2$);

$\nu_{max}$ (thin film, $cm^{-1}$) 1780.0 (C=O), 1444.9 (C-O), 1370.9 ($SO_2$), 1309.9, 1232.3, 1193.6, 1145.2 (C-F), 991.0, 938.3, 893.9, 824.0, 795.0 (C-F), 726.5, 638.7, 562.2, 485.8, 459.2; *m/z* ($EI^+$) calculated for $C_5H_5F_3O_4S$ [$M^+$]; 218.0, found 218.0.

Allyl 2-chloro-2,2-difluoroacetate **74**:[178]



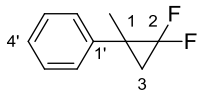

In a 2-neck flask fitted with a Dean-Stark apparatus and thermometer for monitoring the internal temperature of the reaction, chlorodifluoroacetic acid (9.79 g, 75.0 mmol) and allyl alcohol (5.98 g, 103 mmol) in *n*-hexane (10 mL) were stirred with heating 9 hours, maintaining the internal temperature of the reaction mixture between 70 – 75 °C. The reaction mixture was cooled to room temperature, washed with water (2 x 10 mL), dried over anhydrous magnesium sulfate and the solvent removed *in vacuo* to yield allyl 2-chloro-2,2-difluoroacetate as a clear pale yellow oil without the need for further purification (2.85 g, 22 %): $^1$H NMR (400 MHz, $CDCl_3$) $\delta_H$ 6.01-5.91 (*m,* 1H, 2'-H), 5.48-5.37 (*m,* 2H, 3'-$H_2$), 4.83 (*d, J* 5.5 Hz, 2H, 1'-$H_2$); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta_C$ 159.0 (C=O), 129.7 (2'-CH), 120.8 (3'-$CH_2$), 116.8 (C-$F_2$Cl); 68.5 (1'-$CH_2$); $^{19}$F NMR (400 MHz, $CDCl_3$) $\delta_F$ -63.85 (s, 2F, CCl-$F_2$); $\nu_{max}$ (thin film, $cm^{-1}$) 1777.7 (C=O), 1651.1, 1455.2, 1426.1, 1370.4, 1304.7 (C-O), 1166.5, 1119.4 (C-F), 981.6, 940.2, 809.6, 729.6 (C-Cl), 624.2, 551.4; *m/z* ($EI^+$) calculated for $C_5H_5F_2O_2Cl$ [$M^+$]; 170.0, found 170.5.

**General microwave procedure for the addition of difluorocarbene to aryl alkenes:**

All chemicals and solvents were supplied by Sigma Aldrich and Fisher Scientific and were used as received. No prior drying of the reaction vessel was performed and all experiments were run under an air atmosphere. All microwave reactions were performed using a Milestone MicroSYNTH reactor and Q20 vessel with Weflon™ button and magnetic stirring bead. Twist control, rotor control, start parameters and continuous power were all selected. T2 control was used with 80-90 % stirring.

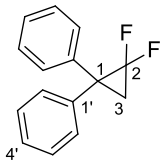
Sodium chlorodifluoroacetate (914 mg, 6.0 mmol) was completely dissolved in 4.0 mL of a 0.5 mmol $mL^{-1}$ THF solution of alkene and exposed to microwave irradiation (300 W, 170 °C, 5 min). After cooling, the reaction mixture was diluted with water (20 mL), extracted with $Et_2O$ (3 x 20 mL), the combined organic extracts dried over anhydrous magnesium sulfate and the solvent removed *in vacuo* to yield the crude products as brown oils. For compounds **80a**, **80d-m** the crude products were purified by column chromatography with 100 % hexane as eluent. For compound **80n** the crude product was purified by column chromatography with 50:1 v/v hexane:EtOAc as eluent.

(2,2-difluoro-1-methylcyclopropyl)benzene **80a**:[198]



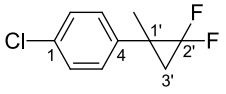

From 2-phenylpropene (236 mg, 2.0 mmol) following the general microwave procedure to yield (2,2-difluoro-1-methylcyclopropyl)benzene as a clear colourless oil (270 mg, 78 %): $R_f$= 0.30 (100 % hexane); $^1$H NMR (400 MHz, $CDCl_3$) $\delta_H$ 7.37-7.25 (*m,* 5H, Ar C<u>H</u>), 1.71-1.66 (*m,* 1H, 3-<u>H</u>$_2$), 1.52 (*dd, J* 3.0, 2.0 Hz, 3H, C<u>H</u>$_3$), 1.43-1.40 (*m,* 1H, 3-<u>H</u>$_2$); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta_C$ 139.1 (1'-<u>C</u>), 128.5 (Ar <u>C</u>H), 128.3 (Ar <u>C</u>H), 127.2 (Ar <u>C</u>H), 114.5 (2-<u>C</u>F$_2$), 31.2 (1-<u>C</u>), 22.5 (3-<u>C</u>H$_2$), 21.4 (<u>C</u>H$_3$); $^{19}$F NMR (400 MHz, $CDCl_3$) $\delta_F$ -132.3-132.7 (*m,* 1F, C<u>F</u>$_2$), -137.3-137.7 (*m,* 1F, C<u>F</u>$_2$); $\nu_{max}$ (thin film, cm$^{-1}$) 2980.7 ($CH_2$), 1499.5, 1468.9 ($CH_2$), 1444.7, 1369.4, 1300.2, 1208.9, 1172.1, 1096.9, 1065.0, 1006.1 (C-F), 932.4, 902.3, 869.0, 764.8, 715.7, 609.9, 544.5, 479.9; *m/z* (EI$^+$) calculated for $C_{10}H_{10}F_2$ [M$^+$]; 168.1, found 168.9; calculated for $C_9H_7F_2$ (M$^+$-$CH_3$); 153.1, found 153.1.

(2,2-difluorocyclopropane-1,1-diyl)dibenzene **80d**:[198]



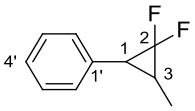

From 1,1-diphenylethene (360 mg, 2.0 mmol) following the general microwave procedure to yield (2,2-difluorocyclopropane-1,1-diyl)dibenzene as a white crystalline solid (412 mg, 87 %): $R_f$= 0.17 (100 % hexane); Mp 73 – 74 °C (lit. 50 – 51 °C); $^1$H NMR (400 MHz, $CDCl_3$) $\delta_H$ 7.41 (*dd, J* 1.5, 7.0 Hz, 4H, 2'/6'-<u>H</u>), 7.31 (*td, J* 1.5, 7.0 Hz, 4H, 3'/5'-<u>H</u>), 7.23 (*tt, J* 1.5, 7.0 Hz, 2H, 4'-<u>H</u>), 2.08 (*t, J* 8.5 Hz, 2H, 3-<u>H</u>$_2$); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta_C$ 138.6 (1'-<u>C</u>), 128.8 (2'/6'-<u>C</u>H), 128.6 (3'/5'-<u>C</u>H), 127.3 (4'-<u>C</u>H), 112.9 (2-<u>C</u>F$_2$), 40.0 (1-<u>C</u>), 23.7 (3-<u>C</u>H$_2$); $^{19}$F NMR (400 MHz, $CDCl_3$) $\delta_F$ -129.88 (*t, J* 8.5 Hz, 2F); $\nu_{max}$ (solid, cm$^{-1}$) 3025.9, 2919.5 ($CH_2$), 1599.6, 1494.2 ($CH_2$), 1447.7, 1438.4, 1367.2, 1301.8, 1280.6, 1207.2, 1070.9, 1027.3 (C-F), 1008.6, 987.9, 912.0, 902.7, 851.0, 831.9, 759.9, 746.4 (Ar CH), 636.2, 609.9, 539.2, 494.2, 475.0; *m/z* (EI$^+$) calculated for $C_{15}H_{12}F_2$ [M$^+$]; 230.1, found 230.0.

1-chloro-4-(2,2-difluoro-1-methylcyclopropyl)benzene **80e**:[209]



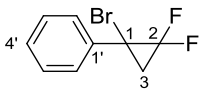
From (4-chlorophenyl)-alpha-methylstyrene (305 mg, 2.0 mmol) following the general microwave procedure to yield 1-chloro-4-(2,2-difluoro-1-methylcyclopropyl)benzene as a clear colourless oil (361 mg, 87 %): $R_f$= 0.37 (100 % hexane); $^1$H NMR (400 MHz, $CDCl_3$) $\delta_H$ 7.31 (*d, J* 8.5 Hz, 2H, 3/5-H), 7.24 (*d, J* 8.5 Hz, 2H, 2/6-H), 1.64 (*ddd, J* 3.5, 7.5, 12.7 Hz, 1H, 3'-$H_2$), 1.49 (*dd, J* 1.8, 3.5 Hz, 3H, C-$H_3$), 1.43 (*ddd, J* 3.5, 7.5, 12.7 Hz, 1H, 3'-$H_2$); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta_C$ 137.6 (1-C), 133.1 (4-C), 129.8 (2/6-CH), 128.7 (3/5-CH), 114.2 (2'-$CF_2$), 30.6 (1'-C), 22.6 (3'-$CH_2$), 21.2 ($CH_3$); $^{19}$F NMR (400 MHz, $CDCl_3$) $\delta_F$ -132.49 (*dd-hex, J* 1.8, 12.7, 150.5 Hz, 1F), -137.62 (*ddhex, J* 1.8, 12.7, 150.5 Hz, 1F); $\nu_{max}$ (thin film, $cm^{-1}$) 2980.0 ($CH_2$), 1493.9, 1469.5 ($CH_2$), 1448.4, 1400.9, 1370.5, 1301.5, 1269.0, 1213.2 (C-F), 1171.9, 1098.3, 1001.9, 932.4, 902.3, 870.0, 827.7, 747.7 (C-Cl), 729.3 (Ar CH), 642.8, 559.9, 518.1, 486.1, 445.6; *m/z* ($EI^+$) calculated for $C_{10}H_9F_2$ [$M^+$-Cl]; 167.1, found: 167.1.

*Trans*-(2,2-difluoro-3-methylcyclopropyl)benzene **80f**:[164]




From *trans*-beta-methylstyrene (236 mg, 2.0 mmol) following the general microwave procedure to yield *trans*-(2,2-difluoro-3-methylcyclopropyl)benzene as a clear pale yellow oil (271 mg, 78 %): $R_f$= 0.33 (100 % hexane); $^1$H NMR (400 MHz, $CDCl_3$) $\delta_H$ 7.32 (*t, J* 7.0 Hz, 2H, 3'/5'-H), 7.25 (*t, J* 7.0 Hz, 1H, 4'-H), 7.19 (*d, J* 7.0 Hz, 2H, 2'/6'-H), 2.28 (*dq, J 6.7, 13.0 Hz,* 1H, 1-H), 1.84 (*d septet, J 1.0, 6.7 Hz,* 1H, 3-H), 1.34 (*dd, J* 1.0, 6.7 Hz, 3H, $CH_3$); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta_C$ 134.3 (1'-C), 128.4 (3'/5'-CH), 127.8 (2'/6'-CH), 126.9 (4'-CH), 114.7 (2-$CF_2$), 34.0 (1-C), 24.3 (3-C), 11.5 ($CH_3$); $^{19}$F NMR (400 MHz, $CDCl_3$) $\delta_F$ -137.86 (*dq, J* 13.0, 164.0 Hz, 2F); $\nu_{max}$ (thin film, $cm^{-1}$) 3029.7 (C-H), 2974.3, 1600.8, 1502.3, 1475.0, 1439.2, 1387.4, 1326.2, 1265.3, 1218.6, 1183.7, 1134.6, 1097.3, 1056.3, 1033.5, 1020.8 (C-F), 1002.4, 984.7, 954.7, 909.2, 861.3, 764.4, 745.3 (Ar CH), 695.1, 652.3, 600.2, 507.6, 474.7; *m/z* ($EI^+$) calculated for $C_{10}H_{10}F_2$ [$M^+$]; 168.1, found 167.8; $C_9H_7F_2$ [M-$CH_3^+$]; 153.1, found 153.0; $C_4H_5F_2$ [M-$C_6H_5^+$]; 91.0, found 90.9.

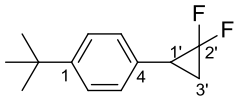
(1-bromo-2,2-difluorocyclopropyl)benzene **80g**:[198]




From alpha-bromostyrene (366 mg, 2.0 mmol) following the general microwave procedure to yield (1-bromo-2,2-difluorocyclopropyl)benzene as a clear colourless oil (363 mg, 76 %): $R_f$= 0.31 (100 % hexane); $^1$H NMR (400 MHz, $CDCl_3$) $\delta_H$ 7.48 (*dd, J* 1.6, 8.2 Hz, 2H, 2'/6'-H), 7.41-7.33 (*m,* 3H,

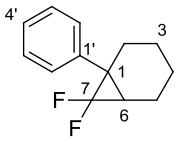
3'/4'/5'-H), 2.25 (*ddd, J* 4.8, 9.5, 18.0 Hz, 1H, 3-$H_2$), 2.08 (*ddd, J* 4.8, 9.6, 14.8 Hz, 1H, 3-$H_2$); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta_C$ 136.2 (1'-C), 129.3 (2'/6'-CH), 129.2 (Ar CH), 128.9 (Ar CH), 109.5 (2-$CF_2$), 34.1 (1-CBr), 26.9 (3-$CH_2$); $^{19}$F NMR (400 MHz, $CDCl_3$) $\delta_F$ 127.17 (*ddd, J* 4.8, 10.7, 150.0 Hz, 1F), 132.10 (*ddd J* 4.8, 13.6, 150.0 Hz, 1F); $\nu_{max}$ (thin film, $cm^{-1}$) 1498.2, 1443.4 ($CH_2$), 1366.3, 1264.4, 1224.2 (C-F), 1059.2, 1025.2, 1011.2, 982.1, 917.1, 896.4, 748.6 (Ar CH), 693.4, 654.2 (C-Br), 607.3; *m/z* ($EI^+$) calculated for $C_9H_7BrF_2$ [$M^+$]; 231.9699, found 232.0; $C_9H_7F_2$ [$M^+$-Br]; 153.1, found 153.0.

1-(*tert*-butyl)-4-(2,2-difluorocyclopropyl)benzene **80h**:[209]




From 4-*tert*-butylstyrene (320 mg, 2.0 mmol) following the general microwave procedure to yield 1-(*tert*-butyl)-4-(2,2-difluorocyclopropyl)benzene as a clear colourless oil (325 mg, 75 %): $R_f$= 0.26 (100 % hexane); $^1$H NMR (400 MHz, $CDCl_3$) $\delta_H$ 7.35 (*d, J 8.5 Hz,* 2H, 3/5-H), 7.16 (*d, J 8.5 Hz,* 2H, 2/6-H), 2.72 (*dt, J* 8.0, 12.0 Hz, 1H, 1'-H), 1.85-1.74 (*m,* 1H, 3'-$H_2$), 1.64-1.55 (*m,* 1H, 3'-$H_2$), 1.31 (*s,* 9H, $^t$Bu $CH_3$); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta_C$ 150.1 (4-C), 130.6 (1-C), 127.7 (2/6-CH), 125.4 (3/5-CH), 112.7 (2'-$CF_2$), 34.5 (C$(CH_3)_3$), 31.3 ($^t$Bu $CH_3$), 26.8 (1'-C), 17.0 (3'-C); $^{19}$F NMR (400 MHz, $CDCl_3$) $\delta_F$ -125.86 (*ddt, J* 4.3, 12.8, 153.5 Hz, 1F), -142.37 (*ddd, J* 4.3, 12.8, 153.5 Hz, 1F); $\nu_{max}$ (thin film, $cm^{-1}$) 2962.8 ($CH_2$), 2868.7, 1519.5, 1467.9, 1409.2, 1378.0, 1364.1, 1324.1, 1303.8 ($CMe_3$), 1269.2, 1230.9, 1188.0, 1112.6, 1086.6, 1043.3 (C-F), 1018.0, 956.0, 932.1, 897.8, 832.9 (Ar CH), 773.8, 719.9, 698.6, 610.6, 549.8, 527.8, 486.4, 464.9, 439.7; *m/z* ($EI^+$) calculated for $C_{13}H_{16}F_2$ [$M^+$]; 210.1, found 210.1; $C_9H_7F_2$ [$M^+$-$C(CH_3)_3$]; 153.1, found 153.0.

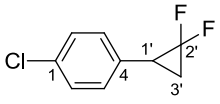
7,7-difluoro-1-phenylbicyclo[4.1.0]heptane **80i**:[165]




From 1-phenyl-1-cyclohexene (316 mg, 2.0 mmol) following the general microwave procedure to yield 7,7-difluoro-1-phenylbicyclo[4.1.0]heptane as a clear pale yellow oil (318 mg, 75 %): $R_f$= 0.26 (100 % hexane); $^1$H NMR (400 MHz, $CDCl_3$) $\delta_H$ 7.34-7.22 (*m,* 5H, Ar CH), 2.20-2.15 (*m,* 1H, 5-H), 2.03-1.96 (*m,* 1H, 2-$H_2$), 1.86-1.73 (*m,* 3H, 2/5/6-$H_2$), 1.49-1.31 (*m,* 4H, 3/4-$H_2$); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta_C$ 141.8 (1'-C), 128.5 (Ar CH), 128.3 (Ar CH), 126.8 (Ar CH), 115.7 (7-$CF_2$), 31.0 (1-C), 27.3 (5-$CH_2$), 23.3 (6-CH), 21.1 (4-$CH_2$), 20.7 (3-$CH_2$), 16.9 (2-$CH_2$); $^{19}$F NMR (400 MHz, $CDCl_3$) $\delta_F$ 127.75 (*dd, J* 16.0, 160.0 Hz, 1F), 143.00 (*d, J* 160.0 Hz, 1F); $\nu_{max}$ (thin film, $cm^{-1}$) 2944.1 (C-H), 2857.1 ($CH_2$),

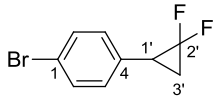
1602.1, 1495.8, 1469.9, 1459.6, 1446.7, 1429.0 ($CH_2$), 1333.0, 1298.5, 1251.3, 1193.9 (C-F), 1094.2, 1073.1, 1046.0, 1014.3, 990.7, 929.8, 896.9, 869.7, 838.4, 817.6, 757.6, 738.9 (Ar CH), 631.5, 615.6, 550.6, 530.3, 503.7, 486.8, 457.1; *m/z* ($EI^+$) calculated for $C_{13}H_{14}F_2$ [$M^+$]; 208.1, found 208.1.

1-chloro-4-(2,2-difluorocyclopropyl)benzene **80j**:



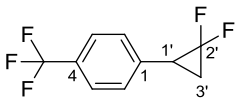

From 4-chlorostyrene (277 mg, 2.0 mmol) following the general microwave procedure to yield 1-chloro-4-(2,2-difluorocyclopropyl)benzene as a clear pale yellow oil (279 mg, 72 %): $R_f$= 0.33 (100 % hexane); $^1$H NMR (400 MHz, $CDCl_3$) $\delta_H$ 7.28 (*d, J 8.5 Hz,* 2H, 3/5-H), 7.13 (*d, J 8.5 Hz,* 2H, 2/6-H), 2.70 (*dt, J* 8.0, 12.5 Hz, 1H, 1'-H), 1.86-1.77 (*m,* 1H, 3'-$H_2$), 1.61-1.59 (*m,* 1H, 3'-$H_2$); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta_C$ 133.1 (1-C), 132.2 (4-C), 129.4 (2/6-CH), 128.7 (3/5-CH), 112.3 (2'-$CF_2$), 26.6 (1'-CH), 17.2 (3'-$CH_2$); $^{19}$F NMR (400 MHz, $CDCl_3$) $\delta_F$ -126.02 (*ddt, J* 4.5, 12.5, 154.5 Hz, 1F), -142.22 (*ddd, J* 4.5, 12.5, 154.5 Hz, 1F); $\nu_{max}$ (thin film, $cm^{-1}$): 1495.8, 1465.9 ($CH_2$), 1405.2, 1380.5, 1298.7, 1230.2, 1188.6, 1095.1, 1040.1, 1016.1 (C-F), 958.0, 930.8, 897.7, 828.4 (Ar CH), 773.1 (C-Cl), 725.4, 640.5, 602.7, 506.5; *m/z* ($EI^+$) calculated for $C_9H_7ClF_2$ [$M^+$]; 188.0, found 188.0; $C_9H_7F_2$ [$M^+$-Cl]; 153.1, found 153.1.

1-bromo-4-(2,2-difluorocyclopropyl)benzene **80k**:[198]



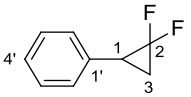

From 4-bromostyrene (366 mg, 2.0 mmol) following the general microwave procedure to yield 1-bromo-4-(2,2-difluorocyclopropyl)benzene as a clear colourless oil (339 mg, 71 %): $R_f$= 0.31 (100 % hexane); $^1$H NMR (400 MHz, $CDCl_3$) $\delta_H$ 7.45 (*d, J 8.5 Hz,* 2H, 3/5-H), 7.09 (*d, J 8.5 Hz,* 2H, 2/6-H), 2.70 (*dt, J* 8.0, 12.5 Hz, 1H, 1'-H), 1.88-1.79 (*m,* 1H, 3'-$H_2$), 1.63-1.60 (*m,* 1H, 3'-$H_2$); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta_C$ 132.7 (1-C), 131.6 (3/5-CH), 129.7 (2/6-CH), 121.1 (4-C), 112.2 (2'-$CF_2$), 26.6 (1'-C), 17.2 (3'-C); $^{19}$F NMR (400 MHz, $CDCl_3$) $\delta_F$ -126.04 (*ddt, J* 4.4, 12.5, 154.0 Hz, 1F), -142.21 (*ddd, J* 4.4, 12.5, 154.0 Hz, 1F); $\nu_{max}$ (thin film, $cm^{-1}$) 2979.9 ($CH_2$), 1492.9, 1463.9 ($CH_2$), 1398.1, 1377.2, 1317.8, 1298.8, 1228.4, 1187.3, 1115.3, 1074.1, 1039.3, 1011.5 (C-F), 956.5, 929.9, 897.0, 825.0 (Ar CH), 766.3, 719.4 ($CH_2$), 621.8, 593.8, 503.6 (C-Br); *m/z* ($EI^+$) calculated for $C_9H_7BrF_2$ [$M^+$]; 232.0, found 231.9; $C_9H_7F_2$ [$M^+$-Br]; 153.1, found 153.0.

1-(2,2-difluorocyclopropyl)-4-(trifluoromethyl)benzene **80l**:



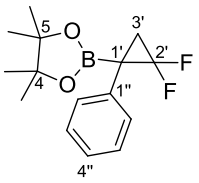

From 4-(trifluoromethyl)styrene (344 mg, 2.0 mmol) following the general microwave procedure to yield 1-(2,2-difluorocyclopropyl)-4-(trifluoromethyl)benzene as a clear colourless oil (306 mg, 67 %): $R_f$= 0.28 (100 % hexane); $^1$H NMR (400 MHz, $CDCl_3$) $\delta_H$ 7.59 (*d, J* 8.0 Hz, 2H, 3/5-H), 7.34 (*d, J* 8.0 Hz, 2H, 2/6-H), 2.80 (*dt, J* 8.0, 12.4 Hz, 1H, 1'-H), 1.95-1.86 (*m,* 1H, 3'-$H_2$), 1.71-1.68 (*m,* 1H, 3'-$H_2$); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta_C$ 137.8 (4-C), 129.5 ($CF_3$), 128.4 (3/5-CH), 125.4 (2/6-CH), 122.7 (1-C), 112.1 (2'-$CF_2$), 27.0 (1'-CH), 17.4 (3'-$CH_2$); $^{19}$F NMR (400 MHz, $CDCl_3$) $\delta_F$ -62.5 (*s,* 3F, $CF_3$), -125.82 (*ddt, J* 4.6, 12.4, 155.0 Hz, 1F, $CF_2$), -142.18 (*ddd, J* 4.6, 12.4, 155.0 Hz, 1F, $CF_2$); $\nu_{max}$ (thin film, $cm^{-1}$): 1680.8, 1623.1, 1524.2, 1468.1 ($CH_2$), 1413.6, 1381.3, 1322.1 (C-F), 1234.8, 1190.2, 1165.0, 1114.6 (C-F), 1069.2, 1038.4, 1018.4, 961.1, 933.7, 898.7, 841.3 (Ar CH), 791.3, 755.4, 728.9 ($CH_2$), 697.6, 629.2, 597.0, 507.0, 479.4; *m/z* ($EI^+$) calculated for $C_{10}H_7F_5$ [$M^+$]; 222.0, found 222.0; $C_9H_7F_2$ [$M^+$-$CF_3$]; 153.1, found 153.0.

(2,2-difluorocyclopropyl)benzene **80m**:[165]



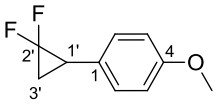

From styrene (208 mg, 2.0 mmol) following the general microwave procedure to yield (2,2-difluorocyclopropyl)benzene as a clear colourless oil (123 mg, 42 %): $R_f$= 0.28 (100 % hexane); $^1$H NMR (400 MHz, $CDCl_3$) $\delta_H$ 7.35-7.22 (*m,* 5H, Ar CH), 2.80-2.73 (*m,* 1H, 1-H), 1.86-1.77 (*m,* 1H, 3-$H_2$), 1.67-1.58 (*m,* 1H, 3-$H_2$); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta_C$ 133.7 (1'-C), 128.5 (Ar CH), 128.0 (Ar CH), 127.2 (Ar CH), 112.6 (2-$CF_2$), 27.2 (1-CH), 17.0 (3-$CH_2$); $^{19}$F NMR (400 MHz, $CDCl_3$) $\delta_F$ -125.86 (*ddt, J* 4.0, 12.0, 164.0 Hz, 1F), -142.38 (*ddd, J* 4.0, 12.0, 164.0 Hz, 1F); $\nu_{max}$ (thin film, $cm^{-1}$) 2926.2 ($CH_2$), 1606.2, 1504.3, 1467.7 ($CH_2$), 1443.4, 1377.4, 1301.0, 1228.6, 1189.9, 1092.7, 1045.5, 1018.7 (C-F), 1001.3, 855.4, 932.4, 910.9, 864.6, 816.7, 778.0, 742.0 (Ar CH), 742.0 ($CH_2$), 615.5, 562.6, 544.1, 504.7; *m/z* ($EI^+$) calculated for $C_9H_8F_2$ [$M^+$]; 154.1, found 154.0.

2-(2,2-Difluoro-1-phenylcyclopropyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane **80n**:[209]



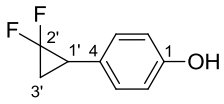

From 1-phenylvinylboronic acid pinacol ester (460 mg, 2.0 mmol) following the general microwave procedure to yield 2-(2,2-Difluoro-1-phenylcyclopropyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane as a white crystalline solid (392 mg, 70 %): $R_f$= 0.07 (50:1 v/v hexane:EtOAc); Mp: 93 – 95 °C (lit. 97 – 99 °C); $^1$H NMR (400 MHz, $CDCl_3$) $\delta_H$ 7.32-7.21 (*m,* 5H, Ar C<u>H</u>), 2.06 (*quin, J* 5.2 Hz*,* 1H, 3'-<u>$H_2$</u>), 1.70 (*dddd, J* 2.5, 5.2, 11.2, 18.6 Hz, 1H, 3'-<u>$H_2$</u>), 1.23 (*s,* 6H, C<u>$H_3$</u>), 1.19 (*s,* 6H, C<u>$H_3$</u>); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta_C$ 136.2 (1''-C), 129.2 (Ar <u>C</u>H), 128.2 (Ar <u>C</u>H), 126.6 (Ar <u>C</u>H), 114.2 (2''-<u>C</u>$F_2$), 84.5 (4/5-C), 24.7 (<u>C</u>$H_3$), 24.5 (1'-<u>C</u>) 24.4 (<u>C</u>$H_3$), 20.5 (3'-<u>C</u>$H_2$); $^{19}$F NMR (400 MHz, $CDCl_3$) $\delta_F$ -125.16 (*ddd, J* 2.5, 11.2, 145.0 Hz, 1F), -132.08 (*ddd, J* 5.2, 11.2, 145.0 Hz, 1F); $\nu_{max}$ (solid, cm$^{-1}$) 2974.0 ($CH_2$), 1730.9, 1601.8, 1494.1, 1446.8 ($CH_2$), 1403.1, 1392.0, 1370.7 (B-O), 1353.7, 1328.9, 1274.6, 1253.2, 1212.3 (B-C), 1167.7, 1144.1, 1111.9 (C=O), 1076.4, 1040.4 (C-F), 1030.2, 1016.1, 1000.5, 955.7, 911.8, 874.7, 847.1, 826.2, 767.3, 744.8 (Ar CH), 698.2, 675.3, 669.1, 645.9, 577.6, 527.5, 491.7, 454.4, 433.1; *m/z* (EI$^+$) calculated for $C_{15}H_{19}BF_2O_2$ [M$^+$]; 280.1, found 280.8.

1-(2,2-difluorocyclopropyl)-4-methoxybenzene **80p**:[198]



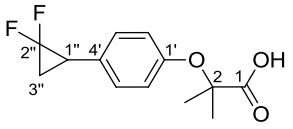

4-Methoxystyrene (268 mg, 2.0 mmol) was converted to 1-(2,2-difluorocyclopropyl)-4-methoxybenzene following the general microwave procedure. An analytically pure sample of 1-(2,2-difluorocyclopropyl)-4-methoxybenzene was obtained as a pale yellow oil by kügelrohr distillation of the crude brown oil: Bp: 93 – 120 °C at 15 mbar (lit. 92 – 95 °C at 15 mbar); $^1$H NMR (400 MHz, $CDCl_3$) $\delta_H$ 7.15 (*d, J* 8.7 Hz, 2H, 2/6-<u>H</u>), 6.87 (*d, J* 8.7 Hz, 2H, 3/5-<u>H</u>), 3.80 (*s,* 3H, OC<u>$H_3$</u>), 2.73-2.65 (*m,* 1H, 1'-<u>H</u>), 1.82-1.73 (*m,* 1H, 3'-<u>$H_2$</u>), 1.58-1.55 (*m,* 1H, 3'-<u>$H_2$</u>); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta_C$ 158.7 (4-<u>C</u>), 129.2 (2/6-<u>C</u>H), 125.6 (1-<u>C</u>), 113.9 (3/5-<u>C</u>H), 112.7 (2'-<u>C</u>$F_2$), 55.3 (O<u>C</u>$H_3$), 26.4 (3'-<u>C</u>$H_2$), 16.9 (1'-<u>C</u>H); $^{19}$F NMR (400 MHz, $CDCl_3$) $\delta_F$ -126.2 (*dtd, J* 3.9, 13.0, 153.5 Hz, 1F), -142.3 (*ddd, J* 4.8, 13.0, 153.5 Hz, 1F); $\nu_{max}$ (thin film, cm$^{-1}$) 2960.4 ($CH_2$), 1838.3, 1746.3, 1613.6, 1583.5, 1515.4 (C-O), 1466.8 ($CH_2$), 1416.8, 1379.0, 1322.1, 1299.0, 1247.8, 1229.7, 1179.1, 1115.3, 1087.7, 1046.1, 1020.1 ($CF_2$), 953.1, 930.1, 896.6, 830.1, 805.5, 742.4 ($CH_2$), 704.7, 609.7, 518.4, 485.7; *m/z* (EI$^+$) calculated for $C_{10}H_{10}F_2O$ [M$^+$]; 184.1, found 184.1; $C_9H_7F_2O$ [M$^+$-$CH_3$] 169.0, found 169.1; $C_9H_7F_2$ [M$^+$-$CH_3O$]; 153.1, found 153.1; $C_3H_3F_2$ [M$^+$-$C_7H_8O$]; 77.1, found 77.0.

4-(2,2-difluorocyclopropyl)phenol **80q**:




4-Methoxystyrene (268 mg, 2.0 mmol) was converted to 4-(2,2-difluorocyclopropyl)phenol following the general microwave procedure in quantitative yield as observed by $^{1}H$ and $^{19}F$ NMR. The crude brown oil containing 1-(2,2-difluorocyclopropyl)-4-methoxybenzene was dissolved in DCM (2 mL) and cooled to 0 °C. To this was added a solution of $BBr_3$ (501 mg, 2.00 mmol) in DCM (2 mL) dropwise and the mixture stirred at 0 °C for 1 hour then room temperature for 1 hour. The reaction was diluted with water (10 mL), the aqueous layer extracted with DCM (2 x 10 mL), the combined organic extracts washed with water (10 mL) and 1N aqueous sodium hydroxide (10 mL) and the combined aqueous layers acidified (HCl). The acidic aqueous solution was extracted with $Et_2O$ (3 x 20 mL), the combined organic extracts dried over anhydrous sodium sulfate and concentrated *in vacuo* to yield 1,1-difluoro-2-(4-phenoxy)cyclopropane as a brown oil without the need for further purification (304 mg, 89 % from 4-methoxystyrene): $^{1}H$ NMR (400 MHz, $CDCl_3$) $\delta_H$ 7.11 (*d, J* 8.5 Hz, 2H, 2/6-H), 6.80 (*d, J* 8.5 Hz, 2H, 3/5-H), 4.55 (*br-s,* 1H, OH), 2.69 (*dt, J* 8.1, 12.6 Hz, 1H, 1'-H), 1.82-1.73 (*m,* 1H, 3'-$H_2$), 1.59-1.58 (*m,* 1H, 3'-$H_2$); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta_C$ 154.6 (1-C), 129.4 (2/6-CH), 125.9 (4-C), 115.4 (3/5-CH), 112.7 (2'-$CF_2$), 26.4 (1'-CH), 16.9 (3'-$CH_2$); $^{19}F$ NMR (400 MHz, $CDCl_3$) $\delta_F$ 126.2 (*ddt, J* 3.8, 12.6, 153.5 Hz, 1F), 142.3 (*ddd, J* 4.8, 12.6, 153.5 Hz, 1F), $\nu_{max}$ (thin film, $cm^{-1}$) 3314.5 (O-H), 1615.2, 1518.3, 1472.0 ($CH_2$), 1439.5, 1378.4, 1314.0, 1229.7, 1190.4, 1113.0, 1045.6 (C-F), 1021.9, 957.8, 932.0, 891.2, 833.0 (Ar CH), 746.3 ($CH_2$), 709.9, 610.1, 518.6, 486.9, 437.9; *m/z* ($EI^+$) calculated for $C_9H_8F_2O$ [$M^+$]; 170.1, found: 170.0; $C_3H_3F_2$ [$M^+$-$C_6H_5O$]; 77.1, found 77.1.

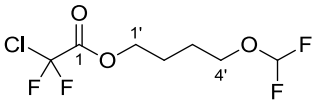
2-(4-(2,2-difluorocyclopropyl)phenoxy)-2-methylpropanoic acid **82**:




Chloroform (226 mg, 1.89 mmol) was added dropwise to a mixture of 4-(2,2-difluorocyclopropyl)phenol (304 mg, 1.78 mmol) and sodium hydroxide (314 mg, 7.85 mmol) in acetone (9 mL) at gentle reflux with stirring for a further 3 hours. The reaction mixture was cooled to 0 °C and filtered and the solid washed with ice-cold acetone. The acetone washings were made basic with aqueous sodium hydroxide and the organic solvent removed *in vacuo*. The aqueous mixture was acidified (HCl) and extracted with $Et_2O$ (3 x 25 mL), the combined organic extracts dried over anhydrous sodium sulfate and the solvent removed *in vacuo* to yield a brown oil (516 mg) which crystallised on standing at -20 °C over night. The crude solid was recrystallised from minimal hot benzene:hexane at 65 °C to yield 2-(4-(2,2-difluorocyclopropyl)phenoxy)-2-methylpropanoic acid as a

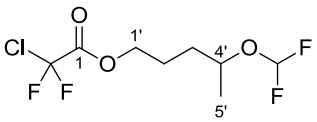
pale brown crystalline solid (209 mg, 41 %): Mp: 94 – 96 °C (lit. 97 – 99 °C); $^{1}$H NMR (400 MHz, $CDCl_3$) $\delta_H$ 9.72 (*br-s,* 1H, $CO_2$-H), 7.14 (*d, J* 8.4 Hz, 2H, 3'/5'-H), 6.90 (*d, J* 8.4 Hz, 2H, 2'/6'-H), 2.70 (*dt, J* 8.4, 12.5 Hz, 1H, 1''-H), 1.85-1.76 (*m,* 1H, 3''-$H_2$), 1.60 (*s,* 6H, $CH_3$), 1.60-1.56 (*m,* 1H, 3''$H_2$); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta_C$ 177.6 (C=O), 153.3 (1'-C), 129.0 (3'/5'-CH), 128.7 (4'-C); 120.6 (2'/6'-CH), 112.5 (2''-$CF_2$), 79.8 (2-C), 26.5 (1''-CH), (25.0 ($CH_3$), 17.2 (3''-$CH_2$); $^{19}$F NMR (400 MHz, $CDCl_3$) $\delta_F$ -126.05 (*ddt, J* 4.0, 12.5, 163.4 Hz, 1F), -142.32 (*ddd, J* 4.8, 12.5, 163.4 Hz, 1F); $\nu_{max}$ (solid, $cm^{-1}$) 2997.0 (O-H), 2910.1 ($CH_2$), 2686.7, 1701.2 (C=O), 1614.0, 1514.6, 1463.0 ($CH_2$), 1418.1, 1382.1, 1369.3, 1324.7, 1287.4, 1234.7, 1180.9, 1153.0 (C-O), 1123.1, 1087.4, 1038.8, 1025.2 ($CF_2$), 938.8, 904.3, 831.8 (Ar CH), 776.6, 748.4 ($CH_2$), 101.0, 645.8, 619.4, 595.4, 582.3, 559.7, 518.2, 480.6; *m/z* (ESI$^+$) calculated for $C_{13}H_{13}F_2O_3Na$ [M+Na$^+$]; 278.0731, found 278.0751 (error = 7.32 ppm).

4-(difluoromethoxy)butyl 2-chloro-2,2-difluoroacetate **83**:



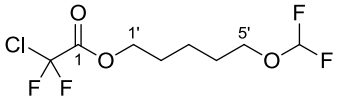

Sodium chlorodifluoroacetate (932 mg, 6.1 mmol) was dissolved in tetrahydrofuran (4 mL) and exposed to microwave radiation (300 W, 160 °C, 5 minutes). The reaction mixture was diluted with water (20 mL) and extracted with $Et_2O$ (3 x 20 mL). The combined organic extracts were dried over anhydrous magnesium sulfate and the solvent removed *in vacuo* give a brown oil (347 mg) which was purified by column chromatography (9:1 v/v hexane:EtOAc) to yield 4-(difluoromethoxy)butyl 2-chloro-2,2-difluoroacetate as an unstable light brown oil (169 mg, 22 %): $R_f$= 0.42 (9:1 v/v hexane:EtOAc); $^{1}$H NMR (400 MHz, $CDCl_3$) $\delta_H$ 6.21 (*t, J 74.5 Hz,* 1H, $CF_2$-H), 4.40 (*t, J 6.1 Hz,* 2H, 1'-$H_2$), 3.91 (*t, J* 6.1 Hz, 2H*,* 4'-$H_2$), 1.92-1.86 (*m,* 2H, C$H_2$), 1.80-1.73 (*m,* 2H, C$H_2$); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta_C$ 159.3 (C=O), 116.8 (2-$CF_2$Cl), 115.9 (C-$F_2$H), 67.8 (1'-C), 62.4 (4'-C), 25.3 ($CH_2$), 24.8 ($CH_2$); $^{19}$F NMR (400 MHz, $CDCl_3$) $\delta_F$ -63.94 (*s,* 2F, 2C$F_2$Cl), -84.36 (*d, J* 74.5 Hz, 2F, C$F_2$H); $\nu_{max}$ (thin film, $cm^{-1}$) 2970.3 ($CH_2$), 1777.1 (C=O), 1469.3 ($CH_2$), 1308.3, 1167.5 (C-O), 1125.0 (C-F), 1070.7, 973.5, 829.9, 729.0,(C-Cl) 627.5, 534.6; *m/z* (EI$^+$) calculated for $C_6H_8ClF_2O_2$ [M$^+$-$CF_2HO$]; 185.0, found 185.0; $C_5H_9F_2O$ [M$^+$-$C_2ClF_2O_2$]; 123.1, found 123.0; $CClF_2$ [M$^+$-$C_6F_2H_9O_3$]; 85.0, found 85.0.

4-(difluoromethoxy)pentyl 2-chloro-2,2-difluoroacetate **85**:



Sodium chlorodifluoroacetate (931 mg, 6.1 mmol) was dissolved in 2-methyl tetrahydrofuran (4 mL) and exposed to microwave radiation (300 W, 160 °C, 5 minutes). The reaction mixture was diluted with water (20 mL) and extracted with $Et_2O$ (3 x 20 mL). The combined organic extracts were dried over anhydrous magnesium sulfate and the solvent removed *in vacuo* to give a brown oil (332 mg) which was purified by column chromatography (9:1 v/v hexane:EtOAc) to yield 4-(difluoromethoxy)pentyl 2-chloro-2,2-difluoroacetate as an unstable brown oil (166 mg, 20 %): $R_f$= 0.38 (9:1 v/v hexane:EtOAc); $^1$H NMR (400 MHz, $CDCl_3$) $\delta_H$ 6.20 (*t, J* 74.7 Hz, 1H, $CF_2\underline{H}$), 5.14-5.08 (*m,* 1H, 4'-$\underline{H}$), 3.89-3.87 (*m,* 2H, 1'-$\underline{H}_2$), 1.83-1.68 (*m,* 4H, 2'/3'-$\underline{H}_2$), 1.40 (*d, J* 6.3 Hz, 3H, 5'-$\underline{H}_3$); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta_C$ 158.9 ($\underline{C}$=O), 116.9 (2-$\underline{C}F_2Cl$), 115.9 ($\underline{C}F_2H$), 76.0 (4'-$\underline{C}$H), 62.6 (1'-$\underline{C}H_2$), 31.9 (2'-$\underline{C}H_2$), 24.8 (3'-$\underline{C}H_2$), 19.5 (5'-$\underline{C}H_3$); $^{19}$F NMR (400 MHz, $CDCl_3$) $\delta_F$ -64.2 (*s,* 2F, C$\underline{F}_2$Cl), -84.3 (*d, J* 74.7 Hz, 2F, C$\underline{F}_2$H); $\nu_{max}$ (thin film, $cm^{-1}$) 2969.4 ($CH_2$), 1773.1 (C=O), 1452.3 ($CH_2$), 1385.1, 1363.6, 1308.5, 1168.9 (C-O), 1134.1 (C-F), 1071.2, 1008.7, 970.8, 864.7, 832.9, 728.0 (C-Cl), 626.9; *m/*z ($EI^+$) calculated for $C_8H_{11}ClF_4O_3$ [$M^+$]; 266.0, found 266.0

5-(difluoromethoxy)pentyl 2-chloro-2,2-difluoroacetate **86**:




Sodium chlorodifluoroacetate (936 mg, 6.1 mmol) was dissolved in tetrahydropyran (4 mL) and exposed to microwave radiation (300 W, 160 °C, 10 minutes). The reaction mixture was diluted with water (20 mL) and extracted with $Et_2O$ (3 x 20 mL). The combined organic extracts were dried over anhydrous magnesium sulfate and the solvent removed *in vacuo* to give a brown oil (388 mg) which was purified by column chromatography (95:5 v/v hexane:EtOAc) to yield 5-(difluoromethoxy)pentyl 2-chloro-2,2-difluoroacetate as an unstable pale yellow oil (181 mg, 22 %): $R_f$= 0.24 (95:5 v/v hexane:EtOAc); $^1$H NMR (400 MHz, $CDCl_3$) $\delta_H$ 6.19 (*t, J 75.1 Hz,* 1H, $CF_2\underline{H}$), 4.67 (*t, J 6.5 Hz,* 2H, 1'-$\underline{H}_2$), 3.86 (*t, J* 6.5 Hz, 2H, 5'-$\underline{H}_2$), 1.80 (*quin*, J 6.5 Hz, 2H, 2'-$\underline{H}_2$), 1.70 (*quin, J* 6.5 Hz, 2H, 4'-$\underline{H}_2$), 1.53 (*quin, J* 6.5 Hz, 2H, 3'-$\underline{H}_2$); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta_C$ 159.3 ($\underline{C}$=O), 116.9 (2-$\underline{C}F_2Cl$), 116.0 ($\underline{C}F_2H$), 68.1 (1'-$\underline{C}H_2$), 63.0 (5'-$\underline{C}H_2$), 28.5 (4'-$\underline{C}H_2$), 27.7 (2'-$\underline{C}H_2$), 21.9 (3'-$\underline{C}H_2$); $^{19}$F NMR (400 MHz, $CDCl_3$) $\delta_F$ -63.99 (*s,* 2F, C$\underline{F}_2$Cl), -84.16 (*d, J* 75.1 Hz, 2F, C$\underline{F}_2$H); $\nu_{max}$ (thin film, $cm^{-1}$) 2964.1 ($CH_2$), 1776.7 (C=O), 1461.3 ($CH_2$), 1363.4, 1307.5, 1168.6 (C-O), 1124.7 (C-F), 1070.9, 1006.6, 973.1, 870.9, 820.1, 728.6 (C-Cl), 627.5; *m/*z ($EI^+$) calculated for $C_8H_{11}ClF_4O_3$ [$M^+$]; 266.0, found 266.8.

## CHAPTER 4: REFERENCES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