Synthesis and Applications of Novel Fluorocyclopropanes

MChem Research Project Report

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# Table of Contents

Abstract 1

Acknowledgements 2

1. Introduction 3
   1.1 Fluorine in Medicinal Chemistry 3
   1.2 Cyclopropanes in Medicinal Chemistry 7
   1.3 Fluorocyclopropanes 11
   1.4 Aims and Objectives 14

2. Results and Discussion 16
   2.1 Strategy 16
   2.2 One-Pot Synthesis of Vinyl Fluorides 24
   2.3 Derivatisation 26
      2.3.1 Nitration 26
      2.3.2 Demethylation 27
      2.3.3 Pd-Catalysed Cross-Couplings 28
   2.4 Facial Polarity 30
   2.5 logP 33
   2.6 Flash Vacuum Pyrolysis 35

3. Conclusions 39

4. Further Work 40
   4.1 Asymmetric Synthesis 40
   4.2 Extended One-Pot Procedure 40
   4.3 Enzymatic Studies 41
4.4 Anti-Cancer Properties of 54

5. Experimental

5.1 General Protocols

5.2 General Synthetic Procedures and Analytical Data

5.2.1 Styrenes

5.2.2 Fluorobromoethanes

5.2.3 Vinyl Fluorides

5.2.4 Trifluorocyclopropanes

5.3 Miscellaneous Experimental Procedures

5.3.1 Nitration of 42a

5.3.2 Demethylation of 42a

5.3.3 Pd-Catalysed Cross-Couplings

5.3.4 Synthesis of Difluorocyclopropanes

5.3.5 Synthesis of Monofluorocyclopropanes 40a and 40b

5.3.6 One-Pot Synthesis of Vinyl Fluorides 37a and 37d

5.3.7 Flash Vacuum Pyrolysis

5.4 Determination of logP

6. References
Abstract

Both fluorine and cyclopropane find great utility in medicinal chemistry. There is a growing need to develop methodologies to access fluorinated cyclopropanes. This work presents the synthesis of a novel trifluorocyclopropylbenzene motif generated in a two-step transformation using safe and readily available reagents. The Ruppert-Prakash reagent (TMS-CF₃) is employed to generate difluorocarbene in situ for a [2+1] cycloaddition. 8 examples were synthesised in 33-93% yield bearing a variety of aromatic substituents. A one-pot synthesis of vinyl fluoride intermediates has been developed; allowing access to this new compound class from corresponding styrenes in two steps, namely bromofluorination-dehydrobromination and cyclopropanation. The versatility of this new structural unit has been demonstrated and is found to be stable under acidic and basic conditions. Nitration and Pd-catalysed cross-coupling reactions proceed cleanly on scaffolds bearing the trifluorocyclopropyl motif; facilitating the synthesis of more complex targets. The logP effect was found to be identical to that of a trifluoromethyl group, suggesting isoelectronic similarities between the two groups. Computational studies reveal a dipole moment (~3.0 D) and the distinct facial polarity exhibited by the new structural motif. Demethylation of an aryl ether derivative to the phenol promotes elimination of the benzylic fluoride to generate the corresponding phenol-cyclopropanol. Anti-cancer properties resulting from this reaction are proposed, whereby nucleophilic DNA may form an adduct with the intermediate phenonium. FVP reactions of these compounds were explored and the trifluoro motif yields the corresponding vinyl fluoride, under FVP conditions.
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Section 1 Introduction

1.1 Fluorine in Medicinal Chemistry

In the decades since the 1970s, the field of organofluorine chemistry has grown steadily. Now, around 20% of pharmaceuticals and 35% of agrochemicals contain fluorine.\(^1\),\(^2\),\(^3\),\(^4\),\(^5\) The realisation that fluorine can selectively enhance the pharmacokinetic and physiochemical properties of a drug candidate has rooted this enigmatic atom in the toolkit of every medicinal chemist.\(^6\),\(^7\) Being small (van der Waals radius 1.47 Å, compared to hydrogen at 1.20 Å) and the most electronegative element (3.98 on the Pauling scale), fluorine has emerged as the most ideal isostere for hydrogen in drug design and development. The role of fluorine in pharmacology has been limited only by the lack of sophisticated methods to access fluorinated compounds.

Although fluorine is the most abundant halogen on earth, and the 13th most abundant element, it primarily exists in mineral form (fluorite, CaF\(_2\)).\(^8\) Very few fluorinated natural products exist. Indeed, the most recent discovery of a fluorinated natural product came over 30 years ago with the identification of 4-fluorothreonine (1) (isolated from the Streptomyces cattleya bacteria).\(^9\),\(^10\) Only five such products are known to contain carbon-bound fluorine.\(^11\) In 2012 diatomic fluorine was found to exist in the natural world; low levels are found contained within rocks of the fluorite mineral, which contain traces of radioactive uranium. Its existence there is only possible because CaF\(_2\) is already in its highest oxidisable state.\(^12\) The scarcity of fluorine-containing organic compounds in nature is likely a result of the low presence of diatomic fluorine in nature. Furthermore, fluoride is a poor nucleophile in water (Nature’s solvent) and there is an absence of biochemical methods to oxidise fluoride to F\(^+\). Thus, the evolutionary process has generally been unable to utilise sources of soluble fluorine.

Possibly the most striking exemplification of fluorine’s affects is observed with monofluoroacetic acid (2). Found naturally in the Southern Hemisphere, this metabolite is responsible for the extreme toxicity of over 40 plants, including the South African Gifblaar.\(^13\) A typical leaf from this plant contains enough 2 to kill several adult humans. The steric similarity of the fluorine atom with hydrogen enables 2 to engage in natural metabolic cycles that normally involve acetic acid (3). Fluoroacetate competitively forms fluoroacetyl CoA with coenzyme A, via condensation at the thiol terminus of CoA to afford the corresponding thioester (Scheme 1). A subsequent cascade of reactions, involving inhibition of the citric acid cycle (a major source of metabolic energy in animals), results in a variety of symptoms including nausea, confusion and seizures. Liberation of fluoride from fluoroacetate contributes to a lowering of calcium...
(hypoglycaemia) due to the strong binding energy of CaF$_2$$^{14}$. When left untreated, the accumulative effect is eventually death.$^{13,15}$

![Diagram of biochemical reactions](image)

**Scheme 1.** Structures of 1 and 3 (top). Mode of incorporation of fluorine into the citric acid cycle (bottom).$^{14}$

Although Nature does not appear to have discovered the utility of fluorine, this element can intrinsically improve pharmacokinetic properties. Fluorine has the ability to increase membrane permeability and conformational bias, whilst also decreasing metabolic clearance of a bioactive compound.$^{16,17,18}$ Hence, fluorine can commonly overcome pharmacological and metabolic hurdles in tandem. As a primary function, fluorine is commonly exploited for its isosteric relationship with hydrogen. The similar size, but differing electronic nature, of fluorine with hydrogen provides a chemical tool to modify biological properties.$^{19,20}$ Because of the similarly in the size of the H/F or CH$_3$/CF$_3$ pairs (and the C-F and C-H bond lengths), the physiological differences imposed by these structural switches are primarily due to their electronics rather than steric contributions. Specifically for the H/F isostere pair, the steric effects are estimated to be marginal in terms of alterations to binding site affinity and perturbation to docking.$^{21}$ Furthermore, fluorine can act as a hydroxyl isostere due to its ability to form (weak) hydrogen bonds.$^{22}$ For example, in the development of 5 as an anti-cancer agent, the use of the H/F isostere pair improved potency by 5-fold compared with 4.$^{23,24,25,26}$ The improved binding resulting from an Ar-H to Ar-F transformation is attributed to a variety of
non-covalent interactions of 5 with ATPase. Primarily, this includes three electrostatic interactions between the 4-fluoro substituent and atoms within the surrounding protein. In addition, it is suspected that π-π stacking between the Ar-F group of 5 and a neighbouring protein salt-bridge is promoted because of the high electronegativity of F.

Figure 2. Fluorine as a hydrogen isostere in the development of 5.23-26

The highly electron withdrawing character of fluorine results in a strongly polarized carbon-fluorine bond that can force a conformational bias upon a fluoroalkane (Figure 3).27 C-F bonds have a characteristically low-lying σ*-antibonding orbital, which is primed to participate in hyperconjugation. The overall effect of this is an equilibrium shift towards the gauche conformer.28 Although modest, the affect is enough to influence conformation in many cases.

Figure 3. The conformational influence of fluorine.27

Although fluorine is observed extensively in marketed pharmaceuticals and agrochemicals, around half of this fluorine is in the form of aromatic substituents. New synthetic methods are required to extend structural diversity beyond the Ar-F group. There are still significant challenges involved with the tactical incorporation of fluorine into organic
molecules.\textsuperscript{20, 30, 31} The use of diatomic fluorine, which is a highly reactive gas, remains challenging and is a tool used only by skilled chemists in the most demanding situations.

The dominance of the aryl substituent as the most popular moiety for fluorine substitution is partly due to its revealing character in QSAR analysis. It is common to investigate and modulate drug metabolism using this group.\textsuperscript{32, 33, 34} The highly electron withdrawing nature of fluorine affords a carbon-bond that, compared to carbon-hydrogen, is highly resistant to oxidative metabolism. Indeed, perfluorinated hydrocarbons are generally inert in the body due to their metabolic stability.\textsuperscript{35, 36} Due to the strength of the C-F bond compared to C-H, fluorine often reduces oxidative metabolism. Hence, if installed at a position of metabolic lability, fluorine will often reduce the rate of metabolic degradation of an administered drug.\textsuperscript{37} This, of course, has the benefit of improving bioavailability by extending the half-life of a compound. Further benefits potentially include reducing the dosage required to elicit a desired biological response.\textsuperscript{38}
1.2 Cyclopropanes in Medicinal Chemistry

In recent decades, the cyclopropane ring has become a common scaffold in drug design. The remarkable rise in popularity of the cyclopropyl moiety is a result of its potential to enhance drug potency through various steric and electronic effects. These primarily include: increased blood-brain-barrier permeability; resistance to metabolism; bio-availability; decreased side-effects; and positive contributions to protein binding. For example, gaseous Cyclopropane (6) itself is a powerful anaesthetic. The first incorporations of cyclopropanes into commercial agents began in the 1960s with monoamine oxidase inhibitors (e.g. tranylcypromine, 7) and opioid antagonists such as nalmetrene (8). Figure 4 illustrates the structural variety of marketed cyclopropyl-compounds (6-11). Currently over 100 pharmaceutical products on the market contain at least one cyclopropane ring. Cyclopropane was also ranked the 10th most abundant ring system in the FDA’s 2012 Orange Book (drug database). At least 100 further examples are in clinical/pre-clinical trial stages.

![Figure 4. Examples of cyclopropane-containing drugs 6-11.](image)

Structurally, cyclopropanes are uniquely interesting molecules. The planar arrangement of three carbon-carbon bonds in a trigonal manner results in a significant deviation of bond angle from the idealised 109.5° for sp³-hydrbridised carbon centres. The resulting ring strain (27.5°)
kcal/mol) is the origin of a substantial thermodynamic driving force.\textsuperscript{46} In addition to ring strain, there is a structural necessity for the ring-substituents (hydrogen or otherwise) to be eclipsed, thus substituents respond to steric stress.

The co-planarity and $60^\circ$ angle of the three carbon-carbon bonds gives rise to an enhanced sp$^2$ character.\textsuperscript{47} C-C and C-H bonds in the ring are shorter than in its linear counterpart, as would be expected in double bonds. Intriguing reactivity arises from this double-bond character. The ring may act as an electrophile (when an electron-withdrawing substituent is present), may be susceptible to catalytic hydrogenation and can even form organometallic complexes.\textsuperscript{48, 49} The reaction of cyclopropane with hydrogen bromide clearly demonstrates the double-bond nature of these three-membered rings. This archaical reaction yields the corresponding linear bromopropane (12), as would be expected in the analogous reaction with a simple alkene (Scheme 2). In addition, there are several known examples of bioactive compounds displaying binding affinity to proteins through an electrostatic interaction of a cyclopropane ring with an electron-rich amino acid (e.g. phenylalanine).\textsuperscript{50, 51, 52}

\begin{center}
\[\text{6} \quad \xrightarrow{\text{HBr}} \quad \text{12}\]
\end{center}

\textbf{Scheme 2.} Reaction of cyclopropane with HBr to give 12.\textsuperscript{48, 49}

Cyclopropanes can also be used as configurationally stable isosteres for C-C double bonds. For example, compound 13 is a kinase inhibitor, which was designed to interfere with the regulation of centriole development for the purpose of inhibiting tumour growth.\textsuperscript{53} Although bioactive, its efficacy was limited by low aqueous-solubility and isomerisation of the potent E-alkene to the less active Z-isomer. Compound 14, the cyclopropane-containing biosterioisomer of 13, has a lower IC$_{50}$ (1.8 vs 4.0 nM) and significantly improved water solubility (1.7 vs <0.1 $\mu$g/ml) due to the configurational stability and increased sp$^3$ character of the cyclopropane.
The cyclopropane can be an ambivalent group with adjustable functions. When employed as a stable unit, it can be seen as a lipophilic and rigid building block which holds functional groups in a defined orientation that may not otherwise be conformationally accessible. Conversely, cyclopropanes can be strategically employed as labile moieties. In this case, they act as an energy source to drive ring-opening metabolic steps and/or to ensure the irreversibility of a metabolic degradation. Cyclopropanes can also act as a store for the release of energy-rich metabolic derivatives.

Intriguingly, these 3-membered rings are rather prevalent in nature. Over 4000 natural cyclopropane-containing compounds have been documented. For example, 1-aminocyclopropanecarboxylic acid (15) is ubiquitous amongst all green plants, where it acts as a precursor to ethylene (an important hormone). One of the most important classes of commercial insecticides (the pyrethroids) is derived from cyclopropane 16, which is easily derivatised by ester linkage at the carboxylic acid terminal. Furthermore, it is not surprising that, given the prevalence of poly-unsaturated fatty acids in living organisms, oligocyclopropanes are also utilised by Nature. For example, U-106305 (17) is a known potent inhibitor of cholesterol ester transferase, isolated from Streptomyces sp (Figure 6). For this reason it may have utility in the treatment of Atherosclerosis, a common disease of the arteries caused by the chronic build-up of cholesterol deposits. In recent years there has been a significant effort directed towards the total synthesis of cyclopropane-containing natural products.
Figure 6. Cyclopropane-containing natural products. 44, 54
1.3 Fluorocyclopropanes

By combining fluorine and cyclopropane together, a useful tool for enhancing bioactivity can be formed. The fluorocyclopropane scaffold is highly relevant in the design and synthesis of biologically active molecules. Synthetically, fluorocyclopropanes present an interesting challenge to organic chemists. The aforementioned structural characteristics of cyclopropanes make direct fluorination of a cyclopropane difficult (i.e. by electrophilic addition or nucleophilic substitution). Instead, fluorocyclopropanes are typically synthesised through cyclopropanation of a fluorinated substrate or a tandem cyclisation-fluorination reaction. Reactions of these types can be grouped into four general areas:

1. Addition of a fluorocarbene to an alkene
2. Addition of a carbene to a vinyl fluoride
3. Nucleophilic fluorination of a cyclopropane
4. Michael-initiated ring closure of an enone

Figure 7. Typical routes to access fluorocyclopropanes

As an example of the potential benefits offered by fluorocyclopropanes in pharmaceutical design, Zosuquidar (20) illustrates the metabolic stability conferred upon compounds containing one of these units. 20 was a stage III clinical trial candidate designed by Eli Lilly for the treatment of multi-drug resistant cancers. This was developed from the hit compound 18 that, although highly bioactive, suffered from rapid degradation under metabolic conditions. Consequently, bioavailability by oral administration was poor. Optimisation of 18 began with the fusion of a cyclopropane ring onto the ethyl linker between the dibenzo skeleton to give 19; leading to a significant improvement in metabolic-stability (to 3 h from 15 minutes). Further modification found that using a difluorocyclopropane increased the half-life to 72 h.
(Figure 8). The stability imparted by the difluorocyclopropane units is likely due to the greater resistance of cyclopropanes to oxidative metabolism compared to the C-H bond.

![Diagram](image)

**Figure 8.** Development of Zosuquidar.

There is relatively little precedence for fluorocyclopropanes in both synthetic and medicinal chemistry. Partly owing to a lack of synthetic methods to access this class of compound, there is also limited literature on the properties and applications of fluorocyclopropanes in medicinal chemistry or otherwise. Some effort has been directed towards designing monofluorinated cyclopropanes however. Much of this area was established by Günter Haufe around the year 2000. Significant headway has been made since then, with the synthesis of highly-functionalised fluorocyclopropanes (e.g. 21-23) now being possible. Sulfono-
sulfoxo-substituted rings can be accessed with ease using diazoacetate derivatives and a Rh catalyst (Scheme 3).\textsuperscript{71} As mentioned previously, compounds of this class can also be accessed through the addition of a fluorocarbene to an alkene. See Scheme 4 for one example of this, where bromofluorocarbene (CFBr) is generated from CHBr\textsubscript{2}F and NaOH in a phase-transfer reaction.\textsuperscript{72, 73} A [2+1] cycloaddition affords the three-membered ring. Michael-initiated ring closure generally requires an enone-type system to allow for conjugate addition of the soft nucleophile (sulfoxonium ylide) generated. Compounds of the general 23 structure (Scheme 5) are generated from an α,β-unsaturated Weinreb amide and \textit{in situ} formation of the corresponding ylide.\textsuperscript{74}

\begin{equation}
\text{Scheme 3. Synthesis of monofluorocyclopropane (21) by addition of carbene to a vinyl fluoride.}\textsuperscript{71}
\end{equation}

\begin{equation}
\text{Scheme 4. Synthesis of monofluorocyclopropane (22) by addition of bromofluorocarbene to an alkene.}\textsuperscript{72, 73}
\end{equation}

\begin{equation}
\text{Scheme 5. Synthesis of monofluorocyclopropane (23) using a Michael-initiated ring closure with a Weinreb amide.}\textsuperscript{74}
\end{equation}
1.4 Aims and Objectives

This work had three aspects:

1. The synthesis of new fluorocyclopropane motifs.
2. Investigation of the properties of new fluorocyclopropane motifs.
3. Exploration of the potential utility of these groups in medicinal chemistry, or otherwise.

The initial synthetic target of this project was mono-fluorinated cyclopropane 28. Interest in this class of compound came from recent literature reports demonstrating the anti-cancer properties of analogous aziridines. Prodrugs such as 1-(4-nitrophenyl)aziridine (24) may be reduced to the corresponding hydroxylamine 25 in vivo by human nitroreductase enzymes (Figure 9). Disproportionation of the hydroxylamine gives an aniline (26). This transformation switches the electronic nature of the ring; the electron-donating arylamine promotes aziridine ring-opening. DNA subsequently acts as a nucleophile to regenerate the aromaticity and afford a DNA-adduct that results in cell death.

![Figure 9. Biological activation of anti-cancer agent 24.](image)

A straightforward mechanism can be imagined for 28 (Figure 10). Reduction in vivo to aniline 29 followed by conjugative elimination of the benzylic fluorine would afford a charged ionic species (30) primed for nucleophilic attack by a DNA-base. Re-aromatisation affords a
DNA mono-adduct (31) that will likely result in cell death. Should further development of this scaffold afford a compound capable of targeting cancer cells specifically, then this class of compound could yield potent and rationally designed anti-cancer prodrug therapies.

**Figure 10.** Proposed mechanism of action for monofluorocyclopropane 28.
Section 2 Results and Discussion

2.1 Strategy

As described in Section 1, the monofluorocyclopropane 28 was the initial synthetic target of this project. Scheme 6 shows the original synthetic route that was designed to access this compound class. A Simmons-Smith cyclopropanation of styrene (32a) with diethylzinc and diiodomethane afforded cyclopropylbenzene (33) in 81% yield. Subsequent bromination with N-bromosuccinimide, under a variety of conditions, generated various undesired products. The likely major product from this reaction is a ring-opened species; however, this product (and the minor products that were also isolated) could not be characterised by NMR spectroscopy or mass-spec analyses. Subsequent synthesis of the fluorocyclopropane 28 was intended to be performed through fluorination of the brominated cyclopropane (34) using a source of nucleophilic fluorine such as AgF₂, followed by nitration of 35.


An alternative strategy was devised to circumvent the need for direct halogenation of a cyclopropane ring. Fluorine was pre-installed in the alkene before an intended cyclisation, under the Simmons-Smith conditions previously discussed. The vinylfluoride 37a was synthesised in
two steps by fluorobromination of styrene using N-bromosuccinimide and NEt₃·3HF, followed by dehydrobromination of 36a with potassium tert-butoxide (Scheme 7).

Scheme 7. Synthetic route towards vinyl fluoride 37a.

Unfortunately, and somewhat to our surprise, Simmons-Smith cyclisation of 37a did not give the anticipated cyclopropane product (38). Only starting material was observed by NMR spectroscopy of the crude reaction mixture (¹H and ¹⁹F). Extended reaction times, increased reaction temperature and increased equivalence of reagents did not improve this outcome. There has been some debate over the exact mechanism by which Simmons-Smith cyclopropanation proceeds. The general consensus is that methylene transfer occurs in a concerted manner. Nucleophilic attack of the alkene on the electrophilic Simmons-Smith reagent (generated in situ from diethylzinc and diiodomethane) may be difficult due to the electron-withdrawing effect of fluorine. Only a handful of Simmons-Smith cyclopropanations on vinyl fluorides have been reported (with all of these being in pharmaceutical patents). In those examples, the transformation is more efficient when an electron-donating substituent is present adjacent to the vinyl fluoride (e.g. OMe).

In addition to the Simmons-Smith cyclisation, further cyclopropanation reactions were attempted on vinyl fluoride substrate 37a (Scheme 8). Although normally reserved for α,β-unsaturated ketones, a Corey-Chaykovsky-type cyclopropanation with sulfoxonium methylide was attempted. Again, only starting material was observed after 3 days at RT or under reflux conditions. Reaction with ethyl diazoacetate (41), catalysed by rhodium(II) acetate, afforded ester 40 as a diastereomeric mixture. This is a known literature protocol; the reaction confirmed the identity and quality of the vinyl fluoride previously synthesised, and the accuracy of laboratory practices.
Fortunately, cyclopropanation of 37a proceeded with difluorocarbene (CF₂) to afford the trifluorocyclopropane 42a as a mixture of stereoisomers. Using the Ruppert-Prakash reagent (43, TMS-CF₃), CF₂ was generated in situ in an auto-catalytic process. A [2+1] cycloaddition of difluorocarbene to the vinyl fluoride forms a trifluorocyclopropane. Figure 11 details the catalytic mechanism for the generation of difluorocarbene from 43; NaI initiates the cycle.

Scheme 8. Attempted reactions to cyclopropanate vinyl fluoride 37a.
Figure 11. Mechanism for CF₂ generation from TMS-CF₃ (43). Initiation by sodium iodide is shown on the left, with the auto-catalytic cycle detailed in blue on the right.

There is almost no precedence in academic literature and patented work for the preparation of trifluorocyclopropanes. Only one example exists in the primary literature, in the form of an α-ketone (44).\(^6\) However, this compound was not isolated (identified only by GC analysis) and was only formed as a by-product. The only remaining examples are found in a small library of patented drugs that contain a heterocyclic trifluorocyclopropane (e.g. 46).\(^7\) This class of compound was synthesised from a vinyl fluoride by generation of difluorocarbene from phenyl(trifluoromethyl)mercury (45) - a highly toxic and expensive (>£30/mg) reagent (Scheme 9). Consequently, the discovery of this simple route to trifluorocyclopropanes represents an advancement in the growing effort to synthesise fluorinated cycloalkanes. For this reason, this new synthetic route was taken forward for further exploration as an alternative to the original target of this project (monofluorocyclopropane 28).
Scheme 9. Previously reported syntheses of trifluorocyclopropanes.\textsuperscript{86,87}

In some cases, the synthetic route used in the creation of a library of examples started from the corresponding para-substituted benzaldehydes 47a-d. Styrenes were used as the initial starting material in the cases where such material was readily available. Appropriate styrenes (32c,e,f,h) were therefore obtained via a Wittig olefination reaction using methyltriphenylphosphonium bromide and \textit{n}-butyllithium. As described before, styrenes were converted to corresponding vinylfluorides (37a-h) \textit{via} fluorobromination and subsequent dehydrobromination. Scheme 10 illustrates the synthetic route. A collection of trifluorocyclopropane examples (42a-g) bearing common aromatic substituents were synthesised following this procedure. In addition, compound 42h was furnished to contain two of the new trifluorocyclopropane units as the para-isomer (Figure 12). Methoxy-substituted vinyl fluoride 37d was made in a one-pot process from the corresponding vinylanisole (see Section 2.3).
Scheme 10. General synthetic route used to access trifluorocyclopropanes 42a-h.
Figure 12. Derivative compounds 42a-h with yields for the final (cyclopropanation) step.

Notably, fluorobromination of nitro-substituted styrene (32c) gave rise to mixture of the 1-fluoro-2-bromo (36c) and 2-fluoro-1-bromo (48) isomers in a 2.8:1.0 (Scheme 11). 48 was not taken forward for further transformation. No conversion was observed using NEt₃·3HF. Rather pyridine hydrogen fluoride was required for fluorobromination of 32c, likely as a result of the nitro-group hindering formation of a suitably long-lived bromonium ion. This result illuminates the mechanism of fluorobromination, wherein the highly electron-withdrawing nitro substituent reduces stabilisation of the partial positive charge at the benzylic position. Hence, there is less preference for nucleophilic attack of fluoride at this position – allowing the formation of the alternative isomer as a minor product.
Scheme 11. Fluorobromination of 32c affords a mixture of isomers.
2.2 One-Pot Synthesis of Vinyl Fluorides

There has long been an interest in synthetic methodology (both academic and industrial) to develop so-called ‘one-pot’ reactions from originally complex syntheses.\textsuperscript{88} The desire for efficient synthetic routes is underscored by the need for reaction pathways to have sensible economics (financial and atomic) and minimal environmental impact.\textsuperscript{88, 90, 91} Moreover, in the development of essential drugs (e.g. Tamiflu (49, Figure 13)), their synthesis must be cheap in order to ensure a supply to developing countries (who may need the materials most)\textsuperscript{92}. One-pot transformations not only minimise waste (solvents, purification and drying materials etc.). By removing intermediary work-ups, these shortened protocols can reduce the overall purification time, and yield losses that result from successive manipulations.

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{tamiflu.png}
\caption{Tamiflu.}
\end{figure}

With this in mind, a telescoped approach to the synthesis of vinylfluoride 37a was attempted (Scheme 12). Fluorobrominated compound 36a was generated following the known procedure described in Section 2.1. Without removal of solvent, work-up or purification, dehydrobromination was initiated by direct addition of KO\textsubscript{t}Bu to the reaction. It was found that 8.0 equivalents of this base – compared to 1.5 equiv for the two-step process - were required to drive the reaction to completion. No reaction was observed until the addition of >6.0 equivalents of KO\textsubscript{t}Bu. This was necessary to quench the residual trimethylamine and succinimide by-products, amongst others, from the previous step. Succinimide is more acidic than fluorobromo compound 36a so will be deprotonated first. Not only does this procedure remove a purification step, but the isolated yield of the one-pot process (76%) was higher than that overall for the corresponding two-step transformation (61%). An identical protocol was carried out on the methoxy substrate 32d to afford vinyl fluoride 37d (82%). However, it would be important to account for the use of extra base in assessing the efficiency improvement of this reaction if it were to be considered for large-scale use.
Given the success of the one-pot preparation of the vinyl fluorides, the next step was to explore the synthesis of trifluorocyclopropanes in one step. Therefore a crude mixture of the vinylfluoride 37a was obtained and without work-up or purification, TMS-CF₃ and NaI (5.0 equivalents each) were added into the reaction pot. Heating for 20 hours did not afford any observable product (42a) by ¹H or ¹⁹F NMR spectroscopy. Increasing to 15 or 20 equivalents of both reagents did not improve the result. Perhaps altering the conditions of the first two steps could lead to a reaction mixture that is suitably clean for performing the final, cyclisation step.

Scheme 12. One-pot synthesis of vinyl fluoride 37a (top), and attempted one-pot synthesis of cyclopropane 47a (bottom).
2.3 Derivatisation

In order to assess the stability and versatility of the new trifluorocyclopropane motif, a series of derivatisation reactions were envisaged. A key area of concern was lability under acidic, basic or high temperature conditions. The strained nature of the ring, together with the electron withdrawing fluorine substituents hinted at a high-energy product that may eliminate HF and/or ring-open under particular conditions. In addition, it was hoped that conditions could be identified that would yield a variety of functionalised building blocks that may have utility in drug discovery programmes.

2.3.1 Nitration

Electrophillic aromatic substitution in the form of nitration was initially explored. Nitration of 42a using ammonium nitrate and trifluoroacetic anhydride proceeded cleanly to give a mixture of isomeric products (42c, 50 and 51) (Scheme 13). Analysis of the reaction mixture by $^{19}$F NMR spectroscopy indicates a conversion to a 1.1:1.0:2.1 ortho/meta/para mixture. The meta product was easily isolated as a pure material by flash column chromatography. However, the ortho and para isomers were recovered as a mixture. The regioselectivity displayed suggests that the trifluorocyclopropane motif has no strong directing powers over the reactivity of 42a towards electrophillic substitution. However, the preference for para indicates a notable steric effect and that a weak inductive effect may be active.

2.3.2 Demethylation

Demethylation of the aryl methyl ether 42d to obtain the corresponding phenol (52) was explored. This would unmask a useful functionality for further extension of the basic scaffold. Boron tribromide was employed as a Lewis acid to perform this transformation. $^1$H and $^{19}$F spectroscopy of the crude product indicated formation of diol 54 (Scheme 14). In their respective NMR experiments, there is a clear upfield shift of the resonances for both protons and fluorines on the cyclopropane after demethylation. All four resonances resolve to the ddd multiplicity that would be expected in 54 (compared with the dddd resonances observed in 42d). Further, a broad singlet that could be assigned to an alcohol was observed at $\delta_{\text{H}}$ 5.04 ppm, and $^{13}$C NMR spectroscopy agrees with the structure of the proposed product. Disappearance of a resonance for the benzylic fluorine (in $^{19}$F NMR) supports the theory of F-elimination. Mass spectrometry would confirm the structure of 54 (analysis by the EPSRC facility in Swansea is forthcoming). The material appeared to be unstable on silica during column chromatography; however, pure material was obtained after reaction work-up when repeating the demethylation with a new sample of boron tribromide.

Scheme 14 also shows a possible mechanism for the formation of this diol species, proceeding via phenolium 53. Considering the similarity of this mechanism to that shown in Section 1.4 for anticancer aziridines and monofluorocyclopropanes, this reaction suggests an interesting area for further studies. In a similar manner to water, DNA could be imagined to act as a nucleophile (in the place of H$_2$O) and thereby form a DNA mono-adduct.
2.3.3 Pd-catalysed Cross-Couplings

Palladium catalysed C-C/C-N bond formation reactions are particularly prominent in the pharmaceutical industry, where they are favoured over stoichiometric catalysts/reagents for their efficiency and versatility. Concise synthetic routes, and mild, selective conditions are characteristic of Pd-catalysed cross couplings that allow access to highly complex drug targets. Some of the most well-known of these reactions include the Sonogashira coupling (for constructing sp-sp^2 bonds) and the Buchwald-Hartwig amination (used to form arylamines). Both of these transformations were performed on the para-bromide substrate 42b (Scheme 15). Coupling to 1-ethynyl-4-propylbenzene (55), with CuI and Pd(PPh_3)_2Cl_2, furnished the 4,4'-substituted diphenylacetylene 56 in an efficient manner. Amination of 42b with morpholine (57) was performed with Pd_2(dba)_3 and BINAP to give analogue 58 in excellent yield (93%).
Scheme 15. Sonogashira (left) and Buchwald-Hartwig (right) cross-couplings performed on 42b.

The high yields of these reactions, and their simple purifications, demonstrate the versatility of the new motif in typical cross-coupling reactions performed in the pharmaceutical and agrochemical industries on a large scale. It is expected from these results that the trifluorocyclopropane motif would be tolerant towards similar reactions, and hence have utility in the powerful Suzuki-Miyaura, Heck and Still transformations, amongst others.
2.4 Facial Polarity

Previous research in the O'Hagan group has highlighted the interesting facial polarity present in some fluorinated cycloalkanes. To probe similar properties in the new trifluorocyclopropane motif, electrostatic surface profiles were generated using Gaussian at the (B3LYP/6-31+G(d,p)) level. The resulting map, shown in Figure 14, illuminates the clear facial polarity of compound 42a.

NMR spectroscopy supports these computational findings (Figure 15). A clear upfield shift of both cyclopropane protons in the $^1$H NMR spectrum is observed in toluene-$d_8$, compared to the NMR experiment run in CDCl$_3$. Such a shift is characteristic of a C-H/$\pi$ interaction between the upper, electropositive face of the cyclopropane ring with the electron-rich $\pi$-system of toluene. Notably, there is a separation of the resonances assigned to the two cyclopropyl protons; suggesting that the proton on the upper face of the cyclopropane ring is affected more by the preferential interaction of toluene with the lower, electronegative face. Also in support of facial polarity is the direction of the dipole vector, as indicated by the blue arrow on Figure 13. It is almost perpendicular to the C-C bond plane of the cyclopropane ring, implying that polarity runs neatly from the electropositive upper face to the electronegative lower face.

Figure 14. Electrostatic map showing facial polarity of 42a; the blue arrow indicates the direction of dipole moment (left). Red indicates an area of high electron-density, and blue an area of lower electron-density. 3D-structure of 42a without electrostatic map (right).
The information obtained through these experiments suggests that the trifluorocyclopropane moiety may orientate the binding, of compounds of this class, to proteins. For example, as with the electrostatic interaction with toluene, 42a may orientate to position the upper face approximately parallel to the phenyl ring of a phenylalanine or tyrosine residues of a protein chain. Similarly in a crystalline structure, 42a may arrange such that the upper (electropositive) face of the trifluorocyclopropane ring is positioned below the phenyl ring of another molecule of itself.

The dipole moment and total energy of the eclipsed and staggered conformations of 42a was also calculated. As would be expected, the staggered conformation is significantly lower in energy (-347 a.u.) than the eclipsed and hence strained, conformer (-643 a.u.). Interestingly, the staggered conformer has a higher dipole moment (3.01 D) than the eclipsed analogue (2.74 D). This is possibly a result of the dipole in the staggered conformer being slightly more aligned with the π-system of the phenyl ring, and therefore benefiting from an electronic contribution.
Figure 15. NMR spectra showing the anisotropic effect of toluene (top). Electrostatic interaction of toluene’s negative face with the electropositive face of compound 42a (bottom).
2.5 logP

One of the most informative predictors of drugability is logP. LogP is the measure of a compound’s partition coefficient between organic and aqueous media (typically water and 1-octanol). Hence, the logP of a drug candidate is an indicator of lipophilicity or, equally, hydrophobicity. Lipinski’s Rule of 5 for determining drug-like characteristics, suggests that a compound should have a logP no greater than 5. Lipinski’s rules do not predict pharmacological activity. Hydrophilic compounds (low logP) will not readily move across lipidic cell-membranes. Whereas compounds with a high partition coefficient (and therefore hydrophobic) are likely to become trapped inside the cell membrane or stick to albumen proteins, where they are sheltered from extra- and intra-cellular fluids. Hence, having an accurate measure of a compound’s logP is a good tool for predicting physico-chemical parameters such as distribution within an organism.

The logP’s of selected compounds (42a, 42b and 42g) containing the new trifluorocyclopropane motif were measured. Traditionally, logP is measured directly as the distribution of a compound between layers of water and 1-octanol; however this can be technically challenging, and instead logP’s were measured by proxy using HPLC.99,100

The retention time of each compound was measured (in triplicate) under a set of standard conditions, and used to calculate logk (HPLC retention factor). For each of the new compounds, the averaged value for logk was plotted on a linear regression derived from measurements taken on reference compounds (59-66 and 33) with known logP. Hence, the logP of new compounds was found by extrapolation on this graph. Comparing cyclopropylbenzene to its fluorinated analogue (42a) there is a clear, and perhaps surprising, indication of an increase in hydrophilicity (Figure 15). This contrasts with the normal behaviour of fluorine, whereby adding fluorines to an alkane generally increases hydrophobicity. However, the induced polarity of this ring system (as described in Section 2.4) would appear to lower logP. Increasing the polarity should improve solubility in water, and makes this moiety more attractive for drug discovery programmes. Notably, the trifluorocyclopropane motif has the same logP as the trifluoromethyl group (42a and 62 logP = 3.2). This suggests that it may have use as a larger isostere than trifluoromethyl, but without an increase in lipophilicity.
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**Figure 16.** logP values for selected reference (green) and new (blue) compounds.
2.6 Flash Vacuum Pyrolysis

Given the interesting bonding and reactivity of cyclopropanes, as described in Section 1.2, we attempted to explore this by means of Flash Vacuum Pyrolysis (FVP). By modern standards, FVP is an archaical but simple technique.\textsuperscript{101, 102, 103} Partly owing to its limitation to unimolecular reactions, and an infrequent use in modern literature, FVP has suffered from a bad reputation in recent times.\textsuperscript{104} However, it can be a valuable method for accessing highly complex products that would otherwise be difficult to obtain through conventional synthesis.\textsuperscript{105, 106, 107} Although FVP employs extreme temperatures, the exposure time is very short and its effects are generally non-destructive. During the FVP process, a substrate is vaporised under high-vacuum before a short exposure to heat (e.g. \(\sim 600 \, ^\circ C\) for 10-20 ms) followed by rapid cooling to condense the reacted material. Chemical transformations almost exclusively occur unimolecularly and so this technique is limited to reactions involving intramolecular rearrangements.

A recent example of its value in synthetic organic chemistry comes from Schobert, Aitken and co-workers in the total synthesis of plant metabolite methylcombretastatin D-2 (68).\textsuperscript{108} Subjecting precursor 67 briefly to 600 °C, resulted in a ring-contraction to generate a 15-membered ring via the extrusion of SO\(_2\) gas (Scheme 16).

Minimal effort has been put into determining the reactivity of cyclopropanes under pyrolytic conditions. However, a publication by Thebtaranonth and co-workers showed ring opening of substituted cyclopropanes to afford dienes (e.g. 69 to 70) under FVP conditions. This proceeds with extrusion of the corresponding carboxylic acid (AcOH, 71).\textsuperscript{109}
In the case of 42a, experiments suggest that retro-cyclopropanation occurs under FVP conditions to yield the vinyl fluoride 37a (Scheme 17). At 500 °C and 600 °C, there is an approximate conversion of 25% and 93%, respectively. This is perhaps not a surprising finding, considering the product will be enthalpically and entropically favourable. Although generally clean, the crude product contained trace amounts of a significant number of by-products that could be observed at the baseline-level of the $^{19}$F NMR spectrum.

Scheme 16. Literature examples of FVP's utility in organic synthesis.$^{108,109}$

Scheme 17. FVP of trifluorocyclopropane 42a affords the corresponding vinyl fluoride. Conversion was determined by $^{19}$F NMR analysis of the crude product.
Due to a lack of precedence for this type of carbene-elimination reaction in the literature, we aimed to trap the expelled CF$_2$ (Scheme 18). The dimerization adduct of CF$_2$ (tetrafluoroethylene) was not observed by $^{19}$F spectroscopy. Styrene was chosen as a nucleophilic carbene trap to be placed in the cold-trap of the FVP system. It was hoped that if difluorocarbene passed through the cold trap, reaction with styrene would proceed to give the analogous difluorocyclopropane 72. Unfortunately, this material was not observed – likely as a result of the short life-span and/or high volatility of difluorocarbene. Additionally, the low temperature of the reaction vessel (79 K) could have limited attainment of the appropriate activation barrier to carbene addition. Alternatively, the conversion to vinyl fluoride 37a may proceed through another mechanism not involving the elimination of difluorocarbene. Further attempts were not carried out. It’s expected that difluorocyclopropane 72 would react similarly, to afford styrene. 72 was synthesised but so far has not been subjected to FVP.

Scheme 18. Attempted carbene trapping experiment.

In addition to experiments with compounds of the new trifluorocyclopropane class, 76 was subjected to FVP conditions as an isolated example from this overall work. Previous research with the dichloro analogue (74) found that a 1,2-shift rearrangement to vinyl chloride 75 occurs upon mild heating (Scheme 19). The difluorocyclopropane 76 was obtained in one-step from norbornene (73) using the Ruppert-Prakash reagent (43), as described before. Although this afforded 76 in a low yield (21%), the method reported here is significantly more efficient than the route previously described in the literature. Posey and Battiste reported a three-step synthesis with an overall yield of 10%. From an initial attempt, it appeared that 76 rearranges...
to give styrene (32a) at 650 °C under FVP conditions. This finding has not been confirmed, but if correct would represent an unprecedented intramolecular rearrangement.

**Scheme 19.** One-step synthesis of 76, and result of subsequent FVP experiment.


**Section 3 Conclusions**

In summary, a concise synthetic route to a new trifluorocyclopropane motif has been designed, and established with the synthesis of 8 examples. The Ruppert-Prakash reagent was found to be a safe and convenient source for the *in situ* generation of difluorocarbene. An existing, two-step, protocol for the synthesis of vinyl fluorides was optimised to a one-pot reaction. A variety of reactions have shown that this new cyclopropane is generally stable, therefore allowing it to find utility in a number of common synthetic transformations. Moreover, this synthetic versatility implies practicality in the pharmaceutical and agrochemical industries.

It has also been shown by computational and NMR studies that this new structure is facially polarised – allowing for predictions on how this motif may orientate in a protein or crystal structure. Furthermore, logP measurements indicate that the trifluorocyclopropyl group is isoelectronic with trifluoromethyl, despite having two additional carbons, suggesting applications in medicinal chemistry. The demethylation of methoxy derivative 42d to afford phenol-cyclopropanol 54 has revealed an interesting area of chemical reactivity with biological relevance. Lastly, it has been demonstrated that the trifluorocyclopropane group reacts under FVP conditions to generate the corresponding vinyl fluoride. This transformation suggests a possible use for the trifluorocyclopropane as a protecting group for vinyl fluorides.
Section 4 Further Work

4.1 Asymmetric Synthesis

Designs for an asymmetric version of the cyclopropanation reaction reported here may require the use of chiral phase-transfer ligands (e.g. cinchona alkaloid 77). It is known that difluorocarbene can be generated under phase-transfer catalysis; perhaps using a chiral catalyst in such a reaction may induce a degree of enantioselectivity to the cyclopropanation of vinyl fluorides.\textsuperscript{111, 112}

Other known enantioselective carbene reactions involve the use of a copper catalyst and a bisoxazoline-type ligand (e.g. 78). Reactions of this type use diazo substrates to generate copper-coordinated carbene \textit{in situ}; this is similar to the Rh-catalysed synthesis of cyclopropylcarboxylate 40 reported here. The chiral ligand forces selectivity upon the direction of attack of this carbene on the substrate (e.g. an alkene).\textsuperscript{113} To the best of our knowledge, such a reaction does not exist with difluorocarbene.

![Figure 17. Structures of ligands 77 and 78.](image)

4.2 Extended One-Pot Procedure

As described in Section 2.2, a one-pot procedure for the synthesis of vinyl fluorides from styrenes has been discovered in this work. Further extending this one-step protocol to the trifluorocyclopropane would make a more time- and cost-efficient process. It would be necessary to optimise the previous step to reduce the amount of residual reagent/by-products that may interfere with the generation or reaction of difluorocarbene. This could involve different reagents, such as NIS as a replacement for NBS, the use of a different fluorinating reagent, or the use of an alternative base.
4.3 Enzymatic Studies

Previous work by O’Hagan and co-workers has demonstrated the interesting behaviour of fluorinated cycloalkanes under metabolic conditions. Understanding how the new trifluoro motif behaves, for example, under oxidative conditions with a P450 enzyme, may illuminate how this group would metabolise in living organisms. Several possible reactions can be predicted, including: hydroxylation at the -CH₂- position of the ring; elimination of HF; and opening of the cyclopropane ring, amongst others.

4.4 Anti-Cancer Properties of 54

As described in Section 2.3.2, the phenol-cyclopropanol 54 displays similar reactivity to the anti-cancer aziridines reported previously. Further investigation into this would primarily involve mechanistic studies to probe formation of the diol and the applicability of such a mechanism to the analogous reaction with DNA.
Section 5 Experimental

5.1 General Protocols

**NMR** spectra were recorded on a Bruker AV 300, Bruker AV 400, Bruker AVII 400, Bruker AVIII-HD 500 or Bruker AVIII 500 instrument. CDCl₃ was used as solvent unless otherwise stated. Chemical shifts are reported in parts per million (ppm). Tetramethysilane (δ 0 ppm) functioned as an external standard for ¹H and ¹³C NMR experiments. CFCl₃ was used as an external standard for ¹⁹F NMR experiments. Where appropriate, solvent signals were used as internal standards and were calibrated as follows: CDCl₃ δ_H 7.26 and δ_C 77.16 ppm, toluene-d₈ δ_H 2.08 ppm. The multiplicity of each resonance has been assigned: e.g. multiplet (m), singlet (s), doublet (d), triplet (t), quartet (q), doublet of doublets (dd), doublet of triplets (dt), doublet of doublet of doublets (ddd), doublet of doublet of doublet of doublets (dddd) etc.

**Chemicals** and non-anhydrous solvents were purchased from Sigma Aldrich, Acros UK, Fisher Chemical or Fluorochem, and were used as received. Anhydrous solvents were obtained from an MRaun SPS-800 solvent purification system.

**Thin Layer Chromatography** was performed on Merck silica gel 60 F₂₅₄, aluminium-backed plates.

**Column Chromatography** was performed using Sigma-Aldrich Analytical Silica gel (60 Å, 230-400 mesh particle size, 40-63 μm) and run with the aid of compressed air.

**Mass Spectrometry** data could not be successfully obtained using standard, in-house, techniques. All data was hence obtained by the EPSRC UK National Mass Spectrometry Facility in Swansea, UK. The instrument used was a Waters Xevo G2-S and the technique was Atmospheric-Pressure Chemical Ionisation (APCI) with an Atmospheric Solids Analysis Probe (ASAP).

**Melting Point** measurements were performed using an Electrothermal IA9100 melting point apparatus.
5.2 General Synthetic Procedures and Analytical Data

5.2.1 Styrenes

*General Procedure A for Wittig Olefination of Benzaldehydes*[^1]:

A flame-dried round-bottomed flask equipped with a magnetic stir bar was charged with methyltriphenylphosphonium bromide (1.9 equiv). The reaction vessel was sealed, then evacuated and backfilled with nitrogen. Anhydrous THF and "BuLi (1.8 equiv) were added sequentially via syringe. The resulting suspension was stirred at 0 °C for 1.5 h, before addition of a solution of the appropriate benzaldehyde (1.0 equiv) in anhydrous THF via syringe. The reaction mixture was stirred at RT for 20 h. After completion, the reaction mixture was quenched with a saturated aqueous solution of NH₄Cl (75 mL) and extracted with diethyl ether (2x100 mL). The combined organic phases were washed with brine, followed by drying over Na₂SO₄, filtration and evaporation of solvent *in vacuo*. Purification by flash column chromatography (petroleum ether/CH₂Cl₂) afforded the appropriate styrene (32c, 32e, 32f, 32h).

![Methyl(4-vinylphenyl)sulfane (32c)](image)

Methyl(4-vinylphenyl)sulfane (32c) was prepared following *General Procedure A*, using methyltriphenylphosphonium bromide (22.46 g, 62.90 mmol, 1.90 equiv), "BuLi (2.5 M, 23.84 mL, 59.6 mmol, 1.80 equiv) in THF (100 mL), and a solution of 4-nitrobenzaldehyde (47a) (5.00 g, 33.11 mmol, 1.00 equiv) in anhydrous THF (50 mL). The reaction mixture was stirred at RT for 20 h. The crude product was purified by flash column chromatography (50% petroleum ether/50% CH₂Cl₂) to afford the title compound (32c) as a yellow oil (2.862 g, 58%).

[^1]: General Procedure A for Wittig Olefination of Benzaldehydes.

1H NMR (400 MHz, CDCl₃) δ_H: 8.19 (2H, d, J = 8.8 Hz, Ar-CH), 7.54 (2H, d, J = 8.8 Hz, Ar-CH), 6.78 (1H, dd, J_Htrans 17.6 Hz, J_Hkiss 10.9 Hz, CH-CH₂), 5.93 (1H, dd, J_Htrans 17.6 Hz, J_Hgem 0.5 Hz, CH-CH₂), 5.50 (1H, dd, J_Hkiss 10.9 Hz, J_Hgem 0.5 Hz, CH-CH₂); 13C NMR (125 MHz, CDCl₃) δ_C: 147.1 (Ar-Ω), 143.8 (Ar-Ω), 126.8 (2xAr-CH), 124.0 (2xAr-CH), 135.0 (CH), 118.6 (CH₂).
4-fluorovinylbenzene (32e) was prepared following General Procedure A, using methyltriphenylphosphonium bromide (27.35 g, 76.60 mmol, 1.90 equiv), t-BuLi (2.5 M, 29.03 mL, 72.58 mmol, 1.80 equiv) in THF (100 mL), and a solution of 4-nitrobenzaldehyde (47b) (5.00 g, 40.32 mmol, 1.00 equiv) in anhydrous THF (50 mL). The reaction mixture was stirred at RT for 20 h. The crude product was purified by flash column chromatography (50% petroleum ether/50% CH₂Cl₂) to afford the title compound (32e) as a colourless oil (2.607 g, 53%).

^1H NMR (400 MHz, CDCl₃) δ_H: 7.41-7.37 (2H, m, Ar-CH), 7.06-6.99 (2H, d, J = 8.8 Hz, Ar-CH), 6.69 (1H, dd, J_HHtrans 17.5 Hz, J_HHcis 10.9 Hz, CH-CH₂), 5.68 (1H, dd, J_HHtrans 17.5 Hz, J_HHgem 0.5 Hz, CH-CH₂), 5.24 (1H, dd, J_HHcis 10.9 Hz, J_HHgem 0.5 Hz, CH-CH₂); ^19F{^1H} NMR (400 MHz, CDCl₃) δ_F: -114.4 (s, Ar-F); ^13C NMR (125 MHz, CDCl₃) δ_C: 162.5 (Ar-CH, d, J = 246.9 Hz), 135.7 (CH), 133.8 (Ar-C, d, J = 3.2 Hz), 127.8 (2xAr-CH, d, J = 8.0 Hz), 115.4 (2xAr-CH, d, J = 21.7 Hz), 113.5 (CH₂).

Methyl(4-vinylphenyl)sulfane (32f) was prepared following General Procedure A, using methyltriphenylphosphonium bromide (26.74 g, 74.90 mmol, 1.90 equiv), t-BuLi (2.5 M, 28.38 mL, 70.96 mmol, 1.80 equiv) in THF (110 mL), and a solution of 4-(methylthio)benzaldehyde (47c) (6.00 g, 39.42 mmol, 1.00 equiv) in anhydrous THF (50 mL). The reaction mixture was stirred at RT for 20 h. The crude product was purified by flash column chromatography (100% petroleum ether) to afford the title compound (32f) as a yellow oil (1.894 g, 32%).

^1H NMR (400 MHz, CDCl₃) δ_H: 7.56-7.50 (2H, m, Ar-CH), 7.44-7.37 (2H, m, Ar-CH), 6.86 (1H, dd, J_HHtrans 17.6 Hz, J_HHcis 10.9 Hz, CH-CH₂), 5.90 (1H, dd, J_HHtrans 17.6 Hz, J_HHgem 0.9 Hz, CH-CH₂), 5.40 (1H, dd, J_HHcis 10.9 Hz, J_HHgem 0.9 Hz, CH-CH₂), 2.68 (3H, s, SCH₃); ^13C NMR
(125 MHz, CDCl₃) δ: 137.9 (Ar-CH), 136.3 (CH), 134.1 (Ar-CH), 127.0 (4xAr-CH), 113.4 (CH₂), 15.9 (CH₃).

1,4-Divinylbenzene (32h) was prepared following General Procedure A, using methyltriphenylphosphonium bromide (10.12 g, 28.36 mmol, 1.90 equiv), "BuLi (1.6 M, 16.79 mL, 26.88 mmol, 1.80 equiv) in THF (35 mL), and a solution of terephthalaldehyde (47d) (2.00 g, 14.93 mmol, 1.00 equiv) in anhydrous THF (35 mL). The reaction mixture was stirred at RT for 20 h. The crude product was purified by flash column chromatography (100% petroleum ether) to afford the title compound (32h) as a colourless oil (1.363 g, 70%).

¹H NMR (400 MHz, CDCl₃) δ:H: 7.39 (4H, s, Ar-CH), 6.72 (2H, dd, JHHtrans 17.6 Hz, JHHcis 10.9 Hz, CH-CH₂), 5.76 (2H, dd, JHHLtrans 17.6 Hz, JHHLgem 0.9 Hz, CH-CH₂), 5.25 (2H, dd, JHHcis 10.9 Hz, JHHLgem 0.9 Hz, CH-CH₂); ¹³C NMR (125 MHz, CDCl₃) δ: 137.6 (2xAr-CH), 136.2 (2xCH), 126.4 (4xAr-CH), 113.8 (2xCH₂).
5.2.2 Fluorobromoethanes

**General Procedure B for Fluorobromination of Styrenes 32a-32h**

A flame-dried round-bottomed flask equipped with a magnetic stir bar was charged with NBS (1.50 equiv). The reaction vessel was sealed, then evacuated and backfilled with nitrogen. Anhydrous CH$_2$Cl$_2$ and the appropriate styrene (1.00 equiv) were added sequentially via syringe. The resulting suspension was cooled to 0 °C and stirred for 30 minutes, followed by addition of NEt$_3$.3HF via syringe. The reaction mixture was warmed to RT, and then stirred for 18 h. After completion, the reaction was quenched with a 28% aqueous solution of NH$_3$ and stirred for 10 minutes. The resulting solution was extracted with CH$_2$Cl$_2$ (3x50 mL) and the combined organic phases were washed sequentially with aqueous dilute HCl (0.1 M, 50 mL) and a saturated aqueous solution of NaHCO$_3$ (50 mL), followed by drying over Na$_2$SO$_4$. After filtration, solvent was removed in vacuo. Purification by flash column chromatography (petroleum ether/CH$_2$Cl$_2$) afforded the appropriate (2-bromo-1-fluoroethyl)benzenes (36a-36h).

(2-bromo-1-fluoroethyl)benzene (36a) was prepared following General Procedure B, using styrene (32a) (5.00 g, 48.0 mmol, 1.0 equiv), N-bromosuccinimide (9.56 g, 52.8 mmol, 1.5 equiv), and NEt$_3$.HF (11.76 mL, 72.00 mmol, 1.5 equiv) in CH$_2$Cl$_2$ (80 mL). The reaction mixture was stirred at RT for 20 h. The crude product was purified by flash column chromatography (100% petroleum ether) to afford the title compound (36a) as a colourless oil (7.209 g, 74%).

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$: 7.45-7.36 (5H, m, Ar-CH$_2$), 5.64 (1H, ddd, $J = 46.8$, 7.9, 4.1 Hz, CHF), 3.74-3.57 (2H, m, CH$_2$Br); $^{19}$F NMR (400 MHz, CDCl$_3$) $\delta$: -174.9 (ddd, $^{2}J_{HF} = 46.8$ Hz, $^{3}J_{HF} = 25.2$ Hz, $^{3}J_{HF} = 15.9$ Hz, CHF); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$: 137.1 (Ar-CH$_3$, d, $J = 20.3$ Hz), 129.3 (1xAr-CH, d, $J = 1.8$ Hz), 128.8 (2xAr-CH), 125.7 (2xAr-CH, d, $J = 6.6$ Hz), 92.8 (CHF, d, $J = 177.9$ Hz), 34.3 (CHBr, d, $J = 28.4$ Hz).
1-bromo-4-(2-bromo-1-fluoroethyl)benzene (36b) was prepared following General Procedure B, using 1-bromo-4-vinylbenzene (32b) (6.00 g, 32.78 mmol, 1.00 equiv), N-bromosuccinimide (8.90 g, 49.17 mmol, 1.50 equiv), and NEt₃.HF (8.02 mL, 49.17 mmol, 1.50 equiv) in CH₂Cl₂ (40 mL). The reaction mixture was stirred at RT for 20 h. The crude product was purified by flash column chromatography (95% petroleum ether/5% CH₂Cl₂) to afford the title compound (36b) as a colourless oil (6.15 g, 67%).

¹H NMR (400 MHz, CDCl₃) δH: 7.89 (2H, d, J=8.4 Hz, Ar-CH), 7.58 (2H, d, J=8.4 Hz, Ar-CH), 5.93 (1H, ddd, J = 46.6, 7.4, 4.5 Hz, CHF), 4.03-3.89 (2H, m, CH₂Br); ¹⁹F NMR (471 MHz, CDCl₃) δF: -174.1 (ddd, JHF = 46.6 Hz, JHF = 24.1 Hz, JHF = 16.5 Hz, CHF); ¹³C NMR (101 MHz, CDCl₃) δC: 137.2 (Ar-CH, d, J = 20.3 Hz), 131.92 (2xAr-CH), 127.4 (2xAr-CH, d, J = 6.7 Hz), 123.6 (Ar-C), 92.0 (CHF, d, J = 178.8 Hz), 33.8 (CHBr, d, J = 28.7Hz); HRMS (APCI+ASAP) calculated for C₈H₇Br₂F [M+H]⁺ m/z 281.8878, found 281.8875.

1-(2-bromo-1-fluoroethyl)-4-nitrobenzene (36c) and 1-(1-bromo-2-fluoroethyl)-4-nitrobenzene (48) were prepared following General Procedure B (expect for the use of HF-pyridine), using 1-nitro-4-vinylbenzene (32c) (0.25 g, 1.83 mmol, 1.00 equiv), N-bromosuccinimide (0.495 g, 2.78 mmol, 1.50 equiv), and HF-pyridine (0.050 mL, 2.78 mmol, 1.50 equiv) in CH₂Cl₂ (7 mL). The reaction mixture was stirred at RT for 20 h. The crude product was purified by flash column chromatography (70% petroleum ether/30% CH₂Cl₂) to
afford the title compounds 36c and 48 as a light yellow oil (0.483 g) and a light yellow oil (0.046 g), respectively (overall 39%).

36c: \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta_{H}: 8.28 (2H, d, ^3J_{HH} = 8.6 \text{ Hz}, \text{Ar-CH})\), 7.56 (2H, d, \(^3J_{HH} = 8.6 \text{ Hz}, \text{Ar-CH}\)) , 5.76 (1H, dt, \(^2J_{HF} = 46.6 \text{ Hz}, ^3J_{HF} = 5.6 \text{ Hz}, \text{C-HF}\)), 3.72 - 3.65 (2H, m, \text{C-H}_2\text{Br}); \(^{19}\)F NMR (470 MHz, CDCl\(_3\)) \(\delta_F: -176.94 \text{ (dt, } ^2J_{HF} = 46.6 \text{ Hz, } ^2J_{HF} = 19.7 \text{ Hz, C-HF)}\); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta_{C}: 148.3 \text{ (Ar-C, d, } ^2J = 20.8 \text{ Hz), 143.9 (Ar-C, d, } J = 20.8 \text{ Hz), 126.7 (2xAr-CH, d, } J = 7.4 \text{ Hz), 124.0 (2xAr-CH), 91.2 (C-HF, d, } J = 180.9 \text{ Hz), 33.4 (C-HBr, d, } J = 27.4 \text{ Hz).}

48: \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta_{H}: 8.26 - 8.20 (2H, m, \text{Ar-CH}), 7.62 - 7.59 (2H, m, \text{Ar-CH}), 5.07 (1H, m, \text{CHBr}), 3.60 - 3.49 (2H, m, \text{CH}_2\text{F}); \(^{19}\)F NMR (470 MHz, CDCl\(_3\)) \(\delta_F: -150.8 - -150.9 \text{ (m, C-HF).}

1-(2-bromo-1-fluoroethyl)-4-fluorobenzene (36e) was prepared following General Procedure B, using 1-fluoro-4-vinylbenzene (32e) (1.00 g, 8.19 mmol, 1.00 equiv), N-bromosuccinimide (2.22 g, 12.29 mmol, 1.50 equiv), and NEt\(_3\),HF (2.00 mL, 12.29 mmol, 1.50 equiv) in CH\(_2\)Cl\(_2\) (20 mL). The reaction mixture was stirred at RT for 20 h. The crude product was purified by flash column chromatography (90% petroleum ether/10% CH\(_2\)Cl\(_2\)) to afford the title compound (36e) as a colourless oil (1.279 g, 71%).

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta_{H}: 7.38 - 7.31 (2H, m, \text{Ar-CH}), 7.17 - 7.06 (2H, m, \text{Ar-CH}), 5.61 (1H, ddd, \(J = 46.4, 7.6, 4.4 \text{ Hz, C-HF}\)), 3.87 - 3.41 (2H, m, \text{CH}_2\text{F}); \(^{19}\)F NMR (471 MHz, CDCl\(_3\)) \(\delta_F: -111.9 - -111.9 \text{ (m, Ar-F), -171.6 (ddd, } ^2J_{HF} = 46.4 \text{ Hz, } ^3J_{HF} = 24.5 \text{ Hz, } ^3J_{HF} = 15.0 \text{ Hz, CHF)}\); \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \(\delta_{C}: 163.1 \text{ (Ar-C, d, } J = 248.2 \text{ Hz), 133.0 (Ar-C, dd, } J = 20.8 \text{ Hz, } J = 3.4 \text{ Hz), 127.8 (2xAr-CH, t, } J = 7.6 \text{ Hz), 115.8 (2xAr-CH, d, } J = 21.8 \text{ Hz), 92.1 (C-HF, d, } J = 178.0 \text{ Hz), 34.1 (C-HBr, d, } J = 29.0 \text{ Hz).}
(4-(2-bromo-1-fluoroethyl)phenyl)(methyl)sulfane (36f) was prepared following General Procedure B, using methyl(4-vinylphenyl)sulfane (32f) (0.75 g, 5.00 mmol, 1.00 equiv), N-bromosuccinimide (1.36 g, 7.50 mmol, 1.50 equiv), and NEt₃·HF (1.22 mL, 7.50 mmol, 1.50 equiv) in CH₂Cl₂ (12 mL). The reaction mixture was stirred at RT for 20 h. The crude product was purified by flash column chromatography (95% petroleum ether/5% CH₂Cl₂) to afford the title compound (36f) as a light yellow oil (0.483 g, 39%).

¹H NMR (400 MHz, CDCl₃) δH: 7.27 (4H, s, Ar-H), 5.69 (1H, ddd, J = 46.8, 7.7, 3.7 Hz, CHF), 3.72-3.50 (2H, m, CH₂Br); ¹⁹F NMR (471 MHz, CDCl₃) δF: -172.6 (ddd, 2JHF = 46.8 Hz, 3JHF = 24.9 Hz, 3JHF = 15.0 Hz, CHF).

4-(2-bromo-1-fluoroethyl)-1,1'-biphenyl (36g) was prepared following General Procedure B, using 1-vinyl-1,1'-biphenyl (32g) (1.00 g, 5.55 mmol, 1.00 equiv), N-bromosuccinimide (1.51 g, 8.32 mmol, 1.50 equiv), and NEt₃·HF (1.36 mL, 8.32 mmol, 1.50 equiv) in CH₂Cl₂ (10 mL). The reaction mixture was stirred at RT for 20 h. The crude product was purified by flash column chromatography (95% petroleum ether/5% CH₂Cl₂) to afford the title compound (36g) as a colourless solid (1.23 g, 80%).

¹H NMR (400 MHz, CDCl₃) δH: 7.64-7.37 (9H, m, Ar-H), 5.68 (1H, ddd, J = 46.5, 7.9, 4.1 Hz, CHF), 4.77-3.61 (2H, m, CH₂Br); ¹⁹F NMR (471 MHz, CDCl₃) δF: -176.6 (ddd, 2JHF = 46.5 Hz, 3JHF = 25.8 Hz, 3JHF = 15.3 Hz, CHF); ¹³C NMR (125 MHz, CDCl₃) δC: 142.2 (Ar-C), 140.3 (Ar-C), 136.0 (Ar-C, d, J = 20.3 Hz), 128.9 (2xAr-C), 127.7 (Ar-C), 127.5 (2xAr-C), 127.1
(2xAr-CH), 126.2 (2xAr-CH, d, J = 6.5 Hz), 92.6 (CHF, d, J = 177.9 Hz), 34.2 (CHBr, d, J = 28.6 Hz); m.p. 55-56 °C.

1,4-bis(2-bromo-1-fluoroethyl)benzene (36h) was prepared following General Procedure B, using 1,4-divinylbenzene (32h) (1.00 g, 7.687 mmol, 1.00 equiv), N-bromosuccinimide (4.17 g, 23.063 mmol, 3.00 equiv), and NEt₃.HF (3.76 mL, 23.06 mmol, 3.00 equiv) in CH₂Cl₂ (20 mL). The reaction mixture was stirred at RT for 20 h. The crude product was purified by flash column chromatography (100% petroleum ether) to afford the title compound (36h) as a colourless solid (7.209 g, 74%).

¹H NMR (400 MHz, CDCl₃) δH: 7.41 (4H, s, Ar-CH), 5.65 (2H, ddd, J = 46.8, 7.5, 4.4 Hz, CHF), 3.82-3.53 (4H, m, CH₂Br); ¹⁹F NMR (470 MHz, CDCl₃) δF: -174.8 (ddd, JHF = 46.8 Hz, 3JHF = 24.5 Hz, 3JHF = 15.7 Hz, CHE); ¹³C NMR (125 MHz, CDCl₃) δC: 138.2 (2xAr-C, d, J = 20.6 Hz), 126.1 (4xAr-CH, d, J = 6.9 Hz), 92.2 (CHF, d, J = 178.7 Hz), 92.3 (CHF, d, J = 178.7 Hz), 34.0 (2xCHBr, d, J = 28.2 Hz); m.p. 92-94 °C.
5.2.3 Vinyl Fluorides

*General Procedure C for Synthesis of Vinyl Fluorides 37a-h*:

A flame-dried round-bottomed flask equipped with a magnetic stir bar was charged with potassium tert-butoxide (1.15-3.00 equiv). The reaction vessel was sealed, then evacuated and backfilled with nitrogen. Anhydrous THF was added via syringe before cooling the resulting suspension to 0°C. After stirring at this temperature for 15 minutes, the appropriate fluorobromoethane (1.00 equiv) was added via syringe. The resulting suspension was allowed to warm to RT, and then stirred for 18 h. After completion, the reaction mixture was filtered and solvent removed *in vacuo*. Purification by flash column chromatography (petroleum ether/CH₂Cl₂) afforded the appropriate vinyl fluoride.

(1-fluorovinyl)benzene (37a) was prepared following General Procedure C, using (2-bromo-1-fluoroethyl)benzene (36a) (5.00 g, 24.60 mmol, 1.00 eq), potassium tert-butoxide (4.12 g, 36.19 mmol, 1.50 eq) and THF (30 mL). The reaction mixture was stirred at RT for 18 h. The crude product was purified by flash column chromatography (100% petroleum ether) to afford the title compound (37a) as a colourless oil (1.506 g, 59%).

1H NMR (400 MHz, CDCl₃) δH: 7.61-6.54 (2H, m, Ar-CH), 7.41-7.34 (3H, m, Ar-CH), 5.04 (1H, dd, 3JHF = 49.8 Hz, 2JHH = 3.5 Hz, CHtrans-Hcis), 4.86 (1H, dd, 3JHF(cis) = 17.3 Hz, 2JHH = 3.5 Hz, CHtrans-Hcis); 19F NMR (471 MHz, CDCl₃) δF: -107.9 (dd, 3JHF(trans) = 49.8 Hz, 3JHF(cis) = 17.3 Hz, CF); 13C NMR (125 MHz, CDCl₃) δC: 162.9 (CF, d, J = 250.5 Hz), 132.0 (Ar-C, d, J = 29.2 Hz), 129.4 (Ar-CH), 128.5 (2xAr-CH), 124.6 (2xAr-CH, d, J = 7.1 Hz), 89.6 (CH₂, d, J = 22.6 Hz).
1-bromo-4-(1-fluorovinyl)benzene (37b) was prepared following General Procedure C, using 1-bromo-4-(2-bromo-1-fluoroethyl)benzene (36b) (2.70 g, 9.65 mmol, 1.00 equiv), potassium tert-butoxide (1.25 g, 11.10 mmol, 1.15 equiv) and THF (25 mL). The reaction mixture was stirred at RT for 18 h. The crude product was purified by flash column chromatography (95% petroleum ether/5% CH₂Cl₂) to afford the title compound (37b) as a colourless oil (0.459 g, 70%).

¹H NMR (400 MHz, CDCl₃) δH: 7.54-7.49 (2H, m, Ar-C₃H), 7.43-7.40 (2H, m, Ar-C₃H), 5.04 (1H, dd, ³JHF(trans) = 49.4 Hz, ²JHH = 3.7 Hz, CHcisHtrans), 4.88 (1H, dd, ³JHF(cis) = 17.7 Hz, ²JHH = 3.7 Hz, CHcisHtrans); ¹⁹F NMR (471 MHz, CDCl₃) δF: -108.0 (dd, ³JHF(trans) = 49.4 Hz, ³JHF(cis) = 17.7 Hz, C𝐹); ¹³C NMR (125 MHz, CDCl₃) δC: 162.0 (C𝐹, d, ³JC(F) = 250.3 Hz), 131.9 (Ar-C, d, J = 29.9 Hz), 131.7 (2xAr-C), 126.2 (2xAr-C, d, J = 7.1 Hz), 90.5 (CH₂, d, J = 22.1 Hz).

1-(1-fluorovinyl)-4-nitrobenzene (37c) was prepared following General Procedure C, using 1-(2-bromo-1-fluoroethyl)-4-nitrobenzene (36c) (1.50 g, 6.07 mmol, 1.00 equiv), potassium tert-butoxide (1.02 g, 9.11 mmol, 1.50 equiv) and THF (50 mL). The reaction mixture was stirred at RT for 18 h. The crude product was purified by flash column chromatography (20% petroleum ether/80% CH₂Cl₂) to afford the title compound (37c) as a colourless solid (0.790 g, 79%).

¹H NMR (400 MHz, CDCl₃) δH: 8.25 (2H, d, J = 8.8 Hz, Ar-CH), 7.72 (2H, d, J = 8.8 Hz, Ar-CH), 5.26 (1H, dd, ³JHF(trans) = 48.3 Hz, ²JHH = 4.0 Hz, CHcisHtrans), 5.10 (1H, dd, ³JHF(cis) = 17.5 Hz, ²JHH = 4.0 Hz, CHcisHtrans); ¹⁹F NMR (471 MHz, CDCl₃) δF: -108.16 (dd, ³JHF(trans) = 48.3 Hz, ³JHF(cis) = 17.5 Hz, C𝐹); ¹³C NMR (125 MHz, CDCl₃) δC: 160.8 (C𝐹, d, J = 250.8 Hz),
148.2 (C-NO₂), 137.8 (Ar-C, d, J = 29.9 Hz), 125.4 (2xAr-CH, d, J = 7.2 Hz), 124.6 (2xAr-CH, d, J = 1.9 Hz), 93.8 (CH₂, d, J = 21.9 Hz); m.p. 62-63 °C.

1-fluoro-4-(1-fluorovinyl)benzene (37e) was prepared following General Procedure C, using 1-(2-bromo-1-fluoroethyl)-4-fluorobenzene (36e) (3.00 g, 13.59 mmol, 1.00 equiv), potassium tert-butoxide (1.91 g, 16.98 mmol, 1.25 equiv) and THF (50 mL). The reaction mixture was stirred at RT for 18 h. The crude product was purified by flash column chromatography (90% petroleum ether/10% CH₂Cl₂) to afford the title compound (37e) as a colourless solid (1.408 g, 74%).

H NMR (500 MHz, CDCl₃) δH: 7.59-7.51 (2H, m, Ar-CH), 7.10-7.03 (2H, m, Ar-CH), 4.96 (1H, dd, 3J_HF(trans) = 49.7 Hz, 2J_HH = 3.6 Hz, CH₃H(trans)), 5.10 (1H, dd, 3J_HF(cis) = 17.9 Hz, 2J_HH = 3.6 Hz, CH₃H(cis)); 19F NMR (471 MHz, CDCl₃) δF: -107.03 (dd, 3J_H,F(trans) = 49.7 Hz, 3J_H,F(cis) = 17.9 Hz, CF), -111.5 (m, Ar-F); 13C NMR (125 MHz, CDCl₃) δC: 163.8 (C,F, d, J = 249.9 Hz), 162.6 (C,F, d, J = 250.4 Hz), 128.0 (2xAr-CH, m), 126.3 (2xAr-CH, t, J = 7.5 Hz), 114.5 (2xAr-CH, d, J = 21.8 Hz), 89.1 (CH₂, d, J = 22.9 Hz).

(4-(1-fluorovinyl)phenyl)(methyl)sulfane (37f) was prepared following General Procedure C, using (4-(2-bromo-1-fluoroethyl)phenyl)(methyl)sulfane (36f) (0.280 g, 1.12 mmol, 1.00 equiv), potassium tert-butoxide (0.158 g, 1.41 mmol, 1.25 equiv) and THF (8 mL). The reaction mixture was stirred at RT for 18 h. The crude product was purified by flash column.
chromatography (90% petroleum ether/10% CH₂Cl₂) to afford the title compound (37f) as a light yellow solid (0.065 g, 35%).

**¹H NMR (400 MHz, CDCl₃)** δ: 7.49-7.43 (2H, m, Ar-CH), 7.26-7.20 (2H, m, Ar-CH), 4.98 (1H, dd, J₁H,F (trans) = 49.8 Hz, J₂H,F (cis) = 17.9 Hz, CH₂cisHtrans), 4.80 (1H, dd, J₁H,F (trans) = 17.9 Hz, J₂H,F (cis) = 49.8 Hz, CH₂cisHtrans); ¹³C NMR (125 MHz, CDCl₃) δ: 162.8 (CF, d, J = 248.8 Hz), 140.6 (Ar-C), 128.3 (Ar-C, d, J = 29.8 Hz), 126.8 (2xAr-CH, d, J = 2.0 Hz), 125.3 (2xAr-CH, d, J = 7.3 Hz), 88.3 (CH₂, d, J = 22.6 Hz), 15.4 (CH₃); m.p. 49-50°C.

4-(1-fluorovinyl)-1,1'-biphenyl (37g) was prepared following General Procedure C, using 4-(2-bromo-1-fluoroethyl)-1,1'-biphenyl (36g) (0.80 g, 2.87 mmol, 1.00 equiv), potassium tert-butoxide (0.371 g, 3.31 mmol, 1.15 equiv) and THF (10 mL). The reaction mixture was stirred at RT for 18 h. The crude product was purified by flash column chromatography (95% petroleum ether/5% CH₂Cl₂) to afford the title compound (37g) as a colourless solid (0.387 g, 68%).

**¹H NMR (400 MHz, CDCl₃)** δ: 7.67-7.62 (6H, m, Ar-CH), 7.46-7.50 (2H, m, Ar-CH), 7.38-7.41 (1H, m, Ar-CH), 5.08 (1H, dd, J₁H,F (trans) = 49.7 Hz, J₂H,F (cis) = 3.5 Hz, CH₂cisHtrans), 4.89 (1H, dd, J₁H,F (trans) = 17.9 Hz, J₂H,F (cis) = 3.5 Hz, CH₂cisHtrans); ¹⁹F NMR (471 MHz, CDCl₃) δ: -108.0 (dd, J₁H,F (trans) = 49.7 Hz, J₂H,F (cis) = 17.9 Hz, CF); ¹³C NMR (125 MHz, CDCl₃) δ: 162.0 (CF, d, J = 250.3 Hz), 130.9 (Ar-C, d, J = 29.9 Hz), 126.2 (2xAr-CH, d, J = 6.9 Hz), 125.0 (2xAr-CH, d, J = 7.0 Hz), 89.6 (CH₂, d, J = 22.5 Hz); m.p. 119-120°C.
1,4-bis(1-fluorovinyl)benzene (37h) was prepared following General Procedure C, using 1,4-bis(2-bromo-1-fluoroethyl)benzene (36h) (1.30 g, 3.96 mmol, 1.00 equiv), potassium tert-butoxide (1.02 g, 9.12 mmol, 3.00 equiv) and THF (30 mL). The reaction mixture was stirred at RT for 18 h. The crude product was purified by flash column chromatography (100% petroleum ether) to afford the title compound (37h) as a colourless oil (0.459 g, 70%).

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 7.56 (4H, s, Ar-$\text{CH}$), 5.08 (2H, dd, $^3$J$_{HF}$ = 49.4 Hz, $^2$J$_{HH}$ = 3.6 Hz, CH$_{\text{trans}}$H$_{\text{cis}}$), 4.90 (2H, dd, $^3$J$_{HF}$ = 17.8 Hz, $^2$J$_{HH}$ = 3.6 Hz, CH$_{\text{trans}}$H$_{\text{cis}}$); $^19$F NMR (471 MHz, CDCl$_3$) $\delta$: -108.3 (dd, $^3$J$_{HF\text{(trans)}}$ = 49.4 Hz, $^3$J$_{HF\text{(cis)}}$ = 17.8 Hz, CF); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$: 162.3 (2xCF, d, $J = 250.3$ Hz), 132.7 (2xAr-C, d, $J = 29.4$ Hz), 124.7 (2xAr-CH, d, $J = 2.2$ Hz), 124.6 (2xAr-CH, d, $J = 2.2$ Hz), 90.5 (2xCH$_2$, d, $J = 22.5$ Hz).
5.2.4 Trifluorocyclopropanes

General Procedure D for Cyclopropanation of Vinyl Fluorides 42a-42h:

A flame-dried round-bottomed flask equipped with a magnetic stir bar was charged with NaI (2.50-5.00 equiv). The reaction vessel was sealed, then evacuated and backfilled with nitrogen. Anhydrous THF, the appropriate vinyl fluoride (1.00 equiv) and trifluoromethyltrimethylsilane (2.50-5.00 equiv) were added sequentially via syringe. The resulting suspension was stirred at 55 °C for 20 h. After completion, the reaction mixture was allowed to cool to RT and solvent was removed in vacuo. The crude residue was diluted with diethyl ether (50 mL) and washed with distilled water (50 mL). The phases were separated and the aqueous layer was extracted with diethyl ether (2x50 mL). The combined organic phases were washed sequentially with saturated aqueous solutions of Na₂SO₃ and NaHCO₃, followed by drying over Na₂SO₄, filtration and evaporation of solvent in vacuo. Purification by flash column chromatography (petroleum ether/CH₂Cl₂) afforded the appropriate 1,2,2-trifluorocyclopropane.

(1,2,2-trifluorocyclopropyl)benzene (42a) was prepared following General Procedure D, using (1-fluorovinyl)benzene (37a) (2.00 g, 16.38 mmol, 1.00 equiv), trifluoromethyltrimethylsilane (6.05 mL, 40.94 mmol, 2.50 equiv), and NaI (6.14 g, 40.94 mmol, 2.50 equiv) in THF (60 mL). The reaction mixture was stirred at 55 °C for 20 h. The crude product was purified by flash column chromatography (100% petroleum ether) to afford the title compound (42a) as a colourless oil (1.506 g, 53%).

¹H NMR (500 MHz, CDCl₃) δ_H: 7.44 (5H, s, Ar-CH), 2.21-2.01 (2H, m, CH₂); ¹⁹F{¹H} NMR (376 MHz, CDCl₃) δ_F: -136.8 (dd, ²J_FF = 167.3 Hz, ³J_FF = 9.6 Hz, CF₂), -141.8 (dd, ²J_FF = 167.3 Hz, ³J_FF = 3.9 Hz, CF₂); ¹⁹F NMR (471 MHz, toluene-d₈) δ_F: -136.8 (ddddd, ²J_FF = 167.3 Hz, ³J_FF = 9.6 Hz, ⁴J_FF = 3.9 Hz, CF₂); ¹³C NMR (125 MHz, CDCl₃) δ_C: 131.1 (Ar-CH, d, J = 21.0 Hz), 129.5 (1xAr-CH, d, J = 21.0 Hz),
2.3 Hz), 128.7 (2xAr-CH, s), 126.9 (2xAr-CH, d, J = 5.0 Hz), 109.3 (C_F, ddd, J = 294.4, 294.1, 12.0 Hz), 78.8 (CF, ddd, J = 233.5, 13.0, 10.2 Hz), 22.2 (CH, dt, J = 12.9, 10.0 Hz); HRMS (APCI+ASAP) calculated for C_9H_7F_3[M+H]^+ m/z 173.0578, found 173.0583.

1-bromo-4-(1,2,2-trifluorocyclopropyl)benzene (42b) was prepared following General Procedure D, using 1-(1-fluorovinyl)-4-bromobenzene (37b) (0.500 g, 2.50 mmol, 1.0 equiv), trifluoromethyltrimethylsilane (0.924 mL, 6.25 mmol, 2.50 equiv), and NaI (0.937 g, 6.25 mmol, 2.50 equiv) in THF (25 mL). The reaction mixture was stirred at 55 °C for 20 h. The crude product was purified by flash column chromatography (90% petroleum ether/10% CH_2Cl_2) to afford the title compound (42b) as a light yellow oil (0.128 g, 66%).

^1H NMR (400 MHz, CDCl_3) δ_H: 7.58-7.56 (2H, d, J = 8.4 Hz, Ar-CH), 7.31-7.28 (2H, d, J = 8.4 Hz, Ar-CH), 2.22-1.98 (2H, m, CH_2); ^19F NMR (471 MHz, CDCl_3) δ_F: -136.9 (dddd, ^2J_{FF} = 167.8 Hz, ^3J_{FF} = 8.3 Hz, ^3J_{FH} = 15.2 Hz, ^3J_{CF} = 5.6 Hz, CF), -141.9 (dddd, ^2J_{FF} = 167.8 Hz, ^3J_{FF} = 3.7 Hz, ^3J_{FH} = 7.1 Hz, ^3J_{CF} = 16.6 Hz, CFF), -181.5 – -182.7 (m, CF); ^13C NMR (125 MHz, CDCl_3) δ_C: 131.9 (2xAr-CH), 130.1 (Ar-CH, d, J = 19.9 Hz), 128.4 (2xAr-CH, d, J = 5.1 Hz), 123.8 (Ar-CH), 108.9 (C_F, ddd, J = 294.8, 294.8, 4.1 Hz), 79.2 (CF, ddd, J = 235.6, 10.6, 2.1 Hz), 22.4 (CH, dt, J = 12.9, 10.0 Hz).

1-nitro-4-(1,2,2-trifluorocyclopropyl)benzene (42c) was prepared following General Procedure D, using 1-(1-fluorovinyl)-4-nitrobenzene (37c) (0.500 g, 2.994 mmol, 1.0 equiv),
trifluoromethyltrimethylsilane (2.21 mL, 14.97 mmol, 5.00 equiv), and NaI (2.24 g, 14.97 mmol, 5.00 equiv) in THF (10 mL). The reaction mixture was stirred at 55 °C for 20 h. The crude product was purified by flash column chromatography (20% petroleum ether/80% CH₂Cl₂) to afford the title compound (42c) as a pale yellow oil (0.480 g, 74%).

**¹H NMR (500 MHz, CDCl₃)** δH: 8.29 (2H, d, J = 9.0 Hz, Ar-CH), 7.55 (2H, d, J = 9.0 Hz, Ar-CH), 2.40-2.11 (2H, m, CH₂); **¹⁹F NMR (471 MHz, CDCl₃)** δF: -137.8 (dddd, 2JFF = 167.8 Hz, 3JFF = 8.5 Hz, 3JFH = 15.3 Hz, 3JFH = 6.8 Hz, CEF), -140.4 (ddd, 2JFF = 167.8 Hz, 3JFF = 2.9 Hz, 3JFH = 6.9 Hz, 3JFH = 16.3 Hz, CEF), -187.3 – -187.4 (m, CF₂); **¹³C NMR (125 MHz, CDCl₃)** δC: 148.1 (Ar-C), 138.5 (Ar-C, d, J = 19.3 Hz), 126.6 (2xAr-CH, d, J = 5.1 Hz), 123.8 (2xAr-CH), 108.7 (CF₂, ddd, J = 299.0, 294.5, 11.0 Hz), 77.4 (CF, ddd, J = 234.5, 12.6, 2.2 Hz), 23.5 (CH₃ dr, J = 13.4, 9.7 Hz); **HRMS (APCI+ASAP)** calculated for C₉H₆F₃NO₂ [M+H]⁺ m/z 218.0429, found 218.0431.

1-methoxy-4-(1,2,2-trifluorocyclopropyl)benzene (42d) was prepared following **General Procedure D**, using 1-(1-fluorovinyl)-4-methoxybenzene (37d) (0.150 g, 0.990 mmol, 1.00 equiv), trifluoromethyltrimethylsilane (0.365 mL, 2.47 mmol, 2.50 equiv), and NaI (0.369 g, 2.47 mmol, 2.50 equiv) in THF (8 mL). The reaction mixture was stirred at 55 °C for 20 h. The crude product was purified by flash column chromatography (80% petroleum ether/20% CH₂Cl₂) to afford the title compound (42d) as a light yellow oil (0.128 g, 64%).

**¹H NMR (500 MHz, CDCl₃)** δH: 7.42-7.38 (2H, m, Ar-CH), 6.97-6.92 (2H, m, Ar-CH), 3.84 (3H, s, CH₃), 2.16-1.91 (2H, m, CH₂); **¹⁹F NMR (471 MHz, CDCl₃)** δF: -135.7 (dddd, 2JFF = 166.4 Hz, 3JFF = 9.7 Hz, 3JFH = 15.6 Hz, 3JFH = 5.5 Hz, CEF), -142.5 (ddd, 2JFF = 166.4 Hz, 3JFF = 5.2 Hz, 3JFH = 7.1 Hz, 3JFH = 16.7 Hz, CEF), -175.0 – -175.2 (m, CF₃); **¹³C NMR (125 MHz, CDCl₃)** δC: 160.7 (Ar-C), 129.5 (2xAr-CH, d, J = 3.7 Hz), 122.8 (Ar-C, d, J = 20.0 Hz), 114.1 (2xAr-CH), 109.5 (CF₂, ddd, J = 295.3, 293.9, 13.4 Hz), 78.6 (CF, ddd, J = 233.5, 12.8, 9.9 Hz), 55.4 (CH₃), 22.2 (CH₃ dr, J = 14.4, 10.1 Hz).
1-fluoro-4-(1,2,2-trifluorocyclopropyl)benzene (42e) was prepared following General Procedure D, using 1-(1-fluorovinyl)-4-fluorobenzene (37e) (0.300 g, 1.76 mmol, 1.00 equiv), trifluoromethyltrimethylsilane (0.792 mL, 5.36 mmol, 2.50 equiv), and NaI (0.804 g, 5.36 mmol, 2.50 equiv) in THF (20 mL). The reaction mixture was stirred at 55 °C for 20 h. The crude product was purified by flash column chromatography (90% petroleum ether/10% CH₂Cl₂) to afford the title compound (42e) as a colourless oil (0.224 g, 67%).

**¹H NMR (500 MHz, CDCl₃)** δH: 7.52-7.37 (5H, s, Ar-CH), 7.17-7.06 (2H, m, Ar-CH₂), 2.21-1.96 (2H, m, CH₂);

**¹⁹F NMR (471 MHz, CDCl₃)** δF: -111.1 - -111.2 (m, Ar-F), -136.3 (dddd, J₁FF = 167.4 Hz, J₂FF = 9.3 Hz, J₃FH = 15.2 Hz, J₃FH = 5.5 Hz, CF₂), -142.31 (dddd, J₁FF = 167.4 Hz, J₂FF = 3.8 Hz, J₃FH = 6.7 Hz, J₃FH = 16.2 Hz, CF₂), -178.5 - -178.6 (m, CE₂);

**¹³C NMR (125 MHz, CDCl₃)** δC: 163.4 (Ar-C, d, J = 249.8 Hz), 129.4 (2xAr-CH, dd, J = 8.8, 4.6 Hz), 115.9 (2xAr-CH, d, J = 21.9 Hz), 108.7 (CF₂, ddd, J = 295.0, 297.1, 12.6 Hz), 78.7 (CF, ddd, J = 233.3, 9.8, 2.2 Hz), 22.3 (CH₂, dt, J = 14.0, 10.2 Hz).

Methyl(4-(1,2,2-trifluorocyclopropyl)phenyl)sulfane (42f) was prepared following General Procedure D, using (4-(1-fluorovinyl)phenyl)(methyl)sulfane (37f) (0.05 g, 0.297 mmol, 1.00 equiv), trifluoromethyltrimethylsilane (0.110 mL, 0.744 mmol, 2.50 equiv), and NaI (0.112 g, 0.744 mmol, 2.50 equiv) in THF (5 mL). The reaction mixture was stirred at 55 °C for 20 h. The
crude product was purified by flash column chromatography (95% petroleum ether/5% CH₂Cl₂) to afford the title compound (42f) as a light yellow oil (0.027 g, 41%).

¹H NMR (500 MHz, CDCl₃) δH: 7.35 (2H, d, J = 8.4 Hz, Ar-CH), 7.29 (2H, d, J = 8.4 Hz, Ar-CH), 2.16-1.94 (2H, m, C₂H₂); ¹³C NMR (101 MHz, CDCl₃) δC: 127.7 (2xAr-CH, d, J = 4.7 Hz), 127.4 (Ar-CH, d, J = 4.7 Hz), 126.1 (2xAr-CH), 123.9 (Ar-C), 109.3 (CF₂, ddd, J = 297.2, 294.5, 10.5 Hz), 22.2 (C₂H₂, dt, J = 13.7, 10.1 Hz), 15.4 (SCH₃); HRMS (APCI+ASAP) calculated for C₁₀H₉F₃S [M+H]⁺ m/z 219.0455, found 219.0455.

4-(1,2,2-trifluorocyclopropyl)-1,1'-biphenyl (42g) was prepared following General Procedure D, using 4-(1-fluorovinyl)-1,1'-biphenyl (37g) (0.180 g, 0.908 mmol, 1.0 equiv), trifluoromethyltrimethylsilane (0.335 mL, 2.27 mmol, 2.5 equiv), and NaI (0.340 g, 2.27 mmol, 2.5 equiv) in THF (10 mL). The reaction mixture was stirred at 55 °C for 20 h. The crude product was purified by flash column chromatography (95% petroleum ether/5% CH₂Cl₂) to afford the title compound (42g) as a pale yellow solid (0.209 g, 93%).

¹H NMR (500 MHz, CDCl₃) δH: 7.67-7.59 (4H, m, Ar-CH), 7.51-7.44 (4H, m, Ar-CH), 7.40-7.36 (1H, m, Ar-CH); ¹³C NMR (101 MHz, CDCl₃) δC: 130.0 (Ar-CH, d, J = 19.7 Hz), 128.9 (2xAr-CH), 127.8 (Ar-CH), 127.4 (2xAr-CH), 127.3 (2xAr-CH), 126.9 (Ar-CH), 126.5 (Ar-CH), 108.9 (CF₂, ddd, J = 294.5, 294.5, 2.5 Hz), 80.0-77.4 (CF, m), 22.4 (CH₂ dt, J = 13.5, 10.1 Hz); m.p. 86-87 °C.
1,4-bis(1,2,2-trifluorocyclopropyl)benzene (42h) was prepared following General Procedure D, using 1,4-bis(1-fluorovinyl)benzene (37h) (0.150 g, 0.904 mmol, 1.00 equiv), trifluoromethyltrimethylsilane (0.726 mL, 4.97 mmol, 5.50 equiv), and NaI (0.756 g, 4.97 mmol, 5.50 equiv) in THF (10 mL). The reaction mixture was stirred at 55 °C for 20 h. The crude product was purified by flash column chromatography (95% petroleum ether/5% CH₂Cl₂) to afford the title compound (42h) as a pale yellow oil (0.079 g, 33%).

¹H NMR (500 MHz, CDCl₃) δ: 7.48 (4H, s, Ar-CH), 2.28-2.01 (4H, m, CH₂); ¹⁹F NMR (471 MHz, CDCl₃) δ: -137.6 (dddd, J_F = 167.6 Hz, J_{FF} = 9.4 Hz, J_{FH} 15.1 Hz, J_{FH} = 6.9 Hz, CFF), -140.3 (dddd, J_F = 167.6 Hz, J_{FF} = 2.8 Hz, J_{FH} = 7.6 Hz, J_{FH} = 16.2 Hz, CFF), -187.22 - -187.45 (m, CF); ¹³C NMR (126 MHz, CDCl₃) δ: 132.4 (2×Ar-C, d, J = 19.6 Hz), 126.8 (4×Ar-CH, d, J = 5.3 Hz), 108.9 (CF₂, ddd, J = 294.7, 293.8, 11.0 Hz), 77.5 (CF, ddd, J = 233.1, 10.0, 2.8 Hz), 22.6 (CH₂, d, J = 13.8, 9.4 Hz).
5.3 Miscellaneous Experimental Procedures

5.3.1 Nitration of 42a

1-nitro-4-(1,2,2-trifluorocyclopropyl)benzene (42c), 1-nitro-3-(1,2,2-trifluorocyclopropyl)benzene (50) and 1-nitro-2-(1,2,2-trifluorocyclopropyl)benzene (51). A flame-dried round-bottomed flask equipped with a magnetic stir bar was charged with ammonium nitrate (0.174 g, 2.56 mmol, 1.10 equiv). The reaction vessel was sealed, then evacuated and backfilled with nitrogen. 42a (0.400 g, 2.32 mmol, 1.00 equiv), acetonitrile (25 mL) and trifluoroacetic anhydride (1.147 mL, 8.12 mmol, 3.50 equiv) were added via syringe. The resulting solution was stirred at 60 °C for 24 h before quenching with an aqueous solution 1 M solution of HCl and washing sequentially with aqueous solution of NaHCO₃ (25 mL) and brine (25 mL). The combined organic layers were dried over Na₂SO₄, filtered and evaporated to dryness in vacuo. Purification of the crude residue by flash column chromatography (30% petroleum ether/70% CH₂Cl₂) afforded the meta-isomer 50 (0.087 g) as a pure material and the para- and ortho-isomers 42c and 51 as a 3.85:1.00 mixture (0.172 g) (overall 48%).

50: ¹H NMR (300 MHz, CDCl₃) δH: 8.25-8.14 (1H, m, Ar-CH), 7.81 – 7.66 (3H, m, Ar-CH), 2.12-1.93 (2H, m, CH₂); ¹⁹F{¹H} NMR (282 MHz, CDCl₃) δF: -133.5 (dd, JFF = 171.9 Hz, JFF 2.6 Hz, CF₂), -142.6 (dd, JFF = 171.9 Hz, JFF 2.6 Hz, CF₂), -187.4 (dd, JFF = 7.2 Hz, JFF = 2.6 Hz, CF²);

42c and 51 mixture (approx. 4:1 isolated): ¹H NMR (300 MHz, CDCl₃) δH: 8.31 (2H, d, J = 8.8 Hz, 42c:Ar-CH), 7.83 – 7.62 (1H, m, 51:Ar-CH), 7.58 (2H, d, J = 8.8 Hz, 42c:Ar-CH), 2.48-2.12 (2.5H, m, 42c and 51:CH₂); ¹⁹F{¹H} NMR (282 MHz, CDCl₃) δF: -137.3 (dd, JFF = 168.5 Hz, JFF 8.8 Hz, JFF 9.0 Hz, 42c:CF₂), -140.7 (dd, JFF = 168.1 Hz, JFF 168.1 Hz, JFF 2.6 Hz, CF₂).
5.3.2 Demethylation of 42d

4-(2,2-difluoro-1-hydroxycyclopropyl)phenol (54). A flame-dried round-bottomed flask equipped with a magnetic stir bar was sealed, then evacuated and backfilled with nitrogen. 42d (0.100 g, 0.546 mmol, 1.00 equiv) and CH₂Cl₂ (18 mL) were added and the solution cooled to 0 °C. Boron tribromide (0.520 mL, 5.46 mmol, 10.00 equiv) was added dropwise over 5 minutes, before stirring at 0 °C for 1 h. After completion, the reaction mixture was warmed to RT, quenched with H₂O (20 mL) and extracted with CH₂Cl₂ (3x30 mL). The combined organic layers were dried over Na₂SO₄, filtered and evaporated to dryness in vacuo to afford the title compound (54) as colourless oil (0.091 g, 90%).

¹H NMR (500 MHz, CDCl₃) δH: 7.35 (2H, d, J = 8.6 Hz, Ar-CH), 6.83 (2H, d, J = 8.6 Hz, Ar-CH), 2.19 (1H, ddd, J = 13.7, 9.4, 4.7 Hz, CH₂H), 2.05 (1H, ddd, J = 13.7, 9.3, 4.7 Hz, CH₃H); ¹⁹F NMR (471 MHz, CDCl₃) δF: -126.9 (ddd, J_FF = 149.2 Hz, J_FH = 11.5 Hz, J_FH = 4.8 Hz, CF₂F), -132.3 (ddd, J_FF = 148.5 Hz, J_FH = 13.1 Hz, J_FH = 4.7 Hz, CF₂F); ¹³C NMR (126 MHz, CDCl₃) δC: 156.3 (Ar-C), 131.0 (2xAr-CH), 128.4 (Ar-C), 115.8 (2xAr-CH), 114.3 (Ar-C), 109.6 (CF₂, t, J = 290.8 Hz), 27.3 (CH₂, t, J = 10.5 Hz).
5.3.3 Pd-Catalysed Cross-Couplings\textsuperscript{115}

1-propyl-4-((4-(1,2,2-trifluorocyclopropyl)phenyl)ethynyl)benzene (56). A flame-dried round-bottomed flask equipped with a magnetic stir bar was charged with PPh\textsubscript{3} (0.058 g, 0.220 mmol, 0.825 equiv), CuI (0.010 g, 0.058 mmol, 0.21 equiv) and Pd(PPh\textsubscript{3})Cl\textsubscript{2} (0.010 g, 0.014 mmol, 0.05 equiv). The reaction vessel was sealed, then evacuated and backfilled with nitrogen. Anhydrous DMF (5.4 mL), NEt\textsubscript{3} (5.4 mL), 1-ethynyl-4-propylbenzene (0.078 g, 0.540 mmol, 0.825 equiv) and 42b (0.070 g, 0.270 mmol, 1.00 equiv) were added via syringe. The resulting suspension was stirred at 80°C for 24 h before quenching with EtOAc and washing sequentially with an aqueous 1M solution of HCl (25 mL), a saturated aqueous solution of NaHCO\textsubscript{3} (25 mL) and brine (25 mL). The combined organic layers were dried over Na\textsubscript{2}SO\textsubscript{4}, filtered and evaporated to dryness in vacuo. Purification of the crude residue by flash column chromatography (75% petroleum ether/25% CH\textsubscript{2}Cl\textsubscript{2}) afforded the title compound (56) as a light yellow oil (0.064 g, 76%).

\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \(\delta_{H}\): 7.61 – 7.55 (2H, m, Ar-C\textsubscript{H}), 7.49 – 7.42 (2H, m, Ar-C\textsubscript{H}), 7.39 (2H, m, Ar-C\textsubscript{H}), 7.20 – 7.14 (2H, m, Ar-C\textsubscript{H}), 2.60 (2H, t, \(J = 7.2\) Hz, C\textsubscript{H\textsubscript{2}}), 2.28 – 1.97 (2H, m, CF-C\textsubscript{H\textsubscript{2}}-CF\textsubscript{2}), 1.74 – 1.57 (2H, m, CH\textsubscript{2}-CH\textsubscript{3}), 0.94 (3H, t, \(J = 7.3\) Hz, CH\textsubscript{3}); \textsuperscript{19}F NMR (471 MHz, CDCl\textsubscript{3}) \(\delta_{F}\): -136.9 (dddd, \(\Delta J_{FF} = 166.9\) Hz, \(\Delta J_{FH} = 15.2\) Hz, \(\gamma J_{FH} = 8.8\) Hz, \(\gamma J_{FH} = 5.7\) Hz, CF\textsubscript{2}), -141.5 (dddd, \(\Delta J_{FF} = 167.1\) Hz, \(\Delta J_{FH} = 16.2\) Hz, \(\gamma J_{FH} = 6.6\) Hz, \(\gamma J_{FH} = 3.8\) Hz, CFE), -182.5 – -185.7 (m, CF); \textsuperscript{13}C NMR (126 MHz, CDCl\textsubscript{3}) \(\delta_{C}\): 143.6 (Ar-C), 131.7 (2xAr-C\textsubscript{H}), 131.6 (2xAr-C\textsubscript{H}), 130.7 (Ar-C, d, \(J = 19.8\)), 128.6 (2xAr-C\textsubscript{H}), 126.6 (2xAr-C\textsubscript{H}, d, \(J = 5.5\) Hz), 124.7 (Ar-C), 120.0 (Ar-C), 109.1 (C\textsubscript{F\textsubscript{2}}, ddd, J = 295.1, 294.2, 11.3 Hz), 91.0 (C≡C), 87.9 (C≡C), 79.6-77.4 (CF, m), 37.99 (CH\textsubscript{2}), 24.36 (CH\textsubscript{3}), 23.51 – 21.80 (m), 13.78 (CH\textsubscript{3}), 23.5-21.8 (CH\textsubscript{3}, m); HRMS (APCI+ASAP) calculated for C\textsubscript{20}H\textsubscript{17}F\textsubscript{3}[M+H]\textsuperscript{+} m/z 315.1360, found 315.1360.
4-(4-(1,2,2-trifluorocyclopropyl)phenyl)morpholine (58). A flame-dried round-bottomed flask equipped with a magnetic stir bar was charged with BINAP (0.037 g, 0.060 mmol, 0.15 equiv), Cs₂CO₃ (0.267 g, 0.637 mmol, 1.60 equiv) and Pd₂dba₃ (0.018 g, 0.020 mmol, 0.05 equiv). The reaction vessel was sealed, then evacuated and backfilled with nitrogen. Anhydrous toluene (6.0 mL), morpholine (0.055 g, 0.637 mmol, 1.60 equiv) and 42b (0.100 g, 0.398 mmol, 1.00 equiv) were added via syringe. The resulting suspension was stirred at 70°C for 24 h before quenching with EtOAc and washing sequentially with an aqueous 1 M solution of HCl (25 mL), a saturated aqueous solution of NaHCO₃ (25 mL) and brine (25 mL). The combined organic layers were dried over Na₂SO₄, filtered and evaporated to dryness in vacuo. Purification of the crude residue by flash column chromatography (70% petroleum ether/30% CH₂Cl₂) afforded the title compound (58) as a light yellow oil (0.095 g, 93%).

¹H NMR (400 MHz, CDCl₃) δH: 7.44 – 7.32 (2H, m, Ar-CH), 6.99 – 6.87 (2H, m, Ar-CH), 3.96 – 3.80 (4H, m, 2xCH₂), 3.31 – 3.12 (4H, m, 2xCH₂), 2.13 – 1.89 (2H, m, CF₂CH₂CF₂); ¹⁹F NMR (471 MHz, CDCl₃) δF: -135.7 (ddddd, JFF = 166.3 Hz, JFH = 14.5 Hz, JFH = 8.7 Hz, JFH = 5.3 Hz, CF₂); -142.6 (ddddd, JFF = 166.4 Hz, JFF = 16.2 Hz, JFH = 11.4 Hz, JFH = 6.2 Hz, CF₂), -178.5 – -178.6 (m, CF₂); ¹³C NMR (126 MHz, CDCl₃) δC: 152.2 (Ar-C), 129.1 (2xAr-CH), 121.3 (Ar-C, d, J = 20.0), 115.0 (2xAr-CH), 108.6 (CF₂, dddd, f = 294.7, 294.9, 10.8 Hz), 79.1-77.9 (CF₂, m), 66.8 (2xOCH₂), 48.5 (2xNCH₂), 22.0 (CH₂, dr, J = 14.8, 10.3 Hz).
5.3.4 Synthesis of Difluorocyclopropanes

(2,2-difluorocyclopropyl)benzene (72) was prepared following General Procedure D, using styrene (32a) (2.50 g, 24.0 mmol, 1.0 equiv), trifluoromethyltrimethylsilane (8.87 mL, 60.0 mmol, 2.5 equiv), and NaI (8.99 g, 60.0 mmol, 2.5 equiv) in THF (80 mL). The reaction mixture was stirred at 55 °C for 20 h. The crude product was purified by flash column chromatography (100% petroleum ether) to afford the title compound (72) as a colourless oil (2.487 g, 67%).

^1H NMR (500 MHz, CDCl₃) δ_H: 7.40-7.33 (2H, m, Ar-CH), 7.33-7.27 (1H, m, Ar-CH), 7.27-7.23 (2H, m, Ar-CH), 2.79 (1H, ddd, J = 13.3, 11.8, 8.1 Hz. CH), 1.91-1.78 (1H, m, CHH), 1.72-1.60 (1H, m, CHH); ^19F NMR (471 MHz, CDCl₃) δ_F: -125.8 (ddd, J_{FF} = 155.2 Hz, J_{FH} = 12.4 Hz, J_{FH}3.6 = Hz, CF₂), -142.4 (ddd, J_{FF} = 154.1 Hz, J_{FH} = 13.0 Hz, J_{FH}5.1 = Hz, CFF); ^13C NMR (125 MHz, CDCl₃) δ_C: 133.7 (Ar-C), 128.5 (2xAr-CH), 128.1 (Ar-CH), 127.2 (Ar-CH), 112.6 (CF₂, t, J = 285.8 Hz), 27.2 (CH, t, J = 11.5 Hz), 17.0 (CH₂, t, J = 10.6 Hz);

(1R,2S,5S)-3,3-difluorotricyclo[3.2.1.0²⁴]octane (76) was prepared following General Procedure D, using norbornene (73) (2.00 g, 21.24 mmol, 1.0 equiv), trifluoromethyltrimethylsilane (7.84 mL, 53.10 mmol, 2.5 equiv), and NaI (7.96 g, 53.10 mmol, 2.5 equiv) in THF (80 mL). The reaction mixture was stirred at 55 °C for 20 h. The crude
product was purified by flash column chromatography (100% petroleum ether) to afford the title compound (76) as a light brown oil (0.642 g, 21%).

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 2.65-2.60 (2H, m, H$_2$), 1.62-1.63 (7H, m, H$_{anti}$, H$_{t}$, CH$_2$), 0.96-0.84 (1H, m, H$_{syn}$). $^{19}$F $\{^1$H} NMR (377 MHz, CDCl$_3$) $\delta$: -119.2 (d, $J = 164.0$ Hz, F$_A$), -139.9 (d, $J = 164.0$ Hz, F$_B$). $^{19}$F NMR (377 MHz, CDCl$_3$) $\delta$: -120.5 (m, F$_A$), -138.7 (m, F$_B$).

5.3.5 Synthesis of Monofluorocyclopropanes 40a and 40b

![Chemical Structures](image)

Ethyl (1$R$,2$R$)-2-fluoro-2-phenylcyclopropane-1-carboxylate (40a) and ethyl (1$S$,2$R$)-2-fluoro-2-phenylcyclopropane-1-carboxylate (40b). A flame-dried round-bottomed flask equipped with a magnetic stir bar was charged with Rh$_2$(OAc)$_4$ (0.011 g, 0.025 mmol, 0.01 equiv). The reaction vessel was sealed, then evacuated and backfilled with nitrogen. Anhydrous CH$_2$Cl$_2$ (2 mL) and 37a (0.300 g, 2.46 mmol, 1.00 equiv) added via syringe, before the dropwise addition of ethyl diazoacetate (0.560 g, 0.492 mmol, 2.00 equiv) over 30 minutes. The resulting solution was stirred for a further 1 hour before quenching with a saturated aqueous solution of NaHCO$_3$ and extraction with CH$_2$Cl$_2$ (3x50 mL). The combined organic layers were dried over Na$_2$SO$_4$, filtered and evaporated to dryness in vacuo. Purification of the crude residue by flash column chromatography (100% petroleum ether) afforded a mixture of diastereomers of the title compound (40a and 40b) as a colourless oil (0.138 g, 27%).

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 7.52 – 7.47 (5H, m, 40b-Ar-CH), 7.46 – 7.30 (5H, m, 40a-Ar-CH), 4.35 – 4.16 (2H, m, 40a-CH$_2$), 3.94 (1H, dd, $J = 7.2$, 1.1 Hz, 40b-CH$_2$), 2.59 (1H, ddd, $J = 18.0$, 10.3, 7.7 Hz, 40b-CH$_3$), 2.33 (1H, ddd, $J = 20.2$, 7.8, 7.0 Hz, 40a-CH$_3$), 2.02 (1H, ddd, $J = 12.4$, 7.7, 7.1 Hz, 40b-CH$_3$), 2.22 (1H, ddd, $J = 9.2$, 7.8, 2.9 Hz, 40a-CH$_3$), 1.84 (1H, ddd, $J = 19.3$, 10.3,
7.1 Hz, 40b-H), 1.66 (1H, ddd, J = 10.5, 9.3, 7.0 Hz, 40a-H), 1.32 (3H, t, J = 7.1 Hz, 40a-CH₃), 1.03 (1H, t, J = 7.1 Hz, 40b-CH₃); ¹⁹F{¹H} NMR (376 MHz, CDCl₃) δ: -188.1 (s, 40a-CH₃), -153.5 (s, 40b-CH₃).

5.3.6 One-Pot Synthesis of Vinyl Fluorides 37a and 37d

![Chemical structure](image)

(1-fluorovinyl)benzene (37a). A flame-dried round-bottomed flask equipped with a magnetic stir bar was charged with NBS (1.91 g, 10.56 mmol, 1.50 equiv). The reaction vessel was sealed, then evacuated and backfilled with nitrogen. Anhydrous CH₂Cl₂ (25 mL) and styrene (32a) (1.00 g, 9.6 mmol, 1.00 equiv) were added sequentially via syringe. The resulting suspension was cooled to 0 °C and stirred for 30 minutes, followed by addition of NEt₃.HF (2.35 mL, 14.4 mmol, 1.50 equiv) via syringe. The reaction mixture was warmed to RT, and then stirred for 4 h before cooling to 0 °C. Potassium tert-butoxide (8.618 g, 76.8 mmol, 8.00 equiv) was added and the resulting suspension was allowed to warm to RT. After 16 h, the reaction mixture was filtered and solvent was removed in vacuo. Purification by flash column chromatography (100% petroleum ether) afforded the title compound 37a as a colourless oil (0.891 g, 76%). Characterisation data agreed with literature, and that previously reported in Section 5.2.3.
1-(1-fluorovinyl)-4-methoxybenzene (37d). A flame-dried round-bottomed flask equipped with a magnetic stir bar was charged with N-bromosuccinimide (4.99 g, 27.54 mmol, 1.50 equiv). The reaction vessel was sealed, then evacuated and backfilled with nitrogen. Anhydrous CH$_2$Cl$_2$ (25 mL) and 1-methoxy-4-vinylbenzene (32d) (2.50 g, 18.631 mmol, 1.0 equiv) were added sequentially via syringe. The resulting suspension was cooled to 0 °C and stirred for 30 minutes, followed by addition of NEt$_3$.3HF (4.49 mL, 27.54 mmol, 1.50 equiv) via syringe. The reaction mixture was warmed to RT, and then stirred for 4 h before cooling to 0 °C. Potassium tert-butoxide (16.72 g, 14.9 mmol, 8.0 equiv) was added and the resulting suspension was allowed to warm to RT. After 16 h, the reaction mixture was filtered and solvent was removed in vacuo. Purification by flash column chromatography (5% petroleum ether/95% CH$_2$Cl$_2$) afforded the title compound 37d as a colourless oil (2.32 g, 82%).

$^1$H NMR (400 MHz, CDCl$_3$) δ$_H$: 7.51-7.46 (2H, m, Ar-$CH$), 6.92-6.86 (2H, m, Ar-$CH$), 5.88 (1H, dd), $^3$J$_{HF\ (trans)}$ = 50.2 Hz, $^2$J$_{HH}$ = 3.2 Hz, CH$_3$.H$_{trans}$, 4.86 (1H, dd), $^3$J$_{HF\ (cis)}$ = 18.4 Hz, $^2$J$_{HH}$ = 3.5 Hz, CH$_3$.H$_{trans}$, 3.85 (3H, s, $CH_3$); $^{19}$F NMR (471 MHz, CDCl$_3$) δ$_F$: -107.1 (dd), $^3$J$_{HF\ (trans)}$ = 50.3 Hz, $^3$J$_{HF\ (cis)}$ = 18.1 Hz, CF; $^{13}$C NMR (125 MHz, CDCl$_3$) δ$_C$: 162.9 (CF, d, $J$ = 248.9 Hz), 160.5 (Ar-$C$), 124.6 (Ar-$C$, d, $J$ = 29.9 Hz), 126.1 (2xAr-$CH$, d, $J$ = 7.2 Hz), 113.8 (2xAr-$CH$), 87.6 ($CH_2$, d, $J$ = 23.2 Hz), 55.3 ($CH_3$).
5.3.7 Flash Vacuum Pyrolysis

42a (29 mg) was subjected to FVP at $5 \times 10^{-2}$ Torr and a specified temperature. At 500 °C and 600 °C, conversions (determined by $^{19}$F NMR spectroscopy) were 25% and 93%, respectively. The reaction mixture was recovered by washing the cold-trap with CDCl$_3$; this sample was used for analysis. At both temperatures, $^1$H and $^{19}$F NMR spectra of the product showed a mixture of starting material 42a and vinyl fluoride 37a. These analyses agree with the data reported for 37a and 42a in Sections 5.2.3 and 5.2.4, respectively.
5.4 Determination of logP

To determine the logP of new compounds by proxy, the retention time for each was determined on a Shimadzu Prominence HPLC System using a Phenomenx Analytical Luna® 5 μm C18(2) 100 Å LC column (250 x 5.5 mm). The flow rate was 1 mL/min and an eluent composition of 60:40 MeCN:H₂O (both containing 0.05 % trifluoroacetic acid) was used. Capacity factor (k) was calculated as follows:

\[ k = \frac{\text{retention time} - \text{dead time}}{\text{retention time}} \]

where dead time is equal to the time for an unretained compound (e.g. MeCN) to travel through the column. The logarithmic of k was plotted against the logP for reference compounds. Hence, plotting the logk for new compounds on the resulting linear regression revealed the logP of new compounds by extrapolation to intercept the x-axis (Graph 1).

Graph 1. logk vs. logP.
<table>
<thead>
<tr>
<th>Compound</th>
<th>logk</th>
<th>logP</th>
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</thead>
<tbody>
<tr>
<td>Phenol\textsuperscript{16}</td>
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<td>1.50</td>
</tr>
<tr>
<td>2-Fluorophenol\textsuperscript{17}</td>
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<td>1.71</td>
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<tr>
<td>Toluene\textsuperscript{18}</td>
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<td>2.73</td>
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<td>α, α, α - Trifluorotoluene</td>
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<td>Naphthalene\textsuperscript{19}</td>
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<td>Cyclopropylbenzene</td>
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<tr>
<td>tert-Butylbenzene</td>
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<td>4.11</td>
</tr>
<tr>
<td>Anthracene\textsuperscript{20}</td>
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<tr>
<td>Pyrene\textsuperscript{20}</td>
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<tr>
<td>42a</td>
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<tr>
<td>42g</td>
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<tr>
<td>42b</td>
<td>1.12</td>
<td>4.47</td>
</tr>
</tbody>
</table>

**Table 1.** logk and logP values for reference and new compounds.
Section 6 References


L. K. Revelle, *Flash Vacuum Pyrolysis*, University of Missouri, St. Louis, 1980.


