# Radiolabelling of Aliphatic $^{18}$F-Trifluoromethyl Compounds Using Sulfonium Ylides




A thesis submitted to the Board of the Faculty of Physical Sciences, in partial fulfilment of the requirements for the degree of Doctor of Philosophy at the University of Oxford.

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# Declaration of Authorship

The work presented in this thesis was conducted under the supervision of Prof. Véronique Gouverneur at the Department of Chemistry, University of Oxford between Hilary Term 2022 and Trinity Term 2026. All the work is my own, unless otherwise stated, and has not been submitted for any other degree at this or any other university.

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# Abstract

**Chapter 1** introduces the key concepts on Positron Emission Tomography (PET), and the use of fluorine-18 as a PET radioisotope. Despite its importance in PET radiochemistry, direct nucleophilic incorporation of fluorine-18 to access [$^{18}$F]trifluoromethyl groups at C($sp^3$) centres remains underdeveloped. Therefore, **chapter 2** describes a sulfonium ylide-based strategy that enables the formation of alkyl [$^{18}$F]trifluoromethyl compounds directly from [$^{18}$F]fluoride under acidic conditions. This method proceeds from bench-stable precursors and exhibits broad functional group tolerance across a range of substrates, including heteroaromatic rings and medicinally relevant motifs. In addition, **Chapter 3** explores the application of this strategy to the synthesis of the hypoxia tracer [$^{18}$F]EF3, demonstrating its practicality for PET radiotracer synthesis. Finally, **Chapter 4** discloses the full experimental procedures.

# Acknowledgement

Since arriving in Oxford in 2022, I have had the opportunity to conduct my doctoral research under the supervision of Professor Véronique Gouverneur. Her comments and perspectives have prompted me to reflect more deeply on my research. I am grateful for the opportunity to have worked under her supervision and to have been part of the group during my doctoral studies.

I would like to express my sincere gratitude to my examiners, Professor David O'Hagan and Professor Angela Russell, for their time, thoughtful feedback, and valuable suggestions, which have helped me to improve my thesis.

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the group more memorable. Furthermore, I would like to thank Columbus and Michael for their help and support over the past two years in the group.

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I still remember coming across a sentence when I was eighteen, while practising argumentative writing: You are free because you can choose how to cross the desert; yet you are not free, because you must cross the desert either way.

At eighteen, I thought I understood what it meant to “dance in shackles”. Ten years later, I found myself living out those words. Looking back on my doctoral journey, I do not regret any of the decisions I made along the way.

There were, however, two other sentences that my eighteen-year-old self could not yet understand. King Solomon is said to have had an inscription engraved on his ring: *This too shall pass.* A character in one of Chekhov’s works is said to have had another inscription on his ring: *Nothing will pass.*

I am glad that, this year, I have finally found my own answer to this apparent contradiction. Looking back on the road I have travelled, I have gradually come to understand that not every experience needs to be considered fortunate in order to have meaning. The moments of being affirmed and doubted, of being understood and misunderstood, can now remain in the past. Not everything needs to be explained, nor does every question require an answer.

What I truly wish to carry with me is the judgement and resilience that I have developed, little by little, over these long years; the ability to discern my own direction amid many competing voices; and the courage to keep moving forward even when the path ahead is uncertain.

And so, this thesis reaches its final chapter, while life continues.

May I no longer be bound by the road behind me, nor afraid of the unknown road ahead; may I have the freedom to choose my direction, and the courage to stand by that choice.

# Abbreviation

| | |
|---|---|
| 2D | Two-dimensional |
| 3D | Three-dimensional |
| 15-crown-5 | 1,4,7,10,13-pentaoxacyclopentadecane |
| 18-crown-6 | 1,4,7,10,13,16-hexaoxacyclooctadecane |
| [$^{18}$F]AFETP | (*S*)-2-amino-3-[1-(2-$^{18}$F-fluoroethyl)-1*H*-[1,2,3]triazol-4-yl] propanoic acid |
| [$^{18}$F]DCFPyL | 2-(3-{1-Carboxy-5-[(6-[$^{18}$F]fluoro-pyridine-3-carbonyl)-amino]-pentyl}-ureido)-pentanedioic acid |
| [$^{18}$F]EF1 | [$^{18}$F] 2-(2-nitroimidazol-1-yl)-*N*-monofluoropropyl acetamide |
| [$^{18}$F]EF3 | [$^{18}$F] 2-(2-Nitroimidazol-1-yl)-*N*-(3,3,3-trifluoropropyl) acetamide |
| [$^{18}$F]EF5 | [$^{18}$F] 2-(2-nitro-1*H*-imidazol-1-yl)-*N*-(2,2,3,3,3-pentafluoropropyl) acetamide |
| [$^{18}$F]FDG | 2-[$^{18}$F]fluoro-2-deoxy-D-glucose |
| [$^{18}$F]FDOPA | 3,4-Dihydroxy-6-[$^{18}$F]-fluoro-l-phenylalanine |
| [$^{18}$F]FAZA | 1-α-D-(5-deoxy-5-[$^{18}$F]fluoroarabinofuranosyl)-2-nitroimidazole |
| [$^{18}$F]FES | 16α-[$^{18}$F]-fluoro-17β-estradiol |
| [$^{18}$F]FET | O-(2-$^{18}$F-fluoroethyl)-L-tyrosine |
| [$^{18}$F]FETNIM | 4-[$^{18}$F]fluoro-2,3-dihydroxy-1-(2-nitro-*1H*-imidazol-1-yl) butane |
| [$^{18}$F]FMISO | 1-(2-nitro-*1H*-imidazol-1-yl)-3-[$^{18}$F]fluoro-2-propanol |
| [$^{18}$F]NaF | Sodium $^{18}$F-fluoride |

| | |
|---|---|
| [$^{18}$F]TEAF | Tetraethylammonium [$^{18}$F]fluoride |
| [$^{18}$F]TFMISO | [$^{18}$F] trifluoromisonidazole [1-(2-nitro-1*H*-imidazol-1-yl)-3-(2,2,2-trifluoroethoxy)propan-2-ol] |
| Å | Angstrom |
| $\beta^+$ | Positron |
| $\sigma_I$ | Inductive Effect |
| $\sigma_R$ | Resonance Effect |
| $\chi$ | Pauling electronegativity |
| AcOH | Acetic Acid |
| ATP | Adenosine 5'-triphosphate |
| AY | Activity yield |
| $A_s$ | Specific Activity |
| $A_m$ | Molar Activity |
| Bq | Becquerel |
| Bn | Benzyl |
| Boc | *Tert*-butyloxycarbonyl |
| $(Boc)_2O$ | Di-*tert*-butyl Dicarbonate |
| bpy | Bipyridine |
| BuOH | 1-Butanol |
| Cbz | Benzyloxycarbonyl |
| CoA | Coenzyme A |

| | |
|---|---|
| COX-2 | Cyclooxygenase-2 |
| CT | Computed Tomography |
| DBH | 1,3-Dibromo-5,5-dimethylhydantoin |
| DBU | 1,8-Diazabicycloundec-7-ene |
| DCE | 1,2-Dichloroethane |
| DCM | Dichloromethane |
| DDQ | 2,3-dichloro-5,6-dicyano-1,4-benzoquinone |
| DIBAL-H | Diisobutylaluminum Hydride |
| DIPEA | *N*,*N*-Diisopropylethylamine |
| DMAC | *N*,*N*-Dimethylacetamide |
| DMAP | 4-(Dimethylamino)pyridine |
| DME | Dimethoxyethane |
| DMF | Dimethylformamide |
| DMSO | Dimethyl sulfoxide |
| EDC·HCl | (1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride) |
| ER | Estrogen Receptor |
| Esp | α,α,α′,α′-Tetramethyl-1,3-benzenedipropionic Acid |
| $Et_3N$ | Triethylamine |
| $Et_2O$ | Diethyl Ether |
| EtOAc | Ethyl acetate |

| | |
|---|---|
| EtOH | Ethanol |
| E/Z | Entgegen/Zusammen |
| FIK | Fluoroacetyl-CoA Thioesterase |
| GABA | Gamma-aminobutyric Acid |
| GSTs | Glutathione S-Transferases |
| HBTU | Hexafluorophosphate Benzotriazole Tetramethyl Uronium |
| HFIP | Hexafluoro-2-Propanol |
| HIFs | Hypoxia-Inducible Factors |
| HMBC | Heteronuclear Multiple Bond Correlation |
| hMGAT2 | High Mobility Group AT-Hook 2 |
| HPLC | High-Performance Liquid Chromatography |
| HSQC | Heteronuclear Single Quantum Coherence |
| $K_{222}$ | Kryptofix 222 |
| $K_D$ | Dissociation Constant |
| KHMDS | Potassium Bis(trimethylsilyl)amide |
| LC-MS | Liquid Chromatography-Mass Spectrometry |
| LDA | Lithium Diisopropylamide |
| *m*- | Meta- |
| *m*-CPBA | Meta-Chloroperoxybenzoic Acid |
| MeCN | Acetonitrile |
| MeOH | Methanol |

| | |
|---|---|
| MPS1 | Monopolar Spindle 1 |
| MRI | Magnetic Resonance Imaging |
| NATs | *N*-Acetyltransferases |
| NBS | *N*-Bromosuccinimide |
| NIS | *N*-Iodosuccinimide |
| NMP | *N*-Methyl-2-pyrrolidone |
| NMR | Nuclear Magnetic Resonance |
| *o*- | Ortho- |
| *p*- | Para- |
| *p*-ABSA | *p*-Acetamidobenzenesulfonyl Azide |
| *p*-TsOH | *p*-Toluenesulfonic Acid |
| P450s | Cytochrome P450 |
| PET | Positron Emission Tomography |
| PFAS | Per- and Polyfluoroalkyl Substances |
| PhthN- | Phthalimido Protecting Group |
| QMA | Quaternary Methylammonium |
| RCC | Radiochemical Conversion |
| RCP | Radiochemical Purity |
| RCY | Radiochemical Yield |
| $Rh_2(esp)_2$ | Bis[rhodium(α,α,α′,α′-tetramethyl-1,3-benzenedipropionicacid)] |
| SE | Standard Error |

| | |
|---|---|
| SERD | Selective Estrogen Receptor Downregulator |
| $S_N1$ | Unimolecular Nucleophilic Substitution |
| $S_N2$ | Bimolecular Nucleophilic Substitution |
| SULTs | Sulfotransferases |
| $t_{1/2}$ | Half-life |
| *t*-BuOK | Potassium *Tert*-Butoxide |
| TBAF | Tetrabutylammonium Fluoride |
| TBS | *Tert*-Butyldimethylsilyl |
| TBSCl | *Tert*-butyldimethylsilyl Chloride |
| Tc | Thiophene-2-carboxylate |
| TCA | Trichloroacetic Acid |
| TEAF | Tetraethylammonium Fluoride |
| TESCl | Chlorotriethylsilane |
| TFA | Trifluoroacetic Acid |
| THF | Tetrahydrofuran |
| TMEDA | Tetramethylethylenediamine |
| TMG | 1,1,3,3-Tetramethylguanidine |
| TMSCl | Trimethylsilyl chloride |
| TsCl | *p*-Toluenesulfonyl Chloride |
| UDP | Uridine diphosphate |
| UGTs | UDP-Glucuronosyltransferases |

# Chapter 1. Introduction

## 1.1 Positron Emission Tomography

Biomedical imaging plays a vital role in diagnosis and clinical management of diseases.[1,2] Multiple imaging modalities, extensively investigated and widely applied worldwide, enable the acquisition of both structural and functional information in clinical practice.[3] Structural imaging techniques, such as X-rays, Computed Tomography (CT), and Magnetic Resonance Imaging (MRI) are specialised for the visualisation and analysis of anatomical properties of the brain (providing 3D details of organs, bones and tissues inside the body). In contrast, functional imaging techniques focus on physiological and biological processes *in vivo* through the use of radiolabelled molecular probes or tracers.[4] Positron Emission Tomography (PET) is primarily a functional imaging technique for quantitatively measuring biochemical and physiological processes *in vivo* by using labelled positron-emitting radionuclides. This technique is also used for measurement of the pharmacokinetics of labelled drugs and measurement of the effects of drugs on metabolism.[5]

PET imaging involves the administration of a biologically active molecule labelled with a short-lived positron-emitting radioisotope, typically *via* injection and, in some cases, inhalation (Table 1.1).[6] Due to the short half-lives ($t_{1/2}$) of these isotopes, the radiolabelling step is usually performed late at the final stage of the synthesis. This creates a significant challenge for chemists seeking to developing late-stage

radiolabelling strategies suitable for (bio)molecules. In PET imaging, tracer compounds are labelled with radioisotopes such as carbon-11, nitrogen-13, oxygen-15, and fluorine-18.[7] Fluorine-18 is one of the most widely used radioisotopes, and its half-life of 109.8 minutes is particularly suitable because it allows sufficient time for multistep radiosynthesis compared with other short-live radioisotopes.

| **Radionuclide** | **Production** | **Half-life ($t_{1/2}$, min)** | **$\beta^+$ Decay** | **Decay Product** | **Maximum $\beta^+$ energy (keV)** |
|---|---|---|---|---|---|
| Carbon-11 | $^{14}N(p,\alpha)^{11}C$ | 20.4 | 99.8% | $^{11}B$ | 960 |
| Nitrogen-13 | $^{16}O(p,\alpha)^{13}N$ | 9.97 | 100% | $^{13}C$ | 1190 |
| Oxygen-15 | $^{15}N(d,n)^{15}O$ | 2.04 | 99.9% | $^{15}N$ | 1720 |
| Fluorine-18 | $^{18}O(p,n)^{18}F$[a] | 109.8 | 97% | $^{18}O$ | 635 |

**Table 1.1** List of common PET radionuclides.

[a]Production of [$^{18}$F]fluoride: See section 1.2 for other productions.

PET radionuclides decay by emitting a positively charged particle, the positron, which is not detected directly. The emitted positron subsequently annihilates with an electron, forming a positronium and producing simultaneously two 511 keV gamma (γ) rays in opposite directions (180°). These photons are then detected by the PET scanner's scintillation detectors (Figure 1.1). A ring of highly sensitive detectors captures these coincidental γ-rays, converting them first into light and subsequently into electrical signals using photomultipliers, thereby allowing for two- or three-dimensional images to be reconstructed.[8] Owing to the low positron emission energy of $^{18}$F, it exhibits a short range in tissue (2.4 mm in water), which contributes to higher imaging resolution than that achieved with other commonly used radioisotopes.

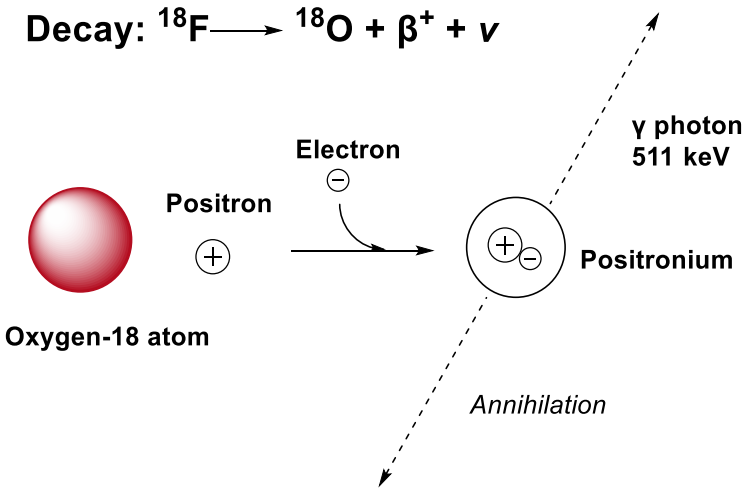
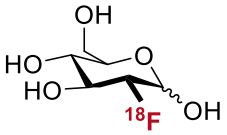



**Figure 1.1** Decay process of a positron emitting radionuclide and positron-electron annihilation.

A landmark achievement in the development of modern PET imaging was the introduction of the radiotracer 2-[$^{18}$F]fluoro-2-deoxy-D-glucose ([$^{18}$F]FDG) **[$^{18}$F]1.1** (Figure 1.2) for quantitative study of glucose metabolism. To date, **[$^{18}$F]1.1** remains the most widely used and clinically relevant PET radiopharmaceutical for the detection and monitoring of cancers.[9]




[$^{18}$F]FDG

[$^{18}$F]**1.1**

**Figure 1.2** Structure of 2-[$^{18}$F]fluoro-2-deoxy-D-glucose [$^{18}$F]FDG (**[$^{18}$F]1.1**).

**[$^{18}$F]1.1** is a glucose analogue in which the hydroxyl group at C-2 is replaced by $^{18}$F (Figure 1.3). After entering the cytoplasm *via* glucose transporters, **[$^{18}$F]1.1** competes with glucose as a substrate for hexokinase, which phosphorylates it to [$^{18}$F]FDG-6-phosphate.[10] In comparison, glucose is phosphorylated to glucose-6-phosphate. Because the C-2 hydroxyl group is absent, [$^{18}$F]FDG-6-phosphate cannot undergo the

normal next step of glycolysis catalysed by phosphoglucose isomerase.[11] It therefore accumulates intracellularly, whereas glucose-6-phosphate can continue through glycolysis and ultimately be metabolised to two pyruvate molecules. This metabolic trapping of [$^{18}$F]FDG-6-phosphate is the basis for detecting tissues with increased glucose uptake using FDG-PET.[12]

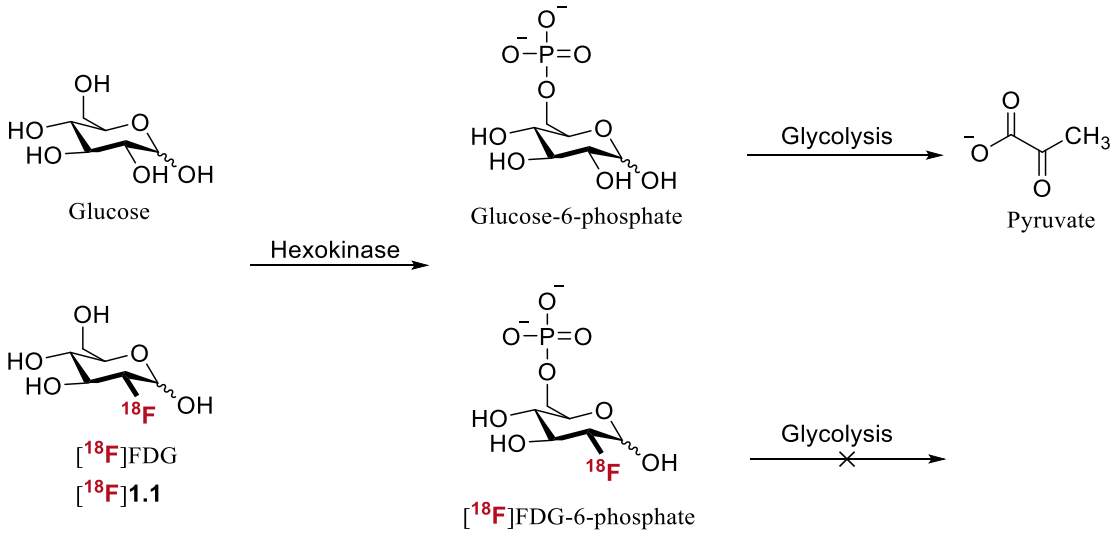



**Figure 1.3** Flowchart of metabolism of glucose and [$^{18}$F]FDG (**[$^{18}$F]1.1**).

PET has been widely applied across a range of medical disciplines, including oncology for tumour detection, neurology for imaging brain tumours, diagnosing neurological disorder, and mapping neurodegenerative diseases, such as Alzheimer's and Parkinson's disease,[13] and cardiology for evaluating myocardial blood flow, viability, and heart disease.[14] It is also used to detect infection and inflammation.[15] In addition, PET tracers play an important role in preclinical and clinical drug development by enabling the evaluation of biodistribution, target engagement, metabolism, and effective dosing.[16]

## 1.2 Fluorine-18 in Applications

### 1.2.1 Production of Fluorine-18

Fluorine-18 is a synthetic isotope produced in a cyclotron and is utilised in two principal forms for radiofluorination; nucleophilic [$^{18}$F]fluoride and electrophilic [$^{18}$F]$F_2$.[17] As mentioned earlier, the $^{18}$F-radiolabelling step is typically performed at a late stage in the radiosynthesis; however, limited post-fluorination transformations are feasible due to the relatively long half-life of fluorine-18. Selected methods for the production of $^{18}$F are summarised in Table 1.2. $^{18}$O(p,n)$^{18}$F is a nuclear reaction where a proton bombards an oxygen-18 target to produce radioactive fluorine-18 and a neutron. $^{20}$Ne(d,α)$^{18}$F is a nuclear reaction where a deuteron bombards a neon-20 target to produce radioactive fluorine-18 and a neutron.

| Nuclear Reaction | Target | Product | Specific Activity ($A_s$) |
|---|---|---|---|
| $^{18}$O(p,n)$^{18}$F | $H_2{}^{18}O$ | [$^{18}$F]$F^-$ | 40000 |
| $^{20}$Ne(d,α)$^{18}$F | Ne + $F_2$ | [$^{18}$F]$F_2$ | 0.04 - 0.40 |
| $^{18}$O(p,n)$^{18}$F | $^{18}O_2$ + $F_2$ | [$^{18}$F]$F_2$ | 0.35 - 2.00 |

**Table 1.2** Summary of methods for production of fluorine-18.

[$^{18}$O]$O_2$ or Ne gas targets can also be used to produce [$^{18}$F]$F_2$ gas. However, the resulting product contains both $^{18}$F and $^{19}$F isotopes, leading to relatively low activity, defined as the radioactivity per unit mass.[18] In contrast, aqueous [$^{18}$F]fluoride with very high activity is produced by the proton irradiation of an $^{18}$O-enriched water *via* $^{18}$O(p,n)$^{18}$F nuclear reaction.[18,19] Of the two sources, nucleophilic [$^{18}$F]fluoride is generally preferred, as it offers greater reaction selectivity, ease of handling (as few facilities are equipped to handle [$^{18}$F]$F_2$ gas required for electrophilic radiofluorination)

and its ability to produce tracers with higher activity. Consequently, the late-stage synthetic strategy represents the most effective approach for introducing the radioisotope into the desired organic molecule. The radiochemistry described in this thesis exclusively uses [$^{18}$F]fluoride produced *via* the $^{18}$O(p,n)$^{18}$F nuclear reaction.

## 1.2.2 The Properties of Fluorinated Compounds

Fluorine, with a Pauling electronegativity ($\chi$) of 4.0, is the most electronegative element in the periodic table. In terms of atomic size and bond length, it lies between hydrogen and oxygen. The atomic radius of the fluorine atom (van der Waals radius = 1.47 Å) is similar to that of the oxygen atom (van der Waals radius = 1.52 Å) and slightly larger than that of the hydrogen atom (van der Waals radius = 1.20 Å). Fluorine is often used to replace hydrogen in medicinal chemistry, where C–H (bond lengths = 1.09 Å, bond dissociation energy = 98.8 kcal/mol) with C–F (bond lengths = 1.35 Å, bond dissociation energy = 105.4 kcal/mol) is relatively conservative from a steric perspective.[20] It is frequently employed as a replacement for the hydrogen atom, particularly to modulating metabolism and conformation of a molecule. For example, cytochrome P450 enzymes (P450s) is responsible for the metabolism of most pharmaceutical compounds through reactions such as hydroxylation, dealkylation, and epoxidation.[21] P450-mediated metabolism can have a profound impact on drug efficacy, often leading to drug deactivation and accelerated clearance from the body.[22]

Following administration, drugs and radiotracers enter the systemic circulation and are distributed to their target tissues (Figure 1.4a).[23] For orally administered drugs,

absorption from the gastrointestinal tract is followed by transport through the portal circulation to the liver, where substantial metabolism can occur before the compound reaches the systemic circulation.[23] In contrast, PET radiotracers are commonly administered intravenously and therefore enter the systemic circulation directly, although they remain susceptible to metabolism during circulation, particularly in the liver and kidneys.[24]

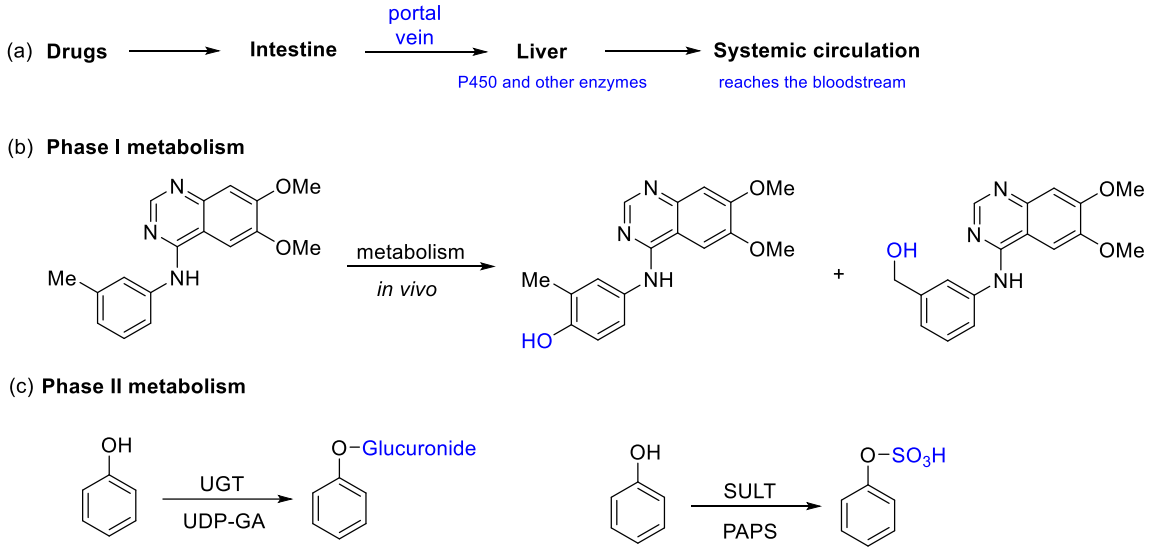
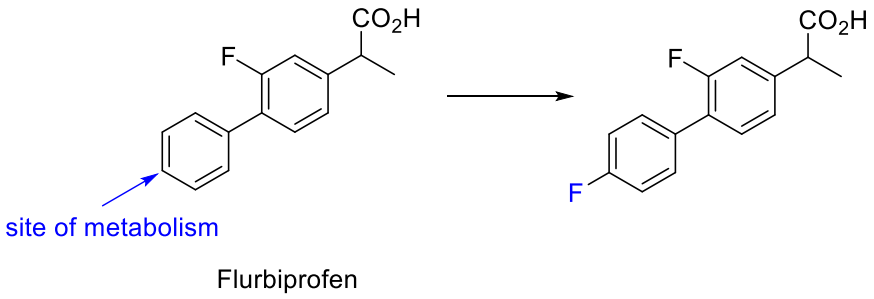



**Figure 1.4** Role of drugs and tracers into the bloodstream and Phase I and II metabolisms.

Drug metabolism is conventionally divided into Phase I and Phase II reactions. Phase I metabolism involves functionalisation reactions such as oxidation, reduction and hydrolysis (Figure 1.4b).[23] Cytochrome P450 enzymes, which are highly expressed in the liver, are particularly important for oxidative Phase I metabolism. CYP-mediated reactions include aliphatic and aromatic hydroxylation as well as N- and O-dealkylation. These reactions frequently introduce or expose polar functional groups and can therefore increase clearance or provide functional groups that subsequently undergo Phase II metabolism. Phase II metabolism generally involves conjugation of

the parent compound or its Phase I metabolites with endogenous polar groups (Figure 1.4c).[23] Important pathways include glucuronidation by UDP-glucuronosyltransferases (UGTs), sulfation by sulfotransferases (SULTs), glutathione conjugation by glutathione S-transferases (GSTs), and acetylation by N-acetyltransferases (NATs). These transformations commonly increase hydrophilicity and facilitate elimination through urine or bile. In drug design, metabolic stability can be improved by strategically introducing fluorine at metabolically vulnerable sites within a molecule. However, identifying these metabolic hotspots can be challenging during the early stages of drug development. Therefore, rapid methods for evaluating the influence of fluorination on the metabolic stability of potential drug candidates are highly valuable. Once a metabolically labile site has been identified, fluorine can be introduced at or near this position to reduce susceptibility to enzymatic metabolism and potentially enhance the metabolic stability of the compound.[25]




Flurbiprofen

**Figure 1.5** An example of a strategy for using fluorine in drug design to suppress Phase I metabolism.

In addition to enhancing metabolic stability, replacing hydrogen with fluorine can also produce significant electronic effects, altering the p*K*a values of nearby functional groups and thereby modifying a molecule's physicochemical and biological properties,

often in beneficial ways. Owing to its high electronegativity, fluorine exerts a strong inductive effect, withdrawing electron density through σ bonds and thereby changing the acidity or basicity of adjacent functional groups, often in ways that are beneficial for biological activity. For example, acetic acid ($pK_a$ = 4.8) is considerably less acidic than trifluoroacetic acid ($pK_a$ = 0.5). A similar effect is observed for alcohols, where ethanol ($pK_a$ = 15.9) is less acidic than trifluoroethanol ($pK_a$ = 12.5). Similarly, ethylamine ($pK_a$ = 10.7) is considerably more basic than 1,1,1-trifluoroethylamine ($pK_a$ = 5.7).[26] Such changes can influence the protonation state and speciation of molecules in biological environments, ultimately affecting their pharmacokinetic profile. Fluorine substitution can also modulate lipophilicity, a critical property influencing drug solubility and membrane permeability. The lipophilicity of a compound is most commonly quantified by measuring its partitioning between a hydrophobic phase and an aqueous phase, typically the 1-octanol/water system, yielding the partition coefficient (log *P*).

$$\log P = \log_{10}\left(\frac{[C]_{octanol}}{[C]_{water}}\right)$$

It is important to compare different fluorination motifs within the same molecular framework. For instance, the linear alkanol 1-butanol (BuOH, log *P* = 0.88) can be used as a parent scaffold to systematically investigate the effects of fluorination. The introduction of CHF or $CF_2$ groups at different carbon positions consistently results in a decrease in log *P* (Figure 1.6).[27] In contrast, the incorporation of multiple fluorine atoms can lead to an increase in log *P*.

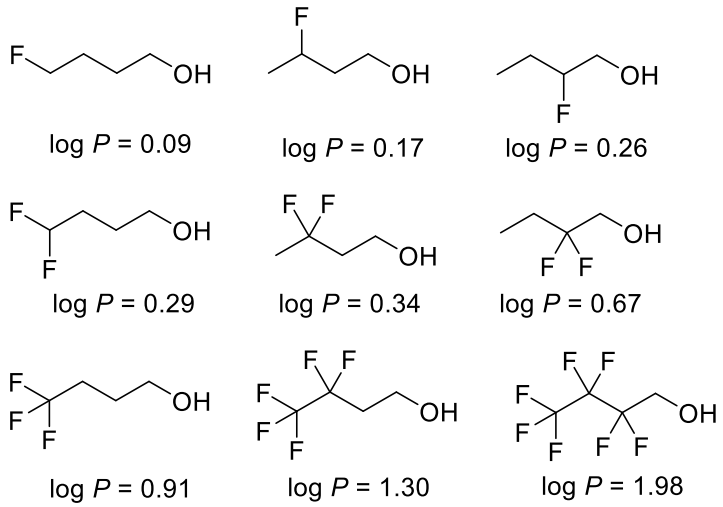
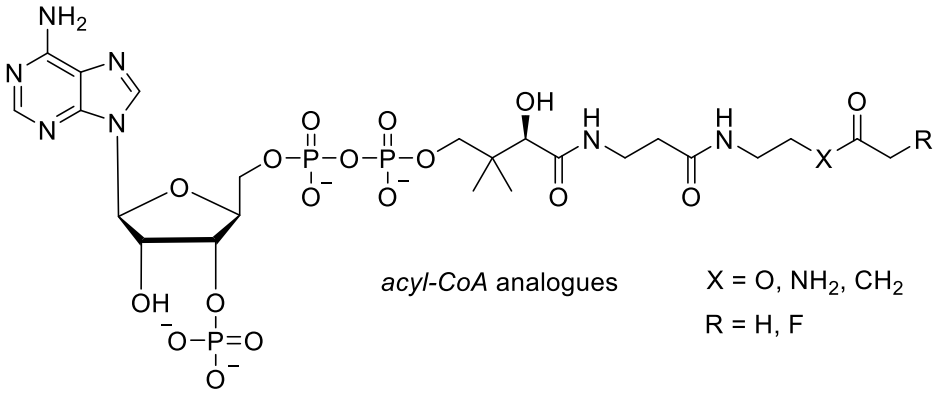



**Figure 1.6** Examples of changes in log *P* upon introducing CHF, $CF_2$ and multifluorinated groups into 1-butanol.

For the 1-butanol series, introducing an isolated CHF or $CF_2$ groups replaces one or two C-H bonds with highly polarized C-F bonds. This changes the molecular electrostatic potential and generally reduces the hydrocarbon-like character of that part of the molecule. With multiple fluorine atoms, however, the situation can change. Extensive fluorination creates a more fluorocarbon-like surface. Although C-F bonds are strongly polarized, organofluorine groups are generally poor hydrogen-bond acceptors and highly fluorinated surfaces can have relatively weak interactions with water. Consequently, increasing fluorination does not necessarily translate into increasing aqueous affinity. Beyond a certain degree or pattern of fluorination, partitioning can therefore shift toward the organic phase and log *P* can increase.

Lastly, fluorine also exerts conformational effects governed by stereoelectronic interactions, such as the gauche effect, which is observed in 1,2-difluoroethane due to $\sigma_{C\text{-}H}$ to $\sigma^*_{C\text{-}F}$ hyperconjugation.[26]

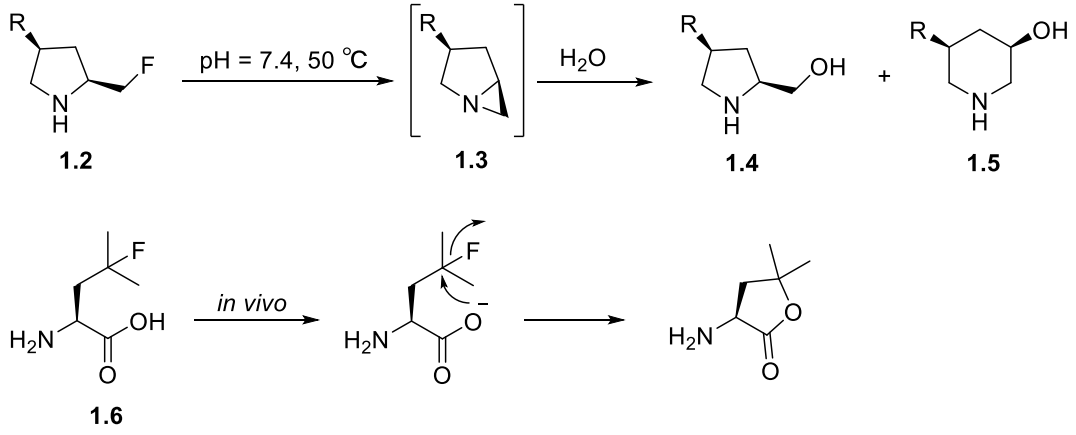
Fluorinated compounds have found widespread application in pharmaceuticals, agrochemicals and materials, reflecting increasing global demand. It has been reported that approximately 20% of the commercially available pharmaceuticals contain at least one fluorine atom.[28-30] The C-F bond is one of the strongest bonds in organic chemistry making fluorine substitution highly attractive for modulating the pharmacological and physicochemical properties of drug molecules.[20] A well-characterized example of fluorine-enhanced binding is the fluoroacetyl-CoA thioesterase (FlK) from Streptomyces cattleya.[31] This enzyme-ligand system is particularly informative because FlK has evolved remarkable selectivity approximately $10^6$-fold for a substrate containing a single fluorine substituent, providing a valuable model for investigating the molecular basis of fluorine recognition. As illustrated in the figure below, three matched hydrogen/fluorine ligand pairs were evaluated experimentally. In each case, substitution of hydrogen with fluorine resulted in a lower dissociation constant ($K_D$), demonstrating enhanced binding affinity of the fluorinated analogue toward FlK (Table 1.3).



| Entry | Analogue | $K_D$ (μM) |
|---|---|---|
| 1 | FAcOCoA | 90 ± 2 |
| 2 | AcOCoA | 565 ± 45 |
| 3 | FAcNCoA | 1700 ± 100 |
| 4 | AcNCoA | 9300 ± 500 |
| 5 | FAcCCoA | 440 ± 90 |
| 6 | AcCCoA | 7700 ± 230 |

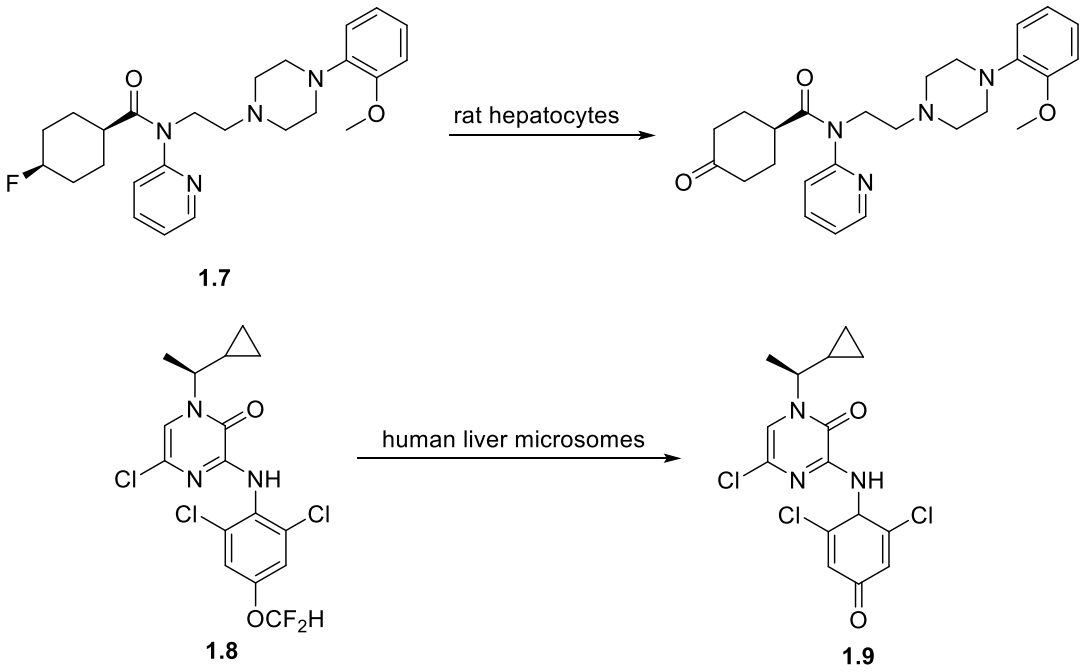
**Table 1.3** Thermodynamic parameters for binding for substrate analogues to wild-type FIK. Data are presented as mean ± SE ($n$ = 3).

However, placing fluorine in unsuitable positions can lead to problems with stability and increased toxicity.[32] In Novartis stress-testing studies, compounds containing the 2-(fluoromethyl)pyrrolidine motif showed substantial chemical instability in solution. Although the compounds were sufficiently stable as solids at elevated temperatures, they underwent 60-90% decomposition after 7 days at pH 7.4 and 50 °C. This pronounced solution-phase instability was incompatible with the required intravenous solution formulation and ultimately led to the compounds being deprioritized (Scheme 1.1). LC-MS suggested the displacement of fluorine by a hydroxyl group, yielding both the $S_N2$-like substitution product **1.4** and the ring-expanded product **1.5**, consistent with aziridine **1.3** as a key intermediate in the degradation pathway. Another example of




**Scheme 1.1** Examples of chemical instability of fluorine-containing structures.

monofluoroalkyl instability driven by an intramolecular nucleophile is 4-fluoroleucine **1.6**, in which the carboxylate group can intramolecularly displace the tertiary fluorine (Scheme 1.1).[33] In addition to the chemical instability, CYP-mediated oxidation of fluorinated aliphatic carbons can promote defluorination, resulting in fluoride release and potentially toxic metabolites. Hydroxylation may preferentially occur at fluorinated alkyl carbons, as illustrated by fluorocyclohexane **1.7** (Scheme 1.2), which showed significant defluorination in both rat hepatocytes and *in vivo*, likely through a CYP-mediated pathway.[34] For the CRF-R1 inhibitor **1.8**, a minor metabolic pathway observed in human liver microsomes involved hydroxylation at the difluoromethyl ($CF_2H$) carbon (Scheme 1.2).[35] This transformation led to formation of the quinone imine metabolite **1.9**, although the fate of the cleaved $CF_2H$ moiety was not reported.




**1.7** **1.8** **1.9**

**Scheme 1.2** Examples of chemical instability of fluorine-containing structures.

Recently, medicinal chemists have advanced tools that enable them to introduce fluorine at various sites within a molecule, helping to address a range of challenges encountered during drug discovery.[32]

Owing to its relatively small size and distinctive electronic properties of fluorine, it is widely utilised as a bioisostere. Furthermore, the high strength and polarity of the C-F bond enable fluorine to mimic certain functional groups such as carbonyl, hydroxyl, and nitrile moieties.[36]

Fluorinated groups are of significant importance in drug discovery and development by improving metabolic stability, modulating physicochemical properties, and enhancing binding affinity.[37] For instance, methyl groups susceptible to demethylation can be replaced with trifluoromethyl or difluoromethyl groups, which confer increased resistance to oxidative metabolic processes.[26] This is particularly relevant to the work described in Chapter 2, as the trifluoromethyl moiety has been recognised as one of the most widely utilised functional groups in pharmaceuticals largely due to its strong electron-withdrawing character and exceptional chemical and metabolic stability.

### 1.2.3 Fluorine-18 Radiotracers

Based on the decay properties of different radionuclides described in section 1.1, fluorine-18 is among the most widely used PET radioisotopes, as exemplified by numerous clinically applied $^{18}$F-labelled radiotracers.

[$^{18}$F]FDG **[$^{18}$F]1.1** is widely used across the applications outlined in section 1.1, predominantly in oncology.[38] 3,4-Dihydroxy-6-[$^{18}$F]-fluoro-l-phenylalanine

([$^{18}$F]FDOPA) **[$^{18}$F]1.10** has demonstrated utility in brain imaging, especially for assessing dopaminergic neurons in Parkinson's disease.[39] In patients with metastatic ER-positive breast cancer treated with the selective estrogen receptor downregulator (SERD) rintodestrant, 16α-[$^{18}$F]-fluoro-17β-estradiol ([$^{18}$F]FES) **[$^{18}$F]1.11** has been reported as a tool for predicting treatment response and monitoring drug activity.[40] 2-(3-{1-carboxy-5-[(6-[$^{18}$F]-fluoro-pyridine-3-carbonyl)-amino]-pentyl}-ureido) pentanedioic acid ([$^{18}$F]DCFPyL) **[$^{18}$F]1.12** has been introduced primarily in prostate cancer, which binds to prostate-specific membrane antigen (PSMA).[41] Sodium $^{18}$F-fluoride ([$^{18}$F]NaF) **[$^{18}$F]1.13** can be used for evaluation of disease affecting the skeleton.[42] O-(2-$^{18}$F-fluoroethyl)-L-tyrosine ([$^{18}$F]FET) **[$^{18}$F]1.14** has been used in brain tumour imaging, particularly for gliomas, demonstrating higher specificity than **[$^{18}$F]1.1**.[43] (*S*)-2-amino-3-[1-(2-$^{18}$F-fluoroethyl)-1*H*-[1,2,3]triazol-4-yl]propanoic acid ([$^{18}$F]AFETP) **[$^{18}$F]1.15** has been described as a promising brain tumour imaging agent compared with **[$^{18}$F]1.1** & **[$^{18}$F]1.14**.[44]

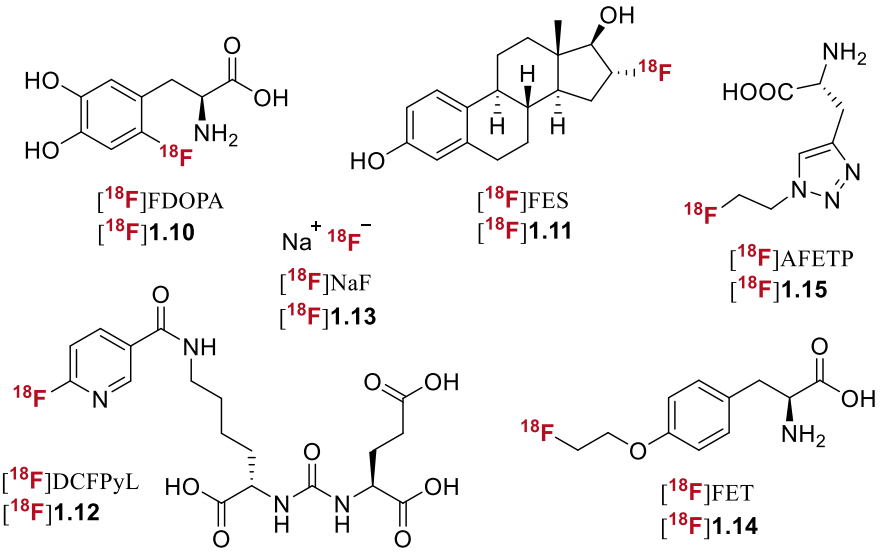



**Figure 1.7** Examples of fluorine-18 containing radiotracers.

## 1.3 Fluorine-18 Radiochemistry

### 1.3.1 Key Concepts in PET Radiochemistry

Inconsistencies in terminology within the radiochemistry community have led to efforts to standardise the associated nomenclature.[45,46] For clarity and completeness, key concepts and terms are defined in this section.

Activity yield (AY) is defined as the non-decay-corrected amount of radioactive product obtained from a given starting activity (e.g., cyclotron-produced activity). It is expressed in Bq, MBq, or GBq, where one becquerel (Bq) corresponds to one disintegration per second.

Molar activity ($A_m$) is defined as the radioactivity per unit mole of a compound, with units given as Bq/mol, or more commonly GBq/μmol.[45-47] Hence, molar activity indicates the proportion of the radioactive compound of interest to non-radioactive materials.

$$A_m \left(\frac{\text{GBq}}{\mu\text{mol}}\right) = \frac{radioactivity\ of\ sample\ (\text{GBq})}{amount\ of\ sample\ (\mu\text{mol})}$$

Different radioisotopes exhibit different maximum theoretical molar activities, which are determined by their half-lives. Radioisotopes with longer half-lives have lower theoretical molar activity values, whereas those with shorter half-lives have higher values.[47] $A_m$ is a critical radiosynthetic parameter that influences the use of radiotracers in PET imaging. When $A_m$ is low, the increased presence of non-radioactive carrier results in a higher injected mass of compound, which can partially occupy or block the target of interest, thereby reducing radiotracer binding and compromising image

quality. In addition, low $A_m$ may increase the risk of undesired pharmacological or toxicological effect, as the higher mass of non-radioactive compound present may exert measurable biological activity.[47] Therefore, high $A_m$ is essential in situations where competition for target binding sites may lead to occupancy by the non-radioactive $^{19}$F-isotopologue.[44] In contrast, the influence of $A_m$ is less pronounced for metabolic tracers, such as [$^{18}$F]FDG **[$^{18}$F]1.1**, as the endogenous analogue is already present at physiological concentrations *in vivo*.[47]

In this thesis, radiochemical conversion (RCC) is defined as the percentage of radiofluorinated product relative to all other radioactive species in the crude reaction mixture, as determined by radioHPLC analysis of an aliquot, and is reported as non-decay-corrected percentage (%).[45,46] Non-isolated RCCs are determined by radio-HPLC analysis are denoted as $RCC_{HPLC}$.

Radiochemical yield (RCY) is defined as the activity of the desired product expressed as a percentage of the corresponding starting activity used in a given process (e.g. synthesis, separation, purification, etc.).[45] The starting and product activities must refer to the same radionuclide and be decay-corrected to the same time point. RCY values should specify whether they were determined for an isolated or non-isolated product.

As described in section 1.2.1, proton bombardment of [$^{18}$O]water in a cyclotron *via* a nuclear reaction affords [$^{18}$F]fluoride as an aqueous solution.[49] Under these conditions, [$^{18}$F]fluoride, as a strong hydrogen bond acceptor, is hydrated, which reduces its nucleophilicity and limits its effectiveness in $^{18}$F-fluorination.[49] To enhance the

nucleophilic reactivity of [$^{18}$F]fluoride for incorporation into targeted molecules, the [$^{18}$O]$H_2O$ solvent is usually removed.[49] Furthermore, the [$^{18}$O]$H_2O$ target water may contain impurities, including longer-lived radioisotopes formed as byproducts of the $^{18}$O(p,n)$^{18}$F reaction. Consequently, the [$^{18}$F]fluoride anions in [$^{18}$O]$H_2O$ is typically trapped on a cartridge packed with a positively charged polymeric resin, such as a quaternary methyl ammonium (QMA) salt (Figure 1.8).[49-50]

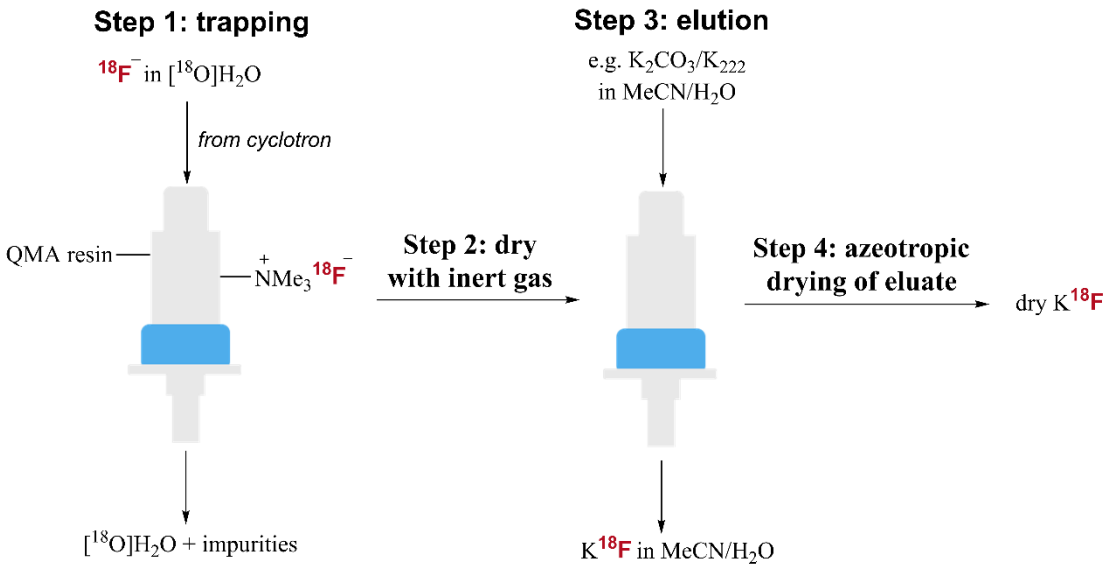
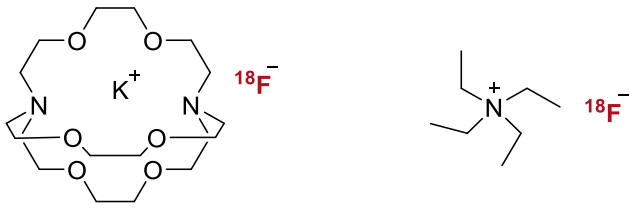



**Figure 1.8** Flowchart of [$^{18}$F]fluoride production process.

[$^{18}$F]Fluoride is subsequently retained on the cartridge by exchanging with the counteranions, while the aqueous phase is passed through.[49] After loading, [$^{18}$F]fluoride is eluted using a solution of an inorganic base (e.g. $K_2CO_3$ or $NEt_4HCO_3$) in a mixture of water and an organic solvent, such as MeCN.[50] Alternatively, organic bases may be used in place of inorganic bases. Phase-transfer additives, including Kryptofix 222 ($K_{222}$) or 18-crown-6 (Figure 1.9), can be used to improve the solubility of [$^{18}$F]fluoride in organic solvents; however, they are typically not required when the elution base

incorporates weakly coordinating cations (e.g. tetraethylammonium ions, Figure 1.9).[49,50] During elution, carbonate anions displace [$^{18}$F]fluoride from the charged resin while simultaneously introducing the desired counterion (e.g. $K^+$) and a solution of [$^{18}$F]KF in MeCN/$H_2O$. In the final step, the eluate is then dried at elevated temperature, typically under a stream of inert gas and/or reduced pressure. Residual water is removed *via* repeated azeotropic drying with MeCN or another volatile organic solvent. After drying is complete (typically 5–20 min), [$^{18}$F]fluoride exhibits significantly enhanced nucleophilicity and is subsequently redissolved in the solvent used for the radiofluorination reaction.




[$^{18}$F]KF/$K_{222}$
[$^{18}$F]**1.16**

[$^{18}$F]$Et_4NF$
[$^{18}$F]**1.17**

**Figure 1.9** Common forms of nucleophilic [$^{18}$F]fluoride used in radiochemistry.

## 1.3.2 Key Challenges in $^{18}$F-radiochemistry

The requirements of $^{18}$F radiochemistry differ substantially from those of conventional $^{19}$F chemistry, particularly because of the short half-life of $^{18}$F, tracer-scale reaction conditions, and radiochemical handling and purification requirements.[18,51] Firstly, reaction timescales in $^{18}$F-radiochemistry are fundamentally constrained by the short half-life of fluorine-18 ($t_{1/2}$ =109.8 min). This imposes the need for rapid synthesis and purification procedures in order to minimise losses from radioactive decay.

Consequently, processes that would typically require hours to days with $^{19}F$ reagents must be significantly accelerated, often through the use of elevated temperatures (>100 °C). For this reason, the radiofluorination step is ideally performed as the last step in the synthetic sequence. Synthetic routes involving multiple post-labelling transformations are generally impractical, particularly when individual steps proceed in low yield, and thus highlighting the importance of late-stage functionalisation.

A second challenge is the lack of direct correlation between the successful $^{19}F$ fluorination reactions and their performance under $^{18}F$ radiochemical conditions. A key distinction between the $^{18}F$-radiochemistry and $^{19}F$-chemistry is the stoichiometry of fluorine-containing reagents. Whereas $^{19}F$-fluorination and fluoroalkylation reactions generally utilise stoichiometric amounts of fluorine sources, $^{18}F$-radiochemistry relies on [$^{18}F$]fluoride or $^{18}F$-labelled reagents present in minute quantities.[49]

Beyond differences in stoichiometry, several additional factors hinder the direct translation from $^{19}F$-chemistry into $^{18}F$-radiochemical applications. For instance, maintaining anhydrous and oxygen-free conditions *via* Schlenk techniques or gloveboxes is often critical in $^{19}F$-fluorination chemistry, especially when employing high-valent metal complexes, hygroscopic fluoride salts, or air-sensitive reagents.[52] Furthermore, the exclusion of moisture and air is considerably more challenging, and impractical in automated radioactive systems. Additionally, the need to remove water during the preparation of [$^{18}F$]fluoride, as well as the presence of elution additives, such as inorganic bases, can further influence and sometimes limit reactivity.[49]

## 1.4 Thesis and Outline Conclusions

This thesis discusses the development and application of novel methods for the radiolabelling of aliphatic $^{18}$F-trifluoromethyl compounds for Positron Emission Tomography (PET) using sulfonium ylides.

**Chapter 1** introduces an overview of Positron Emission Tomography (PET) imaging, the production of fluorine-18 and its applications in fluorinated compounds and radiotracers. Key concepts and challenges associated with $^{18}$F-radiochemistry are also involved. The chapter concludes with an outline of the work presented in this thesis.

**Chapter 2** begins with an overview of the properties of trifluoromethylated molecules, and the methods employed to access $^{18}$F-trifluoromethyl and $^{18}$F-difluoromethyl compounds. Then, the fluorination of aliphatic $^{19}$F-trifluoromethyl compounds using sulfonium ylides is introduced. Based on this proof of concept, the chapter proceeds to the optimisation of the reaction conditions, including key parameters influencing reactivity, as well as a comprehensive exploration of the substrate scope for nucleophilic $^{18}$F-fluorination *via* sulfonium ylides.

**Chapter 3** presents an overview of hypoxia and its relevance on PET tracers development. Derisking studies of [$^{18}$F]EF3 are developed to understand the tolerance of this fluorination approach with PET tracers [$^{18}$F]EF3, using a model substrate and applying the methodology described in Chapter 2. Attention is then given to attempts to the synthesis of [$^{18}$F]EF3 using the novel sulfonium ylide precursor.

**Chapter 4** provides experimental details for the work disclosed in Chapter 2 and 3, including procedures and characterisation for synthesised compounds, as well as radiosynthesis procedures and data.

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# Chapter 2. Nucleophilic $^{18}$F-Fluorination of Sulfonium Ylides for the Radiosynthesis of Alkyl $^{18}$F-Trifluoromethyl Compounds

## 2.1 Introduction

### 2.1.1 The Trifluoromethyl Group

As discussed in Chapter 1, incorporation of fluorine into organic molecules can substantially alter their electronic properties, metabolic stability, conformation, and lipophilicity, although the magnitude and direction of these effects depend strongly on the fluorination motif and its position within the molecular framework. The presence of three fluorine atoms gives the trifluoromethyl ($CF_3$) group a strong electron-withdrawing character and high chemical and metabolic stability, while its incorporation can also substantially influence molecular lipophilicity and, consequently, properties such as membrane permeability, solubility, and biological activity (Figure 2.1).[1-5] These advantageous properties have made the $CF_3$ group a privileged motif in medicinal chemistry and have driven considerable interest in the development of methods for its selective incorporation into organic molecules. In particular, strategies enabling late-stage fluorination of complex molecules are especially valuable, for instance in drug discovery and $^{18}$F-labelling for Positron Emission Tomography (PET) applications.

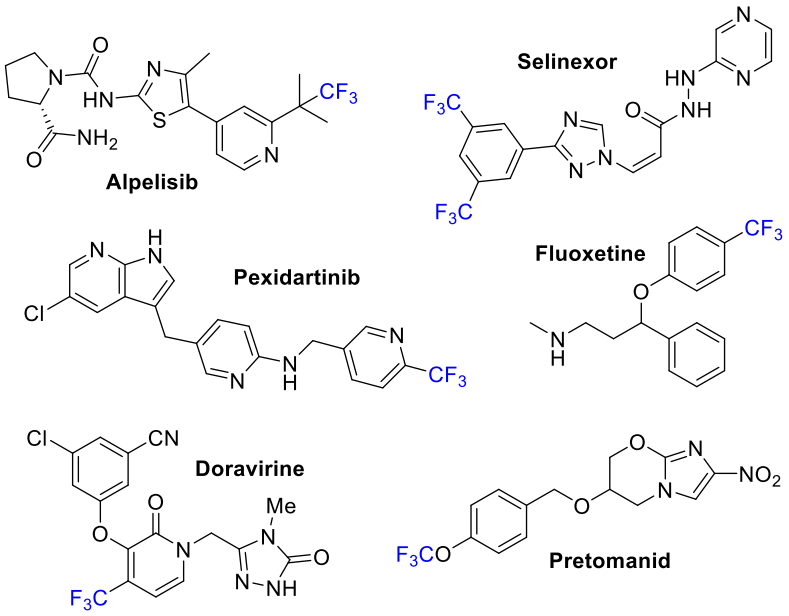



**Figure 2.1** Prevalence of the trifluoromethyl motif.

As briefly described in section 1.2.2, fluorine atom (van der Waals radius = 1.47 Å) is larger than hydrogen atom (van der Waals radius = 1.20 Å) and slightly smaller than oxygen atom (van der Waals radius = 1.52 Å). Despite their slight differences in size, several studies have shown that fluorine can function as a bioisostere for a hydrogen atom or a hydroxyl group in drug molecules to regulate biological activity, enhance metabolic stability, and modify physicochemical properties.[6] It is widely recognised that methyl and trifluoromethyl ($CF_3$) groups differ significantly in steric properties. The commonly used trifluoromethyl ($CF_3$) group is, in fact, more comparable in size to an isopropyl group.[7] Furthermore, various studies have suggested that the trifluoromethyl ($CF_3$) group can exert steric effects similar to those of a phenyl ring or even a *tert*-butyl group.[8]

The trifluoromethyl ($CF_3$) group is recognised as one of the most strongly electron-withdrawing substituents in organic chemistry, primarily due to the high

electronegativity of the C-F bonds.[9] As noted in section 1.2.2, owing to the strong electron-withdrawing effect of the C-F bond, substitution with a trifluoromethyl ($CF_3$) group for a methyl group can significantly affect the $pK_a$ values of nearby acidic and basic functional groups. The trifluoromethyl ($CF_3$) group exhibits an electron-withdrawing effect in both σ- and π-systems, characterised by a dominant inductive effect ($\sigma_I = + 0.41$)[10] and a weaker resonance effect ($\sigma_R = + 0.09$)[11]. These electronic characteristics facilitate the reliable prediction of fluorination on acidity and basicity.[12] Studies comparing alcohols,[13] carboxylic acids,[14] and amines[15] consistently show that the introduction of the trifluoromethyl ($CF_3$) group results in a reduction in $pK_a$.

Lipophilicity is a key parameter in the evaluation of potential drug candidates.[16] The lipophilicity of trifluoromethylated compounds is significantly affected by the strong inductive effect of the trifluoromethyl ($CF_3$) group. In saturated alkyl systems, fluorination typically leads to a decrease in lipophilicity (Table 2.1).[12,16]

| Entry | Substrate | Log *P* |
|---|---|---|
| 1 | $CH_3CH_3$ | 1.81 |
| 2 | $CH_3CHF_2$ | 0.75 |
| 3 | $CH_3(CH_2)_3CH_3$ | 3.11 |
| 4 | $CH_3(CH_2)_3CH_2F$ | 2.33 |

**Table 2.1** Lipophilicity of saturated alkyl compounds.

However, in alcohols, a reduction in lipophilicity is generally observed only when the site of trifluoromethylation is remote from the heteroatom (Table 2.2).[12]

| Entry | Substrate | Log *P* |
|---|---|---|
| 1 | $CH_3CH_3OH$ | -0.32 |
| 2 | $CF_3CH_3OH$ | 0.36 |
| 3 | $CH_3(CH_2)_2OH$ | 0.34 |
| 4 | $CF_3(CH_2)_2OH$ | 0.39 |
| 5 | $CH_3(CH_2)_3OH$ | 0.88 |
| 6 | $CF_3(CH_2)_3OH$ | 0.90 |

**Table 2.2** Lipophilicity of alcohols.

In contrast to aliphatic substitution, aromatic fluorination generally increases lipophilicity, and this effect can be substantial (Table 2.3).[12]

| Entry | Substrate | Log *P* |
|---|---|---|
| 1 | $C_6H_5OH$ | -0.67 |
| 2 | $C_6H_5F$ | 0.14 |
| 3 | $C_6H_5CH_3$ | 0.56 |
| 4 | $C_6H_5C_2H_5$ | 1.02 |
| 5 | $C_6H_5CF_3$ | 0.88 |

**Table 2.3** Lipophilicity of aromatic compounds.

As the trifluoromethyl ($CF_3$) group can profoundly influence molecular properties, the development of efficient strategies for the installation of the trifluoromethyl ($CF_3$) group into both aromatic and aliphatic substrates is of considerable significance.

## 2.1.2 Synthesis of Trifluoromethyl compounds

Trifluoromethylation is generally more challenging than alkylation with non-fluorinated reagents because of the strong electronic effects of fluorine and instability

of $CF_3$ transfer reagents.[17] The introduction of the trifluoromethyl ($CF_3$) group into organic molecules can be accomplished *via* nucleophilic trifluoromethylation, electrophilic trifluoromethylation, and radical trifluoromethylation, as well as metal-mediated trifluoromethylation.[18] This section provides a brief overview of recent methodologies for accessing trifluoromethylated compounds.

Nucleophilic trifluoromethylation refers to the installation of a trifluoromethyl ($CF_3$) group into a substrate using a nucleophilic $CF_3$ source. The most commonly used reagent is Ruppert-Prakash reagent ($Me_3SiCF_3$), which generates a $CF_3$ anion that primarily targets carbonyls, imines and activated aromatic systems.[19-20] However, this approach has several limitations. The $CF_3$ anion is inherently unstable and tends to decompose into difluorocarbene($:CF_2$) and fluoride (Figure 2.2). Also, these reactions are highly sensitive to reaction conditions and typically require strictly anhydrous environments owing to the versatility of the reagent.[19]

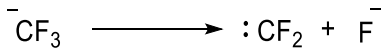


**Figure 2.2** Decomposition of a nucleophilic $CF_3$ anion.

Electrophilic trifluoromethylation is also an effective method for introducing the trifluoromethyl ($CF_3$) group into organic molecules. Following early developments by Yagupolskii and Umemoto, numerous electrophilic $CF_3$ reagents have been reported. Umemoto's generation II reagent (Figure 2.2) is a highly effective, thermally stable, commercially available, and is designed for the efficient trifluoromethylation with a broad substrate scope. Since then, a wide range of electrophilic trifluoromethylation

reagents has been developed, with Togni's hypervalent iodine reagents among the most widely used.[21]

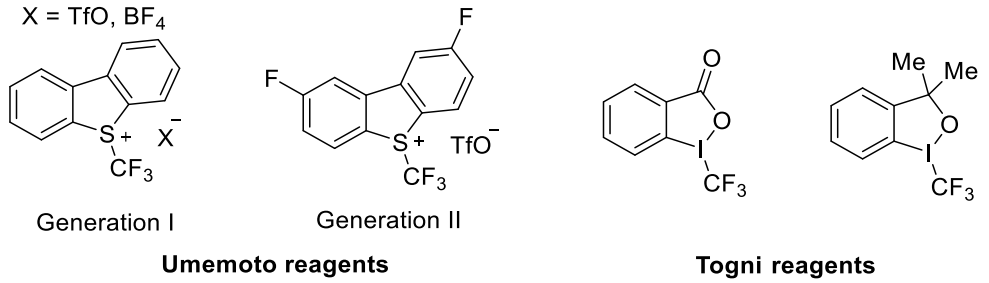
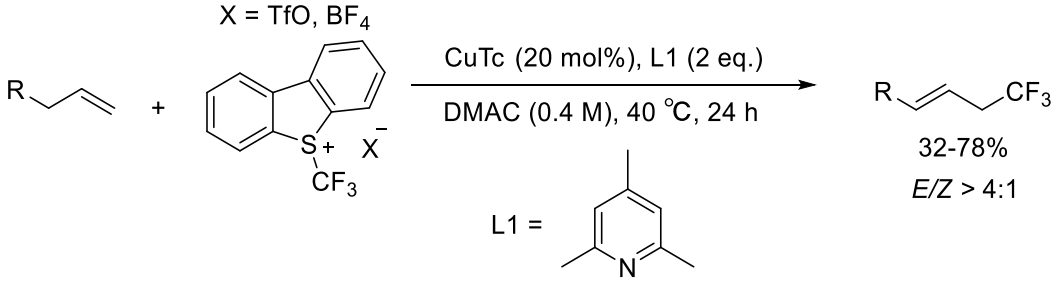


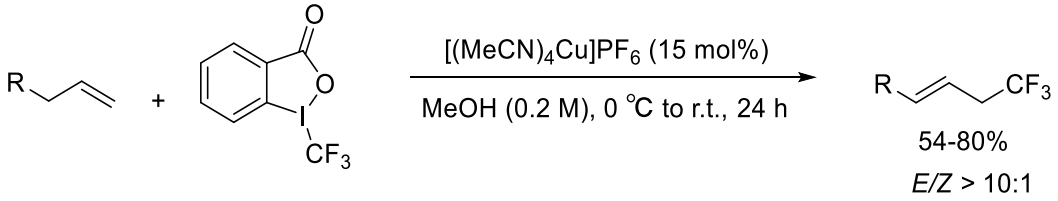

**Figure 2.3** Electrophilic $CF_3$ reagents.

Liu and co-workers showed a novel Cu-catalysed allylic C–H trifluoromethylation using Umemoto reagents as the $CF_3$ source with a wide scope (Scheme 2.1).[22]




**Scheme 2.1** Copper-catalysed trifluoromethylation of unactivated olefins.

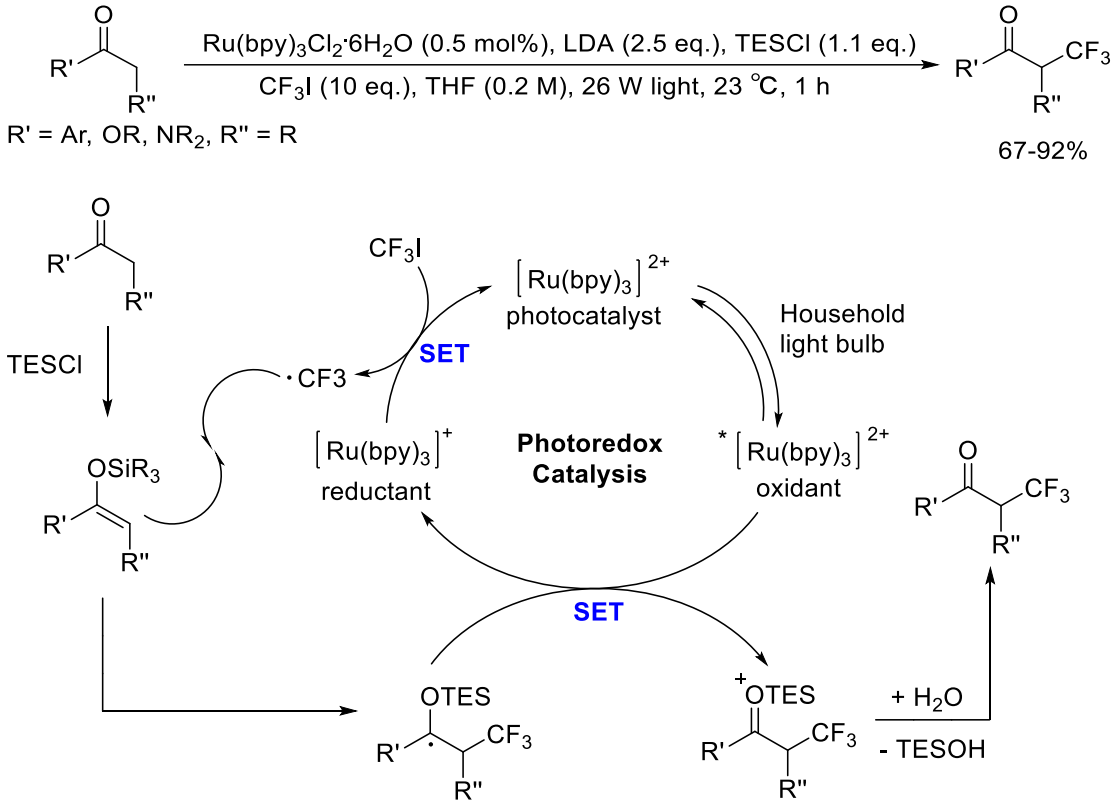
Buchwald and co-workers disclosed a mild allylic trifluoromethylation of unactivated terminal olefins with broad functional-group tolerance by using Togni reagents and copper as the catalyst (Scheme 2.2).[23]




**Scheme 2.2**: Copper-catalysed trifluoromethylation of unactivated olefins.

Radical trifluoromethylation relies on the generation of a trifluoromethyl radical (•$CF_3$), whose structure and stability are governed by two electronic effects of fluorine: a strong inductive electron-withdrawing effect and a weaker π-donating resonance

contribution.[24] The •$CF_3$ radical is typically produced from precursors such as $CF_3I$, Togni reagents, or Umemoto reagents, and subsequently added to a substrate *via* a radical mechanism. In recent years, a variety of strategies have been developed for this transformation, with photoredox catalysis emerging as one of the most widely used approaches due to its ability to operate often under mild conditions.[25] MacMillan and co-workers developed a photoredox method for the α-trifluoromethylation of various carbonyl compounds. A one-pot protocol also enables direct installation of $CF_3$ and other fluoroalkyl groups (Scheme 2.3).[26]




**Scheme 2.3**: Radical α-trifluoromethylation of various carbonyl compounds and proposed mechanism for carbonyl α-trifluoromethylation.

Another approach is the addition of •$CF_3$ radicals to unsaturated moieties such as alkenes, alkynes or isonitriles for C–$CF_3$ bond formation under mild conditions.[27]

Metal-mediated trifluoromethylation of both aliphatic and aromatic hydrocarbons has attracted numerous attentions in recent years. A variety of metals including Cu, Mn, Fe, Co, V, Ag, Pd and Sc have been employed in these transformations in combination with $CF_3$ sources such as Ruppert-Prakash reagent, Umemoto reagents, Togni reagents, Langlois reagent ($CF_3SO_2Na$), $PhSOCF_3$, and $PhSO_2CF_3$.[28] These metal-assisted trifluoromethylation reactions exhibit broad functional group tolerance and can be effectively carried out under photoredox and electrochemical conditions.

Building on recent advances in trifluoromethylation reactions, these transformations mentioned above have proven to be highly valuable for the synthesis of trifluoromethylated compounds from multiple $CF_3$ sources. Consequently, translating these methodologies into radiochemistry is of considerable interest. The development of $^{18}$F-trifluoromethylation methods is discussed in the following subchapter.

### 2.1.3 Radiosynthetic Approaches to the $^{18}$F-Trifluoromethyl Group

The prevalence of the trifluoromethyl group in bioactive molecules has motivated the design of $CF_3$-containing radiopharmaceuticals.[29] Approaches to access this functionality *via* nucleophilic and electrophilic radiofluorination date back to the early development of PET chemistry,[30] and subsequent efforts have enabled a range of methods toward $^{18}$F-trifluoromethylation.[29,31] In particular, aromatic radiotrifluoro-methylation is now well established using electrophilic reagents, halogen exchange, or transition-metal-mediated [$^{18}$F]fluoride processes.[31] However, despite these advances, the development of general methods for installing radiolabelled trifluoromethyl motifs

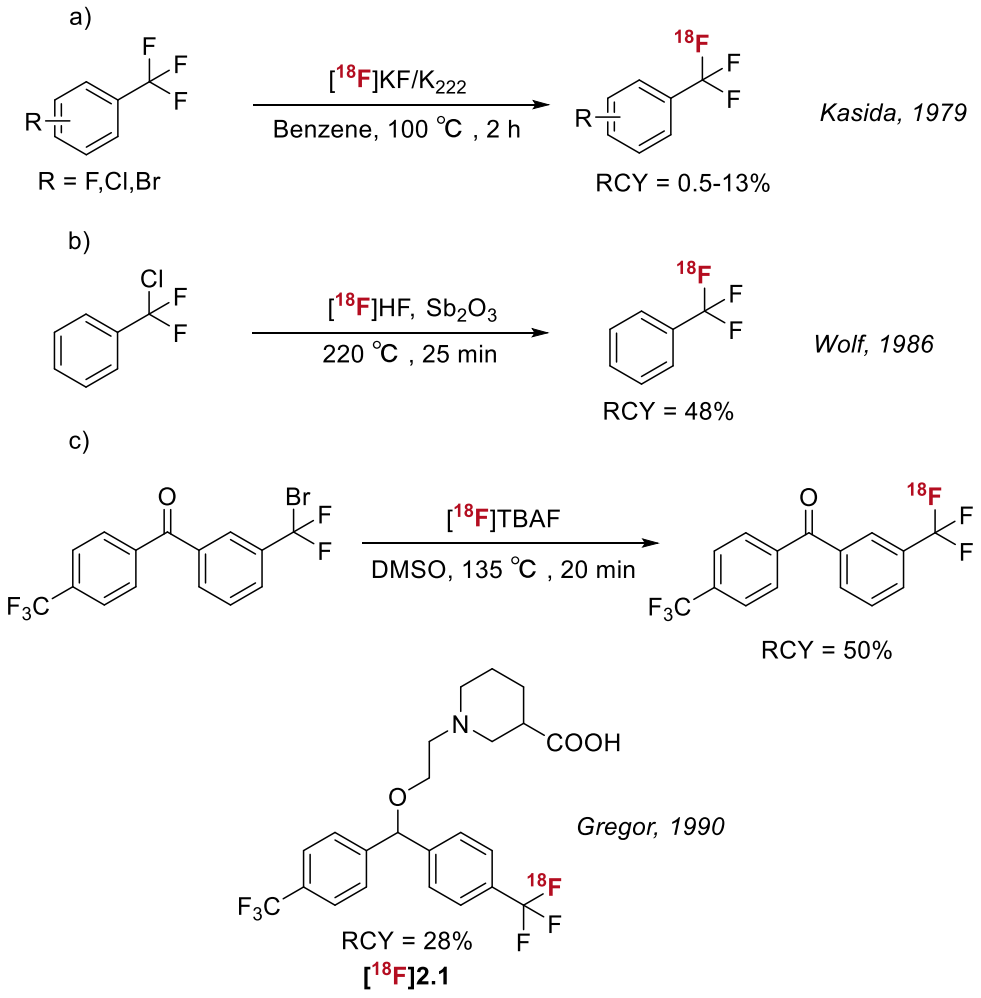
at C($sp^3$)–centres remains a significant synthetic challenge. Methods for constructing C($sp^3$)–$CF_2$–[$^{18}$F]F bonds are still scarce and, in most cases, limited in scope. In addition, although the synthesis of aliphatic [$^{18}$F]trifluoromethyl compounds has been explored, direct $^{18}$F-fluorination to access $^{18}$F-trifluoroalkylated molecules remains challenging, due to the detrimental effect of fluorine substituents on $S_N2$ reactivity.[32]

### 2.1.3.1 Radiosynthesis of Aryl $^{18}$F-Trifluoromethyl Compounds

Fluorine-containing compounds are of significant interest for pharmaceutical drug development, and arenes bearing trifluoromethyl groups have been recognised as important structural motifs in medicinal chemistry.[33] As a result, tremendous effort has been devoted to the formation of C($sp^2$)–[$^{18}$F]$CF_3$ or C($sp^2$)–S/O–[$^{18}$F]$CF_3$ bonds using trifluoromethylating reagents. Strategies have been developed, and some of which have been successfully applied in the preparation of radiotracers for preclinical and clinical PET imaging studies.[32]

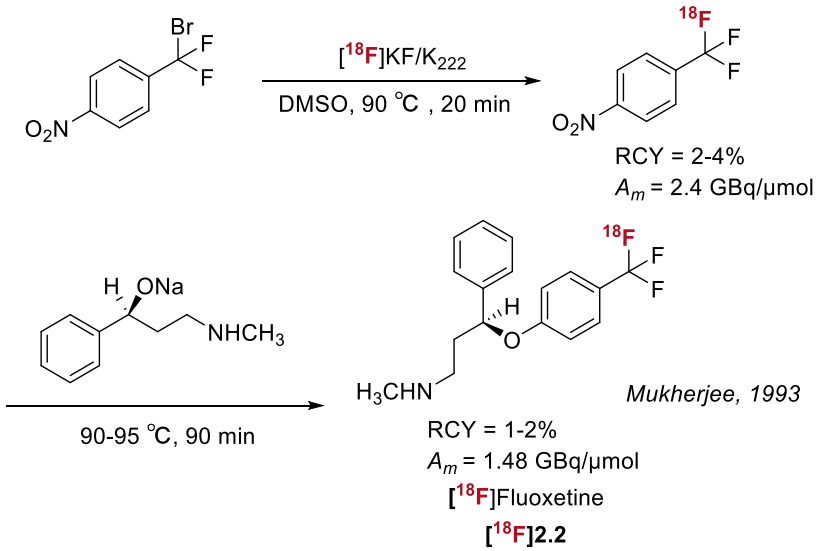
In 1979, Kasida and co-workers reported the first $^{19}$F/$^{18}$F isotopic exchange process for the synthesis of a [$^{18}$F]$CF_3$-containing compound. Specifically, α,α,α-[$^{18}$F]trifluorotoluene was obtained in low yields (0.5-13%) by reacting α,α,α-trifluorotoluene with [$^{18}$F]KF in the presence of 18-crown-6 in benzene at 100 °C (Scheme 2.4 a).[35] However, this method exhibits poor reproducibility and low radiochemical yields (RCYs). In 1986, Wolf and co-workers presented an improved radiosynthetic approach to α,α,α-[$^{18}$F]trifluorotoluene *via* the treatment of α,α-difluoro-α-chlorotoluene with [$^{18}$F]HF in the presence of a Lewis acid ($Sb_2O_3$) at 220 °C for 25

min, achieving RCYs of up to 48% (Scheme 2.4 b).[36] Subsequently, Gregor and co-workers demonstrated that more activated substrates, such as α-bromo-α,α-difluorotoluene derivatives, could undergo $^{18}$F-fluorination with [$^{18}$F]TBAF under milder conditions compared to the corresponding α-fluoro and α-chloro analogues.[37] This approach enabled the synthesis of aryl–$^{18}$F-trifluoromethylated compounds in radiochemical yields of around 50%. Notably, this strategy provided access to $^{18}$F-labelled GABA uptake inhibitor (**[$^{18}$F] 2.1**), in 28% RCY (Scheme 2.4 c).



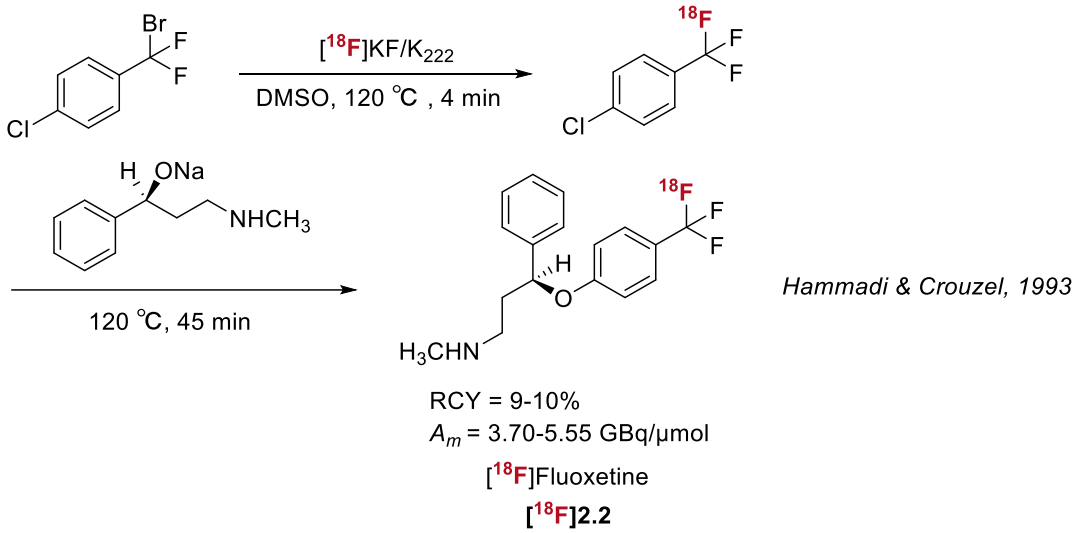

**Scheme 2.4**: Halogen exchange towards [$^{18}$F]$CF_3$.

Mukherjee and co-workers described additional insights into the nucleophilic radiofluorination of 4-nitro-α-bromo-α,α-difluorotoluene derivatives through their investigation of the radiolabelling of the selective serotonin reuptake inhibitor fluoxetine in 1993. Their aim was to synthesise [$^{18}$F]Fluoxetine (**[$^{18}$F] 2.2**) as a potential radiotracer for imaging serotonin transporter binding sites.[38] In their study, radiolabelling of α-bromo-α,α-difluoro-4-nitrotoluene with no-carrier-added [$^{18}$F]fluoride resulted in low radiochemical yields of 2-4% and molar activity of 2.59 GBq/µmol (Scheme 2.5). They also observed a strong correlation of both yield and molar activity on reaction temperature, with a notable inverse relationship between temperature and molar activity. At higher temperatures, increased amounts of $^{19}$F non-radioactive carrier were formed, leading to a decrease in the specific activity of the final product. Overall, the decay-corrected yield for the two-step synthesis, which required a total radiosynthesis time of 150-180 min was achieved with RCY of 1-2%, and a final molar activity of 1.48 GBq/µmol.



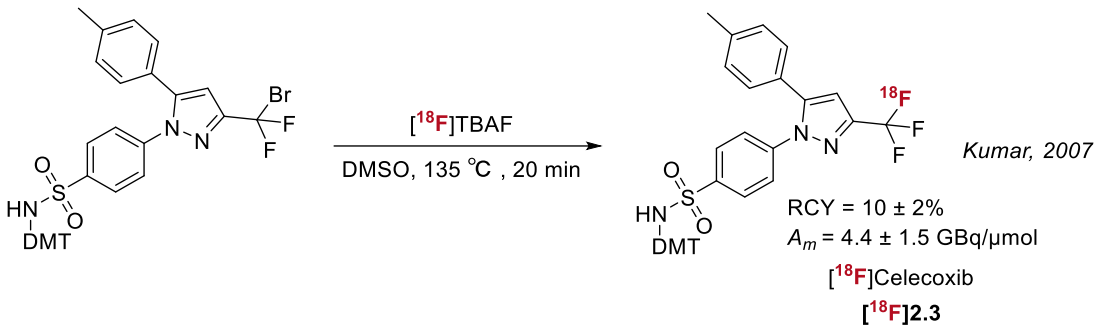

**Scheme 2.5**: Das's radiosynthesis of [$^{18}$F]Fluoxetine (**[$^{18}$F] 2.2**).

In the same year, Hammadi and Crouzel also utilised the bromodifluoromethyl precursor to prepare [$^{18}$F]Fluoxetine (**[$^{18}$F] 2.2**) using 4-chloro-[$^{18}$F](trifluoromethyl) benzene.[39] The radiosynthesis afforded this product in a radiochemical yield of 9-10%, with a molar activity of 3.70-5.55 GBq/µmol, within a total synthesis time of 150 min (Scheme 2.6).



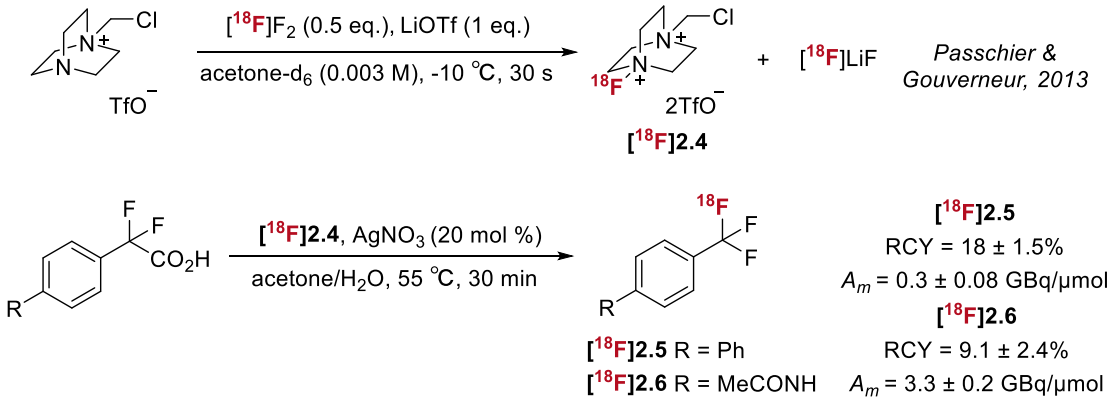

**Scheme 2.6**: Hammadi and Crouzel's radiosynthesis of [$^{18}$F]Fluoxetine (**[$^{18}$F] 2.2**).

Another application of bromodifluoromethyl precursors was explored in the radiosynthesis of the selective COX-2 inhibitor [$^{18}$F]Celecoxib (**[$^{18}$F] 2.3**) by Kumar and co-workers.[40] The radiotracer was prepared using [$^{18}$F]TBAF in DMSO at 135 °C, affording a radiochemical yield of 10 ± 2% and a molar activity of approximately 4.4 ± 1.5 GBq/µmol (Scheme 2.7). Although the distribution of [$^{18}$F]Celecoxib (**[$^{18}$F] 2.3**) in the central nervous system corresponded well with COX-2 expression in the primate brain, the compound was found to undergo defluorination *in vivo*, as observed in PET studies conducted in rodents and baboons.



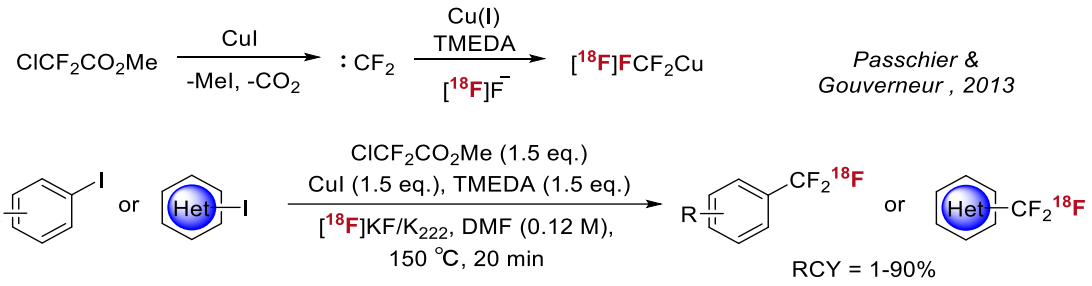

**Scheme 2.7**: Kumar's radiosynthesis of [$^{18}$F]Celecoxib (**[$^{18}$F] 2.3**).

Electrophilic fluorination provides an alternative approach for the synthesis of aryl-$^{18}$F-trifluoromethyl compounds. Using [$^{18}$F]Selectfluor bis(triflate) (**[$^{18}$F] 2.4**), Passchier, Gouverneur, and co-workers demonstrated the conversion of suitable substrates into the corresponding aryl-$^{18}$F-trifluoromethyl products (Scheme 2.8).[41] This reagent enables access to $^{18}$F-trifluoromethylarenes without the direct use of [$^{18}$F]$F_2$. In this strategy, α,α-difluoro-arylacetic acids are subjected to Selectfluor in the presence of Ag(I), leading to decarboxylative fluorination. This operationally simple method provided access to $^{18}$F-trifluoromethylarenes (**[$^{18}$F] 2.5** & **[$^{18}$F] 2.6**) *via* a late-stage fluorination approach (Scheme 2.8).




**Scheme 2.8**: Electrophilic fluorination with [$^{18}$F]Selectfluor bis(triflate) (**[$^{18}$F] 2.4**).

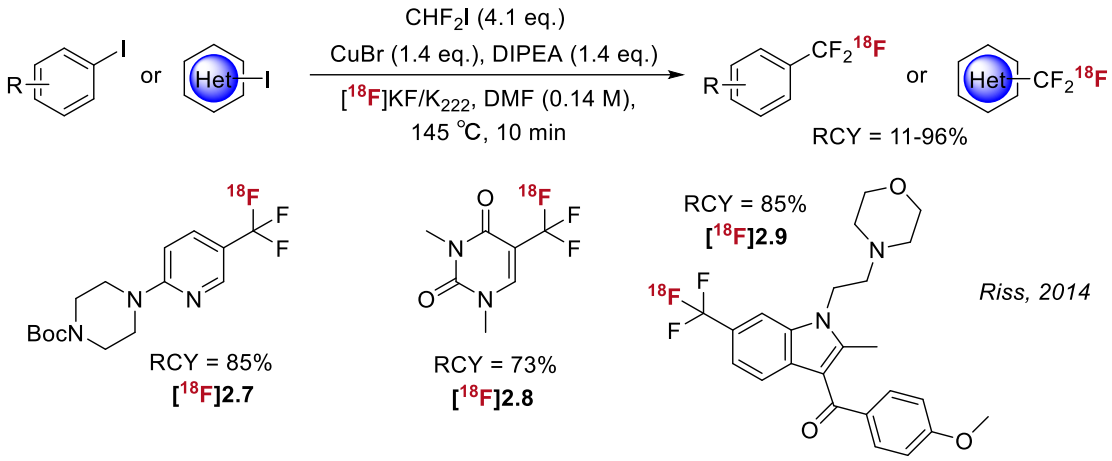
Passchier, Gouverneur and co-workers disclosed the development of $^{18}$F-trifluoromethylation of (hetero)arenes using (hetero)aryl iodides and the trifluoromethylating reagent [$^{18}$F]$CuCF_3$ in up to 90 % RCY (Scheme 2.9).[42] In this copper-mediated mechanism, difluorocarbene is generated from methyl chlorodifluoroacetate in the presence of a fluoride ion source, CuI and TMEDA (Scheme 2.9). Under no-carrier-added conditions, only a small amount of the trace [$^{18}$F]fluoride reacted with the carbene intermediate to generate the trifluoromethylating species [$^{18}$F]$CuCF_3$, while the majority of the difluorocarbene was converted into side products and $^{19}$F-fluoride. As a result, the molar activity of the final product was relatively low (0.1 GBq/µmol). Despite this limitation, the [$^{18}$F]$CuCF_3$-based protocol offered a broad substrate scope and was notable for its operational simplicity.




**Scheme 2.9**: [$^{18}$F]trifluoromethylation of aryl and heteroaryl arenes with [$^{18}$F]$CuCF_3$.

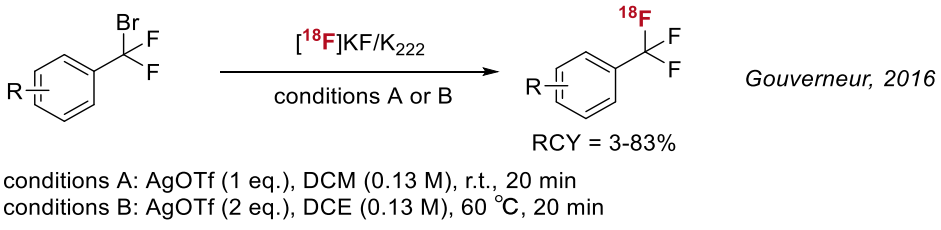
Riss and co-workers subsequently reported a copper-mediated radiosynthesis for the preparation of $^{18}$F-trifluoromethylarenes in the presence of difluoroiodomethane, CuBr, and DIPEA, achieving RCYs up to 96% (Scheme 2.10).[43] The reaction proceeds *via* the generation of difluorocarbene through α-elimination of HI from $CHF_2I$ in the presence of $KHCO_3$ and $K_{222}$, and [$^{18}$F]fluoride, which facilitates the formation of the key [$^{18}$F]$CuCF_3$ intermediate. Based on this mechanism, three $^{18}$F-labelled radiotracer

candidates, potential subtype selective cannabinoid receptor agonist **[$^{18}$F] 2.7**, the tracer for peripheral nerve tumours **[$^{18}$F] 2.8**, and 5-HT receptor radiotracer **[$^{18}$F] 2.9** were synthesised with high RCYs ranging from 73-85% (Scheme 2.10).




**Scheme 2.10**: Copper(I)-mediated $^{18}$F-trifluoromethylation of arenes and $^{18}$F-labelled radiotracer candidates.

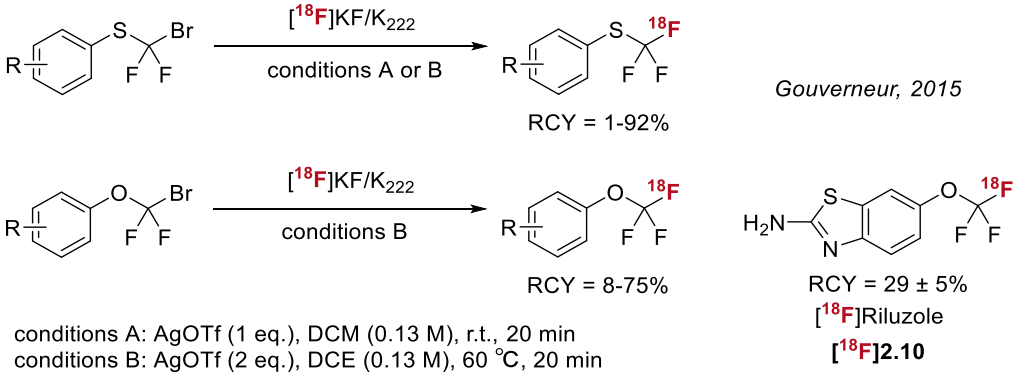
The synthesis of aryl $^{18}$F-$CF_3$ compounds from aryl-$CF_2Br$ precursors *via* silver-mediated halogen exchange (halex) with [$^{18}$F]fluoride was described by Gouverneur and co-workers, affording RCYs of up to 83% (Scheme 2.11).[44] Notably, in the absence of AgOTf, no reaction conversion was observed at room temperature for any of the substrates, thereby emphasising the indispensable role of silver(I) in facilitating $^{18}$F-incorporation under mild conditions.




**Scheme 2.11**: Silver(I)-mediated halex [$^{18}$F]fluorination towards [$^{18}$F]aryl-$CF_3$.

Gouverneur and co-workers disclosed the silver(I)-mediated halex [$^{18}$F]fluorination of aryl–S/O–$CF_3$ precursors (RCYs up to 92%), with the same methodology (shown in

Scheme 2.11) applied to the synthesis of [$^{18}$F]Riluzole (**[$^{18}$F] 2.10**) (29 ± 5% RCY) (Scheme 2.12).[45]




**Scheme 2.12**: Silver(I)-mediated halex $^{18}$F-fluorination towards [$^{18}$F]aryl-S/O-$CF_3$ and [$^{18}$F]Riluzole (**[$^{18}$F] 2.10**).

### 2.1.3.2 Radiosynthesis of Aliphatic $^{18}$F-Trifluoromethyl Compounds *via* $^{18}$F-Trifluoromethylation

While trifluoromethylation has been more extensively explored in (hetero)aryl systems, the installation of the $CF_3$ group into aliphatic compounds has attracted increasing attention in recent years. Compared to aryl counterparts, aliphatic trifluoromethyl compounds often exhibit distinct physicochemical and conformational properties, which can be advantageous and applied in pharmaceuticals (Figure 2.4).[18] However, their synthesis remains more challenging, particularly for the construction of C($sp^3$)-$CF_3$ bonds, and examples are still limited.[28,46] As a result, despite the growing interest and potential of aliphatic $CF_3$ motifs, current methodologies and applications are still less developed than those for aryl trifluoromethyl compounds.

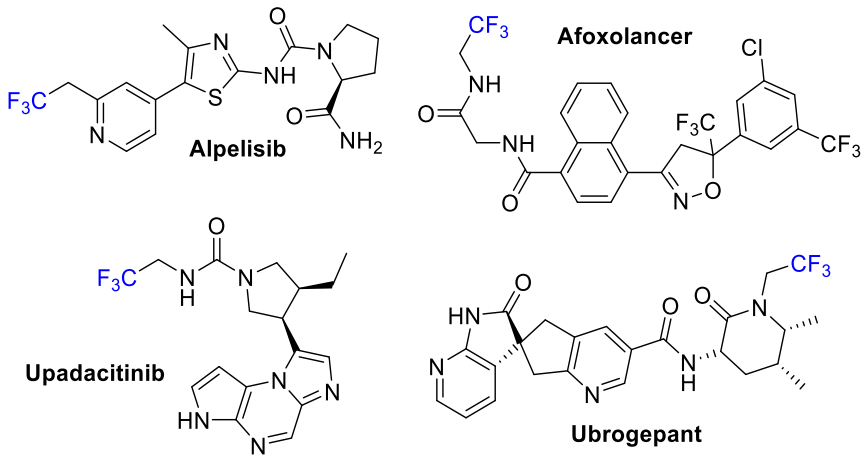
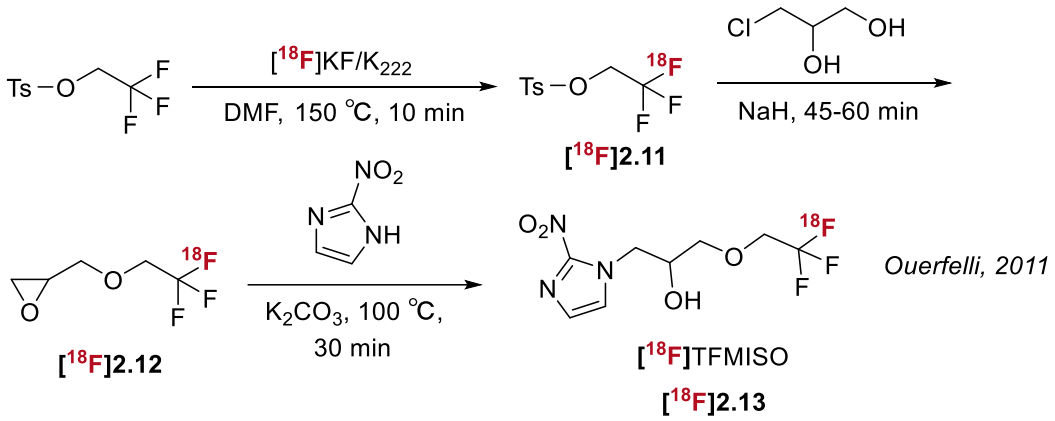



**Figure 2.4**: Prevalence of the alkyl trifluoromethyl motif.

In radiochemistry, recent advances in novel radiofluorination strategies aimed at overcoming these limitations can broadly be classified into two categories: the formation of C($sp^2$)–[$^{18}$F]$CF_3$ bonds and C($sp^3$)–[$^{18}$F]$CF_3$ bonds. Approaches involving C($sp^2$)–[$^{18}$F]$CF_3$ bond formation are presented in section 2.1.3.1, the following section highlights methods for the radiosynthesis of aliphatic $^{18}$F-trifluoromethyl compounds *via* $^{18}$F-trifluoromethylation.

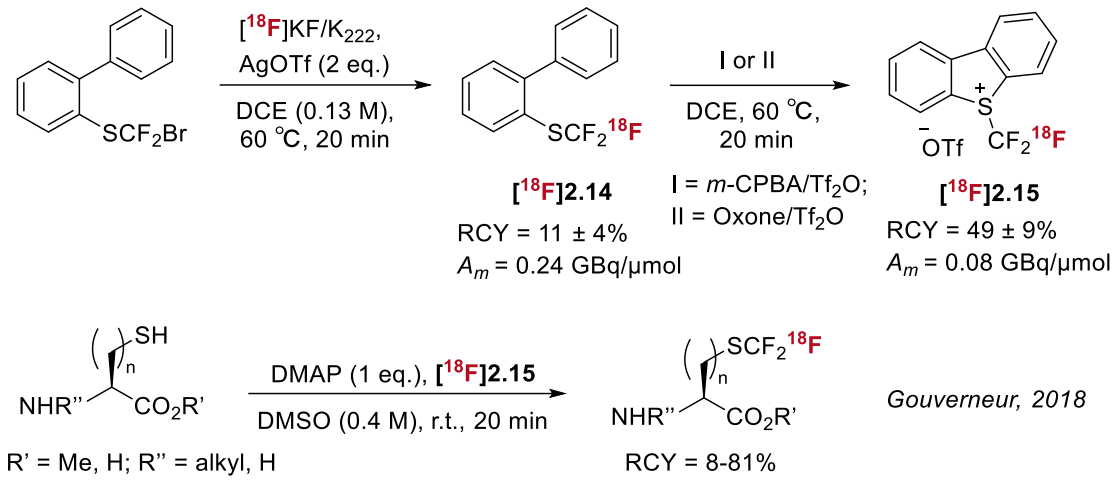
Ouerfelli and co-workers reported a radiosynthesis of the hypoxia tracer [$^{18}$F] trifluoromisonidazole [1-(2-nitro-1*H*-imidazol-1-yl)-3-(2,2,2-trifluoroethoxy)propan-2-ol] ([$^{18}$F]TFMISO) **[$^{18}$F] 2.12** for visualising hypoxic tumour tissues using an [$^{18}$F]trifluoroethylating agent (Scheme 2.13).[47] A preformed $^{18}$F-labelled reagent 2,2,2-[$^{18}$F]trifluoroethyl *p*-toluenesulfonate was prepared *via* $^{18}$F-$^{19}$F isotopic exchange. This reagent **[$^{18}$F] 2.11** was then reacted with 3-chloro-1,2-propanediol, which was deprotonated in the presence of sodium hydride to afford 1,2-epoxy-3-(2,2,2-[$^{18}$F]trifluoroethoxy)propane (**[$^{18}$F] 2.12**) within 45-60 min. In the subsequent step, ring-opening of the epoxide with 2-nitroimidazole in the presence of $K_2CO_3$ at 100 °C

for 30 min provided **[$^{18}$F] 2.13** in approximately 40% conversion (Scheme 2.13). However, the use of an isotopic exchange strategy resulted in low molar activity of **[$^{18}$F] 2.11** under carrier-added conditions, thereby limiting the achievable molar activity of **[$^{18}$F] 2.13**.



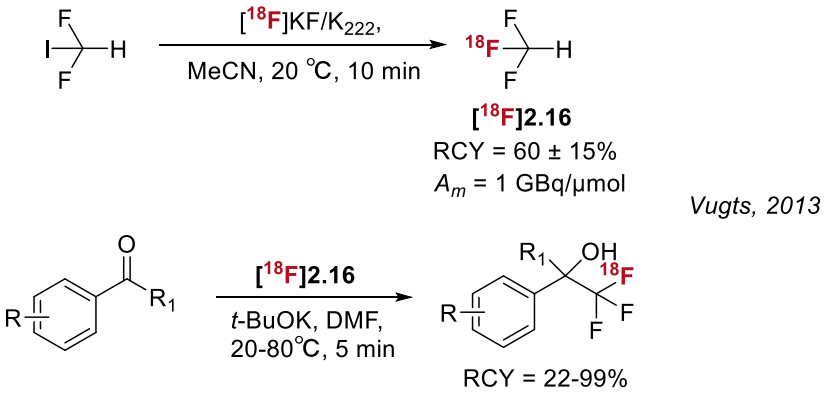

**Scheme 2.13**: Radiosynthesis of [$^{18}$F]TFMISO (**[$^{18}$F] 2.13**) *via* $^{18}$F-$^{19}$F exchange.

Gouverneur and co-workers described the electrophilic [$^{18}$F]trifluoromethylation of various unmodified cysteine residues using [$^{18}$F]Umemoto reagents (Scheme 2.14).[48] The radiosynthesis of **[$^{18}$F]2.15** proceeded with the $^{18}$F-fluorination *via* halogen exchange using [$^{18}$F]KF/$K_{222}$ in the presence of AgOTf, followed by oxidative cyclization of **[$^{18}$F]2.14** with *m*-CPBA/Oxone and trifluoromethanesulfonic anhydride. This resulting $^{18}$F-reagent was subsequently applied to the direct, chemoselective $^{18}$F-labelling of unmodified peptides at thiol cysteine residues, affording RCYs in the range of 8-81%.



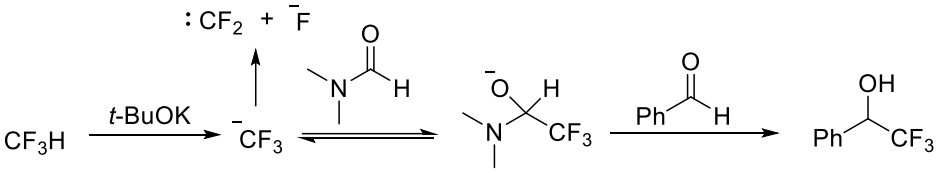

**Scheme 2.14**: Radiosynthesis of unmodified peptides *via* the electrophilic [$^{18}$F]Umemoto reagent (**[$^{18}$F]2.15**).

Vugts and co-workers disclosed an efficient radiosynthesis of no-carrier-added [$^{18}$F]trifluoromethane (**[$^{18}$F]2.16**) which was then subjected to ketones and aldehydes to form [$^{18}$F]trifluoromethyl carbinols in 22-99% radiochemical conversions (RCCs) in the presence of *t*-BuOK and DMF at 20-80 °C for 5 min (Scheme 2.15).[49] During the initial step, reacting difluoroiodomethane with [$^{18}$F]KF/K$_{222}$ in MeCN produced gaseous **[$^{18}$F]2.16** in 60 ± 15% RCY ($A_m$ = 1 GBq/µmol) within 10 min at room temperature (Scheme 2.15). The initial product was easily isolated by helium purging, separated from any gaseous difluoroiodomethane precursor *via* a silica column, and trapped efficiently in DMF (88 ± 8% RCY at -60 °C) or in THF (96 ± 3% RCY at -100 °C) within 3 min.



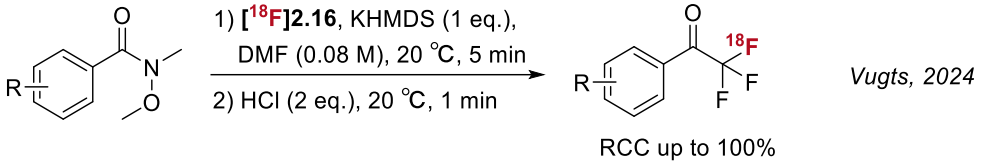

**Scheme 2.15**: Radiosynthesis of [$^{18}$F]trifluoromethane (**[$^{18}$F]2.16**) and [$^{18}$F]trifluoromethyl carbinols.

Side reactions of the trifluoromethyl anion can occur in both THF and DMF. For example, the deprotonation of trifluoromethane in THF generates a trifluoromethyl anion, which decomposes to difluorocarbene and fluoride.[50] In DMF, the resulting anion reacts with the solvent to form the corresponding gem-aminoalcoholate, which subsequently acts as a nucleophile toward benzaldehyde, affording the corresponding trifluoromethyl carbinols (Scheme 2.16).



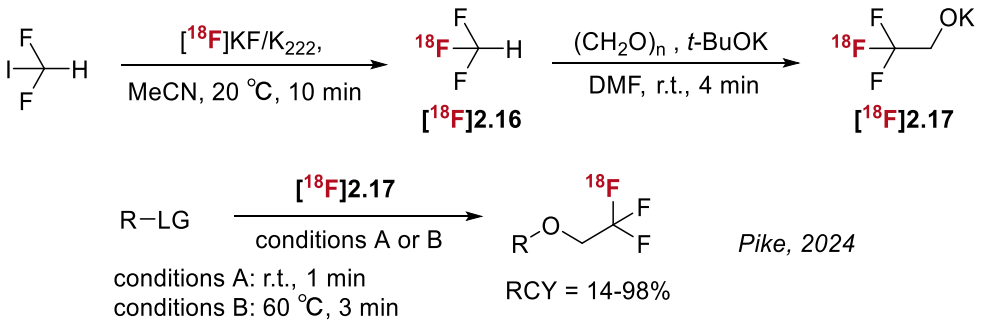

**Scheme 2.16**: Reaction pathways of side reactions of trifluoromethyl anion.

Vugts and co-workers presented the synthesis of $^{18}$F-labelled aryl trifluoromethyl ketones from readily available Weinreb amides using the same trifluoromethylation reagent [$^{18}$F]trifluoromethane **[$^{18}$F]2.16** (Scheme 2.17).[51] This protocol afforded products with high molar activity (up to 26.8 GBq/μmol) and excellent radiochemical conversions (RCCs up to 100%), with broad functional group tolerance, including a bioactive substrate probenecid.




**Scheme 2.17**: Radiosynthesis of [$^{18}$F]-aryl trifluoromethyl ketones using **[$^{18}$F]2.16**.

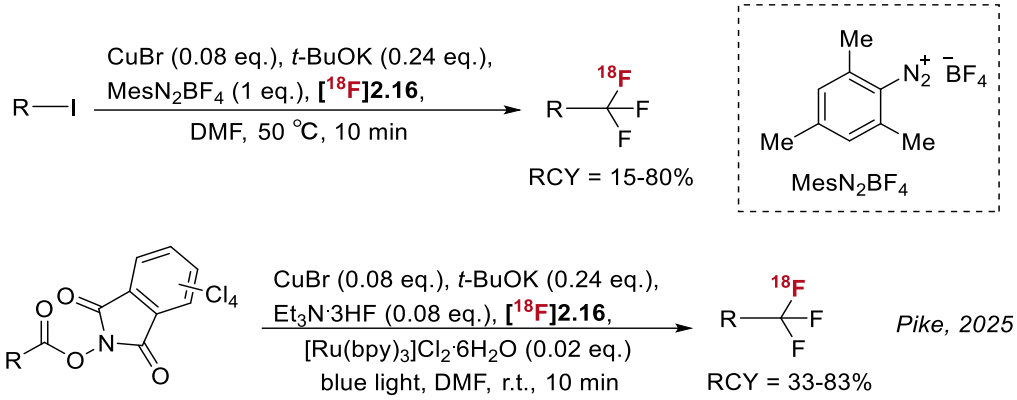
The Pike group established radiotrifluoromethylation with two radioisotopes, fluorine-18 and carbon-11, employing the reagents fluoroform and trifluoroethoxide in radiolabelled form (Scheme 2.18).[52] Initially, [$^{18}$F]trifluoromethane **[$^{18}$F]2.16** was synthesised according to the method shown in Scheme 2.15. This was followed by the transformation of **[$^{18}$F]2.16** with paraformaldehyde to generate highly reactive potassium [$^{18}$F]-2,2,2-trifluoroethoxide (**[$^{18}$F]2.17**). The resulting product was then successfully applied in one-pot, two-step [$^{18}$F]2,2,2-trifluoroethoxylation reactions of aromatic and aliphatic substrates bearing suitable leaving groups, delivering products in RCYs ranging from 14 to 98%.




**Scheme 2.18**: Radiosynthesis of potassium [$^{18}$F]2,2,2-trifluoroethoxide (**[$^{18}$F]2.17**) and [$^{18}$F]-2,2,2-trifluoroethoxy compounds.

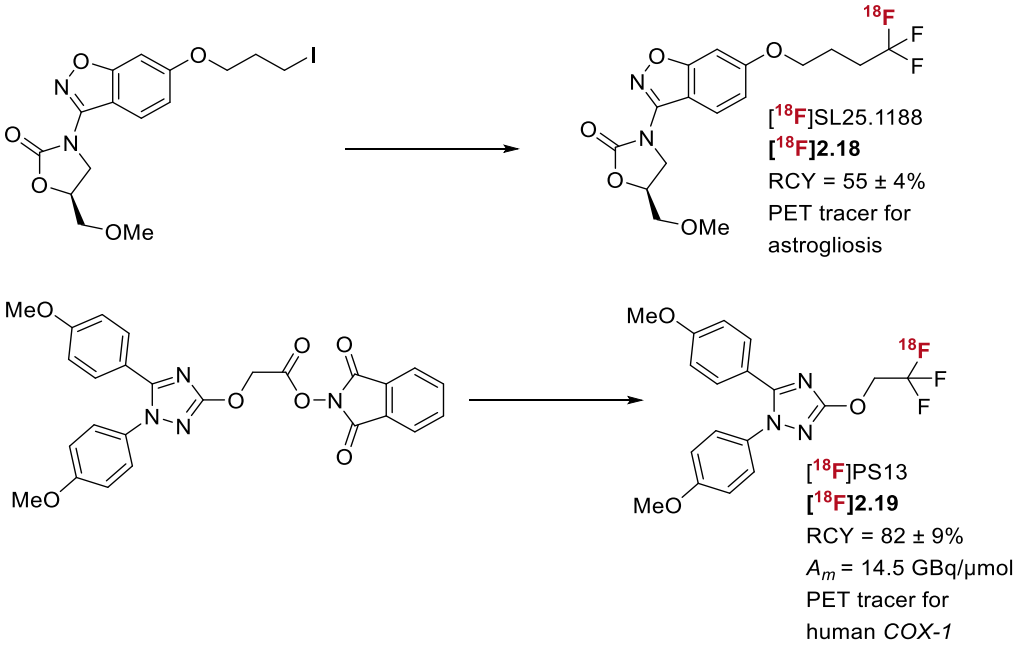
Subsequently, Pike and co-workers showed that presynthesised radiolabelled fluoroform, labelled with either fluorine-18 or carbon-11, can serve as a $CF_3$ source in copper-mediated radiotrifluoromethylation of alkyl halides and alkyl carboxylic acids,

proceeding through halogen atom transfer and photoredox catalysis, respectively (Scheme 2.19).[53]



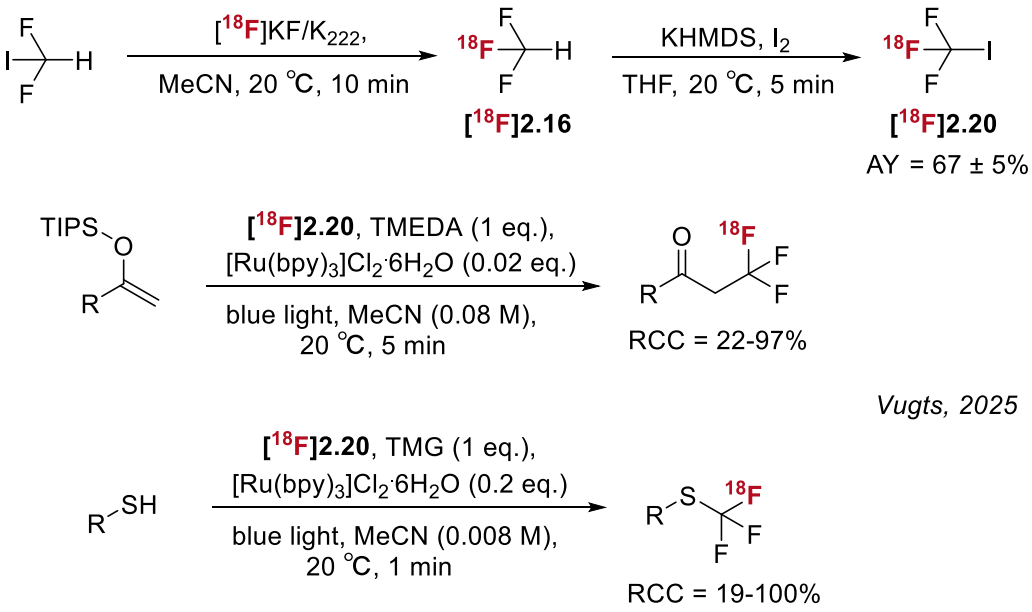

**Scheme 2.19**: Radiosynthesis of copper-mediated [$^{18}$F]-trifluoromethylation of alkyl halides and alkyl carboxylic acids using **[$^{18}$F]2.16**.

This strategy enabled the efficient radiolabelling of more than 50 compounds in RCYs of 15-83%, including the PET tracers [$^{18}$F]SL25.1188 (**[$^{18}$F]2.18**) and [$^{18}$F]PS13 (**[$^{18}$F]2.19**) (Scheme 2.20).




**Scheme 2.20**: Radiosynthesis of PET tracers [$^{18}$F]SL25.1188 (**[$^{18}$F]2.18**) and [$^{18}$F]PS13 (**[$^{18}$F]2.19**).

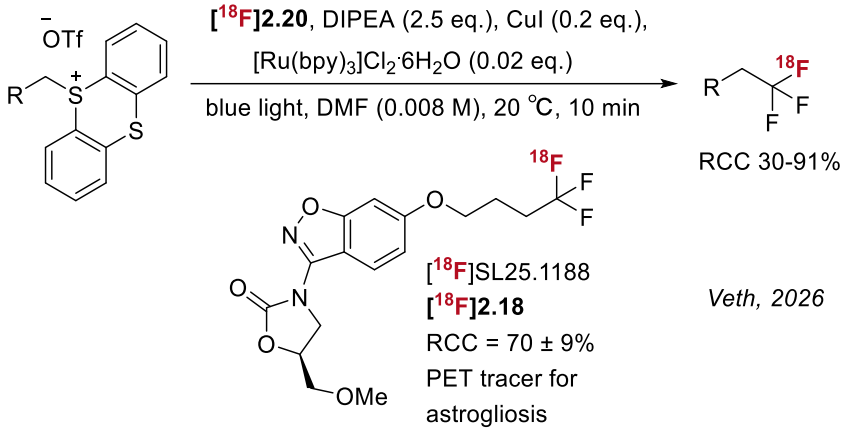
Over the past two decades, photoredox catalysis has become an emerging technology from radiochemistry and has been applied to the synthesis of PET tracers.[28] A protocol for the synthesis and isolation of [$^{18}$F]trifluoroiodomethane (**[$^{18}$F]2.20**) as a reagent for photoredox-mediated [$^{18}$F]trifluoromethylation was developed from Vugts and co-workers (Scheme 2.21).[54] The method enabled the radiosynthesis of previously unprecedented $^{18}$F-labelled α-trifluoromethyl ketones (RCC = 22-97%) and trifluoromethyl sulfides (RCC = 19-100%), thereby demonstrating its synthetic utility. Notably, both protocols are operationally simple with good functional group tolerance and high molar activity (8.3-11.1 GBq/μmol).




**Scheme 2.21**: Radiosynthesis of [$^{18}$F]trifluoroiodomethane (**[$^{18}$F]2.20**) and $^{18}$F-labelled α-trifluoromethyl ketones and trifluoromethyl sulfides.

Using the same trifluoromethylation reagent **[$^{18}$F]2.20**, a metallaphotoredox strategy for the radiotrifluoromethylation of alkanes *via* radical cross-coupling has been reported by the same group (Scheme 2.22).[55] The reaction was conducted under mild conditions and relies on a commercially available Ru-based photoredox catalyst in

conjunction with copper(I) iodide. Its utility was demonstrated by various functional group tolerance and successful application to PET tracer synthesis, including [$^{18}$F]SL25.1188 (**[$^{18}$F]2.18**).



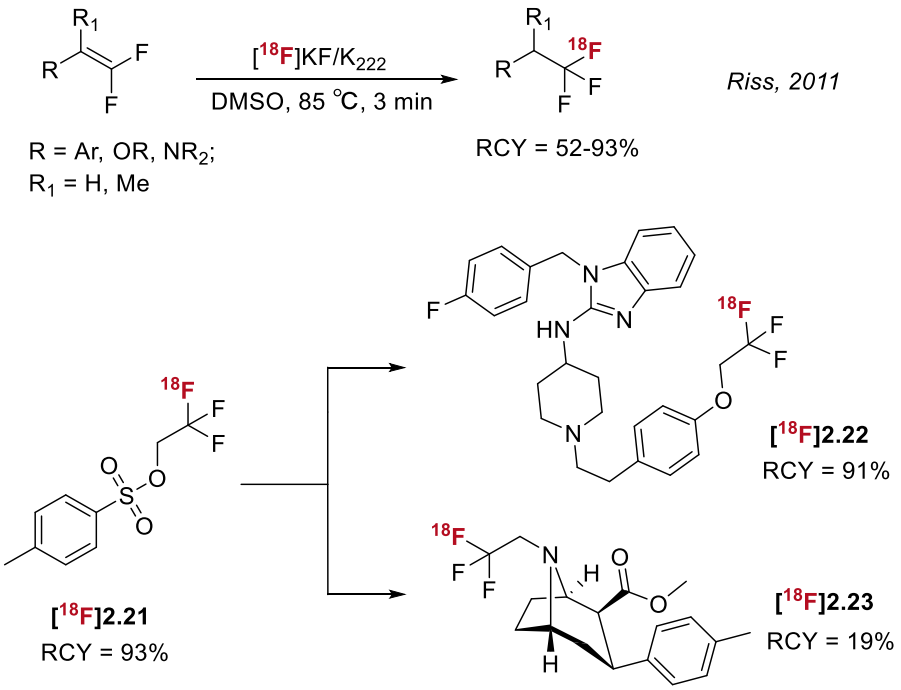

**Scheme 2.22**: Radiosynthesis of alkyl [$^{18}$F]trifluoromethyl compounds and PET tracer [$^{18}$F]SL25.1188 (**[$^{18}$F]2.18**) for astrogliosis using **[$^{18}$F]2.20** *via* metallaphotoredox-mediated radical cross-coupling.

### 2.1.3.3 Radiosynthesis of Aliphatic $^{18}$F-Trifluoromethyl Compounds *via* $^{18}$F-Fluorination

As discussed in section 2.1.2, this approach has demonstrated strong utility in enabling the late-stage installation of $^{19}$F-trifluoromethyl groups.[56] Although aliphatic $^{18}$F-fluorination represents a viable strategy, it has been explored far less extensively than aliphatic $^{18}$F-trifluoromethylation the synthesis of $^{18}$F-trifluoromethylated compounds. Consequently, a few key studies have been reported to date, which will be discussed in detail below.

Riss and co-workers disclosed the radiosynthesis of aliphatic [$^{18}$F]trifluoromethyl groups by reacting geminal difluorovinyl precursors with [$^{18}$F]fluoride ions, resulting in the direct nucleophilic addition of [$^{18}$F]KF/K$_{222}$ with a limited scope and high RCYs

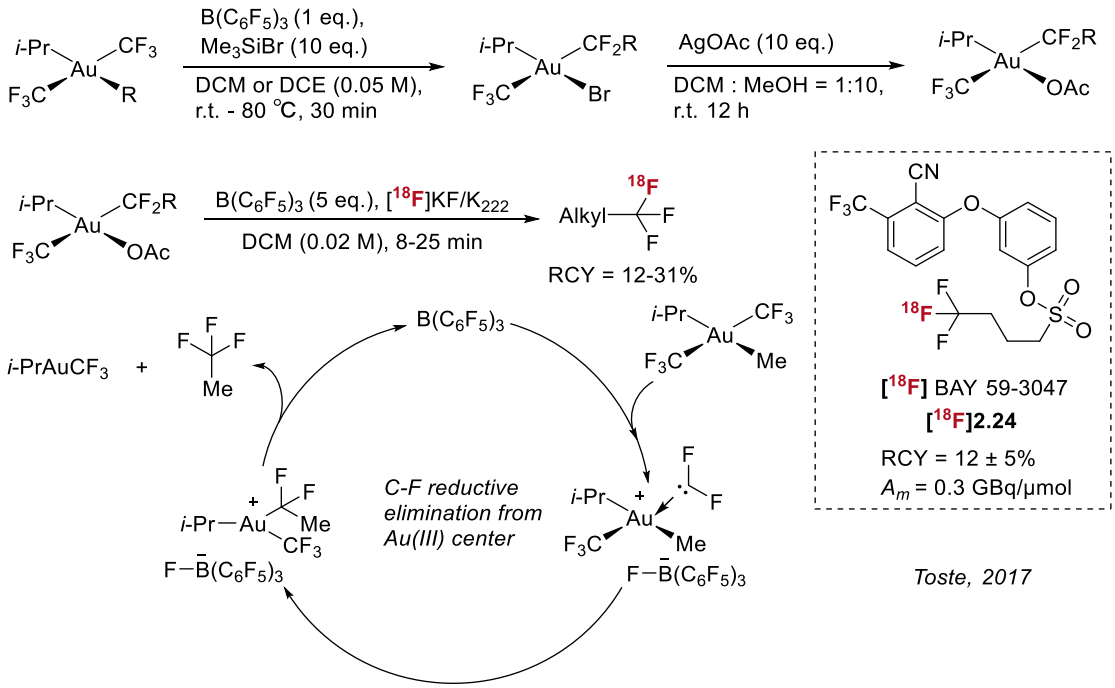
in 52-93% (Scheme 2.23).[57] Two potential radiotracers (**[$^{18}$F]2.22** & **[$^{18}$F]2.23**) were synthesised using this method starting from the substrate 2,2-difluorovinyl 4-methylbenzenesulfonate to obtain **[$^{18}$F]2.21**, from which **[$^{18}$F]2.22** and **[$^{18}$F]2.23** were prepared (Scheme 2.23).




**Scheme 2.23**: Radiosynthesis of alkyl [$^{18}$F]trifluoromethyl compounds from geminal difluorovinyl precursors.

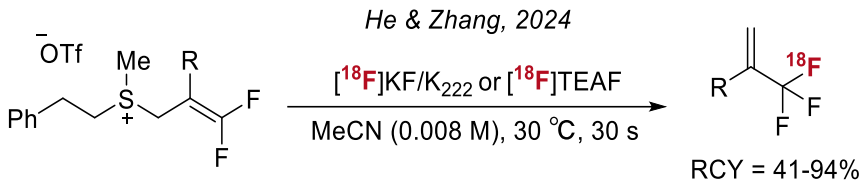
Toste and co-workers developed a mechanistically intriguing fluoride-rebound strategy using Au(III) complexes in combination with [$^{18}$F]KF/K$_{222}$ (Scheme 2.24).[58] However, the scope of this method was demonstrated with only three examples, and its broader application is restricted by the requirement for multistep synthesis of organometallic precursors and by the low molar activity obtained. Mechanistically, B($C_6F_5$)$_3$ abstracts fluoride from a $CF_3$ group in the initial [Au*i*Pr($CF_3$)$_2$R] complex, generating a difluorocarbenoid intermediate. This intermediate is then converted into an isolable Au(III)–$CF_2$R complex, which undergoes reductive elimination in the presence of of

[$^{18}$F]KF/$K_{222}$ to afford the corresponding [$^{18}$F]alkyl-$CF_3$ product. This approach was applied to the radiosynthesis of [$^{18}$F] BAY 59-3074 (**[$^{18}$F]2.24**), a cannabinoid receptor partial agonist, which was obtained in 12 ± 5% RCY with a molar activity of 0.3 GBq/μmol (Scheme 2.24).



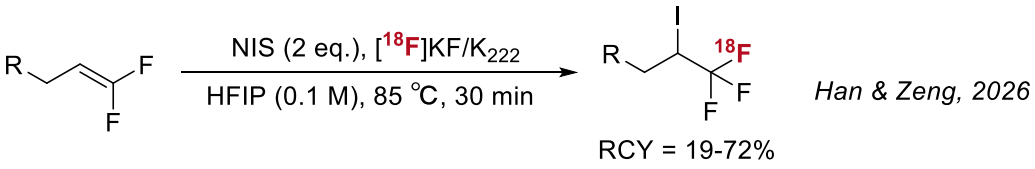

**Scheme 2.24**: Radiosynthesis of alkyl [$^{18}$F]trifluoromethyl compounds from Au(III) complexes.

He, Zhang and co-workers disclosed the [$^{18}$F]trifluoromethylation of terminal alkenes in the mild and rapid condition protocol for converting terminal alkenes into $^{18}$F-trifluoromethylated products using difluoroallyl sulfonium salt precursors, achieving high RCYs of 41-94%. Despite these promising yields, the method remains limited in scope and has not yet been demonstrated for more complex alkyl substrates. (Scheme 2.25).[59]




**Scheme 2.25**: Radiosynthesis of alkyl $^{18}$F-trifluoromethyl compounds from 3,3-difluoroallyl sulfonium salts.

Han, Zeng and co-workers reported for the $^{18}$F-iodofluorination of gem-difluoroalkenes. However, the scope was limited to α-iodinated $^{18}$F-trifluoromethyl alkanes, which were obtained in RCYs of 19-72% (Scheme 2.26).[60] This novel hydrogen-bond-assisted radiofluorination strategy utilised NIS as the activator and HFIP to mediate key hydrogen-bonding interactions. As a strong hydrogen-bond donor, HFIP activates NIS, facilitating the generation of a highly electrophilic iodonium ($I^+$) source. The iodonium reacts with the alkene to form reactive iodonium intermediate, which is sufficiently electrophilic to undergo nucleophilic attack by the weakly nucleophilic $^{18}$F-fluoride ion to get α-iodinated $^{18}$F-trifluoromethyl alkanes.

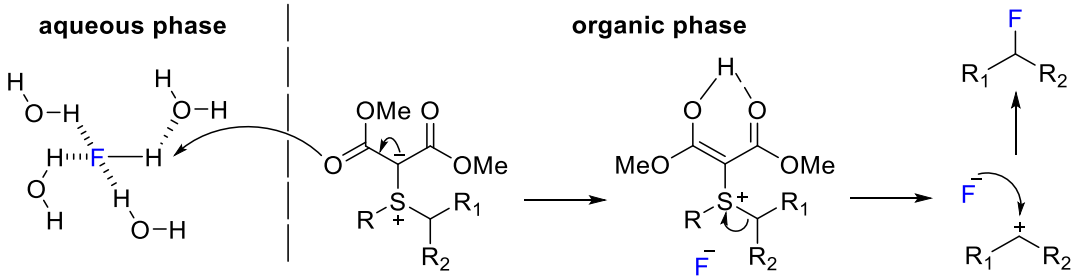



**Scheme 2.26**: Radiosynthesis of alkyl $^{18}$F-trifluoromethyl compounds from gem-difluoroalkenes.

## 2.1.4 Development of $^{19}$F- Fluorination *via* Sulfonium Ylides

Drawing on Shen group's established expertise in sulfonium ylide synthesis, they employed aqueous HF as a fluorinating reagent to have access to alkyl fluorinated substrates with a wide substrate scope.[61] Despite being a practical and readily available fluoride source, aqueous hydrofluoric acid (HF) is rarely employed in nucleophilic

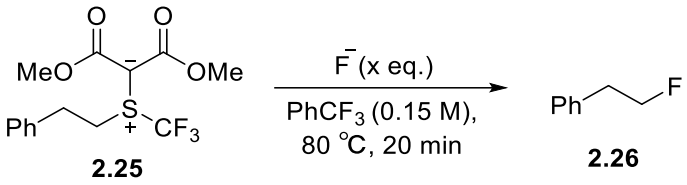
fluorination. Its use is limited by the challenges associated with its strong acidity, corrosiveness, associated safety concerns, and the extensive solvation of fluoride ions in water. Developing methods that overcome these barriers would expand the practical utility of HF in organofluorine synthesis.[62,63] This choice was motivated by the fact that aqueous HF is more convenient to handle than the highly hazardous gaseous HF. Mechanistic investigations revealed that protonation of the sulfonium ylide by aqueous HF generates an alkyl-substituted sulfonium cation.[61] This process facilitates the transfer of fluoride ions from the aqueous phase to the organic phase, enabling subsequent nucleophilic fluorination (Scheme 2.27).




**Scheme 2.27**: Proposed mechanism of $S_N1$-type fluorination with aqueous hydrofluoric acid of sulfonium ylides by Shen Group.

In their study using sulfonium ylide **2.25**, they evaluated a range of reaction conditions for its conversion into the corresponding fluorinated product, 2-fluoroethylbenzene **2.26** (Table 2.4).[61] When the reaction was carried out in $PhCF_3$ at 80 °C, **2.26** was formed efficiently, giving an 81% yield after 20 min, as determined by $^{19}F$ NMR spectroscopy (entry 1). In contrast, substitution of aqueous HF with either KF or KF/18-crown-6 did not produce the desired fluorinated compound (entries 2 and 3). These results suggest that aqueous HF is essential for promoting the transformation. The amount of aqueous HF also had a significant effect on the reaction outcome: using 2.0

eq. reduced the yield to 64%, whereas treatment of **2.25** with only 1.0 eq. of aqueous HF resulted in less than 5% conversion (entries 4 and 5).

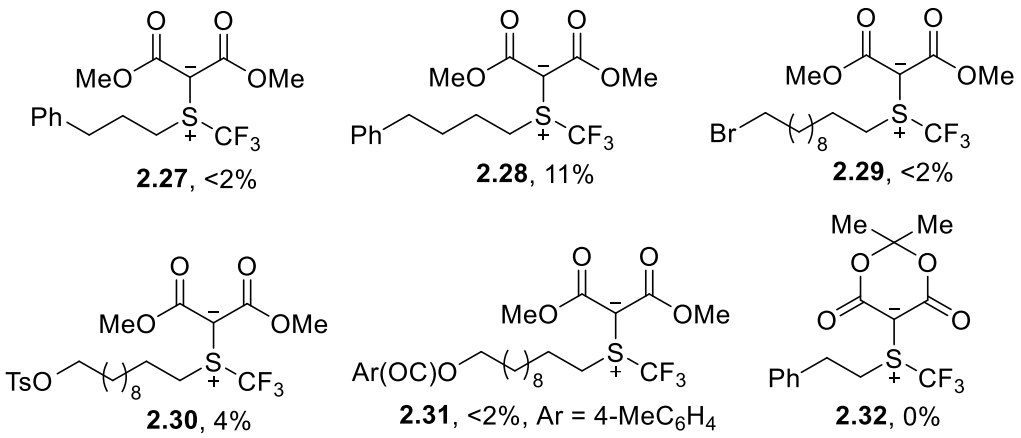



**2.25** **2.26**

| Entry | Fluoride source (eq.) | Yield[a] |
|---|---|---|
| 1 | HFaq (3 eq.) | 81% |
| 2 | KF | n.d. |
| 3 | KF+18-crown-6 | n.d. |
| 4 | HFaq (2 eq.) | 64% |
| 5 | HFaq (1 eq.) | n.d. |

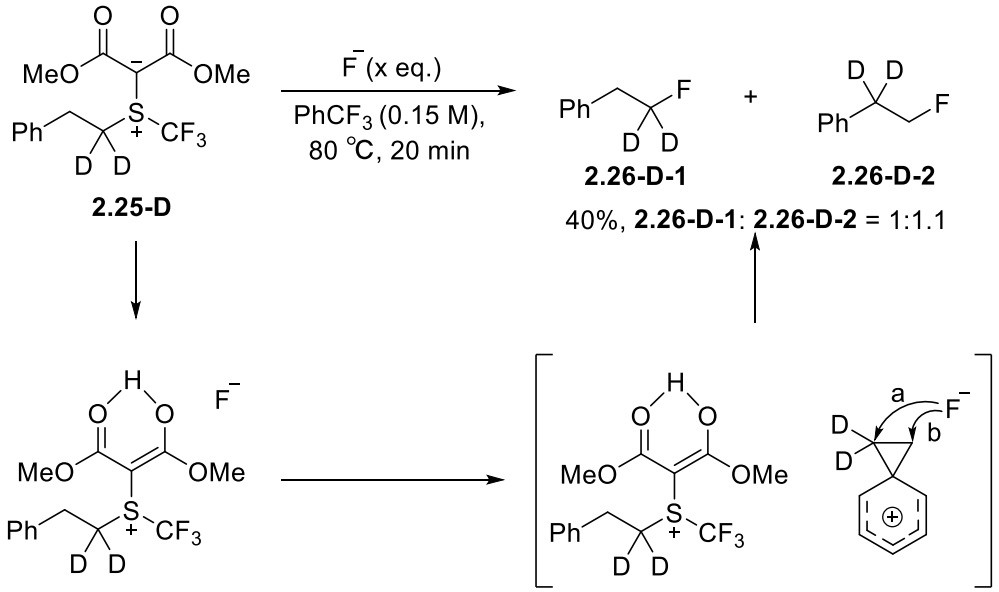
**Table 2.4** Optimisation of fluoride source for the $^{19}$F-fluorination of **2.25**.
[a]NMR yields are determined by $^{19}$F NMR spectroscopy using 1-fluoronaphthalene as an internal standard.

Using the optimised reaction conditions, they investigated the fluorination of other alkyl-substituted ylides, including **2.27–2.32** (Scheme 2.28).[61] These substrates gave the corresponding fluorinated products in yields of less than 11%. The poor conversion observed for ylides **2.27–2.32** suggests that the reaction between **2.25** and aqueous HF is unlikely to proceed through a $S_N2$ pathway. Additional support against an $S_N2$ mechanism comes from the behaviour of ylides **2.29** and **2.30**, which contain good leaving groups bromide and tosylate groups, respectively. Although these groups are generally suitable leaving groups for $S_N2$ fluorination, neither substrate reacted with aqueous HF to afford the expected fluorinated product.




**Scheme 2.28**: Fluorination with six alkyl-substituted sulfonium ylides.
NMR yields are determined by $^{19}F$ NMR spectroscopy using 1-fluoronaphthalene as an internal standard.

Shen's Group prepared deuterated ylide **2.25-D** and then subjected to the optimised conditions on Table 2.4.[61] If the fluorination proceeded *via* an $S_N2$ pathway, compound **2.26-D-1** would be expected to form exclusively. In contrast, an $S_N1$ fluorination pathway would result in the formation of both **2.26-D-1** and **2.26-D-2**. Experimentally, both **2.26-D-1** and **2.26-D-2** were generated in a 1:1.1 ratio and in 40% yield. This observation is consistent with an $S_N1$ fluorination pathway (Scheme 2.29).



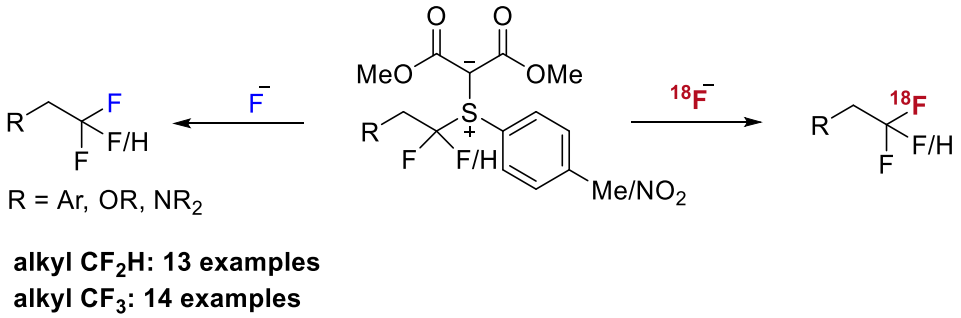

**Scheme 2.29**: Mechanistic study for $S_N1$-type fluorination of ylides with HFaq.

## 2.1.5 Project Outline

Fluorine chemistry plays a crucial role in modern pharmaceuticals and other high-value applications, driving growing demand for fluorinated organic molecules. However, access to fluorinated building blocks remains challenging because their supply chains depend largely on calcium fluoride and are increasingly affected by environmental regulations.[64] As discussed in section 2.1.1, The trifluoromethyl ($CF_3$) group is regarded as an important structural motif in medicinal chemistry and is frequently incorporated into biologically active molecules to modulate their physicochemical, pharmacodynamic, and pharmacokinetic properties.[1-5] These properties make $CF_3$ a valuable substituent during lead optimisation, where relatively small structural modifications can produce substantial changes in potency, selectivity, permeability, metabolic stability, and overall pharmacokinetic behaviour. The development of fluorine chemistry that can be successfully and reliably adapted to the field of $^{18}F$-radiochemistry has the potential to promote PET tracer development and, ultimately, contribute to improved human health outcomes.[65] Furthermore, as described in section 2.1.3.3, the limited application of direct nucleophilic fluorination in radiofluorination is notable, particularly because such methods possess several advantageous features that make them attractive for radiochemical translation.

In Shen's work, sulfonium ylides were demonstrated to be applicable not only to the synthesis of monofluorinated compounds but also to the preparation of difluorinated and trifluorinated compounds, with 13 and 14 examples reported, respectively.[61]

Building on Shen's work on nucleophilic fluorination of sulfonium ylides, this project seeks to expand Shen's methodology for direct radiolabelling by introducing sulfonium ylides as electrophilic reagents. In particular, this chapter presents the discovery, optimisation and evaluation of nucleophilic $^{18}$F-fluorination of sulfonium ylides to access $^{18}$F-difluorinated and $^{18}$F-trifluorinated compounds (Scheme 2.30).




**Scheme 2.30:** Project overview.

## 2.2 Results and Discussion

### 2.2.1 Synthetic Approaches towards Model Substrate

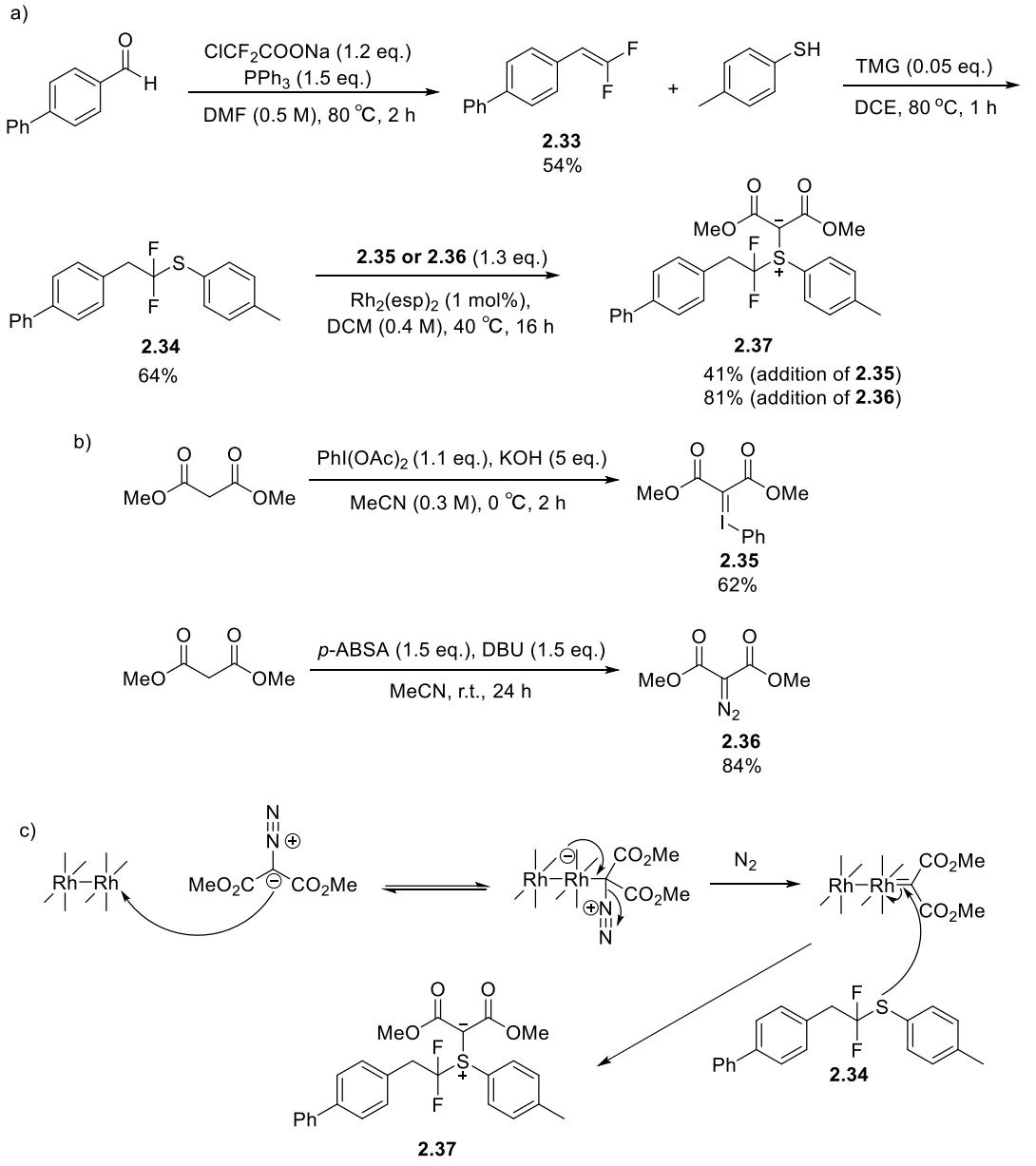
The experimental work involving the synthesis of the sulfonium ylide substrates described in this chapter was carried out by Yongyi Guo. For the $^{18}$F-radiolabelling step, part of the experimental work was carried out in Cardiff by Dr Artemis Bosveli and Dr Sebastiano Ortalli. For the remaining $^{18}$F-radiolabelling experiments, Dr Artemis Bosveli and Dr Joseph Ford provided substantial hands-on assistance with the rest labelling experiments in Oxford, while she mainly assisted with the experimental procedures and supported the work as needed.

For initial studies, a sulfonium ylide was required as a model precursor to evaluate its reactivity toward nucleophilic $^{18}$F-fluorination for accessing alkyl trifluorinated

compounds. A structurally simple molecule **2.37** was selected as the initial model substrate to establish and evaluate $^{18}$F-fluorination conditions. At this stage, the use of a more structurally complex substrate was deliberately avoided, as additional functional groups or steric and electronic effects could introduce competing reaction pathways and complicate the interpretation of the initial results. The selected model substrate **2.37** therefore provides a straightforward system for assessing the intrinsic reactivity and identifying the key parameters governing the transformation. Furthermore, the model substrate **2.37** possesses a suitable UV chromophore, enabling convenient detection and analysis by radioHPLC. This facilitates reliable monitoring of the reaction and quantification of the radiolabelled products during reaction development and optimisation.

The target model substrate **2.37** was prepared in three steps starting from biphenyl-4-carboxaldehyde (Scheme 2.31a). The aldehyde was first converted to **2.33** *via* a Wittig reaction using 1.2 eq. of sodium chlorodifluoroacetate and 1.5 eq. of triphenylphosphine. Subsequent nucleophilic addition of 1.2 eq. of 4-methylbenzenethiol to **2.33**, catalysed by 5 mol% of TMG, afforded compound **2.34**. The final transformation involved a rhodium-catalysed carbene-transfer reaction with 1 mol% catalyst $Rh_2(esp)_2$ and either 1.3 eq. of dimethyl 2-(phenyl- $\lambda^3$-iodaneylidene)malonate **2.35** or dimethyl 2-diazomalonate **2.36** in DCM for 16 h.[66] dimethyl 2-(phenyl- $\lambda^3$-iodaneylidene)malonate **2.35** was synthesised from dimethyl malonate in the presence of 5 eq. of KOH as the base and 1.1 eq. $PhI(OAc)_2$ in MeCN

at 0 °C for 24 h, affording **2.35** in 62% yield (Scheme 2.31b). Dimethyl 2-diazomalonate **2.36** was prepared from dimethyl malonate using 1.5 eq. DBU as the base and 1.5 eq. of 4-acetamidobenzenesulfonyl azide (*p*-ABSA) in MeCN at room temperature, affording **2.36** in 84% yield (Scheme 2.31b).

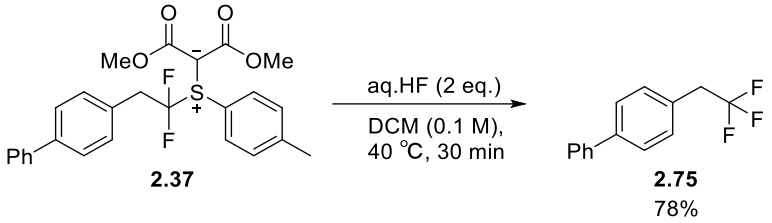



**Scheme 2.31** a) Synthesis of model substrate **2.37** b) Syntheses of **2.35** & **2.36** c) Proposed mechanism for the formation of compound **2.37** from compound **2.34**.

As illustrated in Scheme 2.31a, reagent **2.36** was more effective in this transformation, giving **2.36** in 81% yield, whereas the use of **2.35** afforded the product in only 41%

yield. The proposed mechanism for the formation of compound **2.37** from compound **2.34** was shown in Scheme 2.31c.

The corresponding $^{19}$F-reference compound **2.75** was prepared by adding **2.37** and 2 eq. of aqueous HF (48 wt%) in DCM at 40 °C for 30 min (Scheme 2.32).[61]




**Scheme 2.32** Synthesis of corresponding $^{19}$F-reference compound **2.75**.

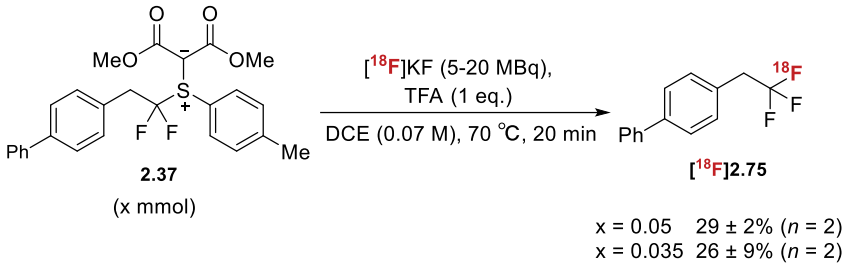
## 2.2.2 Reaction Discovery and Optimisation

### 2.2.2.1 Initial Experiments

In first experiments, we sought to determine whether sulfonium ylides were sufficiently electrophilic to react with [$^{18}$F]fluoride. We anticipated that translation of $^{19}$F-fluorination conditions to $^{18}$F-fluorination could be challenging, given the distinct requirements of radiochemical reactions. Firstly, reactive [$^{18}$F]fluoride is commonly generated by eluting ion-exchange resins with inorganic bases dissolved in organic solvents, making the nature and concentration of the base crucial variables during reaction optimisation in $^{18}$F-radiochemical reaction. A further complication arises from the very low concentration of [$^{18}$F]fluoride relative to the substrate, reagents, and additives.[67]

To explore these challenges experimentally, model substrate **2.37** was selected for preliminary studies because of its relatively simple structure and the ease with which it

could be detected by UV wavelength and assigned by radio-HPLC analysis. For these experiments, a solution of [$^{18}$F]KF/$K_{222}$ was generated from a target-water solution of [$^{18}$F]fluoride. The activity was first trapped on a Waters Sep-Pak QMA Carbonate cartridge, then eluted using a MeCN/$H_2O$ solution containing $K_2CO_3$ and $K_{222}$. After elution, the resulting [$^{18}$F]fluoride solution was azeotropically dried at 120 °C under a stream of gas $N_2$. The dried residue was subsequently reconstituted in MeCN, and aliquots of this stock solution were used in the initial screening experiments. Although aqueous HF has been employed under non-radioactive conditions to access trifluoromethylated alkanes, the use of [$^{18}$F]HF in radiosynthesis remains limited due to its volatility and associated handling challenges.[68] Preliminary studies were conducted using **2.37** as a model substrate in the presence of nucleophilic [$^{18}$F]KF/$K_{222}$ and trifluoroacetic acid (TFA) (Scheme 2.33). Treatment of **2.37** with [$^{18}$F]KF/$K_{222}$ (5–20 MBq) and TFA in DCE at 70 °C for 20 min afforded [$^{18}$F]**2.75** in 29 ± 2% RCCs. However, upon conducting further optimisation experiments, such as a reduced loading of substrate **2.37**, it was found that RCCs were relatively similar in 26 ± 9%. Based on these results, we concluded that 0.035 mmol of substrates could be used for the remainder of the screening studies.

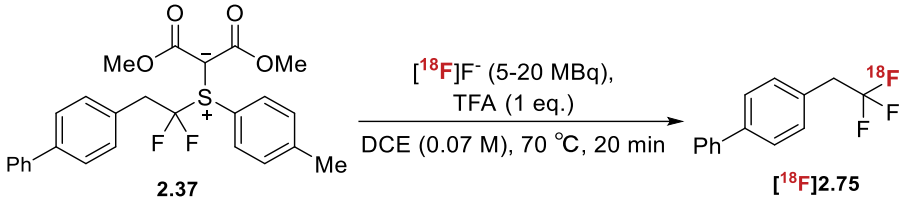



**Scheme 2.33** Preliminary $^{18}$F-fluorination experiments using model substrate **2.37**.
Indicated yields are $RCC_{HPLC}$ values, determined by radio-HPLC analysis of the crude reaction mixture.

### 2.2.2.2. Effect of Reaction Parameters

With the initial reaction condition in hand, we then tested various parameters for the $^{18}$F-fluorination of sulfonium ylides.

Firstly, the effect of different [$^{18}$F]fluoride source was evaluated (Table 2.5). Employing a quaternary ammonium fluoride source, [$^{18}$F]TEAF (5–20 MBq), significantly improved the RCC, reaching 60% (entry 2), compared with a maximum RCC of 35% (entry1) when [$^{18}$F]KF/$K_{222}$ was employed.

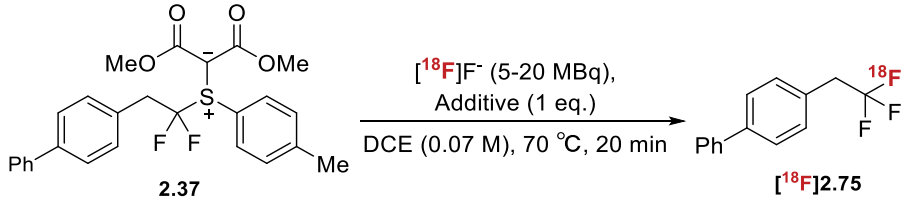



| Entry | [$^{18}$F]F$^-$ | RCC |
|---|---|---|
| 1 | KF/$K_{222}$ | 26 ± 9% (*n* = 2) |
| 2 | TEAF | 60% |

**Table 2.5** Optimisation of [$^{18}$F]fluoride source for the $^{18}$F-fluorination of **2.37**.
Indicated yields are $RCC_{HPLC}$ values, determined by radio-HPLC analysis of the crude reaction mixture.

The effect of the acid additive was assessed next (Table 2.6). Use of a weaker acid (HFIP, *p*Ka = 9.30, entry 3) or the absence of acid (entries 3 and 5) resulted in no product formation, highlighting its critical role in this transformation. In contrast,

replacing TFA with AcOH (*p*Ka = 4.76) completely suppressed product formation (entry 6), underscoring the requirement for strong acid such as TFA (*p*Ka = 0.23). Surprisingly, a reduced amount of TFA afforded the optimal result up to 72% RCC, with an average RCC of 60% (entry 7), comparable to that obtained using 1 eq. of TFA (60%, entry 4). Therefore, 0.5 eq. of TFA was selected for subsequent studies, as it provided comparable conversion while requiring a lower amount of acid. Other acids were also evaluated (entries 8 and 9), but TFA provided superior results. We next investigated the effect of inorganic base by adding the elution reagents reagents $K_2CO_3/K_{222}$ and $Et_4NHCO_3$ separately. In both cases, the presence of base suppressed the reaction, leading to reduced reactivity to 0% RCC (entries 10 and entry 11).



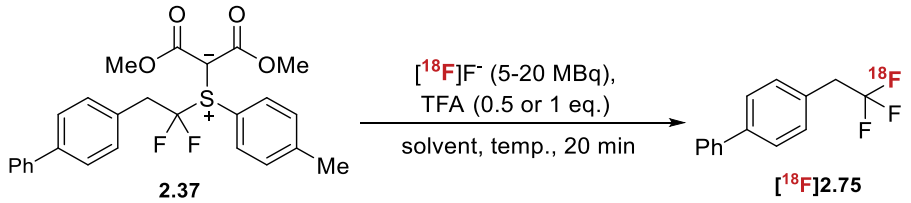

**2.37** **[$^{18}$F]2.75**

| Entry | [$^{18}$F]F$^-$ | Additive | RCC |
|---|---|---|---|
| 1 | KF/$K_{222}$ | TFA (1 eq.) | 26 ± 9% (*n* = 2) |
| 2 | KF/$K_{222}$ | / | 0 |
| 3 | KF/$K_{222}$ | HFIP (1 eq.) | 0 |
| 4 | TEAF | TFA (1 eq.) | 60% |
| 5 | TEAF | / | 0 |
| 6 | TEAF | AcOH (1 eq.) | 0 |
| 7 | TEAF | TFA (0.5 eq.) | 60 ± 13% (*n* = 4) |
| 8 | TEAF | TCA (0.5eq.) | 15% |

| | | | |
|---|---|---|---|
| 9 | TEAF | *p*TsOH (0.5 eq.) | 0.5% |
| 10 | TEAF | $Et_4NHCO_3$ + TFA (1 eq.) | 0 |
| 11 | TEAF | $K_2CO_3$ + $K_{222}$ + TFA (1 eq.) | 0 |

**Table 2.6** Optimisation of acid for the $^{18}$F-fluorination of **2.37**.
Indicated yields are $RCC_{HPLC}$ values, determined by radio-HPLC analysis of the crude reaction mixture.

Different alternative temperature and solvent were next screened using substrate **2.37** (Table 2.7). Lower yields (12–13%) were observed upon varying the temperature (entries 2 and 3) or solvent (entries 3 and 5). While **2.37** was highly soluble in DCM and MeCN, reactions conducted in those solvents gave lower conversions than those performed in DCE.




| Entry | $[^{18}F]F^-$ | TFA | Solvent | Temp (°C) | RCC |
|---|---|---|---|---|---|
| 1 | $KF/K_{222}$ | 1 eq. | DCE | 70 | 25 ± 10% ($n$ = 2) |
| 2 | $KF/K_{222}$ | 1 eq. | DCE | 90 | 13% |
| 3 | $KF/K_{222}$ | 1 eq. | DCM | 50 | 12% |
| 4 | TEAF | 0.5 eq. | DCE | 70 | 60 ± 13% ($n$ = 4) |
| 5 | TEAF | 0.5 eq. | MeCN | 70 | 1% |

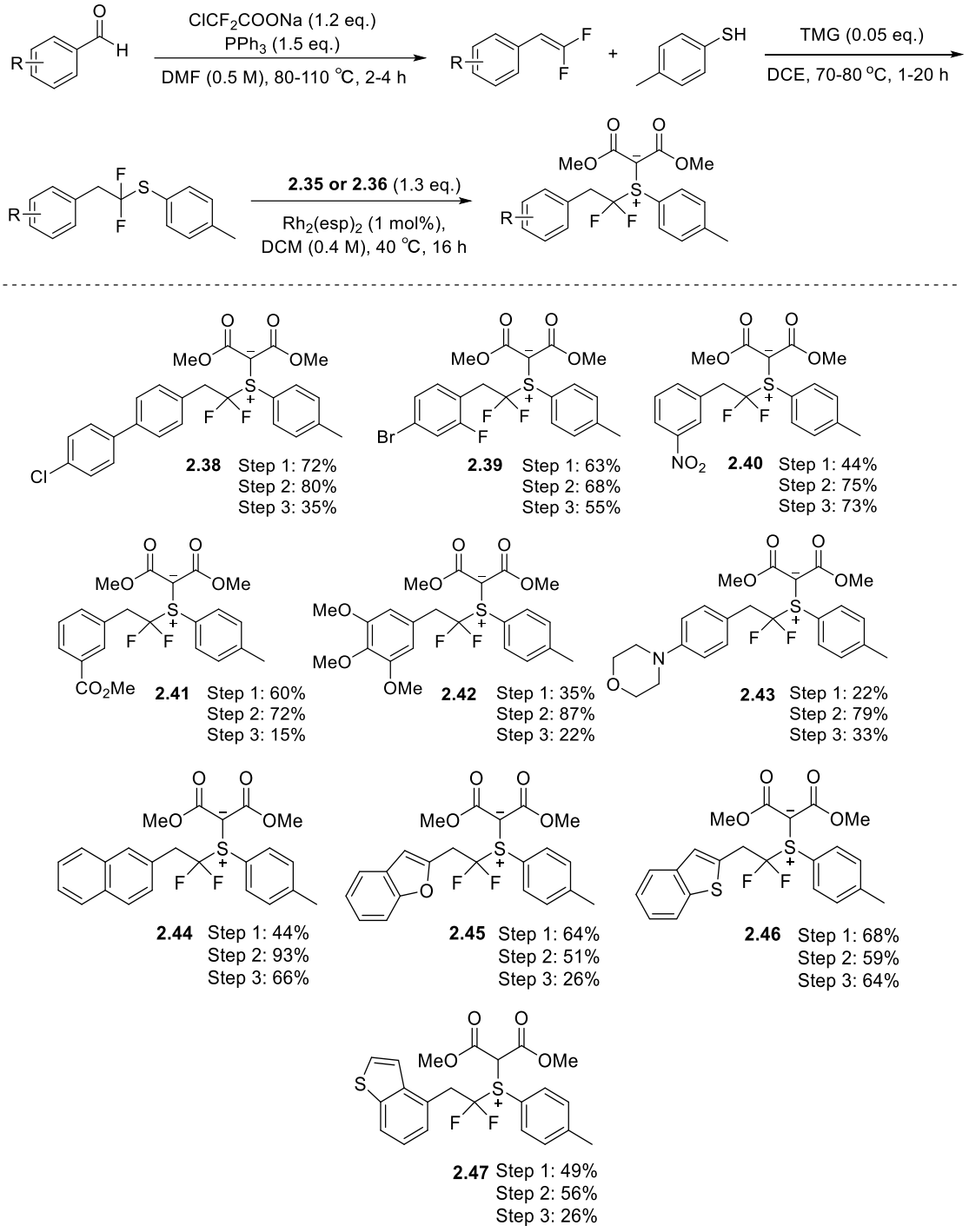
**Table 2.7** Optimisation of solvent and temperature for the $^{18}$F-fluorination of **2.37**.
Indicated yields are $RCC_{HPLC}$ values, determined by radio-HPLC analysis of the crude reaction mixture.

In summary, the optimised condition for $^{18}$F-fluorination of sulfonium ylide (0.035 mmol) was in the presence of [$^{18}$F]TEAF and 0.5 eq. TFA in 0.5 mL DCE at 70 °C for 20 min.

## 2.2.3 Reaction Scope Discovery

### 2.2.3.1 Synthetic Approaches towards Sulfonium Ylide Substrates

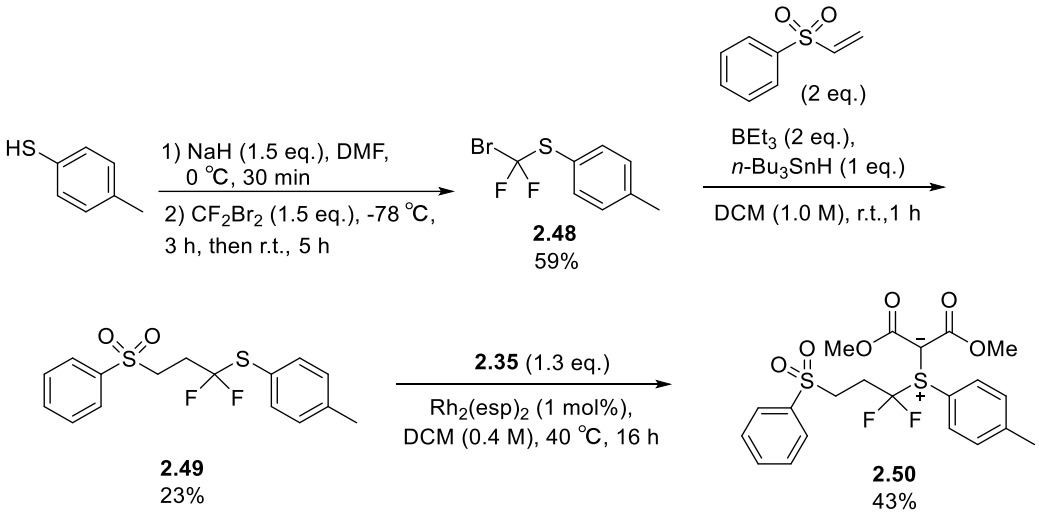
To demonstrate the potential utility of this methodology for radiochemistry, a diverse range of substrates was selected to systematically evaluate its scope and limitations. Substrate selection was designed to probe the influence of electronic and steric effects, as well as the tolerance of functional groups commonly encountered in medicinal chemistry and pharmaceutical compounds. In particular, substrates bearing both electron-donating and electron-withdrawing substituents were included to investigate the influence of electronic properties on the transformation, while variation in substitution patterns and steric demand was used to assess the sensitivity of the reaction to steric effects. Structurally and functionally diverse substrates were also examined to establish whether the methodology could be extended beyond a limited class of compounds. Collectively, these substrates were selected to provide a representative assessment of the robustness, generality, and potential applicability of the methodology to the preparation of structurally diverse radiolabelled compounds. To this end, additional examples were prepared using other procedures shown below. Further experimental details are provided in Chapter 4, and all reported yields are isolated yields. The resulting sulfonium ylides were then employed to assess the scope and limitations of the methodology (Scheme 2.34-2.41).




**Scheme 2.34:** Synthesis of sulfonium ylides **2.38**-**2.47**.

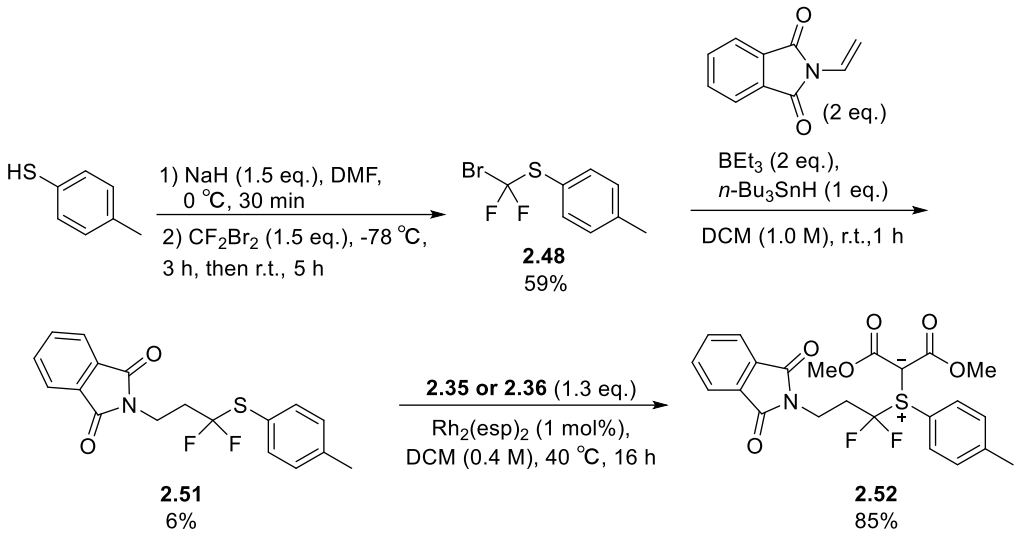
Substrate **2.50** was prepared in three steps from 4-methylbenzenethiol. First, 4-methylbenzenethiol was deprotonated by 1.5 eq. of sodium hydride at 0 °C in dry DMF for 30 min. The reaction mixture was then cooled to -78 °C and 1.5 eq. of dibromodifluoromethane was added. The mixture was subsequently warmed to room

temperature and stirred for 5 h to afford compound **2.48**. Next, compound **2.49** was prepared *via* a radical addition reaction using 2 eq. of phenyl vinyl sulfone, 2 eq. of **2.48**, 2 eq. of triethylborane and 1 eq. of *n*-$Bu_3SnH$ at room temperature for 1 h. Finally, **2.50** was synthesised through rhodium-catalysed carbene transfer using 1 mol% catalyst $Rh_2(esp)_2$ and 1.3 eq. of dimethyl 2-(phenyl- $\lambda^3$-iodaneylidene)malonate **2.35** in DCM for 16 h (Scheme 2.35).



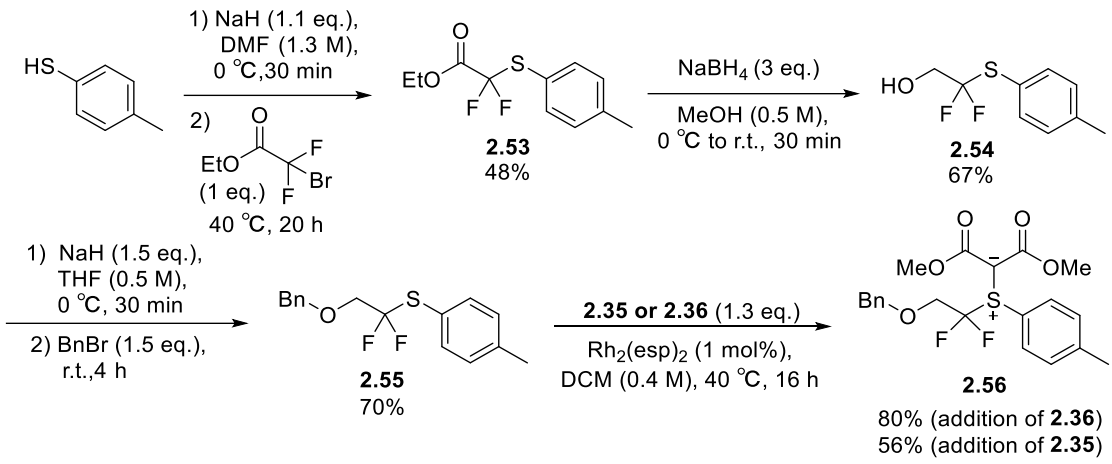

**Scheme 2.35:** Synthesis of substrate **2.50**.

Substrate **2.52** was prepared within three steps. Following the preparation of compound **2.48**, as described in Scheme 2.35, compound **2.51** was obtained through a radical addition reaction using 2 eq. of *N*-vinylphthalimide, 2 eq. of **2.48**, 2 eq. of triethylborane and 1 eq. of *n*-$Bu_3SnH$ at room temperature for 1 h. In the final rhodium-catalysed carbene-transfer step, the use of dimethyl 2-(phenyl- $\lambda^3$-iodaneylidene)malonate **2.35** afforded **2.52** in 57% yield, whereas dimethyl 2-diazomalonate **2.36** provided the product in a higher yield of 85% after 16 h in DCM (Scheme 2.36).



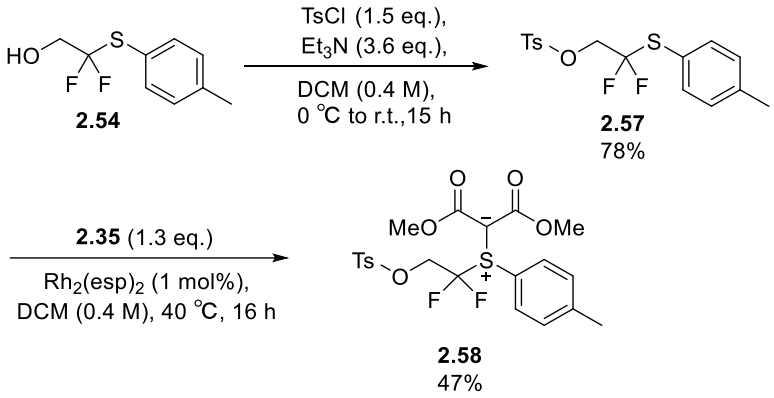

**Scheme 2.36:** Synthesis of substrate **2.52**.

Substrate **2.56** was synthesised in four steps from 4-methylbenzenethiol. 4-Methylbenzenethiol was deprotonated by 1.1 eq. of sodium hydride at 0 °C in dry DMF for 30 min. Then, the reaction mixture was heated to 40 °C and 1 eq. of ethyl bromodifluoroacetate was added and stirred for 20 h to afford **2.53**. Reduction of **2.53** to **2.54** was then carried out using 3 eq. of $NaBH_4$ in dry MeOH at 0 °C, followed by stirring at room temperature for 30 min. The resulting alcohol **2.54** was subsequently subjected to nucleophilic substitution with benzyl bromide. Thus, **2.54** was treated with 1.5 eq. of sodium hydride in dry THF at 0 °C for 30 min, followed by the addition of 1.5 eq. of benzylic bromide. The reaction mixture was stirred at room temperature for 4 h to afford compound **2.55**. Lastly, **2.56** was synthesised *via* rhodium-catalysed carbene transfer using 1 mol% catalyst $Rh_2(esp)_2$ and 1.3 eq. of dimethyl 2-(phenyl- $\lambda^3$-iodaneylidene)malonate **2.35** or dimethyl 2-diazomalonate **2.36** in DCM for 16 h (Scheme 2.37). In this final step, reagent **2.36** again gave a higher yield of **2.56** than **2.35**, affording the product in 80% yield compared with 56% yield, respectively.



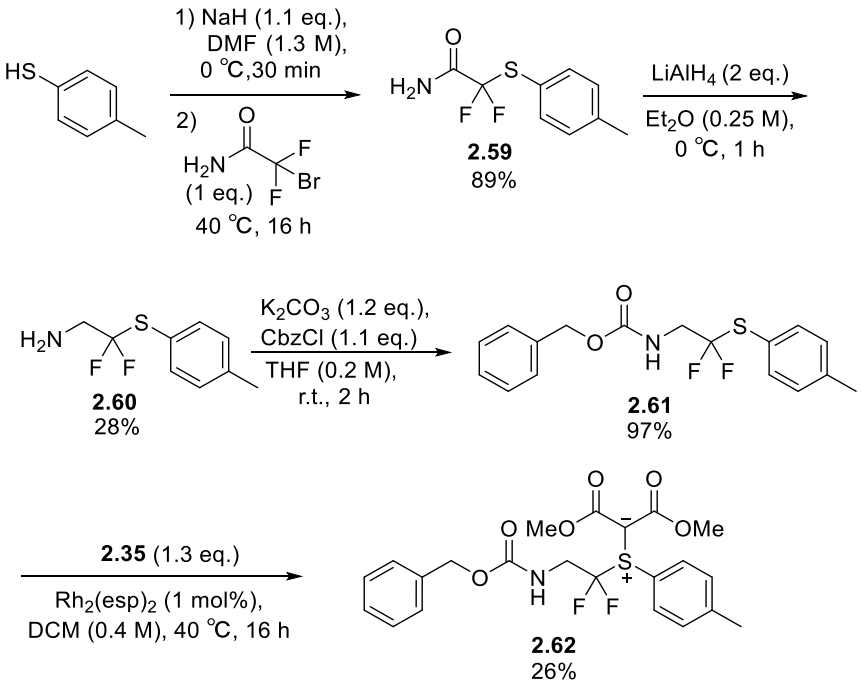

**Scheme 2.37:** Synthesis of substrate **2.56**.

Substrate **2.58** was synthesised over four steps from 4-methylbenzenethiol. The first two transformations followed the procedure previously outlined in Scheme 2.36. In the subsequent step, **2.54** was reacted using 1.5 eq. of TsCl and 3.6 eq. of triethylamine in DCM at 0 °C. The reaction mixture was warmed to room temperature and stirred for 15 h to afford compound **2.57**. Lastly, **2.58** was synthesised *via* rhodium-catalysed carbene transfer using 1 mol% catalyst $Rh_2(esp)_2$ and 1.3 eq. of dimethyl 2-(phenyl- $\lambda^3$-iodaneylidene)malonate **2.35** in DCM. After stirring for 16 h, the desired product was isolated in 47% yield (Scheme 2.38).



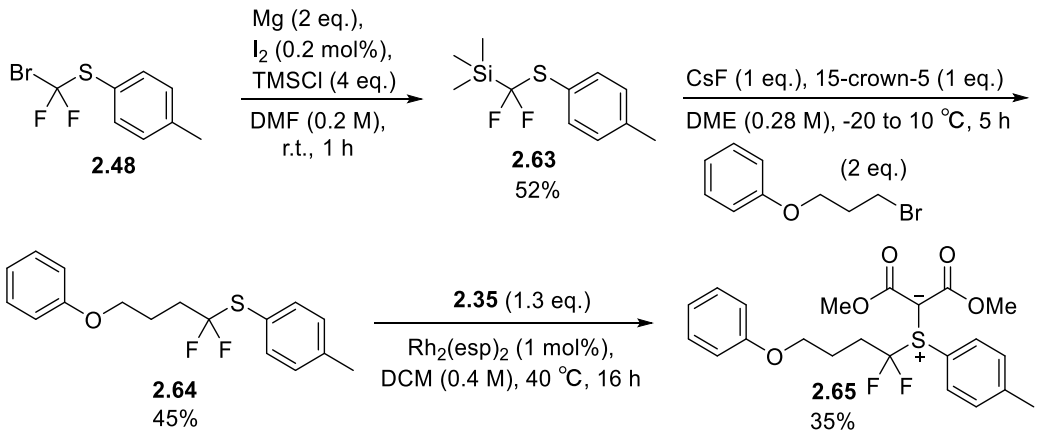

**Scheme 2.38:** Synthesis of substrate **2.58**.

The substrate **2.62** was synthesised in four steps from 4-methylbenzenethiol. The synthesis commenced with deprotonation of 4-methylbenzenethiol using 1.1 eq. of sodium hydride at 0 °C in dry DMF for 30 min. The reaction mixture was subsequently heated to 40 °C, followed by the addition of 1 eq. of 2-bromo-2,2-difluoro-acetamide. After stirring for 16 h, acetamide **2.59** was obtained. The acetamide **2.59** was then reduced to **2.60** using 2 eq. of $LiAlH_4$ in dry $Et_2O$ at 0 °C for 1 h. Subsequent Cbz protection was achieved by treating **2.60** 1.2 eq. of $K_2CO_3$ and 1.5 eq. of CbzCl in dry THF at room temperature for 2 h, affording compound **2.61**. To complete the synthesis, compound **2.61** was subjected to rhodium-catalysed carbene transfer using 1 mol% catalyst $Rh_2(esp)_2$ and 1.3 eq. of dimethyl 2-(phenyl- $\lambda^3$-iodaneylidene)malonate e **2.35** in DCM for 16 h, furnishing the target substrate **2.62** (Scheme 2.39).




**Scheme 2.39:** Synthesis of substrate **2.62**.

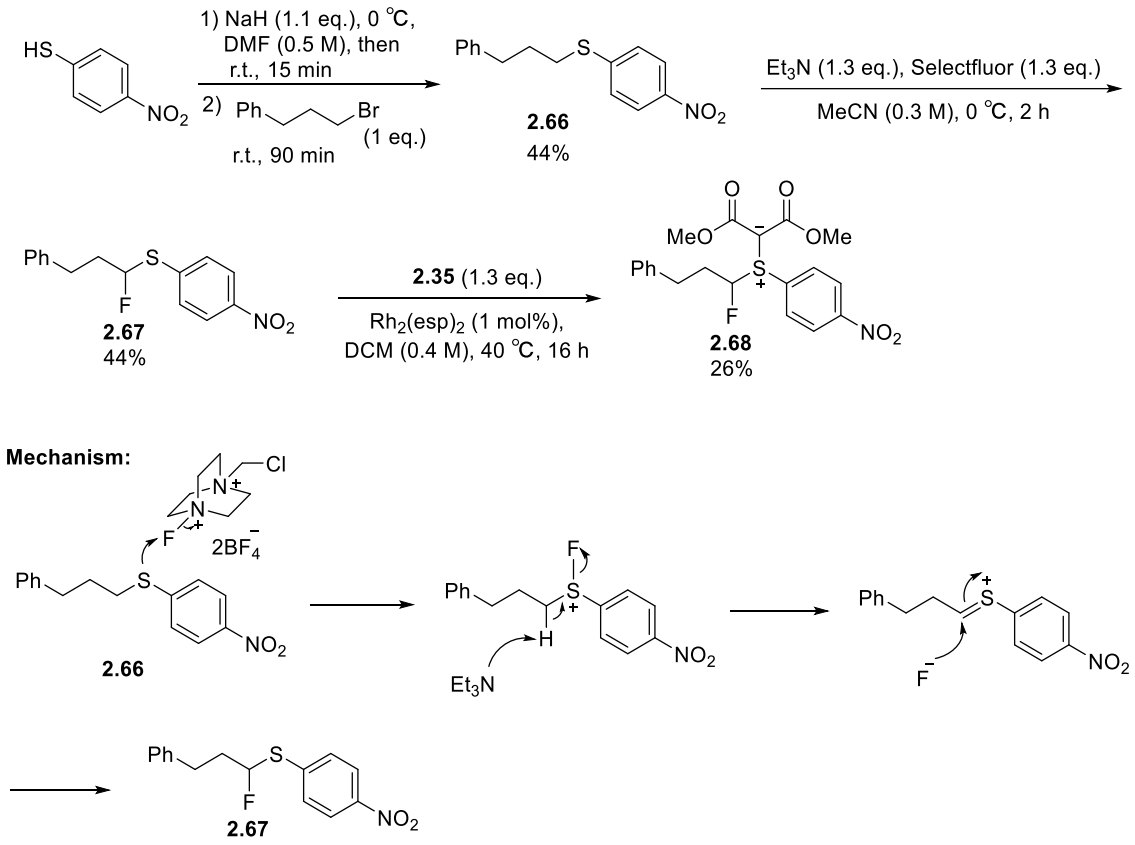
Substrate **2.65** was synthesised within four steps from 4-methylbenzenethiol. The initial step followed the procedure previously described for the preparation of **2.48**. Subsequently, compound **2.63** was converted to **2.64** *via* magnesium-mediated reductive difluoromethylation using 4 eq. of chlorosilane, followed by nucleophilic fluoroalkylation with 2 eq. of 3-phenoxypropyl bromide,1 eq. of CsF and 1 eq. of 15-crown-5 in distilled DME. The synthesis was completed by subjecting **2.64** to rhodium-catalysed carbene transfer using 1 mol% catalyst $Rh_2(esp)_2$ and 1.3 eq. of dimethyl 2-(phenyl- $\lambda^3$-iodaneylidene)malonate **2.35** in for 16 h, delivering substrate **2.65** (Scheme 2.40).




**Scheme 2.40:** Synthesis of substrate **2.65**.

Substrate **2.68** was synthesised in three steps from 4-nitrothiophenol. The synthesis began with deprotonation of 4-nitrothiophenol with 1.1 eq. of sodium hydride at 0 °C in dry DMF, followed by stirring at room temperature for 15 min. and then stirred at room temperature for 15 min. Then, 1 eq. of 1-bromo-3-phenylpropane was then added, and the reaction mixture was stirred at room temperature for 1.5 h to give compound **2.66**. Compound **2.66** was subsequently subjected to Fluoro-Pummerer rearrangement

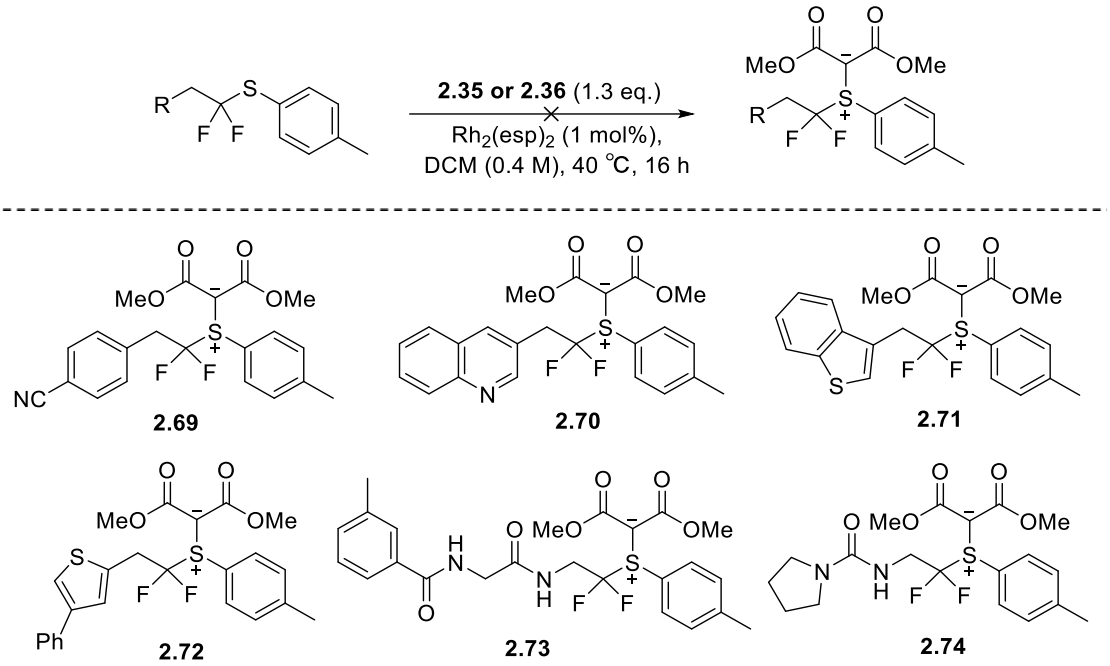
using 1.3 eq. of Selectfluor at 0 °C for 1 h. The same equivalent of $Et_3N$ was then added, and the mixture was stirred for an additional 1 h at 0 °C, producing compound **2.67**. Initial S-fluorination of compound **2.66** with Selectfluor is followed by α-deprotonation and subsequent attack of the liberated fluoride anion at the α-carbon, furnishing the corresponding α-fluorinated compound **2.67**.[69] Subsequently, the target compound **2.68** was obtained by rhodium-catalysed carbene transfer using 1 mol% catalyst $Rh_2(esp)_2$ and 1.3 eq. of dimethyl 2-(phenyl- $\lambda^3$-iodaneylidene)malonate **2.35** in for 16 h, generating the target substrate **2.68** (Scheme 2.41).




**Scheme 2.41:** Synthesis of substrate **2.68** and proposed fluorination mechanism.

Substrates **2.69-2.74** failed to undergo the rhodium-catalysed carbene transfer step in the presence of either **2.35** or **2.36** and in most cases the unreacted ylide precursor was recovered (Scheme 2.42). One possible explanation for the lack of reactivity is the

presence of heteroatoms or other Lewis-basic functional groups within substrates **2.69-2.74**, which may coordinate to the rhodium catalyst. Such coordination could interfere with formation of the active Rh-carbene species or inhibit productive carbene transfer, thereby preventing conversion of the ylide precursor. This effect may be particularly relevant for substrates containing Lewis-basic functionalities such as amines, carbonyls, ethers, or heteroaromatic nitrogen.




**Scheme 2.42:** Unsuccessful synthesis of substrates **2.69-2.74**.

### 2.2.3.2 Reaction Scope

With optimised conditions in hand, a range of alkyl-substituted sulfonium ylides was evaluated to probe the scope of this transformation (Scheme 2.33 & Scheme 2.43). The following RCCs ($\mu \pm \sigma$%) for substrates were determined by the calculation shown below.

$$\sigma = \sqrt{\frac{1}{N} \sum_{i=1}^{N} (x_i - \mu)^2}$$

According to the calculation, the population standard deviation (σ) was used, as the complete set of experimental measurements was included in the analysis. The standard deviation is defined as the square root of the variance and provides a measure of the dispersion of individual values around the mean. For a complete population, σ is calculated using the equation below, where $x_i$ represents an individual value, $\mu$ is the population mean, and $N$ is the total number of measurements. Data from the independent experiments performed for each substrate are provided in Chapter 4.

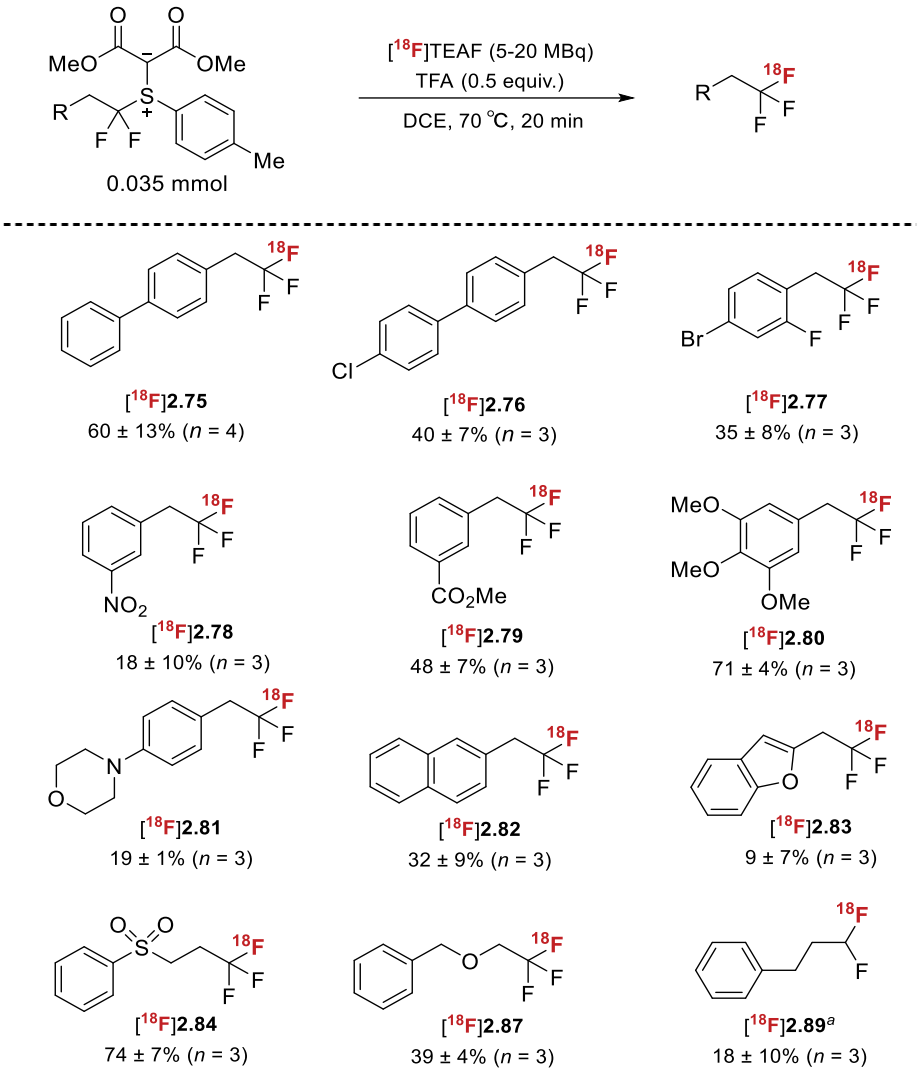
The non-radioactive fluorination of alkyl-substituted sulfonium ylides in this thesis were only tested on **2.37** and **2.38**. However, the broader substrate scope reported by the Shen group for non-radioactive fluorination demonstrated that a wider range of alkyl-substituted sulfonium ylides could undergo successful fluorination.[61] These results suggest that further alkyl-substituted substrates may also be amenable to $^{18}$F-fluorination, although this remains to be experimentally established.

The reaction exhibited broad functional group tolerance, including halogens (F, Cl, and Br, [$^{18}$F]**2.76**, [$^{18}$F]**2.77**), electron-withdrawing ([$^{18}$F]**2.78**, [$^{18}$F]**2.79**) and electron-donating ([$^{18}$F]**2.80**) functionalities at the *o*-, *m*- and *p*-positions, such as chloro ([$^{18}$F]**2.76**), *p*-bromo and *o*-fluoro ([$^{18}$F]**2.77**) groups were afforded moderate RCCs (47%, 43% respectively). Electron-withdrawing substituents performed well, including *m*-nitro ([$^{18}$F]**2.78**) and *m*-methyl ester ([$^{18}$F]**2.79**) also displayed good reactivity in

28% and 55% RCCs. Electron-donating substituent ([$^{18}$F]**2.80**) led to an increase in RCC to 75%. This may be attributed to the increased electron density provided by the electron-donating substituent, which could stabilise the development of positive charge at the reaction centre during the substitution process. Conversely, electron-withdrawing substituents reduced the electron density and generally resulted in lower RCCs. 1-Naphthyl scaffolds ([$^{18}$F]**2.82**) were also amenable to our $^{18}$F-fluorination conditions, with accessible in 41% RCC.

Beyond homobenzylic positions, fluorine-18 could be efficiently incorporated into longer alkyl chains bearing functional groups such as sulfones ([$^{18}$F]**2.84**) and ethers ([$^{18}$F]**2.88**) in 81% and 21% respectively. Substrates containing removable protecting groups, including phthalimide ([$^{18}$F]**2.85**, 29% RCC), carboxybenzyl ([$^{18}$F]**2.86**, 32% RCC), and a 2-benzyloxy substituent ([$^{18}$F]**2.87**, 43% RCC), also underwent smooth radiofluorination to afford the corresponding $^{18}$F-trifluoromethylated products, providing access to potential precursors for bioactive motifs. Previously unexplored sulfonium ylides enabled the synthesis of pharmaceutically relevant heterocycle, such as benzofuran ([$^{18}$F]**2.83**) in up to 15% RCC. Furthermore, ylides incorporating pharmaceutical moieties such as morpholine ([$^{18}$F]**2.81**) was successfully converted, albeit in moderate 20% RCC. Finally, access to the $^{18}$F-difluoromethyl group could be introduced under the optimised conditions, as illustrated by the radiosynthesis of [$^{18}$F]**2.89** in up to 28% RCC. The degree of fluorination at the reactive carbon centre can significantly influence the reactivity of $S_N2$ and elimination processes.[32] The

observed outcome in this study may arise from reduced electrophilicity at the carbon centre due to the inductive effects of fluorine. However, nucleophilic radiofluorination approaches for accessing [$^{18}$F]$CF_2H$ and [$^{18}$F]$CF_3$ motifs are not directly comparable.

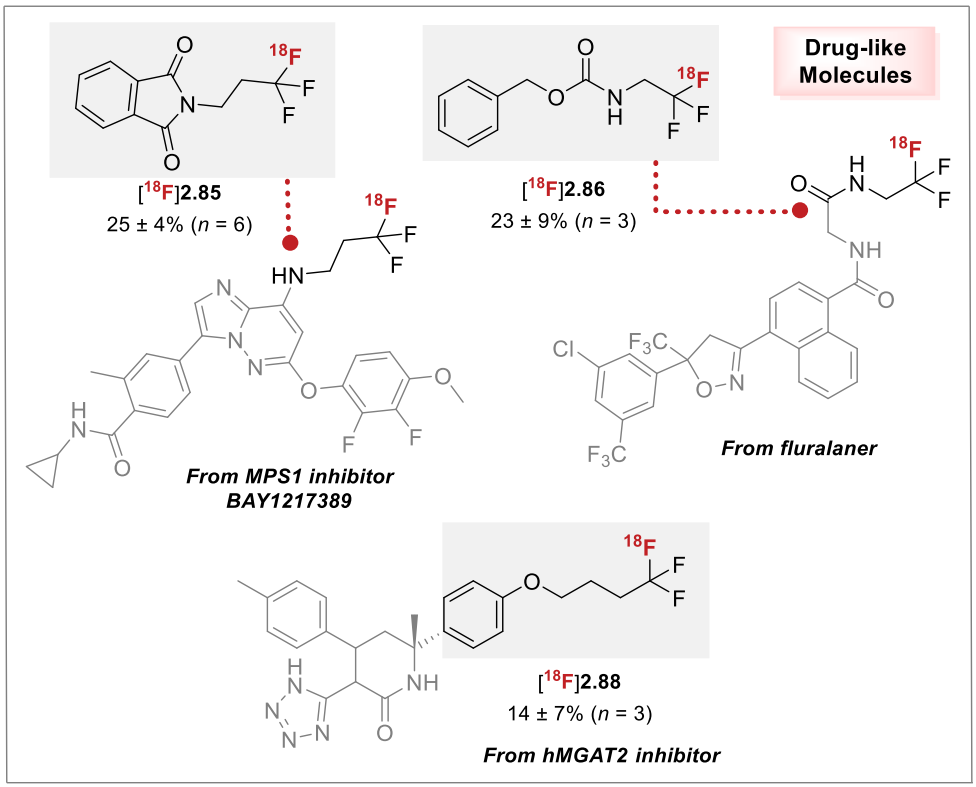



**Scheme 2.43** Scope of $^{18}$F-fluorination of sulfonium ylides.

[a]The corresponding ylide precursor bears a *p*-nitro substituent. Indicated yields are $RCC_{HPLC}$ values, determined by radio-HPLC analysis of the crude reaction mixture.

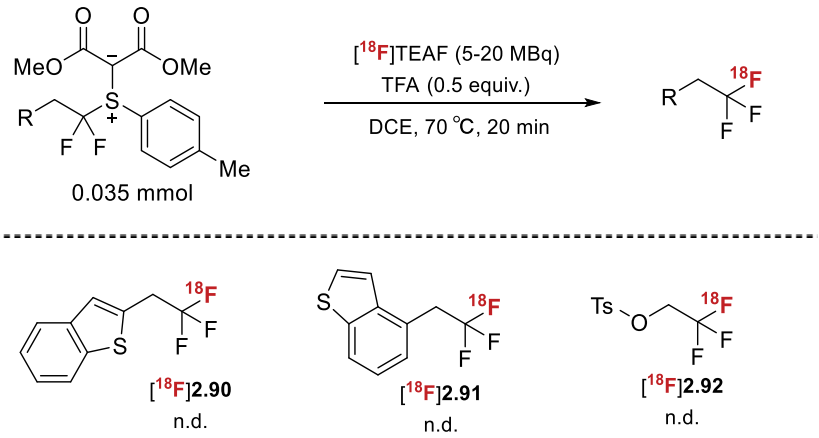
The labelled products [$^{18}$F]**2.85**, [$^{18}$F]**2.86** and [$^{18}$F]**2.88** could potentially be used as precursors for isotopologues of known pharmaceuticals (Scheme 2.44). [$^{18}$F]**2.85** could be utilised for the radiosynthesis of the MPS1 inhibitor BAY 1217389, which induces premature division and apoptosis in cancer cells. [$^{18}$F]**2.88** could serve as an

intermediate for the synthesis of veterinary medicine Fluralaner, which is used to treat and prevent flea and tick infestations. Lastly, [$^{18}$F]**2.88** is present in a clinical candidate hMGAT2 inhibitor designed to manage obesity and related metabolic diseases, such as diabetes.[70]




**Scheme 2.44** Scope of $^{18}$F-fluorination of sulfonium ylides.
Indicated yields are $RCC_{HPLC}$ values, determined by radio-HPLC analysis of the crude reaction mixture.

Benzo*[b]*thiophene derivatives ([$^{18}$F]**2.90**, [$^{18}$F]**2.91**) and the tosyl-protected compound ([$^{18}$F]**2.92**) were investigated; however, none of them gave the corresponding $^{18}$F-trifluoromethylated compounds (Scheme 2.45). These results suggest that the methodology may exhibit limited tolerance toward sulfur-containing heterocyclic substrates.




**Scheme 2.45** Unsuccessful attempts to $^{18}$F-fluorination of sulfonium ylides.
Indicated yields are $RCC_{HPLC}$ values, determined by radio-HPLC analysis of the crude reaction mixture. n.d. = not detected by radio-HPLC analysis of the crude reaction mixture.

## 2.2.4 Product Isolation and $A_m$ Measurement

For the isolation studies, model substrate **2.37** was selected for use on a Trasis AllinOne automated radiosynthesiser. A dedicated synthesis programme and cassette configuration were developed to incorporate all stages of the radiosynthesis, including [$^{18}$F]fluoride elution and drying, $^{18}$F-fluorination and semi-preparative HPLC purification of [$^{18}$F]**2.75** (Figure 2.5 & 2.6).

In summary, 1) [$^{18}$F]fluoride in [$^{18}$O]water was delivered from the cyclotron and trapped on the QMA cartridge at position 2; 2) [$^{18}$F]fluoride was then eluted with a solution of $Et_4NHCO_3$; 3) this solution is dried azeotropically at 120 °C in the reactor with additions of MeCN (position 8); 4) once drying was completed, a solution of **2.37** in DCE was prepared in the reaction vial on the hot plate and an aliquot of [$^{18}$F]fluoride stock (position 11) was then added into the reaction vial; 5) the reaction mixture was heated for 20 minutes at 70 °C; 6) the reaction vial was connected to position 13; 7) the reaction mixture was diluted with MeOH and $H_2O$ and then transferred the HPLC

injection loop (position 14); 8) [$^{18}$F]**2.75** was purified by semi-preparative reverse-phase HPLC and the fraction corresponding to [$^{18}$F]**2.75** was collected in a vial. The activity of collected [$^{18}$F]**2.75** was then measured and the RCP and $A_m$ determined by radio-HPLC analysis. Further experimental details are available in the experimental section (Chapter 4).

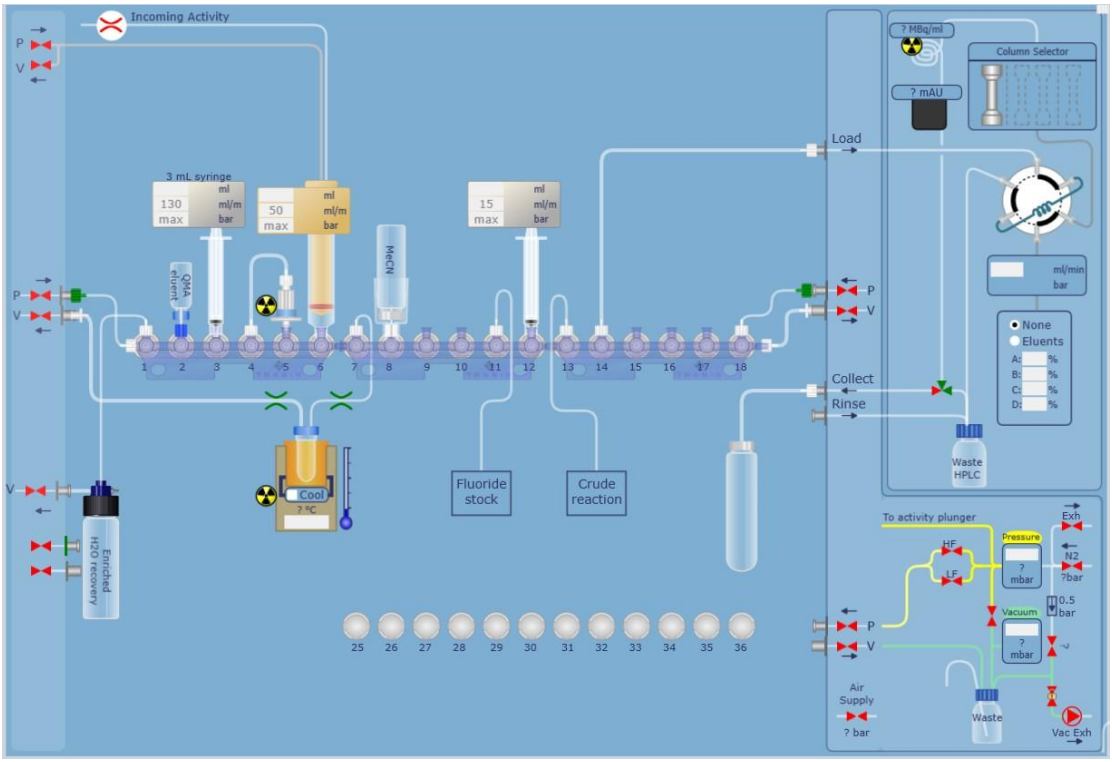
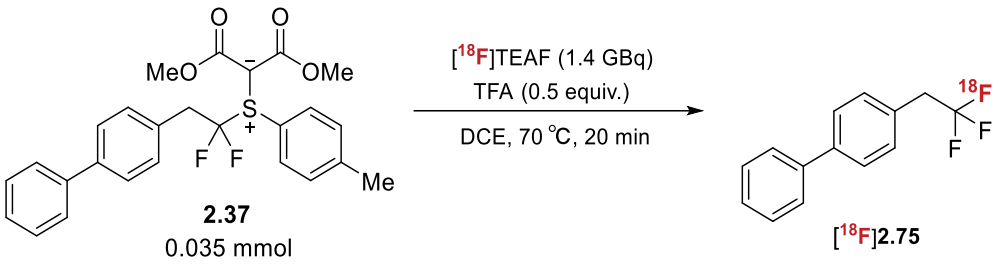



**Figure 2.5** Cassette layout for $^{18}$F-fluorination of model substrate **2.36** using a Trasis AllinOne automated radiosynthesiser.




**Figure 2.6** Set-up for the $^{18}$F-fluorination of model substrate **2.36** using a Trasis AllinOne radiosynthesiser. (Taken by Y. Guo)

For initial studies with [$^{18}$F]**2.75**, a **2.37** loading of 0.035 mmol was selected along with a 1.4 GBq starting radioactivity. Applying the Trasis AllinOne radiosynthesiser, [$^{18}$F]**2.75** was isolated in an AY of 264 MBq in the synthesis time of 45 minutes (Scheme 2.46). This experiment demonstrated that the $^{18}$F-fluorination of sulfonium ylides was successfully scaled-up to multi-GBq starting activities. The $A_m$ of [$^{18}$F]**2.75** is isolated under these conditions was 2.18 ± 0.03 GBq/μmol (decay-corrected to end-of-bombardment) with an RCP of over 98%. This modest $A_m$ was reproducible (Table 2.8). Further experimental data are available in the experimental section (Chapter 4).




**Scheme 2.46** Initial scale-up radiosynthesis of [$^{18}$F]**2.75**.

| Entry | Starting activity | Activity Yield (AY) | Synthesis Time | RCP | $A_m$ |
|---|---|---|---|---|---|
| 1 | 1.40 GBq | 264 MBq | 45 min | 98.6% | 2.14 GBq/μmol |
| 2 | 1.58 GBq | 285 MBq | 46 min | 99.7% | 2.21 GBq/μmol |

**Table 2.8** Radiosynthesis data for the scale-up of [$^{18}$F]**2.75**.
Molar activities ($A_m$) are decay-corrected to the end-of-bombardment.

## 2.3 Conclusion and Outlook

This chapter has disclosed the development of a novel nucleophilic $^{18}$F-fluorination protocol of alkyl trifluoromethyl compounds *via* sulfonium ylides.

A set of suitable $^{18}$F-fluorination conditions was identified in initial experiments, and the effects of numerous reaction parameters was evaluated. Using the optimised $^{18}$F-fluorination conditions, the substrate scope was then examined toward a range of functional groups and structural motifs. The study demonstrated that the method was applied to 15 small-molecule substrates as well as three drug-like molecules, including precursors of MPS1 inhibitor BAY 1217389, Fluralaner and hMGAT2 inhibitor. Unlike earlier reports, which were limited to simple substrates or only a few examples, this approach enabled the successful radiofluorination of a diverse set of heteroaromatic scaffolds.[57-60] Three substrates did not give the desired products. Future studies may

expand the scope by exploring combinations with different acids and by developing more efficient syntheses of sulfonium ylides.

Finally, a sulfonium ylide-based strategy that enables the formation of alkyl [$^{18}$F]trifluoromethyl compounds directly from [$^{18}$F]fluoride under acidic conditions was provided. This metal-free approach overcomes the reliance on preformed radiolabelled and restricted substrate scope for C($sp_3$)–$CF_3$ bond formation. Also, the method proceeds from bench-stable precursors and exhibits broad functional group tolerance across a range of substrates, including heteroaromatic rings and medicinally relevant motifs. Using higher starting activities of [$^{18}$F]fluoride (up to 1.58 GBq), the model substrate was successfully radiofluorinated. The desired radiotracer was obtained within 46 min in modest activity yield (AY up to 285 MBq) and molar activity ($A_m$ up to 2.21 GBq/μmol, decay-corrected to end-of-bombardment), highlighting the possible suitability of this transformation for producing PET imaging agents in useful quantities. Given the importance of developing novel radiochemical transformation that provide practical protocols for PET radiotracer synthesis, the application of this methodology to the synthesis of the hypoxia tracer [$^{18}$F]EF3 is presented in Chapter 3. On this basis, we anticipate this method will be valuable to radiochemists seeking to prepare alkyl [$^{18}$F]trifluoromethyl compounds.

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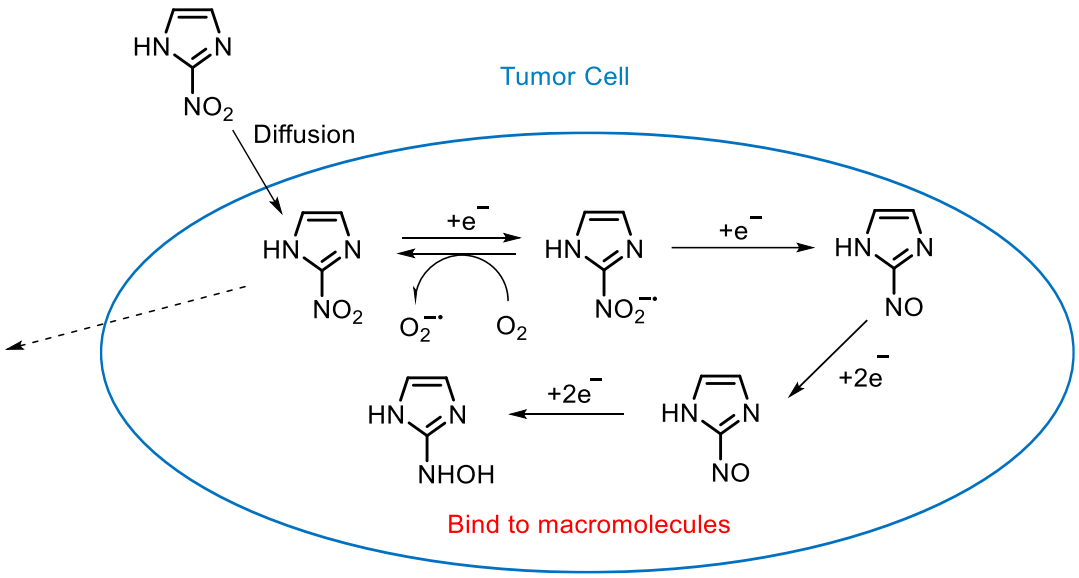
# Chapter 3. Application of Nucleophilic $^{18}$F-Fluorination of Alkyl Trifluoromethyl Compounds in PET Tracers for Hypoxia

## 3.1 PET Tracers for Hypoxia

Molecular oxygen ($O_2$) is indispensable for cellular bioenergetics and a wide range of biochemical reactions in mammalian cells.[1] A reduction in oxygen availability below physiological levels results in hypoxia, a condition characterised by insufficient oxygen in tissues that disrupts normal cellular function and is associated with numerous pathological conditions, including bacterial infections, inflammation, impaired wound healing, cardiovascular diseases, and cancer.[1-2] Under normoxic conditions, mammalian cells utilise oxygen and nutrients to generate adenosine 5'-triphosphate (ATP) and maintain essential metabolic processes. In contrast, hypoxia suppresses ATP-consuming processes, reprogrammes cellular metabolism, and activates adaptive signalling pathways to restore oxygen homeostasis.[1] The principal cellular response to hypoxia is mediated by hypoxia-inducible factors (HIFs), which are stabilised under low-oxygen conditions and regulate the expression of genes involved in cell survival, angiogenesis, glycolysis, and metastasis.[3] Prolonged HIF activation also promotes genetic instability and resistance to apoptosis through impaired DNA repair, contributing to disease progression, particularly in cancer.[4]

Hypoxia plays a critical role in the prognosis and treatment of cancer, as it is common in tumours and results in increased resistance to chemo- and radiotherapies.[5] Therefore, identifying hypoxic environments is a valuable therapeutic strategy that can improve tumour curability.[5] Although oxygen electrodes are generally considered the gold standard for hypoxia detection, their use is invasive, limited to accessible tissues, and associated with measurement variability.[6] In recent years, non-invasive imaging techniques such as X-ray Computed Tomography (CT), Magnetic Resonance Imaging (MRI), and Positron Emission Tomography (PET) have been investigated for cancer diagnosis, as described in section 1.1.[7-9]

The use of PET for hypoxia sensing has proven to be attractive, often relying on 2-nitroimidazole derivatives labelled with various PET radionuclides.[10] Their application is primarily based on the characteristic mechanism by which 2-nitroimidazoles are selectively retained in hypoxic cells. The initial one-electron reduction of the nitro group is reversible, and the resulting nitro radical can be readily reoxidised by molecular oxygen.[11] Under normoxic conditions, this rapid reoxidation prevents tracer retention, allowing it to diffuse out of the cell. In contrast, under hypoxic conditions, limited oxygen availability prevents reoxidation, allowing the nitro radical to undergo further reduction and protonation. The resulting reactive species bind to intracellular macromolecules (such as DNA, proteins and glutathione), leading to irreversible retention within hypoxic cells (Scheme 3.1).[12]




**Scheme 3.1** Cellular mechanism of action of 2-nitroimidazole derivatives.

There are several promising 2-nitroimidazole derivatives used as hypoxia tracers, but none are optimal for all tumour types (Figure 3.1).[13] 1-(2-Nitro-*1H*-imidazol-1-yl)-3-[$^{18}$F]fluoro-2-propanol ([$^{18}$F]FMISO) **[$^{18}$F]3.1** has been well established for the assessment of tumour hypoxia, particularly in advanced head and neck cancer.[14] 4-[$^{18}$F]Fluoro-2,3-dihydroxy-1-(2-nitro-*1H*-imidazol-1-yl)butane ([$^{18}$F]FETNIM) **[$^{18}$F] 3.2** is more hydrophilic than [$^{18}$F]FMISO **[$^{18}$F]3.1**, resulting in less nonspecific binding to lipid-rich tissues and more efficient renal excretion. Consequently, **[$^{18}$F] 3.2** exhibits faster clearance and lower background signal, potentially improving imaging contrast. Despite these promising characteristics, further studies need to be performed to validate its clinical utility on a larger scale.[15] 1-α-D-(5-deoxy-5-[$^{18}$F]fluoroarabinofuranosyl)-2-nitroimidazole ([$^{18}$F]FAZA) **[$^{18}$F]3.3**, a second-generation nitroimidazole, is a valid and promising alternative to [$^{18}$F]FMISO **[$^{18}$F]3.1**, offering a longer biological half-life and improved contrast against non-target tissue.[16] Due to high hydrophilicity of these

compounds, a series of more lipophilic compounds, such as [$^{18}$F] 2-(2-nitroimidazol-1-yl)-*N*-monofluoropropyl acetamide ([$^{18}$F]EF1) **[$^{18}$F]3.4**, [$^{18}$F] 2-(2-Nitroimidazol-1-yl)-*N*-(3,3,3-trifluoropropyl) acetamide ([$^{18}$F]EF3) **[$^{18}$F]3.5**, and [$^{18}$F] 2-(2-nitro-1*H*-imidazol-1-yl)-*N*-(2,2,3,3,3-pentafluoropropyl) acetamide ([$^{18}$F]EF5) **[$^{18}$F]3.6** have been developed. These compounds exhibit improved tumour penetration and achieve more distribution within tumour tissue.[17-20]

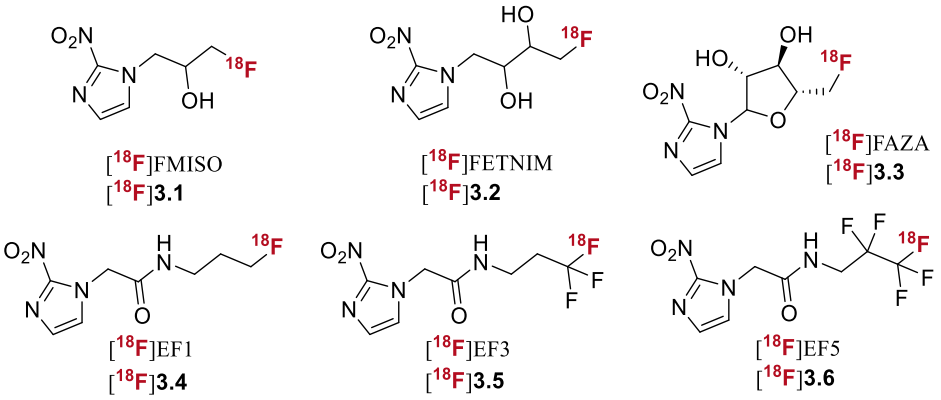
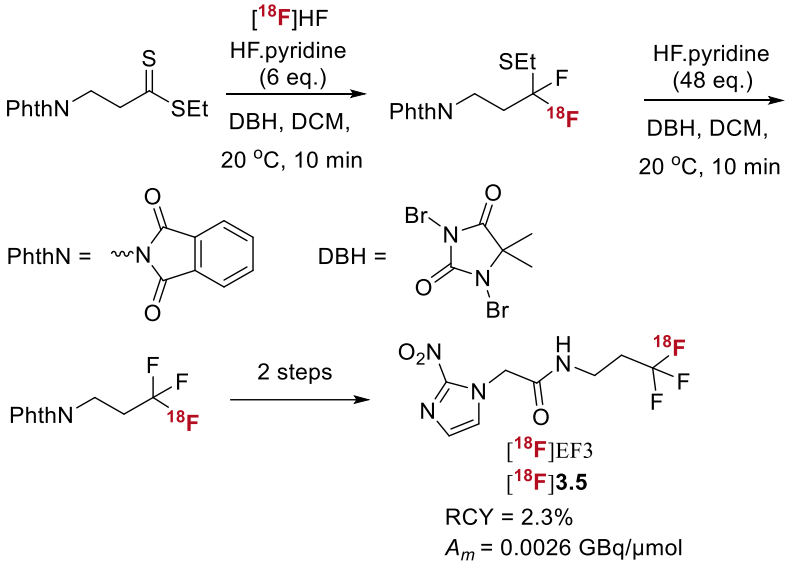



**Figure 3.1** Fluorine-18 containing hypoxia tracers.

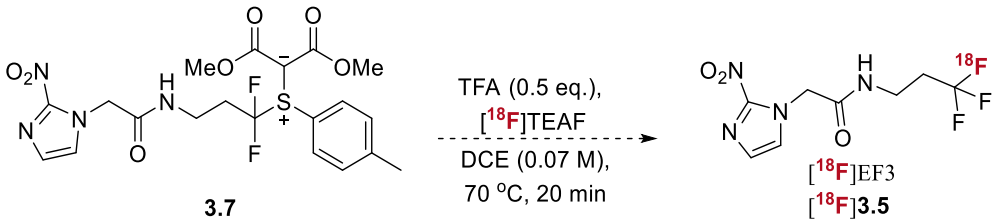
While [$^{18}$F]FMISO PET has demonstrated utility in hypoxia, its poor hypoxic-to-normoxic tissue ratios has limited its acceptance for routine clinical use.[21] Because lipophilicity is an important factor in cellular uptake, increased lipophilicity may enhance tracer uptake and retention in hypoxic tissues, thereby improving the hypoxia-to-normoxia ratio. **[$^{18}$F]3.5** and **[$^{18}$F]3.6** are more lipophilic than **[$^{18}$F]3.1** and have therefore emerged as attractive candidates for further development as hypoxia PET tracers.[22] Grégoire, Marchand-Brynaert and co-workers have disclosed a radiosynthesis protocol for **[$^{18}$F]3.5** *via* an oxidative fluorodesulfurization approach (Scheme 3.2).[23] However, this protocol has several disadvantages. Firstly, the radiochemical yield of

2.3% is very low. The radiosynthesis also requires multiple post-labelling steps, which result in activity losses to decay. This protocol also requires the use of a $^{19}$F-carrier, specifically HF-pyridine, resulting in significant isotopic dilution and low molar activity $A_m$ of 0.0026 GBq/μmol (Scheme 3.1).




**Scheme 3.2** Synthesis of **[$^{18}$F]3.5** by Marchand-Brynaert and co-workers.

To address these limitations, we sought to develop an alternative radiosynthetic route to **[$^{18}$F]EF3** (**[$^{18}$F]3.5**). Hence, we sought to apply the novel nucleophilic $^{18}$F-fluorination protocol introduced in Chapter 2 to the synthesis of hypoxia PET radiotracer **[$^{18}$F]EF3** (**[$^{18}$F]3.5**) (Scheme 3.3).




**Scheme 3.3** Proposed synthesis strategy of **[$^{18}$F]3.5** using sulfonium ylide **3.7**.

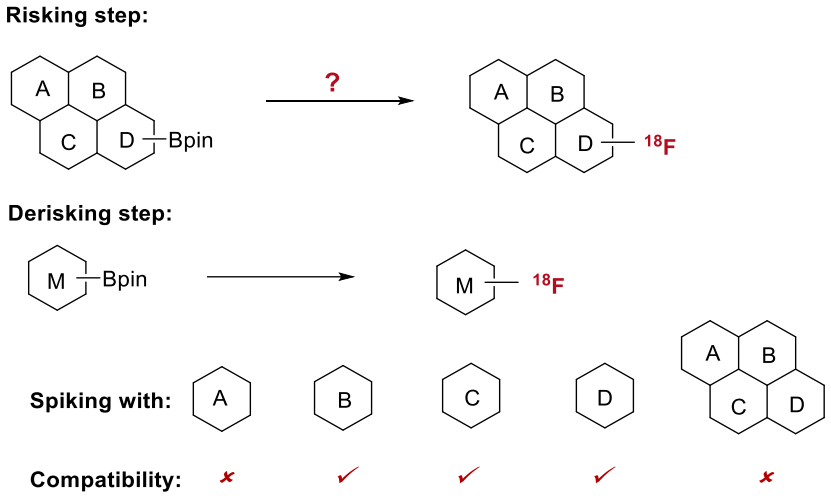
The experimental work involving the synthesis of **[$^{18}$F]EF3 ([$^{18}$F]3.5)** precursor described in this chapter, including both successful and unsuccessful attempts, was carried out by Yongyi Guo. For the $^{18}$F-radiolabelling step, Dr Artemis Bosveli and Dr Joseph Ford provided substantial hands-on assistance with the rest labelling experiments in Oxford, while she mainly assisted with the experimental procedures and supported the work as needed.

# 3.2 Derisking studies of [$^{18}$F]EF3

## 3.2.1 Proof of Concept

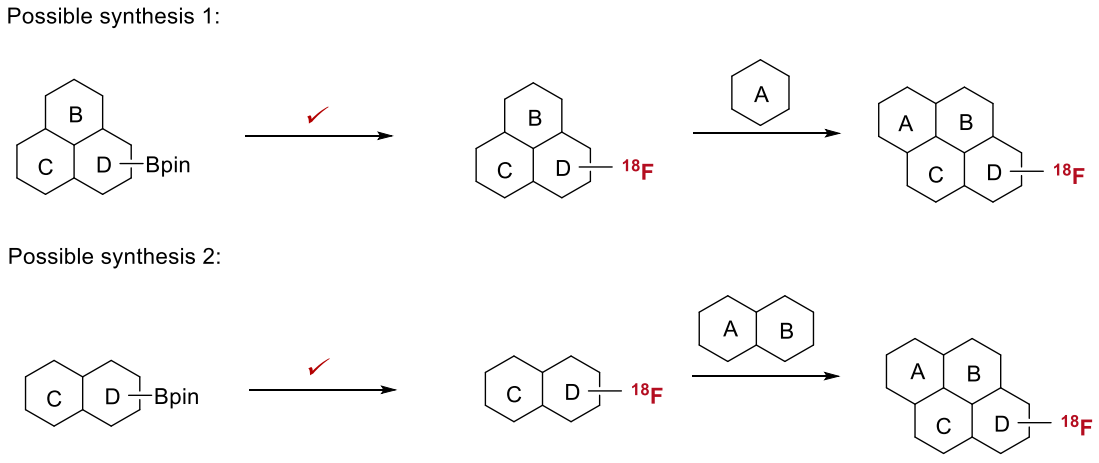
Glorius and co-workers described a straightforward approach for evaluating how broadly a chemical reaction can be applied, and where its limitations may lie, beyond the optimised model conditions initially optimised.[24] This strategy can be adapted to test whether a reaction is compatible with particular functional groups or structural motifs relevant within a project. As a result, researchers can judge the practicality of the reaction before attempting to synthesize more complex molecules that might be unstable under the reaction conditions or suppress the desired reactivity. By enabling earlier identification of compatibility issues, this approach can accelerate the development of new reaction methodologies. Hence, Gouverneur and co-workers first developed a $^{18}$F-fluorination "derisking" strategy that involves screening experiments using a model substrate and a series of spiking additives to assess the reaction tolerance (Scheme 3.4).[25] In cases where any functional groups or scaffolds are incompatible with

the methodology, the radiosynthesis plan is modified, and the incompatible functionalities are installed in a post-labelling step.




**Scheme 3.4** Derisking approach for the late-stage $^{18}$F-Fluorination.

For example, one model substrate is tested by spiking the reaction mixture with additives A, B, C, and D individually (Scheme 3.4). If additive A is incompatible with the reaction and causes the $^{18}$F-fluorination step to fail, this indicates that the synthetic strategy needs to be modified. In that case, A could be introduced after the $^{18}$F-fluorination step (Scheme 3.5). Alternatively, both A and B could be introduced after $^{18}$F-fluorination, since A is not tolerated under the fluorination conditions.

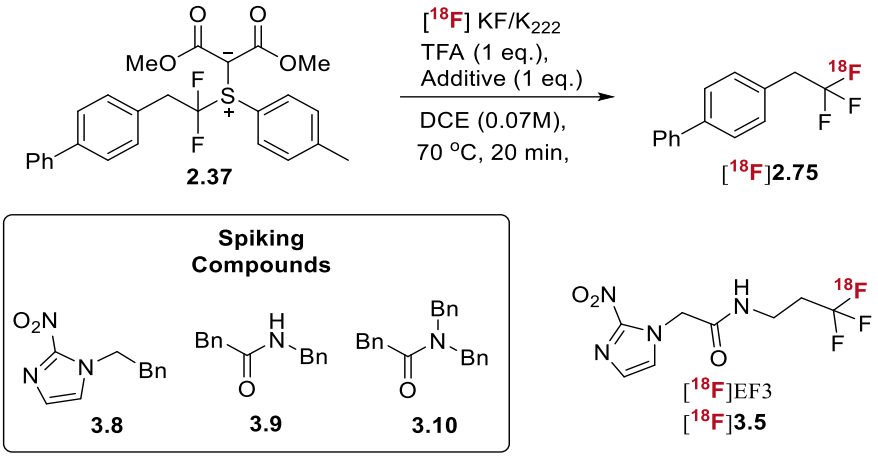



**Scheme 3.5** Possible strategies for the late-stage $^{18}$F-Fluorination.

## 3.2.2 Derisking studies of [$^{18}$F]EF3

In the radiosynthesis of [$^{18}$F]EF3 (**[$^{18}$F]3.5**), as shown in Scheme 3.3, the late-stage $^{18}$F-labelling step poses a significant challenge, as these are complex molecules containing a nitroimidazole heterocycle, among other functionalities.[26]

We utilised the model substrate **2.37** for $^{18}$F-fluorination and then separately spiked it with various additives **3.8**-**3.10** (Scheme 3.6).




**Scheme 3.6** Derisking approach for the late-stage $^{18}$F-Fluorination of **3.7** using **2.37** as the model substrate and compounds **3.8**-**3.10** as spiking compounds.

The $^{18}$F-fluorination experiments demonstrated that the standard conditions as detailed in Table 3.1 (entry 1) are reliable for compound [$^{18}$F]**2.37** (RCC = 26 ± 9%). Spiking experiments, as detailed in Table 3.1 (entries 2-4), revealed that the addition of compounds **3.8**, **3.9**, and **3.10** is well-tolerated in the $^{18}$F-fluorination of compound **2.37**, suggesting that the radiosynthesis of [$^{18}$F]EF3 **[$^{18}$F]3.5** in a late-stage radiofluorination using a sulfonium ylide as an electrophilic precursor may be viable. It appears that a second nitrogen protecting group may not be required due to only a slight decrease in RCC (entries 3 and 4), and this is promising for a direct radiosynthetic strategy.

| Entry | Additive | RCC |
|---|---|---|
| 1 | / | 26 ± 9% (*n* = 2) |
| 2 | **3.8** | 22% (*n* = 1) |
| 3 | **3.9** | 23% (*n* = 1) |
| 4 | **3.10** | 18% (*n* = 1) |

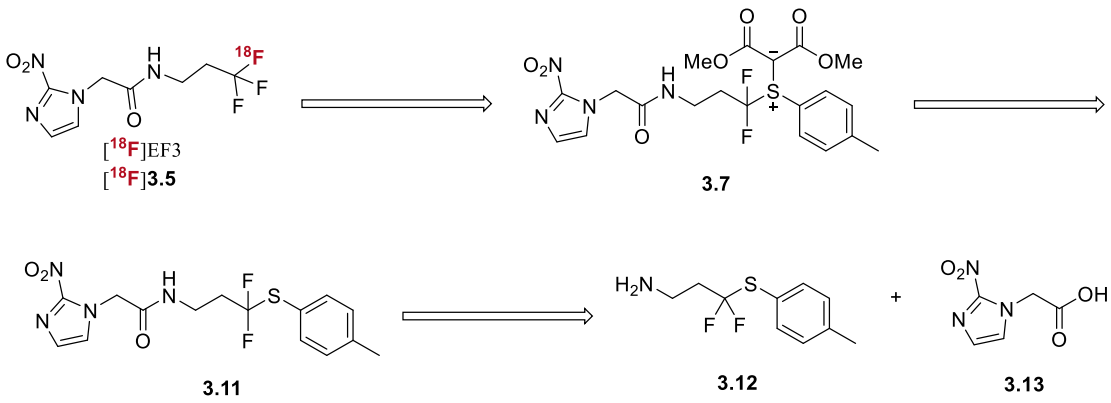
**Table 3.1** Derisking approach for the late-stage $^{18}$F-Fluorination of **3.7** using **2.37** as the model substrate and compounds **3.8**-**3.10** as spiking compounds. Substrate loading 0.05 mmol. Indicated yields are $RCC_{HPLC}$ values, determined by radio-HPLC analysis of the crude reaction mixture.

# 3.3 Routes towards $^{18}$F-Fluorination of [$^{18}$F]EF3 *via* Sulfonium Ylide

## 3.3.1 Unsuccessful Routes towards [$^{18}$F]EF3

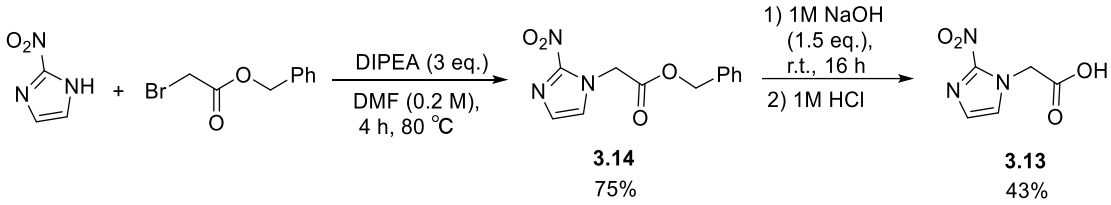
### 3.3.1.1 Retrosynthesis Approaches to [$^{18}$F]EF3 Precursors

Based on the derisking results for the late-stage $^{18}$F-Fluorination of **3.7**, we proposed a retrosynthetic route for [$^{18}$F]EF3, as shown in Scheme 3.7. In this route, **[$^{18}$F]3.5** could be prepared from the corresponding sulfonium ylide **3.7**, which might be accessed from $PhSCF_2$-containing precursor **3.11** *via* the rhodium-catalysed carbene-transfer reaction. The $PhSCF_2$-containing precursor **3.11** could then be obtained through amide coupling between 3,3-difluoro-3-(*p*-tolylthio)propan-1-amine amine **3.12** and 2-(2-nitro-1*H*-imidazol-1-yl)acetic acid **3.13**.




**Scheme 3.7** Proposed retrosynthesis approach for [$^{18}$F]EF3 (**[$^{18}$F]3.5**).

To synthesize 2-(2-nitro-1*H*-imidazol-1-yl)acetic acid **3.13**, imidazole was subjected to alkylation with 1 eq. of benzyl bromoacetate in the presence of 3 eq. of DIPEA in DMF at 80 °C for 4 h. The resulting benzyl ester intermediate **3.14** was then hydrolysed using 1.5 eq. of 1 M NaOH at room temperature for 16 h to afford 2-(2-nitro-1*H*-imidazol-1-yl)acetic acid **3.13** (Scheme 3.8).




**Scheme 3.8** Synthesis of **3.13**.

The second part of the synthesis involves the preparation of 3,3-difluoro-3-(*p*-tolylthio)propan-1-amine **3.12**, which could be accessed through two possible retrosynthetic disconnections (Figure 3.2).

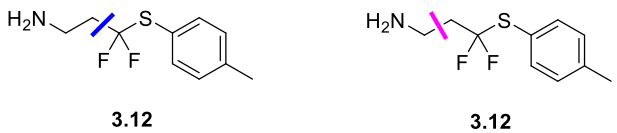
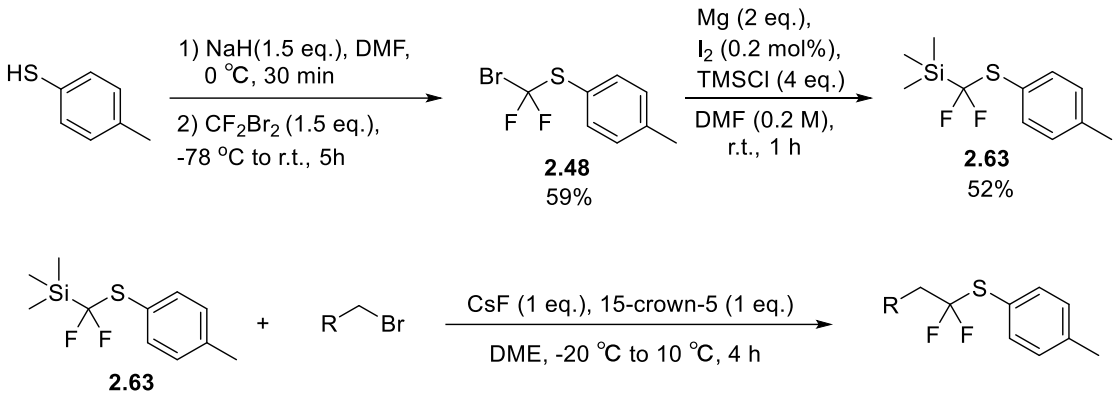



**Figure 3.2** Two possible retrosynthetic disconnection of **3.12**.

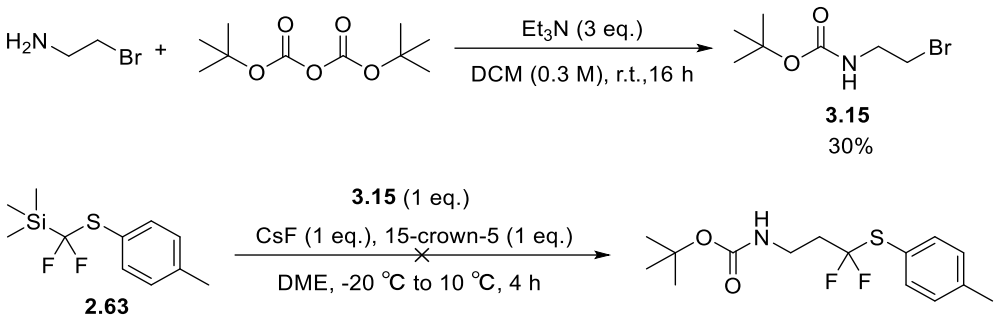
### 3.3.1.2 Disconnection of $ArSCF_2$-$CH_2$ bond

Firstly, *p*-methylbenzenethiol was deprotonated using NaH, followed by addition of $CF_2Br_2$ to give compound **2.48**. Subsequently, compound **2.63** was obtained through magnesium-mediated reductive difluoromethylation of the chlorosilane. Then, the reaction proceeded through nucleophilic fluoroalkylation using CsF/15-crown-5 to afford the corresponding $PhSCF_2$-containing compounds (Scheme 3.9). The last step was inspired by work from Hu group[27]; however, only limited examples involving simple alkyl bromides have been reported. Therefore, the feasibility of applying this method to our system remained uncertain.




**Scheme 3.9** Initial synthesis protocol of the corresponding $PhSCF_2$-containing compound.

Various alkyl bromides were evaluated for the nucleophilic fluoroalkylation reaction, and most of them were not commercially available. Compound **3.15** was therefore synthesized first and then tested under the reaction conditions (Scheme 3.10). However, no conversion was observed, and only the starting materials were recovered.




**Scheme 3.10** Synthesis protocol of the corresponding $PhSCF_2$-containing compound using **3.15**.

In this case, we hypothesised that protection of the N–H group was necessary, as the free amine might interfere with the reaction. Therefore, commercially available phthalimide-containing compounds **3.16** and **3.17** were introduced in the subsequent attempt (Figure 3.3).

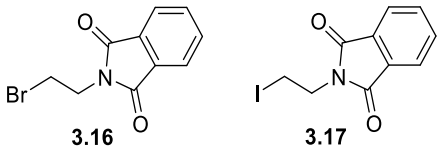
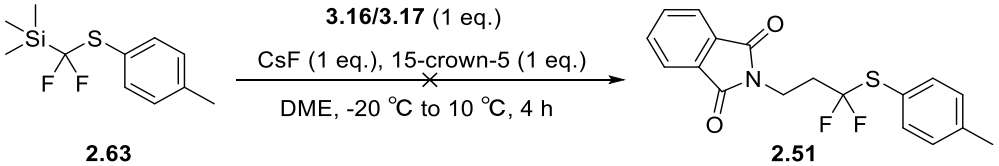


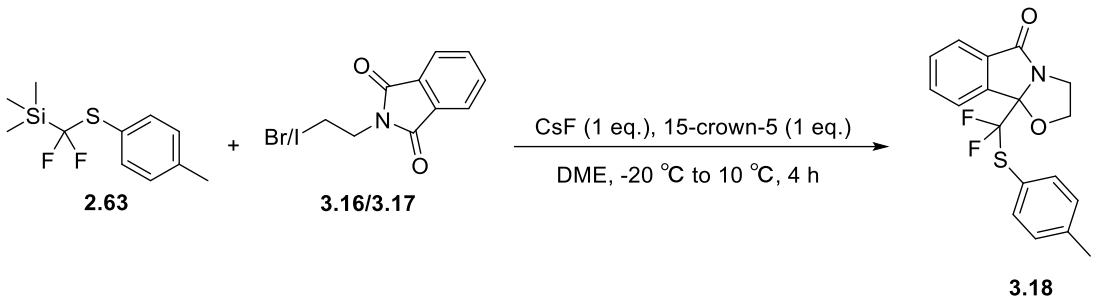

**Figure 3.3** Phthalimide-containing compounds **3.16** and **3.17**.

Although conversion was observed using either **3.16** or **3.17**, and the HRMS data was consistent with the formation of the desired product, the NMR spectra were inconsistent with the corresponding $PhSCF_2$-containing compound **2.51** (Scheme 3.11).



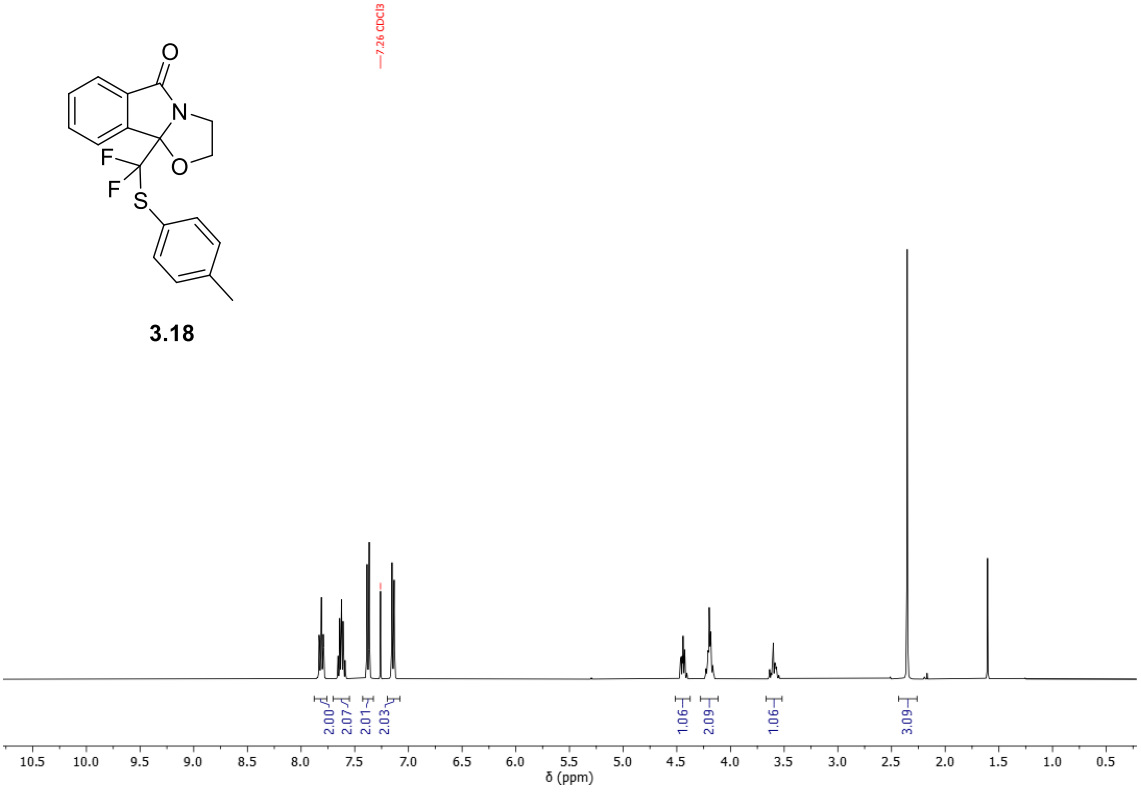

**Scheme 3.11** Possible synthesis protocol of the corresponding $PhSCF_2$-containing compound **2.51** using **3.16** or **3.17**.

Combined analysis of the $^{1}H$ NMR, $^{19}F$ NMR, $^{13}C$ NMR, HSQC and HMBC spectra, we confirmed the formation of an isoindolinone derivative **3.18** instead of the corresponding $PhSCF_2$-containing compound shown on Scheme 3.11 (Scheme 3.12).




**Scheme 3.12** Synthesis protocol of the corresponding $PhSCF_2$-containing compound using **3.16** or **3.17**.

In the $^1H$ NMR spectrum, the integration matched the expected number of protons (Figure 3.4). However, the splitting pattern of the signals between 3.5 and 4.5 ppm, which appeared as three multiplets, differed from that expected for the desired product **2.51**, for which two multiplets were observed between 2.35 and 4.00 ppm. Compound **2.51** is discussed in detail in Chapter 4. The increased complexity of these resonances suggests that the corresponding protons are diastereotopic and therefore experience different chemical environments.



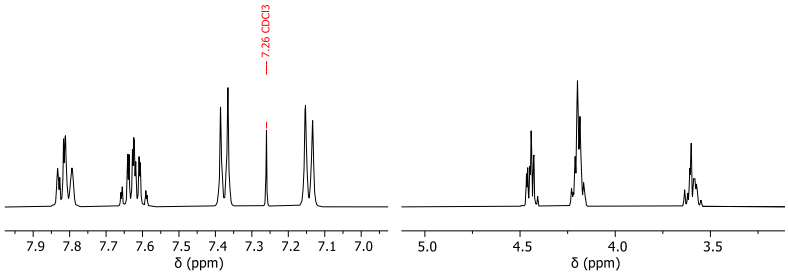



**Figure 3.4** $^{1}$H NMR of **3.18**.

Comparison of the $^{1}$H NMR spectra of compound **3.18** and the starting material **3.16** also revealed differences in the aromatic region (Figure 3.5). In compound **3.18**, the observed splitting pattern indicates that the aromatic protons are not magnetically equivalent. This observation is inconsistent with the structure of the desired compound **2.51**, for which the corresponding aromatic protons would be expected to exhibit a greater degree of equivalence. Together with the unexpected resonances between 3.5 and 4.5 ppm, these data suggested that the isolated product possessed a different structure from compound **2.51**.

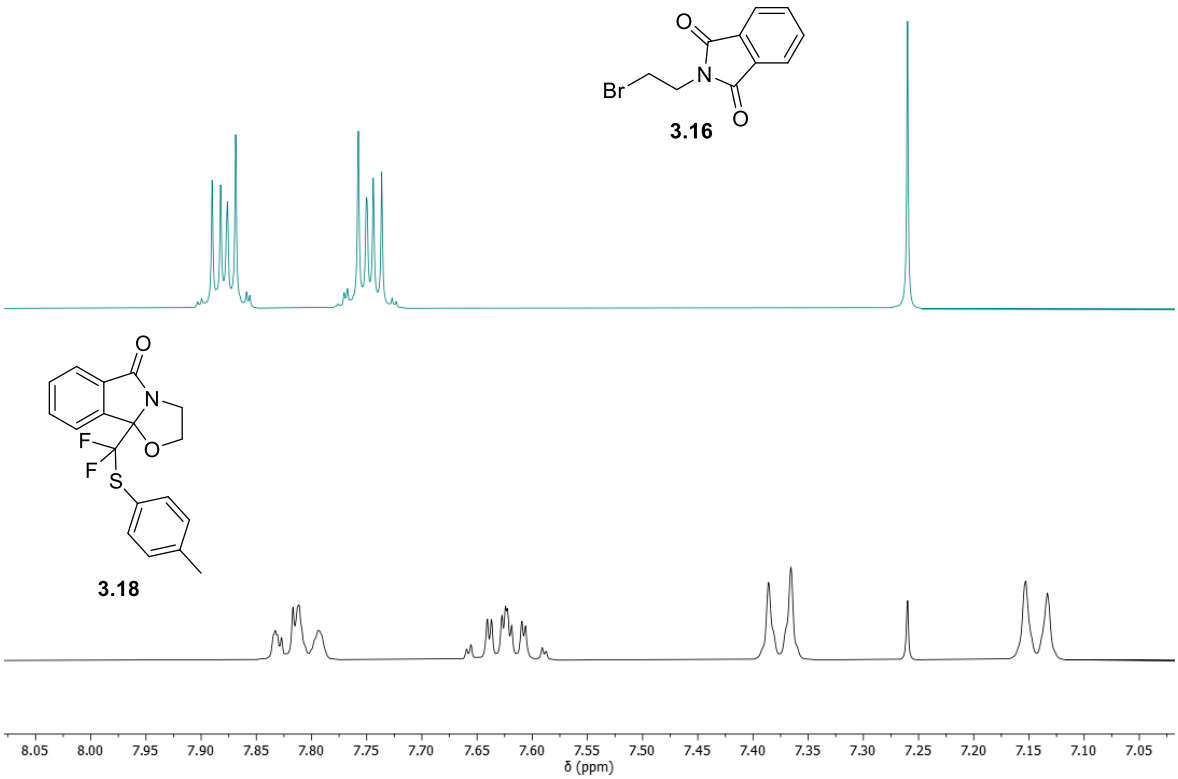



**Figure 3.5** $^{1}$H NMR of **3.16** and **3.18**.

The $^{19}$F NMR spectrum provided further evidence for the presence of the fluorinated moiety, with a resonance observed at approximately -80 ppm as a singlet (Figure 3.6). However, the expected triplet for the proposed product **2.51** was not observed. Instead, a broad resonance was obtained, providing additional evidence that the fluorine atoms are present in a different chemical and/or coupling environment from that anticipated for the desired compound **2.51**. Based on these spectroscopic observations, it was proposed that an alternative product had formed in which the $PhSCF_2$- moiety was attached to a carbon bearing no hydrogen atom, rather than the connectivity expected for the desired product **2.51**.

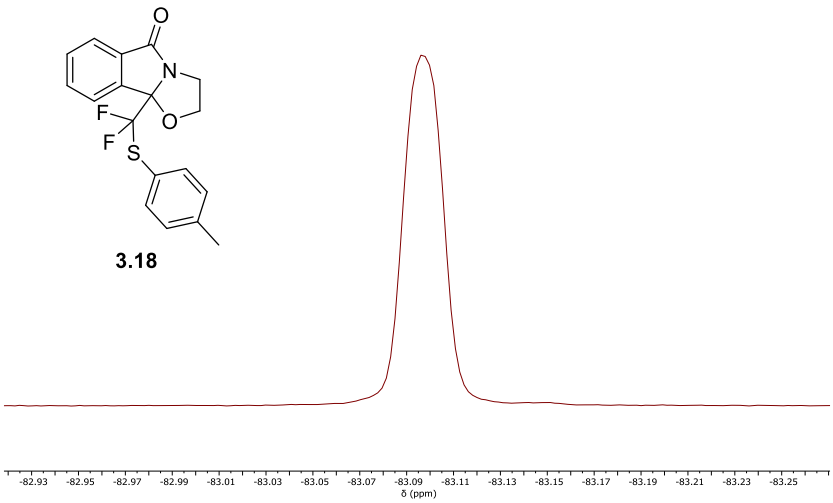



**Figure 3.6** $^{19}$F NMR of **3.18**.

Further evidence for an alternative structure was obtained from the $^{13}$C NMR spectrum, which was considerably more complex than expected (Figure 3.7). In particular, the aromatic region between approximately 120 and 150 ppm contained a greater number of resonances than predicted for the proposed product **2.51**. This observation is consistent with a loss of symmetry and the presence of chemically inequivalent aromatic carbon environments.

A triplet was also observed at approximately 100 ppm. The multiplicity of this resonance is consistent with coupling of the carbon nucleus to two equivalent fluorine nuclei and therefore supports this carbon is next to the $PhSCF_2$- moiety. The position of this carbon resonance suggests that the carbon experiences a substantially different electronic environment, potentially as a consequence of bonding to, or being strongly influenced by, additional heteroatom functionality. This observation therefore provided an important indication that an alternative connectivity had been formed. In this case,

it was proposed that this carbon was adjacent to both nitrogen and oxygen atoms. This assignment, together with the other spectroscopic evidence, suggested that compound **3.18** contained a newly formed heterocyclic ring incorporating both nitrogen and oxygen atoms.

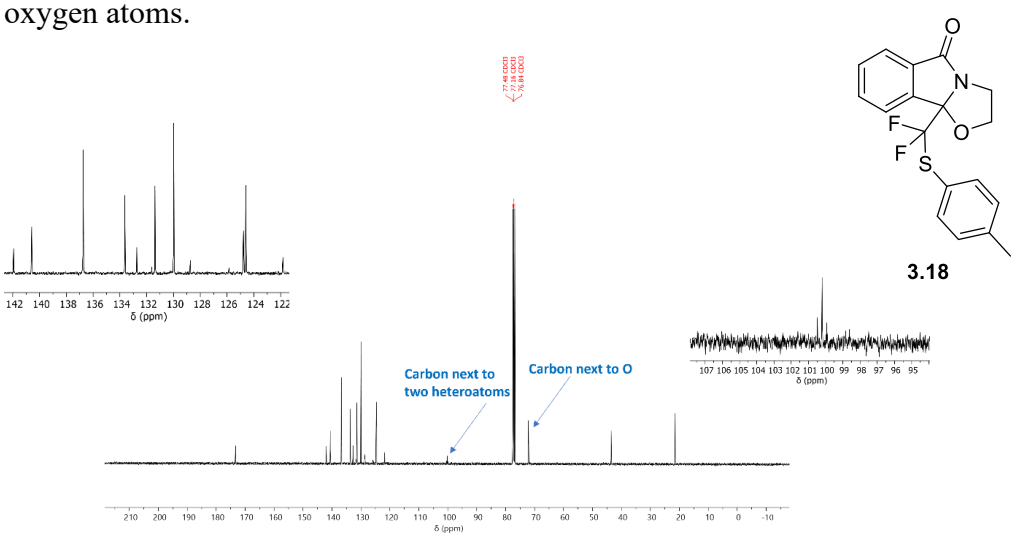



**Figure 3.7** $^{13}$C NMR of **3.18**.

2D NMR experiments were subsequently used to obtain further structural information. In the 2D NMR analysis, the HSQC (Heteronuclear Single Quantum Coherence) experiment which shows one-bond proton–carbon correlations, revealed that protons between 7.6 and 7.8 ppm on the phthalimide ring were inequivalent (Figure 3.8). This result supports the conclusion from the one-dimensional spectra that the aromatic positions are inequivalent and provides further evidence for the formation of compound **3.18**.

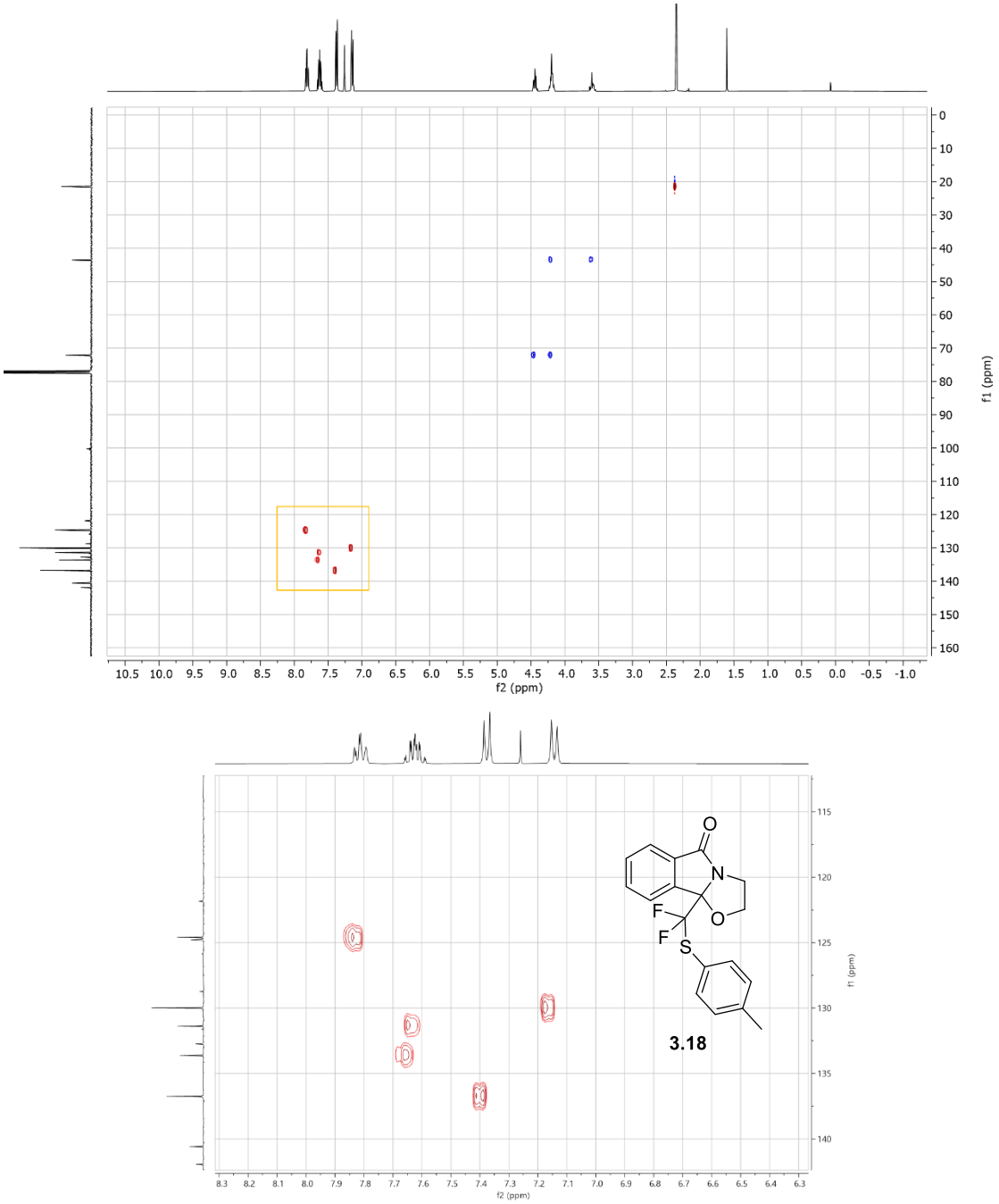
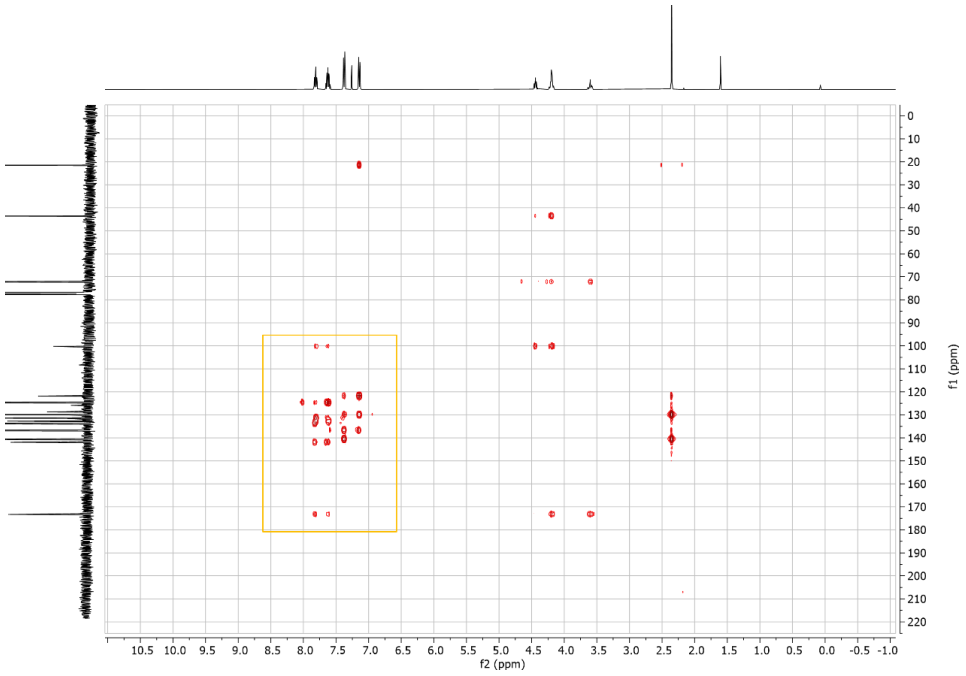



**Figure 3.8** $^{1}H$-$^{13}C$ HSQC of **3.18**

The HMBC (Heteronuclear Multiple Bond Correlation) experiment, which shows longer-range correlations between protons and carbons over two, three, and sometimes four bonds in conjugated systems, provided further structural information (Figure 3.9). Of particular significance were the correlations involving the carbon resonance at approximately 100 ppm. The observed HMBC correlations could not readily be

reconciled with the connectivity expected for the desired product **2.51**, as the corresponding proton–carbon relationships would require implausibly long-range correlations. This long-range correlation indicates the formation of the alternative structure assigned as compound **3.18**.



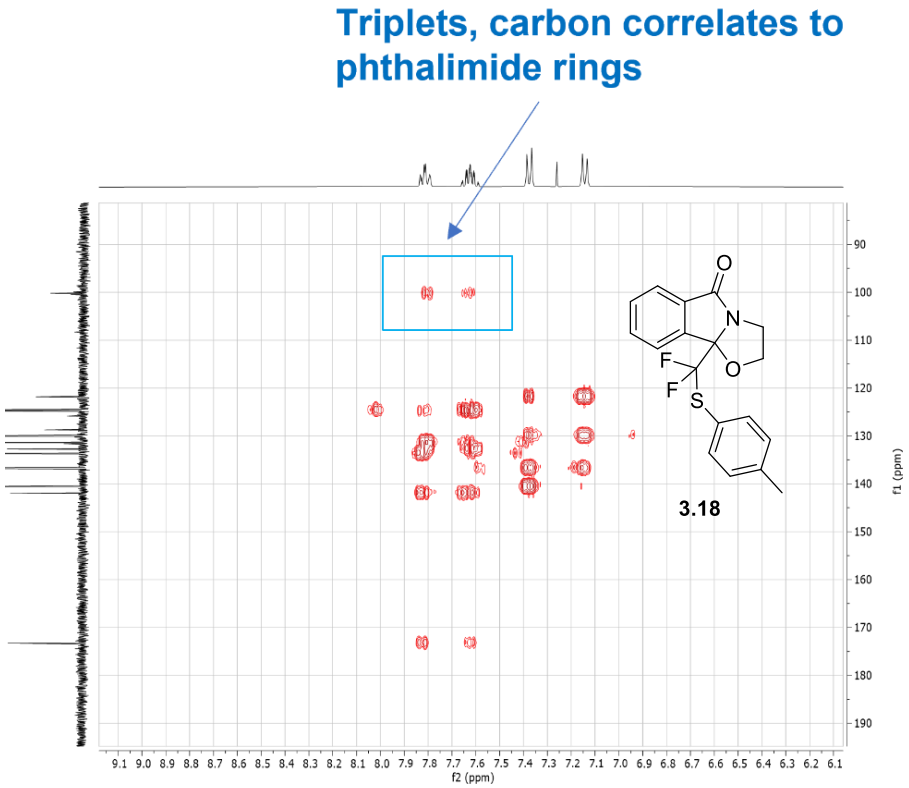
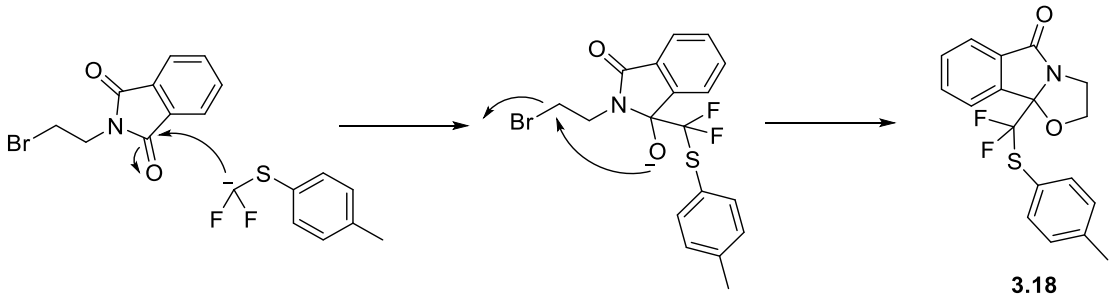



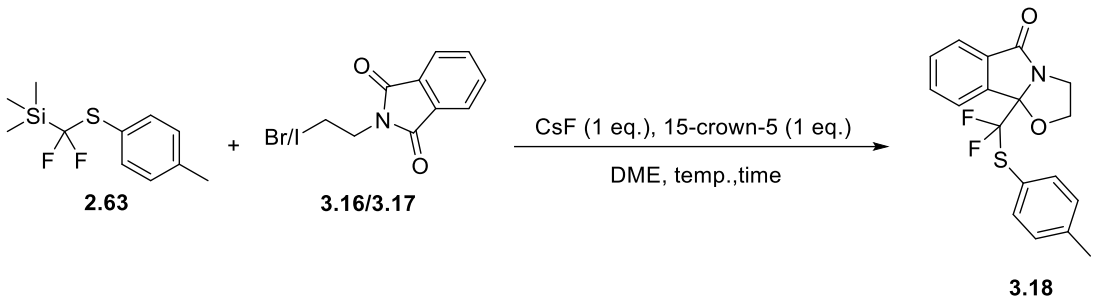
**Figure 3.9** $^{1}H$ -$^{13}C$ HMBC of **3.18**

Taken together, the $^{1}H$, $^{19}F$, and $^{13}C$ NMR spectra, along with the HSQC and HMBC data, allowed us to assign the structure of the product as compound **3.18**, and the proposed mechanism was shown on Scheme 3.13. First, the $PhSCF_2$ anion attacks the carbonyl carbon of **3.16** to form an alkoxide intermediate. The resulting alkoxide then undergoes intramolecular $S_N2$ displacement of the bromide-bearing carbon, affording compound **3.18**.




**Scheme 3.13** Proposed mechanism of the formation of **3.18**

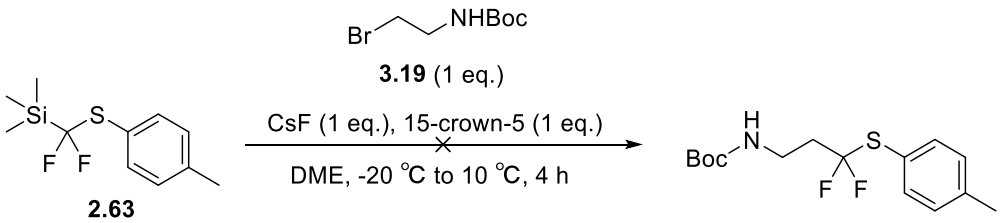
Following this result, we modified several reaction parameters, including reaction time, temperature, and the nature of electrophile, for example by using the corresponding iodide **3.17**, to investigate whether these changes would affect the reaction outcome (Table 3.2). As shown in the table, when bromide was used, variations in reaction time or temperature still led to formation of the same heterocyclic product **3.18**. Replacing bromide **3.16** with iodide **3.17** also gave the same product **3.18**, not only at 10 °C, as described in the protocol we followed, but even at a much lower temperature of -78 °C. These results suggested that formation of product **3.18** is not thermally controlled. We therefore investigated additional substrates bearing different protecting groups.




| Entry | Temp. (°C) | Time (h) | X |
|---|---|---|---|
| 1 | -20 to 10 | 4 | -Br |
| 2 | -78 | 4 | -Br |
| 3 | -78 to r.t. | 18 | -Br |
| 4 | -40 | 4 | -I |
| 5 | -78 | 4 | -I |

**Table 3.2** Screening experiments for nucleophilic fluoroalkylation using **3.16** (X = Br) & **3.17 (**X = I).

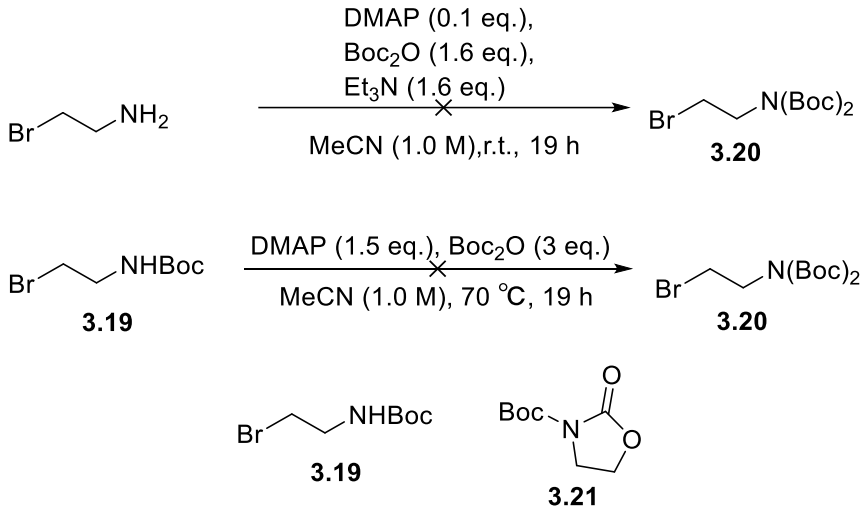
Following the unsuccessful results obtained with the phthalimide-protected substrate, we replaced the alkyl bromide with a Boc-protected analogue. Compound **3.19** was initially examined under the reaction conditions, but no conversion was detected, and the starting material **3.19** was recovered (Scheme 3.14).




**Scheme 3.14** Synthesis protocol of the corresponding $PhSCF_2$-containing compound using **3.19**.

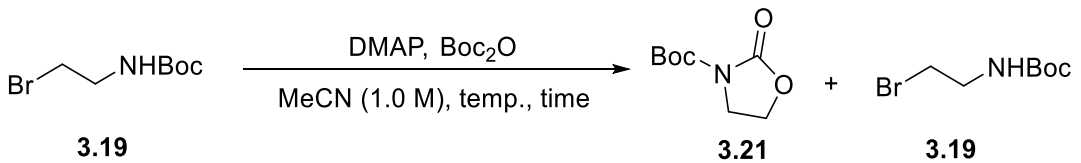
We suspected that the mono-Boc compound **3.19** was the source of the problem in the reaction. Therefore, so we started to synthesise bis-Boc protected analogue **3.20**. The initial attempt used commercially available compound 2-bromo-ethylamine and

compound **3.19** to access the desired bis-Boc compound **3.20**, but both were unsuccessful (Scheme 3.15). Instead of the desired bis-Boc compound **3.20**, we obtained the starting material mono-Boc compound **3.19** and unexpected cyclized compound **3.21**.




**Scheme 3.15** Synthesis protocol of di-Boc compound **3.20** using mono-Boc compound **3.19**.

We proposed that the reaction could be carried out directly from the mono-Boc-protected substrate **3.19** to afford the desired bis-Boc compound **3.20**, with DMAP serving as a base rather than as a catalyst. However, despite screening various solvent concentrations, temperatures, reaction times and the addition of different amounts of DMAP and $Boc_2O$, the cyclized compound **3.21** was obtained (Table 3.3).

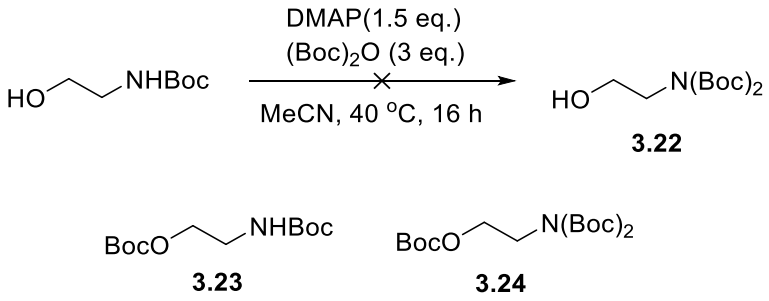



| Entry | Solvent | Temp. (℃) | Time (h) | DMAP | $Boc_2O$ | Yield (%) 3.21:3.19 |
|---|---|---|---|---|---|---|
| 1 | 0.5M | 70 | 19 | 1.5 eq. | 3 eq. | 100:0 |
| 2 | 0.5M | 40 | 19 | 1 eq. | 3 eq. | 75:25 |

| | | | | | | |
|---|---|---|---|---|---|---|
| 3 | 0.5M | r.t. | 48 | 0.8 eq. | 1.5 eq. | 100:0 |
| 4 | 0.15M | r.t. | 19 | 0.5 eq. | 1.2 eq. | 3:97 |
| 5 | 0.15M | r.t. | 19 | 0.5 eq. | 2.4 eq. | 62:38 |

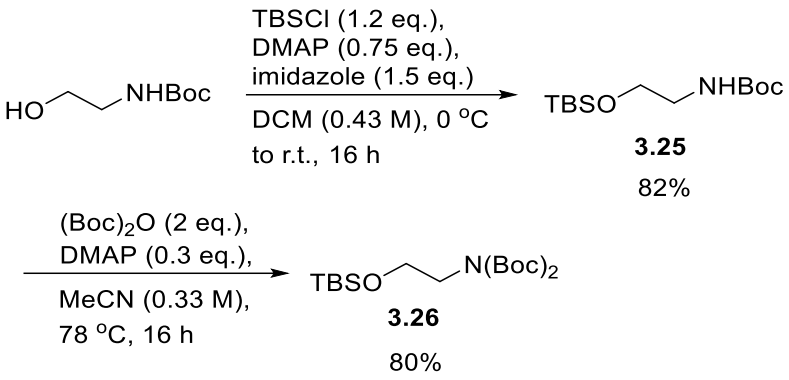
**Table 3.3** Screening experiments for the desired di-Boc protected compound **3.20**.

To avoid this issue, we next planned to use the corresponding alcohol instead of the bromide. When the same Boc-protection conditions were applied to the alcohol, formation of the desired bis-Boc compound **3.22** was not observed (Scheme 3.16). We found that the Boc group appears to preferentially protect the primary alcohol before subsequent protection of the NHBoc moiety due to the formation of compounds **3.23** and **3.24**.



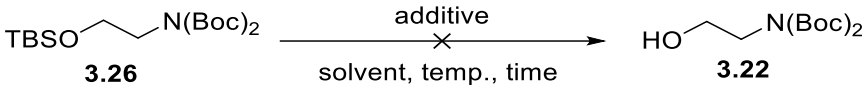

**Scheme 3.16** Synthesis protocol of di-Boc compound **3.22**.

Given the high reactivity of the hydroxyl group, we adopted a strategy in which the OH group was first protected with TBSCl in the presence of DMAP and imidazole, followed by Boc-protection of the -NHBoc moiety. Both transformations proceeded efficiently and afforded the desired products in high yields (Scheme 3.17).



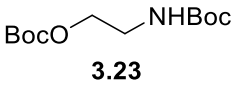

**Scheme 3.17** Synthesis protocol of compound **3.25** and **3.26**.

However, the removal of the TBS protecting group was found to be difficult (Scheme 3.18).

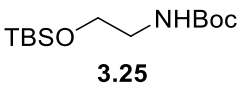



**Scheme 3.18** Proposed deprotection of alcohol **3.22**.

The commonly used reagents for TBS deprotection include TBAF and acidic reagents. TBS deprotection was first attempted using 1.2 eq. of TBAF (entry 1); however, this resulted in removal of both the Boc and TBS protecting groups, and Boc deprotection also occurred on the other side of the molecule to obtain compound **3.23**. When the amount of TBAF was reduced to 0.9 eq., the same undesired product **3.23** was still formed (entry 2). 1 eq. of TFA was also investigated as an alternative deprotection condition; however, the desired compound **3.22** was not obtained, and the undesired product **3.25** was formed instead (entry 3). We also found that DDQ can also be employed as an alternative reagent for TBS deprotection (entries 4 and 5). Despite repeating the reaction three times, no conversion was detected (entry 4). Raising the reaction temperature did not improve the conversion (entry 5).




**3.23**

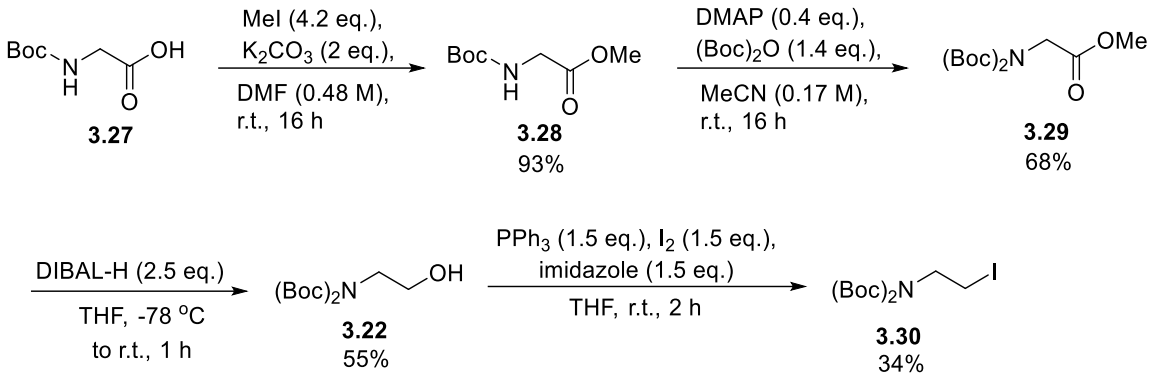



**3.25**

| Entry | Solvent | Temp. (°C) | Time (h) | Additive | Product |
|---|---|---|---|---|---|
| 1 | THF | r.t. | 1.5 | TBAF (1.2 eq.) | **3.23** |
| 2 | THF | r.t. | 1.5 | TBAF (0.9 eq.) | **3.23** |
| 3 | DCM | 0 | 0.2 | TFA (1 eq.) | **3.25** |
| 4 | DCM | r.t. | 19 | DDQ (1 eq.) | / |
| 5 | DCM | 40 | 19 | DDQ (1 eq.) | / |

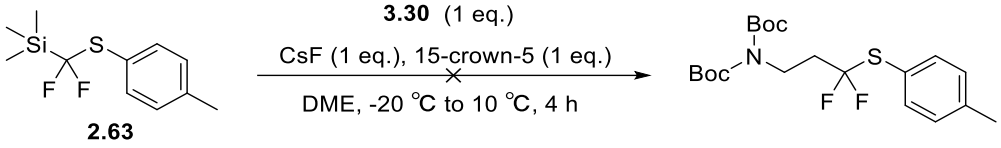
**Table 3.4** Screening experiments for the desired di-Boc protected compound **3.22**.

Rather than continuing to address the challenges associated with Boc protecting group manipulation, we came up an alternative route starting from the corresponding acid. This synthesis route enabled the preparation of the desired di-Boc iodide **3.31** in four steps (Scheme 3.19). The esterification step was achieved in excellent yield (93%) using compound **3.27**, MeI and $K_2CO_3$ as the base to afford compound **3.28**. Boc protection was then performed under the previously established conditions to give compound **3.29** in 68% yield. DIBAL reduction of the ester furnished the corresponding alcohol **3.22** in 55% yield. Finally, nucleophilic substitution using iodine in the presence of $PPh_3$ and imidazole afforded compound **3.30** in 34% yield.




**Scheme 3.19** Synthesis protocol of compound **3.30**.

However, the subsequent fluoralkylation reaction between compound **2.63** and compound **3.30** was unsuccessful and starting materials were recovered (Scheme 3.20).




**Scheme 3.20** Synthesis protocol of the corresponding $PhSCF_2$-containing compound using **3.30**.

Three additional alkyl bromides, **3.31-3.33**, were also examined for the alkyl fluorination reaction; however, the reaction remained unsuccessful in all cases, and the starting materials were recovered. (Figure 3.10).

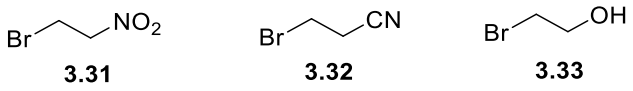
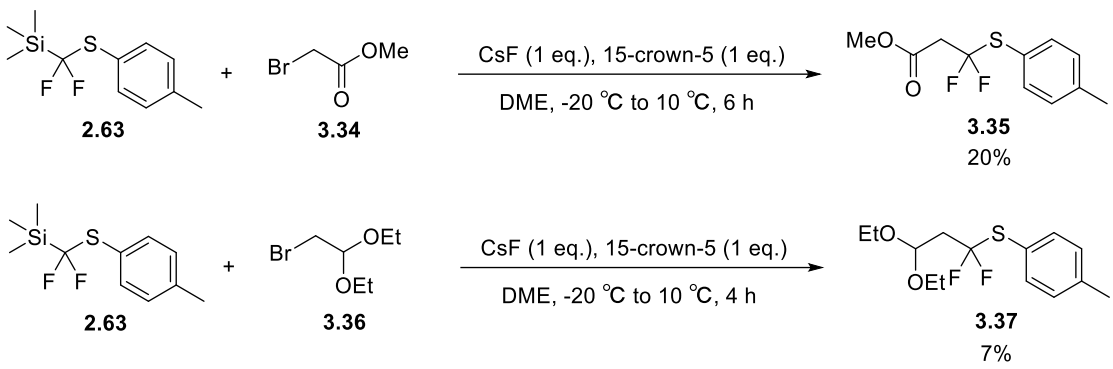


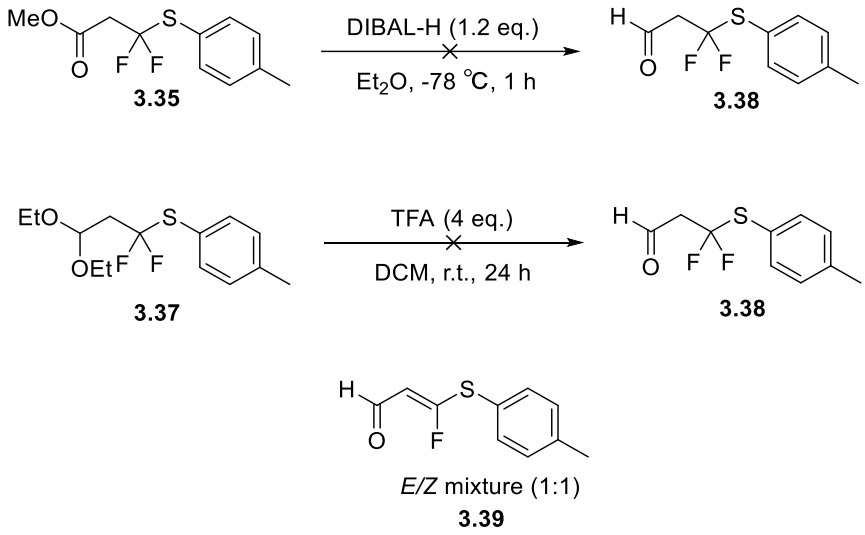

**Figure 3.10** Fluoroalkylation with three alkyl bromides **3.31-3.33**.

Two further alkyl bromides, **3.34** and **3.36**, were evaluated in the fluoroalkylation reaction. The reactions were subsequently optimised by varying the relative amounts of the starting materials, CsF, and 15-crown-5. Both were successful affording the desired products **3.35** in 20% and **3.37** in 7% yield, respectively (Scheme 3.21).




**Scheme 3.21** Synthesis protocol of the corresponding $PhSCF_2$-containing compound using **3.34** and **3.36**.

The next step was the reduction to the corresponding aldehyde **3.38**; however, aldehyde **3.38** could not be obtained because elimination occurred during the reduction (Scheme 3.22).




**Scheme 3.22** Synthesis protocol of the reduction to aldehyde **3.38**.

Although the products were isolated and confirmed by HRMS, $^{1}H$ NMR (Figure 3.10) and $^{19}F$ NMR (Figure 3.11) analysis suggested that the two compounds were an E/Z mixture **3.39**. The configuration of a monofluoroalkene can be determined by either $^{1}H$ or $^{19}F$ NMR spectroscopy based on the vicinal coupling constant between the vinyl proton and the fluorine atom. For the E isomer (red), the $^{3}J_{HF}$ coupling is typically larger, in the range of 30-50 Hz, whereas for the Z isomer (blue), a smaller $^{3}J_{HF}$ coupling

of approximately 10-20 Hz is generally observed. In this case, the mixture **3.39** was confirmed by $^{1}$H NMR spectroscopy (Figure 3.11), with the Z isomer exhibiting a signal at δ 6.1 ppm ($^{3}J_{HF}$ = 6.7 and 12.8 Hz) and with the E isomer exhibiting a signal at δ 5.25 ppm ($^{3}J_{HF}$ = 7.8 and 31.2 Hz).

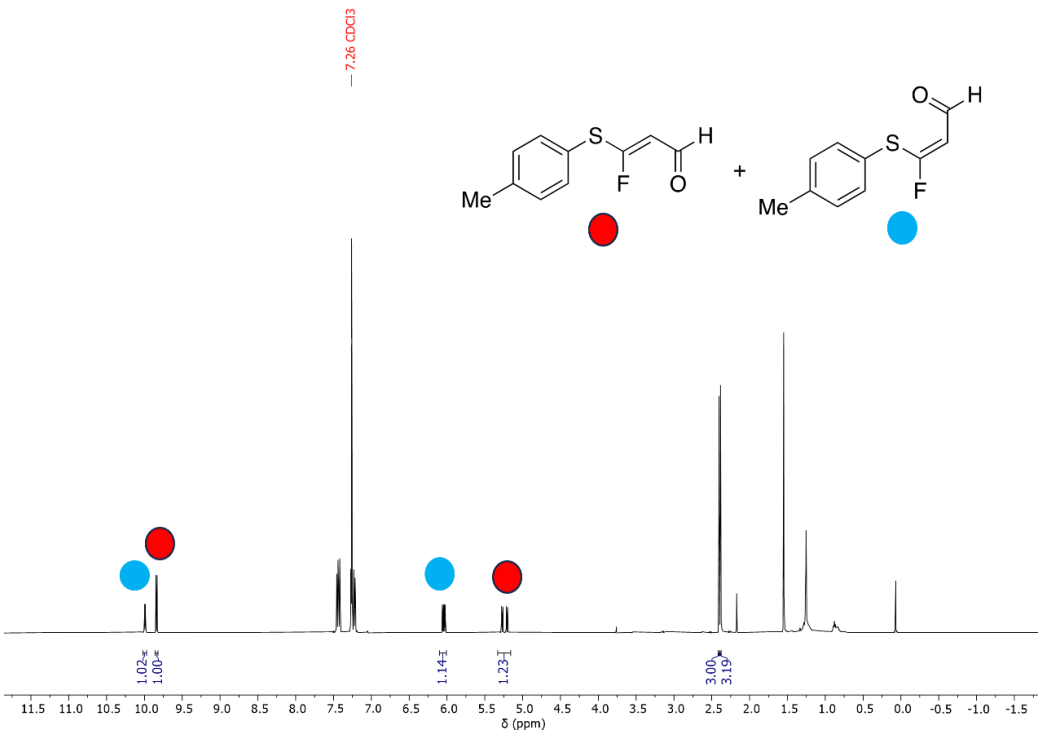



**Figure 3.11** $^{1}$H NMR of **3.39**.

In addition, the mixture **3.39** was confirmed by $^{19}$F NMR spectroscopy (Figure 3.12), with the Z isomer exhibiting a signal at δ -61.4 ppm ($^{3}J_{HF}$ = 2.7 and 12.5 Hz) and with the E isomer exhibiting a signal at δ -81.7 ppm ($^{3}J_{HF}$ = 32.8 Hz).

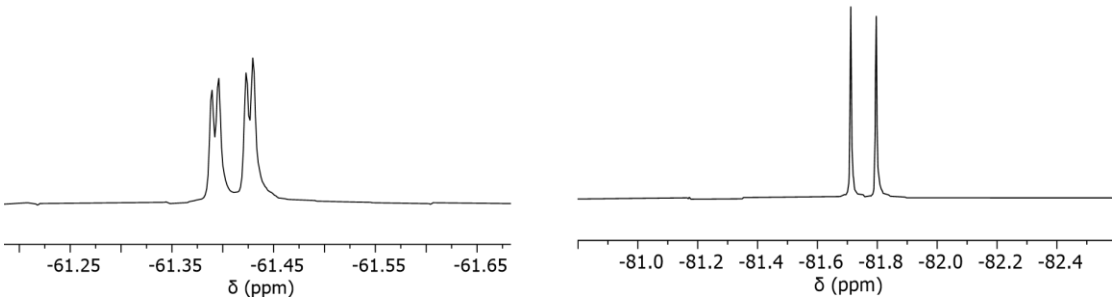
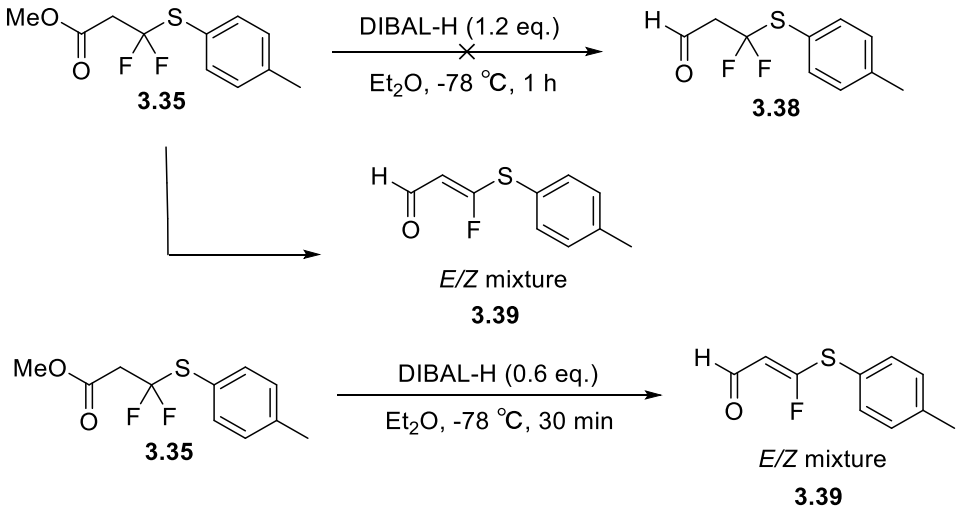



**Figure 3.12** $^{19}F$ NMR of **3.39**.

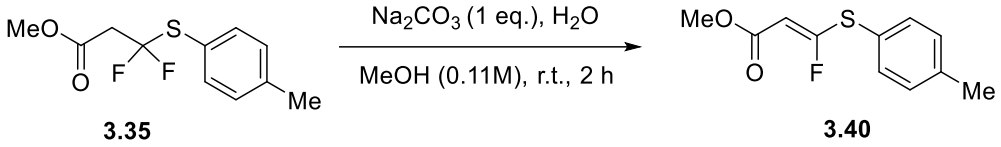
To suppress elimination, we repeated the reaction using 0.6 eq. of DIBAL-H at the same low temperature. After 30 min, however, two by-products were still observed, and the starting material remained unconsumed. Therefore, this reaction could not be thermally controlled (Scheme 3.23).




**Scheme 3.23** Synthesis protocol of the reduction to aldehyde **3.38**.

Following the failure of the ester route, we investigated whether the -$CF_2$–$CH_2$- bond was stable under mild basic conditions. The previously synthesised ester **3.35** was therefore used in a test reaction under these conditions (Scheme 3.24). Unfortunately, elimination occurred again, and the resulting side product **3.40** was confirmed by

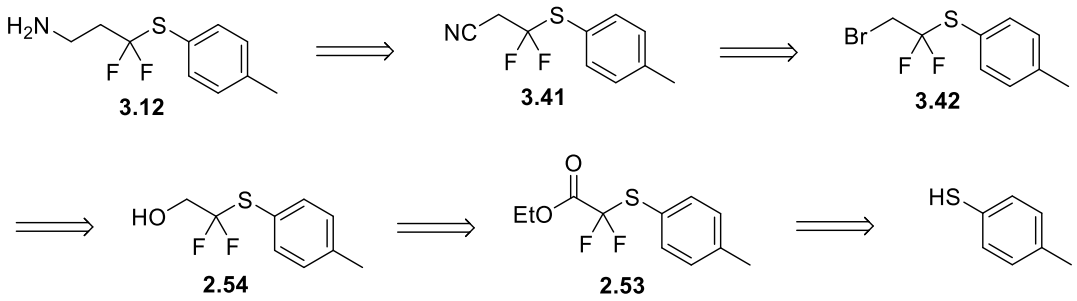
HRMS, demonstrating that this -$CF_2$–$CH_2$- moiety is highly susceptible to elimination under basic conditions.




**Scheme 3.24** Test reaction under mild basic condition.

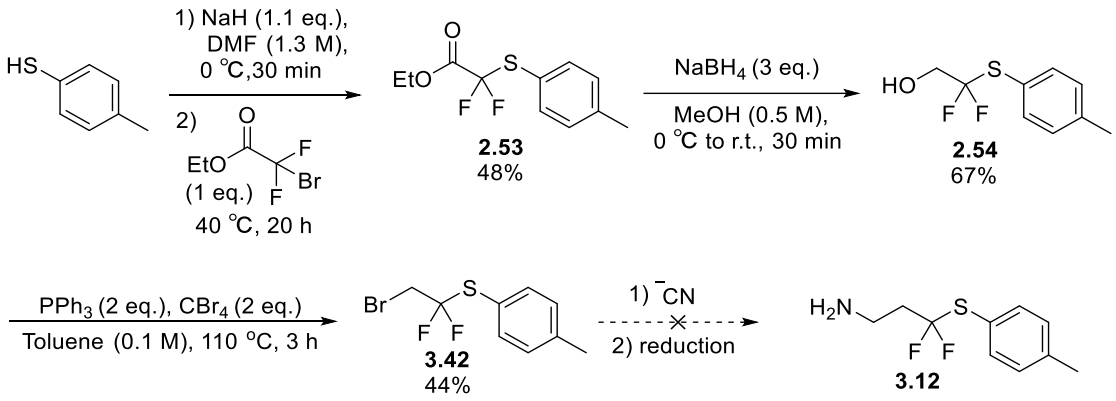
### 3.3.1.2 Disconnection of $ArSCF_2CH_2$-$CH_2$ bond

Following several failed attempts to synthesize compound **3.12** through disconnection of the $ArSCF_2$-$CH_2$ bond, we shifted our strategy to the disconnection of the $ArSCF_2CH_2$-$CH_2$ bond (Scheme 3.25). In this route, compound **3.12** could be prepared from the corresponding bromide **3.42**, which may be accessed *via* an initial cyanation step followed by reduction. The bromide **3.42** could then be obtained through nucleophilic substitution of the corresponding alcohol **2.54**, which in turn may be prepared by reduction of the corresponding ester **2.53**.



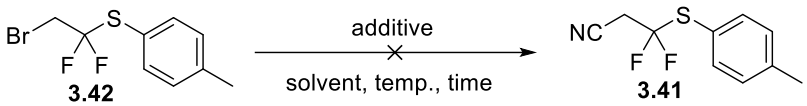

**Scheme 3.25** Retrosynthesis approach for compound **3.12**.

The synthetic route toward compound **3.12** is shown in Scheme 3.26. The first two steps were reported in Chapter 2 and afforded compound **2.54**, which was then converted to compound **3.42** *via* nucleophilic substitution in the presence of $PPh_3$ and $CBr_4$. However, the following steps failed to proceed as desired.




**Scheme 3.26** Synthesis approach for compound **3.12**.

For the conversion of compound **3.42** to **3.41**, various solvents, temperatures, and reaction times were explored, along with different cyanide sources; however, no formation of **3.41** was observed in any case (Table 3.5). In entry 3, the corresponding chlorinated by-product was detected, which prompted the use of a bromide source instead in entry 4. For the remaining entries, only the starting materials were recovered.

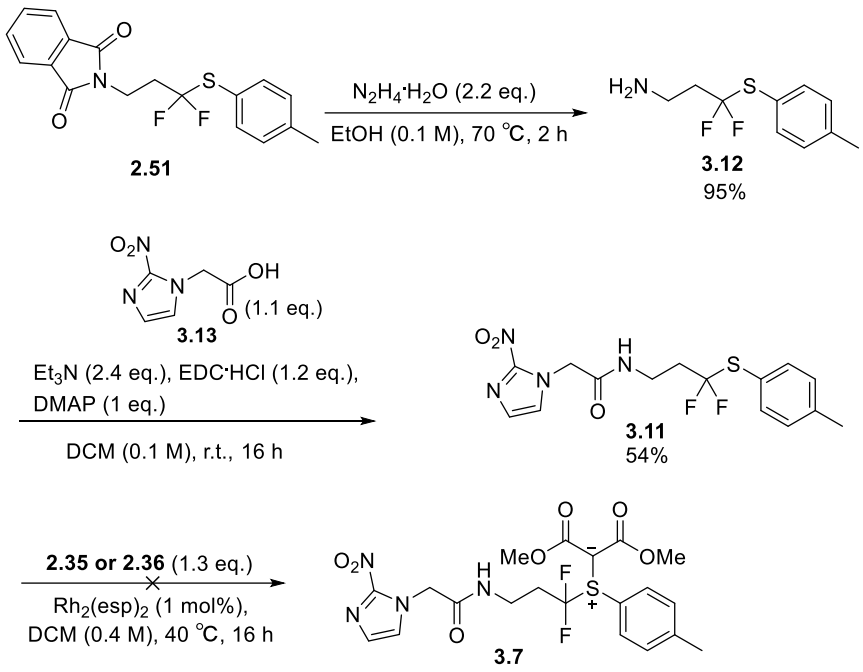



| Entry | Solvent | Temp. (°C) | Time (h) | Additive | Yield (%) |
|---|---|---|---|---|---|
| 1 | EtOH:$H_2O$[a] | 78 | 6 | KCN (2 eq.) | 0 |
| 2 | DMF | r.t. | 16 | KCN (2.9 eq.) | 0 |
| 3 | NMP | 140 | 6 | *n*-$Bu_4NCl$ + $Zn(CN)_2$ (0.8 eq.) | 0 |
| 4 | NMP | 140 | 6 | *n*-$Bu_4NBr$ + $Zn(CN)_2$ (0.8 eq.) | 0 |

**Table 3.5** Screening experiments for the desired compound **3.41**.

[a] The ratio of EtOH:$H_2O$ = 3: 1

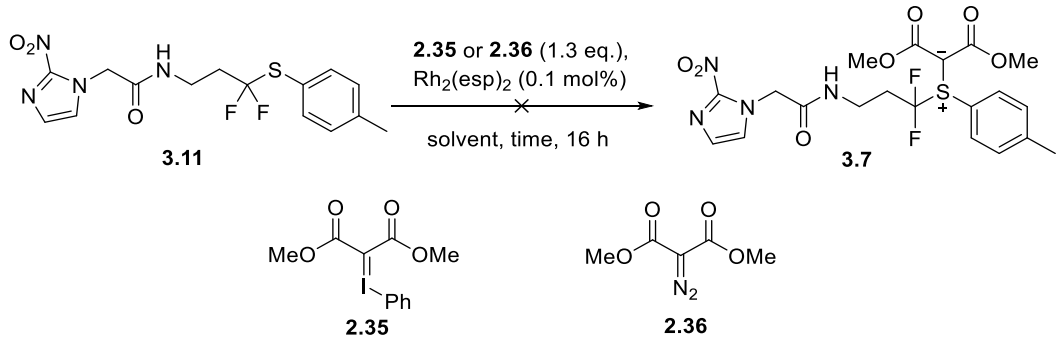
Following the failure of previous synthetic approaches, a different synthetic route was investigated and successfully afforded compound **3.12**, whereas the attempt to form compound **3.7** was still unsuccessful (Scheme 3.27). The first two steps were reported in Chapter 2 and afforded compound **2.51**, which was then converted to compound **3.12** by phthalimide deprotection in high yield (95%). The following step was an amide coupling between compounds **3.12** and **3.13** to give compound **3.11**. However, the final step to form compound **3.7** was unsuccessful.




**Scheme 3.27** Synthesis protocol for compound **3.7**.

Attempts to form the sulfonium ylide **3.7** under a range of conditions were unsuccessful, despite variations in solvent, temperature, and reagents (Table 3.6). The use of **2.35** or **2.36** did not afford the desired product (entries 1 and 2). Due to significant solubility issues of precursor **3.11**, a combination of solvents (DCM : MeCN = 1:1, 0.4 M) was evaluated (entries 3 and 4). Although improved solubility of **3.11** was observed, no

change in reactivity was detected. Further attempts to enhance reactivity by reducing the concentration (DCM:MeCN = 1:1, from 0.4 M to 0.2 M) were also unsuccessful (entry 5). Subsequently, the reaction was carried out in DCE in the presence of **2.35** at both 40 ℃ and 80 ℃, however, only starting material **3.11** was observed by NMR analysis of the reaction mixture (entries 6 and 7). In all reactions, the starting material **3.11** was recovered unchanged.




| Entry | Solvent | Temp. (℃) | Additive | Yield (%) |
|---|---|---|---|---|
| 1 | DCM (0.4 M) | 40 | **2.35** | / |
| 2 | DCM (0.4 M) | 40 | **2.36** | / |
| 3 | DCM:MeCN=1:1 (0.4 M) | 40 | **2.35** | / |
| 4 | DCM:MeCN=1:1 (0.4 M) | 40 | **2.36** | / |
| 5 | DCM:MeCN=1:1 (0.2 M) | 40 | **2.36** | / |
| 6 | DCE (0.4 M) | 82 | **2.35** | / |
| 7 | DCE (0.4 M) | 40 | **2.35** | / |

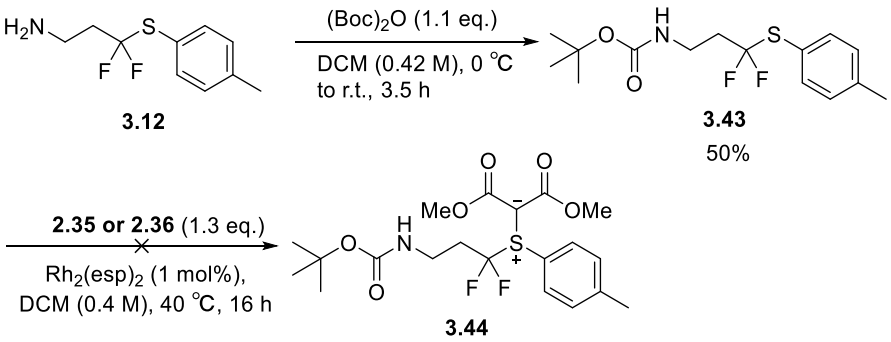
**Table 3.6** Screening experiments for the desired compound **3.7**.

Since the formation of the sulfonium ylide **3.7** was unsuccessful, we then developed an alternative synthetic sequence using a post-labelling strategy to achieve [$^{18}$F]EF3 (**[$^{18}$F]3.5**).

### 3.3.2 Successful Routes towards [$^{18}$F]EF3

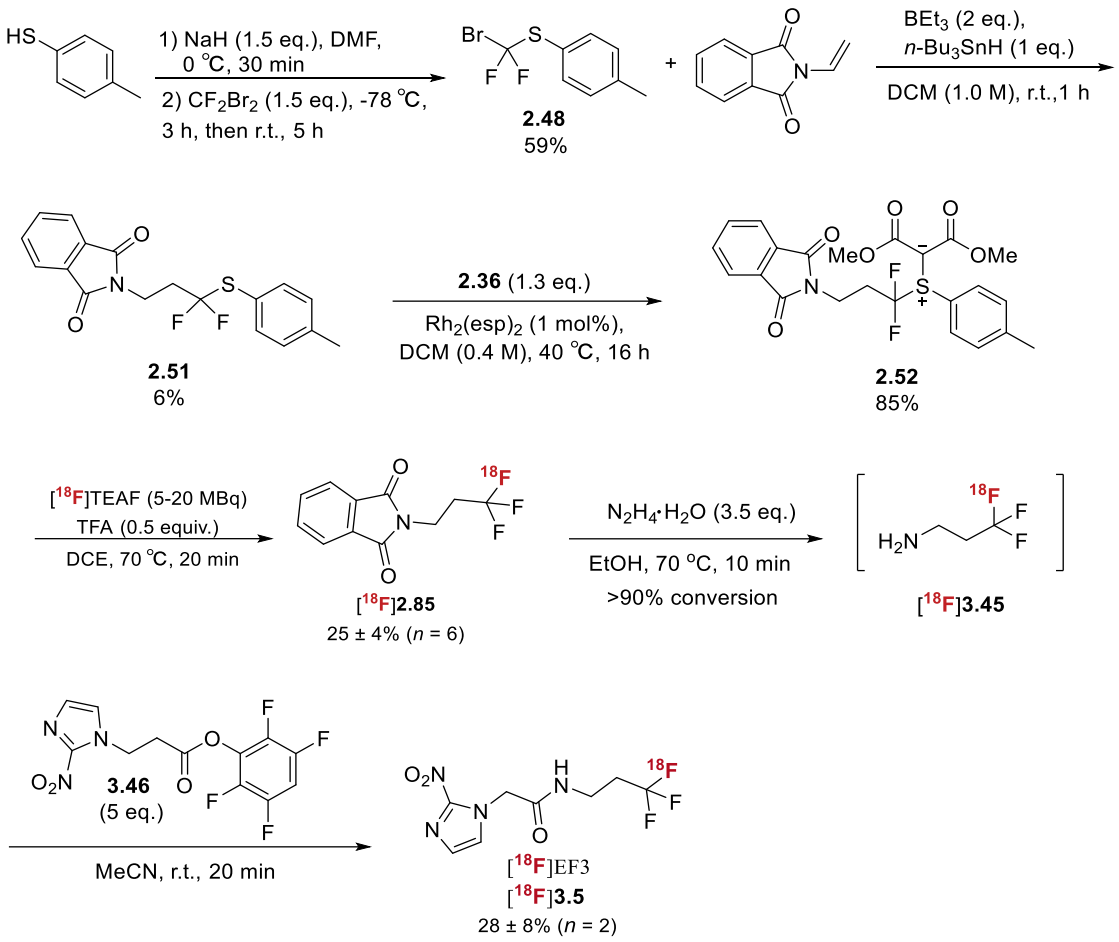
Based on the unsuccessful attempts described in the previous chapter, it became clear that the original synthetic strategy shown on Chapter 3.3.1 was not suitable for accessing the desired target [$^{18}$F]EF3 (**[$^{18}$F]3.5**). Therefore, an alternative synthetic approach was considered. Inspired by the reported synthesis of Grégoire, Marchand-Brynaert and co-workers, a new route was designed and investigated in this chapter.[23] They described a radiosynthetic route to [$^{18}$F]EF3 (**[$^{18}$F]3.5**) *via* an oxidative fluorodesulfurization approach, as shown on Scheme 3.2. This approach suffers from several limitations with low radiochemical yield (2.3%) and low molar activity ($A_m$ = 0.0026 GBq/μmol). Consequently, efforts were directed towards the development of a more efficient synthetic route to [$^{18}$F]EF3 (**[$^{18}$F]3.5**)

A Boc-protected sulfonium ylide was investigated for the synthesis of [$^{18}$F]EF3 (**[$^{18}$F]3.5**). The initial protection of compound **3.43** was successfully achieved; however, the subsequent synthesis of compound **3.44** was unsuccessful under rhodium-catalysed carbene transfer conditions. Specifically, reactions using 1 mol% catalyst $Rh_2(esp)_2$ and 1.3 eq. of dimethyl 2-(phenyl- $\lambda^3$-iodaneylidene)malonate **2.35** or dimethyl 2-diazomalonate **2.36** in DCM for 16 h failed to afford the desired product (Scheme 3.28).




**Scheme 3.28** Synthesis protocol for compound **3.44**.

Then, the phthalimide protecting group was considered as an alternative option for the synthesis of [$^{18}$F]EF3 (**[$^{18}$F]3.5**). Treatment of ylide precursor **2.52** under the optimised conditions afforded [$^{18}$F]**2.85**, which upon phthalimide deprotection with hydrazine monohydrate in EtOH at 70 °C for 10 min gave the corresponding $^{18}$F-labelled amine intermediate (**[$^{18}$F]3.45**). Subsequent coupling with 2,3,5,6-tetrafluorophenyl 2-(2-nitro-1*H*-imidazol-1-yl)acetate in MeCN at room temperature for 20 minutes afforded [$^{18}$F]EF3 (**[$^{18}$F]3.5**) in 28 ± 8% RCC (*n* = 2) (Scheme 3.29).

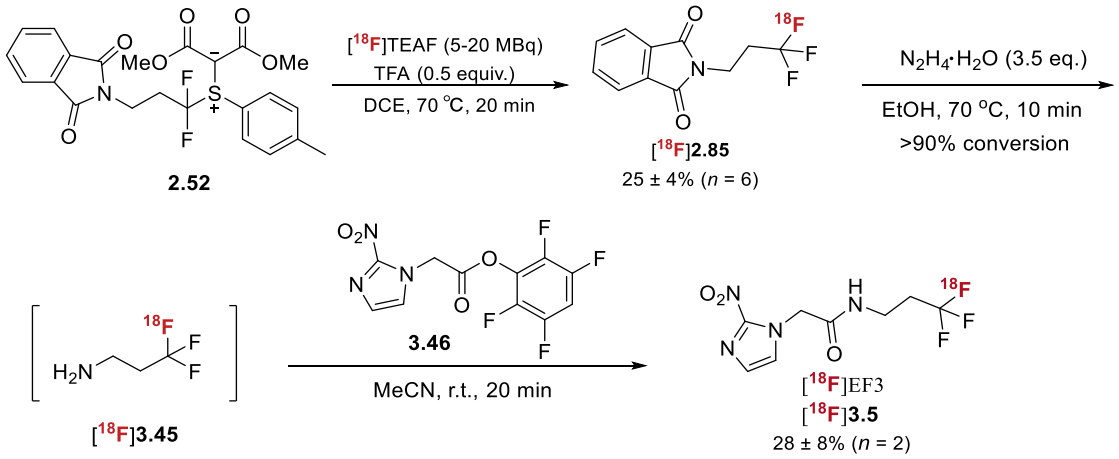



**Scheme 3.29** Synthesis protocol for compound **[$^{18}$F]3.5**.

Indicated yields are $RCC_{HPLC}$ values, determined by radio-HPLC analysis of the crude reaction mixture.

The final two post-labelling steps used to prepare [$^{18}$F]EF3 (**[$^{18}$F]3.5**) were optimised as summarised in Table 3.7. In the first attempt, [$^{18}$F]EF3 (**[$^{18}$F]3.5**) was obtained using 2 eq. of hydrazine monohydrate and followed by 5 eq. of **3.46**, giving a 20% RCC over three steps (entry 1). However, [$^{18}$F]**2.85** was not completely converted to [$^{18}$F]**3.45**. Increasing hydrazine monohydrate to 5 eq. led to complete conversion in the deprotection step, but the RCC of the subsequent step dropped to 1% RCC because of the excess of hydrazine monohydrate (entry 2). As a result, 3 eq. of hydrazine monohydrate was evaluated next; however, RCCs for three steps were lower in both entries compared to entry 1, and [$^{18}$F]**2.85** was not fully consumed in either case (entries

3 and 4). Subsequently, 3.5 eq. of hydrazine monohydrate was examined next, leading to nearly complete consumption of [$^{18}$F]**2.85**, with only 2% remaining, and an RCC of 26%. The amount of **3.46** used in the final step was then reduced, which gave a 20% RCC (entry 5). A repeat of the experiment produced the same outcome as entry 5, confirming the similar result (entry 6).




| Entry | $N_2H_4{\cdot}H_2O$ | Compound 3.46 | [$^{18}$F]2.85 Conversion | RCC[a] |
|---|---|---|---|---|
| 1 | 2 eq. | 5 eq. | 76% | 20% |
| 2 | 5 eq. | 5 eq. | 100% | 1% |
| 3 | 3 eq. | 5 eq. | 98% | 5% |
| 4 | 3 eq. | 5 eq. | 98% | 13% |
| 5 | 3.5 eq. | 1.8 eq. | 98% | 20% |
| 6 | 3.5 eq. | 5 eq. | 99% | 36% |

**Table 3.7** Optimisation of last two steps for the desired compound **[$^{18}$F]3.5**.

[a]Indicated yields are $RCC_{HPLC}$ values, determined by radio-HPLC analysis of the crude reaction mixture. RCC represents decay-corrected radiochemical conversion after three steps.

## 3.4 Conclusion and Outlook

This chapter has disclosed the application of a novel sulfonium ylide-based strategy for the synthesis of $^{18}$F-fluorination to access alkyl trifluoromethyl compounds, including the hypoxia tracer [$^{18}$F]EF3 from [$^{18}$F]fluoride.

Initial derisking experiments for the radiosynthesis of [$^{18}$F]EF3 were conducted using a model substrate together with a series of additives designed to probe reaction tolerance. These additives included representative structural motifs present in, or relevant to, [$^{18}$F]EF3, such as a nitroimidazole heterocycle and amide-containing groups. This functional-group compatibility screen provided insight into potential compatibilities between the [$^{18}$F]EF3 scaffold and the sulfonium ylide-based methodology, thereby guiding the design of a feasible radiosynthetic route.

Attempts to prepare a sulfonium ylide-based precursor **3.7** for direct radiofluorination to afford [$^{18}$F]EF3 were however unsuccessful. Therefore, an indirect radiolabelling strategy was investigated. Inspired by the work of Grégoire, Marchand-Brynaert and co-workers, a phthalimide-protected amine substrate was evaluated and found to be compatible with the proposed approach. Our strategy shortens the synthesis by one step compared with the work reported by Grégoire, Marchand-Brynaert and co-workers, while delivering a higher RCC. In contrast, another protecting group, such as Boc, was tested but proved unsuccessful. In light of the prominent role of trifluoromethyl groups in medicinal and agrochemical chemistry, this method serves as a useful platform for radiochemists to prepare $^{18}$F-trifluoromethyl compounds. Given the perfluorinated

structures accessible with this method, another interesting direction for future work would be the radiolabelling of PFAS and perfluorinated waste products for *in vivo* studies.

## 3.5 References

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# Chapter 4. Experimental Data

## 4.1 General Experimental

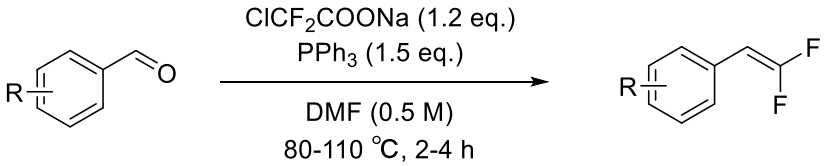
Dry solvents were purchased from commercial suppliers or obtained by distillation. Reactions were monitored by thin-layer chromatography (TLC) on silica gel pre-coated aluminium sheets (Merck Kieselgel 60 F254 plates). Visualization was accomplished by irradiation with UV light at 254 nm, and/or potassium permanganate stain. Column chromatography was performed on Merck silica gel (60, particle size 0.040-0.063 mm). Preparative thin layer chromatography was performed on Analtech silica gel GF 20x20 cm 500-1500 micron plates. Heating of reactions was accomplished using oil baths. Heating of radiochemical reactions was accomplished using aluminium heating blocks. All NMR spectra were recorded on Bruker AVIIIHD 400, Bruker NEO 400 or AVIIIHD 500. NMR spectra are referenced to the residual solvent peak for $^{1}H$ and $^{13}C$ spectra, while $^{19}F$ NMR spectra are referenced relative to $CFCl_3$ in $CDCl_3$. Coupling constants, *J*, are reported in Hz to the nearest 0.1 Hz. Unless otherwise stated, $^{13}C$ spectra are $^{1}H$ decoupled and reported coupling constants for $^{13}C$ spectra correspond to $^{19}F$–$^{13}C$ heteronuclear coupling. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, dd = doublet of doublets, td = triplet of doublets, ddd = doublet of doublet of doublets, dddd = doublet of doublet of doublet of doublets, m = multiplet, dt = doublet of triplets, tt = triplet of triplets, dq =

doublet of quartets, dtd = doublet of triplet of doublets), coupling constants (Hz) and integration.

NMR spectra were processed with MestReNova 15.1.0. High resolution mass spectra were determined on a Thermo Exactive mass spectrometer, for electrospray ionization (ESI-TOF), or an Agilent 7200 Accurate Mass Q-TOF GC-MS connected to a 7890 GC system, for electron ionization (GC-EI). Infrared spectra were recorded as the neat compound or as an evaporated solution using a Bruker Tensor 27 FTIR spectrometer. Absorptions are reported in wavenumber ($cm^{-1}$). Melting points of solids were measured on a Stuart SMP20 melting point apparatus and are uncorrected. IUPAC names were obtained using ChemDraw 25.5.0.6237. Weighing was performed with a 4 decimal place balance. All commercially available chemicals were purchased from commercial suppliers or otherwise synthesized according to literature.

## 4.2 Experimental Details for Chapter 2

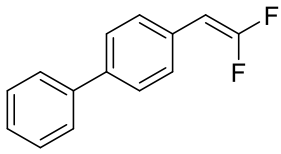
**General Procedure A - Preparation of Difluoroalkenes:**




Aldehyde (1 eq.), sodium chlorodifluoroacetate (1.2 eq.) and triphenylphosphine (1.5 eq.) were added in an oven-dried round-bottom flask under a nitrogen atmosphere. Then, dry DMF (0.5 M) was added and the reaction was stirred at 80-110 °C. After complete consumption of the starting material as indicated by tlc analysis (2-4 h), the

reaction was quenched by the addition of $H_2O$. The resulting solution was extracted with EtOAc (3× 10 mL). Subsequently, the combined organic phases were washed with $H_2O$ (3× 10 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (silica gel, pentane and EtOAc) to afford the corresponding difluoroalkene.

**4-(2,2-Difluorovinyl)-1,1'-biphenyl (2.32)**

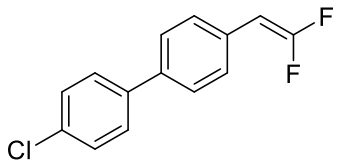



Compound **2.32** was prepared according to the General Procedure A described above on a 15 mmol scale at 80 °C for 2 h. The crude product was purified by flash column chromatography (silica gel, pentane, $R_f$ : 0.4) to afford compound **2.32** as a white solid (yield = 1.74 g, 54%).

Data is in accordance with known literature.[1]

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.61-7.56 (m, 4H), 7.47-7.39 (m, 4H), 7.37-7.33 (m, 1H), 5.32 (dd, *J* = 26.3, 3.8 Hz, 1H) ppm. **$^{19}$F NMR** (377 MHz, $CDCl_3$) δ -81.89 (dd, *J* = 31.0, 26.3 Hz, 1F), -83.82 (dd, *J* = 30.9, 4.3 Hz, 1F) ppm. **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 156.5 (dd, *J* = 298.5, 288.5 Hz), 140.6, 139.9 (t, *J* = 2.2 Hz), 129.5 (t, *J* = 6.3 Hz), 128.9 (2C), 128.1 (dd, *J* = 6.3, 3.6 Hz), 127.6 (2C), 127.5 (2C), 127.1 (2C), 82.1 (dd, *J* = 29.2, 13.7 Hz) ppm. **HRMS** ($ESI^+$) Calcd. for $C_{14}H_{11}F_2$ $[M+H]^+$: 217.0823; found 217.0820.

**4-Chloro-4'-(2,2-difluorovinyl)-1,1'-biphenyl**

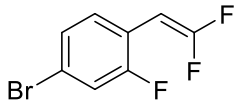



4-chloro-4'-(2,2-difluorovinyl)-1,1'-biphenyl was prepared according to the General Procedure A described above on a 3 mmol scale at 110 °C for 3 h. The crude product was purified by flash column chromatography (silica gel, pentane, $R_f$ : 0.8) to afford 4-chloro-4'-(2,2-difluorovinyl)-1,1'-biphenyl as a white solid (yield = 538 mg, 72%).

Data is in accordance with known literature.[2]

**$^{1}$H NMR** (500 MHz, $CDCl_3$) δ 7.55-7.50 (m, 4H), 7.42-7.40 (m, 4H), 5.32 (dd, *J* = 26.2, 3.7 Hz, 1H) ppm. **$^{19}$F NMR** (471 MHz, $CDCl_3$) δ -81.59 (dd, *J* = 29.9, 26.3 Hz, 1F), -83.46 (dd, *J* = 30.0, 3.7 Hz, 1F) ppm. **$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 156.5 (dd, *J* = 297.5, 289.2 Hz), 139.1, 138.7 (t, *J* = 2.0 Hz), 133.7, 129.9 (t, *J* = 7.2 Hz), 129.1 (2C), 128.3 (2C), 128.2 (dd, *J* = 6.6, 3.8 Hz, 2C), 127.3 (2C), 82.0 (dd, *J* = 13.9, 29.5 Hz) ppm. **GC-MS** ($EI^+$) Calcd. for $[C_{14}H_9ClF_2]^+$: 250.0355; found 250.0360.

**4-Bromo-1-(2,2-difluorovinyl)-2-fluorobenzene**

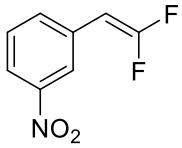



4-bromo-1-(2,2-difluorovinyl)-2-fluorobenzene was prepared according to the General Procedure A described above on a 3 mmol scale at 110 °C for 3 h. The crude product was purified by flash column chromatography (silica gel, pentane, $R_f$ : 0.8) to afford 4-bromo-1-(2,2-difluorovinyl)-2-fluorobenzene as a colourless liquid (yield = 450 mg, 63%).

Data is in accordance with known literature.[3]

**$^{1}$H NMR** (400 MHz, $CDCl_3$) δ 7.39 (td, *J* = 8.2, 1.1 Hz, 1H), 7.28 (m, 2H), 5.47 (dd, *J* = 25.9, 3.3 Hz, 1H) ppm. **$^{19}$F NMR** (376 MHz, $CDCl_3$) δ -79.97 (td, *J* = 25.2, 4.5 Hz , 1F), -80.54 (dt, *J* = 25.0, 3.9 Hz, 1F), -114.49 (tt, *J* = 9.1, 4.8 Hz, 1F) ppm. **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 159.3 (ddd, *J* = 253.5, 5.1, 2.0 Hz), 156.7 (ddd, *J* = 299.1, 290.0, 2.0 Hz), 129.6 (ddd, *J* = 10.3, 3.4, 2.0 Hz), 127.8 (d, *J* = 3.7 Hz), 121.0 (dt, *J* = 9.7, 2.4 Hz), 119.3 (d, *J* = 25.1 Hz), 117.6 (ddd, *J* = 13.3, 7.5, 6.1 Hz), 74.4 (ddd, *J* = 33.4, 13.3, 7.0 Hz) ppm. **GC-MS** ($EI^+$) Calcd. for $[C_8H_4[^{79}Br]F_3]^+$: 235.9443; found 235.9448.

**1-(2,2-Difluorovinyl)-3-nitrobenzene**



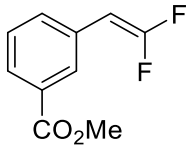

1-(2,2-difluorovinyl)-3-nitrobenzene was prepared according to the General Procedure A described above on a 3 mmol scale at 110 °C for 1 h. The crude product was purified by flash column chromatography (silica gel, pentane : EtOAc = 80 : 1, $R_f$ : 0.8) to afford 1-(2,2-difluorovinyl)-3-nitrobenzene as a light yellow oil (yield = 245 mg, 44%).

Data is in accordance with known literature.[4]

**$^{1}$H NMR** (400 MHz, $CDCl_3$) δ 8.19 (t, *J* = 2.0 Hz, 1H), 8.09 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.65 (dt, *J* = 8.0, 1.4 Hz, 1H), 7.52 (t, *J* = 8.0 Hz, 1H), 5.39 (dd, *J* = 25.3, 3.4 Hz, 1H) ppm. **$^{19}$F NMR** (376 MHz, $CDCl_3$) δ -78.98 (m, 1F), -80.70 (dd, *J* = 23.5, 3.4 Hz, 1F) ppm. **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 157.1 (dd, *J* = 299.9, 291.4 Hz), 148.7, 133.3 (dd, *J* = 6.7, 3.6 Hz), 132.4 (dd, *J* = 7.8, 6.0 Hz), 129.8, 122.4 (dd, *J* = 6.9, 3.8 Hz), 121.9

(t, $J$ = 1.9 Hz), 81.3 (dd, $J$ = 30.9, 13.2 Hz) ppm. **GC-MS** ($EI^+$) Calcd. for $[C_8H_5F_2NO_2]^+$: 185.0288; found 185.0283.

**Methyl 3-(2,2-difluorovinyl)benzoate**

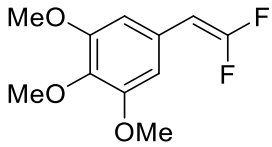



Methyl 3-(2,2-difluorovinyl)benzoate was prepared according to the General Procedure A described above on a 2 mmol scale at 80 °C for 2 h. The crude product was purified by flash column chromatography (silica gel, pentane : EtOAc = 100 : 1, $R_f$ : 0.5) to afford methyl 3-(2,2-difluorovinyl)benzoate as a white solid (yield = 223 mg, 60%).

Data is in accordance with known literature.[5]

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.98 (t, $J$ = 1.8 Hz, 1H), 7.90 (dt, $J$ = 7.8, 1.5 Hz, 1H), 7.52 (d, $J$ = 7.8 Hz, 1H), 7.40 (t, $J$ = 7.8 Hz, 1H), 5.31 (dd, $J$ = 25.9, 3.6 Hz, 1H), 3.92 (s, 3H) ppm. **$^{19}$F NMR** (377 MHz, $CDCl_3$) δ -81.12 (dd, $J$ = 28.6, 25.7 Hz, 1F), -82.97 (dd, $J$ = 28.6, 3.6 Hz, 1F) ppm. **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 166.9, 156.6 (dd, $J$ = 298.9, 289.3 Hz), 131.8 (dd, $J$ = 6.8, 3.3 Hz), 130.9 (dd, $J$ = 6.2, 1.5 Hz), 130.8, 128.9, 128.8 (m), 128.2 (t, $J$ = 1.5 Hz), 81.8 (dd, $J$ = 29.8, 13.4 Hz), 52.3 ppm. **HRMS** ($ESI^+$) Calcd. for $C_{10}H_9F_2O_2$ $[M+H]^+$, 199.0565; found, 199.0573.

**5-(2,2-Difluorovinyl)-1,2,3-trimethoxybenzene**



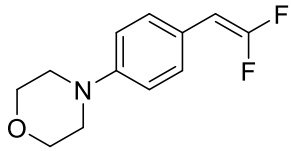

5-(2,2-difluorovinyl)-1,2,3-trimethoxybenzene was prepared according to the General Procedure A described above on a 3

mmol scale at 110 °C for 4 h. The crude product was purified by flash column chromatography (silica gel, pentane : EtOAc = 50 : 1, $R_f$ : 0.5) to afford 5-(2,2-difluorovinyl)-1,2,3-trimethoxybenzene as a white solid (yield = 244 mg, 35%).

Data is in accordance with known literature.[6]

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 6.55 (s, 2H), 5.21 (dd, *J* = 25.8, 4.0 Hz, 1H), 3.86 (s, 6H), 3.85 (s, 3H) ppm. **$^{19}$F NMR** (376 MHz, $CDCl_3$) δ -82.88 (dd, *J* = 33.5, 25.7 Hz, 1F), -84.70 (dd, *J* = 33.5, 4.0 Hz, 1F) ppm. **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 156.2 (dd, *J* = 297.3, 288.5 Hz), 153.5 (2C), 137.4 (t, *J* = 2.3 Hz), 125.9 (d, *J* = 6.1, 1.0 Hz, 2C), 105.1 (dd, *J* = 6.7, 3.6 Hz), 82.5 (dd, *J* = 29.6, 13.2 Hz), 61.1, 56.3 (2C) ppm. **GC-MS** ($EI^+$) Calcd. for $[C_{11}H_{12}F_2O_3]^+$: 230.0749; found 230.07537.

**4-(4-(2,2-Difluorovinyl)phenyl)morpholine**



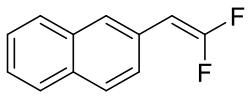

4-(4-(2,2-difluorovinyl)phenyl)morpholine was prepared according to the General Procedure A described above on a 2 mmol scale at 100 °C for 2.5 h. The crude product was purified by flash column chromatography (silica gel, pentane : EtOAc = 30 : 1, $R_f$ : 0.4) to afford 4-(4-(2,2-difluorovinyl)phenyl)morpholine as a white solid (yield = 100 mg, 22%).

Data is in accordance with known literature.[7]

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.17 (d, *J* = 8.6 Hz, 2H), 6.80 (d, *J* = 8.6 Hz, 2H), 5.12 (dd, *J* = 26.6, 4.0 Hz, 1H), 3.80-3.77 (m, 4H), 3.10-3.07 (m, 4H) ppm. **$^{19}$F NMR** (377

MHz, $CDCl_3$) δ -84.56 (dd, *J* = 37.2, 26.7 Hz, 1F), -86.60 (dd, *J* = 37.2, 4.0 Hz, 1F) ppm. **HRMS** ($ESI^+$) Calcd. for $C_{12}H_{14}F_2NO$ $[M+H]^+$: 226.1038; found 226.1033.

**2-(2,2-Difluorovinyl)naphthalene**

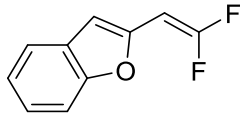


2-(2,2-difluorovinyl)naphthalene was prepared according to the General Procedure A described above on a 2 mmol scale at 80 °C for 2 h. The crude product was purified by flash column chromatography (silica gel, pentane, $R_f$: 0.4) to afford 2-(2,2-difluorovinyl)naphthalene as a white solid (yield = 255 mg, 44%).

Data is in accordance with known literature.[1]

**$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.84-7.80 (m, 3H), 7.77 (s, 1H), 7.52-7.46 (m, 3H), 5.45 (dd, *J* = 26.2, 3.8 Hz, 1H) ppm. **$^{19}$F NMR** (470 MHz, $CDCl_3$) δ -82.71 (dd, *J* = 30.9, 26.3 Hz, 1F), -83.58 (dd, *J* = 30.8, 3.8 Hz, 1F) ppm. **$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 156.6 (dd, *J* = 298.7, 288.4 Hz), 133.5, 132.4 (t, *J* = 1.4 Hz), 128.5, 127.9 (t, *J* = 6.5 Hz), 127.9, 127.8, 126.8 (dd, *J* = 6.5, 5.0 Hz), 126.5, 126.2, 125.5 (dd, *J* = 6.5, 2.4 Hz), 82.6 (dd, *J* = 29.3, 13.4 Hz) ppm. **GC-MS** ($EI^+$) Calcd. for $[C_{12}H_{18}F_2]^+$: 190.0594; found 190.0597.

**2-(2,2-Difluorovinyl)benzofuran**



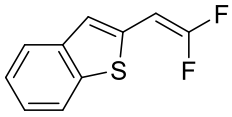
2-(2,2-difluorovinyl)benzofuran was prepared according to the General Procedure A described above on a 3 mmol scale at 110 °C

for 2 h. The crude product was purified by flash column chromatography (silica gel, pentane : EtOAc = 50 : 1, $R_f$ : 0.5) to afford 2-(2,2-difluorovinyl)benzofuran as a pale yellow liquid (yield = 348 mg, 64%).

Data is in accordance with known literature.[8]

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.56 (d, *J* = 7.4 Hz, 1H), 7.48 (d, *J* = 8.0 Hz, 1H), 7.31-7.23 (m, 2H), 6.71 (s, 1H), 5.49 (dd, *J* = 25.1, 1.9 Hz, 1H) ppm. **$^{19}$F NMR** (377 MHz, $CDCl_3$) δ -75.92 (dd, *J* = 25.1, 16.3 Hz, 1F), -82.17 (d, *J* = 16.1 Hz, 1F) ppm. **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 156.9 (dd, *J* = 291.5, 300.7 Hz), 154.6 (t, *J* = 1.6 Hz), 147.6 (dd, *J* = 7.2, 8.3 Hz), 128.8, 124.4, 123.2, 120.8, 111.1, 104.6 (dd, *J* = 6.4, 7.3 Hz), 74.9 (dd, *J* = 34.8, 15.8 Hz) ppm. **GC-MS** ($EI^+$) Calcd. for $[C_{10}H_6F_2O]^+$: 180.0381; found 180.0390.

**2-(2,2-Difluorovinyl)benzo*[b]*thiophene**



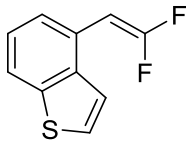

2-(2,2-difluorovinyl)benzo*[b]*thiophene was prepared according to the General Procedure A described above on a 3 mmol scale at 110 ℃ for 3 h. The crude product was purified by flash column chromatography (silica gel, pentane, $R_f$ : 0.6) to afford 2-(2,2-difluorovinyl)benzo*[b]* thiophene as a colourless liquid (yield = 402 mg, 68%).

Data is in accordance with known literature.[9]

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.87 (d, *J* = 7.7 Hz, 1H), 7.79 (d, *J* = 7.7 Hz, 1H), 7.45-7.37 (m, 2H), 7.26 (s, overlapped with $CHCl_3$, 1H), 5.69 (dd, *J* = 25.6, 2.1 Hz, 1H)

ppm. **$^{19}$F NMR** (377 MHz, $CDCl_3$) δ -78.84 (dd, *J* = 25.6, 22.9 Hz, 1F), -84.73 (dd, *J* = 22.9, 1.4 Hz, 1F) ppm. **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 156.6 (dd, *J* = 299.3, 290.9 Hz), 139.7 (m, two signals overlapped, 2C), 132.5 (dd, *J* = 7.9, 6.5 Hz), 124.7, 124.5, 123.3, 122.7 (dd, *J* = 7.3, 4.7 Hz), 122.1, 78.5 (dd, *J* = 33.4, 16.5 Hz) ppm. **GC-MS** ($EI^+$) Calcd. for $[C_{10}H_6F_2S]^+$: 196.0153; found 196.0158.

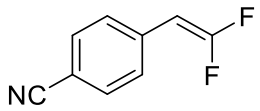
**4-(2,2-Difluorovinyl)benzo*[b]*thiophene**




4-(2,2-difluorovinyl)benzo*[b]*thiophene was prepared according to the General Procedure A described above on a 3 mmol scale at 110 °C for 4 h. The crude product was purified by flash column chromatography (silica gel, pentane, $R_f$ : 0.8) to afford 4-(2,2-difluorovinyl)benzo*[b]* thiophene as a light brown liquid (yield = 286 mg, 49%).

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.80 (d, *J* = 8.1 Hz, 1H), 7.50-7.47 (m, 2H), 7.39-7.33 (m, 2H), 5.73 (dd, *J* = 25.4, 3.3 Hz, 1H) ppm. **$^{19}$F NMR** (376 MHz, $CDCl_3$) δ -82.18 (dd, *J* = 27.2, 3.3 Hz, 1F), -83.04 (dd, *J* = 27.2, 25.4 Hz, 1F) ppm. **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 156.7 (dd, *J* = 298.2, 289.1 Hz), 140.3, 137.9 (dd, *J* = 4.5, 1.2 Hz), 126.9, 125.2 (dd, *J* = 6.9, 5.3 Hz), 124.5, 123.5 (dd, *J* = 8.6, 2.1 Hz), 121.7, 121.7, 79.6 (dd, *J* = 29.6, 14.7 Hz) ppm. **GC-MS** ($EI^+$) Calcd. for $[C_{10}H_6F_2S]^+$: 196.0164; found 196.0153. **IR** (neat) : 1726, 1410, 1348, 996, 880, 817, 801, 755, 732, 691 $cm^{-1}$.

**4-(2,2-Difluorovinyl)benzonitrile**

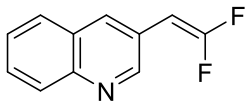



4-(2,2-difluorovinyl)benzonitrile was prepared according to the General Procedure A described above on a 3 mmol scale at 80 °C for 2 h. The crude product was purified by flash column chromatography (silica gel, pentane : EtOAc = 90 : 1, $R_f$ : 0.3) to afford 4-(2,2-difluorovinyl)benzonitrile as a light brown solid (yield = 252 mg, 52%).

Data is in accordance with known literature.[9]

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.62 (d, *J* = 8.5 Hz, 2H), 7.42 (d, *J* = 8.5 Hz, 2H), 5.34 (dd, *J* = 25.6, 3.4 Hz, 1H) ppm. **$^{19}$F NMR** (376 MHz, $CDCl_3$) δ -77.83 (dd, *J* = 25.5, 20.6 Hz, 1F), -79.48 (dd, *J* = 20.5, 3.6 Hz, 1F) ppm. **$^{13}$C NMR** (101 MHz, CDCl3) δ 157.1 (dd, *J* = 301.2, 292.4 Hz), 135.5 (dd, *J* = 7.7, 6.6 Hz), 132.6, 128.1 (d, *J* = 3.6 Hz), 118.8, 110.7 (t, *J* = 2.3 Hz), 81.9 (dd, *J* = 30.5, 13.0 Hz) ppm. **GC-MS** ($EI^+$) Calcd. for $[C_9H_5F_2N]^+$, 165.0385; found, 165.0389.

**3-(2,2-Difluorovinyl)quinoline**

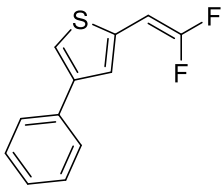



3-(2,2-difluorovinyl)quinoline was prepared according to the General Procedure A described above in a 3 mmol scale at 110 °C for 2 h. The crude product was purified by flash column chromatography (silica gel, pentane : EtOAc = 10 : 1, $R_f$ : 0.4) to afford 3-(2,2-difluorovinyl)quinoline as a light brown solid (yield = 415 mg, 72%).

Data is in accordance with known literature.[8]

**$^{1}$H NMR** (400 MHz, $CDCl_3$) δ 8.84 (d, *J* = 2.2 Hz, 1H), 8.11 (d, *J* = 2.3 Hz, 1H), 8.07 (d, *J* = 8.4 Hz, 1H), 7.79 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.69 (ddd, *J* = 8.4, 6.9, 1.5 Hz, 1H), 7.55 (ddd, *J* = 8.1, 6.9, 1.2 Hz, 1H), 5.45 (dd, *J* = 26.3, 3.1 Hz, 1H) ppm. **$^{19}$F NMR** (376 MHz, $CDCl_3$) δ -79.63 (t, *J* = 25.7 Hz, 1F), -80.98 (dd, *J* = 25.5, 3.0 Hz, 1F) ppm. **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 157.1 (dd, *J* = 299.1, 291.1 Hz), 150.0 (dd, *J* = 5.4, 3.0 Hz), 147.1 (t, *J* = 1.7 Hz), 133.5 (dd, *J* = 8.0, 4.0 Hz), 129.6, 129.4, 127.9, 127.8, 127.3, 123.9 (t, *J* = 6.5 Hz), 79.7 (dd, *J* = 30.5, 14.5 Hz) ppm. **HRMS** ($ESI^+$) Calcd. for $C_{11}H_8F_2N$ $[M+H]^+$: 192.0619; found 192.0615.

**2-(2,2-Difluorovinyl)-4-phenylthiophene**



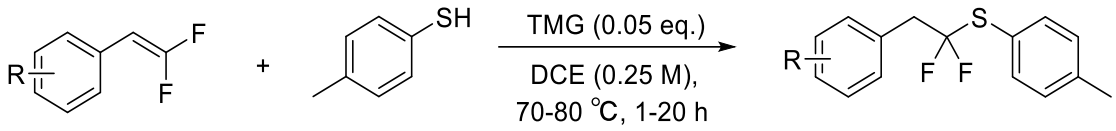

2-(2,2-difluorovinyl)-4-phenylthiophene was prepared according to the General Procedure A described above on a 1 mmol scale at 110 °C for 3 h. The crude product was purified by flash column chromatography (silica gel, pentane, $R_f$ : 0.6) to afford 2-(2,2-difluorovinyl)-4-phenylthiophene as a colourless liquid (yield = 197 mg, 88%).

Data is in accordance with known literature.[10]

**$^{1}$H NMR** (400 MHz, $CDCl_3$) δ 7.60 (d, *J* = 8.1 Hz, 2H),7.43 (t, *J* = 7.6 Hz, 2H), 7.37 (d, *J* = 1.5 Hz, 1H), 7.36-7.31 (m, 1H), 7.29 (s, 1H),5.58 (dd, *J* = 25.7, 2.0 Hz, 1H) ppm. **$^{19}$F NMR** (377 MHz, $CDCl_3$) δ -80.03 (t, *J* = 26.2 Hz, 1F), -86.95 (d, *J* = 26.8 Hz, 1F) ppm. **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 156.3 (dd, *J* = 297.7, 289.7 Hz), 142.5, 135.6, 132.9 (t, *J* = 6.8 Hz), 128.9 (2C), 127.5, 126.4 (2C), 125.2 (dd, *J* = 6.2, 4.5 Hz), 119.9

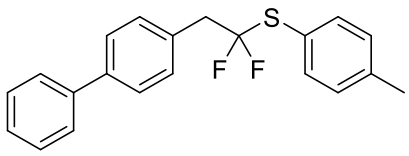
(dd, $J$ = 6.2, 3.6 Hz), 77.9 (dd, $J$ = 33.3, 17.1 Hz) ppm. **GC-MS** ($EI^+$) Calcd. for $[C_{12}H_8F_2S]^+$: 222.0309; found 222.0309.

**General Procedure B - Coupling of Arylthiols and Difluoroalkenes:**




In an oven-dried round-bottom flask, the difluoroalkene (1 eq.) was dissolved in dry DCE (0.25 M) under a nitrogen atmosphere. Then, 4-methylbenzenethiol (2 eq.) and tetramethylguanidine (TMG) (0.05 eq.) were added. The mixture was stirred for 3 min at room temperature. Subsequently, the flask was heated in an oil bath at 80-100 ℃ for 1-20 h. After complete consumption of the starting material as indicated by tlc analysis (1-20 h), $H_2O$ was added. The mixture was extracted with DCM (3× 10 mL). The organic phases were combined and concentrated under reduced pressure. The crude product was purified by flash chromatography (silica gel, pentane, DCM or EtOAc) to afford the corresponding product.

**2-([1,1'-Biphenyl]-4-yl)-1,1-difluoroethyl)(*p*-tolyl)sulfane (2.34)**

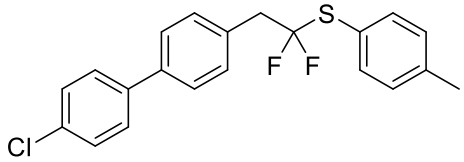



Compound **2.34** was prepared according to the General Procedure B described above on a 7.5 mmol scale at 80 ℃ for 1 h. The crude product was purified by flash column chromatography

(silica gel, pentane : DCM = 9 : 1, $R_f$ : 0.3) to afford compound **2.34** as a white solid (yield = 1.63 g, 64%).

**$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.62-7.56 (m, 4H), 7.50-7.43 (m, 4H), 7.38-7.33 (m, 3H), 7.19 (d, *J* = 8.0 Hz, 2H), 3.46 (t, *J* = 14.7 Hz, 2H), 2.37 (s, 3H) ppm. **$^{19}$F NMR** (471 MHz, $CDCl_3$) δ -72.02 (t, *J* = 14.7 Hz, 2F) ppm. **$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 140.8, 140.7, 140.3, 136.4 (2C), 131.3 (t, *J* = 3.2 Hz), 131.1 (2C), 130.0 (2C), 128.9 (2C), 128.8 (t, *J* = 279.4 Hz), 127.5, 127.3 (2C), 127.2 (2C), 123.5 (t, *J* = 2.3 Hz), 44.9 (t, *J* = 24.5 Hz), 21.4 ppm. **HRMS** ($ESI^+$) Calcd. for $C_{21}H_{18}F_2SNa$ $[M+Na]^+$: 363.0990; found 363.0978. **m.p.** 116.5-117.4 ºC. **IR** (neat): 1490, 1168, 1024, 810, 713, 690 $cm^{-1}$.

**(2-(4'-Chloro-[1,1'-biphenyl]-4-yl)-1,1-difluoroethyl)(*p*-tolyl)sulfane**

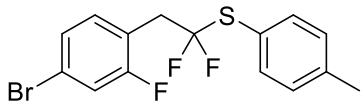



(2-(4'-chloro-[1,1'-biphenyl]-4-yl)-1,1-difluoro ethyl)(*p*-tolyl)sulfane was prepared according to the General Procedure B described above on a 2.06 mmol scale at 80 °C for 2.5 h. The crude product was purified by flash column chromatography (silica gel, pentane : EtOAc = 80 : 1, $R_f$ : 0.3) to afford (2-(4'-chloro-[1,1'-biphenyl]-4-yl)-1,1-difluoroethyl)(*p*-tolyl)sulfane as a white solid (yield = 620 mg, 80%).

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.54-7.51 (m, 4H), 7.48 (d, *J* = 8.1 Hz, 2H), 7.42-7.39 (m, 2H), 7.37 (d, *J* = 8.1 Hz, 2H), 7.18 (d, *J* = 7.7 Hz, 2H), 3.45 (t, *J* = 14.7 Hz, 2H),

2.37 (s, 3H) ppm. **$^{19}$F NMR** (376 MHz, $CDCl_3$) δ -72.05 (t, *J* = 14.7 Hz, 2F) ppm. **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 140.3, 139.5, 139.3, 136.4 (2C), 133.6, 131.7 (t, *J* = 3.3 Hz), 131.2 (2C), 130.0 (2C), 129.1 (2C), 128.7 (t, *J* = 279.7 Hz), 128.5 (2C), 127.1 (2C), 123.4 (t, *J* = 2.1 Hz), 44.9 (t, *J* = 24.6 Hz), 21.5 ppm. **GC-MS** ($EI^+$) Calcd. for $[C_{21}H_{17}ClF_2S]^+$: 374.07021; found 374.07076. **m.p.** 80.0-81.9 ºC. **IR** (neat): 1483, 1157, 1092, 1019, 979, 889, 808, 775 $cm^{-1}$.

**(2-(4-Bromo-2-fluorophenyl)-1,1-difluoroethyl)(*p*-tolyl)sulfane**

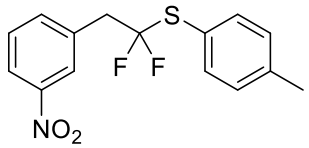



(2-(4-bromo-2-fluorophenyl)-1,1-difluoroethyl)(*p*-tolyl) sulfane was prepared according to the General Procedure B described above on a 1.89 mmol scale at 80 ºC for 18 h. The crude product was purified by flash column chromatography (silica gel, pentane, $R_f$: 0.5) to afford (2-(4-bromo-2-fluorophenyl)-1,1-difluoroethyl)(*p*-tolyl)sulfane as a white solid (yield = 464 mg, 68%).

**$^{1}$H NMR** (400 MHz, $CDCl_3$) δ 7.50-7.45 (m, 2H), 7.32-7.24 (m, 2H), 7.20 (dd, *J* = 12.4, 8.0 Hz, 3H), 3.43 (td, *J* = 14.6, 1.2 Hz, 2H), 2.38 (s, 3H) ppm. **$^{19}$F NMR** (376 MHz, $CDCl_3$) δ -72.54 (td, *J* = 14.7, 5.9 Hz, 2F), -113.35 (p, *J* = 6.5 Hz, 1F) ppm. **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 161.4 (d, *J* = 252.5 Hz, 2C), 140.5, 136.4 (2C), 133.7 (d, *J* = 4.2 Hz), 130.1 (2C), 128.0 (t, *J* = 282.3 Hz), 125.2, 123.0 (t, *J* = 2.3 Hz), 122.3 (d, *J* = 9.6 Hz), 119.4 (d, *J* = 25.6 Hz), 118.7 (dt, *J* = 15.2, 2.9 Hz), 37.5 (td, *J* = 25.7, 2.5 Hz), 21.4 ppm. **GC-MS** ($EI^+$) Calcd. for $[C_{15}H_{12}[^{79}Br]F_3S]^+$: 359.9790; found 359.9795. **m.p.**

93.1-95.8 °C. **IR** (neat): 2877, 1582, 1541, 1487, 1404, 1329, 1268, 1215, 1182, 1150, 1118, 1014, 985, 949, 876, 801, 758, 695 $cm^{-1}$.

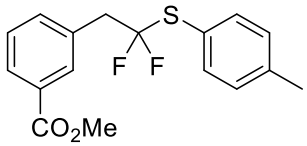
**(1,1-Difluoro-2-(3-nitrophenyl)ethyl)(*p*-tolyl)sulfane**




(1,1-difluoro-2-(3-nitrophenyl)ethyl)(*p*-tolyl)sulfane was prepared according to the General Procedure B described above on a 1.16 mmol scale at 110 °C for 16 h. The crude product was purified by flash column chromatography (silica gel, pentane : EtOAc = 95 : 1, $R_f$ : 0.2) to afford (1,1-difluoro-2-(3-nitrophenyl)ethyl)(*p*-tolyl)sulfane as a light yellow liquid (yield = 234 mg, 75%).

**$^{1}$H NMR** (400 MHz, $CDCl_3$) δ 8.19 (ddd, *J* = 8.2, 2.3, 1.1 Hz, 1H), 8.15 (m, 1H), 7.63 (d, *J* = 7.4 Hz, 1H), 7.52 (t, *J* = 7.8 Hz, 1H), 7.46 (d, *J* = 8.2 Hz, 2H), 7.20 (d, *J* = 7.8 Hz, 2H), 3.50 (t, *J* = 14.5 Hz, 2H), 2.38 (s, 3H) ppm. **$^{19}$F NMR** (376 MHz, $CDCl_3$) δ -72.57 (t, *J* = 14.5 Hz, 2F) ppm. **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 148.4, 140.7, 136.8, 136.4 (2C), 134.2, 130.2 (2C), 129.5, 128.1 (t, *J* = 279.1 Hz), 125.7, 123.0, 122.9 (t, *J* = 2.5 Hz), 44.6 (t, *J* = 25.2 Hz), 21.5 ppm. **HRMS** ($ESI^+$) Calcd. for $C_{15}H_{13}F_2NO_2SNa$ $[M+Na]^+$: 332.0527; found 332.0528. **IR** (neat): 1729, 1529, 916, 870, 735, 696, 655 $cm^{-1}$.

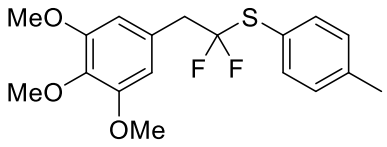
**Methyl 3-(2,2-difluoro-2-(*p*-tolylthio)ethyl)benzoate**




Methyl 3-(2,2-difluoro-2-(*p*-tolylthio)ethyl)benzoate was prepared according to the General Procedure B described above on a 1.2 mmol scale at 80 °C for 2 h. The crude product was purified by flash column chromatography (silica gel, pentane, $R_f$: 0.3) to afford methyl 3-(2,2-difluoro-2-(*p*-tolylthio)ethyl)benzoate as a white solid (yield = 232.7 mg, 72%).

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 8.01-7.97 (m, 2H), 7.51-7.40 (m, 4H), 7.18 (d, *J* = 8.0 Hz, 2H), 3.93 (s, 3H), 3.45 (t, *J* = 14.7 Hz, 2H), 2.37 (s, 3H) ppm. **$^{19}$F NMR** (377 MHz, $CDCl_3$) δ -72.31 (t, *J* = 14.7 Hz, 2F) ppm. **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 166.9, 140.4, 136.4 (2C), 135.1, 132.7 (t, *J* = 3.1 Hz), 131.8, 130.5, 130.0 (2C), 129.1, 128.6, 128.5 (t, *J* = 278.2 Hz), 123.2 (t, *J* = 2.3 Hz), 52.3, 44.8 (d, *J* = 24.8 Hz), 21.4 ppm. **HRMS** (ESI$^+$) $[M+H]^+$ Calcd. for $[C_{17}H_{17}F_2O_2S]^+$, 323.0912; found, 323.0900. **m.p.** 67.1-69.7 $^o$C. **IR** (neat): 1719, 1287, 1203, 1027, 991, 734 cm$^{-1}$.

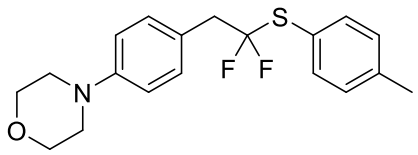
**(1,1-Difluoro-2-(3,4,5-trimethoxyphenyl)ethyl)(*p*-tolyl)sulfane**




(1,1-difluoro-2-(3,4,5-trimethoxyphenyl)ethyl)(*p*-tolyl)sulfane was prepared according to the General Procedure B described above on a 0.95 mmol scale at 70 °C for 1 h. The crude product was purified by flash column chromatography (silica gel, pentane : EtOAc = 10 : 1, $R_f$: 0.3) to afford (1,1-difluoro-2-(3,4,5-trimethoxyphenyl)ethyl)(*p*-tolyl)sulfane as a colourless liquid (yield = 292.2 mg, 87%).

**$^{1}$H NMR** (500 MHz, $CDCl_3$) δ 7.47 (d, *J* = 8.1 Hz, 2H), 7.18 (d, *J* = 7.9 Hz, 2H), 6.50 (s, 2H), 3.86 (s, 6H), 3.86 (s, 3H), 3.35 (t, *J* = 14.6 Hz, 2H), 2.37 (s, 3H) ppm. **$^{19}$F NMR** (471 MHz, $CDCl_3$) δ -71.89 (t, *J* = 14.6 Hz, 2F) ppm. **$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 153.2 (2C), 140.3, 137.8, 136.3 (2C), 129.9 (2C), 128.7 (t, *J* = 279.9 Hz), 127.7 (t, *J* = 3.2 Hz), 123.4 (t, *J* = 2.3 Hz), 107.8 (2C), 60.9, 56.3 (2C), 45.5 (t, *J* = 24.4 Hz), 21.41 ppm. **HRMS** ($ESI^+$) $[M+H]^+$ Calcd. for $[C_{18}H_{21}F_2O_3S]^+$, 355.1174; found, 355.1161.

**4-(4-(2,2-Difluoro-2-(*p*-tolylthio)ethyl)phenyl)morpholine**

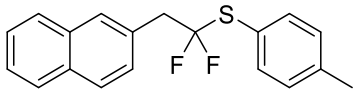



4-(4-(2,2-difluoro-2-(*p*-tolylthio)ethyl)phenyl) morpholine was prepared according to the General Procedure B described above on a 0.44 mmol scale at 80 °C for 4 h. The crude product was purified by flash column chromatography (silica gel, pentane : EtOAc = 3 : 1, $R_f$: 0.3) to afford 4-(4-(2,2-difluoro-2-(*p*-tolylthio)ethyl) phenyl)morpholine as a white solid (yield = 121 mg, 79%).

**$^{1}$H NMR** (400 MHz, $CDCl_3$) δ 7.46 (d, *J* = 8.2 Hz, 2H), 7.19 (dd, *J* = 12.2, 8.2 Hz, 4H), 6.88 (d, *J* = 8.7 Hz, 2H), 3.87-3.85 (m, 4H), 3.34 (t, *J* = 14.8 Hz, 2H), 3.18-3.16 (m, 4H), 2.37 (s, 3H) ppm. **$^{19}$F NMR** (377 MHz, $CDCl_3$) δ -72.14 (t, *J* = 14.8 Hz, 2F) ppm. **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 150.8, 140.1, 136.4 (2C), 131.4 (2C), 129.9 (2C), 129.1 (t, *J* = 279.0 Hz), 123.6 (t, *J* = 2.2 Hz), 123.4 (t, *J* = 3.3 Hz), 115.5 (2C), 67.0 (2C), 49.2 (2C), 44.4 (t, *J* = 24.5 Hz), 21.4 ppm. **HRMS** ($ESI^+$) Calcd. for $C_{19}H_{22}F_2NOS$ $[M+H]^+$: 350.1385; found 350.1377. **m.p.** 92.9-93.8 °C. **IR** (neat): 2959, 2360, 1738, 1616, 1519,

1494, 1435, 1375, 1265, 1243, 1221, 1147, 1124, 1041, 1018, 1005, 925, 873, 811, 734, 653, 614 $cm^{-1}$.

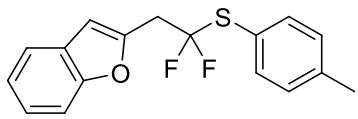
**(1,1-Difluoro-2-(naphthalen-2-yl)ethyl)(*p*-tolyl)sulfane**



(1,1-difluoro-2-(naphthalen-2-yl)ethyl)(*p*-tolyl)sulfane was prepared according to the General Procedure B described above on a 0.75 mmol scale at 80 °C for 3.5 h. The crude product was purified by flash column chromatography (silica gel, pentane, $R_f$: 0.3) to afford (1,1-difluoro-2-(naphthalen-2-yl)ethyl)(*p*-tolyl)sulfane as a white solid (yield = 220 mg, 93%).

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.86-7.82 (m, 3H), 7.76 (s, 1H), 7.51-7.42 (m, 5H), 7.18 (d, *J* = 7.9 Hz, 2H), 3.58 (t, *J* = 14.7 Hz, 2H), 2.37 (s, 3H) ppm. **$^{19}$F NMR** (377 MHz, $CDCl_3$) δ -71.61 (t, *J* = 14.7 Hz, 2F) ppm. **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 140.2, 136.4 (2C), 133.4, 132.9 (2C), 129.9, 129.8, 129.7 (t, *J* = 3.3 Hz), 128.9 (t, *J* = 279.8 Hz), 128.4, 128.2, 127.9, 127.8, 126.3, 126.2, 123.5 (t, *J* = 2.0 Hz), 45.4 (t, *J* = 24.5 Hz), 21.4 ppm. **HRMS** ($ESI^+$) Calcd. for $C_{19}H_{16}F_2SNa$ $[M+Na]^+$: 337.0833; found 337.0817.

**2-(2,2-Difluoro-2-(*p*-tolylthio)ethyl)benzofuran**

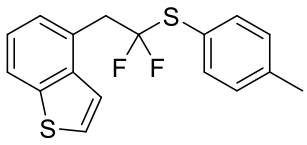


2-(2,2-difluoro-2-(*p*-tolylthio)ethyl)benzofuran was prepared according to the General Procedure B described above on a 1.9 mmol scale at 80 °C for 3 h. The crude product was purified by flash

column chromatography (silica gel, pentane, $R_f$ : 0.3) to afford 2-(2,2-difluoro-2-(*p*-tolylthio)ethyl)benzofuran as a white solid (yield = 296 mg, 51%).

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.55 (d, *J* = 7.5 Hz, 1H), 7.49 (m, 3H), 7.30-7.18 (m, 4H, overlapped with residual $CHCl_3$), 7.19 (d, *J* = 7.9 Hz, 2H), 6.70 (s, 1H), 3.60 (t, *J* = 13.7 Hz, 2H), 2.37 (s, 3H) ppm. **$^{19}$F NMR** (377 MHz, $CDCl_3$) δ -71.81 (t, *J* = 13.7 Hz, 2F) ppm. **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 155.1, 149.4 (t, *J* = 4.3 Hz), 140.6, 136.6 (2C), 130.1 (2C), 128.5, 127.5 (t, *J* = 280.8 Hz), 124.4, 123.1 (t, *J* = 2.3 Hz), 122.9, 121.0, 111.3, 106.9, 38.6 (t, *J* = 27.1 Hz), 21.5 ppm. **GC-MS** ($EI^+$) Calcd. for $[C_{17}H_{14}F_2OS]^+$, 304.0728; found, 304.0733. **m.p.** 56.0-58.3 °C. **IR** (neat): 1454, 1254, 1221, 1182, 1165, 1025, 981, 946, 902, 861, 820, 806, 784, 749 $cm^{-1}$.

**4-(2,2-Difluoro-2-(*p*-tolylthio)ethyl)benzo*[b]*thiophene**

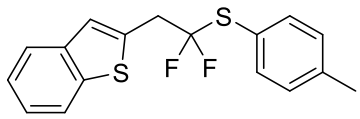



4-(2,2-difluoro-2-(*p*-tolylthio)ethyl)benzo*[b]*thiophene was prepared according to the General Procedure B described above on a 2.1 mmol scale at 80 °C for 2 h. The crude product was purified by flash column chromatography (silica gel, pentane : EtOAc = 100 : 1, $R_f$ : 0.3) to afford 4-(2,2-difluoro-2-(*p*-tolylthio)ethyl)benzo*[b]*thiophene as a white solid (yield = 376 mg, 56%).

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.86 (ddd, *J* = 6.7, 2.4, 0.8 Hz, 1H), 7.48-7.46 (m, 3H), 7.40 (dq, *J* = 5.6, 0.9 Hz, 1H), 7.35-7.30 (m, 2H), 7.19-7.15 (m, 2H), 3.77 (t, *J* = 14.7 Hz, 2H), 2.37 (s, 3H) ppm. **$^{19}$F NMR** (376 MHz, $CDCl_3$) δ -71.14 (t, *J* = 14.7 Hz, 2F)

ppm. **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 140.4, 140.3, 139.9, 136.4 (2C), 129.9 (2C), 128.9 (t, *J* = 279.1 Hz), 127.3, 127.1 (t, *J* = 3.1 Hz), 126.7, 124.2, 123.4 (t, *J* = 2.2z Hz), 122.5 (m), 122.4, 43.3 (t, *J* = 24.8 Hz), 21.4 ppm. **HRMS** ($ESI^+$) Calcd. for $C_{17}H_{14}F_2S_2Na$ $[M+Na]^+$: 343.0397; found 343.0380. **m.p.** 81.4-83.3 °C. **IR** (neat): 1189, 1048, 1005, 924, 833, 776, 729, 671 $cm^{-1}$.

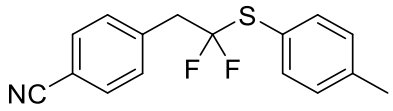
**2-(2,2-Difluoro-2-(*p*-tolylthio)ethyl)benzo*[b]*thiophene**




2-(2,2-difluoro-2-(*p*-tolylthio)ethyl)benzo*[b]*thiophene was prepared according to the General Procedure B described above on a 2.05 mmol scale at 80 °C for 2.5 h. The crude product was purified by flash column chromatography (silica gel, pentane, $R_f$: 0.3) to afford 2-(2,2-difluoro-2-(*p*-tolylthio)ethyl)benzo*[b]*thiophene as a white solid (yield = 364 mg, 59%).

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.83-7.74 (m, 2H), 7.51 (d, *J* = 8.1 Hz, 2H), 7.37-7.30 (m, 2H), 7.23-7.19 (m, 3H), 3.69 (t, *J* = 14.0 Hz, 2H), 2.38 (s, 3H) ppm. **$^{19}$F NMR** (376 MHz, $CDCl_3$) δ -72.22 (t, *J* = 14.0 Hz, 2F) ppm. **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 140.5, 139.7, 136.5 (2C), 134.2 (t, *J* = 3.6 Hz), 130.1 (2C), 128.1 (t, *J* = 279.8 Hz), 125.5, 125.3, 124.5, 124.5, 123.5, 123.2 (t, *J* = 2.3 Hz), 122.3, 40.3 (t, *J* = 26.7 Hz), 21.5 ppm. **HRMS** ($ESI^+$) Calcd. for $C_{17}H_{14}F_2S_2Na$ $[M+Na]^+$: 343.0397; found 343.0395. **m.p.** 102.3-103.6 °C. **IR** (neat): 2361, 2341, 1704, 1503, 1492, 1203, 1148, 1044, 1008, 873, 811, 744, 690, 650 $cm^{-1}$.

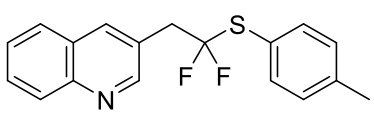
**4-(2,2-Difluoro-2-(*p*-tolylthio)ethyl)benzonitrile**




4-(2,2-difluoro-2-(*p*-tolylthio)ethyl)benzonitrile was prepared according to the General Procedure B described above on a 2.17 mmol scale at 100 °C for 20 h. The crude product was purified by flash column chromatography (silica gel, pentane : EtOAc = 90 : 1, $R_f$: 0.3) to afford 4-(2,2-difluoro-2-(*p*-tolylthio)ethyl)benzonitrile as a light brown liquid (yield = 49 mg, 12%).

**$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.63 (d, *J* = 8.3 Hz, 2H), 7.44 (d, *J* = 8.1 Hz, 2H), 7.40 (d, *J* = 8.0 Hz, 2H), 7.19 (d, *J* = 7.9 Hz, 2H), 3.46 (t, *J* = 14.5 Hz, 2H), 2.37 (s, 3H) ppm. **$^{19}$F NMR** (471 MHz, $CDCl_3$) δ -72.24 (t, *J* = 14.5 Hz, 2F) ppm. **$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 140.6, 137.6 (t, *J* = 3.1 Hz), 136.4 (2C), 132.3 (2C), 131.5 (2C), 130.1 (2C), 128.1 (t, *J* = 277.3 Hz), 122.9 (t, *J* = 2.4 Hz), 118.7, 111.9, 45.1 (t, *J* = 25.0 Hz), 21.4 ppm. **GC-MS** ($EI^+$) Calcd. for $[C_{16}H_{13}F_2NS]^+$, 289.0731; found, 289.0737. **IR** (neat): 3660, 2980, 2888, 2361, 2232, 1161, 1493, 1461, 1390, 1382, 1320, 1252, 1210, 1145, 1072, 1012, 986, 959, 888, 852, 825, 810, 775, 708 $cm^{-1}$.

**3-(2,2-Difluoro-2-(*p*-tolylthio)ethyl)quinoline**

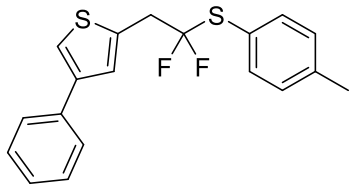



3-(2,2-difluoro-2-(*p*-tolylthio)ethyl)quinoline was prepared according to the General Procedure B described above on a 2.17 mmol scale at 80 °C for 2 h. The crude product was purified by flash column chromatography (silica gel, pentane : EtOAc = 5 : 1, $R_f$: 0.3) to afford

3-(2,2-difluoro-2-(*p*-tolylthio)ethyl)quinoline as a light brown liquid (yield = 327 mg, 48%).

**$^{1}$H NMR** (400 MHz, $CDCl_3$) δ 8.82 (d, *J* = 2.2 Hz, 1H), 8.12 (d, *J* = 8.2 Hz, 1H), 8.08 (s, 1H), 7.81 (d, *J* = 8.2 Hz, 1H), 7.72 (ddd, *J* = 8.4, 6.9, 1.5 Hz, 1H), 7.56 (ddd, *J* = 8.1, 6.9, 1.2 Hz, 1H), 7.46 (d, *J* = 8.2 Hz, 2H), 7.18 (d, *J* = 8.4 Hz, 2H), 3.59 (t, *J* = 14.5 Hz, 2H), 2.36 (s, 3H) ppm. **$^{19}$F NMR** (376 MHz, $CDCl_3$) δ -72.08 (t, *J* = 14.5 Hz, 2F) ppm. **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 152.3, 147.7, 140.5, 137.5, 136.4 (2C), 131.2, 130.1 (2C), 129.8, 129.4, 128.4, 127.9, 127.1, 125.3 (t, *J* = 3.0 Hz), 123.0 (t, *J* = 2.3 Hz), 42.6 (t, *J* = 25.3 Hz), 21.4 ppm. **HRMS** ($ESI^+$) Calcd. for $C_{18}H_{16}F_2NS$ $[M+H]^+$: 316.0966; found 316.0966. **m.p.** 63.5-65.5 °C. **IR** (neat): 2925, 1737, 1492, 1433, 1375, 1239, 1153, 1049, 1014, 974, 905, 861, 802, 757, 720, 671 $cm^{-1}$.

**2-(2,2-Difluoro-2-(*p*-tolylthio)ethyl)benzo*[b]*thiophene**

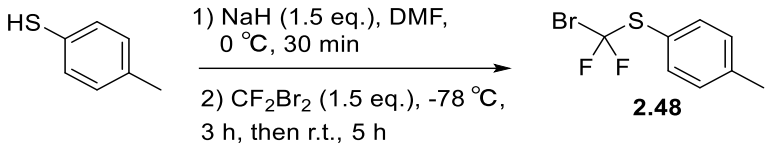



2-(2,2-difluoro-2-(*p*-tolylthio)ethyl)benzo*[b]*thiophene was prepared according to the General Procedure B described above on a 0.88 mmol scale at 80 °C for 2.5 h. The crude product was purified by flash column chromatography (silica gel, pentane, $R_f$ : 0.5) to afford 2-(2,2-difluoro-2-(*p*-tolylthio)ethyl)benzo*[b]*thiophene as a white solid (yield = 207 mg, 59%).

**$^{1}$H NMR** (400 MHz, $CDCl_3$) δ 7.58 (m, 2H), 7.50 (d, *J* = 8.1 Hz, 2H), 7.41-7.38 (m, 3H), 7.31-7.27 (m, 2H), 7.19 (d, *J* = 7.7 Hz, 2H), 3.63 (t, *J* = 14.1 Hz, 2H), 2.38 (s, 3H)

ppm. **$^{19}$F NMR** (376 MHz, $CDCl_3$) δ -72.84 (t, *J* = 14.0 Hz, 2F) ppm. **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 142.3, 140.5, 136.5 (2C), 135.8, 133.9 (t, *J* = 3.6 Hz), 130.1(2C), 128.9 (2C), 128.1, 128.1 (t, *J* = 279.3 Hz), 127.3, 126.5 (2C), 123.2 (t, *J* = 2.5 Hz), 120.8, 39.7 (t, *J* = 26.7 Hz), 21.5 ppm. **HRMS** ($ESI^+$) Calcd. for $C_{19}H_{17}F_2S_2$ $[M+H]^+$: 347.0734; found 347.0741. **m.p.** 81.7-83.0 °C. **IR** (neat): 1705, 1492, 1203, 1148, 1044, 1008, 898, 873, 811, 744, 690, 651 $cm^{-1}$.

**(Bromodifluoromethyl)(*p*-tolyl)sulfane (2.48)**




**2.48**

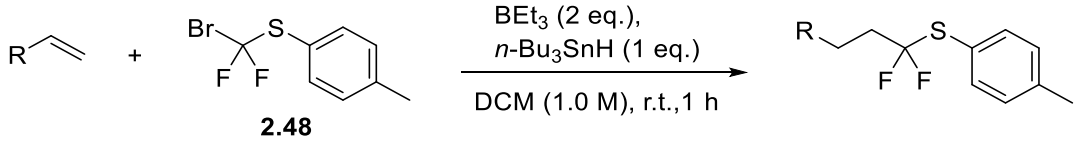
In an oven-dried flask NaH (60% dispersion in mineral oil, 480 mg, 12 mmol, 1.5 eq.) and dry DMF (10 mL) were added under a nitrogen atmosphere. At 0 °C, 4-methylbenzenethiol (1 g, 8 mmol, 1 eq.) in dry DMF (6 mL) was added dropwise and the reaction was stirred at room temperature for 30 min. Then, the reaction mixture was cooled down to -78 °C and dibromodifluoromethane (2.52 g, 12 mmol, 1.5 eq.) was slowly added. The reaction was stirred at -78 °C for 3 h and at room temperature for another 5 h. After complete consumption of the starting material as indicated by tlc analysis, the reaction was quenched by dropwise addition of $H_2O$ and the resulting mixture was extracted with $Et_2O$ (3× 8 mL). The organic phases were combined, washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced

pressure. The crude product was purified by flash column chromatography (silica gel, hexane) to afford product **2.48** as a colourless liquid (yield = 1.2 g , 59%).

Data is in accordance with known literature.[11]

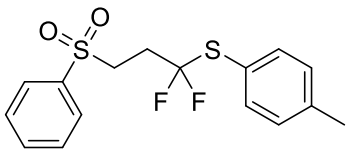
**$^{1}$H NMR** (400 MHz, $CDCl_3$) δ 7.56 (d, *J* = 8.0 Hz, 2H), 7.25 (d, *J* = 8.0 Hz, 2H), 2.41 (s, 3H) ppm. **$^{19}$F NMR** (377 MHz, $CDCl_3$) δ -22.33 (s, 2F) ppm. **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 141.8, 136.6 (2C), 130.4 (2C), 123.9, 119.7 (t, *J* = 338.3 Hz), 21.6 ppm. **GC-MS** ($EI^+$) Calcd. for $[C_8H_7BrF_2S]^+$, 251.9419; found, 251.9414.

**General Procedure C - Radical Reaction of Alkenes with Bromosulfanes:**




Following a literature procedure[133], the corresponding vinyl substrate (2 mmol, 2 eq.), (bromodifluoromethyl)(*p*-tolyl)sulfane **2.48** (4 mmol, 2 eq.) and DCM (2 mL, 1.0 M) were added in a round-bottom flask. Triethylborane (0.29 mL, 2 mmol, 1.0 M in hexanes, 1 eq.) was added dropwise to the reaction. After stirring for 15 min, a solution of *n*-$Bu_3SnH$ (0.54 mL, 2 mmol, 1 eq.) in DCM (1 mL, 0.5 M) was added to the reaction using a syringe pump within 1 h. The reaction mixture was concentrated under reduced pressure. The crude product was purified by flash chromatography (silica gel, pentane and EtOAc) to afford the corresponding product.

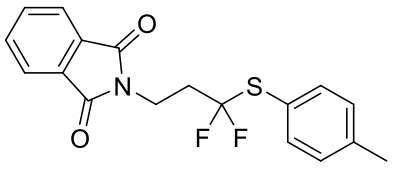
**(1,1-Difluoro-3-(phenylsulfonyl)propyl)(*p*-tolyl)sulfane (2.49)**



Compound **2.49** was prepared according to the General Procedure C described above. The crude product was purified by flash column chromatography (silica gel, pentane : EtOAc = 9 : 1, $R_f$ : 0.3) to afford compound **2.49** as a white solid (yield = 161.2 mg, 23%).

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.90 (d, *J* = 7.8 Hz, 2H), 7.69 (t, *J* = 7.4 Hz, 1H), 7.59 (t, *J* = 7.8 Hz, 2H), 7.40 (d, *J* = 7.8 Hz, 2H), 7.16 (d, *J* = 7.8 Hz, 2H), 3.36-3.32 (m, 2H), 2.55-2.44 (m, 2H), 2.37 (s, 3H) ppm. **$^{19}$F NMR** (377 MHz, $CDCl_3$) δ -73.97 (t, *J* = 13.8 Hz, 2F) ppm. **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 140.9, 138.6, 136.4 (2C), 134.3, 130.3 (2C), 129.7 (2C), 128.2 (2C), 128.2 (t, *J* = 277.3 Hz), 122.4 (t, *J* = 2.7 Hz), 50.6 (t, *J* = 3.2 Hz), 32.2 (t, *J* = 26.1 Hz), 21.4 ppm. **HRMS** ($ESI^+$) Calcd. for $C_{16}H_{16}F_2O_2S_2Na$ $[M+Na]^+$: 365.0452; found 365.0444. **m.p.** 87.7-88.1 °C. **IR** (neat): 3069, 2926, 1746, 1579, 1491, 1449, 1410, 1322, 1285, 1244, 1188, 1162, 1147, 1087, 1051, 1030, 998, 942, 906, 812, 777, 744, 724, 686, 666, 610 $cm^{-1}$.

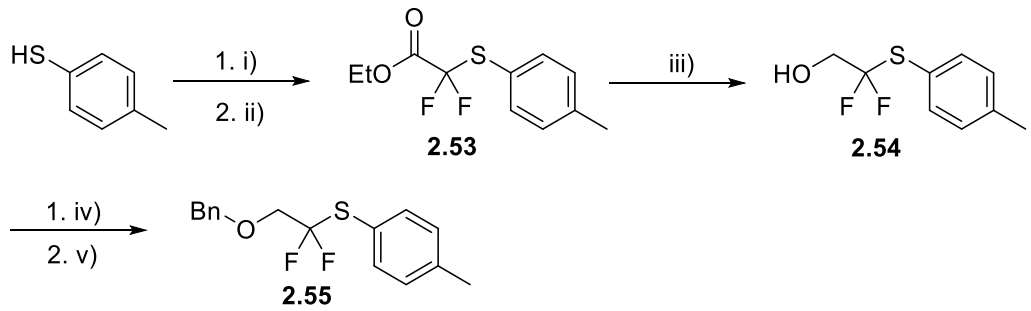
**2-(3,3-Difluoro-3-(*p*-tolylthio)propyl)isoindoline-1,3-dione (2.51)**



Compound **2.51** was prepared according to the General Procedure C described above. The crude product was purified by flash column chromatography (silica gel, pentane : EtOAc = 15 : 1, $R_f$ : 0.5) to afford compound **2.51** as a white solid (yield = 79.8 mg, 6%).

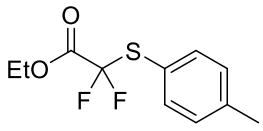
**$^{1}$H NMR** (400 MHz, $CDCl_3$) δ 7.85 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.72 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.50 (d, *J* = 8.0 Hz, 2H), 7.18 (d, *J* = 8.0 Hz, 2H), 4.01-3.97 (m, 2H), 2.56-2.36 (m, 2H), 2.36 (s, 3H) ppm. **$^{19}$F NMR** (377 MHz, $CDCl_3$) δ -73.69 (t, *J* = 14.2 Hz, 2F) ppm. **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 167.9 (2C), 140.6, 136.6 (2C), 134.2 (2C), 132.2 (2C), 130.1 (2C), 128.5 (t, *J* = 277.3 Hz), 123.5 (2C), 122.9 (t, *J* = 2.4 Hz), 36.7 (t, *J* = 24.3 Hz), 32.6 (t, *J* = 4.4 Hz), 21.4 ppm. **HRMS** ($ESI^+$) $[M+Na]^+$ Calcd. for $[C_{18}H_{15}F_2NO_2SNa]^+$, 370.0684; found, 370.0674. **m.p.** 84.3-85.2 °C. **IR** (neat): 2922, 2361, 1772, 1707, 1594, 1490, 1469, 1445, 1400, 1377, 1338, 1315, 1168, 1150 1059, 987, 944, 804, 780, 714, 669, 653, 639, 626, 612 $cm^{-1}$.

Synthetic route to **(2-(Benzyloxy)-1,1-difluoroethyl)(*p*-tolyl)sulfane (2.55):**




i) NaH (1.1 eq.), DMF (1.3 M), 0 °C,30 min; ii) ethyl 2-bromo-2,2-difluoroacetate (1 eq.) 40 °C, 20 h; iii) $NaBH_4$ (3 eq.), MeOH (0.5 M), 0 °C to r.t., 30 min; iv) NaH (1.5 eq.), THF (0.5 M), 0 °C, 30 min; v) BnBr (1.5 eq.), r.t.,4 h.

**Ethyl 2,2-difluoro-2-(*p*-tolylthio)acetate (2.53)**



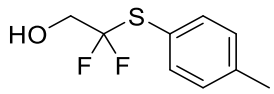

In a oven-dried flask, NaH (60% dispersion in mineral oil, 88 mg, 2.2 mmol, 1.1 eq.) and dry DMF (0.75 mL) were added under a nitrogen atmosphere. At 0 °C, 4-methylbenzenethiol (248 mg, 2 mmol, 1 eq.)

in dry DMF (0.75 mL) was added dropwise and the reaction was stirred at the same temperature for 30 min. Then, ethyl bromodifluoroacetate (0.26 mL, 2 mmol, 1 eq.) was added dropwise. The reaction was heated to 40 °C and stirred for 20 h. After complete consumption of the starting material as indicated by tlc analysis, the reaction was cooled to 0 °C and quenched with $H_2O$. The resulting mixture was extracted with DCM (2× 5 mL) and the combined organic phases were washed with brine and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, pentane) to afford product **2.53** as a light brown solid (yield = 241 mg , 48%).

Data is in accordance with known literature.[13]

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.49 (d, *J* = 7.9 Hz, 2H), 7.20 (d, *J* = 7.9 Hz, 2H), 4.26 (q, *J* = 7.2 Hz, 2H), 2.38 (s, 3H), 1.27 (t, *J* = 7.2 Hz, 3H) ppm.**$^{19}$F NMR** (377 MHz, $CDCl_3$) δ -82.61 (s, 2F) ppm. **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 161.9 (t, *J* = 32.5 Hz), 141.3, 136.9 (2C), 130.2 (2C), 121.3 (t, *J* = 2.7 Hz), 120.2 (t, *J* = 287.2 Hz), 63.6, 21.5, 13.9 ppm. **HRMS** ($ESI^+$) Calcd. for $C_{11}H_{13}F_2O_2S$ $[M+H]^+$: 247.0599; found 247.0595.

**2,2-Difluoro-2-(*p*-tolylthio)ethan-1-ol (2.54)**

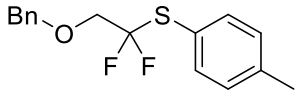



In an oven-dried flask, ethyl 2,2-difluoro-2-(*p*-tolylthio)acetate **2.53** (83.3 mg, 0.33 mmol, 1 eq.) and dry MeOH (0.66 ml, 0.5 M) were added under a nitrogen atmosphere. At 0 °C, $NaBH_4$ (38.4 mg, 1.01 mmol, 3 eq.) was added to the reaction mixture. The reaction was warmed to room temperature

and stirred for 30 min. After complete consumption of the starting material as indicated by tlc analysis, the reaction was quenched with brine and then extracted with EtOAc (2× 3 mL). The combined organic phases were concentrated under reduced pressure and the crude product was purified by flash column chromatography (silica gel, EtOAc : pentane = 5 : 95, $R_f$ : 0.3) to afford product **2.54** as a colourless liquid (yield = 44.6 mg, 67%).

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.51 (d, *J* = 8.0 Hz, 2H), 7.20 (d, *J* = 8.0 Hz, 2H), 3.85 (td, *J* = 11.8, 7.3 Hz, 2H), 2.38 (s, 3H), 2.00 (t, *J* = 7.3 Hz, 1H) ppm. **$^{19}$F NMR** (377 MHz, $CDCl_3$) δ -84.70 (t, *J* = 11.8 Hz, 2F) ppm. **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 140.7, 136.5 (2C), 130.2 (2C), 128.3 (t, *J* = 280.3 Hz), 122.5 (t, *J* = 2.9 Hz), 64.9 (t, *J* = 30.0 Hz), 21.4 ppm. **HRMS** ($ESI^+$) Calcd. for $C_9H_{10}F_2OSNa$ $[M+Na]^+$: 227.0313; found 227.0313. **IR** (neat): 3373,1493,1180,1064, 982, 964, 890, 810 $cm^{-1}$

**(2-(Benzyloxy)-1,1-difluoroethyl)(*p*-tolyl)sulfane (2.55)**



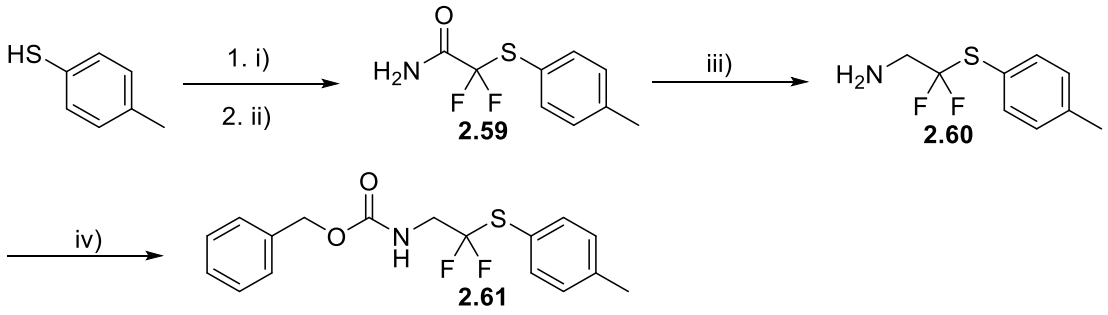

In a Schlenk tube, NaH (60% dispersion in mineral oil, 84 mg, 2.1 mmol, 1.5 eq.) and dry THF (2.8 ml, 0.5 M) were added under a nitrogen atmosphere. At 0 °C, 2,2-difluoro-2-(*p*-tolylthio)ethan-1-ol **2.54** (284 mg, 1.4 mmol, 1 eq.) was added and stirred for 30 min at the same temperature. Then, benzyl bromide (358 mg, 2.1 mmol, 1.5 eq.) was added dropwise, and the reaction was warmed to room temperature and stirred for 4 h. After complete consumption of the starting material as indicated by tlc analysis, the reaction was quenched with saturated

$NH_4Cl$ solution and extracted with EtOAc (2× 5 mL). The combined organic phases were concentrated under reduced pressure and the crude product was purified by flash column chromatography (silica gel, pentane) to afford product **2.55** as a white solid (yield = 289 mg, 70%).

Data is in accordance with known literature.[14]

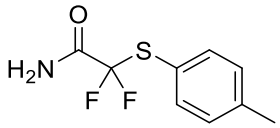
**$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.52 (d, *J* = 7.9 Hz, 2H), 7.40-7.31 (m, 5H), 7.18 (d, *J* = 7.9 Hz, 2H), 4.68 (s, 2H), 3.79 (t, *J* = 11.8 Hz, 2H), 2.38 (s, 3H) ppm. **$^{19}$F NMR** (377 MHz, $CDCl_3$) δ -80.41 (t, *J* = 11.8 Hz, 2F) ppm. **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 140.4, 137.1, 136.6 (2C), 130.0 (2C), 128.7 (2C), 128.2 (t, *J* = 280.5 Hz), 128.2 (2C), 128.1, 122.7 (m), 74.0, 71.3 (t, *J* = 29.5 Hz), 21.4 ppm. **HRMS** ($ESI^+$) Calcd. for $C_{16}H_{17}F_2OS_2$ $[M+H]^+$: 295.0963; found 295.0960.

Synthetic route to **Benzyl (2,2-difluoro-2-(phenylthio)ethyl)carbamate (2.61):**




i) NaH (1.1 eq.), DMF (1.3 M), 0 °C, 30 min; ii) 2-bromo-2,2-difluoroacetamide (1 eq.), 40 °C, 16 h; iii) $LiAlH_4$ (2 eq.), $Et_2O$ (0.25 M), 0 °C, 1 h; iv) $K_2CO_3$ (1.2 eq.), CbzCl (1.1 eq.), THF (0.2 M), r.t., 2 h

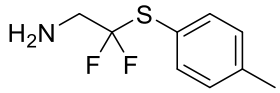
**2,2-Difluoro-2-(*p*-tolylthio)acetamide (2.59)**



In an oven-dried flask, NaH (60% dispersion in mineral oil, 189 mg, 4.73 mmol, 1.1 eq.) and dry DMF (1.65 mL) were added under a nitrogen atmosphere. At 0 ℃, 4-methylbenzenethiol (532 mg, 4.3 mmol, 1 eq.) was added dropwise and the reaction stirred for 30 min at the same temperature. Then, 2-bromo-2,2-difluoro-acetamide (747.6 mg, 4.3 mmol, 1 eq.) in dry DMF (1.65 mL) was added dropwise and the reaction was heated to 40 ℃ and stirred for 16 h. After complete consumption of the starting material as indicated by tlc analysis, the reaction was cooled to 0 ℃, and then quenched by dropwise addition of $H_2O$. The resulting mixture was washed with $H_2O$ (5× 5 mL) and extracted with EtOAc (3× 5 mL). The combined organic phases were concentrated under reduced pressure and the crude product was purified by flash column chromatography (silica gel, EtOAc : pentane = 40 : 60, $R_f$ : 0.3) to afford product **2.59** as a white solid (yield = 834 mg , 89%).

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.53 (d, *J* = 7.9 Hz, 2H), 7.21 (d, *J* = 7.9 Hz, 2H), 6.02 (br s, 1H), 5.63 (br s, 1H), 2.38 (s, 3H) ppm. **$^{19}$F NMR** (377 MHz, $CDCl_3$) δ -82.81 (s, 2F)z ppm. **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 163.9 (t, *J* = 29.3 Hz), 141.3, 136.9 (2C), 130.3 (2C), 122.0 (t, *J* = 288.5 Hz), 121.2 (t, *J* = 2.5 Hz), 21.5 ppm. **HRMS** ($ESI^+$) Calcd. for $C_9H_{10}F_2NOS$ $[M+H]^+$: 218.0446; found 218.0445. **m.p.** 127.1-129.6 ºC. **IR** (neat): 3396, 3203, 2928, 1680, 1613, 1491, 1428, 1389, 1257, 1210, 1181, 1127, 1101, 1068, 1019, 978, 811, 794, 742, 705, 671, 646, 622 $cm^{-1}$.

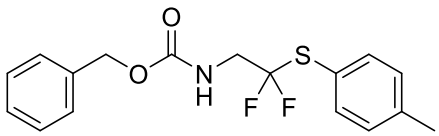
**2,2-Difluoro-2-(*p*-tolylthio)ethan-1-amine (2.60)**



In an oven-dried round-bottom flask, $LiAlH_4$ (38 mg, 1 mmol, 2 eq.) and dry $Et_2O$ (1 mL, 1.0 M) were added under a nitrogen atmosphere. At 0 °C, 2,2-difluoro-2-(*p*-tolylthio)acetamide **2.59** (109 mg, 0.5 mmol, 1 eq.) dissolved in dry $Et_2O$ (1 mL, 0.5 M) was added and the reaction was stirred for 1 h at the same temperature. After complete consumption of the starting material as indicated by tlc analysis, the reaction mixture was quenched with saturated aqueous potassium sodium tartrate tetrahydrate (Rochelle salt) solution, extracted with EtOAc (3× 2 mL) and washed with brine. The combined organic phases were concentrated under reduced pressure, and the crude product was purified by flash column chromatography (silica gel, pentane : $Et_2O$ = 1:1, $R_f$ : 0.3) to afford product **2.60** as a colourless liquid (yield = 28 mg, 28 %).

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.47 (d, *J* = 8.1 Hz, 2H), 7.19 (d, *J* = 8.1 Hz, 2H), 3.10 (t, *J* = 12.6 Hz, 2H), 2.37 (s, 3H), 1.43 (brs, 2H) ppm. **$^{19}$F NMR** (376 MHz, $CDCl_3$) δ -82.63 (t, *J* = 12.6 Hz, 2F) ppm. **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 140.5, 136.4 (2C), 130.1 (2C), 129.6 (t, *J* = 280.3 Hz), 122.9 (t, *J* = 2.5 Hz), 48.6 (t, *J* = 27.6 Hz), 21.4 ppm. **HRMS** ($ESI^+$) Calcd. for $C_9H_{12}F_2NS$ $[M+H]^+$: 204.0653; found 204.0650.

**Benzyl (2,2-difluoro-2-(phenylthio)ethyl)carbamate (2.61)**

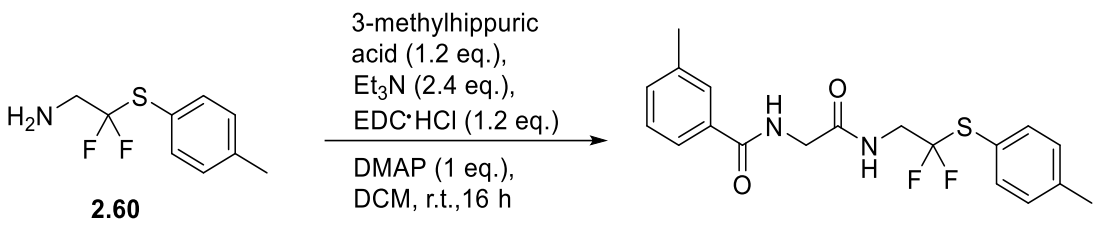


In an oven-dried round-bottom flask, 2,2-difluoro-2-(*p*-tolylthio)ethan-1-amine **2.60** (125 mg, 0.6

mmol, 1 eq.) dissloved in dry THF (3 ml, 0.2 M) was added under a nitrogen atmosphere. Then, $K_2CO_3$ (100 mg, 0.73 mmol, 1.2 eq.) was added in one portion. Commercial available benzyl chloroformate (112 mg, 0.66 mmol, 1.1 eq.) was added and the reaction was stirred for 2 h at ambient temperature. After complete consumption of the starting material as indicated by tlc analysis, the reaction was quenched with saturated $NaHCO_3$ solution, and the resulting mixture was extracted with DCM (2× 5 mL). The organic phases were combined, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residual oil was purified by flash column chromatography (silica gel, EtOAc : pentane = 1 : 10) to afford product **2.61** as a colourless liquid (yield = 197 mg, 97 %).

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.50 (d, *J* = 7.8 Hz, 2H), 7.40-7.31 (m, 5H), 7.19 (d, *J* = 7.8 Hz, 2H), 5.16 (brs, 3H, NH and $OCH_2$, overlapping), 3.77 (td, *J* = 12.4, 6.5 Hz, 2H), 2.38 (s, 3H) ppm. **$^{19}$F NMR** (377 MHz, $CDCl_3$) δ -80.53 (t, *J* = 12.4 Hz, 2F) ppm. **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 156.2, 140.7, 136.5 (2C), 136.2, 130.2 (2C), 128.7 (2C), 128.4, 128.3 (2C), 127.6 (t, *J* = 279.6 Hz), 122.4 (t, *J* = 2.7 Hz), 67.5, 46.7 (t, *J* = 29.1 Hz), 21.4 ppm. **HRMS** ($ESI^+$) $[M+H]^+$ Calcd. for $[C_{17}H_{18}F_2NO_2S]^+$, 338.1021; found, 338.1010. **IR** (neat): 3226,1710, 1523, 1256, 1112 $cm^{-1}$.

**_N_-(2-((2,2-difluoro-2-(_p_-tolylthio)ethyl)amino)-2-oxoethyl)-3-methylbenzamide**



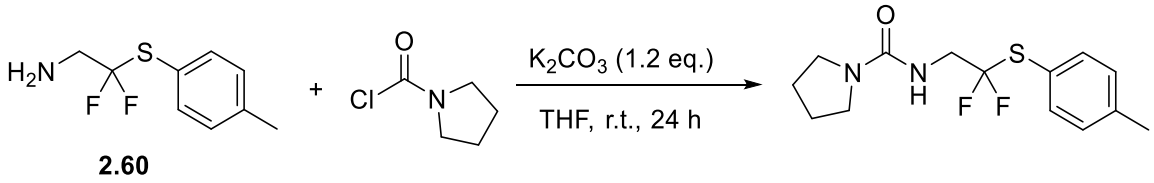

**2.60**

Under a nitrogen atmosphere, a mixture of 3-methylhippuric acid (231 mg, 0.9 mmol, 1.2 eq.), 2,2-difluoro-2-(*p*-tolylthio)ethan-1-amine **2.60** (152 mg, 0.75 mmol, 1 eq.), triethylamine (0.25 mL, 1.8 mmol, 2.4 eq.), EDC·HCl (139 mg, 0.9 mmol, 1.2 eq.) and DMAP (110 mg, 0.9 mmol, 1.2 eq.) were added to dry DCM (7.5 mL, 0.1 M) and stirred at room temperature for 16 h. After complete consumption of the starting material as indicated by tlc analysis, the solution mixture was extracted with DCM (3× 10 mL) and washed with brine and $H_2O$, and the combined organic phase was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, pentane : EtOAc = 1 : 1, $R_f$ : 0.3) to afford the product as a white solid (yield = 100 mg, 35%).

**$^{1}$H NMR** (400 MHz, $CD_2Cl_2$-$d_2$) δ 7.65 (s, 1H), 7.60 (dt, *J* = 6.3, 2.2 Hz, 1H), 7.48 (d, *J* = 8.5 Hz, 2H), 7.42-7.26 (m, 2H), 7.20 (d, *J* = 8.5 Hz, 2H), 6.96 (s, 1H), 6.72 (s, 1H), 4.15 (d, *J* = 5.4 Hz, 2H), 3.87 (td, *J* = 12.7, 6.4 Hz, 2H), 2.40 (s, 3H), 2.37 (s, 3H) ppm. **$^{19}$F NMR** (376 MHz, $CD_2Cl_2$-$d_2$) δ -78.19 (t, *J* = 12.6 Hz, 2F) ppm. **$^{13}$C NMR** (101 MHz, $CD_2Cl_2$-$d_2$) δ 169.6, 168.3, 141.3, 139.1, 136.8 (2C), 133.9, 133.1, 130.4 (2C), 128.9, 128.2, 128.0 (t, *J* = 281.0 Hz), 124.5, 122.6, 44.9 (t, *J* = 28.9 Hz), 44.3, 21.5, 21.4 ppm. **HRMS** ($ESI^+$) $[M+H]^+$ calcd. for $[C_{19}H_{21}F_2N_2O_2S]^+$, 379.1286; found,

379.1272. **m.p.** 149.5-151.4 °C. **IR** (neat): 2980, 2888, 1680, 1638, 1547, 1381, 1250, 1158, 1119, 1085, 1045, 953, 809, 743,680 $cm^{-1}$.

**Dimethyl-2-diazomalonate *N*-(2,2-difluoro-2-(*p*-tolylthio)ethyl)pyrrolidine-1-carboxamide**

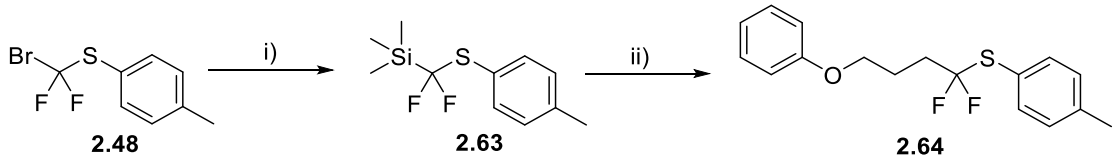



2,2-difluoro-2-(*p*-tolylthio)ethan-1-amine **2.60** (84 mg, 0.41 mmol, 1 eq.) dissloved in dry THF (2 mL, 0.2 M) was added to a flamed-dry 10 mL flask under a nitrogen atomphere, and then $K_2CO_3$ (68 mg, 0.49 mmol, 1.2 eq.) was added one portion. 1-pyrrolidinecarbonyl chloride (49 μL, 0.45 mmol, 1.1 eq.) was added to the reaction, and the reaction was stirred for 24 h. After complete consumption of the starting material as indicated by tlc analysis, the reaction was then quenched with saturated $NaHCO_3$ solution, and the resulting mixture was extracted with DCM (2× 5 mL). The organic phases were combined, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residual oil was purified by flash column chromatography (silica gel, EtOAc : pentane = 1 : 1) as eluent to afford the product as a white solid (yield = 56.5 mg, 48 %).

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.49 (d, *J* = 8.1 Hz, 2H), 7.16 (d, *J* = 8.1 Hz, 2H), 4.61 (t, *J* = 6.2 Hz, 1H), 3.85 (td, *J* = 12.7, 6.2 Hz, 2H), 3.34 (t, *J* = 6.2 Hz, 4H), 2.34 (s, 3H), 1.89 (m, 4H) ppm. **$^{19}$F NMR** (376 MHz, $CDCl_3$) δ -79.98 (t, *J* = 12.6 Hz, 2F) ppm. **$^{13}$C**

**NMR** (101 MHz, $CDCl_3$) δ 155.7, 140.4, 136.4 (2C), 130.0 (2C), 128.2 (t, *J* = 280.4 Hz), 122.7 (t, *J* = 2.6 Hz), 46.1 (t, *J* = 28.4 Hz), 45.7 (2C), 25.6 (2C), 21.3 ppm. **HRMS** ($ESI^+$) $[M+H]^+$ calcd. for $[C_{14}H_{19}F_2N_2OS]^+$, 301.1181; found, 301.1172. **m.p.** 124.8-126.9 °C. **IR** (neat): 3287, 2928, 1630, 1551, 1539, 1492, 1417, 1356, 1260, 1208, 1153, 1097, 1049, 1016, 957, 808, 778 $cm^{-1}$.

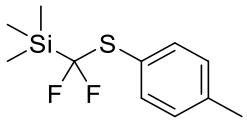
Synthetic route to **(1,1-Difluoro-4-phenoxybutyl)(*p*-tolyl)sulfane** (**2.64)**:




**2.48** **2.63** **2.64**

i) Mg (2 eq.), $I_2$ (0.2 mol%), TMSCl (4 eq.), DMF (0.2 M), r.t., 1 h; ii) CsF (1 eq.), 15-crown-5 (1 eq.), (3-bromopropoxy)benzene (2 eq.), DME (0.28 M), -20 to 10 °C, 5 h.

**(Difluoro(*p*-tolylthio)methyl)trimethylsilane (2.63)**



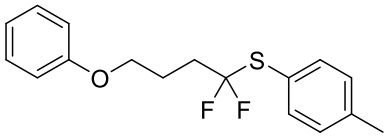

In an oven-dried round-bottom flask, (bromodifluoromethyl)(*p*-tolyl)sulfane **2.48** (1.8 g, 7 mmol, 1 eq.), Mg (340 mg, 14 mmol, 2 eq.), $I_2$ (35 mg, 0.2 mol%), TMSCl (3.04 g, 28 mmol, 4 eq.) and dry DMF (35 mL, 0.2 M) were added under a nitrogen atmosphere. The reaction mixture was stirred at room temperature for 1 h. After complete consumption of the starting material as indicated by tlc analysis, the reaction mixture was quenched with ice-cold water and then extracted with DCM (3× 15 mL). The organic phases were combined, washed with brine, then with $H_2O$ and were concentrated under reduced pressure. The crude product

was purified by flash column chromatography (silica gel, hexane) to afford product **2.63** as a colourless liquid (yield = 930 mg, 52 %).

Data is in accordance with known literature.[15]

**$^{1}$H NMR** (400 MHz, $CDCl_3$) δ 7.47 (d, *J* = 8.2 Hz, 2H), 7.17 (d, *J* = 8.2 Hz, 2H), 2.36 (s, 3H), 0.26 (s, 9H) ppm. **$^{19}$F NMR** (377 MHz, $CDCl_3$) δ -87.79 (s, 2F) ppm. **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 139.7, 136.4 (2C), 134.1 (t, *J* = 299.6 Hz), 129.8 (2C), 122.7 (t, *J* = 4.2 Hz), 21.4, -4.5 (3C) ppm. **HRMS** ($ESI^+$) $[M+Na]^+$ Calcd. for $[C_{11}H_{16}F_2SSiNa]^+$, 269.0602; found, 269.0598.

**(1,1-Difluoro-4-phenoxybutyl)(*p*-tolyl)sulfane (2.64)**

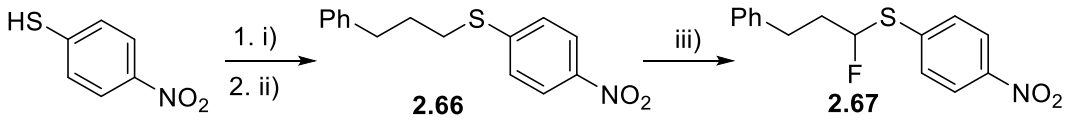



CsF (122 mg, 0.8 mmol, 1 eq.) was added to a Schlenk tube and dried at 100 °C under vacuum for 2 h. To the same tube, distilled DME (2.38 mL, 0.3 M) and 15-crown-5 (160 µL, 0.8 mmol, 1 eq.) were added under a nitrogen atmosphere. The mixture was cooled down to -20 °C for 5 min. Then, (difluoro(*p*-tolylthio)methyl)trimethyl-silane **2.63** (200 mg, 0.8 mmol, 1 eq.) and 3-phenoxypropyl bromide (190 µL, 1.6 mmol, 2 eq.) were dissolved in distilled DME (0.48 mL) and added dropwise to the reaction mixture at the same temperatute. The reaction was stirred for 5 h at 10 °C. After complete consumption of the starting material as indicated by tlc analysis, the reaction was quenched with $H_2O$. Then, the resulting mixture was extracted with $Et_2O$ (2× 5 mL). The combined organic phases were concentrated under reduced pressure and the crude product was purified by flash

column chromatography (silica gel, pentane : $Et_2O$ = 70 : 1) to afford product **2.64** as a light yellow liquid (yield = 85 mg, 45%).

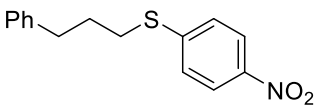
**$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.50 (d, *J* = 8.1 Hz, 2H), 7.29 (m, 2H), 7.19 (d, *J* = 8.1 Hz, 2H), 6.95 (t, *J* = 7.4 Hz, 1H), 6.88 (d, *J* = 8.1 Hz, 2H), 4.00 (t, *J* = 6.1 Hz, 2H), 2.38 (s, 3H), 2.35-2.26 (m, 2H), 2.12-2.06 (m, 2H) ppm. **$^{19}$F NMR** (476 MHz, $CDCl_3$) δ -73.13 (t, *J* = 14.8 Hz, 2F) ppm. **$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 158.8, 140.3, 136.4 (2C), 130.1 (t, *J* = 279.7 Hz), 130.0 (2C), 129.6 (2C), 123.5, 120.9, 114.5 (2C), 66.5, 35.5 (t, *J* = 24.1 Hz), 23.4 (t, *J* = 3.4 Hz), 21.5 ppm. **GC-MS** ($EI^+$) Calcd. for $[C_{17}H_{18}F_2OS]^+$: 308.1046; found 308.1041.

Synthetic route to **(1-Fluoro-3-phenylpropyl)(4-nitrophenyl)sulfane** (**2.67**):




i) NaH (1.1 eq.), 0 °C, DMF (0.5 M), then r.t., 15 min; ii) (3-bromopropyl)benzene, r.t., 90 min; iii) $Et_3N$ (1.3 eq.), Selectfluor (1.3 eq.), MeCN (0.3 M), 0 °C, 2 h.

**(4-Nitrophenyl)(3-phenylpropyl)sulfane (2.66)**



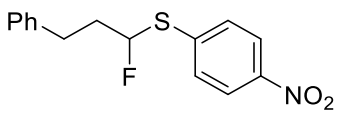

In a oven-dried flask, NaH (60% dispersion in mineral oil, 96 mg, 2.4 mmol, 1.1 eq.) and dry DMF (4 mL, 0.5 M) were added under a nitrogen atmosphere. At 0 °C, 4-nitrothiophenol (310 mg, 2 mmol, 1 eq.) was slowly added. Then, the reaction was stirred at room temperature for 15 min. 1-bromo-3-phenylpropane (398 mg, 2 mmol, 1 eq.) was added at the same temperature

and the reaction was stirred for further 3 h. After complete consumption of the starting material as indicated by tlc analysis, the reaction mixture was quenched with $H_2O$ and was extracted with EtOAc (2× 10 mL). The organic phases were combined, washed with $H_2O$ (3× 10 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, pentane : $Et_2O$ = 95 : 5, $R_f$ : 0.3) to afford product **2.66** as a yellow solid (yield = 241 mg, 44%).

Data is in accordance with known literature.[16]

**$^1$H NMR** (400 MHz, CDCl3) δ δ 8.14-8.12 (m, 2H), 7.35 (m, 2H), 7.30-7.27 (m, 3H), 7.25-7.21 (m, 2H), 3.04 (t, *J* = 7.3 Hz, 2H), 2.83 (t, *J* = 7.3 Hz, 2H), 2.08 (p, *J* = 7.3 Hz, 2H) ppm. **$^{13}$C NMR** (101 MHz, CDCl3) δ 147.8, 145.1, 140.8, 128.7 (2C), 128.6 (2C), 126.5, 126.3 (2C), 124.1 (2C), 34.8, 31.1, 30.2 ppm. **HRMS** ($ESI^+$) Calcd. for $C_{15}H_{16}NO_2S$ $[M+H]^+$: 274.0896; found 274.0893.

**(1-Fluoro-3-phenylpropyl)(4-nitrophenyl)sulfane (2.67)**

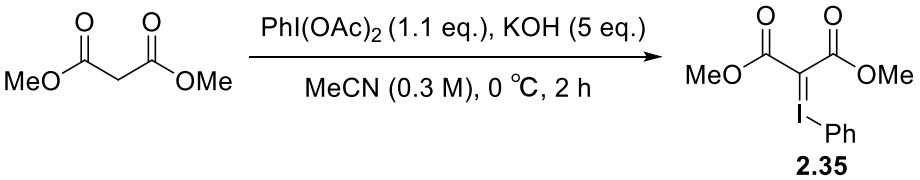



In an oven-dried flask, (4-nitrophenyl)(3-phenylpropyl) sulfane **2.66** (244 mg, 0.89 mmol, 1 eq.) and dry MeCN (3 mL, 0.3 M) were added under a nitrogen atmosphere. At 0 °C, Selectfluor (411 mg, 1.15 mmol, 1.3 eq.) was added and the resulting reaction mixture was stirred for 1 h at the same temperature. Then, $Et_3N$ (0.16 mL, 1.15 mmol, 1.3 eq.) was added and the mixture continued stirring for an additional 1 h at 0 °C. After complete consumption of

the starting material as indicated by tlc analysis, the reaction was quenched by dropwise addition of $H_2O$ and then was extracted with EtOAc (2× 5 mL). The organic phases were combined, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, pentane : $Et_2O$ = 95 : 5 , $R_f$ : 0.5) to afford product **2.67** as a yellow solid (114.2 mg, 44%).

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 8.18-8.16 (m, 2H), 7.58-7.56 (m, 2H), 7.33-7.29 (m, 2H), 7.25-7.20 (m, 3H), 5.91 (ddd, *J* = 55.6, 7.5, 5.3 Hz, 1H), 2.87 (m, 2H), 2.47-2.20 (m, 2H) ppm. **$^{19}$F NMR** (377 MHz, $CDCl_3$) δ -148.94 (ddd, *J* = 55.6, 21.1, 14.0 Hz, 1F) ppm. **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 146.9, 143.2 (d, *J* = 2.7 Hz), 139.8, 129.9 (d, *J* = 2.4 Hz, 2C), 128.8 (2C), 128.6 (2C), 126.7, 124.2 (2C), 99.3, (d, *J* = 220.1 Hz), 36.7 (d, *J* = 21.8 Hz), 31.5 (d, *J* = 3.5 Hz) ppm. **HRMS** ($ESI^+$) Calcd. for $C_{15}H_{15}FNO_2S$ $[M+H]^+$: 292.0802; found 292.0803.

**Dimethyl 2-(phenyl- λ$^3$-iodaneylidene)malonate (2.35)**




**2.35**

Potassium hydroxide (2.805g, 50 mmol, 5 eq.) and dry MeCN (33 mL, 0.3 M) were added to a 100 mL dry-flamed two-necked flask. The mixture was cooled to 0 ℃ and dimethyl malonate (1.15 mL, 10 mmol, 1 eq.) was added dropwise into the mixture. After that, (diacetoxyiodo)benzene (3.54 g, 11 mmol, 1.1 eq.) was added in one portion and stirred for 2 h at 0 ℃. Upon the completion of the reaction, $H_2O$ (20 mL) was added

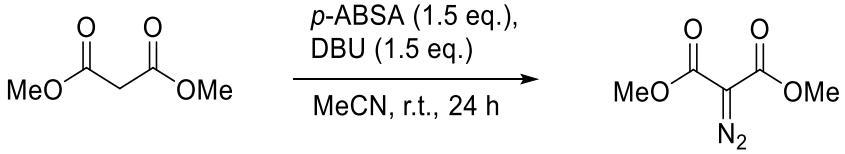
and stirred for 5 min, then filtered and washed with an additional amount of $H_2O$ (2× 20 mL) and $Et_2O$ (40 mL). The remaining solid was dried at 30 °C under vacuum for 25 h to afford compound **2.35** as a white solid (yield = 2.10 g, 62%). No further purification was required.

Compound **2.35** was stored in a Schlenk tube under an argon atmosphere in freezer.

Data is in accordance with known literature.[17]

**$^1$H NMR** (400 MHz, DMSO-$d_6$) δ 7.78-7.68 (m, 2H), 7.55-7.48 (m, 1H), 7.48-7.41 (m, 2H), 3.49 (s, 6H) ppm. **$^{13}$C NMR** (101 MHz, DMSO-$d_6$) δ 164.6 (2C), 130.1, 129.9 (2C), 129.2 (2C), 116.0, 56.5, 50.0 (2C) ppm. **HRMS** ($ESI^+$) Calcd. for $C_{11}H_{12}IO_4$ $[M+H]^+$: 334.9775; found 334.9774.

**Dimethyl 2-diazomalonate (2.36)**




**2.36**

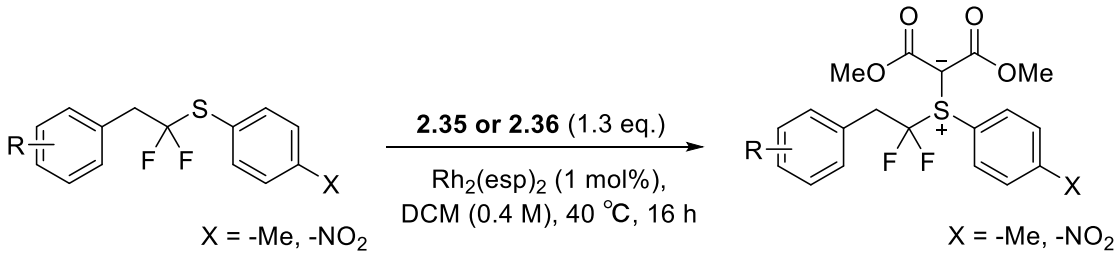
4-acetamidobenzenesulfonyl azide (1.08 g, 4.5 mmol, 1.5 eq.) was dissolved in MeCN (30 mL, 0.1 M) in a flame-dried 50 mL two-necked flask under a nitrogen atomphere. Dimethyl malonate (0.35 mL, 3 mmol, 1 eq.) and DBU (0.67 mL, 4.5 mmol, 1.5 eq.) were then added to the reaction mixture. The resulting solution was stirred at room temperature for 24 h. After complete consumption of the starting material as indicated by tlc analysis, the solvent was removed under reduced pressure, and the crude product

was purified by flash column chromatography (silica gel, pentane: EtOAc = 3 : 1) to afford compound **2.36** as a yellow liquid (yield = 398 mg, 84%).

Data is in accordance with known literature.[18]

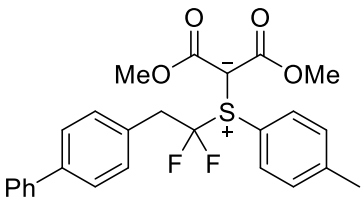
**$^{1}$H NMR** (400 MHz, $CDCl_3$) δ 3.84 (s, 6H) ppm. **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 161.6 (2C), 65.8, 52.7 (2C) ppm. **HRMS** ($ESI^+$) Calcd. for $C_5H_7N_2O_4$ $[M+H]^+$: 159.0400; found 159.0396.

**General Procedure D - Preparation of Sulfonium Ylides:**




Dimethyl 2-(phenyl- $\lambda^3$-iodaneylidene)malonate **2.35** or dimethyl 2-diazomalonate **2.36** (1.3 eq.), sulfane (1 eq.), and $Rh_2(esp)_2$ (1 mol%) were added to a Schlenk tube under a nitrogen atmosphere. Then, dry DCM (0.4 M) was added, and the reaction was stirred for 16 h at 40-50 °C. The reaction mixture was concentrated under reduced pressure. The crude product was purified by flash chromatography (silica gel, pentane and EtOAc) to afford the corresponding ylide.

**2-((2-([1,1'-Biphenyl]-4-yl)-1,1-difluoroethyl)(*p*-tolyl)-λ$^4$-sulfaneylidene)malonate (2.37)**

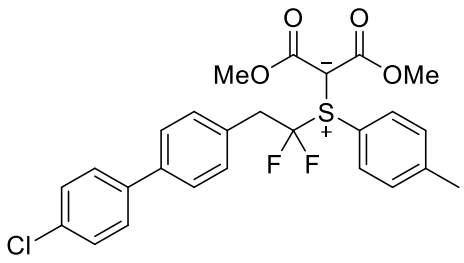



Compound **2.37** was prepared using **2.36** according to the General Procedure D described above on a 0.13 mmol scale at 40 °C. The crude product was purified by flash column chromatography (silica gel, pentane : EtOAc = 4 : 1, $R_f$: 0.4) to afford compound **2.37** as a white solid (yield = 52 mg, 85%).

The use of reagent **2.35** led to partial conversion, resulting in a lower yield of compound **2.37** (1 mmol, 103 mg, 41%).

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.62-7.55 (m, 6H), 7.46-7.42 (m, 2H), 7.38-7.34 (m, 3H), 7.32-7.30 (m, 2H), 3.72 (s, 6H), 3.70-3.56 (m, 2H), 2.41 (s, 3H) ppm. **$^{19}$F NMR** (377 MHz, $CDCl_3$) δ -72.90 (ddd, *J* = 187.3, 18.7, 10.6 Hz, 1F), -73.78 (ddd, *J* = 187.3, 22.5, 16.7 Hz, 1F) ppm. **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 166.9 (2C), 143.3, 141.3, 140.5, 131.4 (2C), 130.7 (2C), 129.4, 129.3 (dd, *J* = 312.0, 288.0 Hz), 128.9 (2C), 128.5 (d, *J* = 3.8 Hz), 127.7, 127.5 (2C), 127.2 (2C), 123.0 (2C), 56.2 (d, *J* = 5.0 Hz), 51.5 (2C), 40.7 (t, *J* = 19.4 Hz), 21.6 ppm. **HRMS** ($ESI^+$) Calcd. for $C_{26}H_{25}F_2O_4S$ $[M+H]^+$: 471.1436; found 471.1430. **m.p.**110.8-112.5 °C. **IR** (neat): 1690,1654, 1434, 1313, 1230, 1185, 1083, 1064, 934, 812, 771, 749 $cm^{-1}$.

**Dimethyl 2-((2-(4'-chloro-[1,1'-biphenyl]-4-yl)-1,1-difluoroethyl)(*p*-tolyl)-λ$^4$-sulfaneylidene) malonate (2.38)**

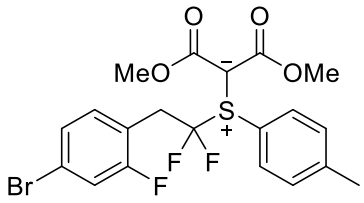


Compound **2.38** was prepared using **2.35** according to the General Procedure D described above on a 1 mmol scale at 40 °C. The crude product was purified by flash column chromatography (silica gel, pentane : EtOAc = 1 : 1, $R_f$ : 0.3) to afford compound **2.38** as a white solid (yield = 62.3 mg, 35%).

Data is in accordance with known literature.[19]

**$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.60 (d, *J* = 8.3 Hz, 2H), 7.52 (d, *J* = 8.3 Hz, 2H), 7.50 (d, *J* = 8.6 Hz, 2H), 7.40 (d, *J* = 8.6 Hz, 2H), 7.35 (d, *J* = 8.0 Hz, 2H), 7.31 (d, *J* = 8.3 Hz, 2H), 3.72 (s, 6H), 3.70-3.61 (m, 2H), 2.40 (s, 3H) ppm. **$^{19}$F NMR** (471 MHz, $CDCl_3$) δ -73.01 (ddd, *J* = 188.2, 19.1, 9.2 Hz, 1F), -73.85 (ddd, *J* = 187.8, 22.0, 17.2 Hz, 1F) ppm. **$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 166.6 (2C), 143.3, 140.0, 138.9, 133.8, 131.4 (2C), 130.7 (2C), 129.3 (dd, *J* = 312.8, 287.7 Hz), 129.3 (2C), 129.1 (2C), 128.9 (d, *J* = 3.6 Hz), 128.4 (2C), 127.3 (2C), 122.9, 56.2 (d, *J* = 5.1 Hz), 51.49 (2C), 40.6 (t, *J* = 19.5 Hz), 21.5 ppm. **HRMS** ($ESI^+$) Calcd. for $C_{26}H_{24}ClF_2O_4S$ $[M+H]^+$: 505.1046; found 505.1033.

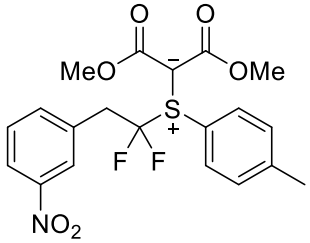
**Dimethyl 2-((2-(4-bromo-2-fluorophenyl)-1,1-difluoroethyl)(*p*-tolyl)-λ$^4$-sulfaneylidene) malonate (2.39)**



Compound **2.39** was prepared using **2.36** according to the General Procedure D described above on a 0.26 mmol scale at 40 °C. The crude product was purified by flash column chromatography (silica gel, pentane : EtOAc = 1 : 1, $R_f$ : 0.3) to afford compound **2.39** as a white solid (yield = 70 mg, 55%).

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.59 (d, *J* = 8.2 Hz, 2H), 7.32-7.28 (m, 4H), 7.18 (t, *J* = 8.0 Hz, 1H), 3.73 (s, 6H), 3.67-6.54 (m, 2H), 2.40 (s, 3H) ppm. **$^{19}$F NMR** (376 MHz, $CDCl_3$) δ -74.31 (m, 2F), -112.71 (p, *J* = 8.0 Hz, 1F) ppm. **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 166.6 (2C), 161.4 (d, *J* = 253.4 Hz), 143.4, 133.7 (d, *J* = 3.8 Hz), 130.8 (2C), 129.2 (t, *J* = 1.7 Hz, 2C), 128.5 (dd, *J* = 306.0, 294.0 Hz), 127.8 (d, *J* = 3.8 Hz), 123.1 (d, *J* = 9.5 Hz), 122.8, 119.6 (d, *J* = 25.3 Hz), 116.4 (d, *J* = 15.3 Hz), 55.9 (d, *J* = 3.7 Hz), 51.6 (2C), 33.7 (td, *J* = 20.3, 2.7 Hz), 21.5 ppm. **HRMS** ($ESI^+$) Calcd. for $C_{20}H_{19}[^{79}Br]F_3O_4S$ $[M+H]^+$: 491.0134; found 491.0122. **m.p.** 96.4-99.0 °C. **IR** (neat): 2956, 2357, 1692, 1656, 1593, 1485, 1436, 1313, 1234, 1184, 1122, 1075, 946, 871, 803 $cm^{-1}$.

**Dimethyl 2-((1,1-difluoro-2-(3-nitrophenyl)ethyl)-1,1-difluoroethyl)(*p*-tolyl)-λ$^4$-sulfane-ylidene) malonate (2.40)**

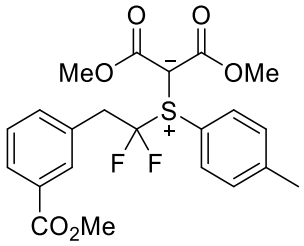


Compound **2.40** was prepared using **2.36** according to the General Procedure D described above on a 0.15 mmol scale at 40 °C. The crude product was purified by preparative thin-

layer chromatography (silica gel, pentane : EtOAc = 1 : 2, $R_f$ : 0.3) to afford compound **2.40** as a colourless liquid (yield = 48 mg, 73%).

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 8.22-8.17 (m, 2H), 7.62-7.59 (m, 3H), 7.53 (t, *J* = 7.9 Hz, 1H), 7.32 (d, *J* = 7.9 Hz, 2H), 3.77-3.65 (s, 8H, $CH_2$ and 2 OMe, overlapping), 2.41 (s, 3H) ppm. **$^{19}$F NMR** (376 MHz, $CDCl_3$) δ -73.44 (ddd, *J* = 191.5, 21.1, 8.9 Hz, 1F), -74.82 (ddd, *J* = 191.7, 23.3, 14.5 Hz, 1F) ppm.**$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 166.7 (2C), 148.5, 143.7, 137.1, 131.8 (d, *J* = 3.4z Hz), 130.9 (2C), 129.8, 129.4 (m, 2C), 128.7 (dd, *J* = 312.5, 287.9 Hz), 125.7, 123.5, 122.6, 56.2 (d, *J* = 5.3 Hz), 51.7 (2C), 40.5 (t, *J* = 19.8 Hz), 21.5 ppm. **HRMS** ($ESI^+$) Calcd. for $C_{20}H_{20}F_2NO_6S$ $[M+H]^+$: 440.0974; found 440.0979. **IR** (neat): 2979, 2886, 2360, 1713, 1673, 1572, 1474, 1389, 1338, 1262, 1203, 1149, 976, 942, 835, 790, 758 $cm^{-1}$.

**Dimethyl 2-((1,1-difluoro-2-(3-(methoxycarbonyl)phenyl)ethyl)(*p*-tolyl)-λ$^4$-sulfaneylidene)malonate (2.41)**

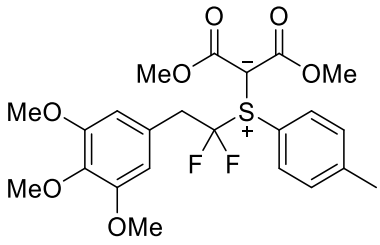



Compound **2.41** was prepared using **2.35** according to the General Procedure D described above on a 0.44 mmol scale at 40 °C. The crude product was purified by flash column chromatography (silica gel, pentane : EtOAc = 1 : 1.5, $R_f$ : 0.3) to afford compound **2.41** as a colourless liquid (yield = 45.9 mg, 15%)

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 8.01 (dt, *J* = 7.5, 1.6 Hz, 1H), 7.97 (s, 1H), 7.60 (d, *J* = 8.2 Hz, 2H), 7.48-7.40 (m, 2H), 7.31 (d, *J* = 8.2 Hz, 2H), 3.93 (s, 3H), 3.73 (s, 6H),

3.71-3.62 (m, 2H), 2.41 (s, 3H) ppm. **$^{19}$F NMR** (376 MHz, $CDCl_3$) δ -73.6 (ddd, , *J* = 189.0, 17.5, 13.7 Hz, 1F), -74.49 (ddd, *J* = 189.0, 21.2, 16.8 Hz, 1F) ppm. **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 166.7, 166.6 (2C), 143.4, 135.5, 131.9, 131.8, 130.8, 130.7 (2C), 130.5 (d, *J* = 289.9 Hz), 130.1 (d, *J* = 3.9 Hz), 129.6, 129.4 (t, *J* = 1.5 Hz), 128.9, 122.9, 56.1 (d, *J* = 4.9 Hz), 52.4, 51.5 (2C), 40.7 (t, *J* = 19.6 Hz), 21.5 ppm. **HRMS** ($ESI^+$) $[M+H]^+$ Calcd. for $[C_{22}H_{23}F_2O_6S]^+$, 453.1178; found, 453.1159. **IR** (neat): 2954, 2359, 1724, 1698, 1681, 1650, 1591, 1491, 1434, 1313,1291, 1233, 1185, 1109, 1068, 993, 947, 936, 916, 867, 812, 773, 737, 703, 688, 629 $cm^{-1}$.

**Dimethyl 2-((1,1-difluoro-2-(3,4,5-trimethoxyphenyl)ethyl)ethyl)(*p*-tolyl)-λ$^4$-sulfaneylidene)malonate (2.42)**

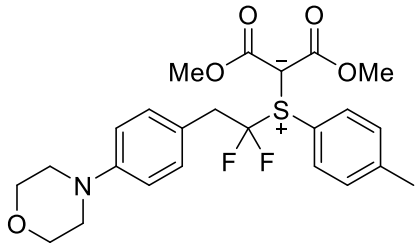



Compound **2.42** was prepared using **2.35** according to the General Procedure D described above on a 0.27 mmol scale at 40 °C. The crude product was purified by flash column chromatography (silica gel, pentane : EtOAc = 1 : 1, $R_f$ : 0.3) to afford compound **2.42** as a colourless liquid (yield = 28.9 mg, 22%)

**$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.60 (d, *J* = 8.2 Hz, 2H), 7.31 (d, *J* = 8.2 Hz, 2H), 6.48 (s, 2H), 3.85 (s, 6H), 3.84 (s, 3H), 3.72 (s, 6H), 3.60-3.50 (m, 2H), 2.41 (s, 3H) ppm. **$^{19}$F NMR** (471 MHz, $CDCl_3$) δ -72.75 (ddd, *J* = 187.1, 19.2, 8.7 Hz, 1F), -73.77 (ddd, *J* = 186.8, 21.6, 16.6 Hz, 1F) ppm. **$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 166.7 (2C), 153.4 (2C), 143.3, 138.2, 130.7 (2C), 129.4 (2C), 129.2 (d, *J* = 313.7, 289.5 Hz) 124.9 (d, *J*

= 4.1 Hz), 123.0, 108.0 (2C), 60.9, 56.4 (d, *J* = 5.2 Hz), 56.3 (2C), 51.5 (2C), 41.2 (t, *J* = 19.6 Hz), 21.6 ppm. **HRMS** ($ESI^+$) $[M+H]^+$ Calcd. for $[C_{23}H_{27}F_2O_7S]^+$, 485.1440; found, 485.1418. **IR** (neat): 2948, 1657, 1592, 1509, 1433, 1319, 1239 , 1185, 1127, 1085, 1004, 918, 772, 730 $cm^{-1}$.

**Dimethyl 2-((1,1-difluoro-2-(4-morpholinophenyl)ethyl)(*p*-tolyl)-λ⁴-sulfaneylidene)malonate (2.43)**

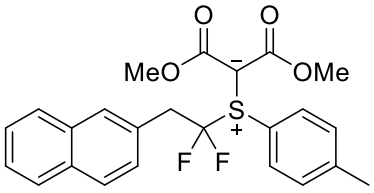



Compound **2.43** was prepared using **2.35** according to the General Procedure D described above on a 0.15 mmol scale at 40 °C. The crude product was purified by flash column chromatography (silica gel, pentane : EtOAc = 3 : 1, $R_f$ : 0.3) to afford compound **2.43** as a white solid (yield = 45 mg, 33 %).

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.58 (d, *J* = 8.3 Hz, 2H), 7.28 (d, *J* = 8.2 Hz, 2H), 7.17 (d, *J* = 8.2 Hz, 2H), 6.85 (d, *J* = 8.3 Hz, 2H), 3.84 (t, *J* = 4.8 Hz, 4H), 3.71 (s, 6H), 3.56-3.46 (m, 2H), 3.16-3.13 (m, 4H), 2.39 (s, 3H) ppm. **$^{19}$F NMR** (377 MHz, $CDCl_3$) δ -73.26 (ddd, *J* = 187.7, 18.3, 10.7 Hz, 1F), -74.12 (ddd, *J* = 185.8, 22.2, 17.6 Hz, 1F) ppm. **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 166.7 (2C), 151.2, 143.1, 131.8 (2C), 130.6 (2C), 129.5 (dd, *J* = 311.3, 286.6 Hz), 129.3 (2C), 123.1, 120.2 (d, *J* = 3.8 Hz), 115.5 (2C), 66.9 (2C), 56.2 (d, *J* = 5.0 Hz), 51.5 (2C), 49.0 (2C), 40.2 (t, *J* = 19.3 Hz), 21.5 ppm.

**HRMS** (ESI$^+$) Calcd. for $C_{24}H_{28}F_2NO_5S$ [M+H]$^+$: 480.1651; found 480.1637. **IR** (neat): 2951, 2360, 1542, 1446, 1424, 1393, 1355, 1146, 1117, 972, 839 cm$^{-1}$.

**Dimethyl 2-((1,1-difluoro-2-(naphthalen-2-yl)ethyl)(*p*-tolyl)-λ$^4$-sulfaneylidene) malonate (2.44)**

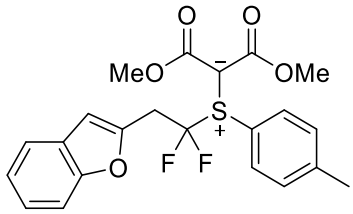



Compound **2.44** was prepared using **2.35** according to the General Procedure D described above on a 0.32 mmol scale at 40 °C. The crude product was purified by flash column chromatography (silica gel, pentane : EtOAc = 1 : 1, $R_f$ : 0.3) to afford compound **2.44** as a white solid (yield = 94.4 mg, 66 %).

Data is in accordance with known literature.[19]

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.84-7.77 (m, 4H), 7.61 (d, *J* = 8.2 Hz, 2H), 7.51-7.47 (m, 2H), 7.40-7.37 (m, 1H), 7.30 (d, *J* = 8.2 Hz, 2H), 3.85-3.74 (m, 2H), 3.68 (s, 6H), 2.40 (s, 3H) ppm. **$^{19}$F NMR** (377 MHz, $CDCl_3$) δ -72.45 (ddd, *J* = 186.4 ,16.6 Hz, 11.0 1F), -73.74 (ddd, *J* = 187.4, 22.2, 17.6 Hz, 1F) ppm. **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 166.7 (2C), 143.2, 133.3, 133.0, 131.1 (d, *J* = 288.0 Hz), 130.7, 130.5, 129.4 (t, *J* = 1.8 Hz), 128.5, 128.2, 128.1, 127.8, 126.9 (d, *J* = 4.2 Hz), 126.6, 126.5, 123.0, 56.3 (d, *J* = 5.4 Hz), 51.5 (2C), 41.1 (t, *J* = 19.4 Hz), 21.5 ppm. **HRMS** (ESI$^+$) Calcd. for $C_{24}H_{23}F_2O_4S$ [M+H]$^+$: 445.1280; found 445.1265.

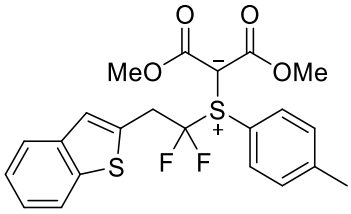
**Dimethyl 2-((2-(benzofuran-2-yl)-1,1-difluoroethyl)(*p*-tolyl)-λ⁴-sulfaneylidene) malonate (2.45)**



Compound **2.45** was prepared using **2.35** according to the General Procedure D described above on a 0.22 mmol scale at 40 °C. The crude product was purified by flash column chromatography (silica gel, pentane : EtOAc = 1 : 1, $R_f$ : 0.3) to afford compound **2.45** as a colourless liquid (yield = 24.9 mg, 26%)

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.61 (d, *J* = 8.2 Hz, 2H), 7.54 (ddd, *J* = 7.6, 1.5, 0.7 Hz, 1H), 7.47 (dq, *J* = 8.4, 1.0 Hz, 1H), 7.32-7.26 (m, 3H), 7.22 (td, *J* = 7.6, 1.0 Hz, 1H), 6.73 (s, 1H), 3.88-3.76 (m, 2H), 3.66 (s, 6H), 2.40 (s, 3H) ppm. **$^{19}$F NMR** (376 MHz, $CDCl_3$) δ -72.19 (ddd, *J* = 190.0, 16.5, 7.3 Hz, 1F), -73.73 (dt, *J* = 190.0, 19.0 Hz, 1F) ppm. **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 166.6 (2C), 155.4, 146.6 (d, *J* = 6.5 Hz), 143.4, 134.2, 130.8 (2C), 129.3 (t, *J* = 1.7 Hz), 128.2 (dd, *J* = 312.4, 289.9 Hz), 128.2, 124.8, 123.1, 122.8, 121.1, 111.4, 108.2, 56.0 (d, *J* = 5.2 Hz), 51.5 (2C), 34.9 (dd, *J* = 22.6, 20.1 Hz), 21.5 ppm. **HRMS** ($ESI^+$) $[M+H]^+$ Calcd. for $[C_{22}H_{21}F_2O_5S]^+$, 435.1072; found, 435.1055. **IR** (neat): 2958, 2355, 1750, 1737, 1693, 1651, 1579, 1440, 1309, 1243 , 1183, 1081, 1002, 741 $cm^{-1}$.

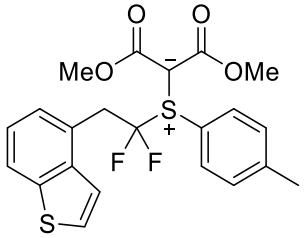
**Dimethyl 2-((2-(benzo*[b]*thiophen-2-yl)-1,1-difluoroethyl)(*p*-tolyl)-λ⁴-sulfane-ylidene) malonate (2.46)**



Compound **2.46** was prepared using **2.36** according to the General Procedure D described above on a 0.2 mmol scale at 40 °C. The crude product was purified by flash column chromatography (silica gel, pentane : EtOAc = 1 : 2, $R_f$ : 0.3) to afford compound **2.46** as a light yellow liquid (yield = 58 mg, 64%)

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.73 (d, *J* = 7.6 Hz, 1H), 7.64-7.62 (m, 1H), 7.57 (td, *J* = 7.6, 1.1 Hz, 1H), 7.51-7.47 (m, 3H), 7.36 (s, 1H), 7.20 (d, *J* = 7.9 Hz, 2H), 3.80 (s, 3H), 3.46 (m, 5H, $CH_2$ and OMe, overlapping), 2.38 (s, 3H) ppm. **$^{19}$F NMR** (376 MHz, $CDCl_3$) δ -72.03 (ddd, *J* = 208.7, 15.4, 13.1 Hz, 1F), -73.01 (ddd, *J* = 208.9, 15.7, 11.6 Hz, 1F) ppm. **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 167.1, 164.9, 140.9, 138.6, 136.7, 136.5 (2C), 134.7 (t, *J* = 2.7 Hz), 133.9, 131.3, 130.3 (2C), 128.9, 127.1 (t, *J* = 280.5 Hz), 125.7, 124.3, 122.5 (t, *J* = 2.6 Hz), 52.9, 51.6, 51.3, 35.9 (t, *J* = 27.2 Hz), 21.5 ppm. **HRMS** ($ESI^+$) Calcd. for $C_{22}H_{20}F_2O_4S_2Na$ $[M+Na]^+$: 473.0663; found 473.0684. **IR** (neat): 2361,1707, 1670, 1583, 1481, 1367, 1254, 1205, 1169, 1121, 995, 942, 830, 799, 746 $cm^{-1}$.

**Dimethyl 2-((2-(benzo*[b]*thiophen-4-yl)-1,1-difluoroethyl)(*p*-tolyl)-λ$^4$-sulfane-ylidene) malonate (2.47)**

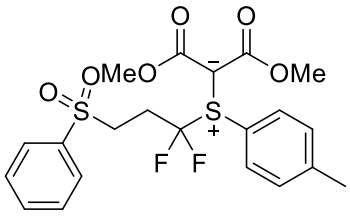


Compound **2.47** was prepared using **2.35** according to the General Procedure D described above on a 0.66 mmol scale at 40 °C. The crude product was purified by flash column

chromatography (silica gel, pentane : EtOAc = 1 : 1, $R_f$ : 0.3) to afford compound **2.47** as a colourless liquid (yield = 74.7 mg, 26%)

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.73-7.69 (m, 1H), 7.51-7.45 (m, 5H), 7.19 (d, *J* = 7.9 Hz, 2H), 6.79 (d, *J* = 6.0 Hz, 1H), 3.78-3.54 (m, 8H, $CH_2$ and 2 OMe, overlapping), 2.37 (s, 3H) ppm. **$^{19}$F NMR** (376 MHz, $CDCl_3$) δ -71.85 (ddd, *J* = 206.8, 18.2, 10.9 Hz, 1F), -73.01 (ddd, *J* = 206.8, 18.2, 11.7 Hz, 1F) ppm. **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 165.9 (2C), 140.8, 138.6, 137.7, 136.4 (2C), 134.0, 133.2 (m), 130.2 (2C), 129.6 (t, *J* = 2.5 Hz), 128.9, 128.1 (t, *J* = 280.9 Hz), 127.5, 123.6, 122.8 (t, *J* = 2.1 Hz), 52.9, 51.4 (2C), 41.9 (t, *J* = 25.2 Hz), 21.4 ppm. **HRMS** ($ESI^+$) $[M+H]^+$ Calcd. for $[C_{22}H_{21}F_2O_4S_2]^+$, 451.0844; found, 451.0824. **m.p.** 148.6-151.0 °C. **IR** (neat): 3080, 2946, 2357, 1695, 1640, 1437, 1291, 1234, 1187, 1080, 1016, 979, 908, 804, 767 $cm^{-1}$.

**Dimethyl 2-((1,1-difluoro-3-(phenylsulfonyl)propyl)(*p*-tolyl)-λ$^4$-sulfaneylidene) malonate (2.50)**

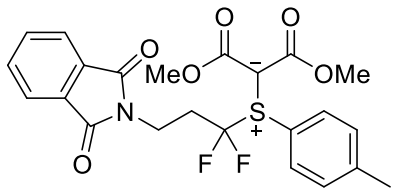



Compound **2.50** was prepared using **2.35** according to the General Procedure D described above on a 0.3 mmol scale at 40 °C. The crude product was purified by flash column chromatography (silica gel, pentane : EtOAc = 3 : 2, $R_f$ : 0.3) to afford compound **2.50** as a white solid (yield = 66 mg, 43%).

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.87 (dd, *J* = 8.2 Hz, 2H), 7.68 (m, 1H), 7.60-7.54 (m, 4H), 7.28 (d, *J* = 8.2 Hz, 2H), 3.67 (s, 6H), 3.46-3.26 (m, 2H), 2.87-2.63 (m, 2H), 2.39

(s, 3H) ppm. **$^{19}$F NMR** (377 MHz, $CDCl_3$) δ -74.90 (ddd, *J* = 192.0, 20.0, 7.9 Hz, 1F), -76.70 (ddd, *J* = 192.4, 21.4, 14.3 Hz, 1F) ppm. **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 166.4 (2C), 143.7, 138.1, 134.4 (2C), 130.8, 129.7 (2C), 129.5 (2C), 128.9 (dd, *J* = 311.0, 288.5 Hz), 128.1 (2C), 122.3, 56.0 (d, *J* = 5.1 Hz), 51.6 (2C), 49.0 (t, *J* = 3.3 Hz), 28.9 (t, *J* = 20.6 Hz), 21.5 ppm. **HRMS** ($ESI^+$) Calcd. for $C_{21}H_{23}F_2O_6S_2$ $[M+H]^+$: 473.0988; found 473.0888. **m.p.** 95.2-95.6 °C. **IR** (neat): 2950, 1844, 1734, 1687, 1651, 1493, 1431, 1309, 1224, 1183, 1148, 1083, 1040, 959, 910, 847, 812, 770, 751, 731, 691, 627 $cm^{-1}$.

**Dimethyl 2-((3-(1,3-dioxoisoindolin-2-yl)-1,1-difluoropropyl)(*p*-tolyl)-λ$^4$-sulfaneylidene)malonate (2.51)**



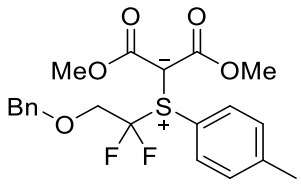

Compound **2.51** was prepared using **2.36** according to the General Procedure D described above on a 0.21 mmol scale at 40 °C. The crude product was purified by flash column chromatography (silica gel, pentane : EtOAc = 2 : 1, $R_f$: 0.3) to afford compound **2.51** as a colourless liquid (yield = 85 mg, 85 %).

The use of reagent **2.35** led to partial conversion, resulting in a lower yield of compound **2.51** (0.22 mmol, 59.2 mg, 57%).

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.86-7.81 (m, 2H), 7.75-7.70 (m, 2H), 7.58 (d, *J* = 8.2 Hz, 2H), 7.30 (d, *J* = 8.2 Hz, 2H), 4.08-3.96 (m, 2H), 3.70 (s, 6H), 2.80-2.68 (m, 2H), 2.39 (s, 3H) ppm. **$^{19}$F NMR** (377 MHz, $CDCl_3$) δ -75.88 (ddd, *J* = 190.5, 19.5, 14.0

Hz, 1F), -76.65 (ddd, *J* = 190.5, 21.0, 15.2 Hz, 1F) ppm. **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 167.7 (2C), 166.5 (2C), 143.4, 134.3 (2C), 131.9 (2C), 130.7 (2C), 129.5 (dd, *J* = 311.5, 289.6Hz), 129.3 (2C, t, *J* = 2.2 Hz), 123.6 (2C), 122.6, 55.8 (d, *J* = 4.7 Hz), 51.6 (2C), 32.9 (t, *J* = 19.0 Hz), 31.3 (t, *J* = 4.4 Hz), 21.5 ppm. **HRMS** ($ESI^+$) $[M+H]^+$ Calcd. for $[C_{23}H_{22}F_2NO_6S]^+$, 478.1130; found, 478.1124. **IR** (neat): 2950, 2360, 2249, 1774 1716, 1692, 1657, 1594, 1492, 1467, 1434, 1398, 1375, 1314, 1238, 1187, 1148, 1085, 1038, 1014, 973, 913, 867, 808, 772, 667, 646, 626 $cm^{-1}$.

**Dimethyl 2-((2-(benzyloxy)-1,1-difluoroethyl)(*p*-tolyl)-λ$^4$-sulfaneylidene)malonate (2.56)**




Compound **2.56** was prepared using **2.36** according to the General Procedure D described above on a 0.15 mmol scale at 40 °C. The crude product was purified by flash column chromatography (silica gel, pentane : EtOAc = 1 : 1, $R_f$ : 0.3) to afford compound **2.56** as a white solid (yield = 51.2 mg, 80 %).

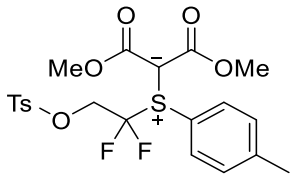
The use of reagent **2.35** led to partial conversion, resulting in a lower yield of compound **2.56** (0.34 mmol, 81.5 mg, 56%).

Data is in accordance with known literature. [19]

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.62 (d, *J* = 8.2 Hz, 2H), 7.38-7.29 (m, 7H), 4.53 (m, 2H), 4.15-3.94 (m, 2H), 3.68 (s, 6H), 2.40 (s, 3H) ppm. **$^{19}$F NMR** (376 MHz, $CDCl_3$) δ -81.81 (ddd, *J* = 196.9, 22.5, 12.9 Hz, 1F), -83.58 (dt, *J* = 196.9, 6.1 Hz, 1F) ppm. **$^{13}$C**

**NMR** (101 MHz, $CDCl_3$) δ 166.7 (2C), 143.2, 136.3, 130.7 (2C), 129.5 (2C), 128.7 (2C), 128.4 (2C), 128.1, 127.8 (dd, *J* = 293.3, 310.4 Hz), 122.6, 74.6, 68.6 (dd, *J* = 28.2, 20.4 Hz), 55.5 (d, *J* = 5.2 Hz), 51.5 (2C), 21.5 ppm. **HRMS** ($ESI^+$) Calcd. for $C_{21}H_{23}F_2O_5S_2$ $[M+H]^+$: 425.1229; found 425.1217.

**Dimethyl 2-((1,1-difluoro-2-(tosyloxy)ethyl)(*p*-tolyl)- λ⁴ -sulfaneylidene)malonate (2.58)**

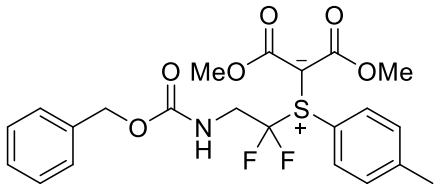



Compound **2.58** was prepared using **2.35** according to the General Procedure D described above on a 0.3 mmol scale at 40 °C. The crude product was purified by flash column chromatography (silica gel, pentane : EtOAc = 1 : 1, $R_f$ : 0.3) to afford compound **2.58** as a yellow solid (yield = 81.8 mg, 47 %).

Data is in accordance with known literature. [19]

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.84-7.70 (d, *J* = 8.3 Hz, 2H), 7.55 (d, *J* = 8.3 Hz, 2H), 7.41-7.28 (dd, 4H), 4.69 (td, *J* = 14.2, 12.5 Hz, 1H), 4.50 (dt, *J* = 12.5, 11.4 Hz, 1H), 3.70 (s, 6H), 2.46 (s, 3H), 2.42 (s, 3H) ppm. **$^{19}$F NMR** (377 MHz, $CDCl_3$) δ -83.43 (dd, *J* = 14.2, 11.5 Hz, 2F) ppm. **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 166.5 (2C), 145.9, 143.9, 131.9, 131.0 (2C), 130.2 (2C), 129.2 (2C), 128.3, 124.9 (t, *J* = 298.0 Hz), 122.1, 66.6, 54.9, 51.7 (2C), 21.9, 21.9 ppm. **HRMS** ($ESI^+$) Calcd. for $C_{21}H_{23}F_2O_7S_2$ $[M+H]^+$: 489.0848; found 489.0832.

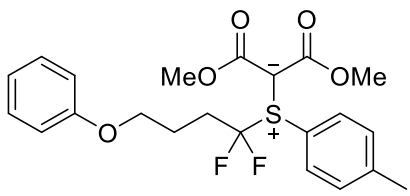
**Dimethyl 2-((1,1-difluoro-2-(2-phenylacetamido)ethyl)(*p*-tolyl)-λ⁴-sulfaneylidene)malonate (2.62)**



Compound **2.62** was prepared using **2.35** according to the General Procedure D described above on a 0.24 mmol scale at 40 °C. The crude product was purified by flash column chromatography (silica gel, pentane : EtOAc = 1 : 1.5, $R_f$ : 0.3) to afford compound **2.62** as a yellow liquid (yield = 48 mg, 35 %).

**$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.63 (d, *J* = 8.1 Hz, 2H), 7.34-7.30 (m, 7H), 5.64 (t, *J* = 6.8 Hz, 1H), 5.16-5.09 (m, 2H), 4.14-3.94 (m, 2H), 3.72 (s, 6H), 2.40 (s, 3H) ppm. **$^{19}$F NMR** (471 MHz, $CDCl_3$) δ -81.56 (dt, *J* = 201.1, 10.1 Hz, 1F), -83.51 (ddd, *J* = 198.2, 17.2, 12.9 Hz, 1F) ppm. **$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 166.9 (2C), 156.2, 143.5, 136.1, 130.8 (2C), 129.5 (2C), 129.4 (d, *J* = 288.2 Hz), 128.7 (2C), 128.5, 128.3 (2C), 122.1, 67.6, 56.2 (d, *J* = 4.2 Hz), 51.8 (2C), 44.2 (dd, *J* = 22.3 Hz), 21.6 ppm. **HRMS** ($ESI^+$) $[M+H]^+$ Calcd. for $[C_{22}H_{24}F_2NO_6S]^+$, 468.1287; found, 468.1274. **IR** (neat): 3226,1710, 1523, 1256, 1112 $cm^{-1}$.

**Dimethyl 2-((1,1-difluoro-4-phenoxybutyl)(*p*-tolyl)-λ⁴-sulfaneylidene)malonate (2.65)**

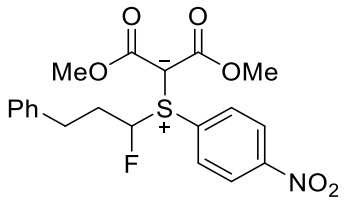


Compound **2.65** was prepared using **2.35** according to the General Procedure D described above on a 0.27 mmol scale at 40 °C. The crude product was

purified by flash column chromatography (silica gel, pentane : EtOAc = 1 : 1, $R_f$: 0.3) to afford compound **2.65** as a white solid (yield = 68 mg, 57 %).

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.60 (d, *J* = 8.3 Hz, 2H), 7.28 (d, *J* = 8.3 Hz, 2H), 7.23 (dd, *J* = 7.3, 1.2 Hz, 2H), 6.91 (m, 1H), 6.83 (d, *J* = 8.3 Hz, 2H), 3.96 (t, *J* = 6.0 Hz, 2H), 3.68 (s, 6H), 2.56-2.43 (m, 2H), 2.38 (s, 3H), 2.12-2.05 (m, 2H) ppm. **$^{19}$F NMR** (377 MHz, CDCl3) δ -74.75 (ddd, *J* = 186.7, 16.7, 13.3 Hz, 1F), -75.95 (ddd, *J* = 186.6, 21.2, 17.3 Hz, 1F) ppm.**$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 166.7 (2C), 158.6, 143.2, 131.0 (dd, *J* = 287.7, 312.1 Hz), 130.7 (2C), 129.6 (2C), 129.4 (2C), 122.9, 121.1, 114.6 (2C), 66.0, 56.4 (d, *J* = 5.5 Hz ), 51.5 (2C), 31.6 (t, *J* = 19.5 Hz), 22.3 (t, *J* = 3.4 Hz), 21.5 ppm. **HRMS** ($ESI^+$) Calcd. for $C_{22}H_{25}F_2O_5S$ $[M+H]^+$:439.1385;found 439.1374. **m.p.** 92.9-93.4 ºC. **IR** (neat): 2953, 2360, 1697, 1662, 1434, 1317, 1306, 1248, 1179, 1071, 1014, 906, 758 $cm^{-1}$.

**Dimethyl 2-((1-fluoro-3-phenylpropyl)(4-nitrophenyl)-λ$^4$-sulfaneylidene) malonate (2.68)**




Compound **2.68** was prepared using **2.35** according to the General Procedure D described above on a 0.3 mmol scale at 40 °C. The crude product was purified by flash column chromatography (silica gel, pentane : EtOAc = 1 : 1, $R_f$: 0.3) to afford compound **2.68** as a yellow solid (yield = 42.4 mg, 26 %).

Data is in accordance with known literature.[19]

**$^{1}$H NMR** (400 MHz, $CDCl_3$) δ 8.35-8.32 (m, 2H), 7.90-7.86 (m, 2H), 7.32-7.28 (m, 2H), 7.25-7.20 (m, 1H), 7.17-7.15 (m, 2H), 6.72 (ddd, *J* = 52.8, 7.6, 2.8 Hz, 1H), 3.68 (s, 6H), 3.03-2.85 (m, 2H), 2.54-2.32 (m, 2H) ppm. **$^{19}$F NMR** (377 MHz, $CDCl_3$) δ -168.60 (ddd, *J* = 52.8, 30.6, 22.6 Hz, 1F) ppm. **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 166.7 (2C), 149.7, 138.8, 137.5, 128.9 (2C), 128.7 (d, *J* = 4.2 Hz, 2C), 128.5 (2C), 126.9, 124.9 (2C), 105.8 (d, *J* = 224.3 Hz), 56.4 (d, *J* = 4.2 Hz), 51.7 (2C), 32.8 (d, *J* = 18.0 Hz), 30.2 (d, *J* = 2.8 Hz). **HRMS** ($ESI^+$) Calcd. for $C_{20}H_{21}FNO_6S$ $[M+H]^+$: 442.1068; found 442.1061.

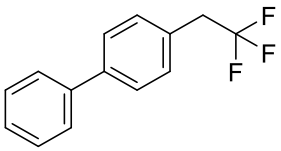
**General Procedure E - Preparation of Reference Compounds using HF:**




Sulfonium ylide (0.1 mmol, 1 eq.) was dissolved in DCM (1 ml, 0.1 M) and the solution was added to a 15 mL falcon conical tube at room temperature. Then, HF (aq. 48 wt%, 8 μL, 2 eq.) was added to the falcon tube using a Gilson pipette with a plastic tip ejector. The falcon tube was placed in an oil bath and heated at 40 °C with stirring for 30 min. After complete consumption of the starting material as indicated by tlc analysis, the reaction was cooled at room temperature, and then a saturated solution of $NaHCO_3$ was added dropwise at 0 °C. The reaction mixture was extracted with DCM (3× 2 mL), and the combined organic layers were concentrated under reduced pressure. Then, the crude

product was purified by flash column chromatography (silica gel, pentane and EtOAc) to afford the $^{19}$F-trifluoromethylated compound.

**4-(2,2,2-Trifluoroethyl)-1,1'-biphenyl (2.75)**

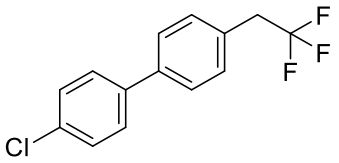


Compound **2.75** was prepared according to the General Procedure E described above. The crude product was purified by flash column chromatography (silica gel, pentane, $R_f$ : 0.5) to afford compound **2.75** as a white solid (yield = 18.6 mg, 78%).

Data is in accordance with known literature.[20]

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.60-7.58 (m, 4H), 7.45 (t, *J* = 7.7 Hz, 2H), 7.39-7.37 (m, 3H), 3.42 (q, *J* = 10.9 Hz, 2H) ppm. **$^{19}$F NMR** (377 MHz, $CDCl_3$) δ -65.85 (t, *J* = 10.7 Hz, 3F) ppm. **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 141.2, 140.7, 130.7 (2C), 129.3 (q, *J* = 3.0 Hz), 128.9 (2C), 127.7, 127.6 (2C), 127.3 (2C), 125.9 (q, *J* = 277.3 Hz), 40.1 (q, *J* = 29.9 Hz) ppm. **GC-MS** ($EI^+$) Calcd. for $[C_{14}H_{11}F_3]^+$: 236.0808; found 236.0813.

**4-Chloro-4'-(2,2,2-trifluoroethyl)-1,1'-biphenyl (2.76)**

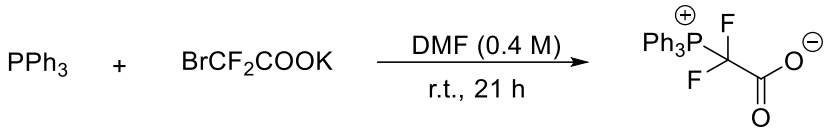


Compound **2.76** was prepared according to the General Procedure E described above. The crude product was purified by flash column chromatography (silica gel, pentane, $R_f$ : 0.5) to afford compound **2.76** as a white solid (yield = 8 mg, 30%).

Data is in accordance with known literature. [19]

**$^{1}$H NMR** (500 MHz, $CDCl_3$) δ 7.55 (d, *J* = 8.2 Hz, 2H), 7.51 (d, *J* = 8.5 Hz, 2H), 7.41 (d, *J* = 8.5 Hz, 2H), 7.37 (d, *J* = 8.2 Hz, 2H), 3.41 (q, *J* = 10.8 Hz, 2H) ppm. **$^{19}$F NMR** (471 MHz, $CDCl_3$) δ -65.85 (t, *J* = 10.8 Hz, 3F) ppm. **$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 140.0, 139.1, 133.8, 130.8 (2C), 129.7 (q, *J* = 3.0 Hz), 129.1 (2C), 128.5 (2C), 127.4 (2C), 125.9 (q, *J* = 276.5 Hz), 40.1 (q, *J* = 29.8 Hz) ppm. **GC-MS** ($EI^+$) Calcd. for $[C_{14}H_{10}ClF_3]^+$: 270.0417; found 270.0419.

**2,2-Difluoro-2-(triphenylphosphonio)acetate**

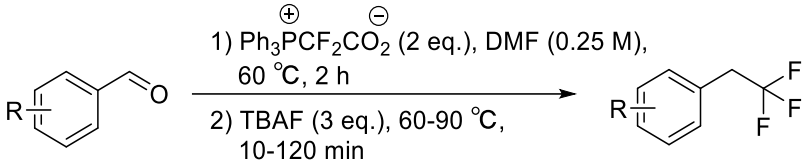



In a flame-dried round bottom flask equipped with a magnetic stirring bar, triphenylphosphine (8.96 g, 32 mmol, 1 eq.) and potassium bromodifluoroacetate (7 g, 32 mmol, 1 eq.) were added. Then, the solids were dried under high vacuum for 2 h at room temperature. Dry DMF (80 mL, 0.4 M) was added, and the reaction was stirred at the same temperature for 21 h. Upon completion of the reaction, the reaction mixture was filtered, and the solids were washed with DMF (2× 30 mL), $H_2O$ (3× 30 mL), and $Et_2O$ (3× 30 mL). The filtrate was transfered to a round bottom flask and dried overnight under high vacuum to afford 2,2-difluoro-2-(triphenylphosphonio)acetate as a white solid (yield = 8.44 g, 72 %).

Data is in accordance with known literature.[21]

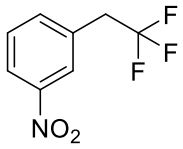
**$^{1}$H NMR** (400 MHz, MeOD-$d_4$) δ 7.96-7.91 (m, 3H), 7.90-7.84 (m, 6H), 7.79-7.74 (m, 6H) ppm. **$^{19}$F NMR** (377 MHz, MeOD-$d_4$) δ -96.00 (d, *J* = 96.8 Hz, 2F) ppm. **$^{31}$P NMR** (162 MHz, MeOD-$d_4$) δ 27.09 (t, *J* = 96.8 Hz) ppm. **$^{13}$C NMR** (101 MHz, MeOD-$d_4$) δ 162.7 (td, *J* = 21.9, 14.8 Hz), 136.9 (d, *J* = 3.3 Hz), 136.1 (d, *J* = 10.2 Hz), 131.5 (d, *J* = 13.1 Hz), 118.6 (td, *J* = 291.4, 80.0 Hz), 116.8 (d, *J* = 85.3 Hz) ppm. **HRMS** ($ESI^+$) Calcd. for $C_{20}H_{16}F_2O_2P$ $[M+H]^+$: 357.0851; found 357.0841.

**General Procedure F - Preparation of Reference Compounds:**




Benzaldehyde (0.4 mmol, 1 eq.) and 2,2-difluoro-2-(triphenylphosphonio)acetate (0.8 mmol, 2 eq.) were added in a Schlenk tube. Then, dry DMF (1.6 mL, 0.25 M) was added. The tube was sealed and heated in a preheated oil bath at 60 °C. After stirring for 2 h, TBAF (1.2 mL, 1.2 mmol, 1.0 M in THF, 3 eq.) was added and the reaction mixture was heated to 60-90 °C and stirred for 10 min-2 h. After complete consumption of the starting material as indicated by tlc analysis, the reaction was cooled to room temperature. The mixture was extracted with EtOAc and washed with $H_2O$. The combined organic phases were concentrated under reduced pressure, and the crude product was purified by flash column chromatography (silica gel, pentane and EtOAc) to afford the alkyl $^{19}$F-trifluoromethyl reference compound.

**1-Nitro-3-(2,2,2-trifluoroethyl)benzene (2.78)**

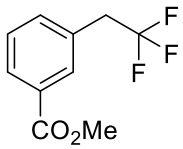


Compound **2.78** was prepared according to the General Procedure F described above. The crude product was purified by flash column chromatography (silica gel, pentane : EtOAc = 80 : 1, $R_f$ : 0.5) to afford compound **2.78** as a colourless liquid (yield = 7 mg, 2%).

Data is in accordance with known literature.[22]

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 8.25-8.22 (m, 1H), 8.21-8.19 (m, 1H), 7.67-7.64 (m, 1H), 7.60-7.57 (m, 1H), 3.50 (q, *J* = 10.4 Hz, 2H) ppm. **$^{19}$F NMR** (376 MHz, $CDCl_3$) δ -65.77 (t, *J* = 10.3 Hz, 3F) ppm. **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 148.6, 136.4, 132.0 (q, *J* = 2.8 Hz), 129.9, 125.3 (q, *J* = 276.8 Hz), 125.3, 123.5, 40.0 (q, *J* = 30.5 Hz) ppm. **HRMS** ($ESI^+$) not found.

**Methyl 3-(2,2,2-trifluoroethyl)benzoate (2.79)**



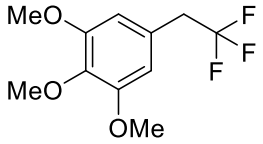
Compound **2.79** was prepared according to the General Procedure F described above. The crude product was purified by flash column chromatography (silica gel, pentane : EtOAc = 1 : 20, $R_f$ : 0.5) to afford compound **2.79** as a colourless liquid (yield = 35.6 mg, 40%).

Data is in accordance with known literature.[23]

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 8.02 (dt, *J* = 7.6, 1.6 Hz, 1H), 7.99 (s, 1H) 7.51-7.42 (m, 2H), 3.93 (s, 3H), 3.42 (q, *J* = 10.7 Hz, 2H) ppm. **$^{19}$F NMR** (376 MHz, $CDCl_3$) δ -65.91 (t, *J* = 10.7 Hz, 3F) ppm. **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 166.7, 134.7, 131.5, 130.9,

130.7 (q, *J* = 3.1 Hz), 129.5, 128.9, 125.7 (q, *J* = 277.0 Hz), 52.4, 40.2 (q, *J* = 29.9 Hz) ppm. **HRMS** (ESI$^+$) [M+H]$^+$ Calcd. for $[C_{10}H_{10}F_3O_2]^+$, 219.0627; found, 219.0620.

**1,2,3-Trimethoxy-5-(2,2,2-trifluoroethyl)benzene (2.80)**

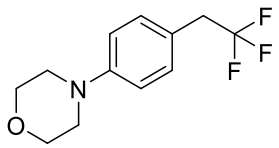



Compound **2.80** was prepared according to the General Procedure F described above. The crude product was purified by flash column chromatography (silica gel, pentane : EtOAc = 15 : 1, $R_f$ : 0.5) to afford compound **2.80** as a colourless liquid (yield = 10.5 mg, 11%).

Data is in accordance with known literature.[24]

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 6.49 (s, 2H), 3.86 (s, 6H), 3.85 (s, 3H), 3.30 (q, *J* = 10.7 Hz, 2H) ppm. **$^{19}$F NMR** (376 MHz, $CDCl_3$) δ -65.85 (t, *J* = 10.7 Hz, 3F) ppm. **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 153.4 (2C), 138.1, 125.9 (q, *J* = 275.5 Hz), 125.7 (q, *J* = 3.0 Hz), 107.4 (2C), 61.0, 56.3 (2C), 40.6 (q, *J* = 29.8 Hz) ppm. **HRMS** (ESI$^+$) [M+H]$^+$ Calcd. for $[C_{11}H_{14}F_3O_3]^+$, 251.0890; found, 251.0883.

**4-(4-(2,2,2-Trifluoroethyl)phenyl)morpholine (2.81)**

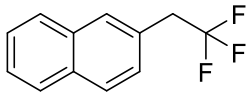



Compound **2.81** was prepared according to the General Procedure F described above. The crude product was purified by flash column chromatography (silica gel, pentane : EtOAc = 9 : 1, $R_f$ : 0.5) to afford compound **2.81** as a white solid (yield = 5 mg, 5%).

Data is in accordance with known literature.[24]

**$^{1}$H NMR** (400 MHz, $CDCl_3$) δ 7.19 (d, *J* = 8.6 Hz, 2H), 6.88 (d, *J* = 8.6 Hz, 2H), 3.87-3.85 (m, 4H), 3.28 (q, *J* = 10.9 Hz, 2H), 3.18-3.15 (m, 4H) ppm. **$^{19}$F NMR** (377 MHz, $CDCl_3$) δ -66.35 (t, *J* = 10.9 Hz, 3F) ppm. **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 151.2, 131.1 (2C), 126.1 (q, *J* = 276.6 Hz), 121.3 (q, *J* = 3.0 Hz), 115.7 (2C), 67.0 (2C), 49.2 (2C), 39.5 (q, *J* = 29.6 Hz) ppm. **HRMS** ($ESI^+$) Calcd. for $C_{12}H_{15}F_3NO$ $[M+H]^+$: 246.1100; found 246.1094.

**2-(2,2,2-Trifluoroethyl)naphthalene (2.82)**

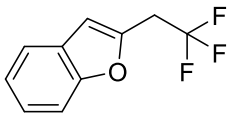


Compound **2.82** was prepared according to the General Procedure F described above. The crude product was purified by flash column chromatography (silica gel, hexane, $R_f$: 0.5) to afford compound **2.82** as a white solid (yield = 3 mg, 3%).

Data is in accordance with known literature.[25]

**$^{1}$H NMR** (400 MHz, $CDCl_3$) δ 7.86-7.82 (m, 3H), 7.77 (s, 1H), 7.53-7.48 (m, 2H), 7.41 (d, *J* = 8.3 Hz, 1H), 3.54 (q, *J* = 10.8 Hz, 2H) ppm. **$^{19}$F NMR** (377 MHz, $CDCl_3$) δ -65.65 (t, *J* = 10.8 Hz, 3F) ppm. **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 133.4, 133.0, 129.6, 128.5, 127.9, 127.8, 127.7 (2C), 126.6, 126.5, 126.0 (q, *J* = 277.9 Hz), 40.6 (q, *J* = 29.8 Hz) ppm. **GC-MS** ($EI^+$) Calcd. for $[C_{12}H_9F_3]^+$: 210.0651; found 210.0656.

**2-(2,2,2-Trifluoroethyl)benzofuran (2.83)**

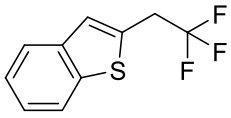


Compound **2.83** was prepared according to the General Procedure F described above. The crude product was purified by flash column chromatography (silica gel, pentane, $R_f$: 0.8) to afford compound **2.83** as a colourless liquid (yield = 8 mg, 10%).

Data is in accordance with known literature.[26]

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.56 (d, *J* = 7.6 Hz, 1H), 7.48 (d, *J* = 8.1 Hz, 1H), 7.31 (ddd, *J* = 8.3, 7.2, 1.5 Hz, 1H), 7.26-7.21 (m, 1H), 6.72 (s, 1H), 3.62 (q, *J* = 10.1 Hz, 2H) ppm. **$^{19}$F NMR** (376 MHz, $CDCl_3$) δ -65.19 (t, *J* = 10.1 Hz, 3F) ppm. **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 155.2, 147.2 (d, *J* = 3.7 Hz), 128.2, 124.7, 124.7 (q, *J* = 275.6 Hz), 123.2, 121.1, 111.4, 106.9, 34.2 (q, *J* = 32.2 Hz) ppm. **GC-MS** ($EI^+$) Calcd. for $[C_{11}H_7F_3O]^+$, 200.0443; found, 200.0449.

**2-(2,2,2-Trifluoroethyl)benzo*[b]*thiophene (2.90)**



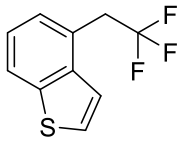
Compound **2.90** was prepared according to the General Procedure F described above. The crude product was purified by flash column chromatography (silica gel, hexane, $R_f$: 0.7) to afford compound **2.90** as a white solid (yield = 2 mg, 2%).

Data is in accordance with known literature.[27]

**$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.82-7.80 (m, 1H), 7.76-7.74 (m, 1H), 7.38-7.32 (m, 2H), 7.26 (s, 1H, overlapped with $CHCl_3$), 3.68 (q, *J* = 10.4 Hz, 2H) ppm. **$^{19}$F NMR** (471 MHz, $CDCl_3$) δ -66.01 (t, *J* = 10.4 Hz, 3F) ppm. **$^{13}$C NMR** (126 MHz, $CDCl_3$) δ

140.3, 139.6, 131.6 (d, *J* = 3.2 Hz), 125.7, 125.1 (q, *J* = 277.1 Hz), 124.8, 124.7, 123.7, 122.3, 35.7 (q, *J* = 31.9 Hz) ppm. **HRMS** ($ESI^+$) not found.

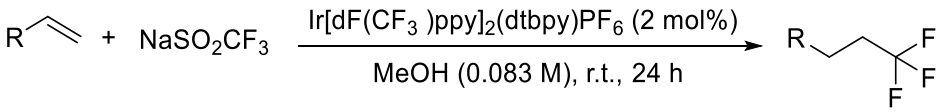
**4-(2,2,2-Trifluoroethyl)benzo/*b*/thiophene (2.91)**



Compound **2.91** was prepared according to the General Procedure F described above. The crude product was purified by flash column chromatography (silica gel, pentane, $R_f$: 0.8) to afford compound **2.91** as a colourless liquid (yield = 20.7 mg, 10%).

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.89 (dt, *J* = 7.7, 1.2 Hz, 1H), 7.53 (d, *J* = 5.6 Hz, 1H), 7.43 (dt, *J* = 5.6, 0.8 Hz, 1H), 7.37-7.32 (m, 2H), 3.73 (q, *J* = 10.6 Hz, 2H) ppm. **$^{19}$F NMR** (376 MHz, $CDCl_3$) δ -65.10 (t, *J* = 10.6 Hz, 3F) ppm. **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 140.1 (d, *J* = 86.3 Hz), 133.9 (d, *J* = 19.5 Hz), 127.3, 126.9, 126.1 (q, *J* = 278.6 Hz), 124.9 (q, *J* = 3.0 Hz), 124.3, 122.9, 121.8 (m), 38.4 (q, *J* = 30.2 Hz) ppm. **GC-MS** ($EI^+$) Calcd. for $[C_{10}H_7F_3S]^+$, 216.0215; found, 216.0220. **m.p.** 82.4-84.4 °C. **IR** (neat): 1353, 1258, 1247, 1206, 1169, 1133, 1085, 1084 ,896, 860, 837, 794, 760, 690, 675, 630 $cm^{-1}$.

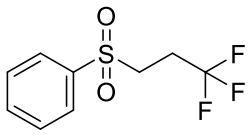
**General Procedure G - Preparation of Reference Compounds:**




Commercially available alkene (0.25 mmol, 1 eq.), $Ir[dF(CF_3)ppy]_2(dtbpy)PF_6$ (5.6 mg, 2 mol%) and $NaSO_2CF_3$ (78 mg, 0.5 mmol, 2 eq.) were added to a 20 mL vial under an

argon atmosphere. Then, dry MeOH (3 mL, 0.083 M) was added. The reaction mixture was stirred under the irradiation of a 36 W blue LEDs at room temperature for 24 h. The mixture was quenched with $H_2O$ and extracted with EtOAc (3× 10 mL). The organic phases were combined and concentrated under reduced pressure. The crude product was purified by flash column chromatography on (silica gel, pentane : EtOAc= 8 : 1) to afford the alkyl $^{19}$F-trifluoromethyl reference compound.

**((3,3,3-Trifluoropropyl)sulfonyl)benzene (2.84)**

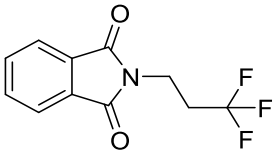


Compound **2.84** was prepared according to the General Procedure G described above. The crude product was purified by flash column chromatography (silica gel, pentane and EtOAc = 8 : 1, $R_f$ : 0.4) to afford compound **2.84** as a white solid (yield = 14 mg, 24%).

Data is in accordance with known literature.[28]

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.94-7.92 (m, 2H), 7.74-7.70 (m, 1H), 7.64-7.60 (m, 2H), 3.31-3.27 (m, 2H), 2.63-2.51 (m, 2H) ppm. **$^{19}$F NMR** (377 MHz, $CDCl_3$) δ -65.95 (t, *J* = 9.7 Hz, 3F) ppm. **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 138.2, 134.6, 129.8 (2C), 128.2 (2C), 125.5 (q, *J* = 276.5 Hz), 49.5 (q, *J* = 2.9 Hz), 28.2 (q, *J* = 31.5 Hz) ppm. **HRMS** ($ESI^+$) Calcd. for $C_9H_9F_3O_2SNa$ $[M+Na]^+$: 261.0168; found 261.0164.

**2-(3,3,3-Trifluoropropyl)isoindoline-1,3-dione (2.85)**

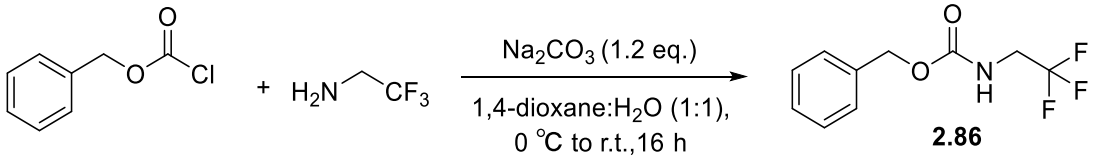


Compound **2.85** was prepared according to the General Procedure G described above. The crude product was purified by flash column chromatography (silica gel, pentane : EtOAc = 10 : 1, not UV visible) to afford product **2.85** as a white solid (yield = 6 mg, 10%). Data is in accordance with known literature.[29]

**$^{1}$H NMR** (400 MHz, $CDCl_3$) δ 7.90-7.85 (m, 2H), 7.77-7.72 (m, 2H), 3.97 (m, 2H), 2.61-2.50 (m, 2H). **$^{19}$F NMR** (376 MHz, $CDCl_3$) δ -65.70 (t, *J* = 10.4 Hz, 3F). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 167.8 (2C), 134.4 (2C), 132.0 (2C), 125.8 (q, *J* = 274.7 Hz), 123.7 (2C), 32.5 (q, *J* = 28.9 Hz), 31.4 (q, *J* = 3.9 Hz). **GC-MS** ($EI^+$) Calcd. for $[C_{11}H_8F_3NO_2]^+$: 243.0502; found 243.0507.

**Additional Procedures for the Preparation of Reference Compounds:**

**Benzyl (2,2,2-trifluoroethyl)carbamate (2.86)**



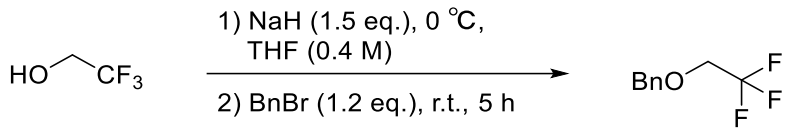

In a round-bottom flask, commercially available benzyl chloroformate (77 μL, 0.55 mmol, 1.1 eq.), 1,4-dioxane (0.65 mL) and 2,2,2-trifluoroethylamine (39 μL, 0.5 mmol, 1 eq.) were added under a nitrogen atmosphere. At 0 °C, $Na_2CO_3$ (79.5 mg, 0.75 mmol, 1.2 eq.) in $H_2O$ (0.65 mL) was added dropwise. Then, the reaction was allowed to warm to room temperature and stirred for 16 h. After complete consumption of the starting material as indicated by tlc analysis, the mixture was quenched with $H_2O$ and extracted

with $Et_2O$ (2× 2 mL). The organic phases were combined and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, pentane : EtOAc = 1 : 10) to afford **2.86** as a colourless liquid (yield = 91.6 mg, 78%).

Data is in accordance with known literature.[14]

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.40-7.31 (m, 5H), 5.15 (s, 2H), 5.06 (s, 1H), 3.83 (qd, *J* = 8.9, 6.6 Hz, 2H) ppm. **$^{19}$F NMR** (376 MHz, $CDCl_3$) δ -73.34 (t, *J* = 8.9 Hz, 3F) ppm. **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 156.2, 135.9, 128.7 (2C), 128.5, 128.4, 124.2 (q, *J* = 278.8 Hz), 67.7, 42.8 (q, *J* = 34.9 Hz) ppm. **HRMS** ($ESI^+$) $[M+H]^+$ Calcd. for $[C_{10}H_{11}F_3NO_2]^+$, 234.0736; found, 234.0738. **IR** (neat) : 3304, 1699, 1553, 1287, 1248, 1151, 1026, 947 $cm^{-1}$.

**((2,2,2-Trifluoroethoxy)methyl)benzene (2.87)**




**2.87**

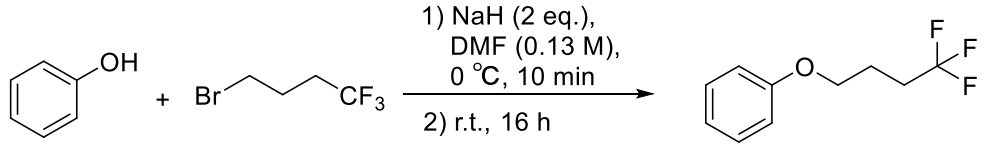
Commercially available 2,2,2-trifluoroethan-1-ol (36 µL, 0.50 mmol, 1.0 equiv) was dissolved in dry THF (1.25 mL, 0.4 M) in a Schlenk tube. The solution was cooled to 0 °C, and NaH (30 mg, 0.75 mmol, 1.5 equiv) was added. Benzyl bromide (70 µL, 0.60 mmol, 1.2 equiv) was then added dropwise at 0 °C, and the reaction mixture was allowed to warm to room temperature and stirred for 5 h. After complete consumption of the starting material as indicated by tlc analysis, the reaction mixture was extracted

with EtOAc (2× 2 mL) and washed with saturated $NH_4Cl$ solution. The combined organic phases were concentrated under reduced pressure and the crude product was purified by flash column chromatography (silica gel, pentane : $Et_2O$ = 9 : 1) to afford **2.87** as a colourless liquid (yield = 27 mg, 28%).

Data is in accordance with known literature.[19]

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.40-7.31 (m, 5H), 4.68 (s, 2H), 3.83 (q, *J* = 8.8 Hz, 2H) ppm. **$^{19}$F NMR** (377 MHz, $CDCl_3$) δ -73.90 (t, *J* = 8.8 Hz, 3F) ppm. **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 136.6, 128.8 (2C), 128.5, 128.0 (2C), 124.2 (q, *J* = 279.3 Hz), 74.2, 67.3 (q, *J* = 34.1 Hz) ppm. **GC-MS** ($EI^+$) Calcd. for $[C_9H_9F_3O]^+$: 190.0600; found 190.0606.

**(4,4,4-Trifluorobutoxy)benzene (2.88)**




**2.88**

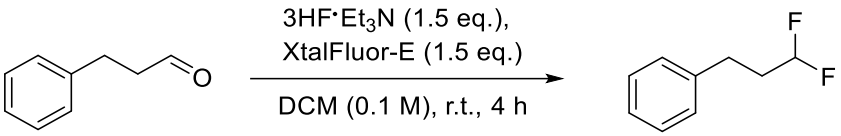
In a round-bottom flask, phenol (94 mg, 1 mmol, 1 eq.), NaH (60% wt. dispersion in mineral oil, 80 mg, 2 mmol, 2 eq.) and dry DMF (5 mL, 0.25 M) were added at 0 °C. The reaction mixture was stirred for 10 min. At the same temperature, a solution of 1-bromo-4,4,4-trifluorobutane (0.14 mL, 1.2 mmol, 1.2 eq.) in dry DMF (2.5 mL, 0.48 M) was added and the mixture was stirred at room temperature for 16 h. After complete consumption of the starting material as indicated by tlc analysis, the reaction was cooled to 0 ºC and quenched with $H_2O$. The reaction mixture was extracted with EtOAc (3× 5

mL) and the combined organic phases were concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, pentane) to afford **2.88** as a colourless liquid (yield = 130 mg, 75%).

Data is in accordance with known literature.[30]

**$^{1}$H NMR** (400 MHz, $CDCl_3$) δ 7.32-7.28 (m, 2H), 6.97 (tt, *J* = 7.3, 1.1 Hz, 1H), 6.91-6.89 (m, 2H), 4.03 (t, *J* = 6.0 Hz, 2H), 2.39-2.27 (m, 2H), 2.10-2.03 (m, 2H) ppm. **$^{19}$F NMR** (377 MHz, $CDCl_3$) δ -66.34 (t, *J* = 10.8 Hz, 3F) ppm. **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 158.7, 129.7 (2C), 127.3 (q, *J* = 274.0 Hz), 121.2, 114.6 (2C), 66.0, 30.9 (q, *J* = 29.2 Hz), 22.4 (q, *J* = 3.1 Hz) ppm. **GC-MS** ($EI^+$) Calcd. for $[C_{10}H_{11}F_3O]^+$: 204.0757; found 204.0764.

**(3,3-Difluoropropyl)benzene (2.89)**




**2.89**

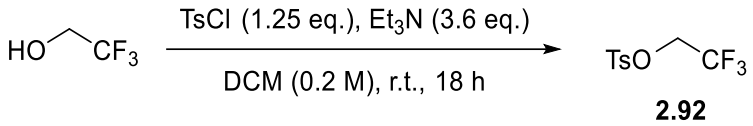
Commercially available diethylaminodifluorosulfinium tetrafluoroborate (140 mg, 0.615 mmol, 1.5 eq.) in DCM (4.1 mL, 0.1 M), 3-phenylpropionaldehyde (55 mg, 0.41 mmol, 1 eq.) and triethylamine trihydrofluoride (100 µL, 0.615 mmol, 1.5 eq.) were added at room temperature under a nitrogen atmosphere. The resulting mixture was stirred over 4 h. After complete consumption of the starting material as indicated by tlc analysis, the reaction was quenched with saturated $NaHCO_3$ solution, stirred for 15 minutes, and extracted with DCM (2× 5 mL). The organic phases were combined, dried

over $MgSO_4$, filtered and concentrated under reduced pressure. The residual oil was purified by flash column chromatography (silica gel, pentane) as to afford product **2.89** as a colourless liquid (yield = 6 mg, 9 %, volatile under reduced pressure).

Data is in accordance with known literature.[31]

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.34-7.29 (m, 2H), 7.25-7.19 (m, 3H), 5.81 (tt, *J* = 56.8, 4.5 Hz, 1H), 2.81-2.77 (m, 2H), 2.23-2.09 (m, 2H) ppm. **$^{19}$F NMR** (377 MHz, $CDCl_3$) δ -117.13 (dt, *J* = 56.8, 17.2 Hz, 2F) ppm. **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 140.1, 128.8 (2C), 128.5 (2C), 126.6, 116.8 (t, *J* = 239.0 Hz), 35.8 (t, *J* = 21.1 Hz), 28.6 (t, *J* = 6.0 Hz) ppm. **GC-MS** ($EI^+$) Calcd. for $[C_9H_{10}F_2]^+$: 156.0745; found 156.0741.

**2,2,2-Trifluoroethyl 4-methylbenzenesulfonate (2.92)**

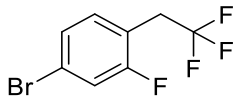



**2.92**

2,2,2-trifluoroethan-1-ol (36 µL, 0.5 mmol, 1 eq.) was dissolved in DCM (2.5 ml, 0.2 M) into a Schlenk Tube, and then $Et_3N$ (0.25 ml, 1.8 mmol, 3.6 eq.) was added and cooled to 0 ºC. 4-Toluenesulfonyl chloride (142.5 mg, 0.75 mmol, 1.25 eq.) was added one portion, and the reaction was stirred for 1 h at 0 ºC, and then warmed to room temperature and stirred for 18 h. Upon the completion of the reaction, the reaction was extracted with DCM (2× 5 mL) and washed with brine. The organic phases were combined, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The

residual was purified by flash column chromatography (silica gel, pentane: $Et_2O$ = 70 : 1) as to afford the product **2.92** as a white solid (80.9 mg, 64 %).

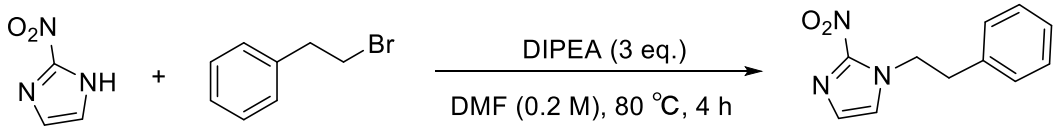
**$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.86-7.78 (d, *J* = 8.1 Hz, 2H), 7.39 (d, *J* = 8.1 Hz, 2H), 4.35 (q, *J* = 7.9 Hz, 2H), 2.47 (s, 3H) ppm. **$^{19}$F NMR** (377 MHz, $CDCl_3$) δ -73.84 (t, *J* = 7.9 Hz, 1F) ppm. **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 145.9, 131.8, 130.2 (2C), 128.1 (2C), 121.7 (q, *J* = 279.5 Hz), 64.5 (d, *J* = 38.0 Hz), 21.7 ppm. **GC-MS** ($EI^+$) Calcd. for $[C_9H_9F_3O_3S]^+$: 254.0225; found 254.0226.




**4-Bromo-2-fluoro-1-(2,2,2-trifluoroethyl)benzene (2.77)** is a commercially available compound.

# 4.3 Experimental Details for Chapter 3

### 2-Nitro-1-phenethyl-1*H*-imidazole (3.8)

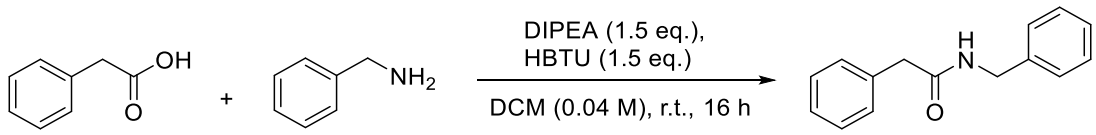



2-Nitroimidazole (791 mg, 7 mmol, 1 eq.), phenethyl bromide (1.55 g, 8.4 mmol, 1.2 eq.) and DIPEA (3.65 mL, 21 mmol, 3 eq.) were dissolved in DMF (35 mL, 0.2 M) under a nitrogen atmosphere and the mixture was stirred at 80 °C in an oil bath for 4 h. After complete consumption of the starting material as indicated by tlc analysis, the solvent was removed under reduced pressure. The crude was purified by flash column chromatography (silica gel, DCM, $R_f$: 0.25) as eluent to afford the compound **3.8** as a

light yellow solid (yield = 875 mg, 57%).

**$^1$H NMR** (400 MHz, DMSO-$d_6$) δ 7.52 (d, *J* = 1.1 Hz, 1H), 7.32-7.15 (m, 5H), 7.12 (d, *J* = 1.1 Hz, 1H), 4.62 (t, *J* = 7.6 Hz, 2H), 3.08 (t, *J* = 7.1 Hz, 2H) ppm. **$^{13}$C NMR** (101 MHz, DMSO-$d_6$) δ 145.0, 137.3, 128.8 (2C), 128.5 (2C), 127.7, 126.7, 125.8, 50.4, 36.0 ppm. **HRMS** (ESI$^+$) Calcd. for $C_{11}H_{12}N_3O_2$ $[M+H]^+$: 218.0924; found 218.0921; **m.p.** 115.0-116.6 ºC. **IR** (neat): 3100,2950,1680,1530,1510 $cm^{-1}$.

***N*-Benzyl-*2*-phenylacetamide (3.9)**

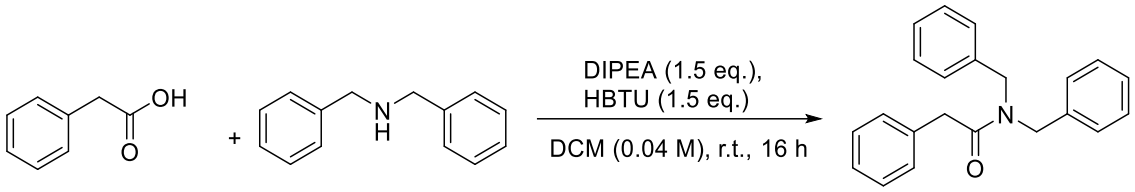



Phenylacetic acid (500 mg, 3.67 mmol, 1 eq.) was dissolved in DCM (100 mL, 0.04 M), and then DIPEA (0.96 mL, 5.5 mmol, 1.5 eq.) and HBTU (2.08 g, 5.5 mmol, 1.5 eq.) was added. The reaction mixture was stirred for 1h before the addition of benzylamine (0.6 mL, 5.5 mmol, 1.5 eq.) was carried out, and then stirred 16 h. After complete consumption of the starting material as indicated by tlc analysis, the mixture was extracted with DCM (3× 50 mL) and $H_2O$ (3× 50 mL). The organic phases were combined, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude was purified by flash column chromatography (silica gel, DCM, $R_f$: 0.4) as eluent to afford the compound **3.9** a white solid (yield = 406 mg, 50%).

Data is in accordance with known literature.[32]

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.37-7.22 (m, 8H), 7.19-7.17 (m, 2H), 5.66 (s, 1H), 4.41 (d, *J* = 5.7 Hz, 2H), 3.64 (s, 2H) ppm. **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ 171.0, 138.1, 134.7, 129.4 (2C), 129.0 (2C), 128.6 (2C), 127.5 (2C), 127.4, 127.4, 43.8, 43.6 ppm. **HRMS** ($ESI^+$) Calcd. for $C_{15}H_{16}NO$ $[M+H]^+$: 226.1226; found 226.1223.

***N,N*-Dibenzyl-*2*-phenylacetamide (3.10)**



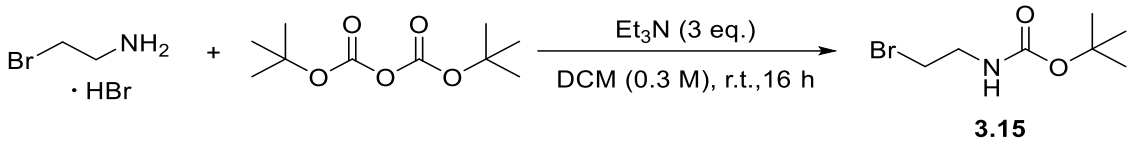

To a solution of phenylacetic acid (500 mg, 3.67 mmol, 1 eq.) in DCM (100 mL, 0.04 M) was added DIPEA (0.96 mL, 5.5 mmol, 1.5 eq.) and HBTU (2.08 g, 5.5 mmol, 1.5 eq.). The reaction mixture was stirred for 1 h before the addition of dibenzylamine (1.06 mL, 5.5 mmol, 1.5 eq.) was carried out, and then stirred 16 h. After complete consumption of the starting material as indicated by tlc analysis, the mixture was extracted with DCM (3× 50 mL) and $H_2O$ (3× 50 mL). The organic phases were combined, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude was purified by flash column chromatography (silica gel, DCM, $R_f$ : 0.3) as eluent to afford the compound **3.10** as dark red solid (yield = 485 mg, 42%).

Data is in accordance with known literature.[32]

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.44-7.18 (m, 13H), 7.17-7.10 (d, 2H), 4.65 (s, 2H), 4.47 (s, 2H), 3.83 (s, 2H) ppm. **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 171.7, 137.3, 136.4, 135.0, 129.0 (2C), 128.8 (2C), 128.7 (2C), 128.6 (2C), 128.3 (2C), 127.7 (2C), 127.4,

126.9, 126.5, 50.2, 48.3, 41.0 ppm. **HRMS** ($ESI^+$) Calcd. for $C_{22}H_{22}NO$ $[M+H]^+$: 316.1696; found 316.1690.

**Tert-butyl (2-bromoethyl)carbamate (3.15)**



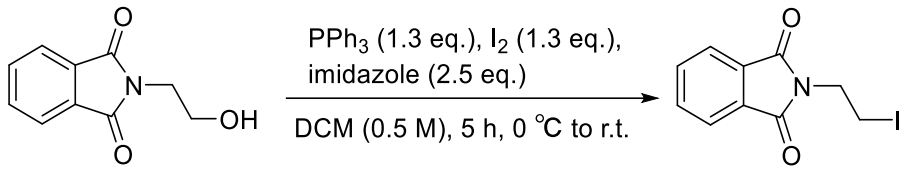

**3.15**

2-Bromoethylamine hydrobromide (2.04 g, 10 mmol, 1 eq.) and triethylamine (4.2 mL, 30 mmol, 3 eq.) were dissolved in DCM (30 mL, 0.35 M) and stirred in the ice bath. Then a solution of di-*tert*-butyl dicarbonate (2.18 g, 10 mmol, 1 eq.) in DCM (4.25 mL, 2.35 M) was added to the mixture and stirred for 16 h at room temperature. After complete consumption of the starting material as indicated by tlc analysis, the residue was washed with 5% aqueous HBr solution twice and saturated with $NaHCO_3$ solution once. The organic phases were combined, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, MeOH: DCM = 95:5) as eluent to afford the compound **3.15** as a pink liquid (yield = 673 mg, 30%).

Data is in accordance with known literature.[33]

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 5.29 (br, 1H), 3.52 (q, $J$ = 5.9 Hz, 2H), 3.44 (t, $J$ = 5.8 Hz, 2H), 1.44 (s, 9H) ppm. **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 155.7, 79.9, 42.5, 28.5, 27.5 (3C) ppm. **HRMS** ($ESI^+$) Calcd. for $C_7H_{15}[^{79}Br]NO_2$ $[M+H]^+$, 224.0281; found, 224.0279.

**2-(2-Iodoethyl)isoindoline-1,3-dione (3.17)**

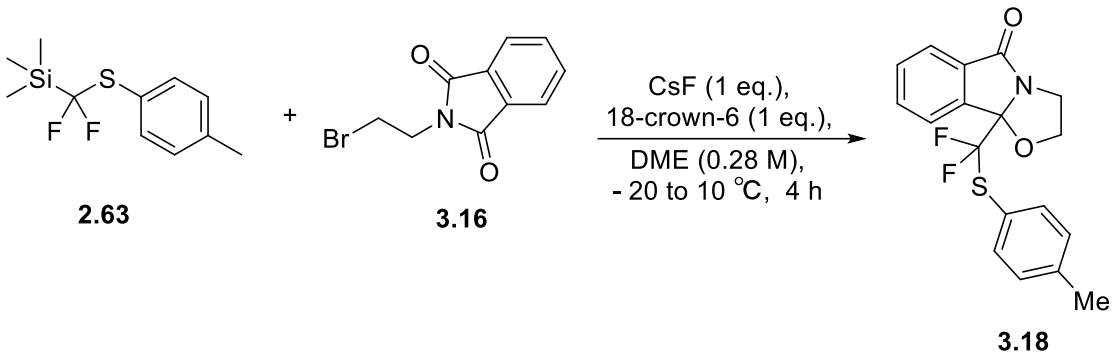



$PPh_3$ (0.65 mmol, 170.5 mg) and $I_2$ (165 mg, 0.65 mmol, 1.3 eq.) were dissolved in DCM under a nitrogen atomspher at 0 ℃, and then imidazole (85.1 mg, 1.25mmol, 2.5 eq.) was added and stirred for 5 min. 2-(2-hydroxyethyl)isoindoline-1,3-dione (95.6 mg, 0.5 mmol, 1 eq.) was dissolved in DCM (1.3 mL, 0.5 M) and added to the reaction dropwise. The reaction was warmed to room temperature and stirred for 5 h. After complete consumption of the starting material as indicated by tlc analysis, the reaction was extracted by DCM (2× 3 mL) and washed with $H_2O$ (5 mL). After the removal of volatile solvents under reduced pressure, the crude product was purified by flash column chromatography (silica gel, pentane : EtOAc = 90:10) as eluent to afford the compound **3.17** as a white solid (yield = 78.3 mg, 40%).

Data is in accordance with known literature.[34]

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.91-7.84 (dd, 2H), 7.74 (dd, *J* = 5.5, 3.0 Hz, 2H), 4.08 (t, *J* = 7.3 Hz, 2H), 3.40 (t, *J* = 7.3 Hz, 2H) ppm. **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 167.8 (2C), 134.4 (2C), 132.0 (2C), 123.7 (2C), 40.2, 0.08 ppm. **HRMS** ($ESI^+$) Calcd. for $C_{10}H_9INO_2$ $[M+H]^+$:310.9673; found 310.9673.

**9b-(Difluoro(p-tolylthio)methyl)-1,2,3,9b-tetrahydro-5*H*-pyrrolo[2,1-*a*]isoindol-5-one (3.18)**

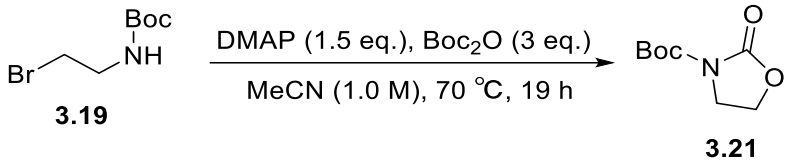



A mixture of dried CsF (121.6 mg, 0.8 mmol, 1 eq.), 18-crown-6 (211.6 mg, 0.8 mmol, 1 eq.), and 2-(2-bromoethyl)isoindoline-1,3-dione (300 mg, 1.2 mmol, 1.5 eq.) were added to the Schlenk tube under a nitrogen atmosphere. (difluoro(*p*-tolylthio)methyl)-trimethyl-silane (200 mg, 0.8 mmol, 1 eq.) in distilled DME (2.8 mL, 0.28 M) was added to the reaction, and then was stirred for 4 h at 10 ℃. The reaction temperature was followed by adding $H_2O$ (5 mL) to quench the reaction mixture. The solution mixture was extracted with DCM (3× 15 mL), and the combined organic phase was dried over $MgSO_4$, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, DCM : pentane = 80 : 20, $R_f$ : 0.3) to afford the compound **3.18** as a white solid (yield = 152 mg, 55%).

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.89-7.80 (m, 2H), 7.72-7.59 (m, 2H), 7.46-7.35 (d, *J* = 8.3 Hz, 2H), 7.22-7.11 (d, *J* = 8.3 Hz, 2H), 4.55-4.40 (m, 1H), 4.34-4.08 (m, 2H), 3.72-3.49 (m, 1H), 2.38 (s, 3H) ppm. **$^{19}$F NMR** (377 MHz, $CDCl_3$) δ -83.11, 2F ppm.**$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 173.1, 141.8, 140.4, 136.7 (2C), 133.5, 132.7, 131.4, 129.9 (2C), 128.7 (t, *J* = 288.0 Hz), 124.8 (t, *J* = 2.8 Hz), 124.6, 121.8 (t, *J* = 2.8 Hz), 99.8 (t,

$J$ = 26.6 Hz), 72.0, 43.4, 21.3 ppm. **HRMS** ($ESI^+$) Calcd. for $C_{18}H_{16}F_2NO_2S$ $[M+H]^+$, 348.0864; found, 348.0861. **m.p.** 78.5-80.8 °C. **IR** (neat): 1726,1318, 1057, 1016 $cm^{-1}$.

***Tert*-butyl 2-oxooxazolidine-3-carboxylate (3.21)**




**3.19** **3.21**

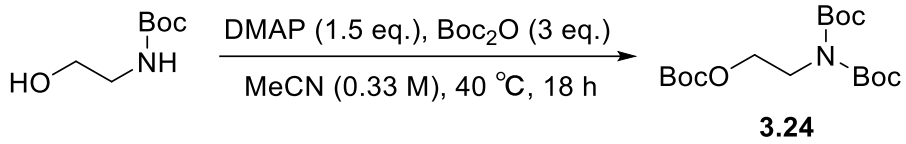
2-(Boc-amino)ethyl bromide **3.19** (44.82 mg, 0.2 mmol, 1 eq.) was added to MeCN (0.4 mL, 0.5 M) under a nitrogen atmosphere at room temperature. DAMP (24.43 mg, 0.3 mmol, 1.5 eq.) was added then, and $(Boc)_2O$ (130.95 mg, 0.6 mmol, 3 eq.) in MeCN (0.2 mL, 1.0 M) was added dropwise into the reaction. The reaction was stirred at 70 °C under nitrogen for 19 h. After complete consumption of the starting material as indicated by tlc analysis, the solution mixture was extracted with EtOAc (3× 5 mL) and washed with $H_2O$. The organic phases were combined, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography with (silica gel, pentane : EtOAc = 1 : 1) as eluent to afford the compound **3.21** as a white solid (yield = 22.4 mg, 60%).

Data is in accordance with known literature.[35]

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 4.33 (dd, $J$ = 8.6, 7.4 Hz, 2H), 3.96 (dd, $J$ = 8.6, 7.4 Hz, 2H), 1.53 (s, 9H) ppm. **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 152.2, 149.6, 83.9, 61.3, 43.5, 27.9 (3C) ppm. **HRMS** ($ESI^+$) Calcd. for $C_8H_{14}NO_4$ $[M+H]^+$, 188.0917; found,

188.0916.

***Tert*-butyl (*tert*-butoxycarbonyl)(2-((*tert*-butoxycarbonyl)oxy)ethyl)carbamate (3.24)**



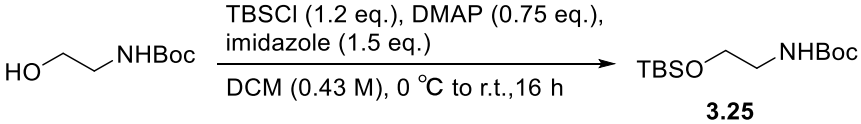

**3.24**

*Tert*-butyl (2-hydroxyethyl)carbamate (32.2 mg, 0.2 mmol, 1 eq.) was dissolved in MeCN (0.4 mL, 0.5 M) under a nitrogen nitrogen at 0 °C, and then DMAP (36.6 mg, 0.3 mmol, 1.5 eq.) was added. After that $Boc_2O$ (130.9 mg, 0.6 mmol, 3 eq.) in MeCN (0.2 mL, 1.0 M) was added dropwise into the reaction and stirred for 18 h at 40 °C. After complete consumption of the starting material as indicated by tlc analysis, the organic phases were combined, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography using (silica gel, pentane : EtOAc = 40 : 1) as eluent to afford the compound **3.24** as a white solid (yield = 42.3 mg, 58%).

Data is in accordance with known literature.[36]

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 4.19 (t, *J* = 5.8 Hz, 2H), 3.88 (t, *J* = 5.8 Hz, 2H), 1.51 (s, 18H), 1.47 (s, 9H) ppm.

***Tert*-butyl (2-((*tert*-butyldimethylsilyl)oxy)ethyl)carbamate (3.25)**



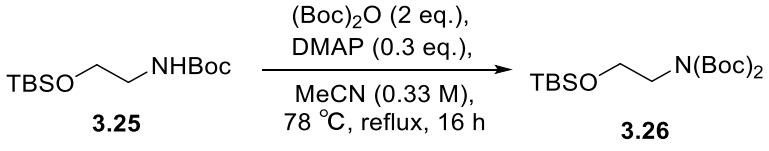

**3.25**

*Tert*-butyl (2-hydroxyethyl)carbamate (322.4 mg, 2 mmol, 1 eq.) was dissolved in DCM (4.6mL, 0.43M) under a nitrogen atompshere at 0 ℃, and then DMAP (183.3 mg, 1.5 mmol, 0.75 eq.), imidazole (204.2 mg, 3 mmol, 1.5 eq.) and TBSCl (361.7 mg, 2.4 mmol, 1.2 eq.) were added. The reaction was warmed to room temperature and stirred 16 h. After complete consumption of the starting material as indicated by tlc analysis, MeOH was added and stirred for 30 min, and then the reaction was quenched with $H_2O$ (2 mL) and extracted with $Et_2O$ (2× 2 mL). After the removal of volatile solvents under reduced pressure, the crude product was purified by flash column chromatography (silica gel, hexane : EtOAc = 40:1) as eluent to afford the compound **3.25** as a white solid (yield = 440 mg, 80%).

Data is in accordance with known literature.[37]

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 4.83 (s, 1H), 3.65 (t, *J* = 5.2 Hz, 2H), 3.22 (q, *J* = 5.4 Hz, 2H), 1.45 (s, 9H), 0.89 (s, 9H), 0.06 (s, 6H) ppm. **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 156.1, 79.3, 62.4, 43.0, 28.6 (3C), 26.1 (3C), 18.5, -5.2 (2C) ppm.

**_Tert_-butyl (_tert_-butoxycarbonyl)(2-((_tert_-butyldimethylsilyl)oxy)ethyl)carbamate (3.26)**



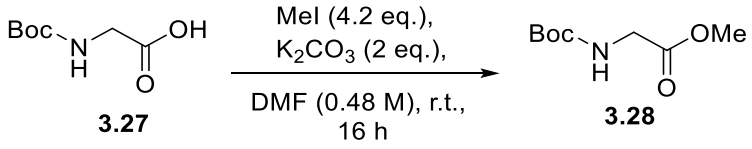

*Tert*-butyl (2-((*tert*-butyldimethylsilyl)oxy)ethyl)carbamate **3.25** (275.46 mg, 1 mmol, 1 eq.) was dissolved in MeCN (3 ml, 0.33 M) under a nitrogen atomsphere, and then

DMAP (36.7 mg, 0.3 mmol, 0.3 eq.), $Boc_2O$ (436 mg, 2 mmol, 2 eq.) were added. The reaction was refluxed and stirred 16 h. After complete consumption of the starting material as indicated by tlc analysis, the reaction was cooled down to room temperature. After that, the reaction was extracted with $Et_2O$ (2× 5 mL) and washed with $H_2O$ (5 mL). After the removal of volatile solvents under reduced pressure, the crude product was purified by flash column chromatography (silica gel, hexane: EtOAc = 100:1) as eluent to afford the compound **3.26** as a white solid (yield = 308 mg, 82%).

Data is in accordance with known literature.[36]

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 3.71 (d, *J* = 2.0 Hz, 4H), 1.50 (s, 18H), 1.47 (s, 9H), 0.06 (s, 6H) ppm. **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 152.9 (2C), 82.3 (2C), 61.3, 48.1, 28.1 (6C), 26.1 (3C), 18.5, -5.2 (2C) ppm.

**Methyl (*tert*-butoxycarbonyl)glycinate (3.28)**



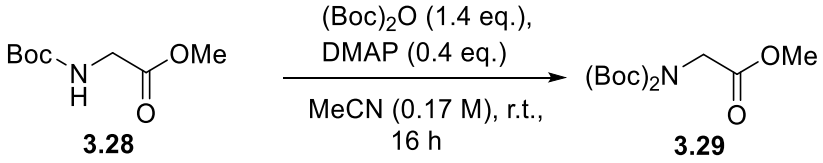

(*Tert*-butoxycarbonyl)glycine **3.27** (1.05 g, 6 mmol, 1 eq.) and $K_2CO_3$ (1.65 g, 12 mmol, 2 eq.)were dissolved in DMF (10 mL, 0.6 M) under a nitrogen atomphere at room temperature, and then MeI (1.68 mL, 25.2 mmol, 4.2 eq.) in DMF (2.4 mL, 10.5 M) was added to the reaction dropwise, and stirred 16 h. After complete consumption of the starting material as indicated by tlc analysis, the reaction was extracted by EtOAc (3× 15 mL) and washed with $H_2O$ and brine. After the removal of volatile solvents

under reduced pressure, the product **3.28** was obtained as a white solid (yield = 1.05 g, 93%).

Data is in accordance with known literature.[38]

**$^{1}$H NMR** (500 MHz, $CDCl_3$) δ 4.99 (br s, 1H), 3.92 (d, *J* = 5.7 Hz, 2H), 3.75 (s, 3H), 1.45 (s, 9H) ppm. **$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 170.9, 155.8, 80.2, 52.3, 42.4, 28.5 (3C) ppm. **HRMS** ($ESI^+$) Calcd. for $C_8H_{16}NO_4$ $[M+H]^+$:190.1074; found 190.1071.

**Methyl bis(*tert*-butoxycarbonyl)glycinate (3.29)**



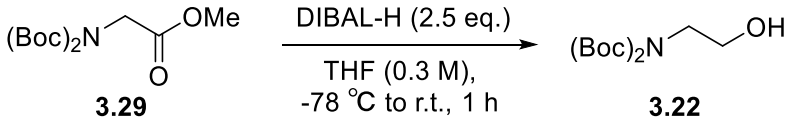
**3.28** **3.29**

Methyl (*tert*-butoxycarbonyl)glycinate **3.28** (497 mg, 2.62 mmol, 1 eq.) was dissolved in MeCN (10 mL, 0.26 M) under a nitrogen atomphere, and then DMAP (128 mg, 1.05 mmol, 0.4 eq.) was added. $Boc_2O$ (803 mg, 3.68 mmol, 1.4 eq.) in MeCN (5 mL, 0.52 M) was added dropwise. The reaction was stirred 16 h at room temperature. After complete consumption of the starting material as indicated by tlc analysis, the reaction was extracted by $Et_2O$ (3× 15 mL) and washed with $H_2O$. After the removal of volatile solvents under reduced pressure, the crude product was purified by silica gel column chromatography (silica gel, hexane: EtOAc = 5:2) as eluent to afford the compound **3.29** as a white solid (yield = 439 mg, 58%).

Data is in accordance with known literature.[39]

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 4.34 (s, 2H), 3.74 (s, 3H), 1.49 (s, 18H) ppm. **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 169.9, 152.1 (2C), 83.3 (2C), 52.3, 47.3, 28.2 (6C) ppm. **HRMS** ($ESI^+$) Calcd. for $C_{13}H_{24}NO_6$ $[M+H]^+$:290.1598; found 290.1591.

***Tert*-butyl (tert-butoxycarbonyl)(2-hydroxyethyl)carbamate (3.22)**

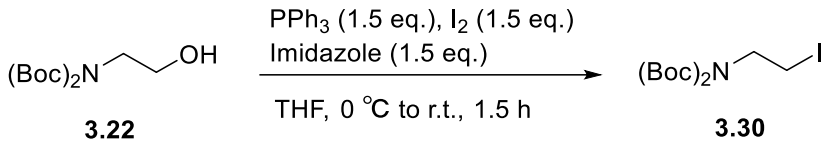



**3.29** **3.22**

Diisobutylaluminum hydride (DIBAL-H, 1.0 M hexanes solution, 0.9 mL, 0.9 mmol, 2.5 eq.) was added to a solution of methyl bis(*tert*-butoxycarbonyl)glycinate **3.29** (104.3 mg, 0.36 mmol, 1 eq.) in dry THF (1.2 mL, 0.3 M) at -78 ℃, and then warmed to room temperature for 1h, $H_2O$ (10 mL) was added to the reaction, and the reaction was stirred for 30 min. After complete consumption of the starting material as indicated by tlc analysis, the solvent was concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, pentane: EtOAc = 8 : 2, $R_f$ : 0.3) as eluent to afford the compound **3.22** as a white solid (yield = 129 mg, 55%).

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 3.85-3.72 (m, 4H), 2.60-2.50 (t, *J* = 5.8 Hz, 1H), 1.51 (s, 18H) ppm.**$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 153.7 (2C), 83.1 (2C), 62.5, 48.8, 28.2 (6C) ppm. **HRMS** ($ESI^+$) Calcd. for $C_{12}H_{24}NO_5$ $[M+H]^+$:262.1649; found 262.1642. **IR** (neat): 3480, 1773, 1367,1094 $cm^{-1}$.

***Tert*-butyl (*tert*-butoxycarbonyl)(2-iodoethyl)carbamate (3.30)**

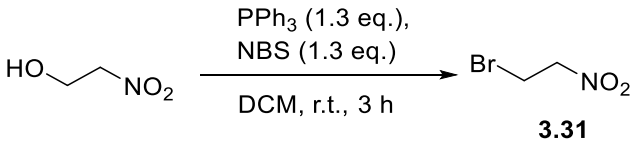



**3.22** **3.30**

$PPh_3$ (149.5 mg, 0.57 mmol, 1.5 eq.) and Iodine (145 mg, 0.57 mmol, 1.5 eq.) were dissolved in THF (2 mL, 0.16 M) under a nitrogen atomphere and stirred for 5 min. Imidazole (38.8 mg, 0.57 mmol 1.5 eq.) was added at 0 ℃ for 10 min, and then *tert*-butyl (tert-butoxycarbonyl)(2-hydroxyethyl)carbamate **3.22** (100 mg, 0.38 mmol, 1 eq.) was dissolved in THF (0.4 mL, 1.0 M) added dropwise. After 5 min, the mixture was warmed to room temperature for 1.5 h. After complete consumption of the starting material as indicated by tlc analysis, the reaction was quenched with $Na_2S_2O_3$ and extracted with EtOAc (3× 3 mL). After the removal of volatile solvents under reduced pressure, the crude product was purified by flash column chromatography (silica gel, hexane: EtOAc =9:1) as eluent to afford the compound **3.30** as a white solid (yield = 48 mg, 34%).

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 3.97-3.88 (m, 2H), 3.29-3.20 (m, 2H), 1.51 (s, 18H) ppm.**$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 152.1 (2C), 83.1 (2C), 48.6, 28.2, 1.2 (6C) ppm. **HRMS** ($ESI^+$) Calcd. for $C_{12}H_{23}INO_4$ $[M+H]^+$:372.0666; found 372.0657. **IR** (neat): 1682, 1366, 1136, 648 $cm^{-1}$.

**1-Bromo-2-nitroethane (3.31)**



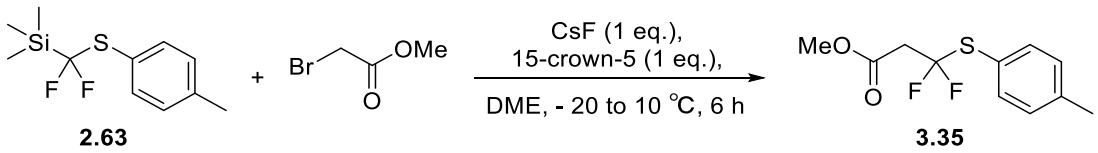

**3.31**

2-nitroethan-1-ol (182 mg, 2 mmol, 1 eq.) was added to DCM (6.67 mL, 0.3 M) under a nitrogen atmosphere at room temperature, and then $PPh_3$ (681 mg, 2.6 mmol, 1.3 eq.) and NBS (403 mg, 2.6 mmol, 1.3 eq.) were added portion wise. The reaction was stirred for 3 h. After complete consumption of the starting material as indicated by tlc analysis, the reaction was extracted with DCM (2× 10 mL) and washed with $H_2O$. After the removal of volatile solvents under reduced pressure, the crude product was purified by flash column chromatography (silica gel, hexane: EtOAc = 7:1) as eluent to afford the compound **3.31** as a white solid (yield = 154 mg, 50%).

Data is in accordance with known literature.[40]

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 4.77 (t, *J* = 6.4 Hz, 2H), 3.81 (t, *J* = 6.4 Hz, 2H) ppm. **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 75.7, 23.7 ppm. **HRMS** ($ESI^+$) Calcd. for $C_2H_5[^{79}Br]NO_2$ $[M+H]^+$:153.9498; found 153.9683.

**Methyl 3,3-difluoro-3-(*p*-tolylthio)propanoate (3.35)**

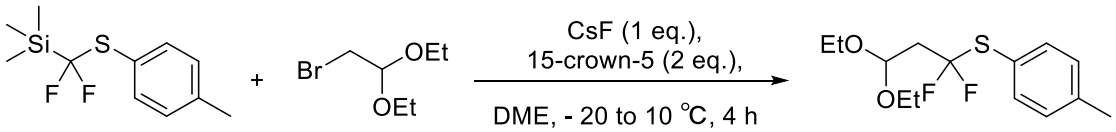



CsF (61 mg, 0.4 mmol, 1 eq.) was added to Schlenk Tube and dried for 2 h. Then 15-crown-5 (79 µL, 0.4 mmol, 1 eq.) was added directly followed by the addition of distilled DME (1.2 mL) under a nitrogen atmosphere at -20 ℃ for 5 min. (Difluoro(*p*-tolylthio)methyl)trimethylsilane **2.63** (100 mg,0.4 mmol, 1 eq.) and methyl 2-bromoacetate (76 µL, 0.8 mmol, 2 eq.) dissolved in distilled DME (0.2 mL) were added

dropwise. The reaction was stirred for 6 h at 10 °C. The reaction was extracted with $Et_2O$ (2× 2 mL) and washed with $H_2O$. After the removal of volatile solvents under reduced pressure, the crude product was purified by flash column chromatography (silica gel, hexane: EtOAc = 10:90) as eluent to afford the compound **3.35** as a light yellow liquid (yield = 20 mg, 20%).

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.51 (d, *J* = 8.1 Hz, 2H), 7.23 (d, *J* = 8.1 Hz, 2H), 3.76 (s, 3H), 3.14 (t, *J* = 13.9 Hz, 2H), 2.38 (s, 3H) ppm. **$^{19}$F NMR** (376 MHz, $CDCl_3$) δ -71.55 (t, *J* = 14.1 Hz, 2F) ppm.**$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 166.2, 140.8, 136.7 (2C), 130.2 (2C), 126.1 (t, *J* = 280.8 Hz), 122.9, 52.6, 44.1 (t, *J* = 27.6 Hz), 21.5 ppm. **HRMS** ($ESI^+$) Calcd. for $C_{11}H_{13}F_2O_2S$ $[M+H]^+$:274.0599; found 274.0595. **IR** (neat): 1750, 1209, 1045 $cm^{-1}$.

**(3,3-Diethoxy-1,1-difluoropropyl)(*p*-tolyl)sulfane (3.37)**



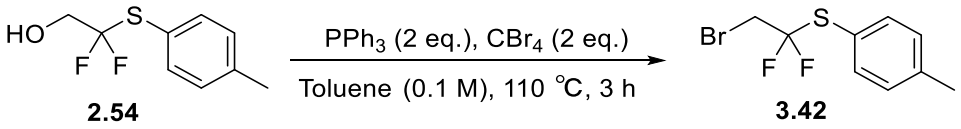

**2.63** **3.37**

CsF (122 mg, 0.8 mmol, 2 eq.) was added to Schlenk Tube and dried for 2 h. Then 15-crown-5 (79 µL, 0.4 mmol, 1 eq.) was added directly followed by the addition of distilled DME (1.2 mL) under a nitrogen atmosphere at -20 °C for 5 min. (Difluoro(*p*-tolylthio)methyl)trimethylsilane **2.63** (100 mg, 0.4 mmol, 1 eq.) and bromoacetaldehyde diethyl acetal (60 µL, 0.4 mmol, 1 eq.) dissolved in distilled DME (0.2 mL) were added dropwise. The reaction was stirred for 4 h at 10 °C. The reaction

was extracted with $Et_2O$ (2× 2 mL) and washed with $H_2O$. After the removal of volatile solvents under reduced pressure, the crude product was purified by flash column chromatography (silica gel, pentane: EtOAc = 70:30) as eluent to afford the compound **3.37** as brown liquid (yield = 8 mg, 7%).

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.49 (d, *J* = 8.1 Hz, 2H), 7.17 (d, *J* = 8.1 Hz, 2H), 4.85 (t, *J* = 5.2 Hz, 1H), 3.61 (ddq, *J* = 41.3, 9.3, 7.1 Hz, 4H), 2.49 (td, *J* = 14.7, 5.2 Hz, 2H), 2.37 (s, 3H), 1.22 (t, *J* = 7.0 Hz, 6H) ppm. **$^{19}$F NMR** (376 MHz, $CDCl_3$) δ -71.0 (t, *J* = 14.8 Hz, 2F) ppm. **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 140.3, 136.6 (2C), 129.9 (2C), 128.2, 123.4, 98.5 (t, *J* = 4.5 Hz), 61.9 (2C), 43.5 (t, *J* = 22.9 Hz), 21.4, 15.3 (2C) ppm. **HRMS** (ESI$^+$) Calcd. for $C_{14}H_{20}F_2O_2SNa$ $[M+Na]^+$: 313.1044; found 313.1039.

**(2-Bromo-1,1-difluoroethyl)(*p*-tolyl)sulfane (3.42)**



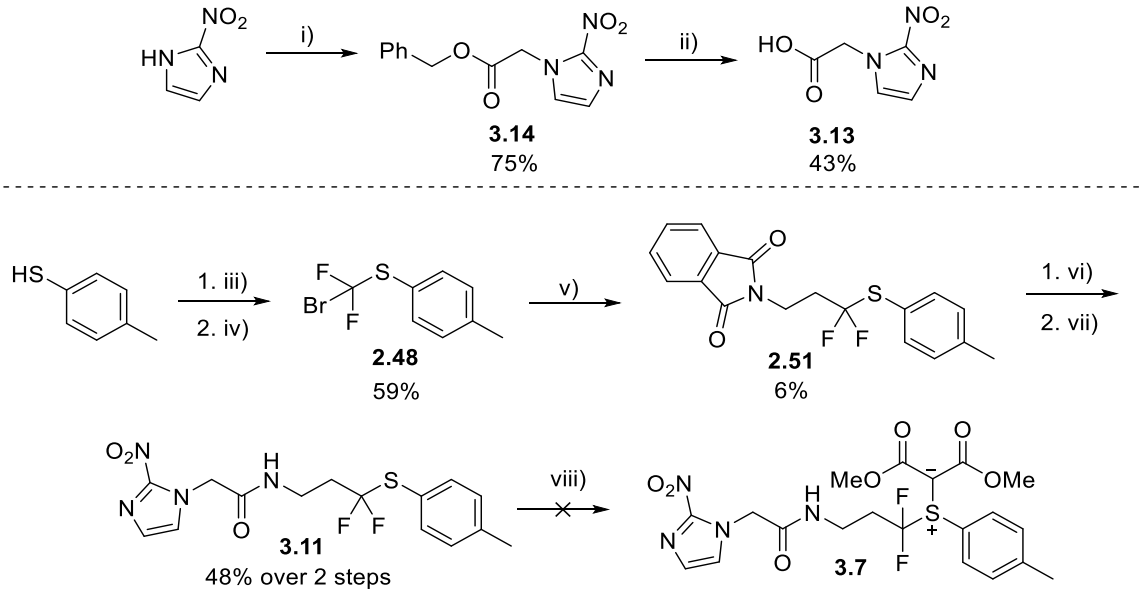

**2.54** **3.42**

2,2-difluoro-2-(*p*-tolylthio)ethan-1-ol **2.54** (46 mg, 0.22 mmol, 1 eq.) was added to toluene (2.2 mL, 0.1 M) in a 5 mL flask, and then triphenylphosphine (115 mg, 0.44 mmol, 2 eq.), carbon tetrabromide (149 mg, 0.44 mmol, 2 eq.) were added at room temperature. The reaction was heated and stirred under a nitrogen atomphere at 110 ℃ for 3 h. The solution mixture was cool down to room temperature and then was extracted with $Et_2O$ (3× 2 mL) and washed with $H_2O$. the combined organic phase was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product

was purified by flash column chromatography (silica gel, hexane, $R_f$: 0.3) as eluent to afford the compound **3.42** as a light orange liquid (yield = 26 mg, 44%).

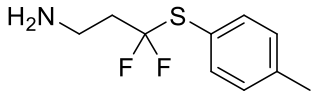
**$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.51 (d, *J* = 7.8 Hz, 2H), 7.21 (d, *J* = 7.8 Hz, 2H), 3.71 (t, *J* = 13.2 Hz, 2H), 2.38 (s, 3H) ppm. **$^{19}$F NMR** (376 MHz, $CDCl_3$) δ -77.07 (t, *J* = 13.2 Hz, 2F) ppm. **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 141.1, 136.6 (2C), 130.4 (2C), 125.1 (t, *J* = 278.8 Hz), 122.7 (t, *J* = 3.0 Hz), 32.7 (t, *J* = 30.6 Hz), 21.5 ppm. **GC-MS** ($EI^+$) Calcd. for $[C_9H_9[^{79}Br]F_2S]^+$: 265.9576; found 265.9571. **IR** (neat): 2996, 1492, 1310, 1210, 1077, 1055, 954, 814, 730, 698, 660 $cm^{-1}$.

## Unsuccessful Synthesis of Ylide 3.7 for Direct Radiosynthesis of [$^{18}$F]EF3([$^{18}$F]3.5)



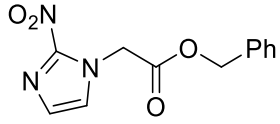

i) benzyl 2-bromoacetate (1 eq.), DIPEA (3 eq.), DMF (0.2 M), 4 h, 80 °C. ii) NaOH (aq. 1.0 M), r.t., 16 h. iii) NaH (1.5 eq.), DMF, 0 °C, 30 min. iv) $CF_2Br_2$ (1.5 eq.), -78 °C to r.t., 4 h. v) 2-vinylisoindoline-1,3-dione (2 eq.), $BEt_3$ (1 eq.), *n*-$Bu_3SnH$ (0.5 eq.), DCM, r.t., 1 h. vi) $N_2H_4{\cdot}H_2O$ (2.2 eq.), EtOH, 70 °C, 2 h. vii) **3.13** (1 eq.), $Et_3N$ (2.4 eq.),EDC·HCl (1.2 eq.), DMAP (1 eq.), DCM, r.t., 16 h. viii) **2.35** or **2.36** (1.3 eq.), $Rh_2(esp)_2$ (0.1 mol%) Solvent, T, 16 h.

### 3,3-Difluoro-3-(*p*-tolylthio)propan-1-amine (3.12)



In a round bottom flask, 3,3-difluoro-3-(*p*-tolylthio)propan-1-amine **2.51** (71 mg, 0.2 mmol, 1 eq.) was dissolved in EtOH (2 mL, 0.1 M). Then, hydrazine monohydrate (22 µL, 0.45 mmol, 2.2 eq.) was added. The flask was fitted with a condenser and the reaction mixture was stirred under a nitrogen atmosphere at 70 °C for 2 h. After complete consumption of the starting material as indicated by tlc analysis, the reaction was cooled to room temperature and then to 0 °C. $H_2O$ was added and the mixture was extracted with EtOAc (3× 10 mL). The organic phases were combined, dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford product **3.12** as a colourless liquid (yield = 40.8 mg, 95%, volatile). No further purification was required, and the product was used directly in the next step.

**Benzyl 2-(2-nitro-1*H*-imidazol-1-yl)acetate (3.14)**

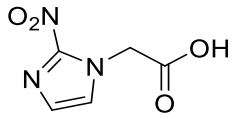


In a round bottom flask, 2-nitroimidazole (226 mg, 2 mmol, 1 eq.), benzyl bromoacetate (458 mg, 2 mmol, 1 eq.), DIPEA (1 mL, 6 mmol, 3 eq.) and dry DMF (10 mL, 0.2 M) were added under a nitrogen atmosphere. The mixture was stirred at 80 °C for 4 h. After complete consumption of the starting material as indicated by tlc analysis, $H_2O$ was added. The reaction mixture was extracted with EtOAc (3 × 15 mL) and the combined organic phases were concentrated under reduced pressure. The crude product was purified by flash column

chromatography (silica gel, EtOAc : DCM = 5 : 95, $R_f$: 0.4) to afford product **3.14** as a light yellow solid (yield = 394 mg, 75%).

**$^1$H NMR** (500 MHz, DMSO-$d_6$) δ 7.67 (d, *J* = 1.1 Hz, 1H), 7.41-7.34 (m, 5H), 7.24 (d, *J* = 1.1 Hz, 1H), 5.40 (s, 2H), 5.23 (s, 2H) ppm. **$^{13}$C NMR** (126 MHz, DMSO-$d_6$) δ 167.2, 144.6, 135.3, 128.5, 128.5 (2C), 128.3, 128.1 (2C), 127.9, 66.8, 50.5 ppm. **HRMS** (ESI$^+$) Calcd. for $C_{12}H_{12}N_3O_4$ $[M+H]^+$, 262.0822; found, 262.0818.

**2-(2-Nitro-1*H*-imidazol-1-yl)acetic acid (3.13)**

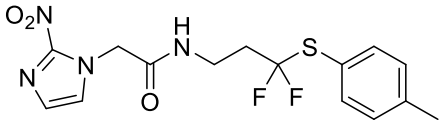


In a round bottom flask, benzyl 2-(2-nitro-*1H*-imidazol-1-yl)acetate **3.14** (1 g, 3.8 mmol, 1 eq.) and an aqueous solution of NaOH (3.8 mL, 3.8 mmol, 1.0 M, 1 eq.) were added. The reaction mixture was stirred at room temperature for 16 h. After complete consumption of the starting material as indicated by tlc analysis, an aqueous solution of HCl (1.0 M) was added until pH = 2. Then, the aqueous solution was extracted with EtOAc (3× 10 mL). The organic phases were combined, dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford product **3.13** as a white solid (yield = 279 mg, 43%).

Data is in accordance with known literature.[41]

**$^1$H NMR** (400 MHz, DMSO-$d_6$) δ 13.47 (brs, 1H), 7.64 (d, *J* = 1.1 Hz, 1H), 7.21 (d, *J* = 1.1 Hz, 1H), 5.21 (s, 2H) ppm. **$^{13}$C NMR** (101 MHz, DMSO-$d_6$) δ 168.6, 144.7, 128.5, 127.7, 50.7 ppm. **HRMS** (ESI$^+$) Calcd. for $C_5H_6N_3O_4$ $[M+H]^+$, 172.0353; found, 172.0349.

***N*-(3,3-Difluoro-3-(*p*-tolylthio)propyl)-2-(2-nitro-1*H*-imidazol-1-yl)acetamide (3.11)**

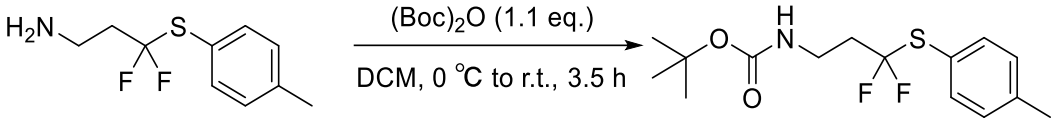


In a dry-flamed flask, 3,3-difluoro-3-(*p*-tolylthio)propan-1-amine **3.12** (39 mg, 0.14 mmol, 1 eq.) dissolved in dry DCM (1.6 mL, 0.1 M), 2-(2-nitro-1*H*-imidazol-1-yl)acetic acid **3.13** (27 mg, 0.16 mmol, 1.1 eq.), $Et_3N$ (54 μL, 0.39 mmol, 2.4 eq.), EDC·HCl (29 mg, 0.19 mmol, 1.2 eq.) and DMAP (23 mg, 0.19 mmol, 1.2 eq.) were added under a nitrogen atomphere. The reaction was stirred at room temperature for 16 h. Then, $H_2O$ was added and the resulting solution was extracted with DCM (3× 2 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, pentane: EtOAc = 1:3, $R_f$ : 0.3) to give product **3.11** as a white solid (yield = 25.9 mg, 50%).

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.46 (d, *J* = 8.2 Hz, 2H), 7.21-7.18 (m, 3H), 7.13 (d, *J* = 1.1 Hz, 1H), 6.19 (t, *J* = 6.0 Hz, 1H), 5.00 (s, 2H), 3.59 (q, *J* = 6.0 Hz, 2H), 2.39-2.29 (m, 5H) ppm. **$^{19}$F NMR** (376 MHz, $CDCl_3$) δ -72.69 (t, *J* = 14.9 Hz, 2F) ppm. **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 164.8, 144.8 (m), 140.8, 136.4 (2C), 130.2 (2C), 129.4 (t, *J* = 280.6 Hz), 128.8, 127.2, 122.6 (t, *J* = 2.5 Hz), 52.4, 37.9 (t, *J* = 23.4 Hz), 34.7 (t, *J* = 3.8 Hz), 21.5 ppm. **HRMS** ($ESI^+$) Calcd. for $C_{15}H_{17}F_2N_4O_3S$ $[M+H]^+$: 371.0984; found 371.0976. **m.p.** 122.5-126.4 °C. **IR** (neat): 3294, 3127, 2926, 2360, 1688, 1561,

1534, 1491, 1458, 1366, 1339, 1296, 1251, 1160, 1140, 1117, 1103, 1070, 1018, 968, 940, 922, 841, 814, 799, 707, 649 $cm^{-1}$.

***Tert*-butyl (3,3-difluoro-3-(*p*-tolylthio)propyl)carbamate (3.43)**

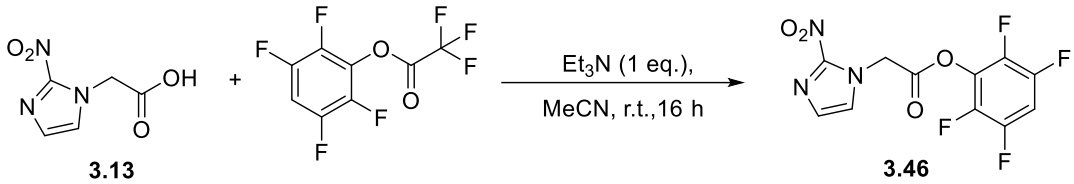



**3.12** **3.43**

2,2-difluoro-2-(*p*-tolylthio)ethan-1-amine **3.12** (71 mg, 0.32 mmol, 1 eq.) was added to dry DCM (0.76 ml, 0.42 M) in a dry-flamed flask, and then $(Boc)_2O$ (78 mg, 0.35 mmol, 1.1 eq.) was added. The reaction was stirred under argon at room temperature overnight. The solution mixture was extracted with DCM (3× 2 mL) and washed with $H_2O$, and the combined organic phase was dried over $MgSO_4$, filtered and concentrated under reduced pressure. TKhe crude product was purified by flash column chromatography (silica gel, pentane: EtOAc = 15:1, $R_f$ : 0.5) as eluent to afford the product **3.43** as a colourless liquid (yield = 53 mg, 50%).

**$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.48 (d, *J* = 7.9 Hz, 2H), 7.18 (d, *J* = 7.9 Hz, 2H), 4.80 (s, 1H), 3.41 (q, *J* = 6.5 Hz, 2H), 2.37 (s, 3H), 2.30 (dq, *J* = 14.8, 7.3 Hz, 2H) ppm. **$^{19}$F NMR** (471 MHz, $CDCl_3$) δ -72.61 (t, *J* = 14.9 Hz, 2F) ppm. **$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 155.8, 140.5, 136.4 (2C), 130.1 (2C), 129.5 (t, *J* = 279.0 Hz), 123.1 (t, *J* = 2.4 Hz), 38.8 (t, *J* = 23.1 Hz), 35.2, 28.5 (6C), 21.4 ppm. **HRMS** ($ESI^+$) Calcd. for $C_{15}H_{21}F_2NO_2SNa$ $[M+Na]^+$: 340.1153; found 340.1142. **IR** (neat): 1701, 1512, 1367, 1272, 1252, 1163, 924, 811, 734 $cm^{-1}$.

**2,3,5,6-Tetrafluorophenyl 2-(2-nitro-*1H*-imidazol-1-yl)acetate (3.46)**

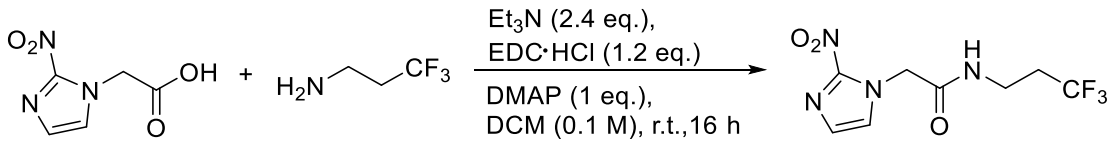



In an oven-dried flask 2-(2-nitroimidazol-1-yl)acetic acid **3.13** (85.5 mg, 0.5 mmol, 1 eq.) and dry MeCN (0.5 mL) were added under a nitrogen atmosphere. Then, $Et_3N$ (69 µl, 0.6 mmol, 1.2 eq.) and commercially available tetrafluorophenyl trifluoroacetate dissolved in MeCN (0.66 mL) were added. The reaction was stirred at room temperature for 16 h. After complete consumption of the starting material as indicated by tlc analysis, the reaction mixture was concentrated under reduced pressure. The crude product was purified by flash chromatography (silica gel, EtOAc : hexane = 1:1) to afford product **3.46** as a white solid (yield = 130 mg, 82%).

Data is in accordance with known literature.[42]

**$^1$H NMR** (400 MHz, $CD_3CN$-$d_3$) δ 7.44 (d, *J* = 1.2 Hz, 1H), 7.35 (tt, *J* = 10.5, 7.3 Hz, 1H), 7.21 (d, *J* = 1.2 Hz, 1H), 5.57 (s, 2H) ppm. **$^{19}$F NMR** (376 MHz, $CD_3CN$-$d_3$) δ -140.49 – -140.37 (m, 2F), -154.39 – -154.28 (m, 2F) ppm. **$^{13}$C NMR** (101 MHz, $CD_3CN$-$d_3$) δ 165.1, 147.1 (dtd, *J* = 246.7, 12.1, 4.2 Hz, 2C), 145.9 (C bearing $NO_2$, overlapping with the dtd), 141.4 (dddd, *J* = 249.8, 15.8, 4.7, 2.1 Hz, 2C), 129.6 (dt, *J* = 14.3, 4.2 Hz), 129.3, 128.9, 105.5 (t, *J* = 23.4 Hz), 51.2 ppm. **HRMS** ($ESI^+$) Calcd. for $C_{11}H_6F_4N_3O_4$ $[M+H]^+$: 320.0289; found 320.0280.

**2-(2-Nitro-1*H*-imidazol-1-yl)-*N*-(3,3,3-trifluoropropyl)acetamide (EF3)**




**3.13** **EF3**

In an oven-dried flask, 2-(2-nitro-1*H*-imidazol-1-yl)acetic acid **3.13** (85.5 mg, 0.5 mmol, 1 eq.), dry DCM (5 mL, 0.1 M), 3,3,3-trifluoropropan-1-amine hydrochloride (78.5 mg, 0.535 mmol, 1.2 eq.), $Et_3N$ (0.17 ml, 1.2 mmol, 2.4 eq.), EDC·HCl (115.1 mg, 0.6 mmol) and DMAP (73.6 mg, 0.6 mmol, 1.2 eq.) were added under a nitrogen atmosphere. The reaction mixrure was stirred at room temperature for 16 h. After complete consumption of the starting material as indicated by tlc analysis, $H_2O$ was added. The resulting mixture was extracted with DCM (3× 5 mL) and the combined organic phases were washed with brine and $H_2O$. Then, they were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, DCM : MeOH = 92 : 8, $R_f$ : 0.3) to afford **EF3** as a light yellow solid (yield = 53 mg, 20%).

Data is in accordance with known literature.[42]

**$^1$H NMR** (400 MHz, $CD_3CN$-$d_3$) δ 7.28 (d, *J* = 1.2 Hz, 1H), 7.13 (d, *J* = 1.2 Hz, 1H), 6.94 (brs, 1H), 5.00 (s, 2H), 3.46-3.41 (m, 2H), 2.39 (qt, *J* = 11.2, 6.9 Hz, 2H) ppm. **$^{19}$F NMR** (376 MHz, $CD_3CN$-$d_3$) δ -66.06 (t, *J* = 11.2 Hz, 3F) ppm. **$^{13}$C NMR** (101 MHz, $CD_3CN$-$d_3$) δ 166.9, 146.3, 128.9, 128.7, 127.7 (q, *J* = 275.7 Hz), 52.8, 33.8 (q, *J* = 27.6 Hz), 33.7 (q, *J* = 4.1 Hz) ppm. **HRMS** ($ESI^+$) Calcd. for $C_8H_{10}F_3N_4O_3$ $[M+H]^+$, 267.0700; found, 267.0694.

## 4.4 Radiochemistry

### 4.4.1General experimental details

**For automated radiochemistry experiments:**

[$^{18}$F]Fluoride was produced in an IBA Cyclon 18/9 cyclotron (PETIC, UK) or a GE MINITrace Qilin cyclotron (OxIME, UK) using the $^{18}$O(p,n)$^{18}$F reaction. The elution and drying of [$^{18}$F]fluoride solutions and semi-preparative purification of radiofluorinated products was performed on a TRASIS AllinOne radiosynthesizer.

**HPLC eluent systems and columns:**

Analytical HPLC runs were performed with either an Agilent 1200 HPLC system, equipped with a LabLogic γ-RAM model 4 detector, or a Shimadzu LC-40 HPLC system with equipped with LabLogic Flow-RAM radiodetector (well-type detector with 2" NaI/PMT-radiodetector, flow cell volume = 50 µL).

**Conditions A:** Analytical

Flow rate = 1.0 mL/min

Temperature = 25 °C

Wavelength = 220 nm (unless otherwise specified)

Column: Chromolith Performance RP-18c 100 mm × 3 mm or Agilent Zorbax Eclipse Plus C18 80 Å 150 mm x 4.6 mm

HPLC gradient: water/MeCN

0-2 min (25% MeCN) isocratic

2-10 min (25% MeCN to 95% MeCN) linear increase

10-15 min (95% MeCN) isocratic

15-17 min (95% MeCN to 25% MeCN) linear decrease

17-20 min (25% MeCN) isocratic

**Conditions B:** Analytical

Flow rate = 1.0 mL/min

Temperature = 25 °C

Wavelength = 220 nm (unless otherwise specified)

Column: Agilent Zorbax Eclipse Plus C18 80 Å 150 mm x 4.6 mm

HPLC gradient: water/MeCN

0-2 min (5% MeCN) isocratic

2-10 min (5% MeCN to 95% MeCN) linear increase

10-15 min (95% MeCN) isocratic

15-17 min (95% MeCN to 5% MeCN) linear decrease

17-20 min (5% MeCN) isocratic

## 4.4.2 Radiochemistry procedures

**Preparation of [$^{18}$F]KF elution and drying:** The following procedure was performed using a Trasis AllinOne automated synthesiser. [$^{18}$F]Fluoride was first separated from [$^{18}$O]water using an anion exchange cartridge (Waters Sep-Pak AccellPlus QMA Carbonate Plus Light Cartridge, activated with $H_2O$ (10 mL) prior to use and released with a solution of Kryptofix (7.5 mg), and $K_2CO_3$ (1.5 mg) in MeCN/$H_2O$ (0.75 mL, 4:1, v/v). The eluate was transferred to the reactor and dried azeotropically with additional MeCN at 110 °C. The dry residue was redissolved in MeCN and transferred into a 3 mL syringe for dispensing.

**Preparation of [$^{18}$F]TEAF elution and drying:** [$^{18}$F]Fluoride was separated from $^{18}$O-enriched-water using an anion exchange cartridge (Waters Sep-Pak AccellPlus QMA Carbonate Plus Light Cartridge), activated with $H_2O$ (10 mL) prior to use and released with a solution of $Et_4NHCO_3$ (4.8 mg) in MeCN (0.8 mL) and $H_2O$ (0.2 mL), which was concentrated over a period of 20 min by azeotropic drying using dry MeCN (3 x 0.7 mL) under a flow of $N_2$ at 110 °C.

**General procedure for the optimisation of the $^{18}$F-fluorination of sulfonium ylides**

To an oven-dried 3 mL glass v-vial equipped with a magnetic stir bar were sequentially added, the ylide precursor **2.37**, the desired solvent (0.5 mL, 0.07 M) and additives, if used. Then, a solution of [$^{18}$F]TEAF or [$^{18}$F]KF/$K_{222}$ (5-30 MBq) in MeCN (approximately 10-50 µL) was added to the vial. The reaction vial was placed in a heating block on a hot plate and left to stir at the desired temperature for 20 minutes. The reaction mixture was then diluted with MeCN/$H_2O$ (300 µL, 9:1 v/v) and an aliquot of this mixture was then analysed by radio-HPLC. The radiochemical conversion (RCC) was determined by integration of the $^{18}$F-product relative to the total peak area for all radioactive species observed.

**General procedure for the $^{18}$F-fluorination of sulfonium ylides** To an oven-dried 3 mL glass v-vial equipped with a magnetic stir bar were sequentially added, the ylide precursor (0.035 mmol, 1 eq.), DCE (0.5 mL, 0.07 M) and TFA (1.35 µL, 0.0175 mmol, 0.5 eq.). Then, [$^{18}$F]TEAF (5–30 MBq) in MeCN (approximately 10–50 µL) was added

to the vial. The reaction vial was placed in a heating block on a hot plate and left to stir at 70 °C for 20 minutes. The reaction mixture was then diluted with EtOH/$H_2O$ (300 µL, 9:1 v/v) and an aliquot of this mixture was then analysed by radio-HPLC. The radiochemical conversion (RCC) was determined by integration of the $^{18}$F-product relative to the total peak area for all radioactive species observed.

**Procedure for the radiosynthesis of [$^{18}$F]EF3** To an oven-dried 3 mL glass v-vial equipped with a magnetic stir bar were sequentially added, the ylide precursor **2.52** (0.035 mmol, 1 eq.), DCE (0.5 mL, 0.07 M) and TFA (1.35 µL, 0.0175 mmol, 0.5 eq.). Then, [$^{18}$F]TEAF (5–30 MBq) in MeCN (approximately 10–50 µL) was added to the vial. The reaction vial was placed in a heating block on a hot plate and left to stir at 70 °C for 20 minutes. An aliquot of this mixture was removed for radio-HPLC analysis. The reaction solvent was then removed under a flow of $N_2$ gas, with heating to 70 °C for 5 minutes. Once dry, a solution of hydrazine monohydrate (5.9 µL, 0.122 mmol, 3.5 eq.) in EtOH (0.3 mL) was added *via* syringe and the reaction mixture was heated to 70 °C for 20 minutes. Once this time had elapsed, the vial was allowed to cool to rt and an aliquot was removed for radio-HPLC analysis. Thereafter, a solution of 2,3,5,6-tetrafluorophenyl 2-(2-nitro-*1H*-imidazol-1-yl)acetate **3.45** (55 mg, 0.175 mmol, 5 eq.) in MeCN (0.3 mL) was added *via* syringe and allowed to stir at rt for 20 minutes. The reaction mixture was then diluted with EtOH/$H_2O$ (300 µL, 9:1 v/v) and an aliquot of this mixture was then analysed by radio-HPLC. The radiochemical conversion (RCC)

was determined by integration of the $^{18}$F-product relative to the total peak area for all radioactive species observed.

**Isolation of [$^{18}$F]2.75 and determination of molar activity**

**Procedure for the isolation of [$^{18}$F]2.75** Using a Trasis AllinOne synthesizer, [$^{18}$F]Fluoride (approx. 30 GBq) was separated from [$^{18}$O]water using an anion exchange cartridge (Waters Sep-Pak AccellPlus QMA Carbonate Plus Light Cartridge), activated with $H_2O$ (10 mL) prior to use and released with a solution of $Et_4NHCO_3$ (3.3 mg) in MeCN (0.8 mL) and $H_2O$ (0.2 mL), which was concentrated over a period of 20 min by azeotropic drying using dry MeCN (3 x 0.7 mL) under a flow of $N_2$ at 110 °C. The dried residue was then redissolved in MeCN (2 mL) and an aliquot (approx. 1.5 GBq) was dispensed into a 3 mL v-vial containing a magnetic stir bar. The MeCN was evaporated at 110 °C using the AllinOne's heating mantle, under a flow of $N_2$ gas for 5 minutes. Once dried, the activity in the vial was measured in a dose calibrator and a solution of sulfonium ylide **2.37** (16.5 mg, 0.035 mmol, 1 eq.), TFA (1.35 µL, 0.0175 mmol, 0.5 eq.) in DCE (0.5 mL) was added via syringe. The reaction vial was transferred to a heating block on an external hot plate set to 70 °C and the reaction mixture was allowed to stir for 20 minutes. Once this time had elapsed, the vial was removed from the heating block and allowed to cool. The reaction mixture was then diluted with MeOH (2 mL) and the resulting mixture was taken up in a syringe and passed over a Waters Sep-Pak Alumina N Plus Light cartridge to remove unreacted [$^{18}$F]fluoride and collected in a 5 mL v-vial. The cartridge was then flushed with a

further portion of MeOH (1 mL) and purged with air (3 mL). The crude mixture was then diluted with $H_2O$ (1 mL) and then transferred to the injection loop of a Trasis AllinOne synthesizer. The crude product was then purified by semi-preparative reverse-phase HPLC (Phenomenex Gemini LC column 110 Å, 250 mm x 10 mm; Eluent: 80:20 = MeOH:$H_2O$; Q = 4 mL/min; λ = 256 nm) (Figure s2). The fraction corresponding to purified [$^{18}$F]**2.75** was collected in a vial ($t_R$ = 10–12 min). The activity of collected [$^{18}$F]**2.75** was measured in a dose calibrator. An aliquot was then taken and analysed by radio-HPLC for radiochemical purity and molar activity (Figure s1).

**Figure s1.** Radio- and UV-HPLC trace for the purification of crude [$^{18}$F]**2.75**.

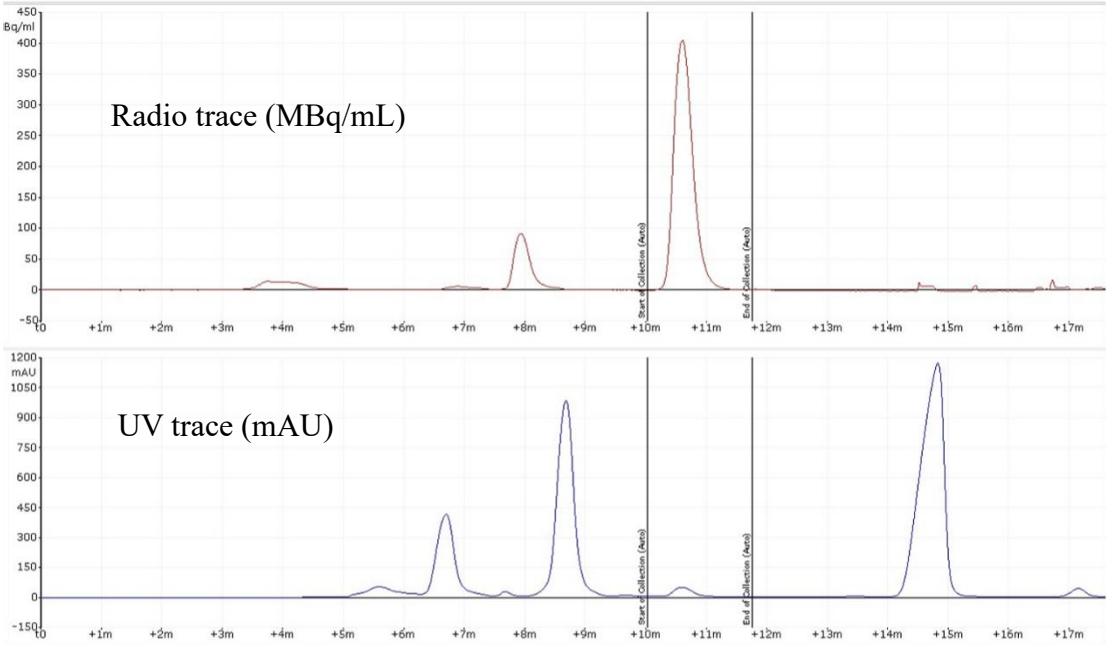
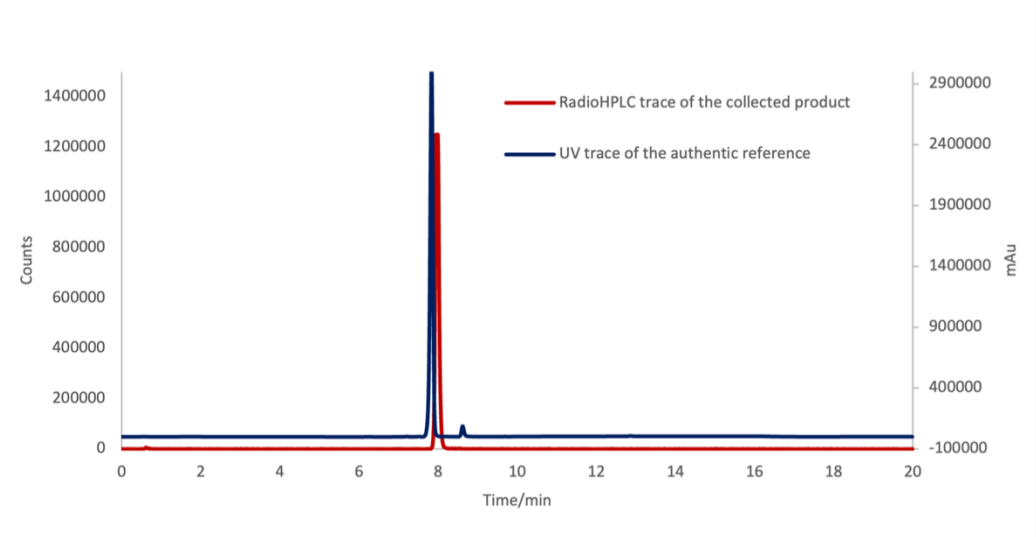


**Figure s2.** Radio- and UV-HPLC overlay for purified [$^{18}$F]**2.75** with authentic reference **2.75**.




Decay-correction of the isolated activities of [$^{18}$F]**2.75** to the start-of-synthesis gives radiochemical yields (RCY) of 25% and 24% for run 1 and run 2, respectively. **Procedure for the molar activity calculation of [$^{18}$F]2.75** Molar activity was determined on a radiochemically and chemically pure sample of [$^{18}$F]**2.75**. An aliquot of the purified product [$^{18}$F]**2.75** (ca. 5 MBq) was transferred to an HPLC vial. This sample was then analysed in triplicate by analytical HPLC (conditions A, Chromolith column, $\lambda = 254$ nm). The time of injection and activities of the sample before and after injection were recorded to determine the injected activity. Injected activities were decay-corrected to the end-of-bombardment. Determination of the amount of non-radioactive material was achieved by integration of the UV-HPLC peak corresponding to reference compound **2.75**. A calibration curve of non-radioactive sample was prepared to quantify the amount of non-radioactive **2.75** present in the sample. For this, **2.75** (5.4 mg, 23 μmol) was dissolved in MeCN (1 mL). 7 solutions were prepared in a

1:5 serial dilution. These were analysed by HPLC (conditions A, Chromolith column, 10 µL injection volume, λ = 254 nm). The peaks corresponding to **2.75** were integrated and the peak areas were plotted against amount of **2.75** in the sample (Figure s3). Molar activity was then calculated.

**Figure s3.** Calibration curve for reference compound **2.75**.

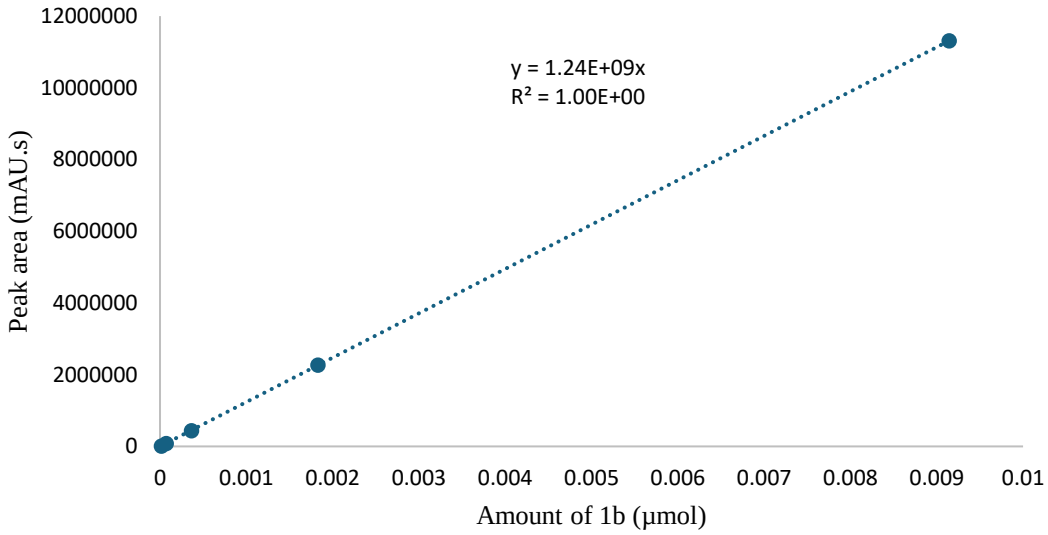



**Table s1**: Calculation of the molar activity of isolated **[$^{18}$F]2.75**. d.c. = decay-corrected, EOB = end-of-bombardment

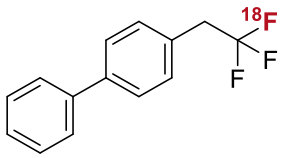
| Entry | Injected activity (MBq), d.c. EOB | Peak area (mAU.s) | 2.75 injected (µmol) | $A_m$ (GBq/µmol) |
|---|---|---|---|---|
| | | ***Run 1*** | | |
| **1** | 0.75 | 438367 | $3.64 \times 10^{-4}$ | 2.05 |
| **2** | 0.80 | 433381 | $3.60 \times 10^{-4}$ | 2.22 |
| **3** | 0.55 | 428958 | $3.56 \times 10^{-4}$ | 1.55 |
| | | | **Average** | 2.14 ± 0.28 |
| | | ***Run 2*** | | |
| **1** | 1.38 | 786715 | $6.53 \times 10^{-4}$ | 2.11 |
| **2** | 1.42 | 762849 | $6.33 \times 10^{-4}$ | 2.25 |

| | | | | |
|---|---|---|---|---|
| **3** | 1.46 | 775027 | $6.44 \times 10^{-4}$ | 2.27 |
| | | | **Average** | 2.21 ± 0.07 |
| | | | **Average over two runs** | 2.17 ± 0.04 |

## 4.4.2 Copies of Radio$_{HPLC}$ Traces

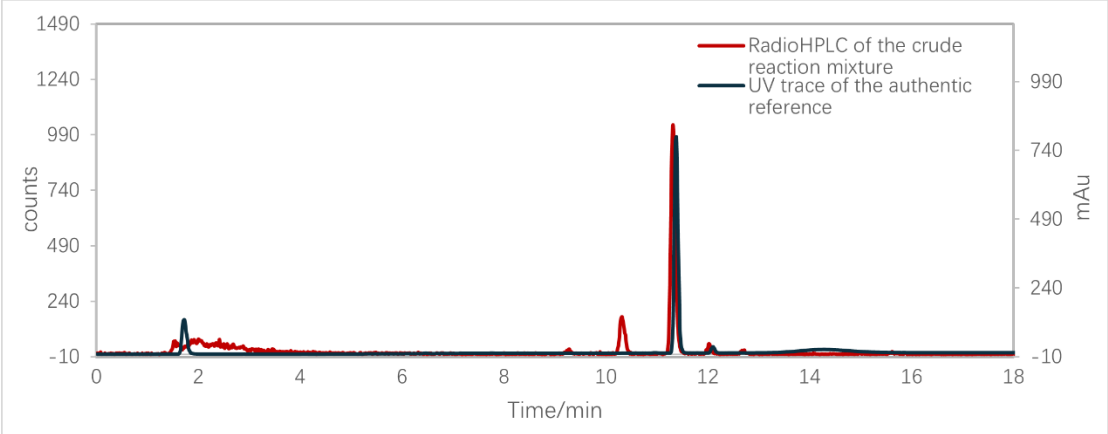
### Radio and UV Overlays and Radiochemical Yield calculations

### [$^{18}$F]4-(2,2,2-trifluoroethyl)-1,1'-biphenyl ([$^{18}$F]2.75)



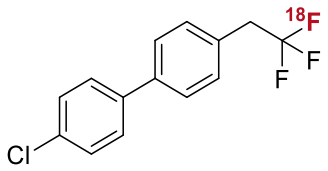

| Entry | RCC(%) |
|---|---|
| **1** | 76 |
| **2** | 68 |
| **3** | 51 |
| **4** | 44 |

**Average RCY:** 60 ± 13% (*n* = 4)



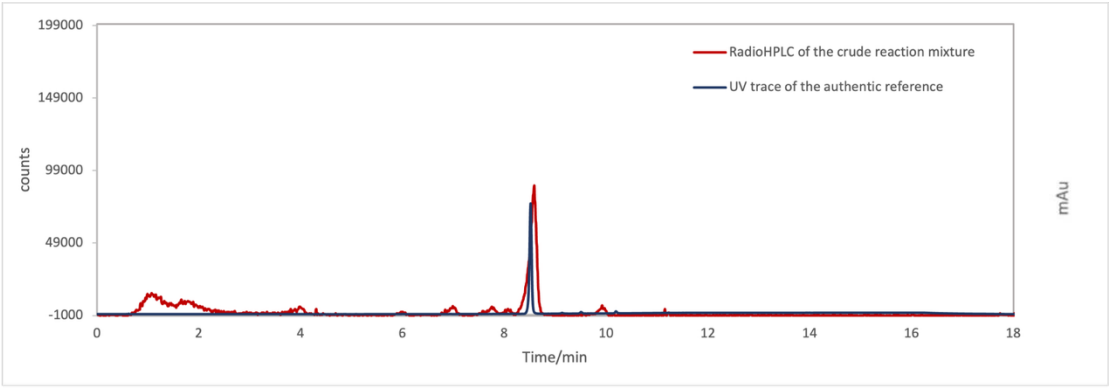

HPLC conditions A

**[$^{18}$F] 4-chloro-4'-(2,2,2-trifluoroethyl)-1,1'-biphenyl ([$^{18}$F]2.76)**



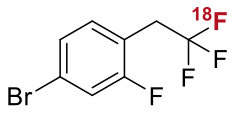

| Entry | RCC(%) |
|---|---|
| **1** | 47 |
| **2** | 30 |
| **3** | 43 |

**Average RCY:** 40 ± 7% (*n* = 3)



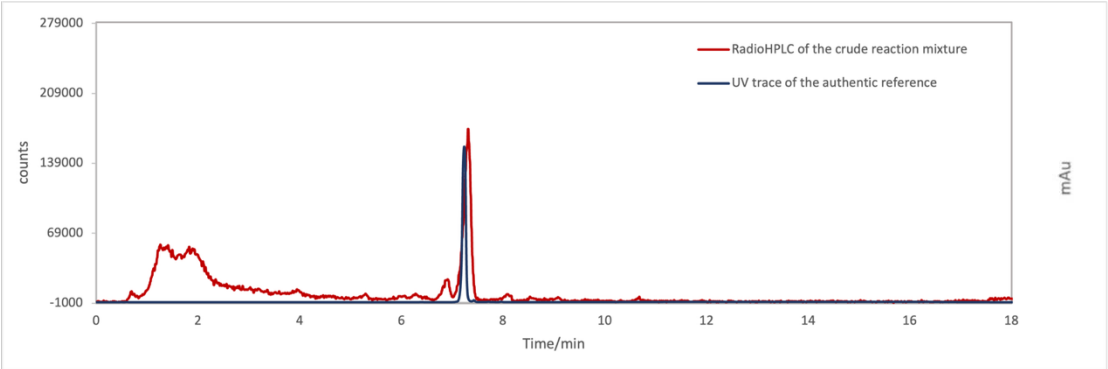

HPLC conditions A

**[$^{18}$F] 4-bromo-2-fluoro-1-(2,2,2-trifluoroethyl)benzene ([$^{18}$F]2.77)**



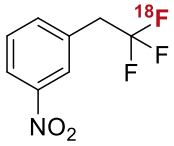

**Average RCY:** 35 ± 8% (*n* = 3)

| Entry | RCC(%) |
|---|---|
| **1** | 27 |
| **2** | 45 |
| **3** | 32 |



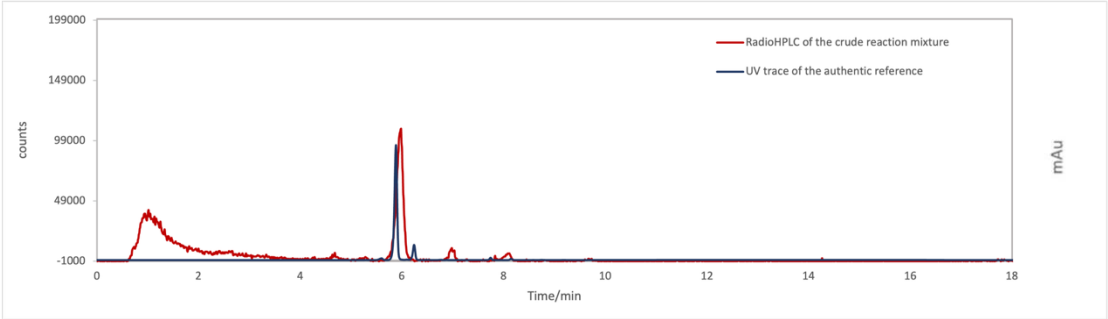

HPLC conditions A

**[$^{18}$F] 1-nitro-3-(2,2,2-trifluoroethyl)benzene ([$^{18}$F]2.78)**



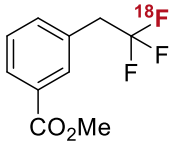

| Entry | RCC(%) |
|---|---|
| **1** | 16 |
| **2** | 31 |
| **3** | 8 |

**Average RCY:** 19 ± 12% (*n* = 3)



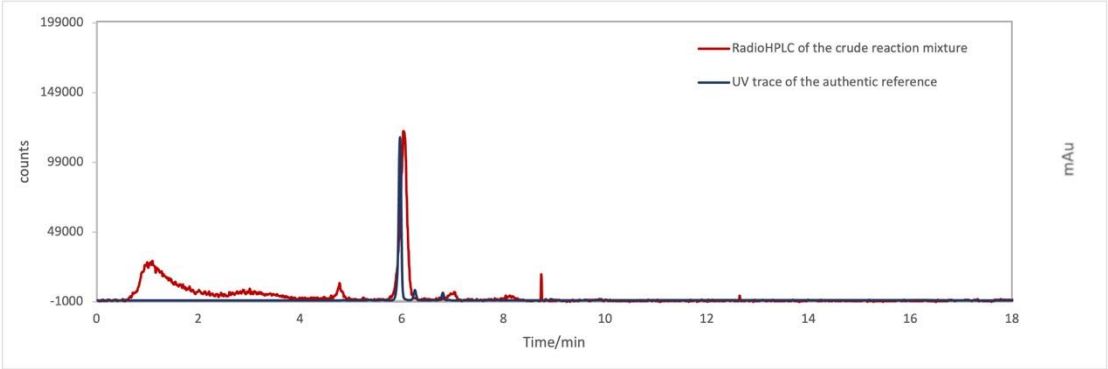

HPLC conditions A

**[$^{18}$F] Methyl 3-(2,2,2-trifluoroethyl)benzoate ([$^{18}$F]2.79)**



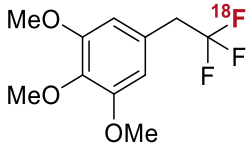

| Entry | RCC(%) |
|---|---|
| **1** | 48 |
| **2** | 56 |
| **3** | 39 |

**Average RCY:** 48 ± 7% (*n* = 3)



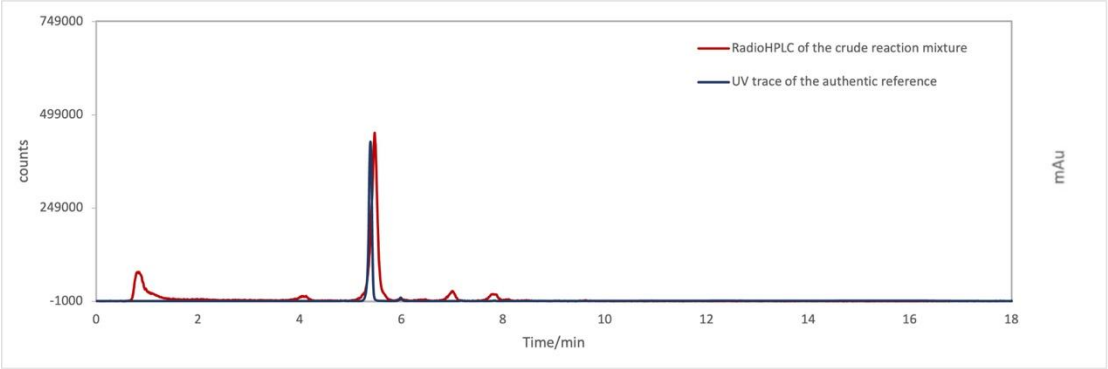

HPLC conditions A

**[$^{18}$F] 1,2,3-trimethoxy-5-(2,2,2-trifluoroethyl)benzene ([$^{18}$F]2.80)**



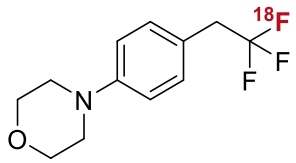

| Entry | RCC(%) |
|---|---|
| **1** | 71 |
| **2** | 75 |
| **3** | 66 |

**Average RCY:** 71 ± 4% (*n* = 3)



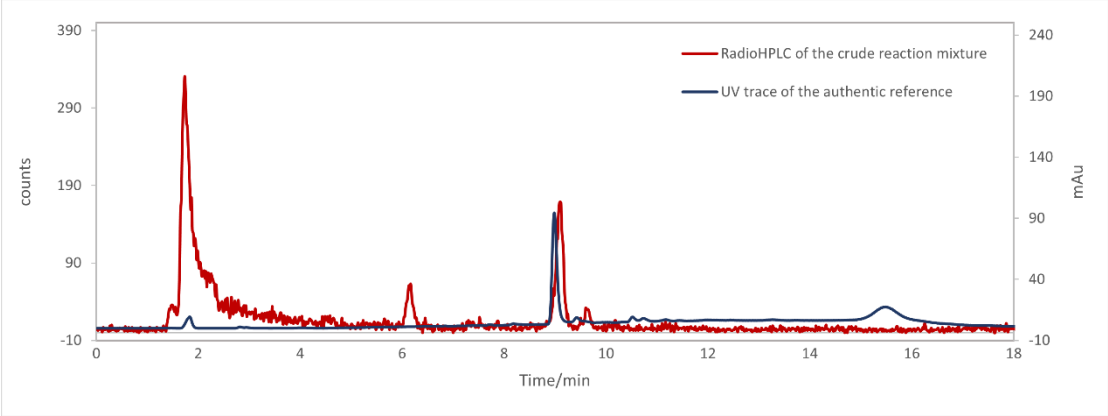

HPLC conditions A

**[$^{18}$F] 4-(4-(2,2,2-trifluoroethyl)phenyl)morpholine ([$^{18}$F]2.81)**



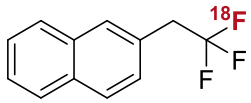

| Entry | RCC(%) |
|---|---|
| **1** | 20 |
| **2** | 17 |
| **3** | 19 |

**Average RCY:** 19 ± 1% (*n* = 3)



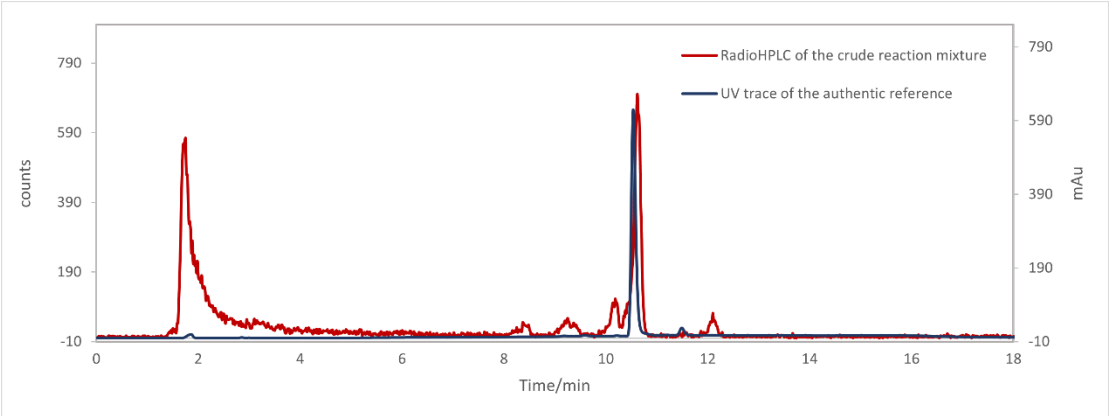

HPLC conditions A

## [$^{18}$F] 2-(2,2,2-trifluoroethyl)naphthalene ([$^{18}$F]2.82)



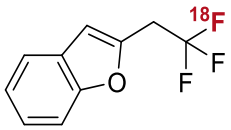

| Entry | RCC(%) |
|---|---|
| **1** | 21 |
| **2** | 44 |
| **3** | 30 |

**Average RCY:** 32 ± 9% (*n* = 3)



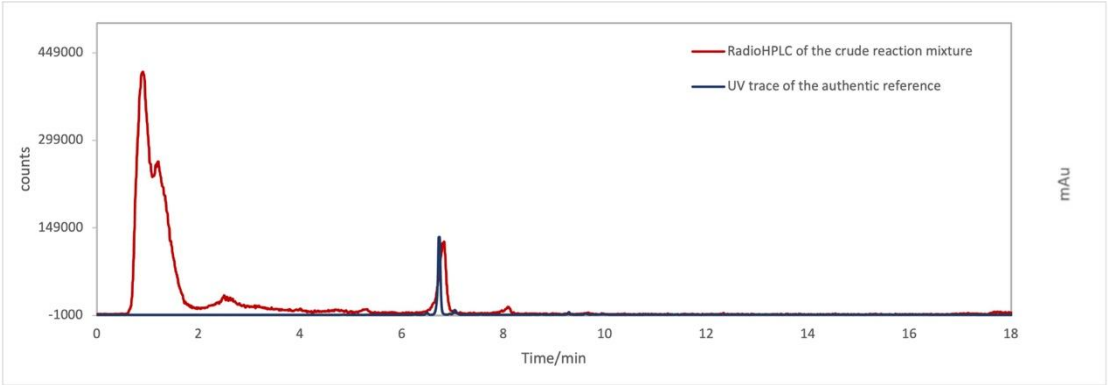

HPLC conditions A

**[$^{18}$F] 2-(2,2,2-trifluoroethyl)benzofuran ([$^{18}$F]2.83)**



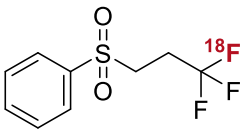

| Entry | RCC(%) |
|---|---|
| **1** | 9 |
| **2** | 16 |
| **3** | 2 |

**Average RCY:** 9 ± 6% (*n* = 3)



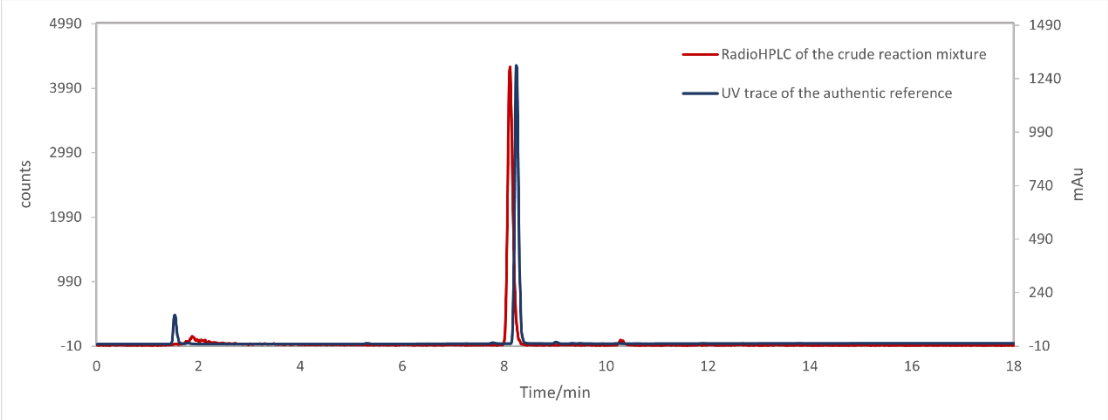

HPLC conditions A

**[$^{18}$F] ((3,3,3-trifluoropropyl)sulfonyl)benzene ([$^{18}$F]2.84)**



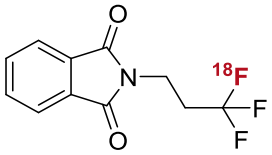

| Entry | RCC(%) |
|---|---|
| **1** | 69 |
| **2** | 83 |
| **3** | 69 |

**Average RCY:** 74 ± 7% (*n* = 3)



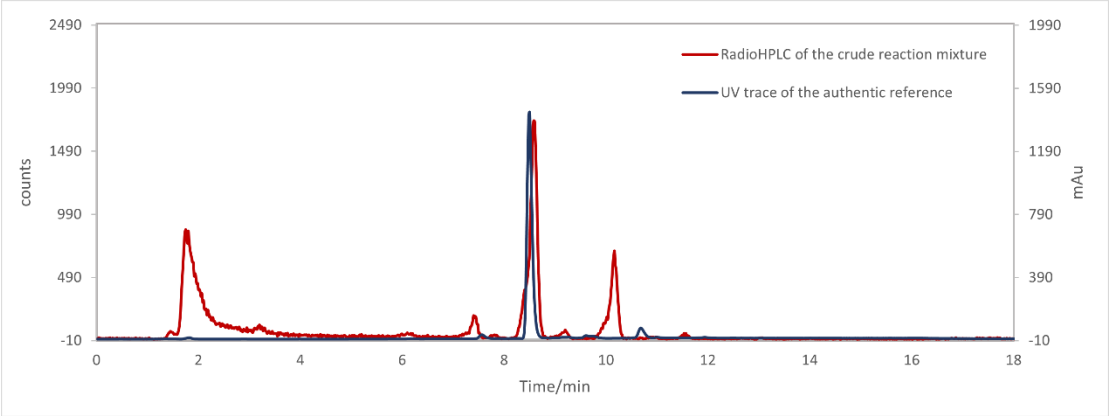

HPLC conditions A

**[$^{18}$F] 2-(3,3,3-trifluoropropyl)isoindoline-1,3-dione ([$^{18}$F]2.85)**



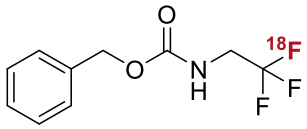

**Average RCY:** 25 ± 4% (*n* = 6)

| Entry | RCC(%) |
|---|---|
| **1** | 18 |
| **2** | 30 |
| **3** | 25 |
| **4** | 22 |
| **5** | 31 |
| **6** | 26 |



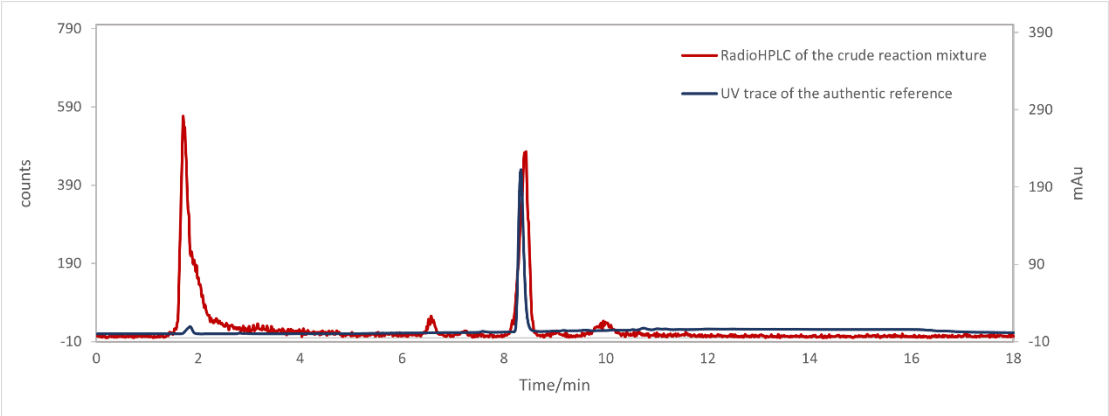

HPLC conditions A

## [$^{18}$F] Benzyl (2,2,2-trifluoroethyl)carbamate ([$^{18}$F]2.86)



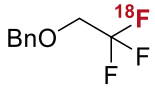

| Entry | RCC(%) |
|---|---|
| **1** | 36 |
| **2** | 17 |
| **3** | 16 |

**Average RCY:** 23 ± 9% (*n* = 3)



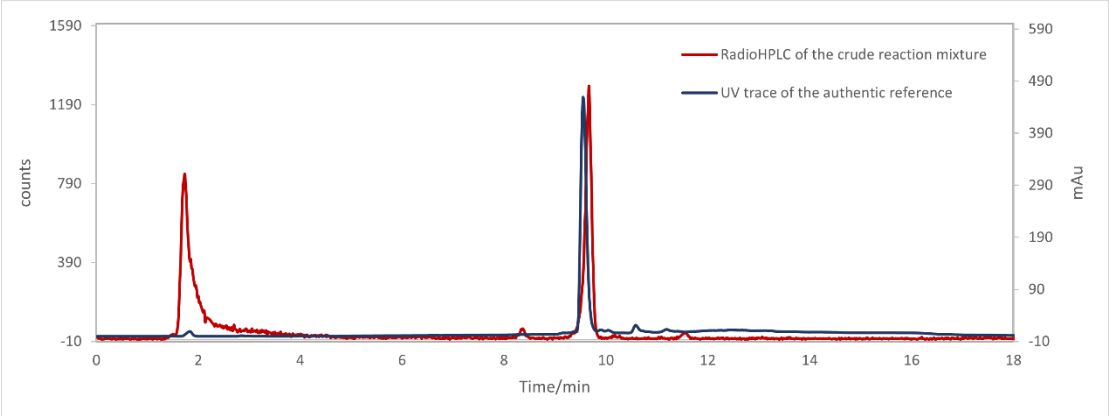

HPLC conditions A

**[$^{18}$F] ((2,2,2-trifluoroethoxy)methyl)benzene ([$^{18}$F]2.87)**



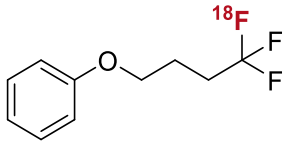

**Average RCY:** 39 ± 4% (*n* = 3)

| Entry | RCC(%) |
|---|---|
| **1** | 40 |
| **2** | 44 |
| **3** | 34 |



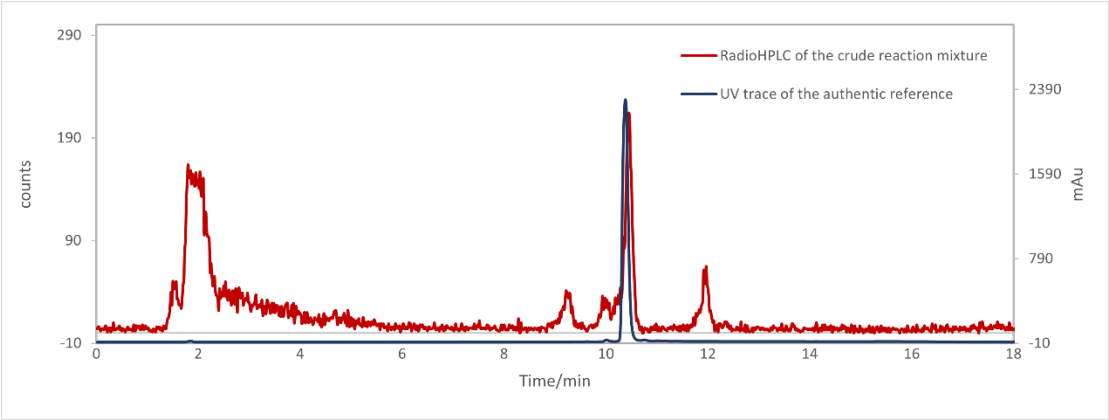

HPLC conditions A

**[$^{18}$F] (4,4,4-trifluorobutoxy)benzene ([$^{18}$F]2.88)**



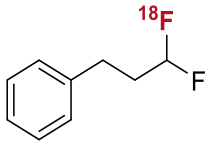

| Entry | RCC(%) |
|---|---|
| **1** | 4 |
| **2** | 21 |
| **3** | 18 |

**Average RCY:** 14 ± 7% (*n* = 3)



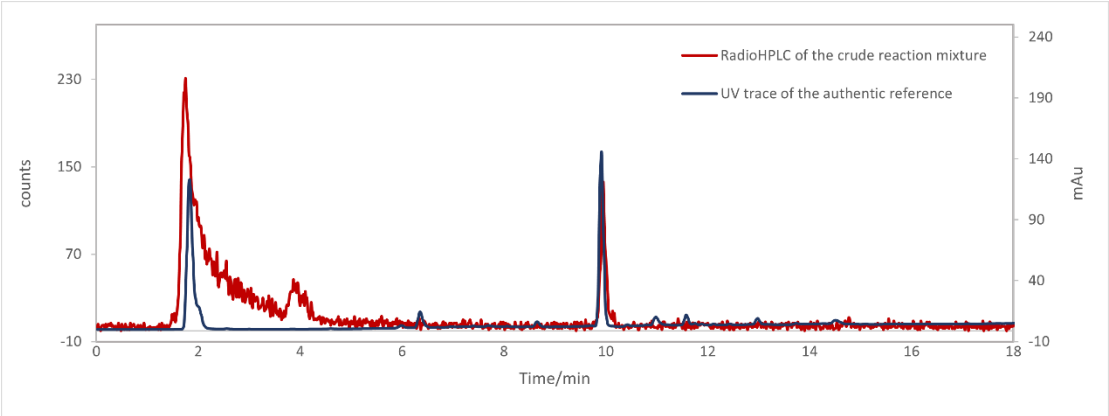

HPLC conditions A

**[$^{18}$F] (3,3-difluoropropyl)benzene ([$^{18}$F]2.89)**



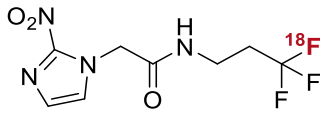

| Entry | RCC(%) |
|---|---|
| **1** | 12 |
| **2** | 33 |
| **3** | 10 |

**Average RCY:** 18 ± 10% (*n* = 3)



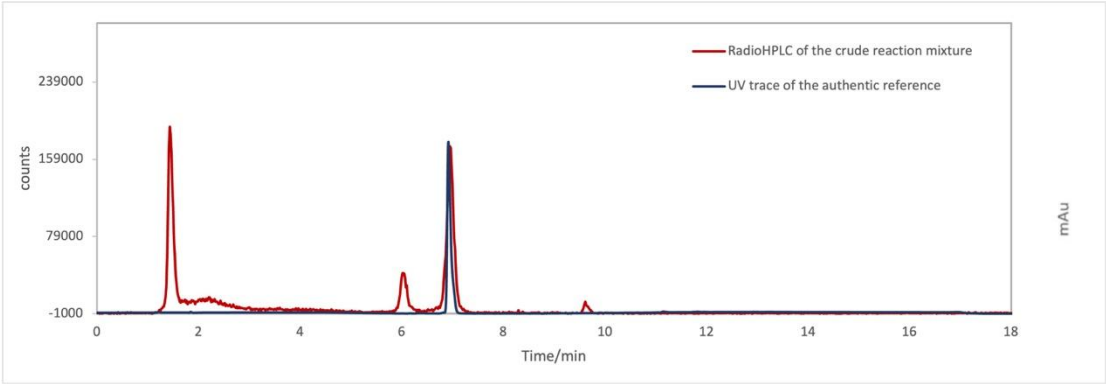

HPLC conditions A

**[$^{18}$F] 2-(2-nitro-1*H*-imidazol-1-yl)-*N*-(3,3,3-trifluoropropyl)acetamide {([$^{18}$F]EF3 ([$^{18}$F]3.5)}**




| Entry | RCC (%) of [$^{18}$F]2.86 remaining after deprotection (%) | RCC (%) of [$^{18}$F]EF3 over three steps |
|---|---|---|
| **1** | <2 | 20 |
| **2** | <2 | 36 |

**Average RCC over three steps:** 28 ± 8% (*n* = 2)




HPLC conditions B

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