New Methods for F-18 Radiolabelling



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Author’s Declaration

The work presented in this thesis was conducted at the Chemistry Research Laboratory at the University of Oxford under the supervision of Professor Véronique Gouverneur, between Trinity Term 2017 and Trinity Term 2021. All the work is my own, except where otherwise stated, and has not been submitted for any other degree at this or any other university.

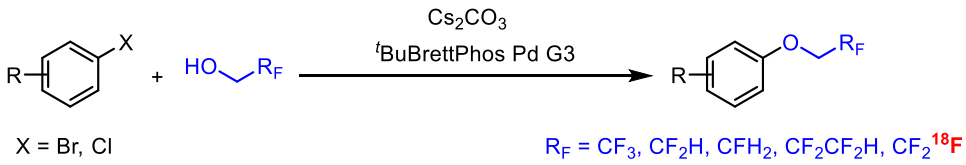
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Abstract

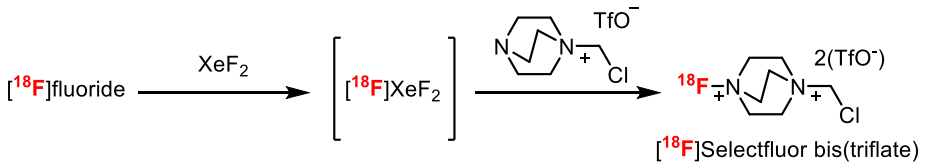
Chapter 1 – Introduction briefly introduces the fundamental principles of positron emission tomography (PET). The different isotopes commonly employed in PET are compared, before examples of fluorine-18 (F-18) radiotracers are presented. Various concepts in F-18 radiochemistry are then discussed, including methods for the production of F-18. Key developments in methods for ^{18}F-labelling small molecules are then presented. Finally, the aims of this thesis are summarised.

Chapter 2 – Palladium-Catalysed C–O Cross-Coupling and Applications in ^{18}F-Radiochemistry presents the optimisation and scope of a palladium-catalysed C–O cross-coupling between aryl halides and fluorinated alcohols to prepare fluorinated alkyl aryl ethers. Application of the reaction in ^{18}F-radiochemistry is also presented, including a novel radiosynthesis of [^{18}F]trifluoroethanol, and subsequent palladium-mediated cross-coupling with aryl bromides.

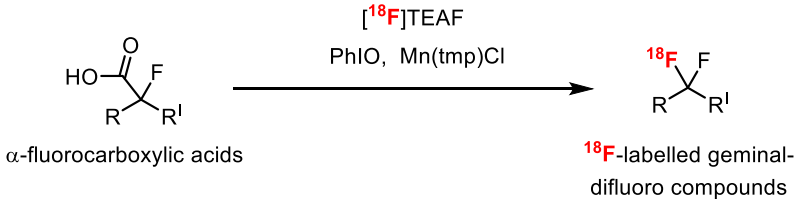


Chapter 3 – Preparation of [^{18}F]Selectfluor from [^{18}F]Fluoride presents work aimed at preparing [^{18}F]Selectfluor bis(triflate) from [^{18}F]fluoride. This research comprises studies of the synthesis of [^{18}F]xenon difluoride from [^{18}F]fluoride, and subsequent reaction with

monoquaternised 1,4-diazabicyclo[2.2.2]octane salts to afford [^{18}F]Selectfluor bis(triflate) and related F-TEDA reagents. The characterisation of [^{18}F]Selectfluor bis(triflate) and a preliminary application of the reagent are also described.



Chapter 4 – ^{18}F-Fluorodecarboxylation for Preparing ^{18}F-Labelled Geminal-Difluoro Compounds presents the preliminary investigations into use of [^{18}F]Selectfluor bis (triflate) and [^{18}F]xenon difluoride for the ^{18}F-fluorodecarboxylation of α-fluorinated carboxylic acids to prepare ^{18}F-labelled geminal-difluoro compounds. The development of a more efficient method using [^{18}F]fluoride and a manganese mediator is then presented, along with a preliminary reaction scope.



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Abbreviations

AMF	Ammonium formate
APCI	Atmospheric pressure chemical ionization
BOC	*Tert*-butoxycarbonyl
BPin	Pinacol boronic ester
C-11	Carbon-11
C18	Stationary phase attached with molecules that have 18 carbon atoms
CT	Computed tomography
DABCO	1,4-diazabicyclo(2.2.2)octane
DBU	1,8-Diazabicyclo(5.4.0)undec-7-ene
DCE	1,2-Dichloroethane
$(DHQ)_2Pyr$	Hydroquinine 2,5-diphenyl-4,6-pyrimidinediyl diether
diCy-18-C-6	Dicyclohexano-18-crown-6
DME	1,2-Dimethoxyethane
DMF	Dimethylformamide
DMI	1,3-Dimethyl-2-imidazolidinone
DMSO	Dimethyl sulfoxide
DPPF	1,1'-Bis(diphenylphosphino)ferrocene
EDG	Electron-donating group
equiv.	Equivalents
ESI	Electrospray ionisation
EWG	Electron-withdrawing group
F-18	Fluorine-18
F-19	Fluorine-19
FDOPA	6-Fluoro-L-DOPA
FDG	Fluorodeoxyglucose

FET	Fluoroethyl-L-tyrosine
F-TEDA	*N*-fluoro triethylenediamine derivative
GLUTs	Glucose transporter
h	hours
HMPA	Hexamethylphosphoramide
HPLC	High-performance liquid chromatography
HRMS	High resolution mass spectroscopy
imp	Impurity
IR	Infrared
K_{222}	Kyrptofix-222
LAT	L-type amino acid transporter
LDA	Lithium diisopropylamide
LED	Light-emitting diode
LRMS	Low resolution mass spectroscopy
MA	Molar activity
mCPBA	meta-Chloroperoxybenzoic acid
Min	Minutes
Mn(tmp)Cl	Mn(III) meso-tetra(2,4,6-trimethylphenyl)porphine chloride
MP	Melting point
MRI	Magnetic resonance imaging
MTBE	Methyl *tert*-butyl ether
MTDB	7-Methyl-1,5,7-triazabicyclo(4.4.0)dec-5-ene
N-13	Nitrogen-13
NFSI	*N*-fluorobenzenesulphonimide
NML	*N*-methyl lansoprazole
NMM	*N*-methylmorpholine
NMR	Nuclear magnetic resonance
NMRY	Nuclear magnetic resonance yield
$[(NpNMe_3)_2C_2O_4]$	Bis(neopentyltrimethylammonium) oxalate

O-15	Oxygen-15
Pd G3	Generation three Buchwald pre-catalyst
PET	Positron emission tomography
PIDA	(Diacetoxyiodo)benzene
ppm	Parts per million
PPTS	Pyridinium p-toluenesulfonate
Py·9HF	Pyridine nonahydrofluoride
QMA	Quaternary methylated ammonium
RadioHPLC	Radio high-performance liquid chromatography
RadioTLC	Radio thin layer chromatography
RCC	Radiochemical conversion
RCP	Radiochemical purity
RCY	Radiochemical yield
RBF	Round bottom flask
RP-HPLC	Reverse-phase high-pressure liquid chromatography
rt	Room temperature
Selectfluor	1-Chloromethyl-4-fluoro-1,4-diazoniabicyclo(2.2.2)octane bis(tetrafluoroborate)
S_NAr	Nucleophilic aromatic substitution
TBAF	Tetrabutylammonium fluoride
TBAOTs	Tetrabutylammonium tosylate
TCA	Trichloroacetic acid
TEAF	Tetraethylammonium fluoride
TFA	Trifluoroacetic acid
TFAA	Trifluoroacetic anhydride
TLC	Thin layer chromatography
Tol-BINAP	2,2’-Bis(di-p-tolylphosphino)-1,1’-binaphthyl
TSPO	Translocator protein
UV	Ultraviolet
wrt	With respect to

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Chapter 1

Introduction to Positron Emission Tomography and ^{18}F-Radiochemistry

This chapter briefly introduces the fundamental principles of positron emission tomography (PET). The different isotopes commonly employed in PET are compared before examples of fluorine-18 (F-18) radiotracers are presented. Various concepts in F-18 radiochemistry are then discussed, including methods for the production of F-18. Key developments in methods for ^{18}F-labelling small molecules are then presented. Finally, the aims of this thesis are summarised.

1.1 Positron Emission Tomography

1.1.1 Introduction to Positron Emission Tomography

Positron emission tomography (PET) is a non-invasive molecular imaging technique that enables *in vivo* imaging of biological processes. PET requires use of a molecular probe (radiotracer) labelled with a positron emitting isotope, most commonly fluorine-18 (F-18). Relative to other common imaging methods, PET is unique in its high sensitivity, with scanners able to detect picomolar to nanomolar concentrations of radiotracers.[1] Unlike ultrasound, magnetic resonance imaging (MRI), and computed tomography (CT), which primarily provide structural information, PET provides information at the molecular level.[2] Indeed, the ability of PET to probe biochemical processes is important as diseases typically manifest in biological changes before structural changes.[2] PET is used in the clinical setting to monitor disease states including for diagnosis and assessment of treatment response, and pre-clinically to investigate drug biodistribution and receptor binding.

In PET imaging, a radiotracer is administered to the subject, and within the subject's body a proton in the radioisotope decays to a neutron with the emission of a positron and a neutrino (Figure 1). The positron travels a short distance in the surrounding tissue, before encountering an electron and annihilating with the emission of two anti-parallel 511 keV

γ-photons. These photons are detected by a ring of scintillation detectors surrounding the subject. The coincident detection of these two photons enables determination of the location of the annihilation event, and hence also that of the radiotracer. These readouts are processed to generate a 3D image of the distribution of the radiotracer within the subject. PET and CT images are commonly acquired together (PET-CT) so that the functional information obtained from the former can be precisely mapped in an anatomical context using structural information from the latter.

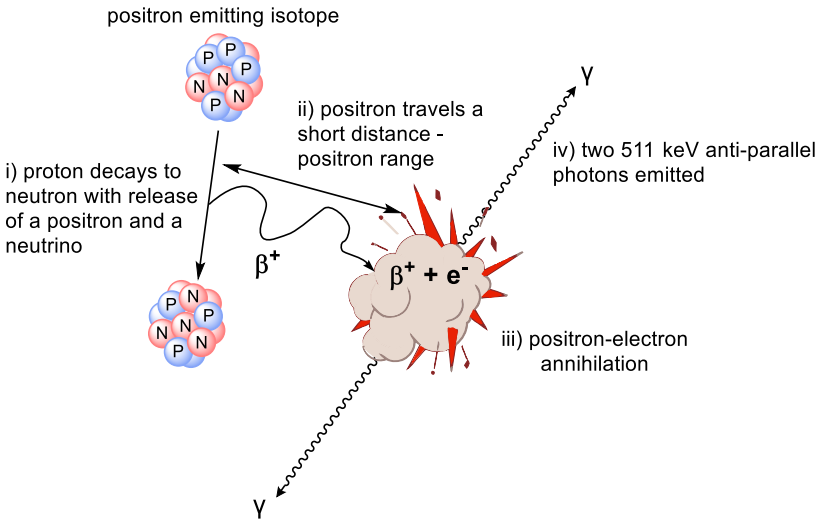


Figure 1: Decay of a positron emitting isotope and positron annihilation.

1.1.2 Radioisotopes Used in PET

The different nuclear properties of radioisotopes are important to consider for applications in PET (Table 1). The half-life defines the time taken for the radioactivity of a radioisotope to fall to half of its initial value. While carbon, nitrogen, and oxygen are ubiquitous in biomolecules and drugs, the short half-lives of their positron emitting isotopes C-11 (20.3 minutes), N-13 (10.0 minutes) and O-15 (2.0 minutes) present a logistical challenge to their application in PET imaging. Radiotracers labelled with these isotopes must be produced and used on-site before loss of radioactivity to decay. In

contrast, the 109.8 minute half-life of F-18 is significantly longer. This is advantageous as it allows time for more complex radiotracer synthesis, enables multiple radiotracer doses to be prepared, and provides time for radiotracers to be transported for use at satellite clinics that lack radiochemistry facilities. Nonetheless, the half-lives of C-11, N-13, O-15, and F-18 require that radiosyntheses incorporating these nuclei are fast and efficient.

The distance that the emitted positrons of a radioisotope travel before annihilation is the positron range, quantified as the mean positron range (Table 1, R_{mean}). This distance is dependent on both the energy of the positron, quantified as the maximum positron energy (E_{max}), and the medium through which they travel, for example water or tissue. As different radioisotopes have different positron energies, they also have different positron ranges. Higher positron ranges result in more blurring of the PET image, as it is the site of annihilation that is detected in PET rather than the site of positron emission (Figure 1). Blurring effects are most obvious with high energy emitters such as Rb-82. Due to the low positron range of F-18, its relatively long half-life, and its high positron decay ratio, F-18 is the most commonly used radioisotope in PET. For the remainder of this chapter, radiochemistry will be discussed specifically in the context of F-18.

Table 1: Physical properties of relevant positron emitting isotopes.[3,4,5,6] E_{max} = maximum positron energy in MeV, R_{mean} = mean positron range in water, in mm.

Isotope	Half-life	% β^+ decay	E_{max} (MeV)	R_{mean} (mm)
C-11	20.3 min	99	0.97	1.1
N-13	10.0 min	100	1.20	1.5
O-15	2.0 min	100	1.74	2.5
F-18	109.8 min	97	0.64	0.6
Cu-64	12.7 h	18	0.65	0.7
Ga-68	68.1 min	89	1.90	2.9
Rb-82	1.3 min		3.38	5.9
Zr-89	78.4 h	23	0.89	1.3

1.1.3 Fluorine-18 Radiotracers

The most widely used radiotracer in clinical PET is [^{18}F]fluorodeoxyglucose ([^{18}F]FDG, Figure 2). As an analogue of glucose, [^{18}F]FDG is taken up into cells via glucose transporters (GLUTs), and is then phosphorylated by hexokinase to afford [^{18}F]FDG-6-phosphate. Expression of GLUTs and hexokinase is generally higher in cancerous cells than in normal cells. Unlike glucose, further glycolysis of [^{18}F]FDG-6-phosphate is inhibited, due to the absence of the 2-hyroxyl group present in glucose. In normal cells, glucose-6-phosphate/[^{18}F]FDG-6-phosphate can be dephosphorylated and then exit the cell. However, expression of glucose-6-phosphatase is usually significantly decreased in cancerous cells. [^{18}F]FDG-6-phosphate hence accumulates in cancerous cells.[7] [^{18}F]FDG is therefore used in oncology for tumour diagnosis, staging, treatment monitoring, and radiation therapy planning.

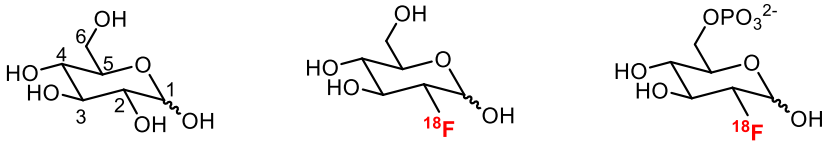


Figure 2: Glucose and [^{18}F]FDG, the most commonly used radiotracer in PET imaging.

Many other F-18 labelled radiotracers are used in clinical PET imaging, a selection of which are shown in Figure 3. 6-[^{18}F]Fluoro-L-DOPA ([^{18}F]FDOPA) is used for imaging the dopaminergic system in the human brain for the diagnosis of Parkinson's disease and other neuropsychiatric diseases. [^{18}F]FDOPA accumulation in the brain reflects the functional integrity of presynaptic dopaminergic synthesis, which is compromised in patients with Parkinson's disease.[8] Another application of [^{18}F]FDOPA is in neuroendocrine tumour imaging. [^{18}F]Fluoromisonidazole ([^{18}F]FMISO) is used in

oncology for visualising tumour hypoxia, which is closely associated with chemotherapy and radiotherapy resistance. It is therefore used to predict treatment outcome and monitor treatment response in cancer patients.[9] [^{18}F]Florbetapir is used in the diagnosis of Alzheimer's disease, as it has a high binding affinity to beta amyloid peptides, the main component of amyloid plaques that play a key role in the disease's pathogenesis.[10] [^{18}F]PSMA-1007 is used in the diagnosis of prostate cancer.[11] [^{18}F]Flumazenil is used to quantify the density of central benzodiazepine receptors.[12]

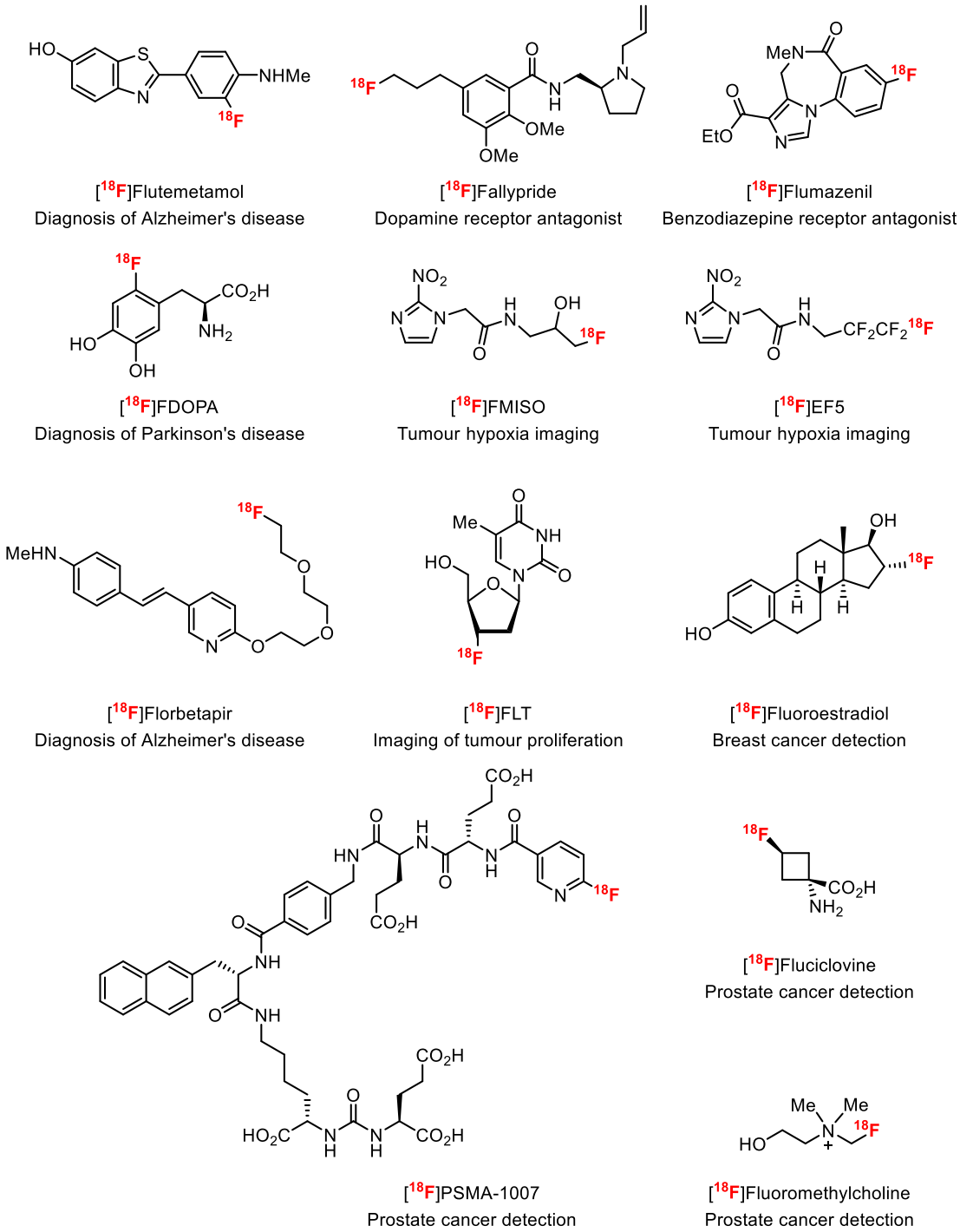


Figure 3: Representative F-18 radiotracers used in clinical PET.

1.2 Concepts and Considerations in ^{18}F-Radiochemistry

1.2.1 Molar Activity

Molar activity quantifies the radioactivity per mole of a radiotracer (typically quoted in GBq μmol^{-1}). The F-18 isotopologue of a radiotracer represents a negligible quantity of

the total sample, with the bulk accounted for by the non-radioactive F-19 isotopologue. The molar activity effectively describes the isotopic composition of the sample, with a higher ratio of the F-18 isotopologue manifesting in higher molar activity.

$$\text{molar activity (GBq } \mu\text{mol}^{-1}) = \frac{\text{radioactivity of compound (GBq)}}{\text{total quantity of compound } (\mu\text{mol})}$$

Molar activity is dependent on the method used to produce F-18 (see Section 1.2.3) and on the radiosynthetic route to the tracer. While the maximum theoretical molar activity for F-18 is 63,000 GBq µmol^{-1},[13,3] such values are never obtained for ^{18}F-labelled radiotracers. This is due to unavoidable isotopic dilution with F-19 from reagents, water, solvents and transport vessels during production and transport of F-18, and during radiotracer synthesis. Different applications of PET have different molar activity requirements, and so it is an important parameter to consider. For example, imaging of low density neuroreceptors requires tracers with high molar activity, otherwise the receptors become saturated with the non-radioactive tracer isotopologue leading to poor image contrast. In addition, for tracers prepared with low molar activity, a higher dose (in mole) must be administered to achieve a given quantity of radioactivity, potentially leading to unwanted pharmacological effects. In contrast to receptor binding studies, biodistribution studies do not require radiotracers with high molar activity.[14]

1.2.2 Radiochemical Conversion and Radiochemical Yield

As [^{18}F]fluoride is produced in nanomole to picomole quantities, it is the limiting reagent in radiosyntheses. Reaction yields are therefore quoted with respect to [^{18}F]fluoride. Radiochemical conversion (RCC) quantifies the radioactivity of the ^{18}F-labelled product as a fraction of all F-18 containing components in the crude reaction mixture. This is determined by analysing a sample of the crude reaction mixture by radioTLC (to

determine the conversion of [^{18}F]fluoride) and radioHPLC (to determine the distribution of ^{18}F-labelled products). Use of radioHPLC alone to determine RCC can be inaccurate due to retention of [^{18}F]fluoride on the stationary phase.[15]

$$\% \text{ RCC} = \frac{\%\text{purity by radioHPLC (excluding fluoride)} \times \%\text{conversion by radioTLC}}{100}$$

The radiochemical yield (RCY) quantifies the radioactivity of the isolated and formulated ^{18}F-labelled product as a fraction of the starting activity of [^{18}F]fluoride. The RCY is generally significantly lower than the RCC for a given reaction, as large losses of radioactivity can occur during purification and drying of [^{18}F]fluoride (see Section 1.2.4), during purification by preparative HPLC, during formulation of the final product, and due to decay. These losses are not accounted for in the RCC. Prior to 2017, the terms RCC and RCY where poorly defined and somewhat ambiguous, however since then various consensus have standardised radiochemical nomenclature to defined the terms as described above.[16,17] In the production of radiotracers, RCYs as low as 1% are still sufficient for dosing patients; hundreds of gigabecquerel of [^{18}F]fluoride can be produced in a cyclotron run, while patients generally are administered with less than 500 megabecquerel of a radiotracer.[18]

$$\% \text{ RCY} = \frac{\text{radioactivity of isolated final product}}{\text{starting radioactivity}} \times 100$$

1.2.3 Production of F-18

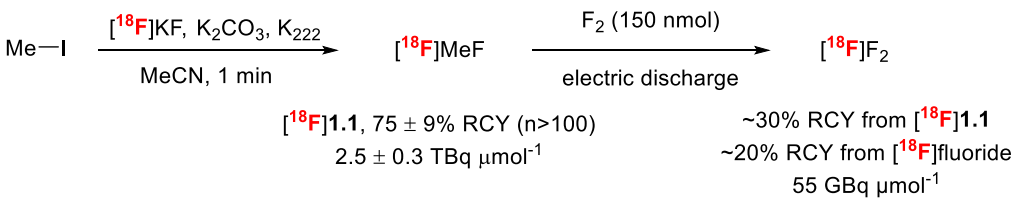
Both [^{18}F]fluoride and [^{18}F]F_2 gas can be produced using a cyclotron, but the former is far more common as it can be prepared in higher molar activity and is easier to manipulate. [^{18}F]Fluoride is produced by the ^{18}O(p,n)^{18}F nuclear reaction; proton bombardment of [^{18}O]H_2O affords [^{18}F]fluoride as a solution in [^{18}O]H_2O with a molar activity of around

5000 GBq µmol^{-1} (Table 2, Method A). The counterion of [^{18}F]fluoride is dependent on the metal of the target chamber and entrance foil in the cyclotron.[19] The desired counterion is introduced during subsequent purification and drying of [^{18}F]fluoride prior to radiosynthesis (see Section 1.2.4).

Table 2: Methods for the cyclotron production of F-18. A_m = molar activity

Method	Product	Target	Nuclear Reaction	A_m (GBq µmol^{-1})
A	[^{18}F]fluoride	[^{18}O]H_2O	^{18}O(p,n)^{18}F	5000
B	[^{18}F]F_2	[^{18}O]O_2 + F_2	^{18}O(p,n)^{18}F	0.60
C	[^{18}F]F_2	Ne + F_2	^{20}Ne(d,α)^{18}F	0.13
D	[^{18}F]F_2	[^{18}O]H_2O	^{18}O(p,n)^{18}F	55

Method D:



There are various methods for preparing [^{18}F]F_2 gas. One method exploits the ^{18}O(p,n)^{18}F nuclear reaction (Table 2, Method B);[20] proton bombardment of [^{18}O]oxygen gas in an aluminium target produces F-18 which deposits onto the target surface. F_2 gas carrier diluted with krypton gas is then introduced, and a second proton irradiation induces isotopic exchange with the deposited F-18 to afford [^{18}F]F_2 gas.[20] The required use of carrier F_2 gas results in a low molar activity of around 0.60 GBq µmol^{-1}. [^{18}F]F_2 gas can also be produced via the ^{20}Ne(d,α)^{18}F nuclear reaction, achieved by deuteron irradiation of a Nickel target containing a mixture of F_2 gas and neon gas (Table 2, Method C).[21] The use of carrier F_2 gas is required for recovery of the radioactivity, and results in low molar activity of up to 0.13 GBq µmol^{-1}.

An alternative method for producing [^{18}F]F_2 gas in high molar activity is via an isotopic exchange reaction between a very small quantity (150 nmol) of F_2 gas carrier and high molar activity [^{18}F]fluoromethane ([^{18}F]**1.1**) in an electrical discharge chamber (Table 2, Method D).[22] [^{18}F]**1.1** can be prepared with a molar activity of 2.5 ± 0.3 TBq µmol^{-1} by the reaction of [^{18}F]fluoride (produced in high molar activity via Method A) with iodomethane. The subsequent isotopic exchange affords [^{18}F]F_2 gas with a molar activity of up to 55 GBq µmol^{-1}. However, due to the specialised equipment required for this procedure, it has not been widely adopted. It is however used at the Turku PET Centre in Finland for the synthesis of radiotracers.[23] Solin and co-workers have since disclosed various refinements of the post-target production of [^{18}F]F_2 gas; vacuum ultraviolet photons generated by a commercially available excimer laser can be used in place of an electrical discharge for the isotopic exchange between [^{18}F]**1.1** and F_2.[24] This simplified setup may facilitate other PET centres to adopt this method for producing [^{18}F]F_2 gas. Solin and co-workers have also reported that SF_6 carrier gas can be used in place of highly reactive F_2 carrier gas. Applying a high voltage electric discharge to a mixture of [^{18}F]**1.1**, xenon gas and SF_6 gas resulted in formation [^{18}F]F_2, which could be used to prepare [^{18}F]FDOPA with a molar activity of up to 2.2 ± 0.5 GBq µmol^{-1} (n=5).[25]

1.2.4 Trapping, Elution, and Drying of [^{18}F]Fluoride

As discussed in Section 1.2.3, [^{18}F]fluoride is produced as a solution in [^{18}O]H_2O with an ill-defined counterion. Prior to use in radiosynthesis, the [^{18}F]fluoride is typically purified to remove impurities from production, to install the desired counterion, and to remove [^{18}O]H_2O to facilitate drying. This is typically achieved using an anion exchange cartridge composed of methylated quaternary ammonium groups bound to a solid support (QMA cartridge, Figure 4). Upon passing the target water through the QMA cartridge,

[^{18}F]fluoride exchanges with anions on the cartridge and is retained, while the [^{18}O]H_2O and non-ionic impurities pass through. [^{18}F]Fluoride is then eluted using a solution of a base, which is typically potassium carbonate in a mixture of acetonitrile and water. The carbonate anion exchanges with [^{18}F]fluoride, releasing [^{18}F]KF, which is then dried by heating under a flow of nitrogen gas. Typically, additional acetonitrile is added to azeotrope the water and thus expedite drying. Due to the poor solubility of [^{18}F]KF in organic solvents, Kryptofix-222 is typically added to the elution solution to bind the potassium cation for increased solubility.

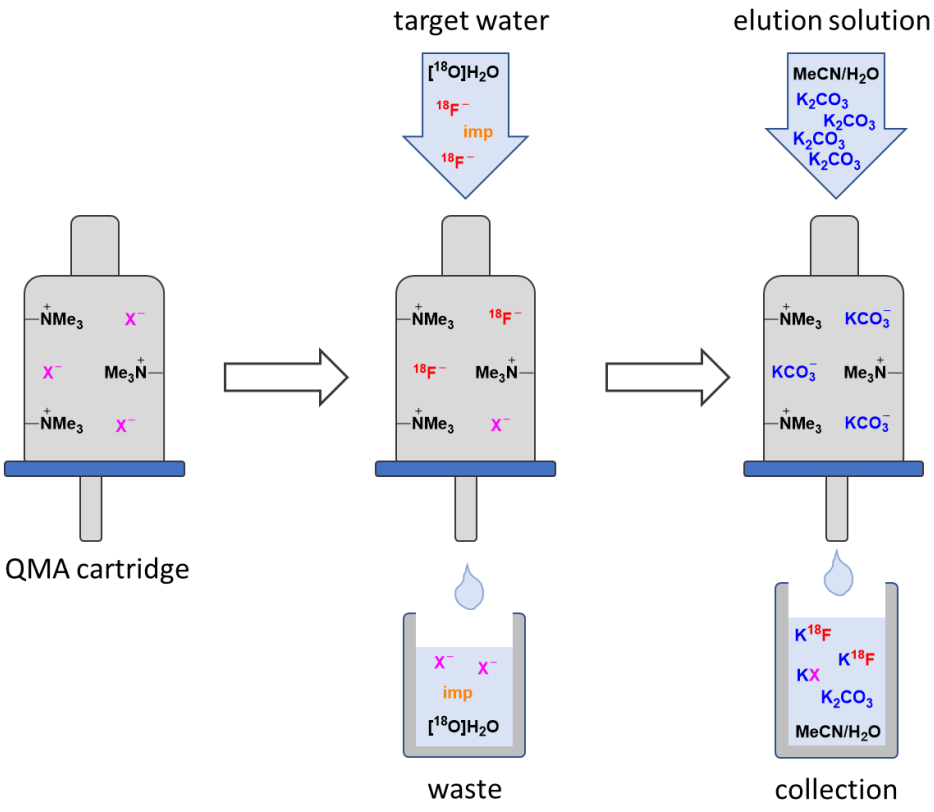


Figure 4: Purification of [^{18}F]fluoride using a quaternary methyl ammonium (QMA) cartridge. imp = impurity

There are various sources of impurities during the [^{18}F]fluoride purification process. Due to the nanomole to picomole quantity of [^{18}F]fluoride in the target water, only a small

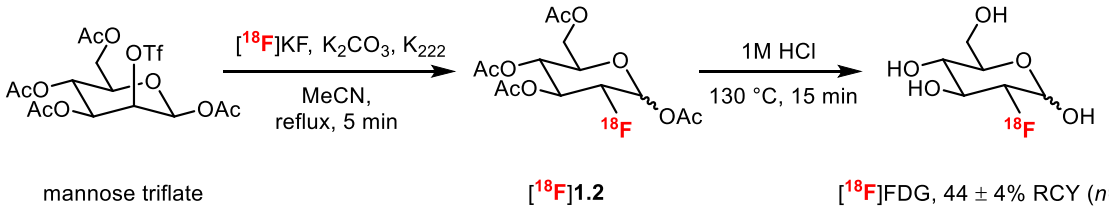
fraction of the anions originally on the QMA cartridge (Figure 4, X^-) are displaced by [^{18}F]fluoride, and therefore the remainder of these anions are eluted into the collection vial by the basic elution solution along with [^{18}F]fluoride. In addition, some of the base used in the elution solution will also pass through the cartridge. Both the base used to equilibrate the QMA cartridge, and the base in the elution solution can therefore have a large effect on the reactivity of the dry [^{18}F]fluoride, as can the presence of Kryptofix-222. Various elution protocols other than K_2CO_3/Kryptofix-222 have therefore been developed. Use of weaker bases than carbonate such as oxalate and bicarbonate is common for reactions which are base sensitive.[26] Alternatively, the Hayashi group have reported using small self-packed QMA columns enables [^{18}F]fluoride to be eluted with reduced quantities of K_2CO_3/Kryptofix-222.[27] Use of organic soluble bases such as tetraethylammonium bicarbonate is common and obviates the need for a phase transfer agent such as Kryptofix-222.[28,29] Organic bases including 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) have also been shown to efficiently elute [^{18}F]fluoride, and do not require use of a phase transfer agent.[30] Non-aqueous protocols for eluting [^{18}F]fluoride have been developed, obviating the need for repeated azeotropic drying cycles. This can be achieved by eluting [^{18}F]fluoride with solutions of tetraalkylammonium bases in alcohol solvents. The resulting [^{18}F]fluoride solutions can be used directly in radiofluorination reactions.[31,32] In Chapter 3, the effect of the elution protocol on the labelling of [^{18}F]xenon difluoride is discussed.

1.3 Reactions for Introducing Fluorine-18

1.3.1 Aliphatic ^{18}F-Fluorination using [^{18}F]Fluoride

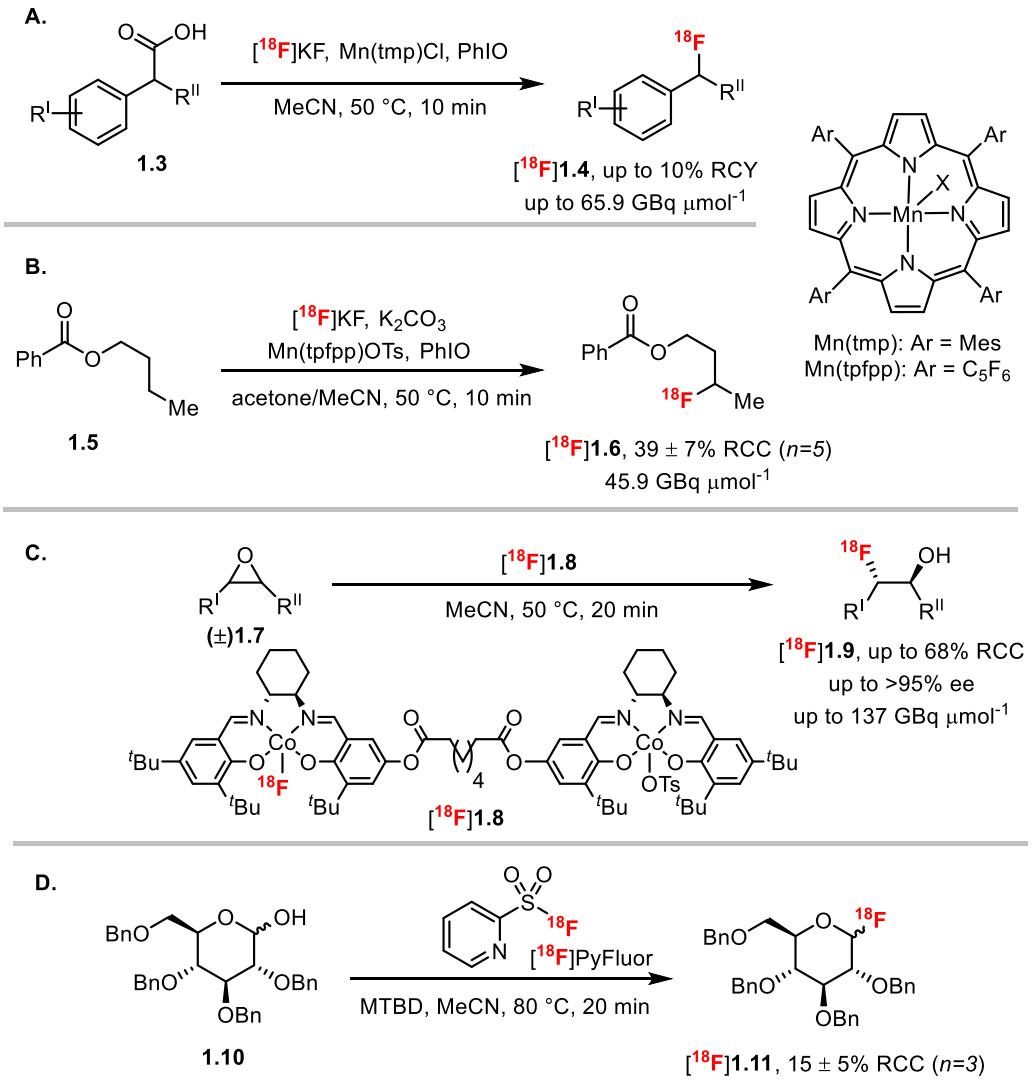
Formation of C(sp^3)–^{18}F bonds is typically achieved by nucleophilic substitution reactions between [^{18}F]fluoride and an aliphatic substrate bearing a suitable leaving group such as

triflate, mesylate, tosylate or a halide. This affords the ^{18}F-labelled product in high molar activity.[33] The reactivity of alkyl electrophiles towards nucleophilic substitution varies considerably between substrate classes with the order; primary benzylic > primary aliphatic >> secondary aliphatic.[26] These reactions can be sensitive to the [^{18}F]fluoride elution conditions, as the base can result in elimination rather than substitution. The most widely used PET radiotracer [^{18}F]FDG is synthesised via nucleophilic radiofluorination of mannose triflate to afford [^{18}F]**1.2**, followed by ester hydrolysis (Scheme 1).[34,35]



Scheme 1: Synthesis of [^{18}F]FDG via reaction of mannose triflate with [^{18}F]KF/K_{222}, reported by Hamacher, Coenen and Stocklin.[34]

More recent methods for C(sp^3)–^{18}F bond formation from [^{18}F]fluoride include manganese porphyrin-mediated ^{18}F-fluorodecarboxylation of phenylacetic acids **1.3** (Scheme 2A, see Chapter 4 for manganese porphyrin-mediated radiosynthesis of geminal-difluoroalkanes),[36] manganese porphyrin-mediated C–H ^{18}F-fluorination (Scheme 2B),[37] enantioselective synthesis of fluorohydrins [^{18}F]**1.9** by reaction of chiral cobalt fluoride [^{18}F]**1.8** with racemic epoxides (±)**1.7** (Scheme 2C),[38] and ^{18}F-deoxyfluorination of carbohydrate **1.10** using [^{18}F]PyFluor ((Scheme 2D).[39]



Scheme 2: A. Manganese porphyrin-mediated ^{18}F-fluorodecarboxylation, reported by the Groves group.[36] B. Manganese porphyrin-mediated C–H ^{18}F-fluorination, reported by the Groves group.[37] Cobalt-mediated enantioselective synthesis of ^{18}F-fluorohydrins, reported by the Doyle group.[38] ^{18}F-Deoxyfluorination using [^{18}F]PyFluor, reported by the Doyle Group.[39] MTBD = 7-methyl- 1,5,7-triazabicyclo[4.4.0]dec-5-ene.

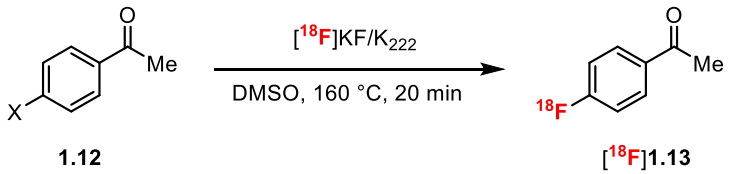
1.3.2 Aromatic ^{18}F-Fluorination using [^{18}F]Fluoride

1.3.2.1 Nucleophilic Aromatic Substitution

^{18}F-Labelling of aryl fluorides can be achieved via nucleophilic aromatic substitution (S_NAr) reactions with [^{18}F]fluoride. These reactions are carried out in polar aprotic solvents at high temperature.[40] The reactivity of different leaving groups in S_NAr has been measured for preparing [^{18}F]**1.13** (Table 3).[41] The following order was determined; iodide

< bromide < chloride < NMe_3 ~ NO_2. Nitro and trimethylammonium groups are most commonly employed in the synthesis of radiotracers.

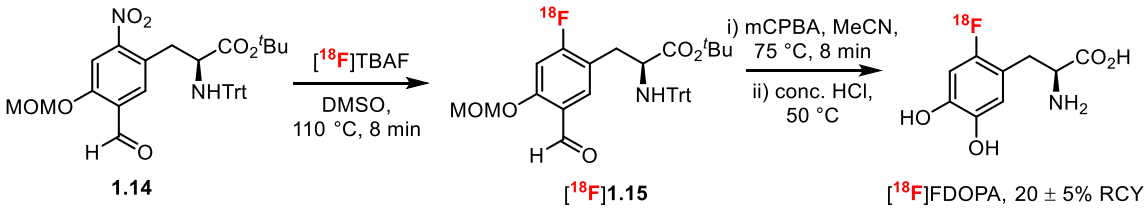
Table 3: Effect of leaving group on RCC in S_NAr with [^{18}F]fluoride, reported by the Hashizume group.[41]



1.12 [^{18}F]**1.13**

X	% RCC
I	2
Br	4
Cl	28
NMe_3^+ TfO^-	34
NO_2	34

A major limitation of radiofluorination via S_NAr is that only substrates with activating electron withdrawing groups ortho or para to the leaving group are reactive. Post-labelling functional group manipulations are therefore often required using this approach, for example in one synthesis of [^{18}F]FDOPA (Scheme 3).[42] The aldehyde substituent in **1.14** enables the S_NAr reaction, however the group ultimately has to be converted to a hydroxyl motif in the final product.

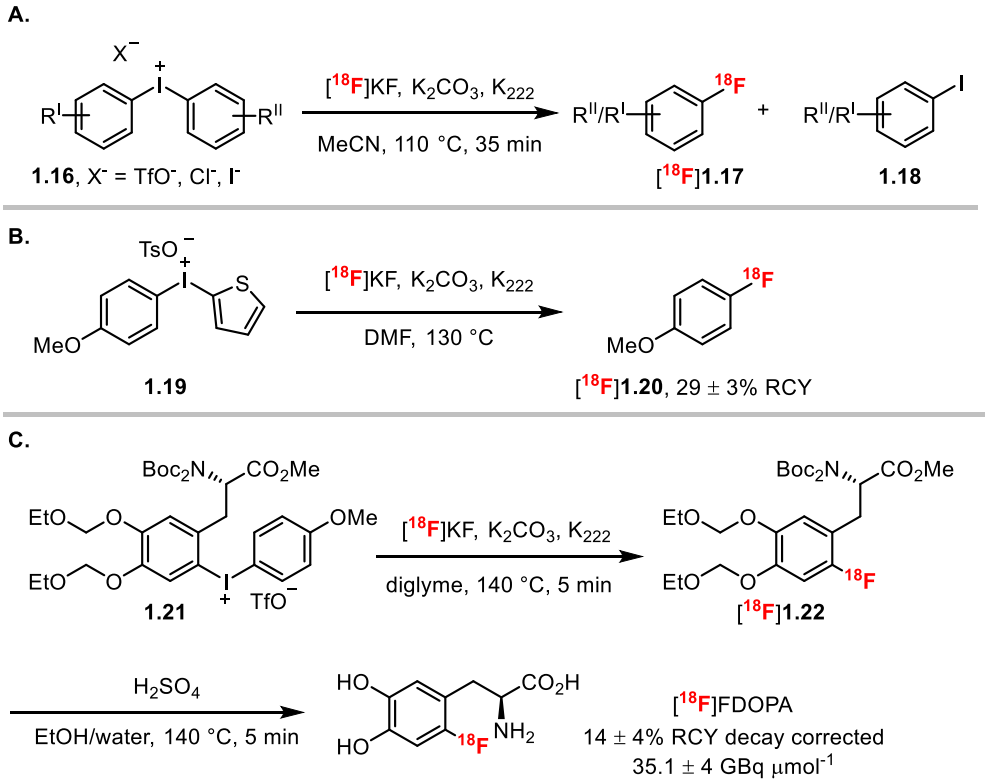


1.14 [^{18}F]**1.15** [^{18}F]FDOPA, 20 ± 5% RCY

Scheme 3: Synthesis of [^{18}F]FDOPA via nucleophilic aromatic substitution with [^{18}F]fluoride.[42] *MOM = methoxymethyl, Trt = trityl, TBAF = tetrabutylammonium fluoride, mCPBA = meta-chloroperoxybenzoic acid.*

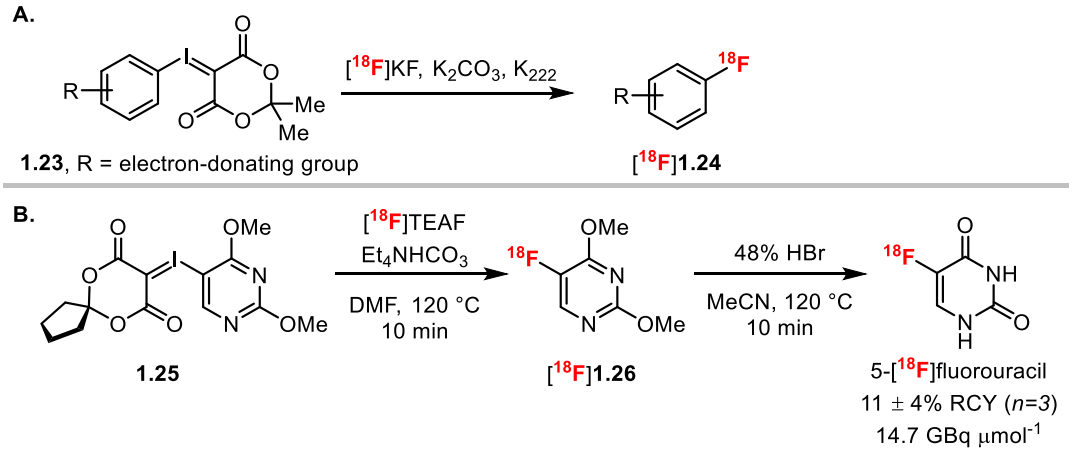
1.3.2.2 ^{18}F-Fluorination of Diaryliodonium Salts and Iodonium Ylides

This scope limitation of radiofluorination via S_NAr prompted the development of more general methods for preparing ^{18}F-labelled aryl fluorides. Pike and Aigbirhio showed that diaryliodonium salts **1.16** undergo reaction with [^{18}F]fluoride to afford ^{18}F-fluoroarenes [^{18}F]**1.17** and an iodoarene **1.18** by-product (Scheme 4A).[43] Using this method, electron rich and neutral ^{18}F-fluoroarenes can be prepared, which are not accessible via S_NAr. For non-symmetrical diaryliodoniums, mixtures of the two possible ^{18}F-fluoroarenes can be formed. ^{18}F-Fluorination generally occurs on the less electron rich ring.[40] Diaryliodoniums bearing a non-reactive by-standing arene such as 2-thiophene (**1.19**) have been developed to increase selectivity towards formation of the desired ^{18}F-fluoroarene (Scheme 4B).[44] The mechanism of the reaction has been proposed to proceed via [^{18}F]fluoride ligation to I(III) followed by intramolecular nucleophilic attack of fluoride at the aryl ipso carbon.[45] This method has been used in the preparation of various radiotracers, including [^{18}F]FDOPA (Scheme 4C).[46]



Scheme 4: A. Early work on the radiofluorination of diaryliodonium salts with [^{18}F]fluoride, reported by Pike and Aigbirhio.[43] B. Chemoselective radiofluorination of aryl 2-thienyl iodonium salts with [^{18}F]fluoride, reported by the Coenen group.[44] C. Application of a diaryliodonium salt in the synthesis of [^{18}F]DOPA, reported by Elsinga and co-workers.[46]

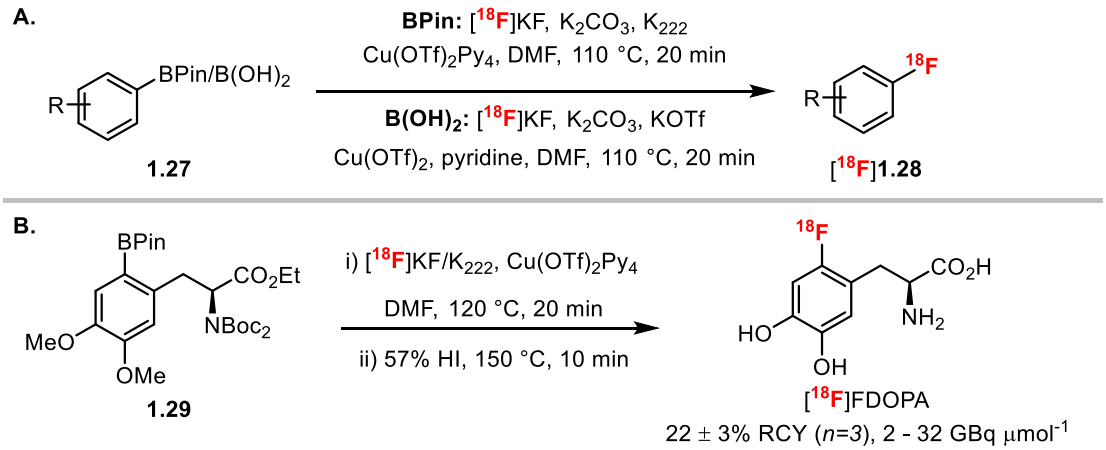
Satyamurthy and Barrio have shown that iodonium ylides **1.23** react with [^{18}F]fluoride to form ^{18}F-fluoroarenes [^{18}F]**1.24** (Scheme 5A).[47] Computational studies supported that iodonium ylides display high chemoselectivity for radiofluorination on the aromatic ring rather than on the dicarbonyl auxiliary, hence circumventing the regioselectivity challenges when using diaryliodonium salts.[48] Vasdev, Liang and co-workers showed that spirocyclic iodonium ylides (such as **1.25**) afforded higher RCYs than those derived from Meldrum's acid (**1.23**), and applied the reaction to the synthesis of radiopharmaceuticals including 5-[^{18}F]fluorouracil (Scheme 5B).[49]



*Scheme 5: A. Radiofluorination of Meldrum's acid derived iodonium ylides **1.23** with [^{18}F]fluoride, reported by Satyamurthy and Barrio.[47] Radiofluorination of spirocyclic iodonium ylides, reported by Vasdev, Liang and co-workers.[49] TEAF = tetraethylammonium fluoride.*

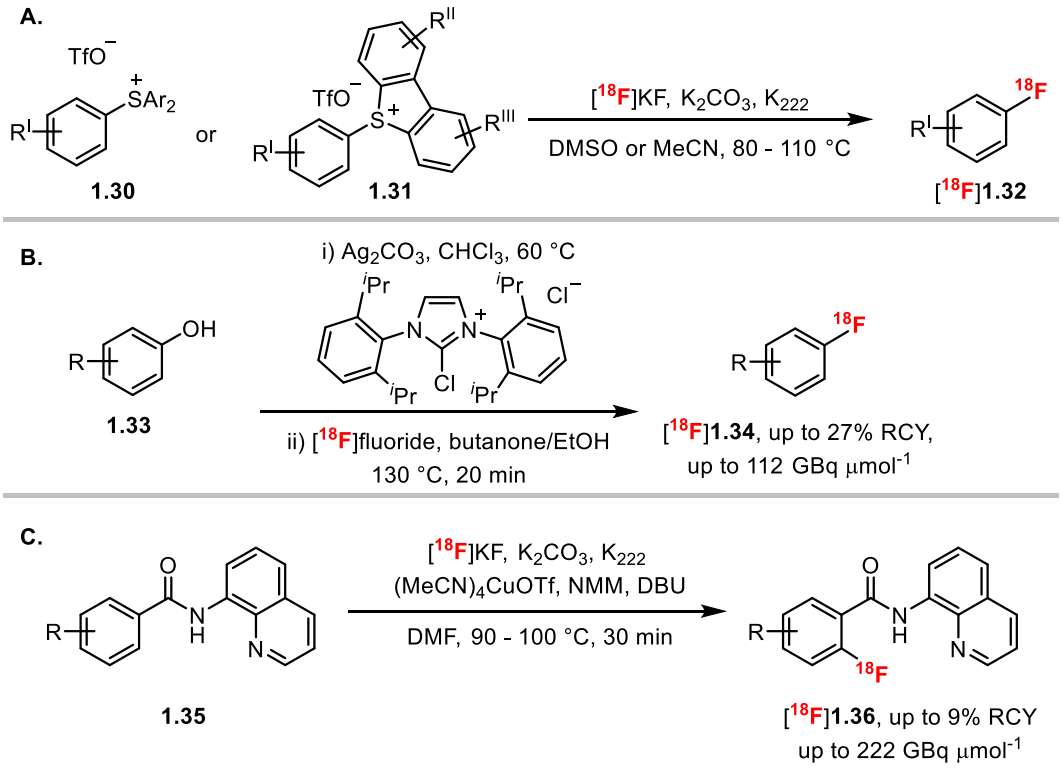
1.3.2.3 Copper-Mediated Radiofluorination of Aryl Boronic Acids / Esters

The Gouverneur have shown that aryl boronic esters **1.27** react with [^{18}F]fluoride in the presence of copper to afford the corresponding ^{18}F-fluoroarenes **1.28**.[50] A similar procedure from the Sanford group enables formation of ^{18}F-fluoroarenes from aryl boronic acids mediated by copper.[51] These procedures are particularly practical given the availability of aryl boronic acids / esters and the variety of methods for their preparation.[52,53] Similar to the I(III) chemistry described in Section 1.3.2.2, these radiofluorination methods enable direct synthesis of ^{18}F-fluoroarenes with diverse electronics, providing a route to products not accessible by simple nucleophilic aromatic substitution. This methodology has been applied in a streamlined synthesis of [^{18}F]FDOPA (Scheme 6).[54]



Scheme 6: A. Radiosynthesis of ^{18}F-fluoroarenes by copper-mediated reaction of [^{18}F]fluoride and aryl boronic esters and acids, reported independently by the Gouverneur group, and Sanford, Scott and co-workers.[50,51] B. Synthesis of [^{18}F]FDOPA from an aryl boronic ester precursor, reported by the Gouverneur group.[54]

Various other methods have been developed for aromatic ^{18}F-fluorinations using [^{18}F]fluoride, including S_NAr with triarylsulphonium **1.30** / dibenzothiophenium salts **1.31** (Scheme 7A),[55,56,57] ^{18}F-deoxyfluorination of phenols **1.33** (Scheme 7B),[58] and copper-mediated directed C–H ^{18}F-fluorination of aminoquinolinamides **1.35** (Scheme 7C).[59] Use of [^{18}F]Selectfluor for preparing an ^{18}F-labelled pyrazole via C–H fluorination is discussed in Chapter 3.

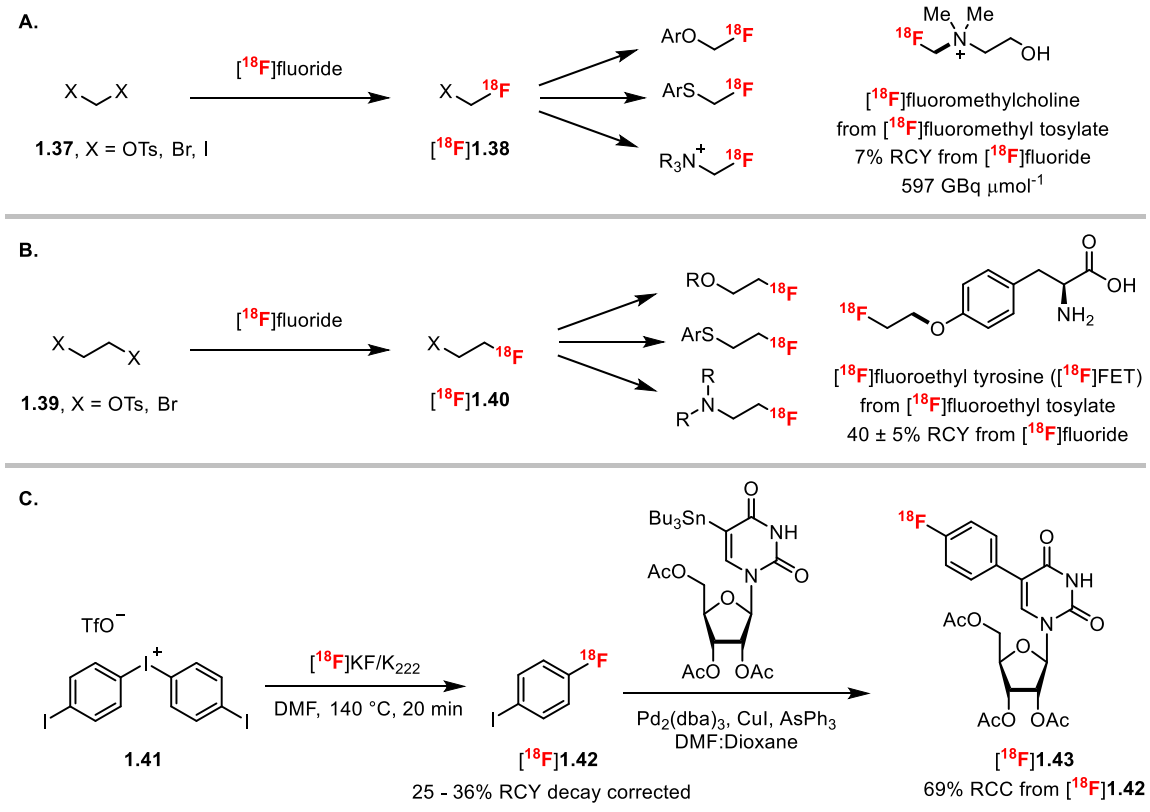


Scheme 7: A. ^{18}F-Fluorination of triarylsulphoniums / aryl dibenzothiopheniums.[55,56,57] B. ^{18}F-Deoxyfluorination of phenols, reported by the Ritter group.[58] C. Copper-mediated directed C–H radiofluorination, reported by the Sanford, Scott and co-workers.[59] NMM = N-methylmorpholine.

1.3.3 ^{18}F-Fluorination Using Building Blocks Prepared from [^{18}F]Fluoride

Hitherto, methods for direct installation of fluorine-18 into molecules of interest have been described. A complimentary approach is to first synthesise an ^{18}F-labelled building block or reagent, which can then be coupled to a molecule of interest. This approach can allow ^{18}F-labelling of molecules bearing sensitive functional groups that might not be compatible with the harsh conditions used for radiofluorinations with [^{18}F]fluoride. This approach is particularly useful for the labelling of sensitive biomolecules.[60] Common F-18 labelled reagents include the fluoromethylating agents **1.38** [^{18}F]fluoromethyl tosylate, [^{18}F]fluoromethyl bromide and [^{18}F]fluoromethyl iodide (Scheme 8A), and fluoroethylating agents **1.40** [^{18}F]fluoroethyl tosylate and [^{18}F]fluoroethyl bromide (Scheme 8B).[61] These reagents are prepared by nucleophilic radiofluorination of the corresponding difunctionalised precursors **1.37** and **1.39** respectively. They are used for

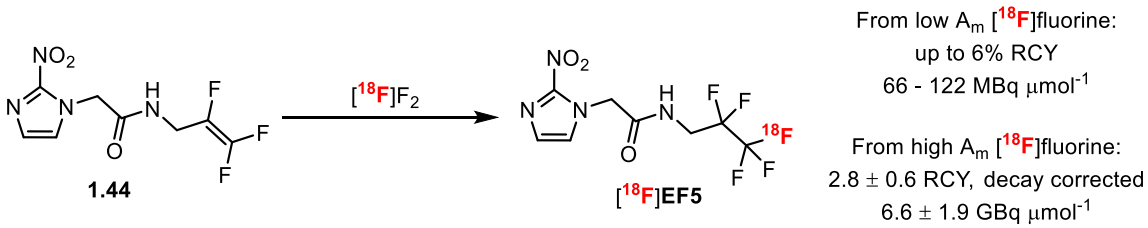
the ^{18}F-fluoroalkylation of phenols, thiophenols and amines. For example, [^{18}F]fluoromethylcholine can be prepared by alkylation of the corresponding tertiary amine with [^{18}F]fluoromethyl tosylate (Scheme 8A),[62] and [^{18}F]fluoroethyl tyrosine ([^{18}F]FET) can be prepared by alkylation of L-tyrosine with [^{18}F]fluoroethyl tosylate.[63] ^{18}F-Labelled building blocks can also be introduced via cross-coupling reactions,[64] for example [^{18}F]**1.42** can be coupled with stannanes using palladium as reported in the synthesis ^{18}F-labelled nucleoside [^{18}F]**1.43** (Scheme 8C).[65] Application of palladium-mediated C–O cross-coupling for reaction of aryl halides with [^{18}F]trifluoroethanol is discussed in Chapter 2.



*Scheme 8: A. Synthesis of ^{18}F-fluoromethylating reagents, and use in synthesis of [^{18}F]fluoromethylcholine.[62] B. Synthesis of ^{18}F-fluoroethylating reagents, and use in synthesis of [^{18}F]FET.[63] C. Synthesis of [^{18}F]**1.42** , and use in cross-coupling for ^{18}F-labelling of nucleoside [^{18}F]**1.43**, reported by Wüst and Kniess.[65]*

1.3.4 ^{18}F-Fluorination Using [^{18}F]F_2 Gas

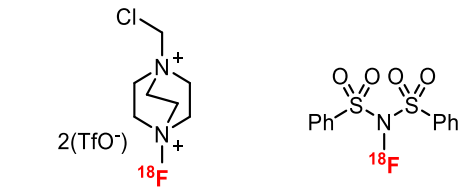
The majority of radiofluorinations are conducted using nucleophilic [^{18}F]fluoride, as it can be produced in high molar activity and is conveniently manipulated as a solution as discussed in Section 1.2.3. Indeed many radiotracers are designed specifically so they can be prepared easily from [^{18}F]fluoride.[66] In so doing, the structural diversity of radiotracers is reduced. There are fluorinated motifs that cannot be prepared from [^{18}F]fluoride. For example the radiotracer [^{18}F]EF5, used in the imaging of tumour hypoxia, is prepared by addition of [^{18}F]F_2 gas to **1.44**.[14] No method for preparing [^{18}F]EF5 via nucleophilic radiofluorination has been reported, highlighting the importance of electrophilic fluorinating agents in radiochemistry. Using [^{18}F]F_2 gas produced via the ^{20}Ne(d,α)^{18}F nuclear reaction, [^{18}F]EF5 was produced with a molar activity of 66 to 122 MBq μmol^{-1},[67] while using high molar activity [^{18}F]F_2 gas produced post-target, a molar activity of 6.6 GBq μmol^{-1} was measured.[68]



Scheme 9: Synthesis of [^{18}F]EF5, using low molar activity [^{18}F]F_2 gas,[67] and using high molar activity [^{18}F]F_2 gas.[68] A_m = molar activity.

Due to the highly reactive nature of F_2 gas, functional group tolerance and selectivity in reactions with F_2 are poor. Thus preparations of the reagents [^{18}F]Selectfluor[69] and [^{18}F]NFSI[70] have been developed to enable more controlled electrophilic radiofluorination (Figure 5). The huge number of F-19 fluorination methodologies developed using these reagents suggests great potential in F-18 radiochemistry. These

reagents provide the opportunity to access radiochemical space not attainable via nucleophilic radiofluorination. However, widespread use of these reagents has been hampered by the required use of $[^{18}F]F_2$ for their synthesis. In Chapter 3, a more comprehensive discussion on electrophilic ^{18}F-fluorination is presented, followed by research on the synthesis of [^{18}F]Selectfluor from [^{18}F]fluoride.



[^{18}F]Selectfluor bis(triflate) [^{18}F]NFSI

Figure 5: ^{18}F-Labelled electrophilic fluorinating agents [^{18}F]Selectfluor and [^{18}F]NFSI.

1.4 Outlook and Work in This Thesis

Enormous progress has been made in developing methodologies for radiofluorination as summarised in this chapter. Yet still the variety of methods used in F-18 radiochemistry are narrow, and composed largely of nucleophilic aliphatic fluorinations and fluorinations of functionalised aromatic precursors. Relying on these methods limits diversity in radiotracer design. This thesis discusses research on development of new methodologies for introducing F-18 labels. In Chapter 2, work is presented on developing C–O cross-coupling of aryl halides with fluorinated alcohols. Translation of the procedure to enable introduction of [^{18}F]trifluoroethanol is then presented. To the best of our knowledge, C-O cross-coupling for introducing F-18 labels has not been explored previously. This methodology enables ^{18}F-labelling of widely available aryl bromides. In Chapter 3, the labelling of [^{18}F]Selectfluor bis(triflate) from [^{18}F]fluoride is presented. While [^{18}F]Selectfluor has been labelled previously, the required use of $[^{18}F]F_2$ limited

adoption of the method by the radiochemical community. Application of [^{18}F]Selectfluor for the C–H radiofluorination of the pyrazole ring of celecoxib is also discussed. In Chapter 4, preliminary results on preparing ^{18}F-labelled geminal-difluoroalkanes via ^{18}F-fluorodecarboxylation are presented. Radiosynthesis of polyfluorinated alkyl motifs is underexplored despite the prevalence of these motifs in drug molecules.

Chapter 2

Palladium-Catalysed C–O Cross-Coupling and Applications in ^{18}F-Radiochemistry

This chapter first introduces the applications of fluorinated alkyl aryl ethers, and then presents reported methods to prepare these motifs. The optimisation and scope of a palladium-catalysed C–O cross-coupling between aryl halides and fluorinated alcohols to prepare fluorinated alkyl aryl ethers is discussed. Application of the reaction in ^{18}F-radiochemistry is also presented, including a novel radiosynthesis of [^{18}F]trifluoroethanol, and subsequent palladium-mediated cross-coupling with aryl halides. The work presented in this chapter is published; Szpera, R.; Isenegger, P. G.; Ghosez, M.; Straathof, N. J. W.; Cookson, R.; Blakemore, D. C.; Richardson, P.; Gouverneur, V. Synthesis of Fluorinated Alkyl Aryl Ethers by Palladium-Catalyzed C–O Cross-Coupling. *Org. Lett.* **2020**, *22* (16), 6573–6577. All experiments in Section 2.3 were conducted by R. Szpera, apart from the synthesis, isolation, and characterisation of substrates **2.56B** (quinoxaline) and **2.57B** (quinoline), which was conducted by M. Ghosez. All non-radioactive experiments in Section 2.4 were conducted by R. Szpera. Dr. P. Isenegger made one batch of **2.82** (menthol trifluoroacetate), and R. Szpera made a second batch. All ^{18}F-labelling experiments were conducted by R. Szpera and Dr. P. G. Isenegger. Dr. N. Straathof, Dr. F. Guibbal and Dr. J. Sap assisted with some of the ^{18}F-labelling experiments.

2.1 Introduction

2.1.1 Fluorinated Alkyl Aryl Ethers

Fluorinated alkyl aryl ethers are prevalent in medicinal chemistry and in agrochemistry due to fluorine's ability to modulate molecular properties such as metabolic stability and lipophilicity.[71] While the most common of these motifs are trifluoromethyl and difluoromethyl ethers which have been the subject of intense research interest,[72,73,74] other fluorinated alkyl aryl ethers are also encountered in industrially relevant molecules

(Figure 6). The 2,2,2-trifluoroethyl ether unit is found in the multibillion-dollar proton pump inhibitor lansoprazole, in the benign prostate hyperplasia treatment silodosin, and in the antiarrhythmic flecainide, amongst other drugs. The 2,2,-difluoroethyl ether unit is found in penoxsulam, the most sold rice herbicide in the world. Various other fluorinated alkyl aryl ethers are encountered in drugs such as the 2,2,3,3-tetrafluoropropyl ether motif in the experimental Alzheimer's drug idalopirdine. The presence of fluorine in these motifs presents the opportunity for ^{18}F-radiolabelling and PET imaging. [^{18}F]Lansoprazole and [^{18}F]*N*-methyl lansoprazole ([^{18}F]NML) have been used as Tau imaging agents in PET.[75,76] The ^{18}F-fluoroethyl ether unit is also widely encountered in PET radiotracers, such as in [^{18}F]fluoroethyl tyrosine ([^{18}F]FET) used in tumour detection, and in [^{18}F]FEPPA, a translocator protein (TSPO) ligand.[61,77]

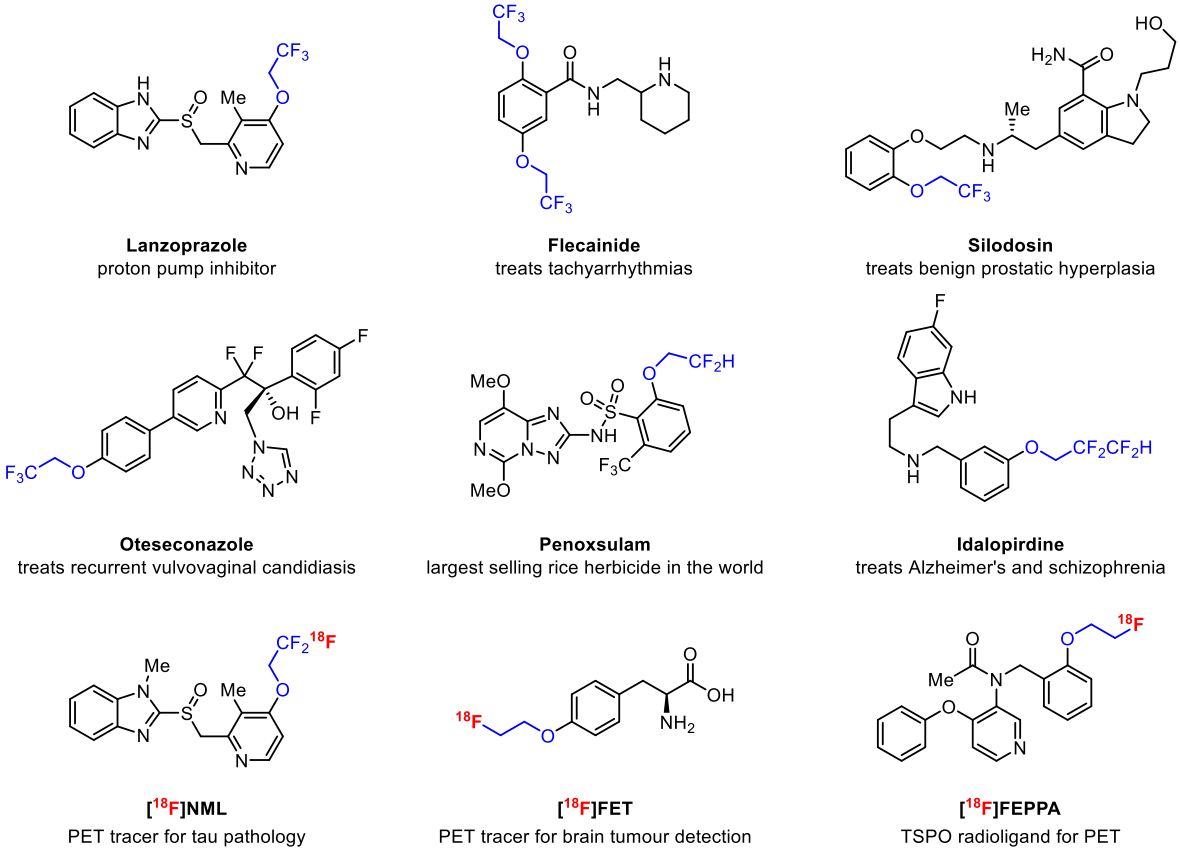
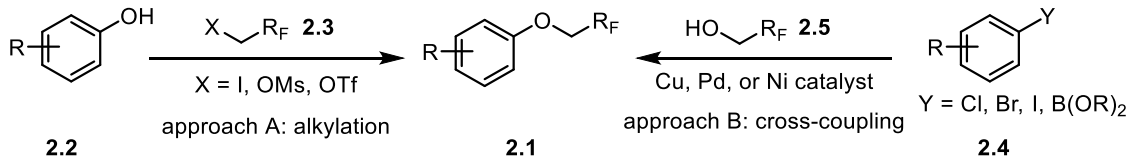


Figure 6: Fluorinated alkyl aryl ethers in medicinal chemistry and agrochemistry.

2.1.2 Overview of Methods for Preparing Fluorinated Alkyl Aryl Ethers

Various methods have been developed for the synthesis of fluorinated alkyl aryl ethers **2.1**. Two common approaches are reaction of phenols/phenolates **2.2** with fluoroalkyl sulphonates/iodides **2.3** (approach A, Scheme 10),[78,79] and metal-catalysed cross-coupling of aryl halides/boronic acids/boronic esters **2.4** with fluorinated alcohols **2.5** (approach B, Scheme 10). Alkylation reactions avoid the use of expensive metals however require stoichiometric quantities of toxic alkylating reagents which are often made from the fluorinated alcohols (in the case of fluoroalkyl mesylates/triflates). In cross-coupling reactions the alcohol can be used directly. The presence of fluorine is detrimental to both these approaches; S_N2 reactivity at carbon beta to fluorine is reduced, and so harsh conditions (e.g. 140 °C in hexamethylphosphorous triamide, HMPT)[79] are required in alkylation approach, while fluorine reduces the nucleophilicity of alcohols which can make cross-couplings challenging (see Section 2.3.3).



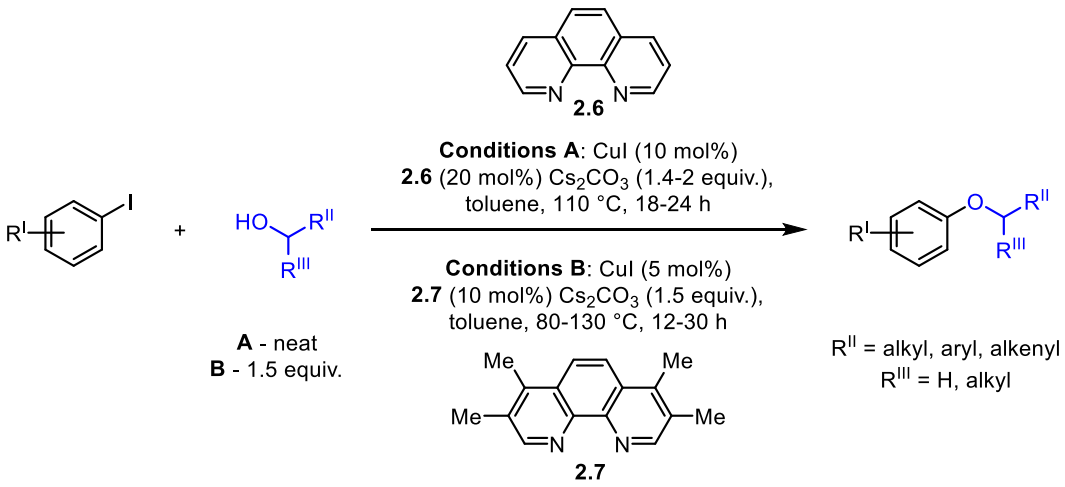
Scheme 10: Approaches for fluorinated alkyl aryl ether synthesis

C–O cross-coupling of aryl halides and alcohols (including fluorinated alcohols) has been reported under copper and palladium catalysis. While copper is cheaper, lower catalyst loadings and milder conditions are used in palladium-catalysed approaches as a result of significant ligand development.[80] Most copper-catalysed procedures require a large excess of the fluorinated alcohol or dry conditions and would therefore be difficult to translate for ^{18}F-radiolabelling. Nickel catalysis has also been exploited for C–O cross-coupling, however due to challenges with C–O reductive elimination from nickel(II), the

scope is currently limited to activated electron-poor aryl halides.[81,82] An overview of copper and palladium catalysed C–O cross-coupling is presented below.

2.1.3 Copper-Mediated C–O Cross-Coupling with Fluorinated Alcohols

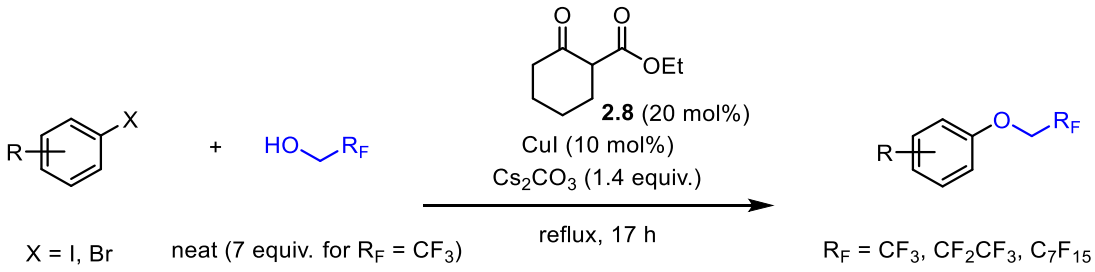
Early work on copper-catalysed C–O cross-coupling was conducted in the Buchwald group. Aryl iodides could be coupled with alcohols used in large excess and neat in the presence of 10 mol% copper iodide and 20 mol% 1,10-phenanthroline **2.6** (Conditions A, Scheme 11).[83] Subsequently the same group reported that the related ligand 3,4,7,8-tetramethyl-1,10-phenanthroline **2.7** alleviates the necessity of using excess neat alcohol for coupling with aryl iodides (Conditions B, Scheme 11). The beneficial effect of the methyl substituents was attributed to the increased solubility of the copper-ligand complex in toluene, and/or the increased sigma-donating ability of the nitrogens. However, aryl bromides still could not be cross-coupled without a large excess of alcohol.[84] No coupling with fluorinated alcohols was reported.



Scheme 11: Early work on copper-catalysed C–O cross-coupling with aryl iodides, enabled by 1,10-phenanthroline ligands, reported by the Buchwald group.[83,84]

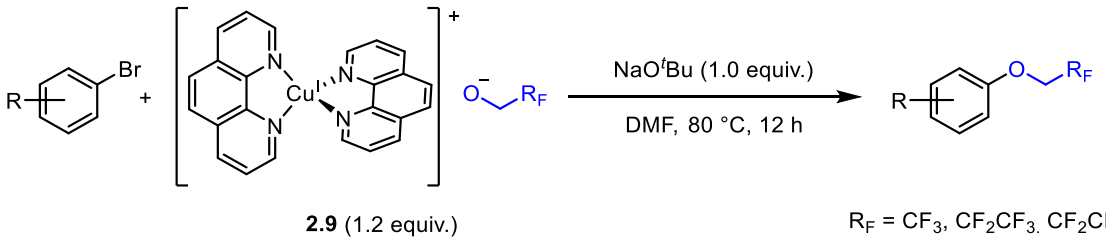
Legros and Crouse reported copper-catalysed coupling of fluorinated alcohols with aryl iodides and bromides. β-keto ester **2.8** was a more effective ligand for this purpose

(Scheme 12).[85] Both electron-rich and poor aryl iodides and bromides with various substitution patterns are compatible, however this method still required the use of neat alcohol.



Scheme 12: Copper-catalysed coupling of aryl iodides and bromides with fluorinated alcohols, reported by Legros, Crousse, and co-workers.[85]

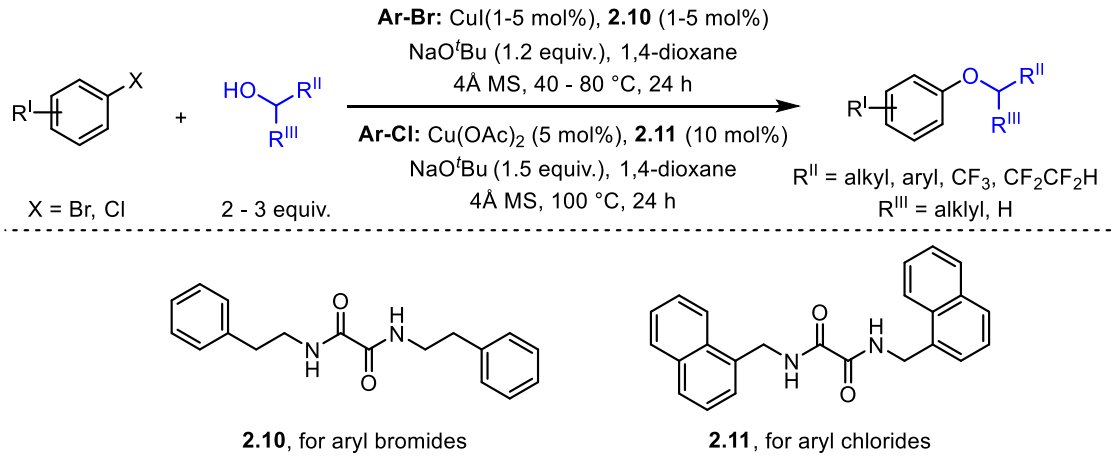
Reaction of stoichiometric 1,10-phenanthroline ligated copper(I) fluoroalkoxide complexes **2.9** with (hetero)aryl bromides has been reported by the Weng group (Scheme 13).[86] This approach enables coupling with a much broader range of (hetero)aryl bromides than the methods previously discussed. This method can be used for introducing various fluorinated alkyl ether motifs including 2,2,2-trifluoroethyl and 2,2,3,3,3-pentafluoropropyl. However, stoichiometric use of copper reagents **2.9**, which requires synthesis and storage at -30 °C, limit the practicality of the approach.



Scheme 13: Reaction of copper(I) fluoroalkoxide complexes with (hetero)aryl bromides, reported by the Weng group.[86]

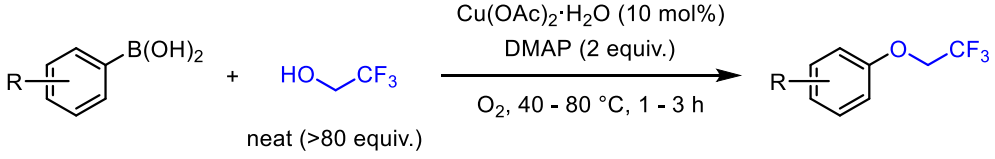
A significant advance in copper-catalysed C–O cross-coupling was reported by the Ma group, who found oxalic diamide ligands **2.10** and **2.11** enabled alcohols to be coupled

with aryl bromides and chlorides without requiring the alcohol to be used neat (Scheme 14).[87] Previous work in the same group had shown that oxalic diamides are excellent ligands in copper-catalysed arylations of other nucleophiles such as amines.[88] The Ma group demonstrated their C–O coupling method was compatible with the fluorinated alcohols 2,2,2-trifluoroethanol and 2,2,3,3-tetrafluoropropanol. The method does however still use multiple equivalents of alcohol. Whether the reaction functions in short durations applicable for F-18 radiochemistry was not investigated.



Scheme 14: Copper-catalysed C–O cross-coupling without use of neat alcohol, enabled by oxalic diamide ligands, reported by the Ma Group.[87]

The Chan-Lam coupling of (hetero)aryl boronic acids with 2,2,2-trifluoroethanol, under copper catalysis has been reported.[89,90] While the scope of (hetero)aryl boronic acids is broad, the reaction requires the use of neat 2,2,2-trifluoroethanol (>80 equivalents, Scheme 15).

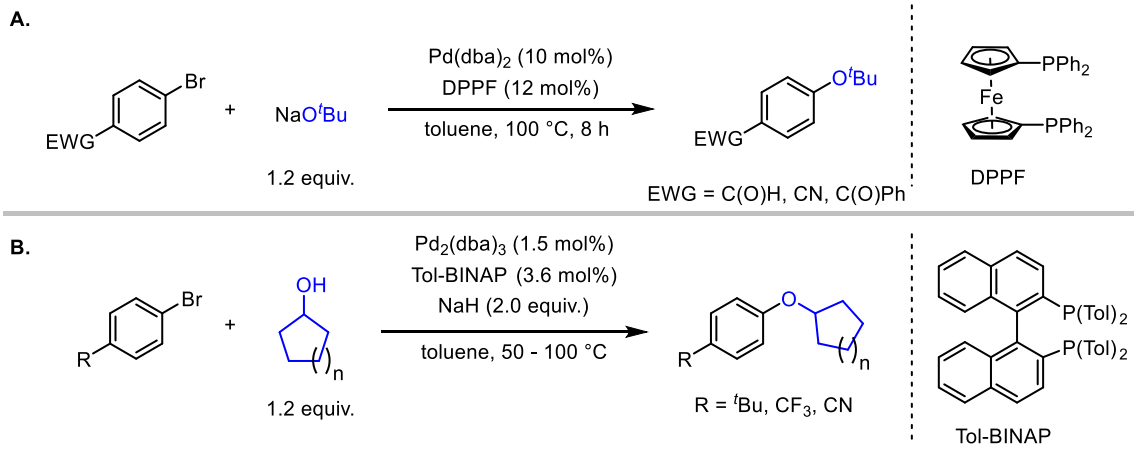


Scheme 15: Chan-Lam coupling of (hetero)aryl boronic acids with 2,2,2-trifluoroethanol, reported by Wu and co-workers.[89]

2.1.4 Palladium-Catalysed C–O Cross-Coupling: Bidentate Phosphine Ligands

Palladium-catalysed C–O cross-coupling has been used extensively for aryl ether synthesis, with modern methods exhibiting broad reaction scopes. Before discussing application in coupling with fluorinated alcohols, a brief overview of the development of palladium-catalysed C–O cross-coupling is presented.

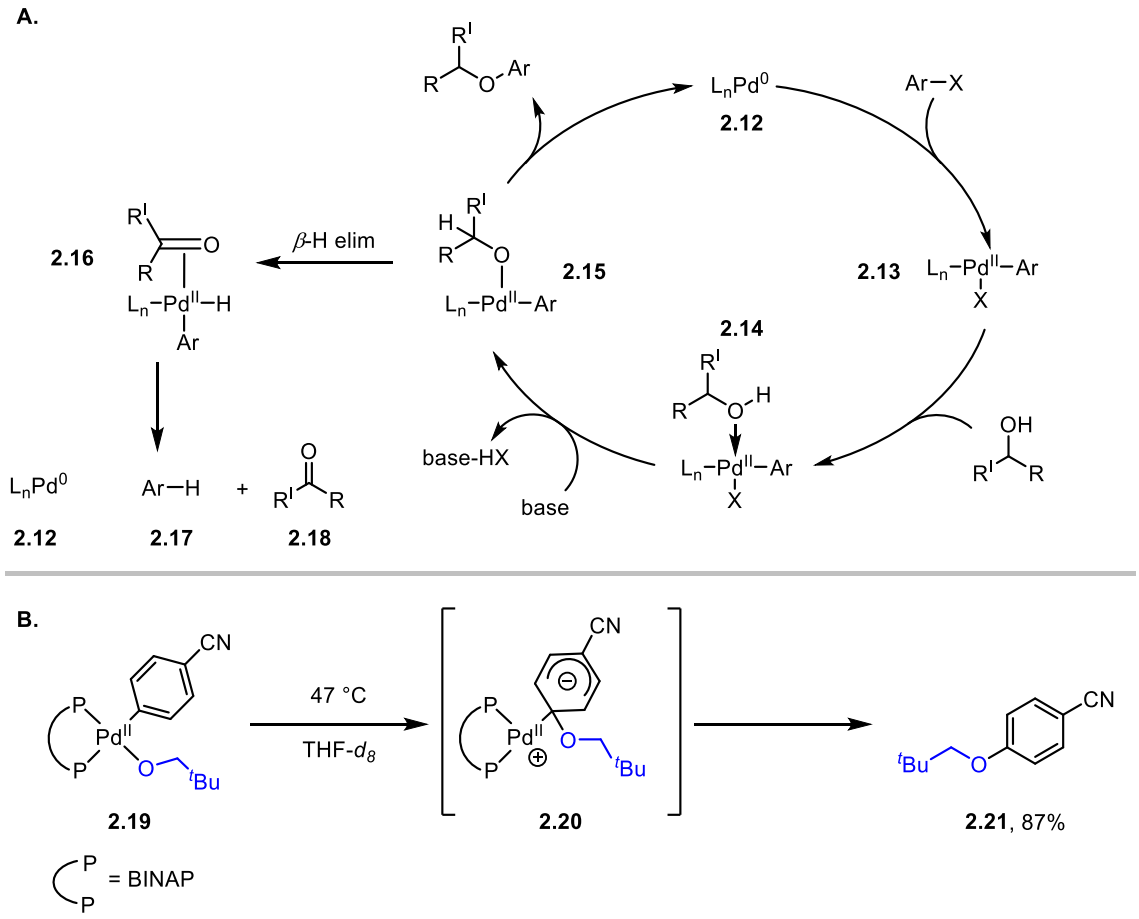
Early work on palladium catalysed C–O cross-coupling of alcohols and phenols with aryl halides was conducted in the Buchwald and Hartwig groups.[91,92,93,94] This research was facilitated by concurrent developments in palladium-catalysed C–N cross-coupling within the same groups.[95,96,97] The key innovations came in ligand design, which over time resulted in highly general cross-coupling methods. Bidentate phosphines were the first class of ligands reported for C–O cross-coupling. The Hartwig group reported a palladium-catalysed cross-coupling of electron-deficient aryl bromides and sodium *tert*-butoxide using 1,1′-bis(diphenylphosphino)ferrocene (DPPF, Scheme 16A).[91] The Buchwald group then reported that (*S*)-(-)-2,2′-bis(di-*p*-tolylphosphino)-1,1′-binaphthyl (Tol-BINAP) enabled C–O cross-coupling of aryl bromides with tertiary alcohols and secondary cycloalkanols (Scheme 16B).[94]



Scheme 16: A. Palladium catalysed intermolecular C–O cross-coupling of electron-poor aryl bromides with sodium tert-butoxide reported by the Hartwig group.[91] B. Palladium catalysed

intermolecular C–O cross-coupling of aryl bromides with alcohols reported by the Buchwald group.[94]

Studies in the Buchwald group suggested a mechanism whereby C–O bond formation occurs via C–O reductive elimination from a palladium(II) (aryl)alkoxide complex **2.15** (Scheme 17A).[93,98] This complex forms by oxidative addition of the aryl halide to LPd(0) **2.12**, followed by alcohol coordination and deprotonation. A competing pathway of β-hydride elimination from palladium alkoxide **2.15** can occur, affording the palladium(II) hydride **2.16**, which can then undergo C–H reductive elimination to afford the protodehalogenated arene **2.17** and aldehyde/ketone **2.18**. This competing pathway limited the substrate scope of methods using DPPF and Tol-BINAP to tertiary alcohols/alkoxides which cannot undergo β-hydride elimination such as *tert*-butoxide (Scheme 16A), or secondary alcohols for which β-hydride elimination is slow such as cycloalkanols (Scheme 16B). In addition, only aryl halides with electron-withdrawing groups undergo cross-coupling. This is because C–O reductive elimination from **2.19** proceeds via a nucleophilic attack of the palladium bound alkoxide at the ipso-carbon of the palladium bound aryl group, resulting in a build-up of negative charge on the aromatic ring in the intermediate/transition state **2.20** (Scheme 17B). [93,98] These limitations in aryl halide and alcohol scope prompted development of new ligands to enable more general C–O cross-coupling.

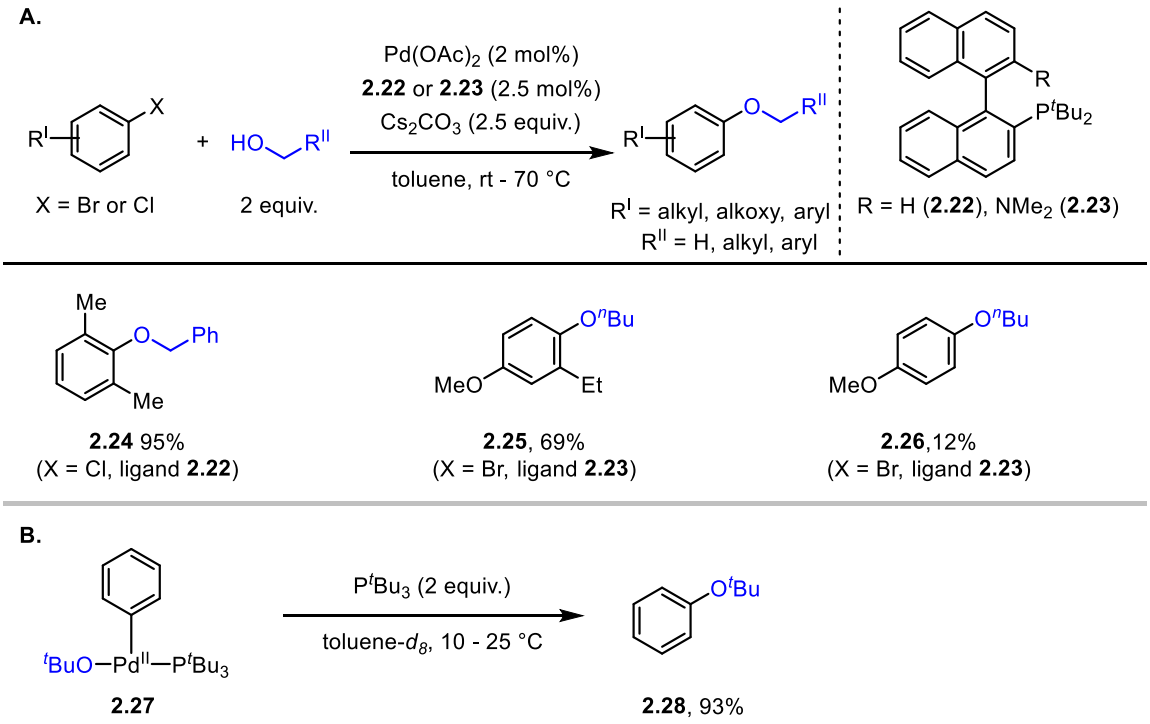


Scheme 17: A. General mechanism for palladium-catalysed C–O cross-coupling.[99] B. Mechanism of thermal C–O reductive elimination from palladium(aryl)alkoxides, reported by the Buchwald group.[93,98]

2.1.5 Palladium-Catalysed C–O Cross-Coupling: Bulky Monophosphine Ligands

The scope of cross-coupling between aryl halides and alcohols was significantly expanded by use of monophosphine ligands with bulky substituents at phosphorus. The Buchwald group reported use of dialkylbiaryl monophosphine ligands **2.22** and **2.23**, which enabled coupling with primary alcohols for the first time, and also enabled use of aryl halides without electron-withdrawing groups (**2.24** and **2.25**, Scheme 18A).[99] Mechanistic work in the Hartwig group showed that when using bulky monophosphine ligands, C–O reductive elimination occurs from a three coordinate T-shaped palladium alkoxide complex **2.27** (Scheme 18B).[100] This C–O reductive elimination is faster than that from four coordinate bisphosphine ligated palladium complexes such as **2.19** (Scheme 17B),

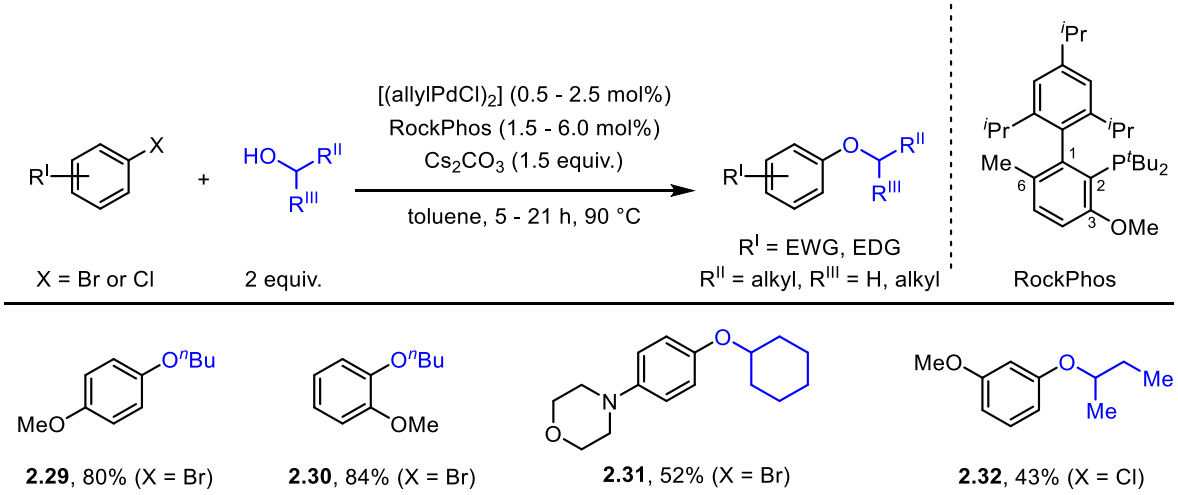
and so more challenging substrates could be coupled. However, using ligand **2.22** or **2.23** the scope was still limited in that only electron-rich or neutral aryl halides with ortho-substitution afforded good yields (**2.24** and **2.25** vs **2.26**). Ortho-substitution enhances the rate of C–O reductive elimination relative to β-hydride elimination. In addition, secondary alcohols could not be coupled.



Scheme 18: A. C–O cross-coupling of primary alcohols enabled by use of bulky monophosphine ligands, reported the by Buchwald group.[99] B. C–O reductive elimination from a T-shaped palladium complex ligated by a bulky monophosphine, reported by the Hartwig group.[100]

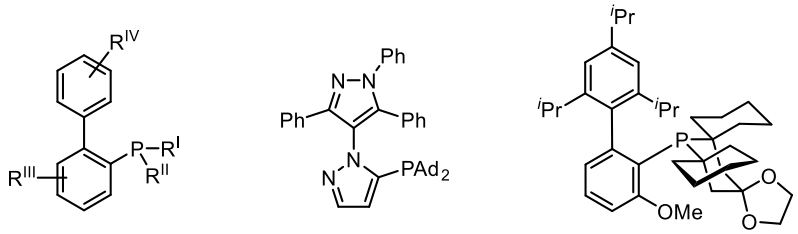
Subsequently, the Buchwald group reported the first highly general palladium catalysed C–O cross-coupling, in which the ligand RockPhos enabled intermolecular cross-coupling of primary alcohols (**2.29** and **2.30**, Scheme 19) and both cyclic and acyclic secondary alcohols (**2.31** and **2.32**).[101] Diverse aryl halides were tolerated, including electron-rich substrates without ortho-substitution (**2.29** and **2.32**). The substituents at the 3- and 6-

positions of RockPhos induce conformational rigidity in its palladium complexes, which in turn facilitates C–O reductive elimination.



Scheme 19: Highly general palladium-catalysed C–O cross-coupling with primary and secondary alcohols using RockPhos, reported by the Buchwald group.[101] EWG = electron-withdrawing group, EDG = electron-donating group.

The efficiency of Buchwald's dialkylbiaryl ligands inspired the development of related ligands (Figure 7). The Beller group reported the dialkylheteroaryl phosphine ligand Ad-BippyPhos for coupling of aryl halides with primary alcohols and methanol.[102,103] The Shekhar group have reported biaryl phosphorinane ligands for palladium-catalysed C–O and C–N cross-coupling.[104] In these ligands, instead of having two separate alkyl substituents at phosphine, the phosphine is incorporated into a phosphorinane ring. The synthesis of these ligands does not require the use of copper, a known contaminant in dialkylbiaryl phosphines. In addition, ligands **2.33** outperformed Buchwald ligands in selected benchmarking cross-coupling reactions.



Buchwald ligands
R^{I} = alkyl, R^{II} = alkyl
R^{III} = alkyl or alkoxy
R^{IV} = alkyl

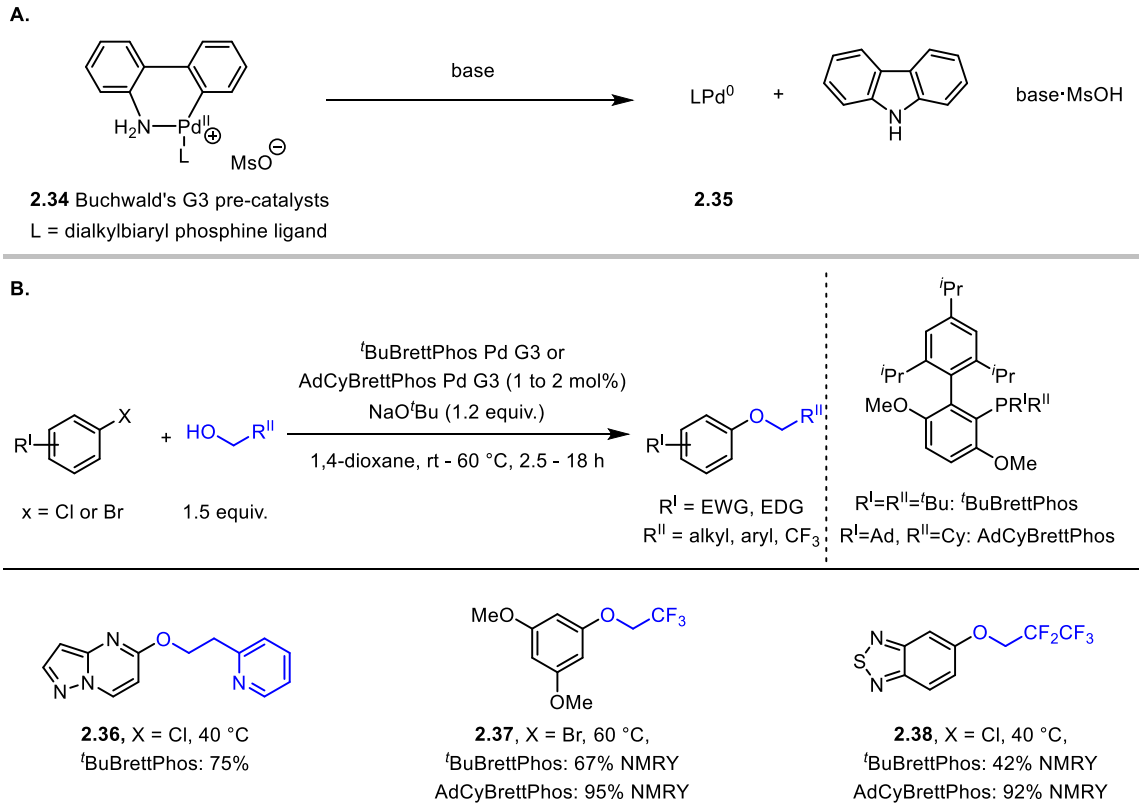
Ad-BippyPhos

2.33

Figure 7: Other ligands used in palladium-catalysed C–O cross-coupling. [102,103,104]

2.1.6 Palladium-Catalysed C–O Cross-Coupling: Buchwald Pre-catalysts

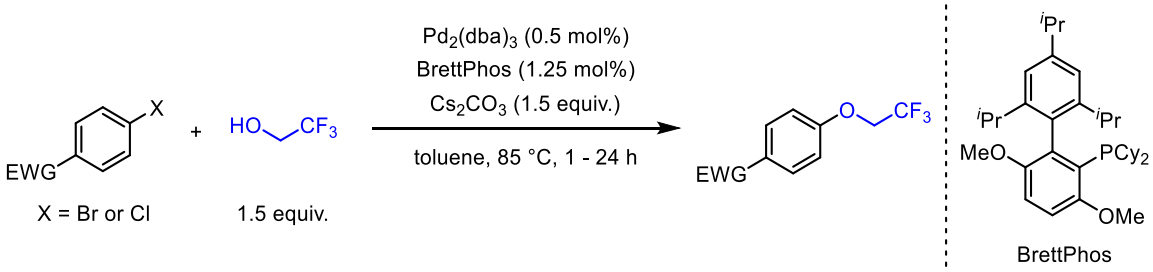
Formation of catalytically active Pd(0)-ligand complexes from Buchwald's dialkylbiaryl phosphine ligands can be inefficient. The Buchwald group have therefore developed a series of air and moisture stable Pd(II) precatalysts, that form the active Pd(0)-ligand complexes in situ upon base-induced C–N reductive elimination (Scheme 20A).[105] These precatalysts also increase operational simplicity, as a single reagent is added rather than the ligand and palladium source separately. Buchwald and co-workers have reported that the generation three precatalysts (G3) derived from ^{t}BuBrettPhos and AdCyBrettPhos enabled coupling of a wide range of electron-rich and poor aryl halides with primary alcohols (Scheme 20B).[106] Two examples with fluorinated aliphatic alcohols were disclosed (**2.37** and **2.38**). The authors reported that for these more challenging coupling partners, AdCyBrettPhos Pd G3 gave superior yields to ^{t}BuBrettPhos Pd G3. Recently, the Buchwald group reported that AdCyBrettPhos Pd G3 also efficiently couples secondary alcohols with diverse aryl halides.[107]



Scheme 20: A. Activation of Buchwald's G3 precatalysts.[105] B. Buchwald's G3 precatalysts in C–O cross-coupling.[106] EWG = electron-withdrawing group, EDG = electron-donating group. NMRY = NMR yield.

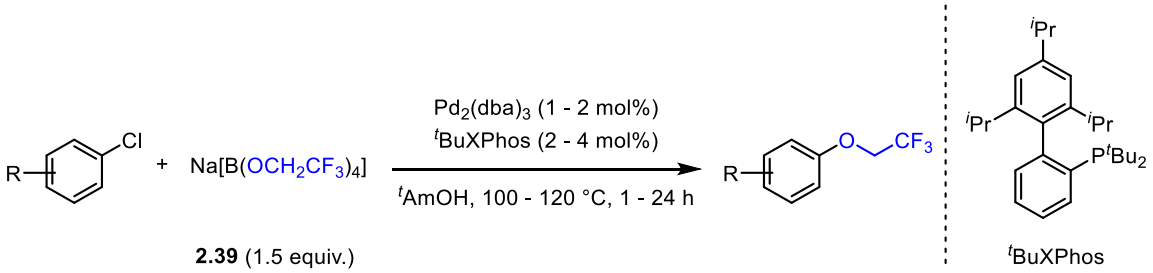
2.1.7 Palladium-Catalysed C–O Cross-Coupling with Fluorinated Alcohols

Various methods have been developed specifically focused on the introduction of fluorinated alcohols by palladium-catalysed C–O cross-coupling. The Singh group have reported the palladium-catalysed cross-coupling of aryl bromides and chlorides with 2,2,2-trifluoroethanol using the ligand BrettPhos (Scheme 21),[108] and subsequently also with ^{t}BuXPhos and JohnPhos.[109] However, in each case the scope was limited to aryl halides bearing para electron-withdrawing groups.



Scheme 21: Palladium-catalysed cross-coupling of aryl halides with 2,2,2-trifluoroethanol using BrettPhos as ligand, reported by the Singh group.[108]

The Novák group have reported palladium-catalysed cross-coupling of (hetero)aryl chlorides with sodium tetrakis(2,2,2-trifluoroethoxy)borate **2.39** as a trifluoroethoxy source (Scheme 22).[110] Examples with both electron-poor and rich aryl chlorides are provided, in addition to a range of activated and non-activated heteroaryl chlorides. Use of the borate salt reagent rather than the parent alcohol enables the coupling to proceed in the absence of additional base, however is disadvantageous in that the reagent needs to be prepared, and requires multiple equivalents of the fluorinated alcohol.

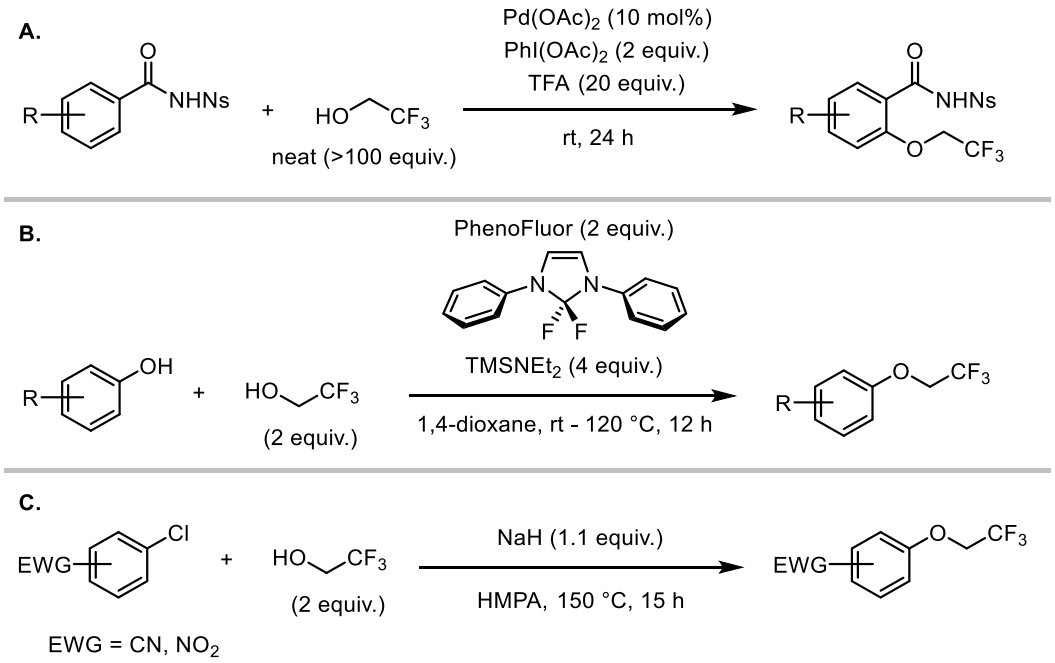


*Scheme 22: Palladium catalysed cross-coupling of (hetero)aryl chlorides with sodium tetrakis(2,2,2-trifluoroethoxy)borate **2.39** as a trifluoroethoxy source, reported by the Novák group.*[110]

2.1.8 Other Methods to Prepare Fluorinated Alkyl Aryl Ethers:

In addition to the above methods, palladium-catalysed C–H trifluoroethoxylation (Scheme 23A),[111] and coupling of phenols with alcohols using PhenoFluor have also been reported for preparing fluorinated alkyl aryl ethers (Scheme 23B).[112] Nucleophilic

aromatic substitution of aryl halides with fluorinated alcohols is known too, but such reactions are highly substrate dependent (Scheme 23C).[113]



Scheme 23. A. Palladium-catalysed C–H trifluoroethoxylation, reported by the Ji and Li groups.[111] *B. Coupling of phenols with alcohols using PhenoFluor, reported by the Ritter group.*[112] *C. Nucleophilic aromatic substitution of electron-poor aryl halides with fluorinated alcohols, reported by the Idoux and Gupton groups.*[113] *HMPA = hexamethylphosphoramide.*

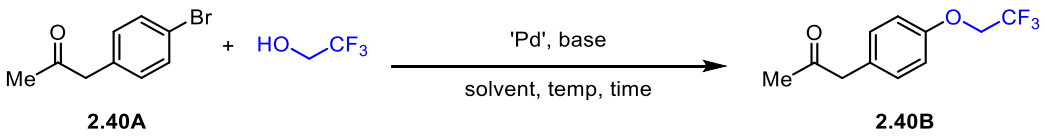
2.2 Aims of This Work

We sought to develop a broad-in-scope C–O cross-coupling between aryl halides and fluorinated alcohols, and to apply the method for ^{18}F-radiolabelling. Specifically, our aim was to prepare ^{18}F-trifluoroethyl ethers by cross-coupling of aryl halides with [^{18}F]trifluoroethanol. This approach to ^{18}F-radiolabelling via C–O cross-coupling has not been reported previously. While there are various methods for the synthesis of fluorinated alkyl aryl ethers as discussed hitherto, each have limitations or would be difficult to translate for use in ^{18}F-radiolabelling. Copper-catalysed C–O cross-couplings require a large excess of fluorinated alcohol and/or are sensitive to water. Palladium-catalysis was therefore explored instead. Previously reported palladium-catalysed approaches focusing on fluorinated alcohols have been compatible only with activated electron-poor aryl halides. Other palladium-catalysed C–O cross-couplings have not investigated parameters important for translation to radiochemistry such as short reaction durations and sensitivity to water. To enable easy translation for use in ^{18}F-radiochemistry, we aimed to develop a cross-coupling that was fast, did not require a large excess of fluorinated alcohol, and was robust in not requiring rigorously inert conditions. Such reaction characteristics would equally be useful for introducing non-radioactive fluorinated alcohols.

2.3 Results and Discussion: Palladium-Catalysed C–O Cross-Coupling

2.3.1 C–O Cross-Coupling Optimisation

We began by investigating the cross-coupling between 2,2,2-trifluoroethanol and aryl bromide **2.40A** (Scheme 24). This coupling is challenging due to i) the mildly acidic α-protons of **2.40A**, ii) the lack of an activating conjugated para electron-withdrawing group on **2.40A**, and iii) the low nucleophilicity of the fluorinated alcohol.



2.40A **2.40B**

Scheme 24: Model reaction for palladium-catalysed C–O cross-coupling of 2,2,2-trifluoroethanol and aryl bromides

2.3.1.1 Reaction analysis

Optimisation reactions were analysed by quantitative ^{19}F NMR (Figure 8). The crude reaction mixture was first filtered through celite to remove insoluble components such as the base and halide salts. The filtrate was not concentrated to avoid loss of 2,2,2-trifluoroethanol. α,α,α-Trifluorotoluene was added as an internal NMR standard, and an aliquot of the filtrate was taken, diluted with $CDCl_3$ and analysed by quantitative ^{19}F NMR. The integration of the α,α,α-trifluorotoluene peak at approximately -62.9 ppm was compared with that of the product **2.40B** at between -74.0 and -74.3 ppm, enabling calculation of the yield. The shift at -74.0 ppm was confirmed to be that of the product by isolation of the product by flash chromatography and characterisation by ^{1}H NMR, ^{13}C NMR, ^{19}F NMR and high-resolution mass spectroscopy. Remaining 2,2,2-trifluoroethanol was observed at -77.4 ppm. Under most conditions screened, the only components observed by ^{19}F NMR were the product and 2,2,2-trifluoroethanol. For reactions that did not afford **2.40B**, only unconsumed 2,2,2-trifluoroethanol was observed. Trifluoroacetaldehyde / trifluoroacetaldehyde hydrate, which could result from unproductive β-hydride elimination from an intermediate palladium(II) alkoxide, were not observed.

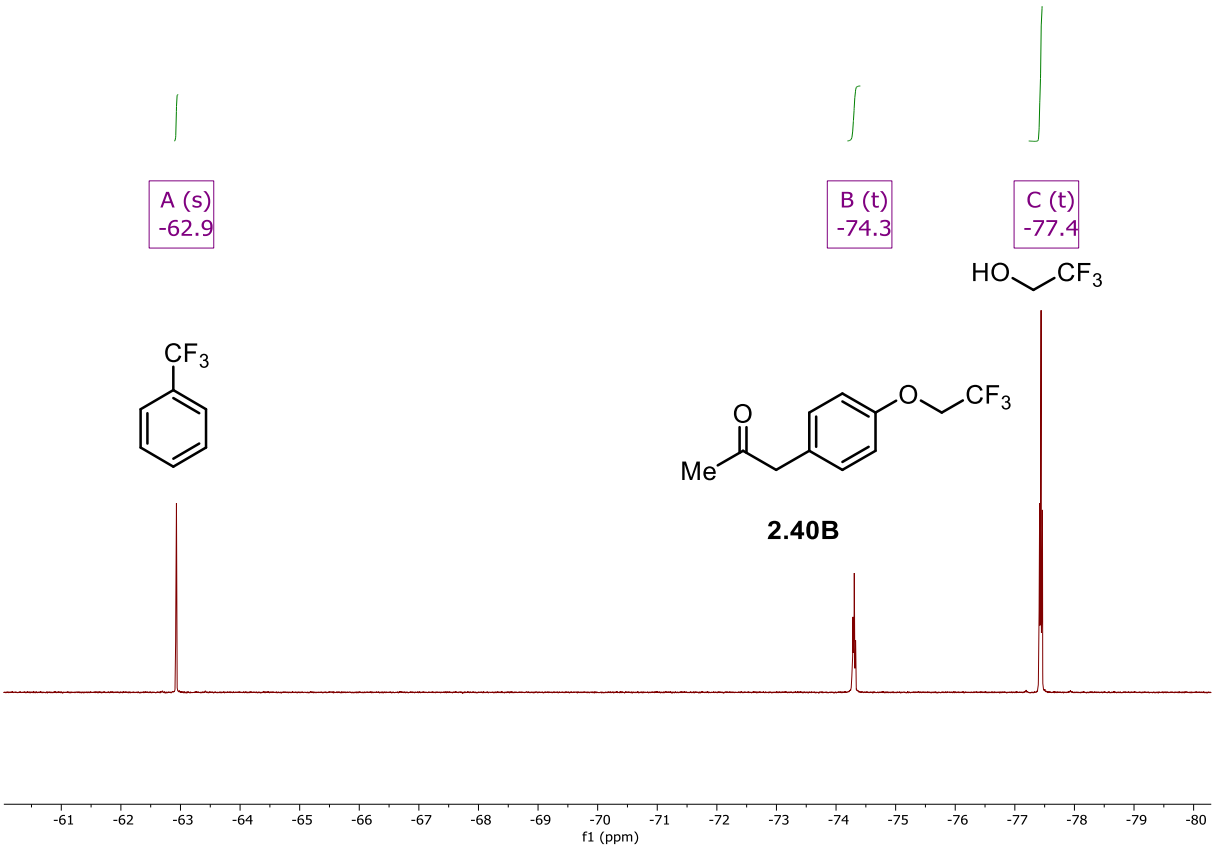


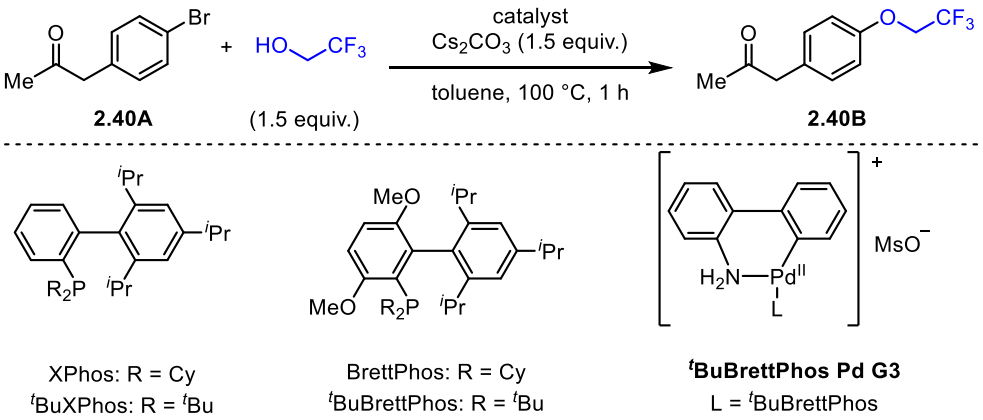
Figure 8: Quantitative ^{19}F NMR analysis of screening reactions

2.3.1.2 Catalyst Optimisation

Under conditions similar to those previously reported by the Singh group (for C–O cross-coupling of 2,2,2-trifluoroethanol and activated aryl bromides) using BrettPhos, $Pd_2(dba)_3$ and cesium carbonate (Scheme 21),[108] no product was observed as expected (Table 4, Entry 1). Use of ^{t}BuXPhos, reported for coupling of fluorinated alcohols with activated aryl bromides and coupling of sodium tetrakis(2,2,2-trifluoroethoxy)borate with aryl chlorides (Scheme 22),[110] afforded none of the desired product (Entry 3). Of the ligands screened, only Buchwald's ^{t}BuBrettPhos ligand was found to be effective, affording the **2.40B** in 51% yield after heating at 100 °C for 1 hour (Entry 4). An increase to 70% yield was achieved through use of Buchwald's commercially available precatalyst ^{t}BuBrettPhos Pd G3 (Entry 5, see Section 2.1.6 for a discussion on Buchwald's

precatalysts).[105] In addition to affording a high yield of **2.40B**, use of a precatalyst is convenient as both the ligand and palladium source are added in a single reagent.

*Table 4: Screening of catalysts for palladium-catalysed C–O cross-coupling of aryl bromide **2.40A** with 2,2,2-trifluoroethanol. [a]Yields determined by quantitative ^{19}F NMR using α,α,α-trifluorotoluene as an internal standard.*



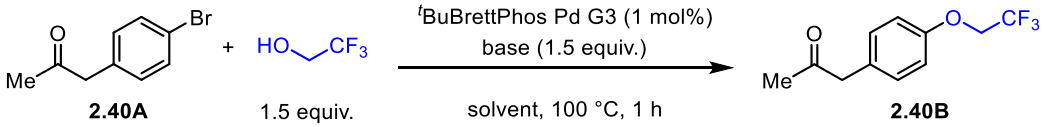
Entry	Catalyst	% Yield[a]
1	BrettPhos (1.25 mol%), $Pd_2(dba)_3$ (0.5 mol%)	0
2	XPhos, (1.25 mol%), $Pd_2(dba)_3$ (0.5 mol%)	0
3	^{t}BuXPhos, (1.25 mol%), $Pd_2(dba)_3$ (0.5 mol%)	0
4	^{t}BuBrettPhos, (1.25 mol%), $Pd_2(dba)_3$ (0.5 mol%)	51
9	^{t}BuBrettPhos Pd G3 (1.0 mol%)	70

2.3.1.3 Base Optimisation

Bases were screened next. Sodium carbonate afforded no coupled product (Table 5, Entry 2), while potassium carbonate afforded just 8% of the product (Entry 3). Enhanced reaction rates with cesium carbonate over other carbonates in such cross-couplings are well documented and attributed to higher solubility in organic solvents.[114] In contrast to sodium and potassium carbonate, tripotassium phosphate was effective, affording the coupled product in 70% yield, the same as obtained with cesium carbonate (Entry 4). The low cost of this base (£40.20 for 500 g from Sigma Aldrich on 22.09.2020) makes it an

attractive alternative to cesium carbonate (£273.00 for 500 g from Sigma Aldrich on 22.09.2020) for larger scale reactions. The strong base sodium *tert*-butoxide with 1,4-dioxane as solvent (conditions similar to those reported by Buchwald)[106] was also tested. This resulted in a decreased yield of 48% (Entry 5). Compared to weaker inorganic bases, strong bases allow for shorter durations and lower temperatures in cross-coupling reactions.[114] However, strong bases can also lead to undesired side reactions, such as Claisen condensation for ester containing substrates, and thus can limit functional group compatibility.[115]

*Table 5: Screening of bases for palladium-catalysed C–O cross-coupling of aryl bromide **2.40A** with 2,2,2-trilfuoroethanol. [a]Yields quantified by ^{19}F NMR using α,α,α-trifluorotoluene as an internal standard.*



Entry	Base	Solvent	% Yield[a]
1	Cs_2CO_3	toluene	70
2	Na_2CO_3	toluene	0
3	K_2CO_3	toluene	8
4	K_3PO_4	toluene	70
5	NaO^tBu	1,4-dioxane (80 °C, 16 h)	48

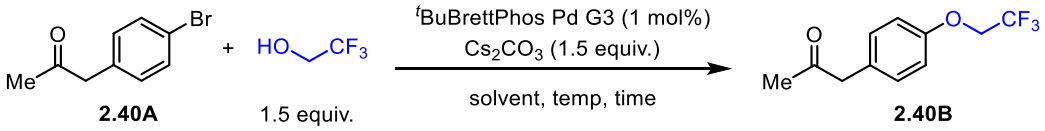
2.3.1.4 Solvent, Temperature, and Duration Optimisation

Solvents other than toluene were next tested in combination with cesium carbonate as base.[a] Use of 1,4-dioxane afforded the product in 61% yield (Table 6, Entry 2). Using *tert*-amyl alcohol just 33% yield was obtained (Entry 3). While these solvents afforded lower

[a] While potassium trisphosphate is cheaper than cesium carbonate, for some substrates it gave a slightly lower yield (see Section 2.3.2.5). Therefore cesium carbonate was used for the main scope.

yields than obtained with toluene (70%), they could serve as alternatives for substrates which are not soluble in toluene; substrate insolubility is one of the most common reasons for the failure of palladium catalysed cross-coupling reactions.[114] Maintaining the duration at 1 hour, but reducing the reaction temperature from 100 °C to 80 °C resulted in a reduced yield of 34% (Entry 4). Similarly, maintaining the temperature at 100 °C but reducing the duration from 1 hour to 30 minutes resulted in a reduced yield of 48% (Entry 5).

*Table 6: Screening of solvent, temperature and duration for palladium-catalysed C–O cross-coupling of aryl bromide **2.40A** with 2,2,2-trilfuoroethanol. [a]Yields quantified by ^{19}F NMR using α,α,α-trifluorotoluene as an internal standard.*



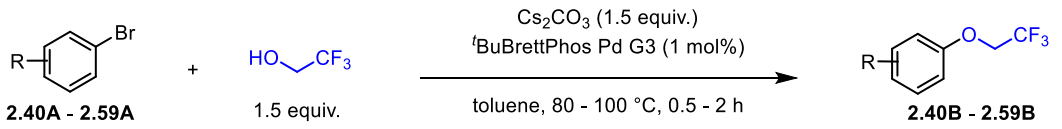
Entry	Solvent	Temp (°C)	Duration (h)	% Yield[a]
1	toluene	100	1	70
2	1,4-dioxane	100	1	61
3	*tert*-amyl alcohol	100	1	33
4	toluene (80 °C)	80	1	34
5	toluene (30 min)	100	0.5	48

To summarise, the screening experiments determined the optimal conditions to be use of ^{t}BuBrettPhos Pd G3 in toluene at 100 °C for 1 hour, with either cesium carbonate or tripotassium phosphate as base. In addition, 1,4-dioxane could serve as an alternative solvent, albeit affording a slightly reduced yield.

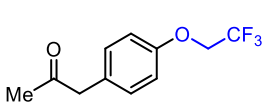
2.3.2 Substrate Scope

2.3.2.1 Aryl Bromides

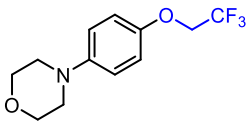
With the optimised coupling conditions in hand, the scope of aryl bromides was investigated (Scheme 25). Various electron-rich aryl bromides, which are more challenging substrates in C–O cross-coupling reactions, afforded the desired products in excellent yield within 0.5 to 2 hours (substrates **2.41B** to **2.43B**). Substrates **2.42A**, **2.47A**, and **2.52A**, which gave no product under Prasad's conditions using BrettPhos,[108] afforded the desired products in moderate to excellent yield under the conditions herein. By doubling the equivalents of 2,2,2-trifluoroethanol and Cs_2CO_3, a double cross-coupling with 1,4-dibromobenzene afforded **2.44B** in 76% yield. A wide range of electron-deficient aryl bromides afforded the coupled products in excellent yield, with various functional groups being well tolerated, including nitrile (**2.45B**), ester (**2.46B**, **2.48B**), nitro (**2.47B**) and sulphone (**2.49B**) groups. For these electron-deficient substrates, the reaction temperature could be decreased to 80 °C without reducing the yield. The temperature could also be reduced to 80 °C for electronically neutral substrates **2.53A** and **2.54A**. While the reaction with model substrate **2.40A** afforded a lower yield at 80 °C than at 100 °C (34% vs 70% NMR yield, Table 6), substrate **2.41A** with a more electron-donating morpholinyl substituent afforded no product at 80 °C. Various medicinally relevant heteroaryl bromides were also coupled effectively, including pyrimidine **2.55A**, quinoxaline **2.56A**, quinoline **2.57A** and pyridines **2.58A** and **2.59A**. The reaction temperature could be reduced to 80 °C for quinoxaline **2.56A**, quinoline **2.57A**, and the activated cyano-substituted pyridine **2.59A**.



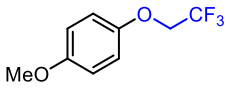
2.40A - 2.59A **2.40B - 2.59B**



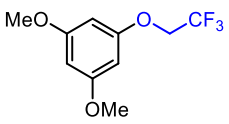
2.40B, 66%, 100 °C



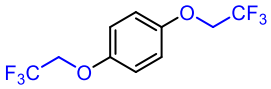
2.41B, 80%, 100 °C
0%, 80 °C



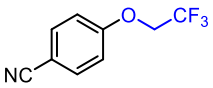
2.42B, 85%, 100 °C



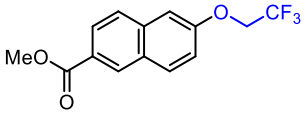
2.43B, 89%, 100 °C



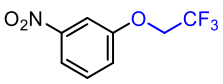
2.44B, 76%,[a] 100 °C



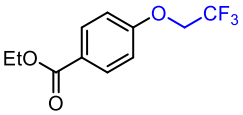
2.45B, 93%,[b] 80 °C



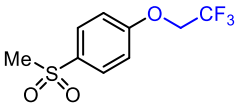
2.46B, 93%, 80 °C



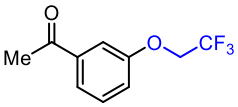
2.47B, 87%, 80 °C



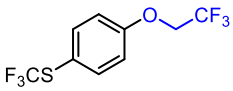
2.48B, 97%, 80 °C



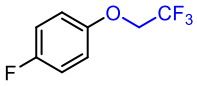
2.49B, 87%, 80 °C



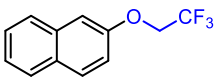
2.50B, 50%, 80 °C



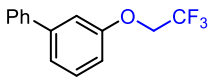
2.51B, 83%, 80 °C



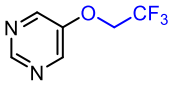
2.52B, 46%, 85 °C



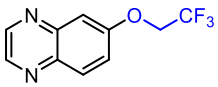
2.53B, 85%, 80 °C



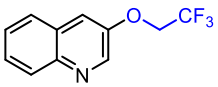
2.54B, 95%, 80 °C



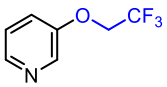
2.55B, 90%, 100 °C



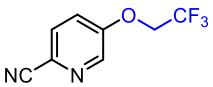
2.56B, 99%,[b] 80 °C



2.57B, 90%, 80 °C



2.58B, 42%,[c] 100 °C



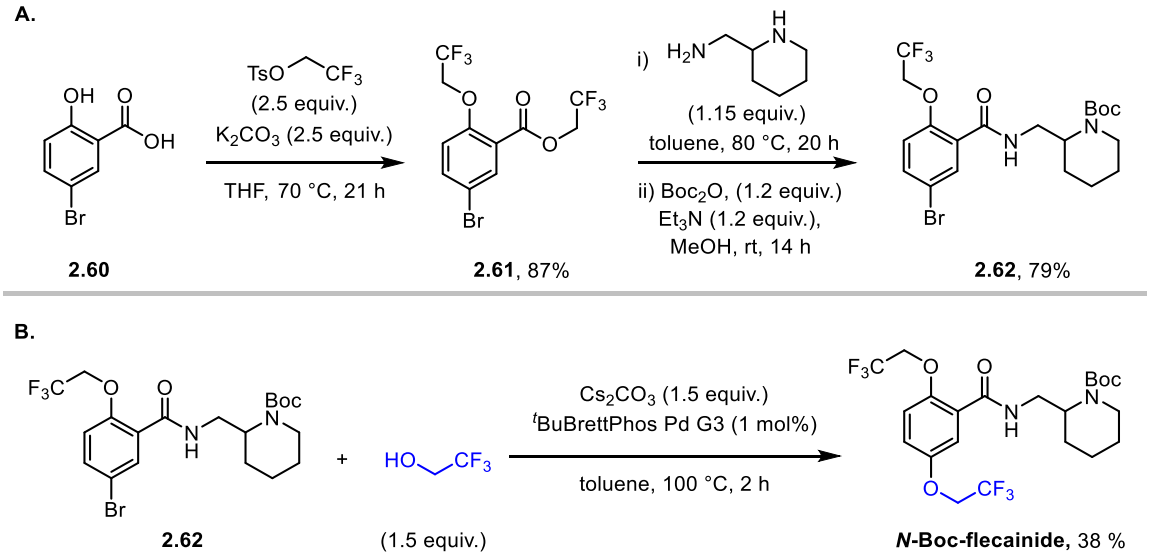
2.59B, 93%, 80 °C

Scheme 25: Scope of C–O cross-coupling of aryl bromides with 2,2,2-trifluoroethanol. [a]2 mol% [t]BuBrettPhos Pd G3, 3 equiv. of Cs_2CO_3 and 2,2,2-trifluoroethanol used. [b]Yield determined by quantitative ^{19}F NMR. [c]Reaction duration 4 hours.

2.3.2.2 *N*-Boc-Flecainide

The method was applied for the preparation of Boc-protected flecainide, a drug used in the treatment of cardiac arrythmia, with the foresight of preparing [^{18}F]flecainide by cross-coupling with [^{18}F]trifluoroethanol. The novel aryl bromide precursor **2.62** was prepared by adapting a method reported for the synthesis of flecainide (Scheme 26A).[116]

Bis-alkylation of commercially available 5-bromo-2-hydroxybenzoic acid **2.60** with 2,2,2-trifluoroethyl tosylate afforded **2.61**. Amide formation by nucleophilic acyl substitution of the electron-deficient ester, followed by Boc-protection afforded the desired aryl bromide **2.62**. Indeed **2.62** coupled with 2,2,2-trifluoroethanol at 100 °C under the standard conditions to afford *N*-Boc-flecainide in 38% yield (Scheme 26B). While it may also be possible to install both trifluoroethyl ether motifs in a single transformation from the dibromoarene, this would be difficult to translate for ^{18}F-radiolabelling where the ^{18}F-labelled reagent is the limiting reagent. An alternative approach would be to install the trifluoroethoxy group ortho to the benzamide by C–O cross-coupling, however this was not tested.

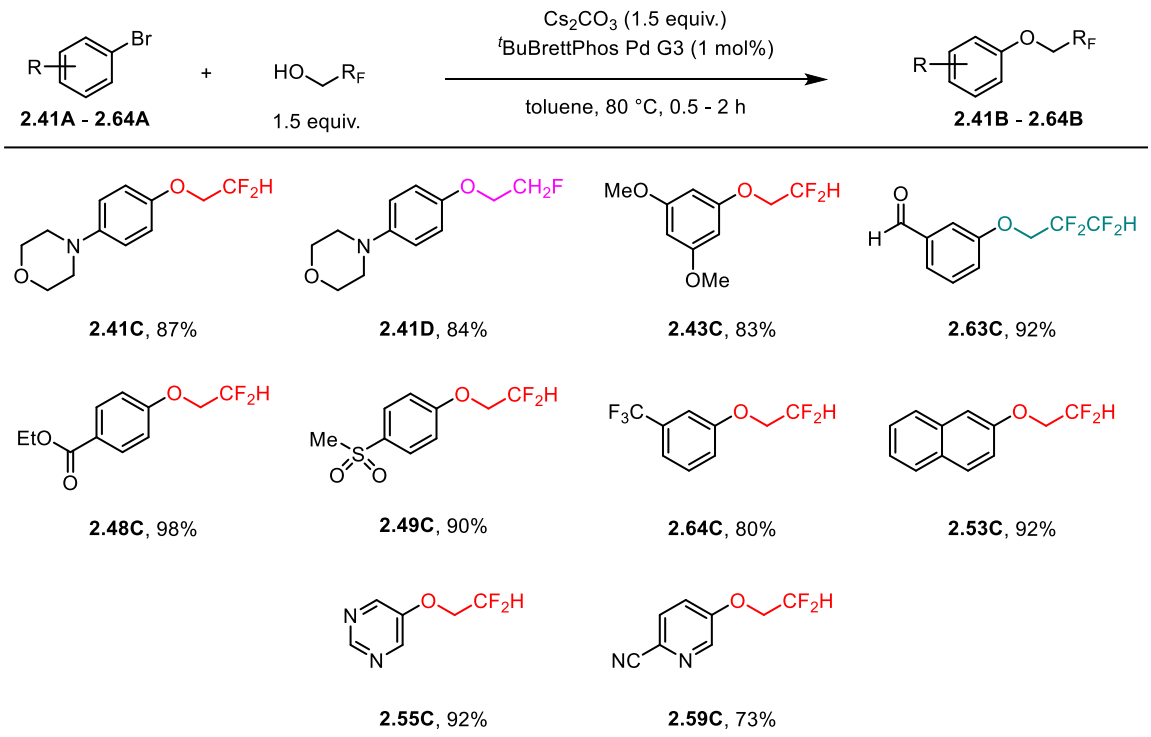


Scheme 26: A. Synthesis of N-Boc-flecainide precursor. B. Cross-coupling with 2,2,2-trifluoroethanol to prepare N-Boc-flecainide.

2.3.2.3 Other Fluorinated Alcohols

In addition to 2,2,2-trifluoroethanol, various other fluorinated alcohols coupled effectively under the optimised conditions (Scheme 27). Notably, 2,2-difluoroethanol and 2-fluoroethanol underwent coupling with electron-rich aryl bromides at 80 °C (**2.41C**,

2.41D and **2.43C**) rather than requiring 100 °C as was the case for coupling with 2,2,2-trifluoroethanol. This highlights the increased difficulty of cross-coupling with 2,2,2-trifluoroethanol.

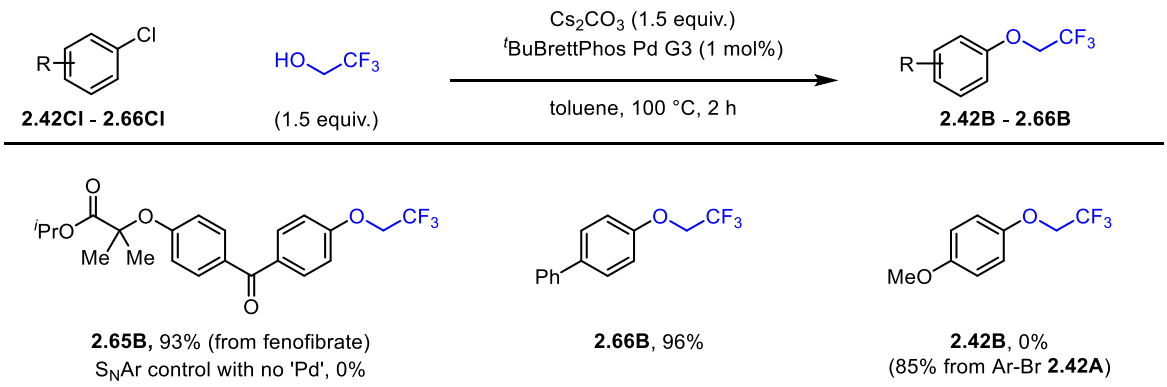


Scheme 27: Scope of C–O cross-coupling with various other fluorinated alcohols.

2.3.2.4 Aryl Chlorides

Aryl chlorides are typically more challenging substrates than aryl bromides in palladium-catalysed cross-coupling reactions, due in part to their slower oxidative addition to palladium(0).[117,118] Nonetheless the abundance of commercially available aryl chlorides makes them attractive substrates, and so their reactivity towards C–O bond formation was investigated (Scheme 28). The drug fenofibrate, used to treat abnormal blood lipid levels, features an aryl chloride with a para electron-withdrawing ketone. Fenofibrate underwent coupling with 2,2,2-trifluoroethanol at 100 °C to afford **2.65B** in 93% yield. A control experiment in the absence of palladium yielded no product, confirming that the

product forms via cross-coupling rather than via nucleophilic aromatic substitution. Electronically neutral aryl chloride **2.66Cl** also coupled effectively forming product **2.66B** in 96% yield at 100 °C. Electron-rich aryl chloride **2.42Cl** failed to afford the desired cross-coupled product at 100 °C. This is in stark contrast to the corresponding aryl bromide **2.42A** which afforded the cross-coupled product in 85% yield at 100 °C (Scheme 25). Based on these results, aryl chlorides appear to be suitable coupling partners for electron-poor and electronically neutral aromatics, but not for electron-rich aromatics, which require a bromide handle instead.

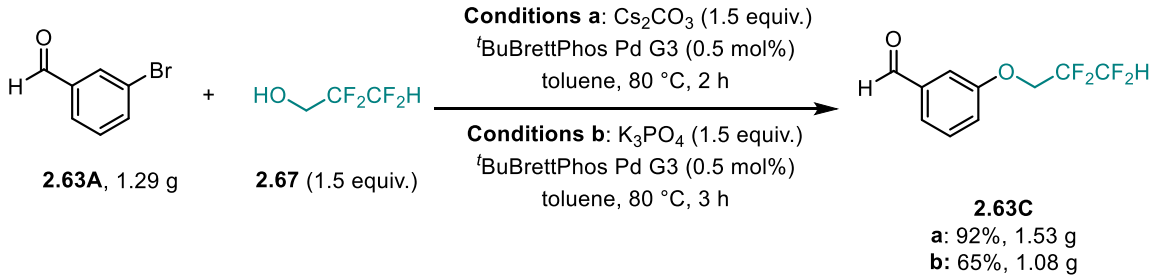


Scheme 28: Scope of C–O cross-coupling of aryl chlorides with 2,2,2-trifluoroethanol.

2.3.2.5 Scale-Up

The coupling reaction was scaled up to prepare 1.53 g of **2.63C** from 2,2,3,3-tetrafluoropropanol **2.67** and 3-bromobenzaldehyde **2.63A** in 92% yield (Conditions A, Scheme 29). **2.63C** is an intermediate in the synthesis of idalopirdine, an investigational drug for the treatment of Alzheimer's disease (Figure 6). **2.63C** is normally prepared in two steps by tosylation of the fluorinated alcohol **2.67,** followed by reaction with 3-hydroxybenzaldehyde.[119] Using our cross-coupling, the catalyst loading was reduced to 0.5 mol% without detrimental effect on the yield. A gram-scale reaction was also run using 0.5 mol% catalyst with tripotassium phosphate as base (shown to be

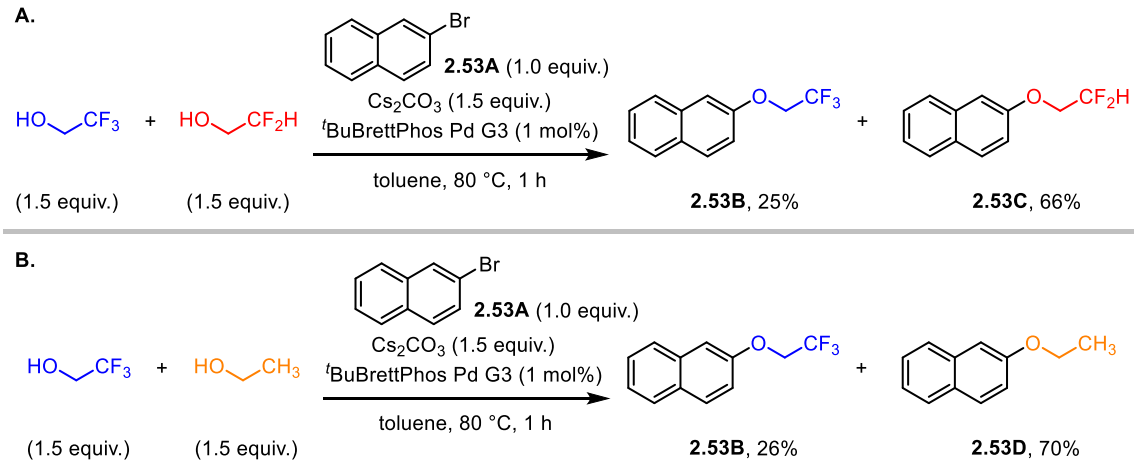
effective in Table 5), which is significantly cheaper than cesium carbonate and hence preferable on large-scale (Conditions B, Scheme 29). Under these conditions the product was isolated in 65% yield.



*Scheme 29: Scale-up reaction of C–O cross-coupling to prepare **2.63C**, an intermediate in the synthesis of idalopirdine.*

2.3.3 Competition Experiments

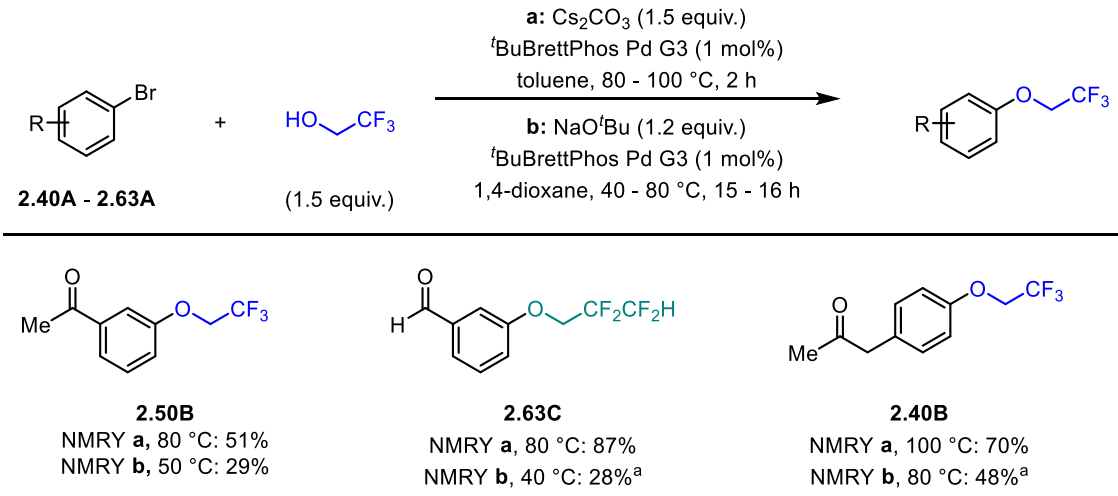
As discussed above, cross-coupling of electron-rich aryl bromides with 2,2-difluoroethanol could be performed at 80 °C while coupling with 2,2,2-trifluoroethanol required heating at 100 °C, suggesting that the latter alcohol is less reactive under the C–O cross-coupling conditions. The two alcohols were compared directly in a competition experiment coupling with electronically neutral 2-bromonaphthalene **2.53A** at 80 °C (Scheme 30A). As expected, the difluoroethyl ether **2.53C** was formed in a higher yield of 66%, while the trifluoroethyl ether **2.53B** was formed in only 25% yield. A competition experiment comparing 2,2,2-trifluoroethanol with ethanol gave similar results, affording the ethyl ether **2.53D** in 70% yield, and **2.52C** in 26% yield (Scheme 30B). The lower yields of trifluoroethyl ether **2.53C** is likely due to the reduced nucleophilicity of 2,2,2-trifluoroethanol, as a result of the electron-withdrawing CF_3 group.[93]



*Scheme 30: Competition experiments coupling 2-bromonaphthalene **2.53A** A. 2,2,2-trifluoroethanol vs 2,2-difluoroethanol. B. 2,2,2-trifluoroethanol vs ethanol.*

2.3.4 Comparison to Other Methods

The C–O cross-coupling method developed in this chapter was compared to a similar method previously reported by the Buchwald group (Scheme 31).[106] In our hands, substrates **2.50A**, **2.63A**, and **2.40A** afforded higher NMR yields of the coupled products using cesium carbonate in toluene (as per the conditions reported within) than when sodium *tert*-butoxide and 1,4-dioxane were used.



Scheme 31: Comparison of conditions for C–O cross-coupling. NMRY = NMR yield. [a]Reaction set-up in an N_2 filled glovebox.

2.4 Results and Discussion: Application of C–O Cross-Coupling for ^{18}F-Radiolabelling

2.4.1 Introduction

2.4.1.1 ^{18}F-labelled Fluorinated Alkyl Aryl Ethers

^{18}F-Labelled fluorinated alkyl aryl ethers are common motifs in radiochemistry, particularly ^{18}F-fluoroethyl ethers and ^{18}F-fluoromethyl ethers.[61] ^{18}F-Trifluoroethyl ethers are less common, but have still received considerable attention (Figure 9A). These motifs are typically prepared by reaction of phenols/phenolates with an ^{18}F-fluoroalkylating reagent (Figure 9B). ^{18}F-Fluoroethylations are typically carried using [^{18}F]fluoroethyl tosylate [^{18}F]**2.69** and [^{18}F]fluoroethyl bromide,[61] while ^{18}F-trifluoroethylations are achieved using [^{18}F]trifluoroethyl tosylate [^{18}F]**2.71**.[120] These reagents can be synthesised from [^{18}F]fluoride (Figure 9C and D). We sought to apply the C–O cross-coupling discussed hitherto to enable an alternative disconnection to ^{18}F-labelled fluorinated alkyl aryl ethers, by coupling of aryl halides with ^{18}F-labelled alcohols (Figure 9B).

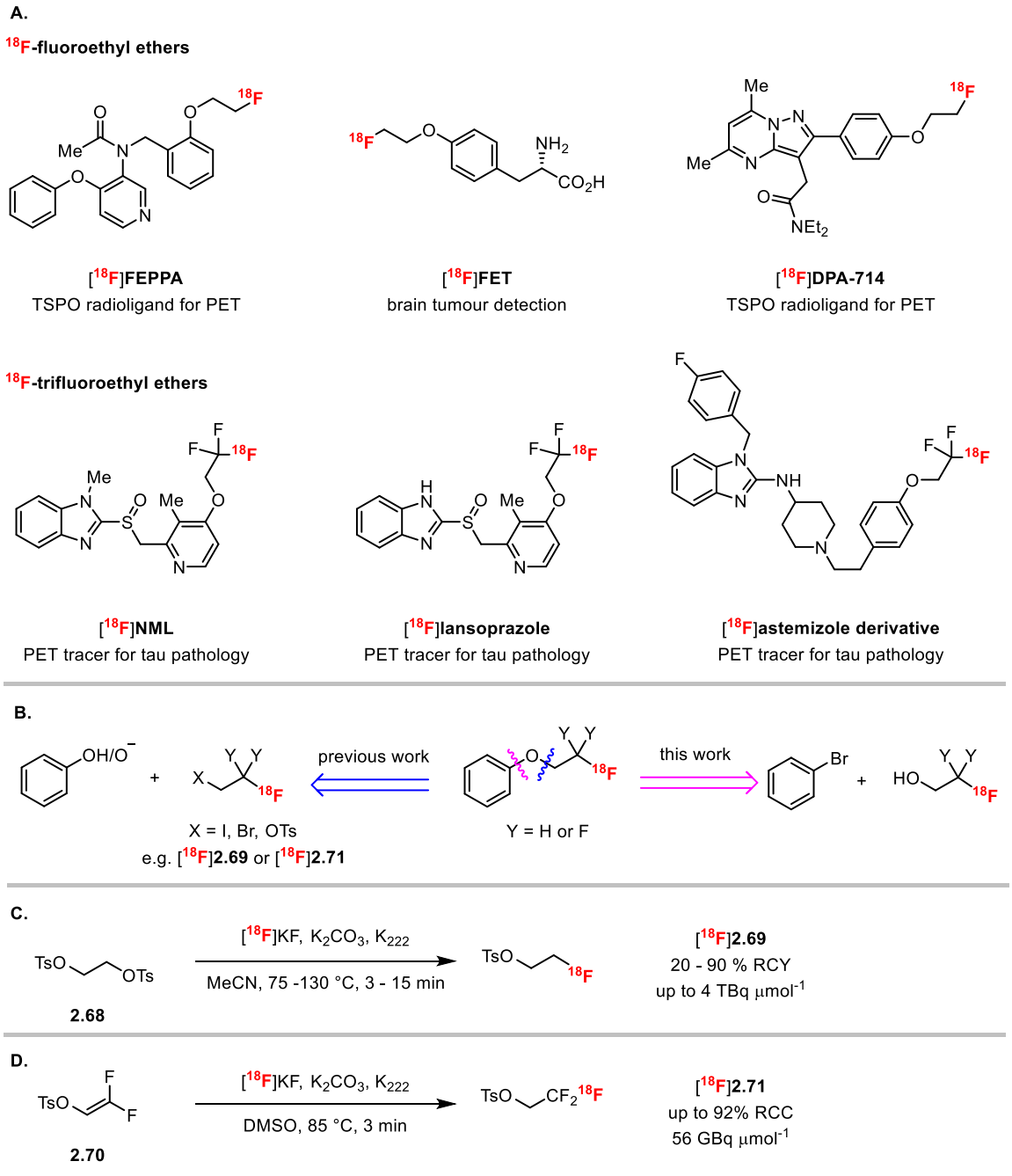


Figure 9: A. ^{18}F-Labelled fluorinated alkyl aryl ethers in PET tracers B. Previous work on preparation of ^{18}F-labelled fluorinated alkyl aryl ethers by alkylation of phenols/phenolates, and this work on preparation by cross-coupling of aryl bromides with ^{18}F-labelled fluorinated alcohols. C. Preparation of [^{18}F]fluoroethyl tosylate.[121,122] D. Preparation of [^{18}F]trifluoroethyl tosylate, reported by the Riss group.[123,124]

2.4.1.2 Palladium-Catalysed Cross-Coupling in ^{18}F-Radiochemistry

Palladium-catalysed cross-coupling reactions can be used for the introduction of labelled building blocks into radiotracers. Such reactions are relatively common for the introduction of carbon-11 by coupling with [^{11}C]methyl iodide and [^{11}C]carbon

monoxide.[64] Introduction of ^{18}F-labelled building blocks via palladium-catalysed cross-coupling has received less attention, however there are some reports on C–C and C–N cross-coupling for this purpose.[64,125] To the best of our knowledge, C–O cross-coupling for introducing ^{18}F-labelled alcohols has not been previously reported.

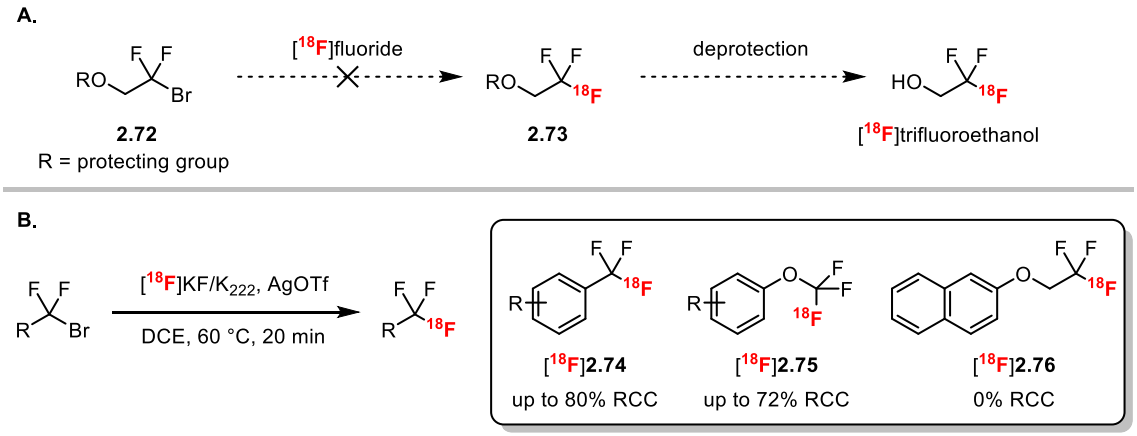
2.4.2 This Work

Having established a C–O cross-coupling with a broad scope and relatively short reaction duration, we sought to apply the method for ^{18}F-radiolabelling by coupling with [^{18}F]trifluoroethanol. While phenols are widely used as handles for introducing ^{18}F-labelled motifs,[61] our approach would provide an alternative route to ^{18}F-labelled alkyl aryl ethers from widely available aryl halides for the first time. While [^{18}F]trifluoroethanol was chosen as the coupling partner for proof-of-concept, the method should be applicable to other ^{18}F-labelled alcohols such as [^{18}F]fluoroethanol.[126]

2.4.3 Synthesis of [^{18}F]Trifluoroethanol

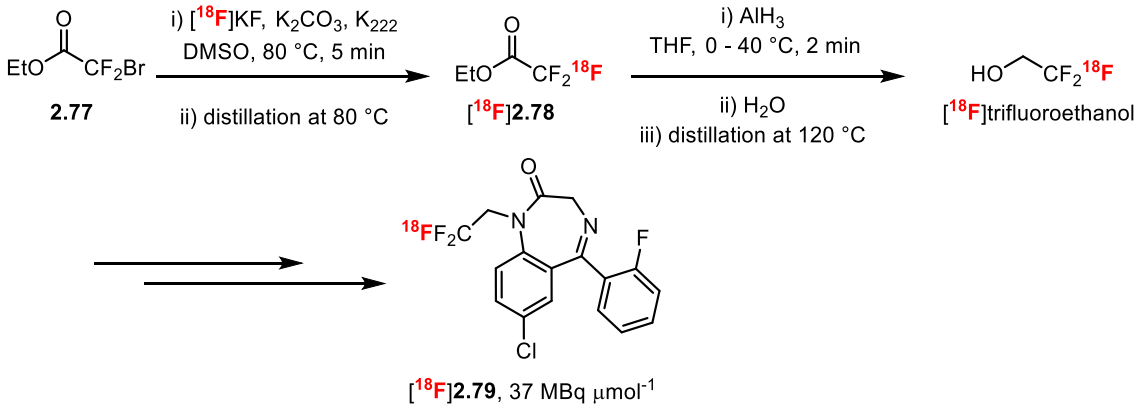
2.4.3.1 Potential Approaches

Synthesis of [^{18}F]trifluoroethanol by nucleophilic radiofluorination of an O-protected bromodifluoroethanol substrate **2.72** was considered (Scheme 32A). Indeed, synthesis of ^{18}F-trifluoromethyl ([^{18}F]**2.74**) and ^{18}F-trifluoromethoxy ([^{18}F]**2.75**) groups via reaction of bromodifluoromethyl compounds with [^{18}F]KF/K_{222} in the presence of silver triflate has been reported (Scheme 32B).[127,128] However, previous unpublished work in the Gouverneur group has shown that bromodifluoroethyl ethers are unreactive under these conditions ([^{18}F]**2.76**), so an alternative approach was required.[129]



Scheme 32: A. Unviable route to [^{18}F]trifluoroethanol. B. Nucleophilic radiofluorination for preparing [^{18}F]CF_3 motifs.

Before this work there was a single procedure in the literature for the synthesis of [^{18}F]trifluoroethanol, reported by Johnström and Stone-Elander (Scheme 33).[130] Use of bromodifluoroacetate **2.77** (rather than a bromodifluoroethyl ether) enables formation of the ^{18}F-CF_3 group in [^{18}F]**2.78** group via nucleophilic radiofluorination. Subsequent reduction affords [^{18}F]trifluoroethanol. Johnström and Stone-Elander go on to form [^{18}F]trifluoroethyl triflate and ultimately [^{18}F]**2.79**. RCYs are not quoted in the work. There are drawbacks to this synthesis; i) use of distillations for purification, which are typically irreproducible and potentially hazardous due to release of gaseous radioactivity, and ii) use of aluminium hydride as the reducing agent, which has to be prepared *in situ* from $LiAlH_4$ and H_2SO_4 and requires careful handling. We sought to revisit this general approach to [^{18}F]trifluoroethanol, in order to address its shortcomings.



Scheme 33: Previously reported synthesis of [^{18}F]trifluoroethanol, by the Johnström and Stone-Elander.

2.4.3.2 Trifluoroacetate Ester Stability

Purification of the [^{18}F]trifluoroacetate intermediate is required to remove remaining bromodifluoroacetate starting material after reaction with [^{18}F]fluoride. To avoid purification by distillation, which can suffer from poor reproducibility, we sought to use reverse-phase HPLC, as is typical for purification of ^{18}F-labelled reagents and radiotracers. To facilitate detection by HPLC, UV-active [^{18}F]phenyl trifluoroacetate [^{18}F]**2.80** was initially selected as the target, which would then be reduced to afford [^{18}F]trifluoroethanol. However, **2.80** was found to hydrolyse during purification by silica chromatography. Benzyl trifluoroacetate **2.81** was more stable and could be isolated by silica chromatography. However, during analysis of **2.81** by HPLC (water/acetonitrile, Phenomenex Synergi Hydro-RP column), significant degradation to benzyl alcohol was observed. Indeed, the Szabó group have reported their attempt to label [^{18}F]**2.81**, and found that the ester underwent hydrolysis under the reaction conditions, resulting in only 2% RCC.[131] The Szabó group reported that (-)-menthol trifluoroacetate **2.82** has improved stability, and could be ^{18}F-labelled in 64% RCC. This is likely due to the bulkiness of the menthol group slowing the hydrolysis of the ester. The Szabó group used [^{18}F]**2.82** to synthesise ^{18}F-trifluoroacetamides by reaction with primary amines. Due to its increased

stability, ester [^{18}F]**2.82** was investigated as an intermediate towards [^{18}F]trifluoroethanol.

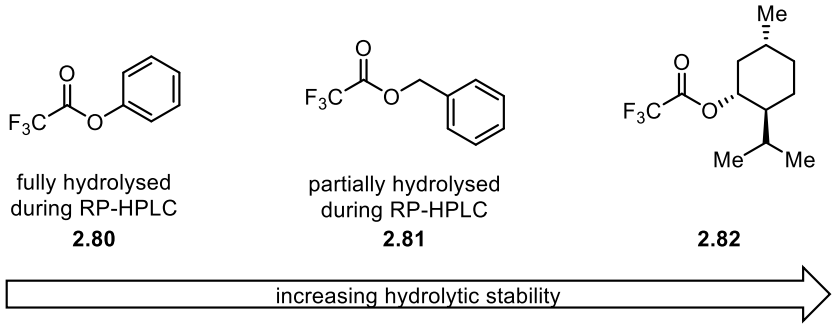
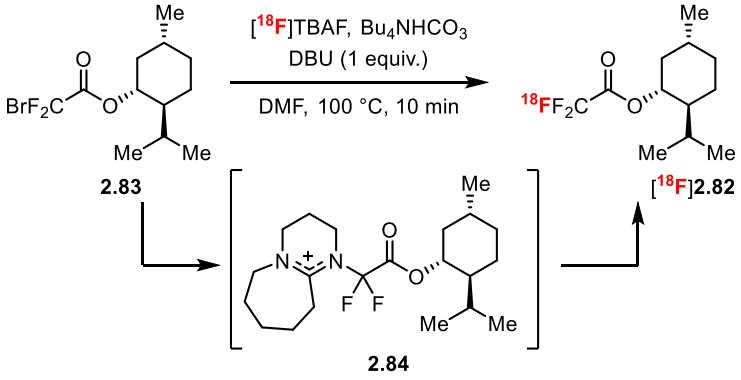


Figure 10: Trifluoroacetate esters investigated for hydrolytic stability. RP-HPLC = reverse-phase HPLC.

2.4.3.3 Optimisation of (-)-menthol [^{18}F]trifluoroacetate Synthesis

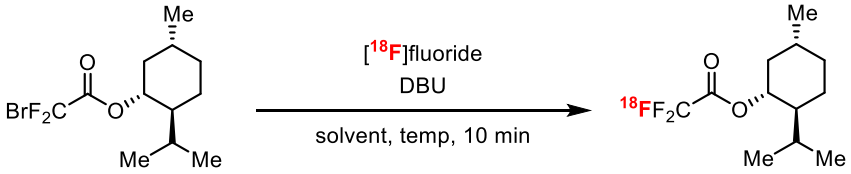
Synthesis of (-)-menthol [^{18}F]trifluoroacetate [^{18}F]**2.82** has previously been reported by the Szabó group by radiofluorination of (-)-menthol bromodifluoroacetate **2.83** with [^{18}F]TBAF in the presence of 1,8-diazabicyclo(5.4.0)undec-7-ene (DBU) in dimethylformamide (DMF, Scheme 34). The authors propose that DBU acts as a nucleophilic mediator in the reaction, displacing the bromide to form **2.84** before being displaced by [^{18}F]fluoride. These conditions were investigated for the synthesis of [^{18}F]**2.82** towards [^{18}F]trifluoroethanol.



Scheme 34: Synthesis of (-)-menthol [^{18}F]trifluoroacetate, reported by the Szabó group.[131]

In our hands, labelling of [^{18}F]**2.82** proceeded with 18% RCC under the conditions reported by the Szabó group (Table 7, Entry 1).[131] The conditions were reoptimised to increase the RCC, using ~20 MBq aliquots of [^{18}F]fluoride solution. Decreasing the equivalents of DBU from 1.0 to 0.5 had little effect on RCC (Entry 1 vs Entry 2), but removing DBU entirely led to a significantly lower RCC of 6% (Entry 3). The observed beneficial effect of DBU is consistent with the work of the Szabó group. Decreasing the temperature to 80 °C resulted in a lower RCC (Entry 4 vs Entry 2). Lowering the loading of the (-)-menthol bromodifluoroacetate **2.83** from 0.06 mmol to 0.03 mmol and changing from [^{18}F]TBAF to [^{18}F]tetraethylammonium fluoride ([^{18}F]TEAF) also resulted in a lower RCC (Entry 5). Increasing the starting material loading was beneficial, with 0.24 mmol of **2.83** affording an RCC of 45% (Entry 7). Changing the solvent to acetonitrile resulted in a lower RCC of 22% (Entry 8), however an increase to 51% RCC was observed when 1,3-dimethyl-2-imidazolidinone (DMI) was used (Entry 9).

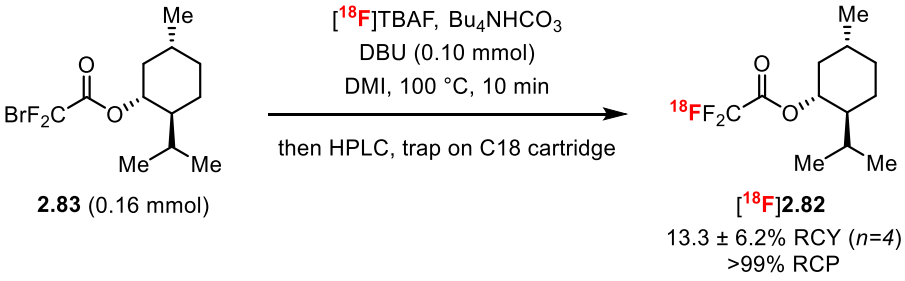
Table 7: Optimisation of (-)-menthol [^{18}F]trifluoroacetate synthesis. Screening reactions run with ~20 MBq aliquots of [^{18}F]fluoride. TBAF = tetrabutylammonium fluoride, TEAF = tetraethylammonium fluoride, DBU = 1,8-diazabicyclo(5.4.0)undec-7-ene, DMI = 1,3-dimethyl-2-imidazolidinone.



2.83 [^{18}F]**2.82**

Entry	[^{18}F]fluoride	Solvent	Temp (°C)	SM (mmol)	DBU (mmol)	RCC (*n=2*)
1	[^{18}F]TBAF	DMF	100	0.06	0.06	18
2	[^{18}F]TBAF	DMF	100	0.06	0.03	16
3	[^{18}F]TBAF	DMF	100	0.06	0	6
4	[^{18}F]TBAF	DMF	80	0.06	0.03	10
5	[^{18}F]TEAF	DMF	100	0.03	0.03	7
6	[^{18}F]TBAF	DMF	100	0.12	0.06	29
7	[^{18}F]TBAF	DMF	100	0.24	0.12	45
8	[^{18}F]TBAF	MeCN	80	0.24	0.12	22
9	[^{18}F]TBAF	DMI	100	0.24	0.12	51

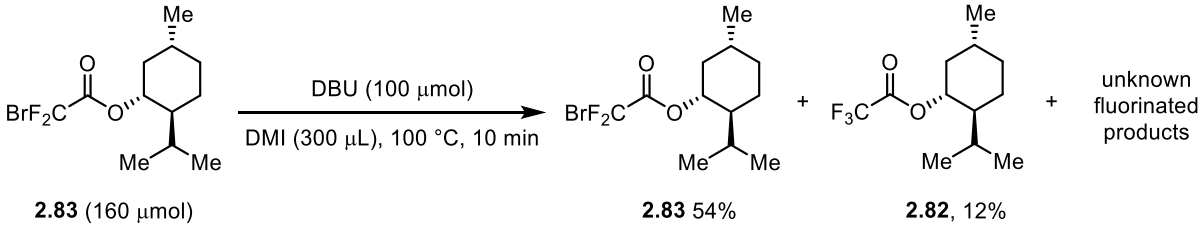
Upon scale-up of the labelling reaction using a full-batch of trapped and eluted [^{18}F]fluoride of between 2.5 and 5.0 GBq, the non-decay corrected RCY of [^{18}F]**2.82** was 13.3 ± 6.2% (*n=4*) (Scheme 35). The RCY was measured as the radioactivity trapped on C18 cartridge post-HPLC, as a percentage of the initial radioactivity of dry [^{18}F]fluoride. The RCY varied considerably between repeats of the same conditions. In one instance an RCY of 24% was recorded, however typically the RCY was closer to 10%. HPLC was effective in separating [^{18}F]**2.82** from the bromodifluoroacetate precursor **2.83**, which eluted shortly after.



*Scheme 35: Synthesis and isolation by HPLC of [^{18}F]**2.82**. RCY is non-decay corrected.*

2.4.3.4 Background Reactivity Under the ^{18}F-Labelling Conditions:

Submitting (-)-menthol bromodifluoroacetate **2.83** to the ^{18}F-labelling conditions in the absence of [^{18}F]fluoride resulted in considerable consumption of (-)-menthol bromodifluoroacetate **2.83**, and formation of trifluoroacetate **2.82** in 12% yield (Scheme 36). Various other unidentified fluorinated products were also observed by ^{19}F NMR. Formation of trifluoroacetate **2.82** in the absence of an external fluoride source indicates that the CF_2Br group of **2.83** can release fluoride. In the ^{18}F-labelling reaction, this results in isotopic dilution of [^{18}F]**2.82**, reducing the molar activity. Similar background reactivity was reported by Szabó and Schou in labeling ^{18}F-trifluoroacetamides.[131] They found that this background reactivity could be decreased by lowering the loading of the bromodifluoroacetamide precursor. However, lowering the loading of (-)-menthol bromodifluoroacetate **2.83** significantly decreased the RCC of [^{18}F]**2.82** (Entry 5, Table *7*), and so this approach was not pursued.

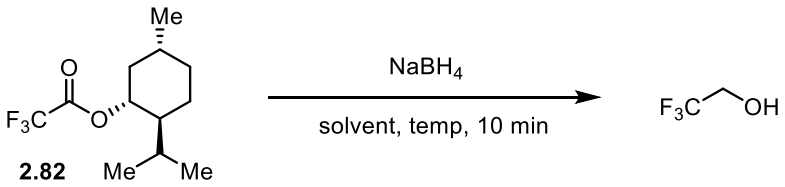


*Scheme 36: Background reactivity resulting in formation of (-)-menthol trifluoroacetate **2.82**. DMI = 1,3-dimethyl-2-imidazolidinone.*

2.4.3.5 Post-HPLC Reformulation and Solvent Selection

After HPLC purification, (-)-menthol [^{18}F]trifluoroacetate [^{18}F]**2.82** was obtained as a solution in water/acetonitrile. [^{18}F]**2.82** was then trapped on a C18 cartridge and eluted with the desired solvent. Choice of solvent here was important; after reduction of [^{18}F]**2.82** to [^{18}F]trifluoroethanol, change of solvent by evaporation and re-solvation would be impossible due to the volatility of 2,2,2-trifluoroethanol (boiling point of 74-75 °C reported by Alfa Aesar). Post-reduction solvent change by dilution with water, trapping on a C18 cartridge, and re-elution would introduce a large amount of water which would be difficult to remove from [^{18}F]trifluoroethanol and interfere with the cross-coupling reaction (see Table 10). Therefore it was important to elute [^{18}F]**2.82** with a solvent which would enable reduction to [^{18}F]trifluoroethanol, and also be suitable for the palladium-mediated cross-coupling reaction. The optimal solvent found for the cross-coupling reaction was toluene, however toluene was a poor solvent for the sodium borohydride reduction of ester **2.82** (Entry 5, Table 8). Instead, 1,4-dioxane was chosen as it performed well in both the cross-coupling reaction and the sodium borohydride reduction (Table 8).

Table 8: Optimisation of reduction of (-)-menthol trifluoroacetate. Yields determined by quantitative ^{19}F NMR after filtration though a syringe filter and dilution with $CDCl_3$. α,α,α-Trifluorotoluene was used as internal standard.



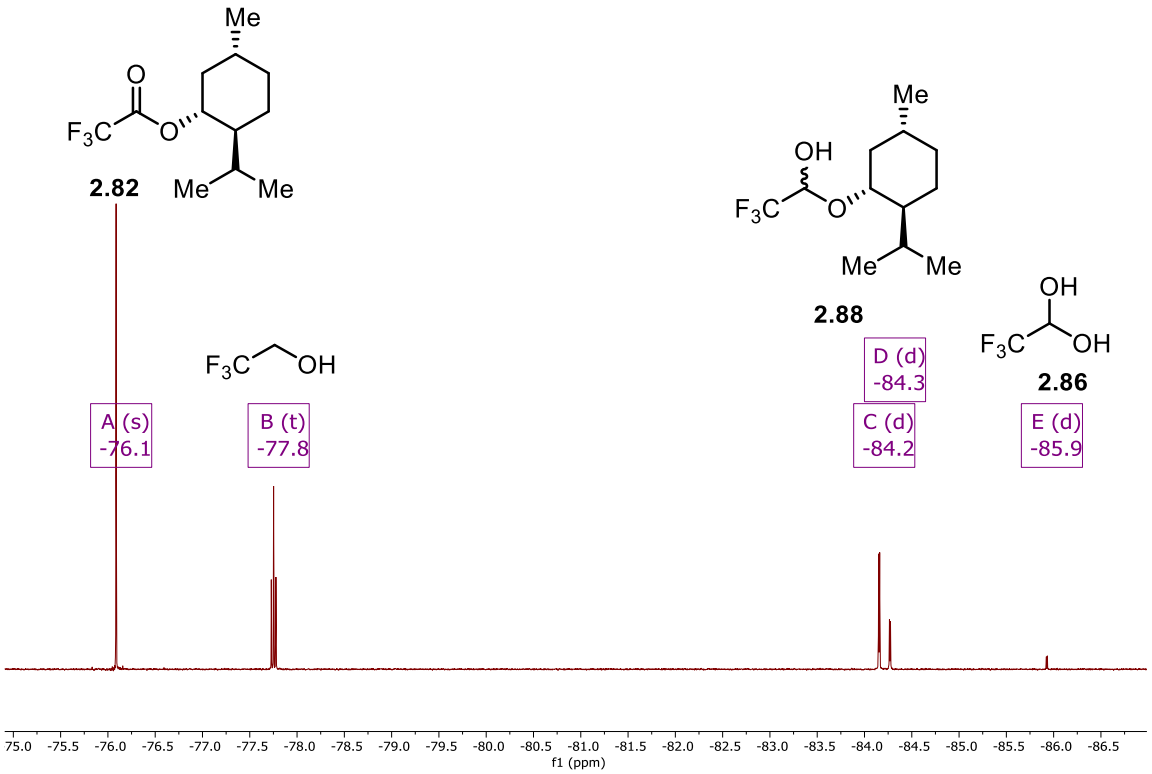
Entry	Solvent	$NaBH_4$ (equiv.)	Temp (°C)	% Yield
1	1,4-dioxane, 0.1 vol% water	1	rt	34
2	1,4-dioxane, 0.1 vol% water	3	rt	62
3	1,4-dioxane, 0.1 vol% water	3	60	74
4	1,4-dioxane (<10 ppm water)	3	60	<2
5	toluene, 0.1 vol% water	3	60	0

2.4.3.6 Reduction of [^{18}F]**2.82** to [^{18}F]Trifluoroethanol

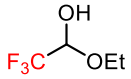
While aluminium hydride (prepared in situ from lithium aluminium hydride and sulfuric acid) has been previously used for reducing [^{18}F]ethyl trifluoroacetate [^{18}F]**2.78** to [^{18}F]trifluoroethanol (Scheme 33), we sought to use a commercially available and more easily handled reducing agent. Treatment of (-)-menthol trifluoroacetate **2.82** with 1 equivalent of sodium borohydride in 1,4-dioxane with 0.1 vol% water at room temperature was trialled (Entry 1, Table 8). ^{19}F NMR analysis of the crude reaction mixture showed the presence of multiple species (Figure 11A). Both starting material and 2,2,2-trifluoroethanol were observed, in addition to three doublets at -84.2, -84.3 and -85.9 ppm, each with J = 4.0 Hz. The peak at -85.9 ppm is consistent with the reported shift of -86.3 ppm (d, J = 4.3 Hz) for trifluoroacetaldehyde hydrate **2.86** (Figure 11B).[132] The shift of -84.2 ppm (d, J = 3.8 Hz) for **2.85**,[b] a hemiacetal of trifluoroacetaldehyde, is close to the peaks observed at -84.2 and -84.3 ppm. These peaks therefore likely arise from the two diastereomeric (-)-menthol derived hemiacetals **2.88**. No peak was

[b] ^{19}F NMR measured in $CDCl_3$ for trifluoroacetaldehyde ethyl hemiacetal purchased from Fluorochem.

observed in the region expected for trifluoroacetaldehyde **2.87** (-81.8 ppm, d, *J* = 3.1 Hz).[133] The hemiacetals **2.88** and hydrate **2.86** arise from partial reduction of ester **2.82**. Indeed the partial reduction of ethyl trifluoroacetate **2.78** to hydrate **2.86** with sodium borohydride has been previously reported in water at 15 – 18 °C (Figure 11C).[134] While partial reduction of esters is uncommon due to the higher electrophilicity of intermediate aldehydes relative to esters, the formation of hydrate **2.86** and hemiacetal **2.88** likely prevents reduction to the alcohol. Indeed the equilibrium between trifluoroacetaldehyde and its hemiacetals/hydrates is known to favour the latter species due to the electron-withdrawing nature of the CF_3 group.[135] By using three equivalents of $NaBH_4$ and increasing the temperature to 60 °C, complete consumption of (-)-menthol trifluoroacetate **2.82** was achieved, with only 2,2,2-trifluoroethanol observed in the ^{19}F NMR (Entry 3, Table 8). Conducting the reaction under strictly anhydrous conditions using 1,4-dioxane with less than 10ppm of water resulted in very poor conversion to 2,2,2-trifluoroethanol (Entry 4, Table 8).

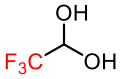


B.



2.85

-84.2 ppm, (d, *J* = 3.8 Hz)



2.86

-86.3 ppm, (d, *J* = 4.3 Hz)

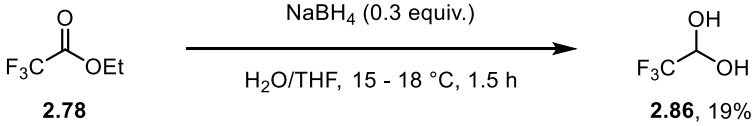


2.87

-81.8 ppm, (d, *J* = 3.1 Hz)

not observed

C.



2.78 **2.86**, 19%

*Figure 11: A. ^{19}F NMR of reaction mixture resulting from treatment of (-)-menthol trifluoroacetate **2.82** with $NaBH_4$ (1 equiv.) at rt °C for 10 minutes in 1,4-dioxane with 0.1 vol% water. B. ^{19}F NMR shifts of trifluoroacetaldehyde **2.87** and the corresponding hydrate **2.86** reported in the literature, and measured for a commercial sample **2.85**.[132133] C. Reported partial reduction of ethyl trifluoroacetate **2.78** to trifluoroacetaldehyde hydrate **2.86** with sodium borohydride.[134]*

Similarly, when performing the reduction of (-)-menthol [^{18}F]trifluoroacetate [^{18}F]**2.82**, sufficient heat and sodium borohydride equivalents were required to ensure complete reduction to [^{18}F]trifluoroethanol reproducibly. In some cases when the reduction was

performed at 40 °C, a third product was observed by radioHPLC in addition to [^{18}F]trifluoroethanol and [^{18}F]**2.82** (blue trace, Figure 12). This is likely to be either hydrate ^{18}F]**2.86** or hemiacetal [^{18}F]**2.88**. In one instance when this unknown radioactive species was observed by analytical radioHPLC, additional sodium borohydride was added to the reaction mixture, and the duration was extended. RadioHPLC showed the unknown species was consumed, and only [^{18}F]trifluoroethanol was observed. By performing the reduction using 10 mg (0.27 mmol) of sodium borohydride at 60 °C, complete reduction of [^{18}F]**2.82** was consistently achieved affording [^{18}F]trifluoroethanol in 98 ± 1% RCC (n=5) from [^{18}F]**2.82** (green trace, Figure 12).

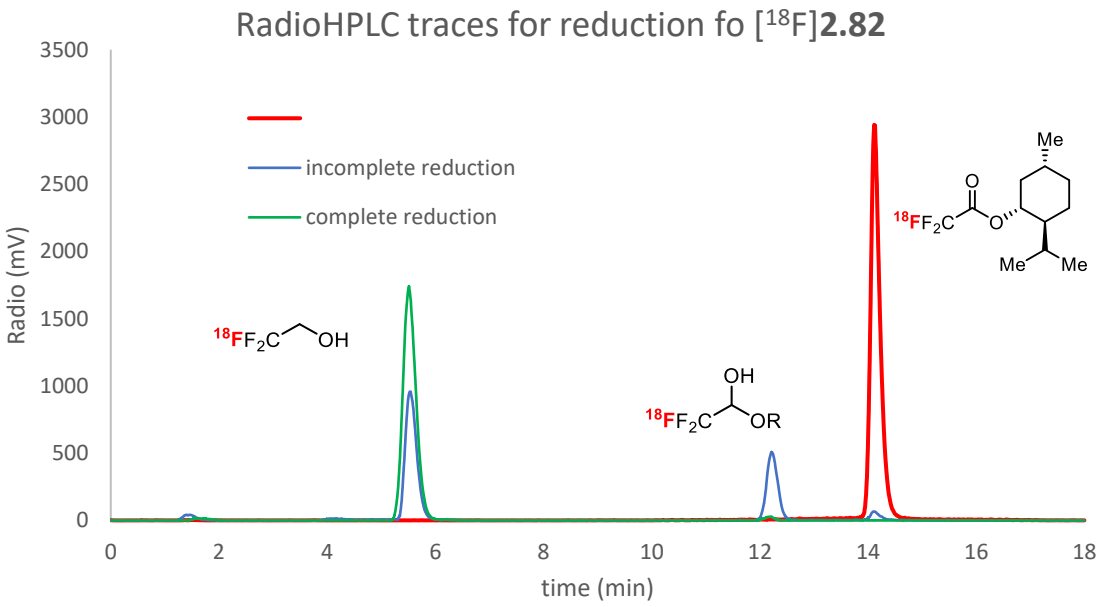


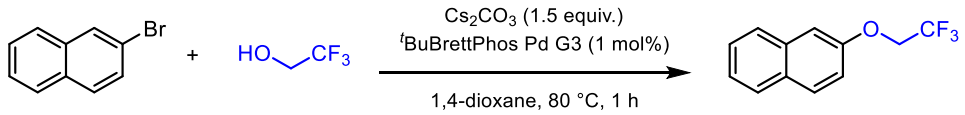
*Figure 12: Stacked ^{18}F-radiotraces. Orange: Radiochemically pure (-)-menthol [^{18}F]trifluoroacetate [^{18}F]**2.82** post semi-prep HPLC. Blue: Analysis after incomplete reduction of [^{18}F]**2.82** with $NaBH_4$ (10 mg) at 40 °C, with some formation of [^{18}F]trifluoroethanol, in addition to an intermediate species at around 12 minutes, and unconsumed [^{18}F]**2.82**. Green: Complete reduction to [^{18}F]trifluoroethanol with 98% RCC using $NaBH_4$ (10 mg) at 60 °C.*

2.4.3.7 [^{18}F]Trifluoroethanol Purity

After the reduction of [^{18}F]**2.82** to [^{18}F]trifluoroethanol with sodium borohydride, the mixture was passed through a Sep-Pak Silica Light cartridge to remove salts. In addition

to [^{18}F]trifluoroethanol, the resulting 1,4-dioxane solution also contained (-)-menthol from the reduction of [^{18}F]**2.82**. However, this was inconsequential as (-)-menthol was found not to be detrimental when spiked into the C–O cross-coupling reaction (Table 9).

Table 9: Effect of (-)-menthol on cross-coupling



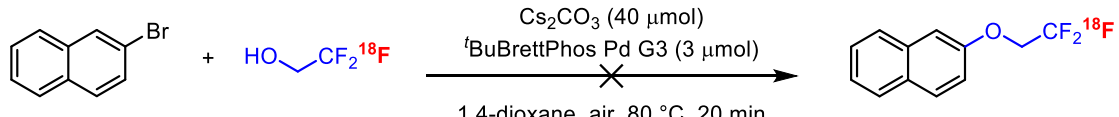
2.53A 1.5 equiv. **2.53B**

Entry	Additive	% Yield
1	none	94
2	(-)-menthol (1.5 equiv.)	91

2.4.4 Palladium-Mediated Cross-Coupling with [^{18}F]trifluoroethanol

2.4.4.1 Initial Attempts

Initial attempts to couple [^{18}F]trifluoroethanol with 2-bromonaphthalene **2.53A** failed, with only unreacted [^{18}F]trifluoroethanol observed by radioHPLC. It was speculated that this was due to either water or air present in the reaction.



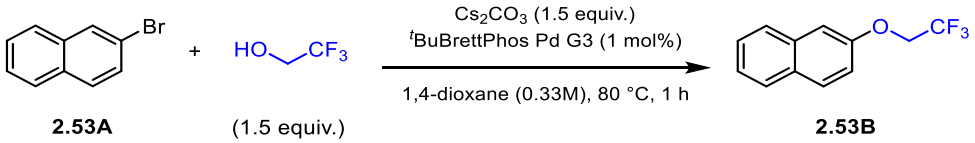
2.53A (30 or 120 μmol) 'wet' [^{18}F]**2.53B**

*Scheme 37: Failed attempts to cross-couple [^{18}F]trifluoroethanol, under air without removal of water. Reaction tested using both 30 and 120 μmol of **2.53A**.*

The tolerance of the cross-coupling of 2,2,2-trifluoroethanol with 2-bromonaphthalene **2.53A** towards these factors was therefore investigated (Table 10). For cross-coupling with non-radiolabelled alcohols, the reaction is typically carried out under an N_2 atmosphere using dry (<10 ppm water) toluene. Indeed, using dry 1,4-dioxane (10 ppm water) as solvent with a nitrogen atmosphere **2.53B** was obtained in 94% yield by quantitative ^{19}F NMR (Entry 1). However, such stringently inert conditions are difficult to

recreate in the radiochemical lab, particularly as (-)-menthol [^{18}F]trifluoroacetate [^{18}F]**2.82** is purified by reverse-phase HPLC using a mobile phase of water and acetonitrile. When the water content was increased to 1 vol%, the reaction still afforded **2.53B** however with a reduced yield of 41% (Entry 2). Increasing to 5 vol% of water reduced the yield further to 5% (Entry 3). These results show the reaction does not require rigorously anhydrous conditions to function, but that with high water content the reaction is almost entirely inhibited. Using dry 1,4-dioxane under an atmosphere of air yielded the **2.53B** in 21% (Entry 4). Therefore to enable cross-coupling with [^{18}F]trifluoroethanol, exclusion of water and air from the reaction was investigated.

Table 10: Tolerance of the palladium catalysed C–O cross-coupling towards water and air. Water content for entry 1 and 4 determined by Karl Fischer titration. Yields determined by quantitative ^{19}F NMR, with α,α,α-trifluorotoluene as internal standard.



2.53A (1.5 equiv.) **2.53B**

Entry	Water Content	Equiv. Water	Atmosphere	% Yield
1	5 ppm	-	N_2	94
2	1 vol%	1.67	N_2	41
3	5 vol%	8.33	N_2	5
4	5 ppm	-	air	21

2.4.4.2 Removing Water Post-HPLC

The main source of water in the cross-coupling was from the [^{18}F]trifluoroethanol solution. This originated from water left on the C18 cartridge (Waters Sep-Pak C18 Plus Short cartridge) after trapping of the HPLC effluent containing (-)-menthol [^{18}F]trifluoroacetate [^{18}F]**2.82** (Figure 13). The volume of water eluted from the C18 cartridge with 1,4-dioxane following the procedure for preparing [^{18}F]trifluoroethanol was investigated. This was estimated by first passing 5 mL of 9:1 water/acetonitrile (the

approximate composition of the HPLC effluent after dilution with water) through a C18 cartridge, followed by 1 mL of air, and then eluting the cartridge with 2 mL of dry 1,4-dioxane (<10 ppm water). Quantitative ^{1}H NMR was then used to determine the water content of the 1.75 mL of eluate as 13 vol%, equating to 0.23 mL of water. This water would be carried through to the final [^{18}F]trifluoroethanol solution. This is well above the 5 vol% water content found to almost entirely inhibit C–O cross-coupling (Entry 3, Table 10).

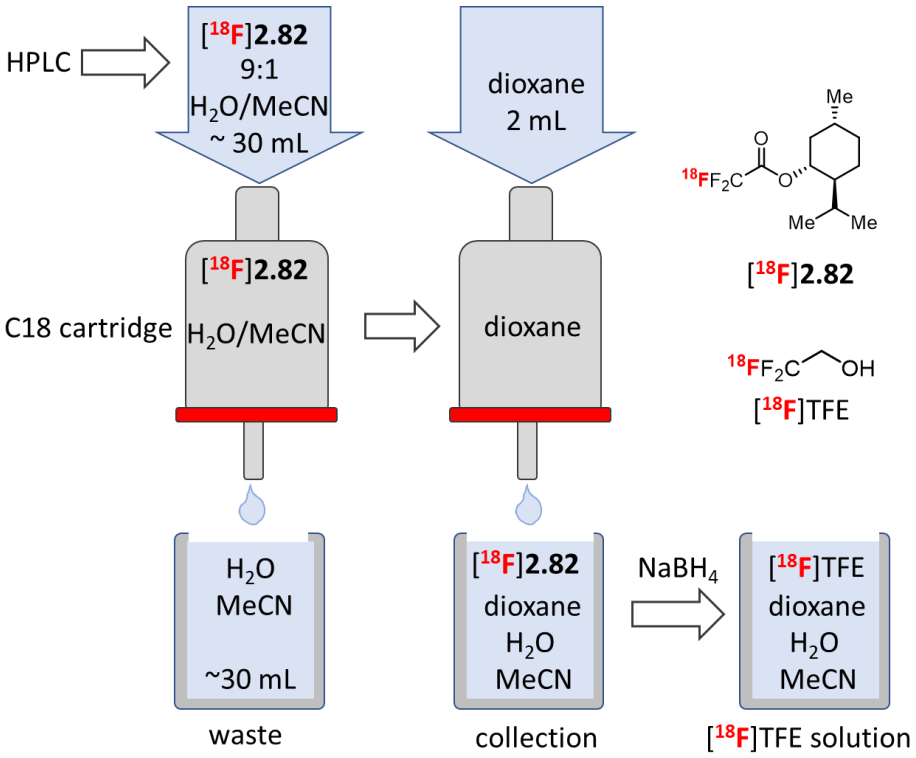


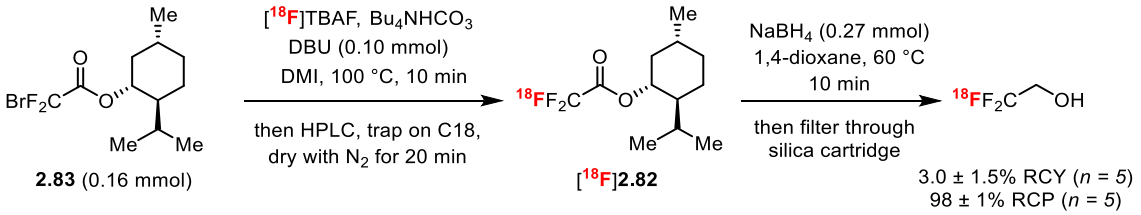
Figure 13: Origin of water in the [^{18}F]trifluoroethanol solution.

Various approaches were tested for removing water after C18 trapping. Eluting the C18 cartridge with THF (low boiling point azeotrope with water: 64 °C, 5% water) followed by azeotropic drying at 65 °C under a nitrogen flow resulted in a 97% loss of radioactivity. Various other drying techniques were trialled using **2.82** in 9:1 water/acetonitrile trapped on a C18 cartridge. Elution with 1,4-dioxane through a Sep-Pak Dry Sodium Sulfate

cartridge in series with the C18 cartridge was ineffective, with the resulting solution containing over 5 vol% water, determined by Karl-Fischer analysis. The same approach was tested using 2-methyltetrahydrofuran, which has a lower solubility in water (14 g per 100 g water at 20 °C[136]) and might therefore be dried more easily by the Sulfate cartridge. However, this also afforded a solution containing over 5 vol% water. Elution with pentane, which has a far lower water solubility (3.8 mg per 100 g water at 25 °C), afforded a biphasic water-pentane mixture, showing that the Sep-Pak Dry Sodium Sulfate cartridges were ineffective for this purpose. A dry solution (<100 ppm) of **2.82** was obtained by eluting the C18 cartridge with pentane through a Sep-Pak Alumina Plus Long Cartridge. However, this was ineffective when performed in the radiochemical lab as significant radioactivity was retained on the cartridges (79% of radioactivity collected by HPLC was lost on the cartridges). The most effective way to remove the water was to dry the C18 cartridge under a flow of nitrogen. Drying for 30 minutes under a nitrogen flow of 1.6 to 1.8 L min^{-1}, followed by elution with dry 1,4-dioxane (<10 ppm water) afforded an eluate with just 300 ppm of water. When this was tested in the radiochemical lab, drying for longer than 20-25 minutes resulted in a rapid drop in radioactivity on the cartridge beyond that of decay (a radio detector was attached to the cartridge). Drying was therefore typically carried out for no longer than 20 minutes.

2.4.4.3 [^{18}F]Trifluoroethanol Synthesis Summary

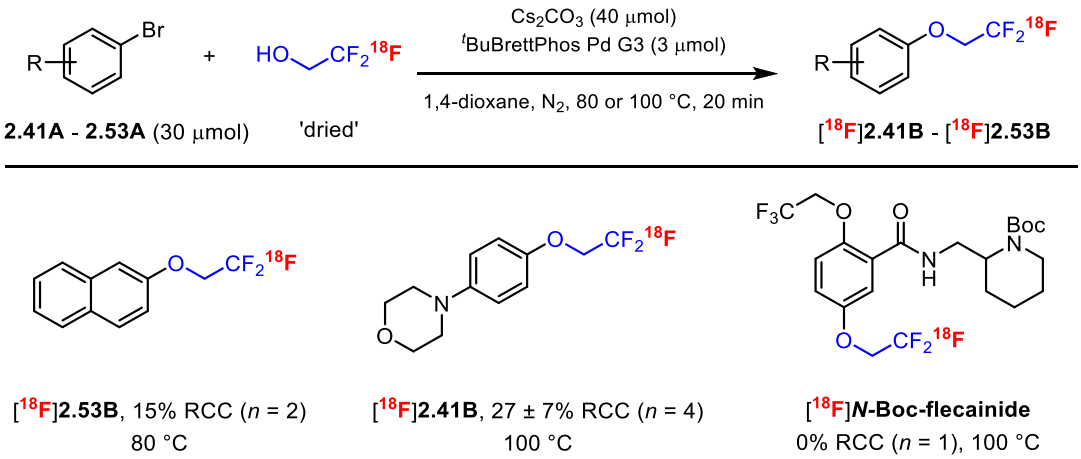
The synthesis of [^{18}F]trifluoroethanol discussed above, including the drying of intermediate [^{18}F]**2.82** on the C18 cartridge under a flow of nitrogen, afforded a non-decay corrected RCY of 3.0 ± 1.5% (*n = 5*) from dry [^{18}F]fluoride, with a radiochemical purity (RCP) of 98 ± 1% (*n = 5*) (Scheme 38).



Scheme 38: Final synthesis of [^{18}F]trifluoroethanol. RCY is non-decay corrected.

2.4.4.4 Cross-Coupling Under Nitrogen After Removal of Water

The reactions were placed under an N_2 atmosphere by flushing the V-vials with nitrogen after addition of solid reagents. This, in combination with removal of water from the C18 cartridge post-HPLC as discussed above, enabled cross-coupling of [^{18}F]trifluoroethanol with aryl bromides to form products [^{18}F]**2.53B** and [^{18}F]**2.41B** (Scheme 39). Analysis of the reaction mixtures by radioHPLC showed the labelled product, unreacted [^{18}F]trifluoroethanol and traces of [^{18}F]fluoride. Cross-coupling was attempted to prepare [^{18}F]*N*-Boc-flecainide (see Section 2.3.2.2 for synthesis of the aryl bromide precursor and cross-coupling with 2,2,2-trifluoroethanol), however this was unsuccessful. Indeed, in cross-coupling with 2,2,2-trifluoroethanol, the yield of *N*-Boc-flecainide (38%) was significantly lower than that for the 2-napthyl product **2.53B** (85%) and the 4-morpholinyl product **2.41B** (80%). Due to low RCYs obtained in preparing [^{18}F]trifluoroethanol, further substrate scope was not investigated.



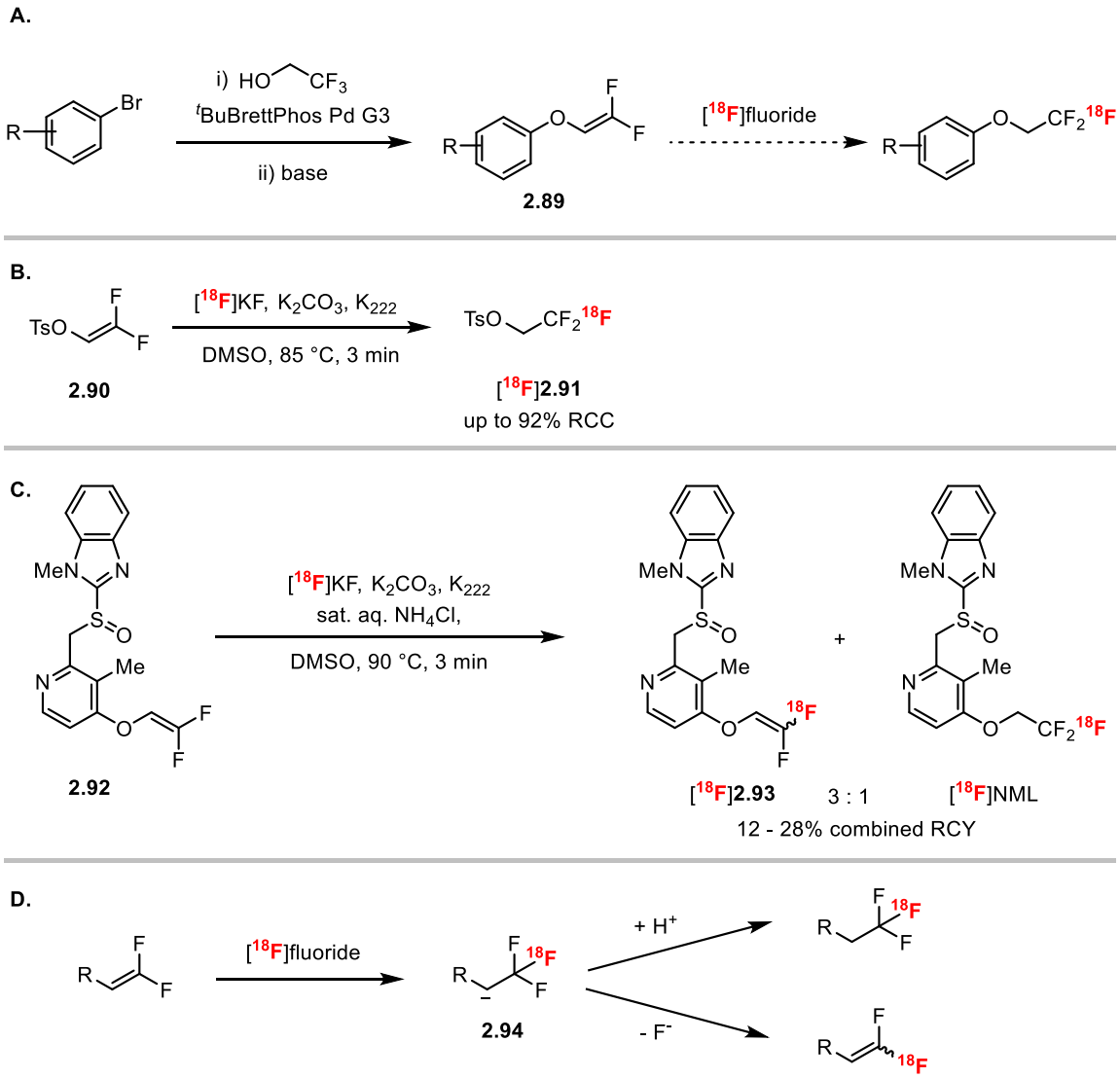
Scheme 39: Palladium-mediated cross-coupling using 'dry' [^{18}F]trifluoroethanol. For [^{18}F]N-Boc-flecainide, the reaction mixture was treated with 300 µL of TFA and heated at 100 °C for 10 minutes after the cross-coupling, but neither [^{18}F]N-Boc-flecainide nor the deprotected product were detected by radioHPLC.

2.4.5 Synthesis and Application of Geminal-Difluorovinyl Ethers

2.4.5.1 Introduction

The cross-coupling of aryl bromides with [^{18}F]trifluoroethanol discussed above provides an alternative to the ^{18}F-fluoroalkylation of phenols for preparing ^{18}F-labelled alkyl aryl ethers. However, this approach requires synthesis of the ^{18}F-labelled alcohol followed by cross-coupling. Due to the short half-life of F-18, direct methods for radiofluorination are preferable. An alternative approach to prepare [^{18}F]trifluoroethyl aryl ethers in a single step from [^{18}F]fluoride was investigated. We proposed that geminal-difluorovinyl ethers **2.89** might undergo reaction with [^{18}F]fluoride to afford [^{18}F]trifluoroethyl aryl ethers (Scheme 40A). The requisite geminal-difluorovinyl ethers **2.89** could be prepared from the corresponding aryl bromides by cross-coupling with 2,2,2-trifluoroethanol followed by elimination of hydrogen fluoride. The Riss group have shown that [^{18}F]fluoride adds to geminal-difluoroalkene **2.90** to afford [^{18}F]trifluoroethyl tosylate [^{18}F]**2.91** with high RCC (Scheme 40B).[124123] Scott and Riss have shown that [^{18}F]NML can be labelled from **2.92** using a similar strategy (Scheme 40C). However, using the conditions Riss reported for

preparing [^{18}F]**2.91** (heating with [^{18}F]KF/K_{222} in dry DMSO), the ^{18}F-labelled geminal-difluorovinyl ether [^{18}F]**2.93** was obtained as the major product (ratio of between 10:1 and 100:1 [^{18}F]**2.93 :** [^{18}F]NML, 1 – 3% combined RCY). This is presumably due to addition of [^{18}F]fluoride followed by elimination of ^{19}F-fluoride (Scheme 40D). To favour formation of [^{18}F]NML, Scott and co-workers tested various protic additives to trap the intermediate carbanion **2.94**. Addition of ammonium chloride facilitated the reaction, but [^{18}F]NML was still formed with poor selectivity (3:1 [^{18}F]**2.93 :** [^{18}F]NML**,** 12 – 28% combined RCY).[7576]

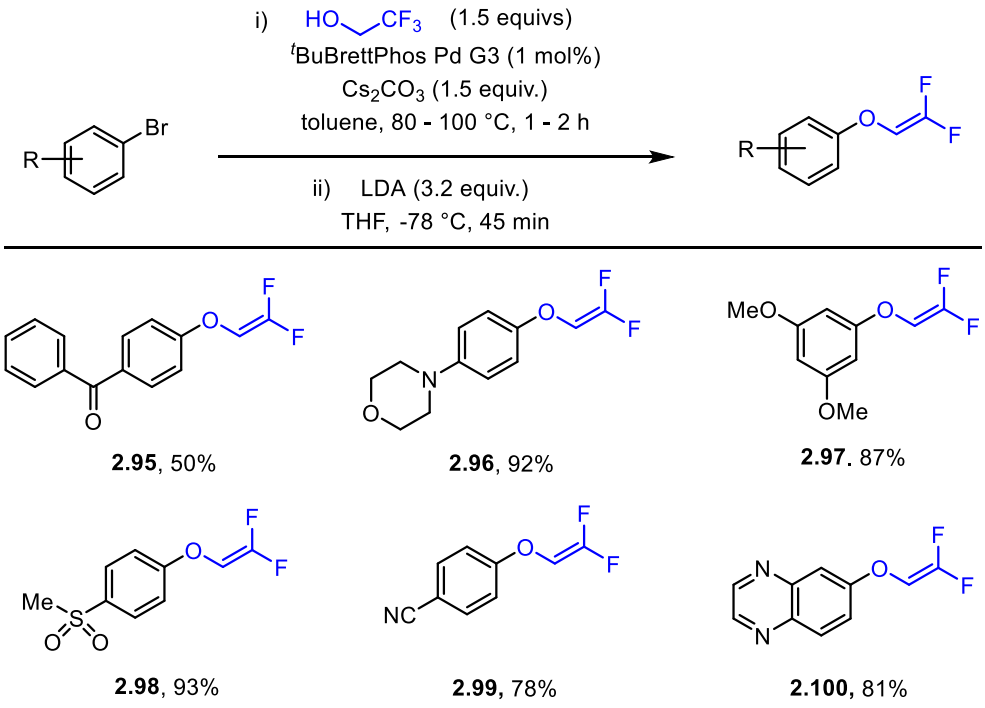


*Scheme 40: A. Our proposed approach to [^{18}F]trifluoroethyl ethers from aryl bromides, via geminal-difluorovinyl ethers **2.89**. B. Preparation of [^{18}F]trifluoroethyl tosylate [^{18}F]**2.91** by*

*addition of [^{18}F]fluoride to 1,1-difluoroalkene **2.90**, reported by the Riss group.[124,123] C. Radiosynthesis of [^{18}F]NML, reported by Scott, Riss and co-workers.[75] D. Proposed reaction mechanism.*

2.4.5.2 Synthesis of Geminal-Difluorovinyl Ethers

Geminal-difluorovinyl ethers were prepared from aryl bromides using a simple telescoped procedure; cross-coupling with 2,2,2-trifluoroethanol under the conditions developed within this chapter, followed by celite filtration, solvent switch to THF, and elimination of hydrogen fluoride with lithium diisopropylamide (Scheme 41). Using this method, a selection of electron-poor, neutral, and electron-rich geminal-difluorovinyl ethers were prepared (**2.95** – **2.100**).



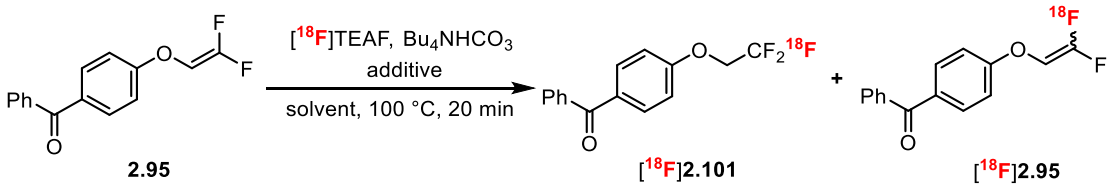
Scheme 41: Preparation of geminal-difluorovinyl ethers from aryl bromides.

2.4.5.3 Optimisation of ^{18}F-Labelling

When geminal-difluorovinyl ether **2.95** was treated with [^{18}F]fluoride in anhydrous DMSO, the major product was the ^{18}F-labelled geminal-difluorovinyl ether [^{18}F]**2.95**, with only 2% RCC to the desired product [^{18}F]**2.101** observed (Entry 1, Table 11) . This is

consistent with the observations from Scott and Riss' work on preparing [^{18}F]lansoprazole.[75,76] Using DMSO containing 2400 ppm of water, the desired product [^{18}F]**2.101** was obtained in 11% RCC (Entry 2). The additional water acts as a proton source to quench to intermediate carbanion. Other proton sources were tested using anhydrous DMSO. Using 1 equivalent (relative to **2.95**) of isopropanol or *tert*-butanol, [^{18}F]**2.101** was formed in 8% and 6% RCC respectively (Entries 3 and 4). Under all these conditions (Entries 1 to 4), the ^{18}F-labelled geminal-difluorovinyl ether [^{18}F]**2.95** was formed in over 80% RCC. Using 100 equivalents of isopropanol, no formation of either [^{18}F]**2.95** or [^{18}F]**2.101** was observed (Entry 5). This is likely due to the reduced nucleophilicity of [^{18}F]fluoride as a result of hydrogen bonding with isopropanol.[30] Similarly, addition of 1 equivalent of pyridinium para-toluene sulphonate resulted in no reaction (Entry 6). Use of dry 1,2-dimethoxyethane (DME) as solvent afforded [^{18}F]**2.101** in 10% RCC, and [^{18}F]**2.95** in 81% RCC (Entry 7). Using 1 vol% water in DME, the desired product [^{18}F]**2.101** was formed in 31% RCC, with formation of [^{18}F]**2.95** reduced to 33% (Entry 8). Using a slightly modified procedure, in which residual acetonitrile was removed prior to addition of **2.95** and DME ([^{18}F]TEAF was dispensed as a solution in acetonitrile), a significant reduction in RCC to 6% was observed (Entry 9).

*Table 11: Optimisation of synthesis of [^{18}F]trifluoroethyl ether [^{18}F]**2.101** from [^{18}F]fluoride. RCC values averaged over two runs. PPTS = pyridinium para-toluene sulphonic acid. [a]MeCN, in which the [^{18}F]TEAF was dispensed, was removed by heating under flow of N_2 before addition of **2.95** and DME. [b]Reaction performed at 80 °C. RCC determined by RadioHPLC and RadioTLC. DME = 1,2-dimethoxyethane, TEAF = tetraethylammonium fluoride. RCCs are averaged over two runs of the same conditions.*



Entry	Solvent	Water content	Additive (1 equiv.)	% RCC [^{18}F]2.101	% RCC [^{18}F]2.95
1	DMSO	35 ppm	none	2	87
2	DMSO	2400 ppm	none	11	81
3	DMSO	35 ppm	^{i}PrOH	8	85
4	DMSO	35 ppm	^{t}BuOH	6	81
5	DMSO	35 ppm	^{i}PrOH (100 equiv.)	0	0
6	DMSO	35 ppm	PPTS	0	0
7	DME	117 ppm	none	10	81
8	DME	1 vol%	none	31	33
9[a]	DME	1 vol%	none	6	4

This data suggests that direct addition of [^{18}F]fluoride to geminal-difluorovinyl ethers is indeed possible, however the formation of the labelled trifluoroethyl ether [^{18}F]**2.101** is accompanied by significant formation of the labelled geminal-difluorovinyl ether [^{18}F]**2.95**. Due to the similarly in structure of these species, they were difficult to separate via reverse-phase HPLC. This would complicate purification of a radiotracer prepared via this method. Scott and Riss have however reported separating [^{18}F]NML from the ^{18}F-labelled geminal-difluorovinyl ether [^{18}F]**2.93** using a perfluorophenyl capped stationary phase.[75]

2.5 Conclusions

A C–O cross-coupling between fluorinated alcohols and aryl halides has been developed, catalysed by ^{t}BuBrettPhos Pd G3 and using cesium carbonate as base. Electron-rich, neutral, and poor aryl bromides are compatible, as are electron-neutral and poor aryl chlorides. A wide range of functional groups on the aryl halide are tolerated. Various fluorinated alcohols couple effectively under the reaction conditions. The method was also applied for ^{18}F-radiolabelling; [^{18}F]trifluoroethanol was prepared using a newly developed synthesis, and was coupled with aryl bromides. Key to the success of the coupling with [^{18}F]trifluoroethanol was minimising the water content, and flushing the reaction vial with nitrogen. To the best of our knowledge, this represents the first example of C–O cross-coupling for ^{18}F-radiolabelling. While we focused our efforts on synthesising and coupling [^{18}F]trifluoroethanol, the insights gained should enable coupling with other ^{18}F-labelled alcohols such as [^{18}F]fluoroethanol, which can be prepared with a far greater molar activity of over 100 GBq μmol^{-1}.[126] Proof-of-concept of an alternative approach to ^{18}F-trifluoroethyl ethers by adding [^{18}F]fluoride directly to geminal-difluorovinyl ethers was also presented, including a telescoped procedure to access the precursors from aryl bromides.

Chapter 3

Preparation of [^{18}F]Selectfluor from [^{18}F]Fluoride

This chapter introduces prior work on the ^{18}F-labelling of electrophilic fluorinating reagents, before discussing research aimed at preparing [^{18}F]Selectfluor bis(triflate) from [^{18}F]fluoride. This research comprises studies of the synthesis of [^{18}F]xenon difluoride from [^{18}F]fluoride, and subsequent reaction with monoquaternised 1,4-diazabicyclo[2.2.2]octane salts to afford [^{18}F]Selectfluor bis(triflate) and related F-TEDA reagents. The characterisation of [^{18}F]Selectfluor bis(triflate) and a preliminary application of the reagent are also described. All non-radioactive experiments described in this chapter were conducted by R. Szpera. All ^{18}F-labelling experiments were conducted by R. Szpera with assistance from Dr. G. Destro, Dr. J. Sap and A. W. J. Poh.

3.1 Introduction

3.1.1 Electrophilic ^{18}F-Fluorinating Reagents

The use of [^{18}F]fluoride for preparing ^{18}F-labelled radiotracers is preferred to use of [^{18}F]F_2 gas for multiple reasons. [^{18}F]Fluoride can be produced in high molar activities of up to 5000 GBq μmol^{-1}, while [^{18}F]F_2 gas is typically only available in up to 0.6 GBq μmol^{-1}, or 55 GBq μmol^{-1} via post-target production (see Section 1.2.3).[22] [^{18}F]Fluoride is conveniently handled as an aqueous solution, enabling easy manipulation using standard apparatus and procedures. As an aqueous solution, [^{18}F]fluoride can be easily transported from a site equipped with a cyclotron, to satellite radiochemistry facilities which lack production capacity. In contrast, [^{18}F]F_2 is a gas and therefore requires special equipment and handling, and is difficult to transport.

While the use of [^{18}F]fluoride is preferred in F-18 radiochemistry, many modern fluorination reactions can only be accomplished with electrophilic sources of fluorine derived from F_2. Use of [^{18}F]F_2 for such electrophilic radiofluorinations is complicated by

its high reactivity and low selectivity.[137] In light of this, syntheses of various ^{18}F-labelled electrophilic fluorinating agents have been reported, such as [^{18}F]Selectfluor bis(triflate) and [^{18}F]NFSI (Figure 14).[69,70] These reagents are more selective than [^{18}F]F_2 gas,[137,138] and their ^{19}F-isotopologues have well established reactivities which can be exploited.[139,140] However, most electrophilic ^{18}F-fluorinating reagents are prepared from [^{18}F]F_2 gas. Therefore, the limitations associated with use of [^{18}F]F_2 gas, including availability, manipulation difficulties / requirement for specialised equipment, and low molar activity also apply for these reagents.

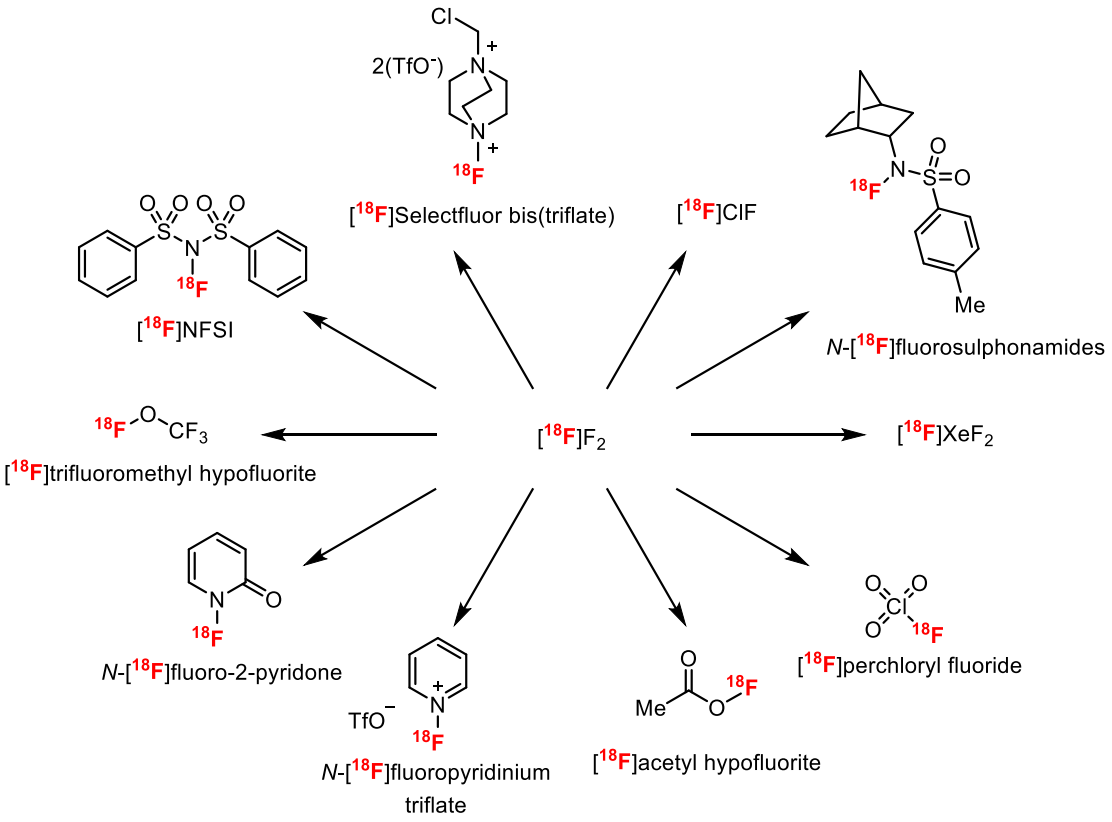
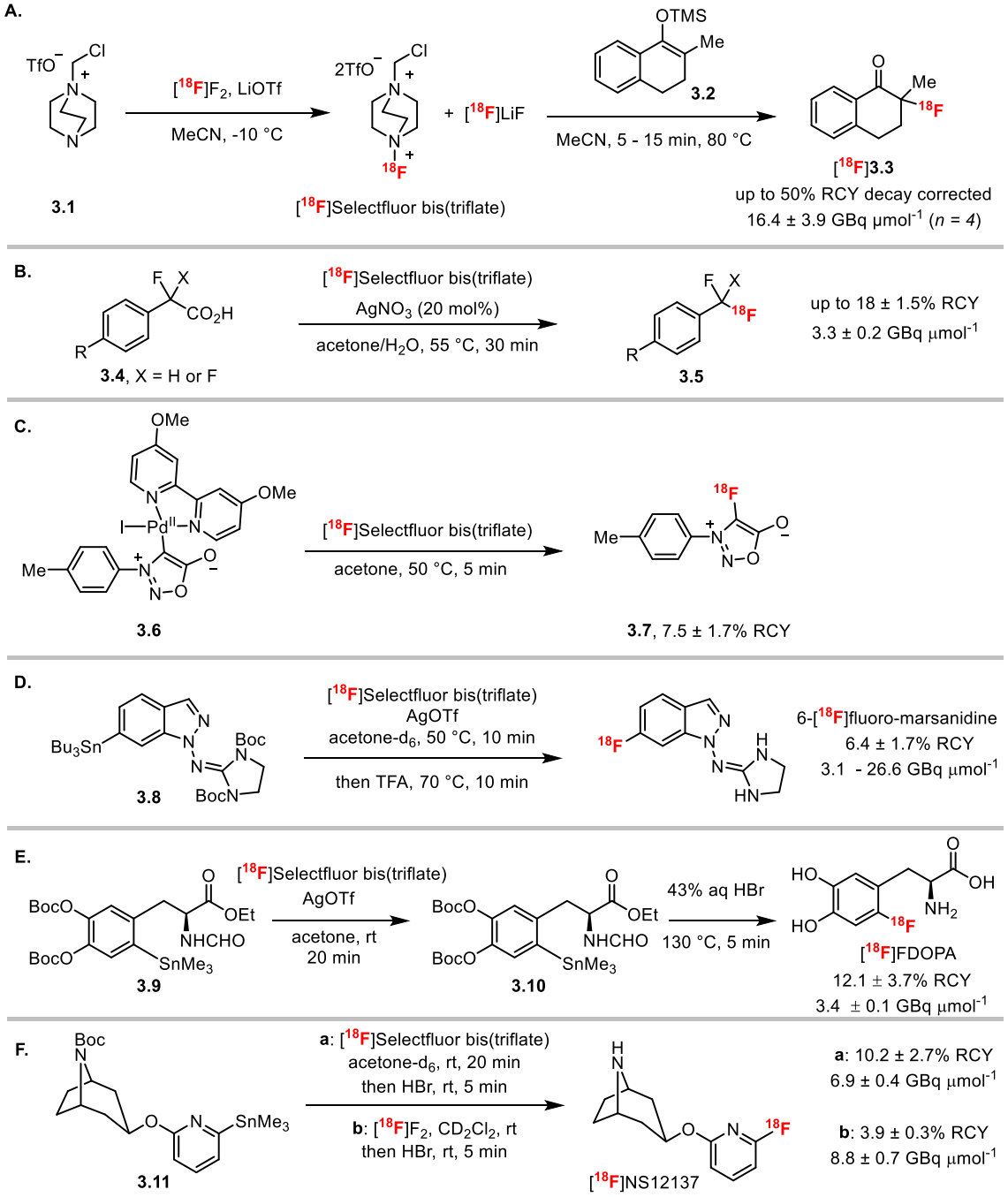


Figure 14: Electrophilic ^{18}F-fluorinating reagents labelled from [^{18}F]F_2 gas. References: [^{18}F]NFSI,[70] [^{18}F]Selectfluor,[69] [^{18}F]ClF,[141] N-[^{18}F]fluoro-N-alkylsulphonamides,[142] [^{18}F]XeF_2,[143] [^{18}F]perchloryl fluoride,[144] [^{18}F]acetyl hypofluorite,[145] N-[^{18}F]fluoropyridinium triflate,[146] N-[^{18}F]fluoro-2-pyridone,[147] [^{18}F]trifluoromethyl hypofluorite.[148]

3.1.1.1 [^{18}F]Selectfluor

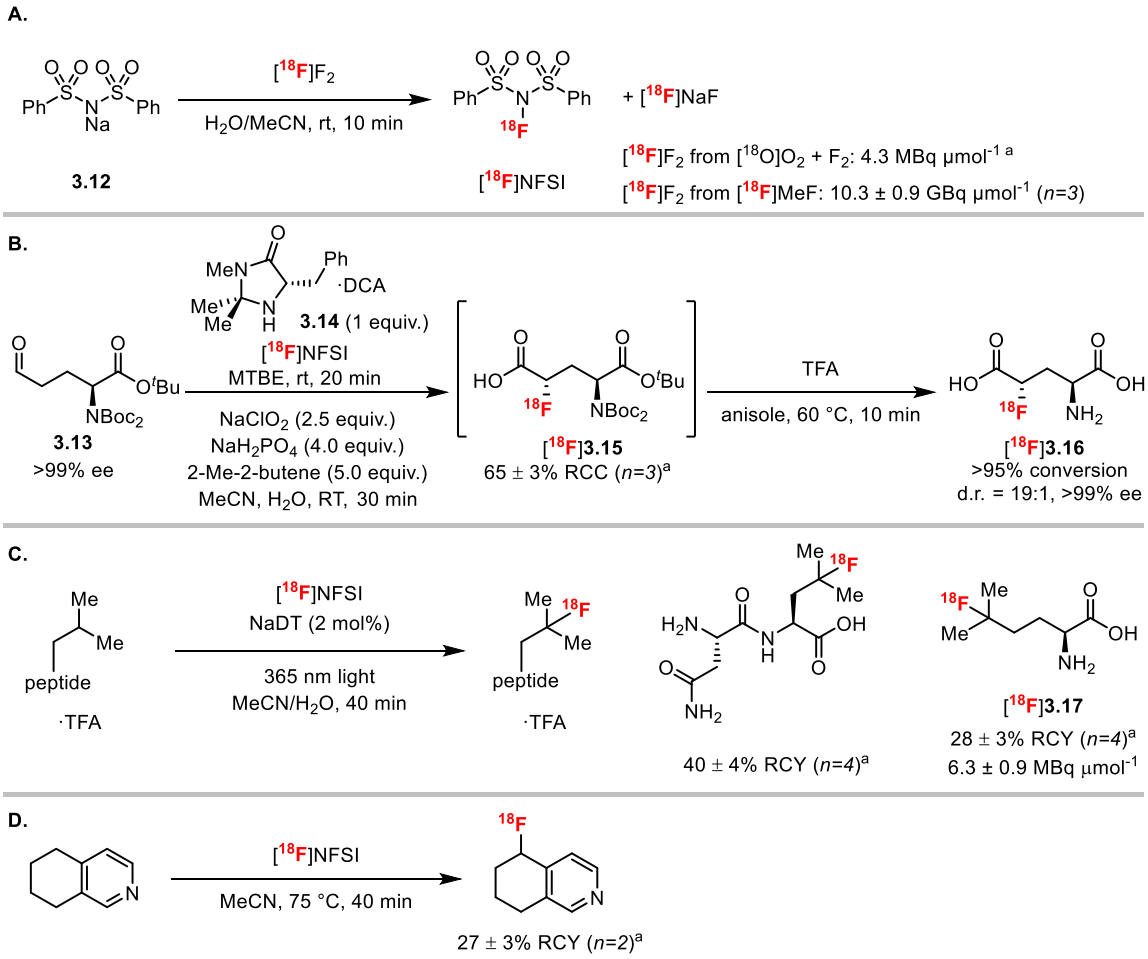
Solin, Luthra, Gouverneur and co-workers have reported the preparation of [^{18}F]Selectfluor bis(triflate) by reaction of 1-(chloromethyl)-1,4-diazabicyclo[2.2.2]octan-1-ium triflate **3.1** and lithium triflate with [^{18}F]F_2 gas in acetonitrile at -10 °C (Scheme 42A).[69] The ^{18}F-fluorination is instantaneous with concomitant formation of [^{18}F]lithium fluoride. The labelled reagent can be used directly as a solution in acetonitrile without purification. Due to the lack of UV-chromophore on [^{18}F]Selectfluor, the molar activity was measured after reaction with silyl enol ether **3.2**. The α-fluorinated ketone [^{18}F]**3.3** was obtained with a molar activity of 16.4 ± 3.9 GBq μmol^{-1}. [^{18}F]Selectfluor bis(triflate) has since been applied for various transformations that would be difficult to accomplish with [^{18}F]fluoride, including silver mediated decarboxylative radiofluorination of α-fluorinated phenyl acetic acids **3.4** for preparing di- and trifluoromethyl arenes [^{18}F]**3.5** (Scheme 42B),[137] radiofluorination of an aryl palladium(II) complex **3.6** (Scheme 42C),[149] and radiofluorination of aryl stannanes **3.8**, **3.9** and **3.11** for preparing the radiotracers 6-[^{18}F]fluoro-marsanidine, [^{18}F]FDOPA (radiosynthesis from [^{18}F]fluoride is now well known for this tracer)[46] and [^{18}F]NS12137 respectively (Scheme 42D, E and F).[138,150,151] These radiotracers were synthesised from [^{18}F]Selectfluor prepared using post-target produced [^{18}F]F_2 gas, and hence their molar activities are higher than that of [^{18}F]F_2 produced from [^{18}O]O_2. In the preparation of [^{18}F]NS12137, the Solin group compared [^{18}F]F_2 and [^{18}F]Selectfluor for the ^{18}F-fluorodestannylation of **3.11** (Scheme 42F). [^{18}F]Selectfluor afforded fewer by-products and the desired product in significantly higher RCY, highlighting the increased selectivity in electrophilic fluorinations using [^{18}F]Selectfluor.[138]



Scheme 42: A. Radiosynthesis of [^{18}F]Selectfluor bis(triflate), reported by Solin, Luthra, Gouverneur and co-workers.[69]. B. Decarboxylative radiofluorination for preparing di and trifluoromethylarenes, reported by Luthra, Passchier, Solin, Gouverneur and co-workers.[137] C. Radiofluorination of an organopalladium complex, reported by Solin, Gouverneur, Taran, and co-workers.[149] TFA = trifluoroacetic acid. D, E, and F. Radiofluorination of aryl stannanes, reported by the Solin group.[150,138,151]

3.1.1.2 [^{18}F]NFSI

The Gouverneur group have also reported the synthesis of [^{18}F]NFSI, by reaction of sodium dibenzenesulphonimide **3.12** with [^{18}F]F_2 gas in water and acetonitrile (Scheme 43A).[70] After azeotropic drying to remove water, [^{18}F]NFSI was redissolved in a solvent of choice for subsequent reaction, without purification. [^{18}F]NFSI has been used in various transformations that could not be carried out using [^{18}F]fluoride, including enantioselective α-fluorination of aldehydes mediated by chiral oxazolidinone **3.14**. This method was applied to the stereoselective synthesis of the radiotracer (2S,4R)-4-[^{18}F]fluoroglutamic acid [^{18}F]**3.16** (Scheme 43B).[152] [^{18}F]NFSI has also been used for the C–H fluorination of unprotected amino acids and peptides using a decatungstate photocatalyst. This method was applied for preparing (S)-5-[^{18}F]fluorohomoleucine [^{18}F]**3.17** which has shown promise as radiotracer for imaging L-type amino acid transporter (LAT, Scheme 43C).[153,154,155] [^{18}F]NFSI has also been used heterobenzylic C–H fluorination (Scheme 43D).[156]



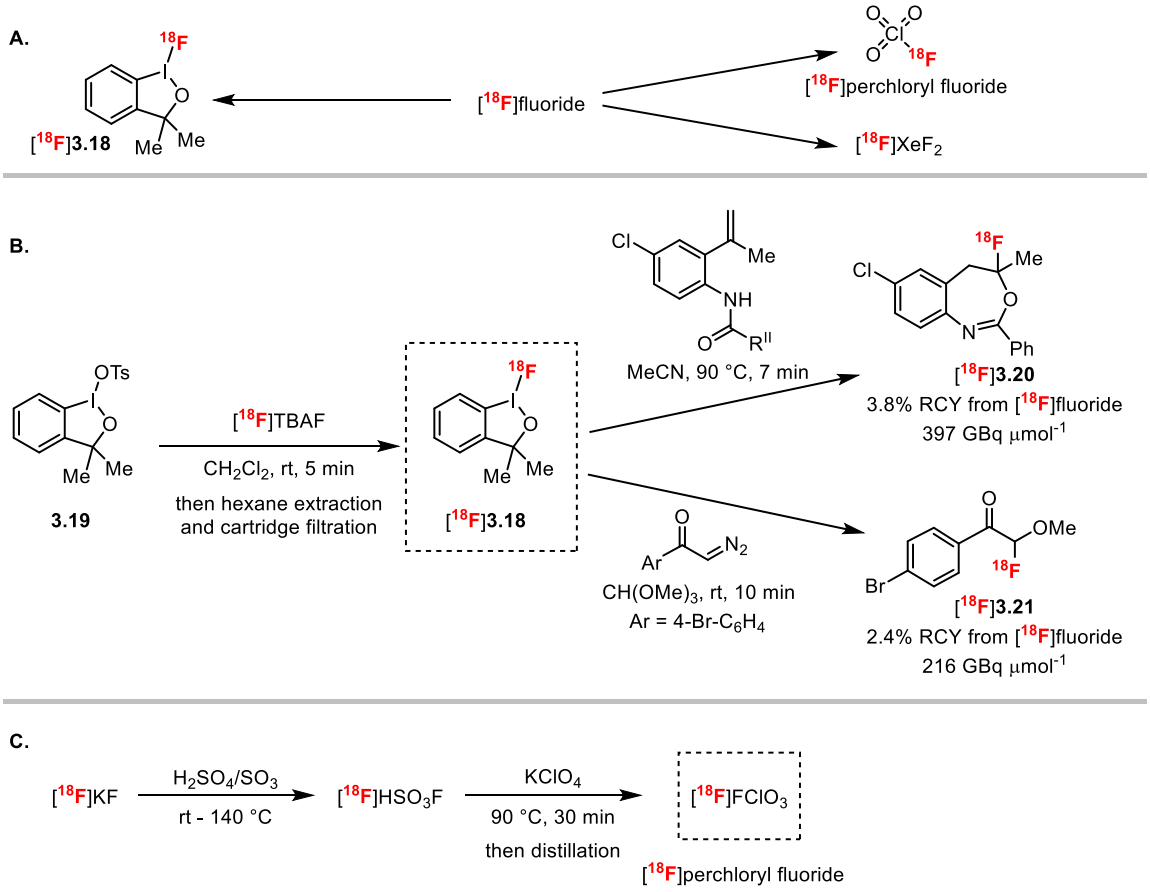
*Scheme 43: A. Synthesis of [^{18}F]NFSI from [^{18}F]F_2 gas, reported by Luthra, Gouverneur and co-workers.[70] [a]molar activity measured for α-fluoro-α-methyltetralone [^{18}F]**3.3** after reaction with α-methyltetralone trimethylsilyl enol ether **3.2**. B. Enantioselective α-radiofluorination of aldehydes, reported by the Gouverneur group.[152] DCA = dichloroacetic acid, MTBE = methyl tert-butyl ether, ee = enantiomeric excess. C. Light-mediated C–H radiofluorination of unprotected peptides, reported by the Britton Group.[154] TFA = trifluoroacetic acid, NaDT = sodium decatungstate. D. Heterobenzylic C–H radiofluorination, reported by the Britton group.[156] [a]Determined from radioactivity of [^{18}F]NFSI.*

The molar activity of electrophilic ^{18}F-fluorinating reagents derived from [^{18}F]F_2 gas is dependent on the method used to produce the [^{18}F]F_2 gas. Using high molar activity [^{18}F]F_2 gas prepared post-target from [^{18}F]fluoromethane, the Solin group have reported that [^{18}F]NFSI can be obtained with a molar activity of 10.3 ± 0.9 GBq µmol^{-1} (Scheme 43A).[24] Similarly, [^{18}F]Selectfluor bis(triflate) can be prepared with a high molar activity of 16.4 ± 3.9 GBq µmol^{-1} using this method.[69] In contrast, when low molar activity [^{18}F]F_2

gas is used, prepared by proton bombardment of [^{18}O]O_2, [^{18}F]NFSI is obtained with a much lower molar activity of around 4 MBq µmol^{-1} (measured for α-fluoro-α-methyltetralone [^{18}F]**3.3** after reaction with α-methyltetralone trimethylsilyl enol ether **3.2**).[70] As discussed previously, synthesis of high molar activity [^{18}F]F_2 gas from [^{18}F]fluoromethane is a process that requires specialised equipment, and so is not yet a general solution to the problem of low molar activity [^{18}F]F_2 gas and derived reagents.

3.1.2 Electrophilic ^{18}F-Fluorinating Reagents Prepared from [^{18}F]Fluoride

Preparing electrophilic ^{18}F-fluorinating reagents from [^{18}F]F_2 gas as described above enables selective electrophilic ^{18}F-fluorination reactions, however the widespread adoption of these reagents has been hampered by the required use of [^{18}F]F_2 gas for their synthesis. Preparation of electrophilic ^{18}F-reagents from [^{18}F]fluoride is far more desirable yet highly challenging, and only limited progress has been made to date (Scheme 44A). The hypervalent iodine reagent [^{18}F]**3.18** has been prepared by nucleophilic ^{18}F-fluorination of the corresponding tosylate **3.19** (Scheme 44B). [^{18}F]**3.18** has been applied for intramolecular ^{18}F-fluorocyclization forming [^{18}F]**3.20** with a molar activity of 397 GBq µmol^{-1},[157] and ^{18}F-oxyfluorination of diazoketones affording [^{18}F]**3.21** with a molar activity of 216 GBq µmol^{-1}.[158] While these molar activities are excellent, the applications are niche. Synthesis of the electrophilic reagent [^{18}F]perchloryl fluoride has been reported from [^{18}F]fluoride, but the method is limited by poor reproducibility and low RCYs (Scheme 44C).[159]

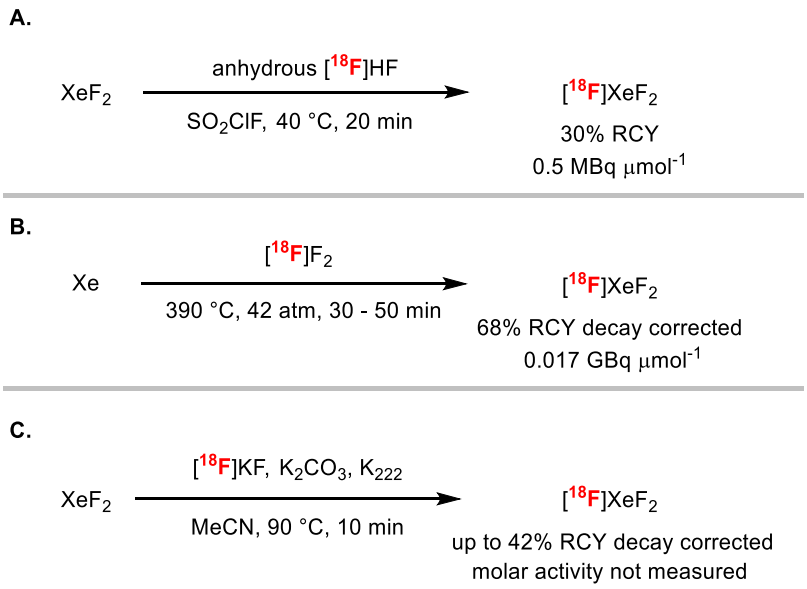


*Scheme 44: A. Reported electrophilic ^{18}F-fluorinating reagents prepared from [^{18}F]fluoride. B. Synthesis and reactivity of ^{18}F-labelled iodine(III) reagent [^{18}F]**3.18**, reported by the Szabó group.[157,158] C. Synthesis of [^{18}F]perchloryl fluoride, reported by the Hiller group.[159]*

3.1.2.1 [^{18}F]Xenon Difluoride

Xenon difluoride is a crystalline white solid which has found use as a highly reactive electrophilic fluorinating agent.[160] Radiosynthesis of [^{18}F]xenon difluoride was first reported by the Schrobilgen group by isotopic exchange between xenon difluoride and anhydrous [^{18}F]hydrogen fluoride (Scheme 45A).[161] Due to the large quantity of xenon difluoride required for this process (680 µmol) and the addition of hydrofluoric acid (300 µmol), [^{18}F]xenon difluoride was obtained with a low molar activity of under 0.5 MBq µmol^{-1}. Subsequently, the Schrobilgen group reported that reaction of xenon gas and [^{18}F]F_2 gas at high temperature and pressure also affords [^{18}F]xenon difluoride, with a higher molar activity of up to 0.017 GBq µmol^{-1} (Scheme 45B).[143] While pioneering,

these approaches were limited in practicality, with synthesis from [^{18}F]hydrogen fluoride requiring multiple distillations and cryogenic temperatures, and synthesis from [^{18}F]F_2 gas requiring high temperatures and pressures, and handling of gaseous radioactivity.



Scheme 45: Methods for preparing [^{18}F]xenon difluoride. A. From anhydrous [^{18}F]hydrogen fluoride, reported by the Schrobilgen group.[161] B. From [^{18}F]F_2 gas, reported by the Schobilgen group.[143] C. From [^{18}F]fluoride, reported by the Pike group.[162]

The Pike group reported the first practical method for [^{18}F]xenon difluoride synthesis, by reaction of xenon difluoride with [^{18}F]fluoride in the form of either [^{18}F]KF/K_{222}, [^{18}F]CsF or [^{18}F]CsF/K_{222} (Scheme 45C).[163,162] Pike and co-workers demonstrated gigabecquerel scale synthesis of [^{18}F]xenon difluoride by heating [^{18}F]KF/K_{222} and xenon difluoride in acetonitrile at 90 °C for 10 minutes. In these isotopic exchange reactions, high loadings of between 56 and 253 μmol of xenon difluoride were required for formation of [^{18}F]xenon difluoride, inevitably resulting in poor molar activity due to isotopic dilution. The molar activity was not reported. Work from the Schrobilgen group showed that the reaction of [^{18}F]KF/K_{222} and xenon difluoride is likely to proceed via exchange between xenon difluoride and *in situ* generated [^{18}F]hydrogen fluoride or [^{18}F]bifluoride (HF_2^-),

rather than by direct exchange with [^{18}F]fluoride. Formation of hydrogen fluoride occurs by reaction of xenon difluoride with Kryptofix-222 or the solvent. Formation of bifluoride can occur by reaction of KF/K_{222} with acetonitrile or dichloromethane solvents.[164] Few applications of [^{18}F]xenon difluoride have been reported. In 1982, [^{18}F]xenon difluoride was reported for the synthesis of [^{18}F]FDG,[165] however this route has long since been superseded by synthesis from [^{18}F]fluoride.[35] The use of [^{18}F]xenon difluoride for preparing ^{18}F-labelled α-fluorinated ketones has also been reported.[162]

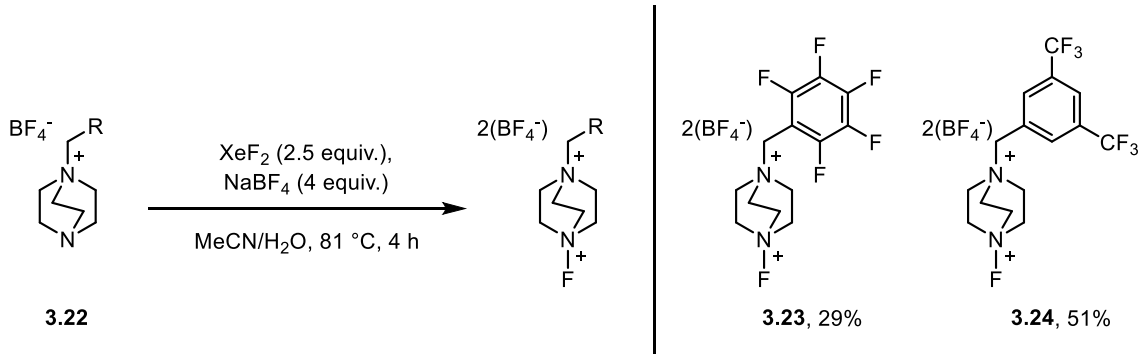
Each of the electrophilic fluorinating agents labelled from [^{18}F]fluoride have limitations; hypervalent iodine reagent [^{18}F]**3.18** has only niche applications, and the synthesis of [^{18}F]perchloryl fluoride suffers from poor reproducibility and low RCYs as discussed. Preparation of [^{18}F]xenon difluoride suffers from poor reproducibility and presumably low molar activity. In addition, xenon difluoride is highly reactive (oxidising) and known to even react with solvents, limiting its utility as a broadly applicable electrophilic fluorinating reagent.[166] Finally, none of these reagents have as widely established reactivity profiles as the more common fluorinating agents Selectfluor and NFSI.[139,140]

3.2 Results and Discussion

3.2.1 Introduction

The Toste group have reported the use of xenon difluoride to synthesise *N*-fluorotriethylenediamine (F-TEDA) reagents **3.23** and **3.24** from the corresponding monoquaternised 1,4-diazabicyclo[2.2.2]octane derivatives (hereafter referred to as DABCOnium salts) **3.22** (Scheme 46).[167] This provides a convenient method for preparing bespoke F-TEDA reagents in the lab, which are otherwise usually synthesised from F_2 gas.

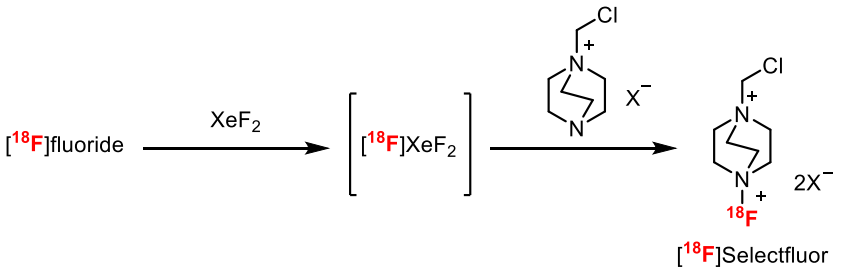
The Toste group used these bespoke reagents in enantioselective fluorocyclisation reactions.



Scheme 46: Synthesis of F-TEDA reagents using xenon difluoride, reported by the Toste group.[167]

3.2.2 Aims of This Work

This work aimed to develop a synthesis of [^{18}F]Selectfluor from widely available, easily handled, high molar activity [^{18}F]fluoride. Given that the Pike group have shown xenon difluoride can be radiolabelled from [^{18}F]fluoride, and that the Toste group have shown that F-TEDA reagents can be prepared from xenon difluoride, we postulated that [^{18}F]Selectfluor could be prepared from [^{18}F]fluoride in one-pot via in situ formation of [^{18}F]xenon difluoride (Scheme 47).



Scheme 47: Proposed synthesis of [^{18}F]Selectfluor from [^{18}F]fluoride via [^{18}F]xenon difluoride.

3.2.3 Formation of N–F Reagents Using Xenon Difluoride

While Selectfluor classically features tetrafluoroborate (BF_4^-) counterions, in a radiochemical setting the presence of these anions has been shown to reduce product

molar activity, presumably by release of fluoride.[168] Triflate (TfO^-) was therefore chosen as a less labile counteranion, which is also sufficiently resistant to oxidation by xenon difluoride (Figure 15).

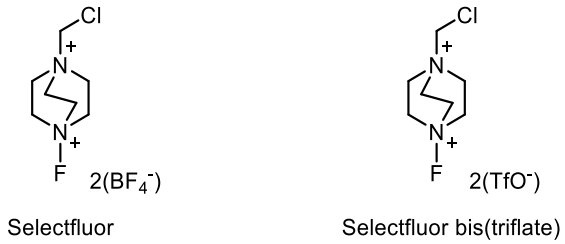


Figure 15: Selectfluor and Selectfluor bis(triflate)

3.2.3.1 Proof of Concept and Characterisation of Selectfluor In Situ

Prior to attempting the radiosynthesis of [^{18}F]Selectfluor from [^{18}F]xenon difluoride, the reaction was investigated with F-19 reagents. Reaction of xenon difluoride with two equivalents of *N*-chloromethyl DABCOnium triflate **3.1** in acetonitrile for 20 minutes at room temperature afforded Selectfluor bis(triflate) in 24% NMR yield (Figure 16). ^{19}F NMR of the crude reaction mixture showed a broad singlet at 48.2 ppm, characteristic of F-a of Selectfluor.[169] The yield of Selectfluor bis(triflate) was determined by quantitative ^{19}F NMR (Figure 16), comparing the integration of F-a with that of α,α,α-trifluorotoluene used as an internal standard. Reaction yields were calculated with respect to xenon difluoride, which would be the limiting reagent in a radiochemical setting. The amount of xenon difluoride remaining in the reaction mixture was also quantified using ^{19}F NMR.

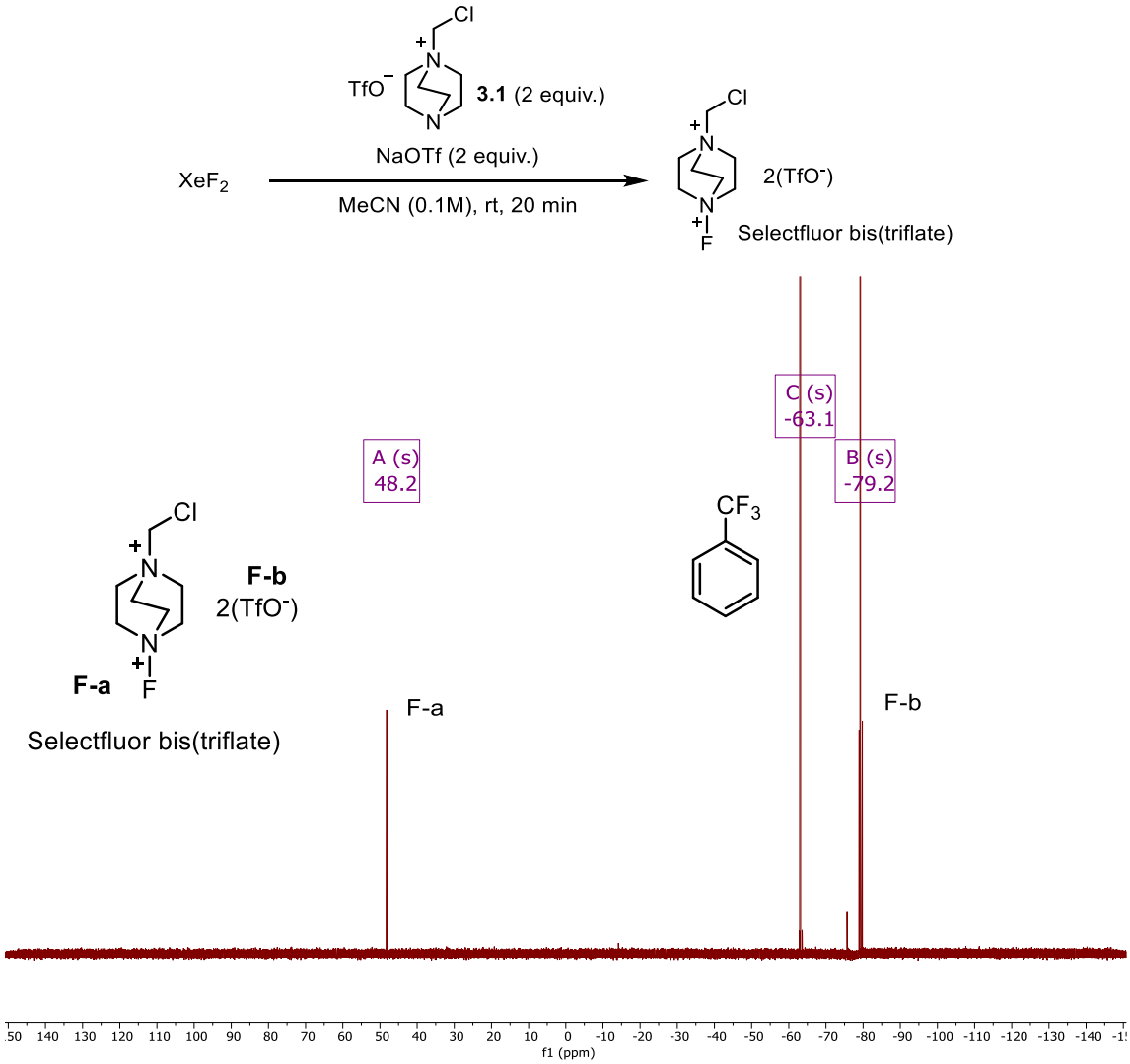


Figure 16: Quantification of Selectfluor bis(triflate) yields using quantitative ^{19}F NMR.

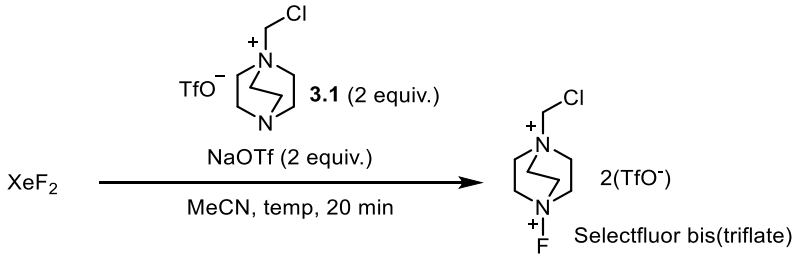
3.2.3.2 Optimisation of Selectfluor bis(triflate) Synthesis from Xenon Difluoride

The factors affecting the yield of Selectfluor bis(triflate) from xenon difluoride were investigated (Table 12). These optimisation reactions were run for 20 minutes, as long durations are undesirable in F-18 radiochemistry due to radioactive decay. Sodium triflate was added to the reactions so that Selectfluor was formed as the bis(triflate) salt rather than a mixed salt with both fluoride and triflate counterions. The sodium fluoride by-product is insoluble in acetonitrile (1.2 mgL^{-1} at 25 °C).[170]

Initially the effect of the concentration of xenon difluoride was investigated (Table 12). This is an important consideration, as to maximise the molar activity of [^{18}F]xenon difluoride and thus [^{18}F]Selectfluor, we aimed to use a low loading of xenon difluoride in the reaction with [^{18}F]fluoride to minimise isotopic dilution (see Section 3.2.4). The reaction to prepare Selectfluor must therefore proceed efficiently at low concentrations of xenon difluoride. At 0.1 M with respect to xenon difluoride, a 24% yield of Selectfluor bis(triflate) was obtained with respect to xenon difluoride (Entry 1).[c] The yield decreased to 10% when the concentration was reduced to 0.05 M (Entry 2). Conversely the yield increased up to 34% and 41% at 0.2 M and 0.4 M concentrations respectively (Entries 3 and 4). Such high concentrations would be difficult to translate to a radiochemical setting without using a high loading of xenon difluoride or performing the reaction in a microfluidic device.[171,162] At lower concentrations, more xenon difluoride remained in the reaction mixture after 20 minutes, suggesting the reaction is slower. The effect of temperature while maintaining a xenon difluoride concentration of 0.1 M was investigated. Running the reaction at 60 °C or 80 °C, resulted in an increased yield of 38%, demonstrating that higher temperature can compensate for lower xenon difluoride concentrations (Entries 6 and 7). Similarly, the yield of the reaction at 0.05 M concentration increased to 27% when run at 60 °C (Entry 8).

[c] To achieve a higher degree of reproducibility in these reactions, xenon difluoride was added as a stock solution in acetonitrile.

Table 12: Effect of concentration and temperature on Selectfluor bis(triflate) synthesis from xenon difluoride. Reactions run with 0.05 mmol of XeF_2.

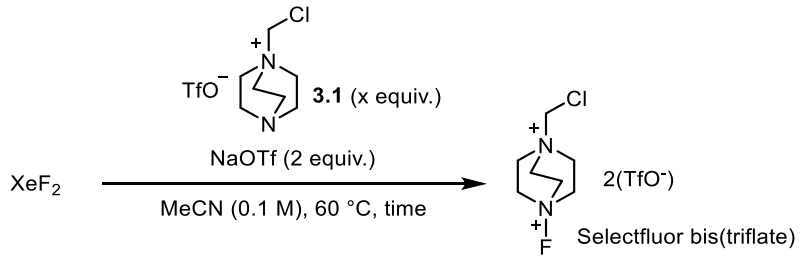


Entry	Temp	[XeF_2] (M)	%XeF_2 Remaining	Yield
1	rt	0.1	45	24
2	rt	0.05	65	10
3	rt	0.2	24	34
4	rt	0.4	22	41
5	40 °C	0.1	31	34
6	60 °C	0.1	11	38
7	80 °C	0.1	6	38
8	80 °C	0.05	23	27

The effect of the stoichiometry of DABCOnium triflate **3.1** was investigated; use of fewer equivalents would be desirable to reduce impurities. This is an important consideration, as [^{18}F]Selectfluor was used without removal of remaining starting material (see Section 3.2.5). Maintaining the concentration at 0.1 M and the temperature at 60 °C, the yield decreased to 22% when only 1.0 equivalent of **3.1** was used, with 48% of xenon difluoride remaining (Entry 2, Table 13). Little change in yield was observed by increasing from 2.0 to 3.0 or 4.0 equivalents of **3.1** (Entries 3 and 4). The time dependence of the reaction was investigated; the yield decreased to 33% when the duration was decreased to 5 minutes (Entry 5). Increasing the duration to 1 hour resulted in an increase in yield to 43% (Entry 6). Various other factors were investigated. The reaction was not highly sensitive to water; use of 10 vol% water in acetonitrile as solvent afforded Selectfluor

bis(triflate) in 31% yield (Entry 7). The slight reduction in yield is probably due to competitive oxidation of water by xenon difluoride ($XeF_2 + H_2O \rightarrow 2HF + Xe + 1/2O_2$).[172] Use of deuterated acetonitrile also afforded Selectfluor bis(triflate) in 38% yield (Entry 8). Finally, use of a plastic reaction vessel instead of a borosilicate glass vessel also resulted in a yield of 38% (Entry 9). Reactions of xenon difluoride can be sensitive to reaction vessel material.[173]

Table 13: Effect of other variables on Selectfluor bis(triflate) synthesis from xenon difluoride. Reactions run with 0.05 mmol of XeF_2.



Entry	3.1 (equiv.)	Duration (mins)	Other Changes	%XeF_2 Remaining	Yield
1	2.0	20	-	11	38
2	1.0	20	-	48	22
3	3.0	20	-	0	39
4	4.0	20	-	0	35
5	2.0	5	-	28	33
6	2.0	60	-	1	43
7	2.0	20	10 vol% H_2O	0	31
8	2.0	20	In MeCN-d_3	7	38
9	2.0	20	plastic vessel	20	38

3.2.3.3 Generation of Hydrogen Fluoride

^{1}H NMR and mass spectroscopy analysis (ESI+) showed the crude reaction mixtures were composed predominantly of Selectfluor bis(triflate) and starting material **3.1**. However, proton resonances for **3.1** in the crude mixtures were significantly deshielded compared

to those for the isolated material (Figure 17A). The deshielding of H-a in the crude mixture may be due to acidification of the reaction medium. This could occur by degradation of xenon difluoride to hydrogen fluoride, via either oxidation of adventitious water, or reaction with the C–H bonds of **3.1** or acetonitrile.[174] In the screening reactions in Table 12 and Table 13, the yield of Selectfluor was lower than the consumption of xenon difluoride, hence some of the latter is consumed unproductively. A singlet was observed in the ^{19}F NMR of the crude reaction mixtures at approximately -183 ppm (in a mixture of 5:3 acetonitrile and deuterated acetonitrile), consistent with the reported shift for hydrogen fluoride in acetonitrile.[175] When *N*-chloromethyl DABCOnium triflate **3.1** was titrated with hydrogen fluoride (0.125 M in acetonitrile, prepared from 48% aqueous hydrogen fluoride) H-a was deshielded in ^{1}H NMR to a shift-range consistent with those measured for the crude optimisation reactions (Figure 17B). These data supports the hypothesis that some xenon difluoride undergoes decomposition to hydrogen fluoride over the course of the reaction.

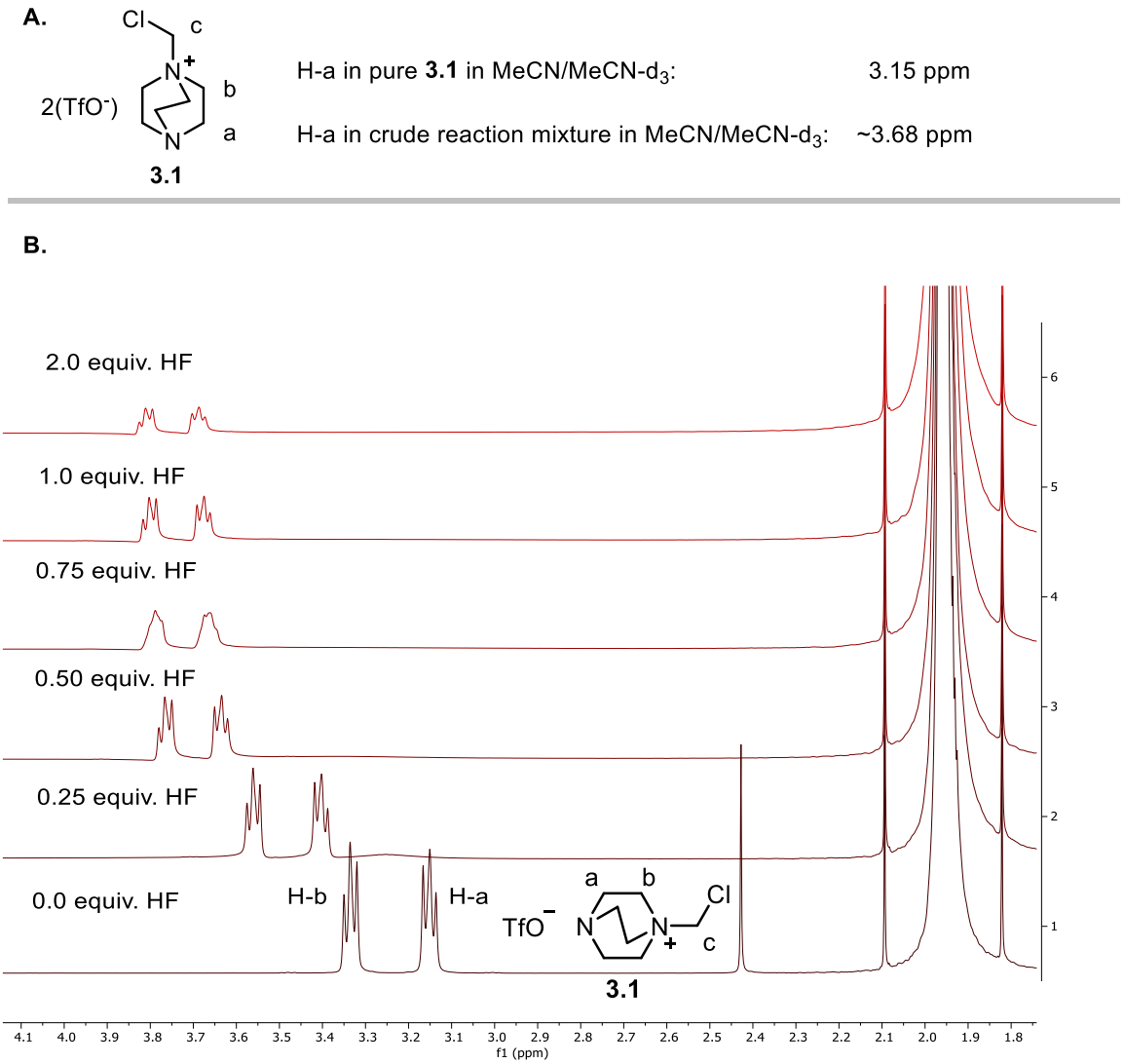


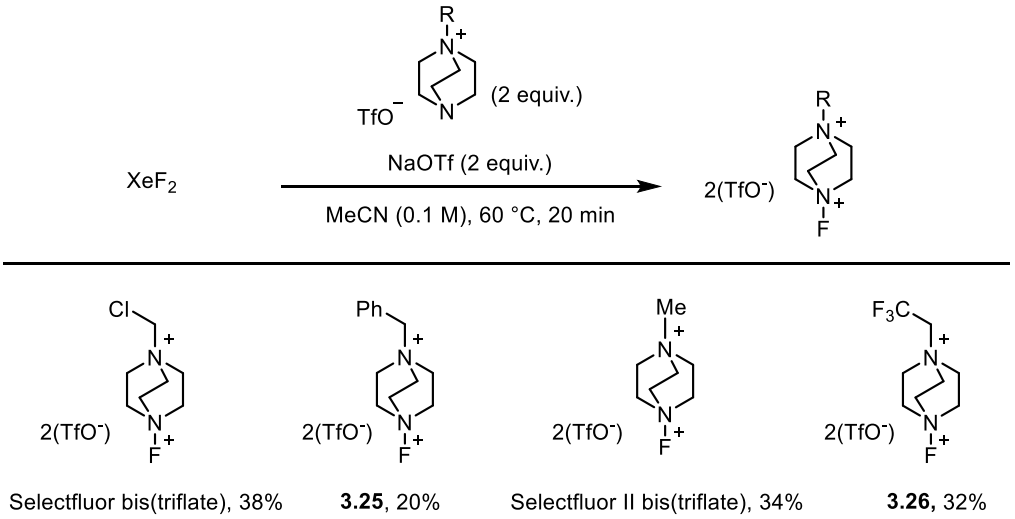
*Figure 17: A: ^{1}H NMR chemical shifts of H-a for a pure sample of **3.1**, and for **3.1** in the crude reaction mixture. B. Stacked ^{1}H NMR spectra of triflate **3.1** following addition hydrogen fluoride (0 to 2 equivalents).*

3.2.3.4 Preparation of Other F-TEDA Reagents from Xenon Difluoride

As reported by Banks and co-workers in their seminal work on F-TEDA reagents, the quaternising alkyl group on nitrogen enables the reactivity to be modulated.[176] Whilst the *N*-chloromethyl analogue Selectfluor is by far the most common F-TEDA reagent, the *N*-methyl analogue Selectfluor II (Scheme 48) is also common and commercially available. In some reactions, Selectfluor II has been shown to afford higher yields than Selectfluor, such as in the radical fluorination of aliphatic C–H bonds reported by the Tang

group.[177] Various other F-TEDA reagents were disclosed by the Banks group, including the *N*-trifluoroethyl reagent **3.26** which was reported to be the most reactive of those prepared.

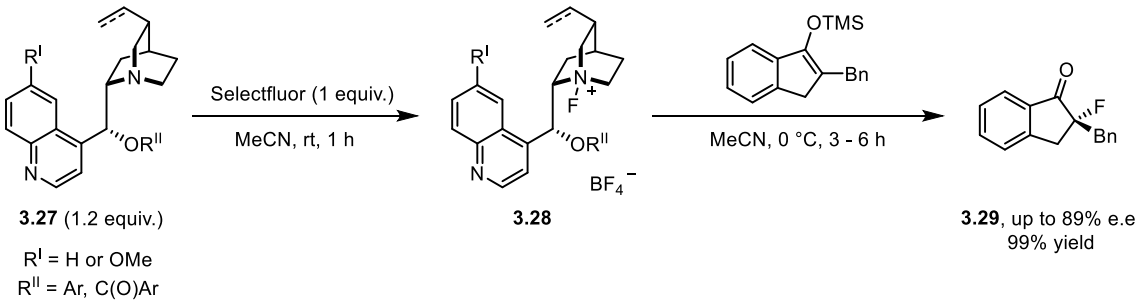
The use of [^{18}F]xenon difluoride to prepare different ^{18}F-labelled F-TEDA reagents in addition to [^{18}F]Selectfluor was considered. The influence of the quaternising group on nitrogen on the yield of the F-TEDA reagent from xenon difluoride was therefore investigated (Scheme 48). The quaternising group was found to have an influence on reactivity, however no obvious trend with regards to the electronic properties of the group was observed. Notably, of the substrates tested, Selectfluor bis(triflate) was formed in the highest yield at 38%. Synthesis of *N*-benzylated F-TEDA **3.25** was investigated, as its UV-absorbance (and retention on C18 columns) would facilitate analysis of the radiochemical reactions by HPLC (see Section 3.2.5.2). **3.25** was obtained in 20% yield. The *N*-methyl and *N*-trifluoroethyl substituted DABCOniums afforded the corresponding F-TEDA reagents Selectfluor II bis(triflate) and **3.26** in 34% and 32% respectively. It should be noted that upon repeating the synthesis of these F-TEDA reagents the yields varied, however the trend of which was formed in the highest yield was consistent. This data supports the feasibility of preparing a range of ^{18}F-labelled F-TEDA reagents from [^{18}F]fluoride.



Scheme 48: Effect of quaternising group on the yield of F-TEDA reagents from xenon difluoride.

3.2.3.5 Preparation of Chiral N–F Reagents from Xenon Difluoride

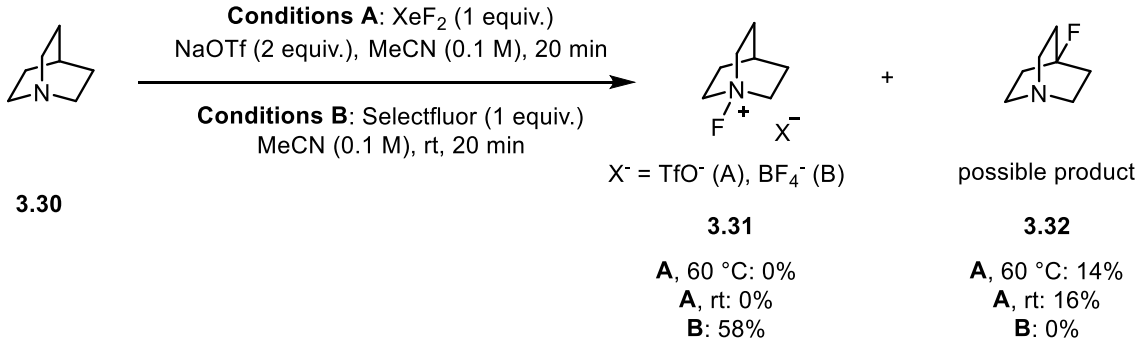
The use of chiral *N*-fluorocinchona alkaloid derivatives **3.28** has been reported in various enantioselective electrophilic fluorination reactions, such as α-fluorination of silyl enol ethers (Scheme 49).[178,179,180,181] These reagents can be prepared in situ by fluorination of the parent cinchona alkaloid derivative **3.27** with Selectfluor.



Scheme 49: Enantioselective electrophilic fluorination mediated by chiral cinchona alkaloid derivatives, reported by the Shibata group.[178]

Use of the corresponding ^{18}F-labelled reagents for enantioselective ^{18}F-labelling reactions was considered. While such reagents might be prepared from [^{18}F]Selectfluor, direct synthesis from [^{18}F]xenon difluoride would be preferable. A model reaction of xenon difluoride with quinuclidine (the bicyclic core of the cinchona alkaloids) was therefore

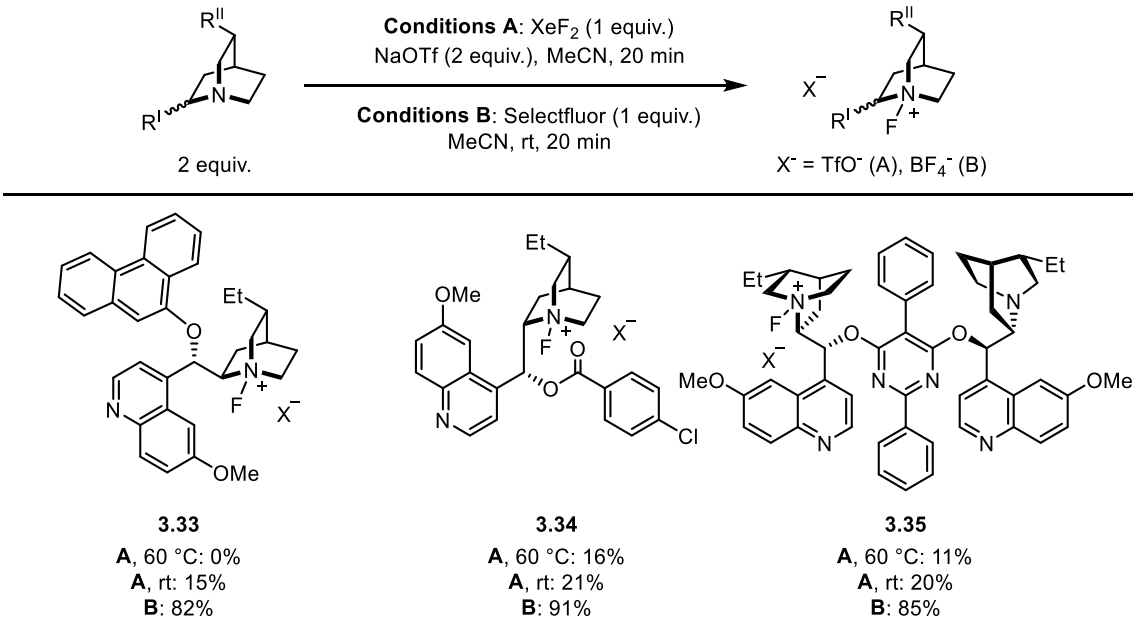
investigated (Scheme 50). Upon addition of xenon difluoride to quinuclidine in acetonitrile at room temperature, an exothermic reaction took place immediately. However, no *N*-fluoroquinuclidine **3.31** was observed immediately by ^{19}F NMR, or after 20 minutes at either 60 °C or at room temperature. The xenon difluoride was entirely consumed at both temperatures, and a new species was observed by ^{19}F NMR at -149.7 ppm (16% yield at room temperature, 14% yields at 60° C). This species could result from C–H fluorination at the tertiary position of quinuclidine, affording **3.32**. Indeed the ^{19}F NMR shift is consistent with that of structurally related tertiary alkyl fluorides,[182] and a product with mass corresponding to **3.32** was observed by mass spectroscopy (LRMS ESI+ m/z: $[M+H]^+$ Calcd for $C_7H_{13}FN$ 130.2; Found 130.2). Fluorination of tertiary C–H bonds with xenon difluoride has been reported in the literature.[183] This result is in stark contrast to that using Selectfluor, which afforded *N*-fluoroquinuclidine **3.31** in 58% yield after 20 minutes at room temperature, with no formation of **3.32**.[184]



Scheme 50: Reaction of xenon difluoride and Selectfluor with quinuclidine.

Despite unsuccessful attempts to prepare *N*-fluoroquinuclidine **3.31** with xenon difluoride, the reactivity of various cinchona alkaloid derivatives was tested (Scheme 51). Reaction of xenon difluoride with hydroquidine-9-phenanthyrl ether at 60 °C did not

afford any of the corresponding *N*-fluorinated compound **3.33**, yet the xenon difluoride was fully consumed. For this cinchona alkaloid derivative, in addition to the tertiary C–H bond of the quinuclidine ring, xenon difluoride may react with the electron rich phenanthryl ring. Performing the reaction at room temperature afforded the *N*-fluorinated product **3.33** in 15% yield with respect to xenon difluoride. Treatment of hydroquinine-4-chlorobenzoate with xenon difluoride at 60 °C afforded the corresponding *N*-fluorinated compound **3.34** in 16% yield, while 21% yield was obtained at room temperature. The cinchona alkaloid derivative $(DHQ)_2Pyr$ underwent fluorination to afford **3.35** in 11% yield at 60 °C, and 20% yield at room temperature. The higher yields obtained at lower temperatures contrasts with the trend observed for preparing Selectfluor. This may be due to the presence of more oxidation sensitive functional groups in these cinchona alkaloid derivatives. In stark contrast to xenon difluoride, Selectfluor afforded **3.33**, **3.34** and **3.35** each in over 80% yield (Conditions B). Compounds **3.33**, **3.34** and **3.35** were characterised in solution by mass spectroscopy (ESI+) and ^{19}F NMR, with spectra consistent with those reported in the literature.[180,185] Further reaction optimisation with xenon difluoride was not pursued, however this data suggests the potential of preparing chiral electrophilic ^{18}F-fluorinating agents from [^{18}F]fluoride via [^{18}F]xenon difluoride. The compatibility of this reaction with a range of chiral amines could facilitate optimisation of enantioselective ^{18}F-fluorinations by changing the amine scaffold. The stark difference in yields of *N*-fluorinated products when using xenon difluoride and Selectfluor highlight their different reactivities.



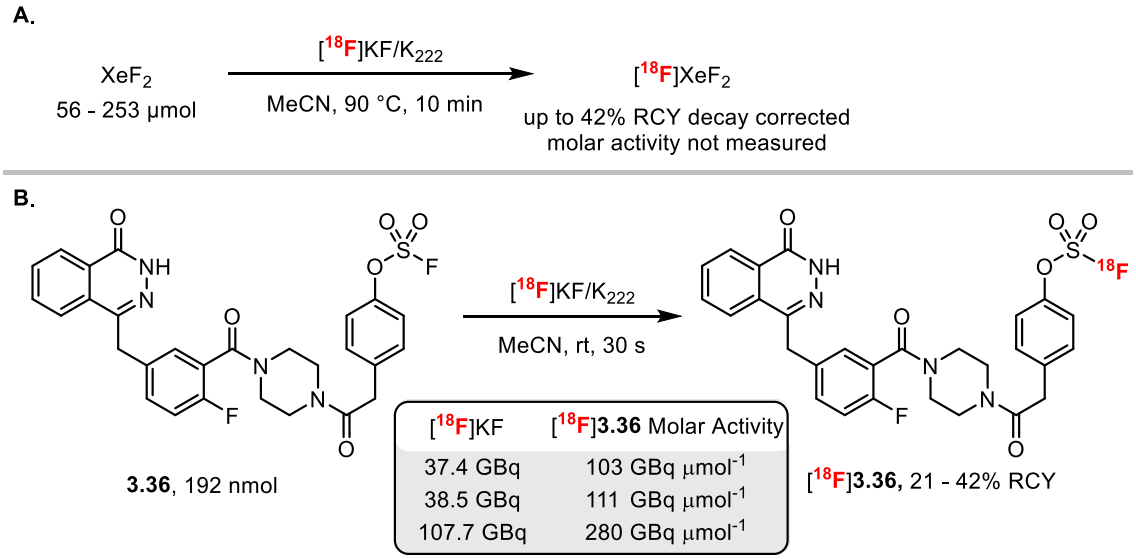
Scheme 51: Reaction of xenon difluoride or Selectfluor with quinuclidine and chiral cinchona alkaloid derivatives.

3.2.4 Preparation of [^{18}F]Xenon Difluoride

3.2.4.1 Stability of Xenon Difluoride Towards Reagents Used for Eluting [^{18}F]Fluoride

The Pike group reported preparing [^{18}F]xenon difluoride via isotopic exchange, using high loadings of xenon difluoride of up to 253 µmol (Scheme 52A).[162] The molar activity was not measured in this report, but low values are expected in isotopic exchange reactions using such high quantities of the F-19 substrate.[120] High molar activities can be achieved in isotopic exchange reactions by using low F-19 substrate loading and high amounts of starting radioactivity. Indeed, recent work from Sharpless, Yang, Wu and co-workers showed that aryl fluorosulphonates such as **3.36** can be ^{18}F-labelled via isotopic exchange in molar activities of up to 280 GBq µmol^{-1}, decay corrected to end of synthesis (Scheme 52B).[186] This was achieved using a high starting activity of 108 GBq of [^{18}F]KF, and a low substrate loading of 172 nmol of **3.36**. The molar activity of [^{18}F]**3.36** scaled approximately linearly with the quantity of starting radioactivity. Lowering the loading of

xenon difluoride is likely to increase the molar activity of [^{18}F]xenon difluoride and ultimately [^{18}F]Selectfluor. We speculated that the high loadings of xenon difluoride required in the protocol reported by Pike and co-workers could be partly due to decomposition of some of the xenon difluoride under the labelling conditions.



Scheme 52: A. The Pike group's conditions for labelling [^{18}F]xenon difluoride from [^{18}F]fluoride.[162] *B. High molar activity radiosynthesis of aryl [^{18}F]fluorosulphates via isotopic exchange, reported by Sharpless, Yang, Wu and co-workers.*[186]

The stability of xenon difluoride was investigated using ^{19}F NMR. Solutions of xenon difluoride in acetonitrile are known to be stable in borosilicate glass vessels for days at room temperature.[187] However reaction of xenon difluoride with [^{18}F]fluoride requires elevated temperature. Heating a 0.1 M solution of xenon difluoride in anhydrous acetonitrile in borosilicate glass at 80 °C for 20 minutes resulted in negligible degradation (Entry 1, Table 14). As absolute exclusion of water is challenging to achieve in a radiochemical setting, the stability of xenon difluoride while heated in 10 vol% water in acetonitrile was tested; 29% degradation was observed (Entry 2). This result is consistent with xenon difluoride's ability to oxidise water.[172]

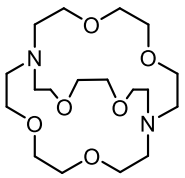
In the work of Pike and co-workers, a mixture of Kryptofix-222 and K_2CO_3 is used to formulate [^{18}F]KF/K_{222} from [^{18}F]fluoride. The base is required for formation of [^{18}F]KF, while Kryptofix-222 solubilises [^{18}F]KF in organic solvents.[d] Due to the picomolar quantities of [^{18}F]fluoride, Kryptofix-222 and K_2CO_3 are present in large excess. We investigated the stability of xenon difluoride towards these reagents. When xenon difluoride was heated with a mixture of K_2CO_3 and Kryptofix-222 in acetonitrile at 80 °C, complete degradation of xenon difluoride was observed (Entry 3). Similarly, when xenon difluoride was heated with Krptofix-222 (1 equivalent), complete degradation of xenon difluoride was observed (Entry 4). Using 0.25 equivalents of Krptofix-222 still resulted in complete degradation of xenon difluoride (Entry 5). Schrobilgen has reported previously on the reactivity of xenon difluoride with Kryptofix-222.[164] When xenon difluoride was heated with 0.25 equivalents of K_2CO_3, 23% degradation was observed (Entry 6). This data shows that both the solubilising agent (Kryptofix-222) and the base (K_2CO_3) used in the work of the Pike group react with xenon difluoride. We therefore investigated the stability of alternative solubilising agents and bases towards xenon difluoride. We speculated that xenon difluoride, as a strong oxidant, is not compatible with the tertiary amine moieties in Kryptofix-222. Pike and co-workers have reported that labelling of xenon difluoride does not work using [^{18}F]KF in the absence of Kryptofix-222, due to the insolubility of [^{18}F]KF in acetonitrile.[162] We hypothesised that a crown ether lacking amine

[d] In the work of the Pike group, the [^{18}F]fluoride is not purified and dried using a QMA cartridge. Instead, K_2CO_3 and Kryptofix-222 are added directly to the [^{18}F]fluoride in [^{18}O]H_2O, and the mixture is dried using microwave heating. This enables a lower quantity of base to be used than when a QMA cartridge is used. However, use of a QMA cartridge is preferable because i) it expedites the drying process, ii) it removes impurities from the production of F-18, and iii) it enables easier translation to automated synthesis modules.

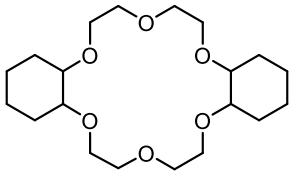
groups might be less reactive towards xenon difluoride, while still solubilising [^{18}F]KF. Dicyclohexano-18-crown-6 (diCy-18-C-6) is commonly used for solubilizing [^{18}F]KF.[188] Mixing xenon difluoride with diCy-18-C-6 and K_2CO_3 resulted in 70% decomposition of xenon difluoride (Entry 7). This is a marked improvement on the 100% decomposition using Kryptofix-222 with K_2CO_3. Mixing equimolar quantities of diCy-18-C-6 and xenon difluoride resulted in just 18% degradation (Entry 8). When 0.25 equivalents of diCy-18-C-6 were used, less than 1% degradation of xenon difluoride was observed (Entry 9). The increased degradation observed for the mixture of diCy-18-C-6 and K_2CO_3 (Entry 7) vs K_2CO_3 alone (Entry 6) is likely due to the higher solubility of the carbonate in the presence of diCy-18-C-6. Stability of xenon difluoride towards a mixture of potassium oxalate and diCy-18-C-6 (Entry 10), and potassium oxalate alone (Entry 11) was similar to that for potassium carbonate. Potassium oxalate can be used as a less basic alternative to potassium carbonate for eluting [^{18}F]fluoride.[128]

Table 14: Stability of XeF_2 towards reagents typically used for eluting [^{18}F]fluoride. XeF_2 (0.1 M) heated at 80 °C with the additive in dry acetonitrile for 20 minutes. Decomposition measured using quantitative ^{19}F NMR with α,α,α-trifluorotoluene as internal standard.

Entry	Additive	Equivalents	% XeF_2 Decomposition
1	none		<1
2	Water	56	29
3	2:1 K_{222}/K_2CO_3	0.50/0.25	100
4	K_{222}	1.0	100
5	K_{222}	0.25	100
6	K_2CO_3	0.25	23
7	2:1 diCy-18-C-6/K_2CO_3	0.50/0.25	70
8	diCy-18-C-6	1.0	18
9	diCy-18-C-6	0.25	<1
10	2:1 diCy-18-C-6/ $K_2C_2O_4.H_2O$	0.5/0.25	63
11	$K_2C_2O_4.H_2O$	0.25	11



Kryptofix-222
K_{222}

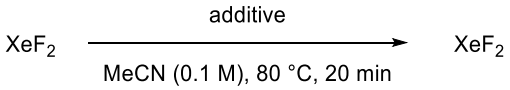


dicyclohexano-18-crown-6
diCy-18-C-6

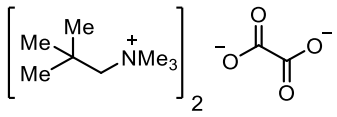
While the use of [^{18}F]KF for radiolabelling reactions requires a cryptand or crown ether for solubilisation, tetraalkylammonium fluorides such as tetraethylammonium [^{18}F]fluoride ([^{18}F]TEAF) and tetrabutylammonium [^{18}F]fluoride ([^{18}F]TBAF) do not as they are already soluble in most organic solvents. These [^{18}F]fluoride salts are typically prepared using tetraethylammonium bicarbonate and tetrabutylammonium bicarbonate respectively.[29] While one equivalent of tetraethylammonium bicarbonate lead to complete consumption of xenon difluoride (Entry 1, Table 13) using 0.25 equivalents, only 45% degradation was observed (Entry 2). Other tetraalkylammonium salts were

tested. Use of tetrabutylammonium phosphate monobasic afforded similar results, with complete decomposition using 1 equivalent (Entry 3), and 66% decomposition with 0.25 equivalents (Entry 4). The stability of xenon difluoride to the oxalate dianion was tested by treatment with bis(neopentyltrimethylammonium) oxalate ([$(NpNMe_3)_2C_2O_4$] (neither the tetrabutylammonium nor tetraethylammonium salts are commercially available). Complete decomposition was observed using 1 equivalent (Entry 5), and 81% decomposition with 0.25 equivalents (Entry 6). Recent literature reports have shown that non-basic tetralkylammonium salts such as tetrabutylammonium tosylate (TBAOTs) can also be used to prepare [^{18}F]TBAF.[31] Treatment of xenon difluoride with 1 equivalent of TBAOTs resulted in only 6% degradation (Entry 7).

Table 15: Stability of XeF_2 towards tetraalkylammonium salts.



Entry	Additive	Equivalents	% XeF_2 Decomposition
1	$Et_4N\ HCO_3$	1.0	100
2	$Et_4N\ HCO_3$	0.25	45
3	$Bu_4N\ H_2PO_4$	1.0	100
4	$Bu_4N\ H_2PO_4$	0.25	66
5	$[(NpNMe_3)_2C_2O_4]$	1.0	100
6	$[(NpNMe_3)_2C_2O_4]$	0.25	81
7	TBAOTs	1.0	6



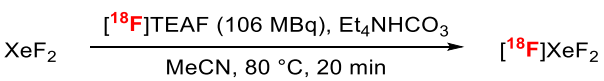
bis(neopentyltrimethylammonium) oxalate
$[(NpNMe_3)_2C_2O_4]$

This data shows that when choosing a base for the formation of [^{18}F]fluoride, the nature of both the cation and anion, and the stoichiometry relative to xenon difluoride each influence the extent of degradation of xenon difluoride. Use of potassium bases requires a solubilising agent. Kryptofix-222 is inappropriate for this purpose, but diCy-18-C-6 is an alternative that is more stable towards xenon difluoride. Tetraalkylammonium bases do not require a solubilising agent. Carbonate, bicarbonate, monobasic phosphate and oxalate bases each lead to significant degradation of xenon difluoride. However, the extent of degradation can be minimised by reducing the quantity of the base. Tetrabutylammonium tosylate leads to minimal degradation of xenon difluoride. These results prompted us to investigate the effect of the nature and quantity of base in the reaction of [^{18}F]fluoride with xenon difluoride. We speculated that by minimising degradation of xenon difluoride in the reaction with [^{18}F]fluoride, we would be able to use a lower loading of xenon difluoride and thus increase molar activity.

3.2.4.2 Analysis of [^{18}F]Xenon Difluoride by HPLC

When investigating different [^{18}F]fluoride elutions for preparing [^{18}F]xenon difluoride, it became apparent that measured RCCs for [^{18}F]xenon difluoride varied significantly depending on the composition of the mobile phase used for the HPLC analysis. When aqueous ammonium formate/acetonitrile was used, measured RCCs were significantly lower than when water/acetonitrile was used (Table 16).

Table 16: Effect of HPLC mobile phase composition on measured [^{18}F]XeF_2 RCC.



Entry	Mobile Phase	% RCC
1	55% H_2O / 45% MeCN	73
2	55% 25 mM aqueous NH_4HCO_2 / 45% MeCN	16

Initially it was thought this discrepancy was due to faster degradation of [^{18}F]xenon difluoride with a mobile phase of aqueous ammonium formate / acetonitrile than with water / acetonitrile. The stability of xenon difluoride towards different mobile phases was therefore studied with ^{19}F NMR (Figure 18). Xenon difluoride was found to be completely stable over 7 hours as a 12.5 mM solution in 1:1 acetonitrile / deuterated acetonitrile, consistent with previous reports.[187] A 12.5 mM solution of xenon difluoride in a 1:1 mixture of acetonitrile / deuterium oxide resulted in slow decomposition, with xenon difluoride halving in concentration over approximately 5 hours. Concomitant formation of hydrogen / deuterium fluoride was observed between -169 and -171 ppm by ^{19}F NMR. A solution of 12.5 mM xenon difluoride and 12.5 mM ammonium formate in 1:1 acetonitrile / deuterium oxide degraded over approximately the same time frame. Under these conditions, formation of fluoride (presumably ammonium fluoride) at -129.3 ppm in ^{19}F NMR accompanied xenon difluoride decomposition. This data suggests that ammonium formate makes little difference to the rate of xenon difluoride decomposition. Under all conditions tested, the decomposition is slow on the HPLC timescale; xenon difluoride elutes in under 5 minutes with the HPLC conditions used in this work.

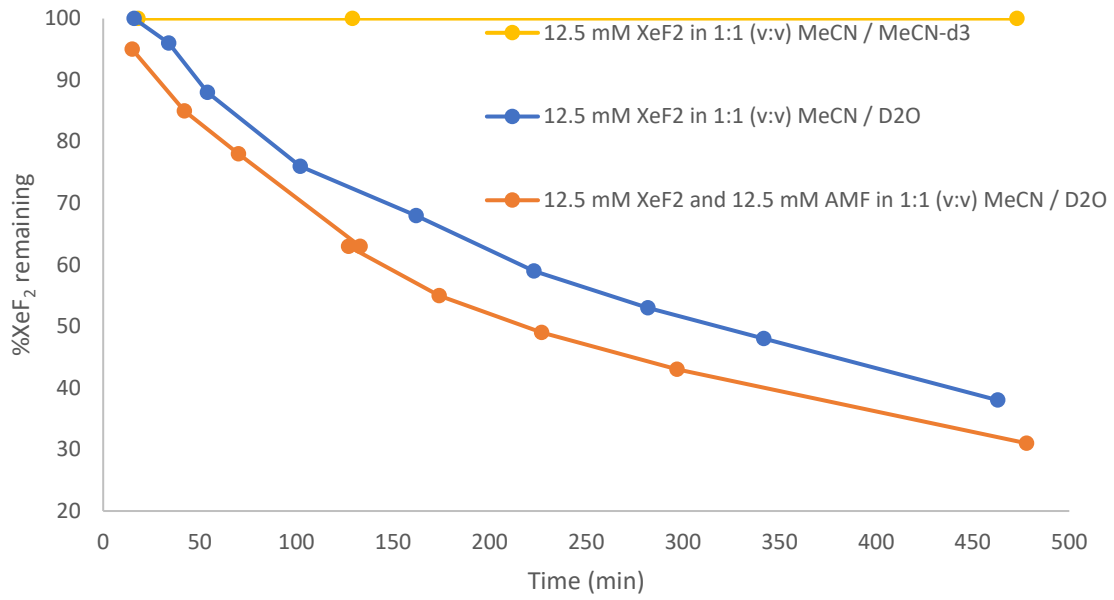


Figure 18: Degradation of xenon difluoride in various solvent/additive mixtures, mimicking the mobile phase conditions used for HPLC analysis. Data obtained using quantitative ^{19}F NMR with α,α,α-trifluorotoluene as internal standard. AMF = ammonium formate.

The stability of xenon difluoride towards different mobile phases was also investigated by comparison of HPLC UV peak area. Consistent and highly reproducible (4 repeated injections for each condition) UV peak areas for xenon difluoride were obtained when 30 µL of a 25 mM solution of xenon difluoride in acetonitrile was injected into the HPLC, using either 55% water / 45% acetonitrile or 55% 25 mM aqueous ammonium formate / 45% acetonitrile as mobile phase (Table 17). A 5 mM xenon difluoride solution afforded similarly consistent results with both mobile phases. For both 25 mM and 5 mM xenon difluoride solutions, only a very slight decrease in mean UV area (<2%) was observed when aqueous ammonium formate was used as mobile phase compared to when water was used. Together with the NMR data, these results suggest that the difference in extent of degradation of xenon difluoride is insignificant and does not account for the large differences in RCCs observed between the different mobile phases.

Table 17: Integration of XeF_2 UV peak after HPLC analysis with different mobile phases. SD = standard deviation. AMF = ammonium formate

Mobile Phase	[XeF_2] (mM)	Mean±SD (*n=4*)
55% H_2O, 45% MeCN	25	51.63±0.21
55% 25mM AMF, 45% MeCN	25	51.32±0.20
55% H_2O, 45% MeCN	5	10.72±0.04
55% 25mM AMF, 45% MeCN	5	10.55±0.02

Instead we hypothesized that the RCCs measured in the absence of ammonium formate may be overestimated due to retention of [^{18}F]hydrogen fluoride on the C18 column. [^{18}F]Hydrogen fluoride/hydrogen fluoride may form over the course of the labelling reaction by decomposition of [^{18}F]xenon difluoride/xenon difluoride, resulting in acidification of the reaction mixture. It has been shown that [^{18}F]hydrogen fluoride / [^{18}F]fluoride is significantly retained on C18 columns when the mobile phase pH is 3 or below.[15] Under these conditions fluoride exists predominantly as hydrogen fluoride (hydrogen fluoride pKa = 3.17 in water).[189] In contrast, very little retention is observed at pH 5 and above. Due to the negligible buffering capacity of water / acetonitrile, injection of small quantities of hydrogen fluoride would result in significant acidification of the mobile phase, and therefore retention of [^{18}F]hydrogen fluoride/ [^{18}F]fluoride on the C18 column. In contrast, a mobile phase of 55:45 25 mM ammonium formate : acetonitrile has buffering capacity at pH 5 and is thus somewhat more resistant to pH change upon injection of [^{18}F]hydrogen fluoride / hydrogen fluoride.[190] RCYs measured for [^{18}F]xenon difluoride post HPLC-purification (performed using ~10 MBq of crude [^{18}F]xenon difluoride on an analytical HPLC column using either water or ammonium formate with acetonitrile) were close to the RCCs measured using ammonium formate in the mobile

phase (e.g. RCC measured as 35%, RCY = 30%), supporting the accuracy of analysis using this mobile phase.

3.2.4.3 Optimisation of [^{18}F]Fluoride Elution for Preparing [^{18}F]Xenon Difluoride

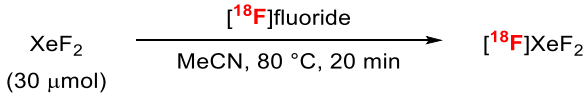
Various [^{18}F]fluoride elutions were tested for the labelling of xenon difluoride. As xenon difluoride is sensitive to the quantity of base and solubilising agent present, each screening reaction was performed with the full quantity of [^{18}F]fluoride eluted from the QMA cartridge (rather than using aliquots of an [^{18}F]fluoride elution which only contain a fraction of the elution base/solubilising agent). For each elution, the elution efficiency (EE) was monitored so that the minimum quantity of eluting agents to obtain an EE of over 80% were used. We anticipated that minimising the quantity of base would have two beneficial effects; i) less xenon difluoride would be degraded reacting with the base enabling lower loadings to be used, and ii) as discussed previously, Schrobilgen and co-workers have proposed that the F-18 species undergoing exchange with xenon difluoride under the conditions reported by the Pike group is [^{18}F]hydrogen fluoride.[164] Using a lower quantity of base would minimise neutralisation of in situ generated [^{18}F]hydrogen fluoride, promoting formation of [^{18}F]xenon difluoride. The elution efficiency was calculated as the eluted and dried radioactivity (decay-corrected to when the radioactivity trapped on the cartridge was measured) as a fraction of the radioactivity initially trapped on the QMA cartridge.

$$\%\ \text{elution efficiency} = \frac{\text{eluted and dried radioactivity (decay corrected)}}{\text{radioactivity initially on QMA cartridge}} \times 100$$

30 µmol of xenon difluoride was used in each reaction. No [^{18}F]xenon difluoride was formed when Kryptofix-222 and K_2CO_3 were used to elute [^{18}F]fluoride (Table 18, Entry 1). No xenon difluoride was detected by UV, suggesting complete degradation. This is

consistent with the data presented in Table 14, which shows that xenon difluoride is completely degraded by just 0.25 equivalents of Kryptofix-222. In reaction of [^{18}F]KF / Kryptofix-222 with 30 µmol of xenon difluoride, over 0.4 equivalents of Kryptofix-222 (12.5 µmol) are present relative to xenon difluoride. [^{18}F]Fluoride elution using diCyhex-18-C-6 in place of Kryptofix-222 was less efficient, requiring more elution solution to recover the radioactivity (Entry 2). Nonetheless, [^{18}F]xenon difluoride was obtained in 13% RCC. This is consistent with the lower extent of xenon difluoride degradation using diCyhex-18-C-6 compared to Kryptofix-222 in Table 14. Use of diCyhex-18-C-6 with potassium oxalate monohydrate instead of potassium carbonate resulted in reduced RCC (Entry 3). [^{18}F]Fluoride elution with tetraethyl ammonium bicarbonate was less efficient, requiring 10 µmol to achieve the threshold of 80% EE. [^{18}F]Xenon difluoride was obtained in 16% RCC (Entry 4). [^{18}F]Fluoride recovery with TBAOTs in acetonitrile / water was poor, with only 9% EE using 7.5 µmol (Entry 5). Using ethanol enabled over 80% EE with just 3.75 µmol of TBAOTs. This elution afforded [^{18}F]xenon difluoride in 25% RCC (Entry 6). Using [$(NpNMe_3)_2C_2O_4$] in ethanol, over 80% EE was obtained with just 2.5 µmol. This elution afforded [^{18}F]xenon difluoride in 27% RCC (Entry 7). These latter two elutions clearly afforded higher RCCs of [^{18}F]xenon difluoride than other elutions.

Table 18: Effect of [^{18}F]fluoride elutions for labelling [^{18}F]XeF_2. diCy-18-C-6 = dicyclohexyl-18-crown-6. For each elution, a QMA carbonate light cartridge was used, pre-activated with 10 mL of water. See experimental section for further details. EE = elution efficiency.

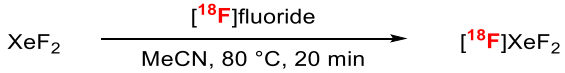


Entry	Solubilising agent/base	Solvent	µmol for >80% EE	EE	% RCC
1	2.5:1 Kryptofix-222/K_2CO_3	8:2 MeCN:H_2O	12.5, 5	93	0
2	2.5:1 diCy18-C-6/K_2CO_3	8:2 MeCN:H_2O	18.8, 7.5	93	13
3	2.5:1 dicy-18-C-6/$K_2C_2O_4.H_2O$	8:2 MeCN:H_2O	18.8, 7.5	91	3
4	Et_4N HCO_3	8:2 MeCN:H_2O	10	85	16
5	TBAOTs	8:2 MeCN:H_2O	7.5	9	-
6	TBAOTs	EtOH	3.75	90	25
7	[$(NpNMe_3)_2C_2O_4$]	EtOH	2.5	81	27

Radiosynthesis of [^{18}F]xenon difluoride using TBAOTs and [$(NpNMe_3)_2C_2O_4$] elutions was further investigated. We sought to determine to what extent the loading of xenon difluoride could be reduced. Using 2.5 µmol of [$(NpNMe_3)_2C_2O_4$] in ethanol to elute [^{18}F]fluoride, [^{18}F]xenon difluoride was formed in 16% RCC from 15 µmol of xenon difluoride (Entry 2). The loading could be reduced further to 7.5 µmol and 5 µmol, affording 12% (Entry 3) and 4% (Entry 4) RCCs respectively. When 3.75 µmol of xenon difluoride was used, no [^{18}F]xenon difluoride was detected. No xenon difluoride was observed by UV indicating complete degradation. This data supports the dependence of xenon difluoride degradation on the ratio of elution base to xenon difluoride. As speculated, the molar activity of [^{18}F]xenon difluoride increased as the loading of xenon difluoride was reduced; using 30 µmol of xenon difluoride a molar activity of 0.9 MBq μmol^{-1} was measured (Entry 1), while using 7.5 µmol resulted in a molar activity of

2.1 MBq µmol^{-1} (Entry 3).[e] The effect of the starting radioactivity of [^{18}F]fluoride on the molar activity was also investigated. Using 9.48 GBq of [^{18}F]fluoride with 40 µmol of xenon difluoride resulted in a modest increase in molar activity to 9.4 MBq µmol^{-1}. This data suggests the molar activity does not scale linearly with the starting radioactivity. However, any conclusions must be drawn very cautiously from this preliminary data, as the molar activities and RCCs were measured for a single experiment (*n=1*); in general the RCC of [^{18}F]xenon difluoride was found to vary considerably between repeats of the same reaction.

Table 19: Effect of XeF_2 loading on RCC and molar activity in preparing [^{18}F]XeF_2. A_m = molar activity. Molar activities decay-corrected to the end of the labelling reaction. [^{18}F]Fluoride radioactivity reported as the dried radioactivity.



Entry	Elution	µmol XeF_2	% RCC	[^{18}F]Fluoride (MBq)	A_m (MBq µmol^{-1})
1	[(NpNMe$_3$)$_2$C$_2$O$_4$]	30	35	85	0.9
2	[(NpNMe$_3$)$_2$C$_2$O$_4$]	15	16	101	0.9
3	[(NpNMe$_3$)$_2$C$_2$O$_4$]	7.5	12	94	2.1
4	[(NpNMe$_3$)$_2$C$_2$O$_4$]	5	4	77	-
5	[(NpNMe$_3$)$_2$C$_2$O$_4$]	3.75	0	90	-
6	[(NpNMe$_3$)$_2$C$_2$O$_4$]	40		9480	9.4
7	TBAOTs	30	33	120	0.8
8	TBAOTs	7.5	0	62	-
9	TBAOTs	3.75	0	72	-

[e] The molar activities measured for entries 1 and 2 of Table 19 are the same despite having used different loadings of xenon difluoride. However, the accuracy of the molar activity in entry 2 is probably low due to the small quantity of radioactivity collected (0.2 MBq) and the insensitivity of the Capintec dose calibrator. For a higher degree of accuracy, this experiment should be repeated so that more radioactivity is collected in the molar activity measurement.

When [^{18}F]fluoride was eluted using TBAOTs, no [^{18}F]xenon difluoride was detected when 7.5 µmol (Entry 7, Table 19) or 5 µmol (Entry 8) of xenon difluoride were used, and no xenon difluoride was observed by UV, indicating degradation. These results appear to contradict the data in Table 15, which show xenon difluoride is stable towards TBAOTs. However, we speculated that anion exchange of tosylate with carbonate (from the QMA carbonate cartridge) may occur during [^{18}F]fluoride elution. To test this, a solution of 3.75 µmol of TBAOTs in deuterated methanol was passed through a QMA carbonate cartridge, preactivated with 10 mL of water. ^{1}H NMR of the eluate showed the presence of the tetrabutylammonium cation, however no tosylate was observed (Figure 19). IR analysis of the eluate showed a strong absorption in the C=O region at 1660 cm^{-1} (similar to that measured for cesium carbonate at 1630 cm^{-1}), which was absent in the IR of TBAOTs. These data confirm anion exchange has occurred, and suggest the eluate contains tetrabutylammonium carbonate/bicarbonate. Indeed, the data in Table 15 shows xenon difluoride to be unstable towards tetraethylammonium bicarbonate. The complete degradation of 7.5 µmol of xenon difluoride using TBAOTs but not with [$(NpNMe_3)_2C_2O_4$] (Entry 7 vs 3, Table 19) may be explained by the higher quantity of TBAOTs used to reach the threshold EE of 80% (3.75 µmol for TBATOs vs 2.5 µmol for [$(NpNMe_3)_2C_2O_4$]). Therefore more base is present in the eluate when TBAOTs is used.

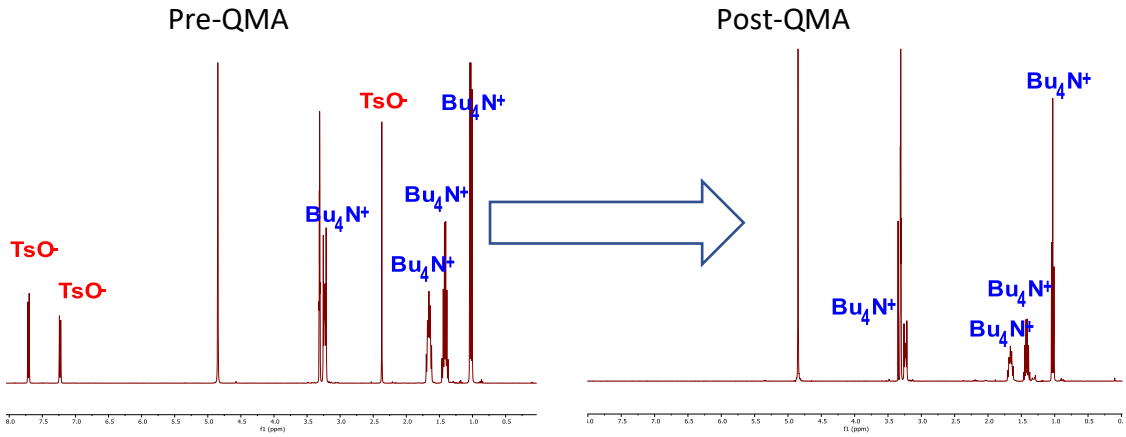


Figure 19: ^{1}H NMR, showing anion exchange as TBAOTs is passed through a QMA carbonate cartridge.

This anion exchange between tosylate and carbonate highlights the importance of the nature of the counteranion on the QMA cartridge. While the QMA cartridges used in this work come paired with carbonate anions, this can be changed by equilibrating the cartridge prior to trapping of [^{18}F]fluoride. The effect of the cartridge counteranion on the [^{18}F]fluoride EE, and on the labelling of [^{18}F]xenon difluoride was investigated (Figure 20). TBAOTs and $[(NpNMe_3)_2C_2O_4]$ / $[(Bu_4N)_2C_2O_4]$ were used for eluting the [^{18}F]fluoride.[f] Previous experiments showed that xenon difluoride is stable towards sulphonates (Table 15). We therefore tested using a QMA cartridge modified with the mesylate anion (by equilibration with aqueous potassium mesylate). However no [^{18}F]fluoride was recovered using TBAOTs. Recovery was also very poor with $[(Bu_4N)_2C_2O_4]$. Using a QMA cartridge modified with the bicarbonate anion resulted in poor [^{18}F]fluoride recovery with TBAOTs, yet recovery was high when $[(Bu_4N)_2C_2O_4]$ was used. When the non-modified carbonate

[f] $[(Bu_4N)_2C_2O_4]$ and $[(NpNMe_3)_2C_2O_4]$ were both used as tetraalkylammonium oxalate sources, and are expected to behave similarly as they differ only in their *N*-alkyl groups. Availability dictated which salt was used. Eventually, $[(NpNMe_3)_2C_2O_4]$ was favoured as it is commercially available.

cartridge was used, [^{18}F]fluoride recovery was high with both TBAOTs and [$(NpNMe_3)_2C_2O_4$]. [^{18}F]Fluoride recovery was also high for both TBAOTs and [$(Bu_4N)_2C_2O_4$] when the cartridge was modified with potassium oxalate.

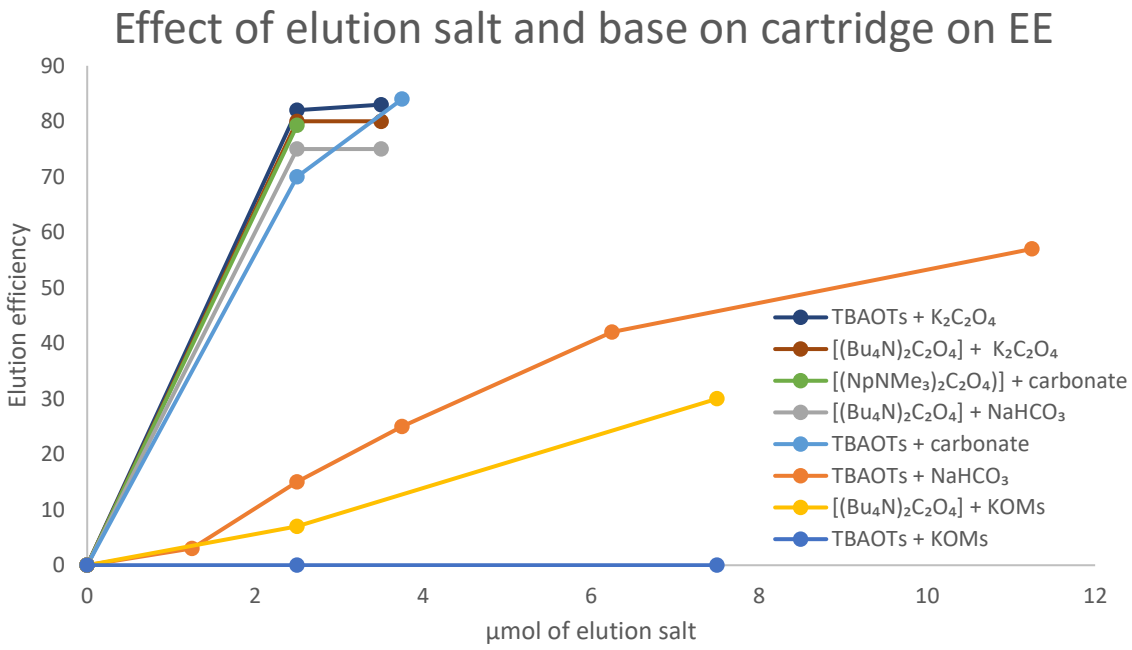
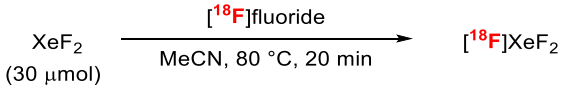


Figure 20: Effect of elution salt and cartridge anion on [^{18}F]fluoride EE. EE values calculated for eluted radioactivity before drying and without decay-correction. In the legend, the elution salt is listed first, followed by the base used to equilibrate the cartridge.

For the elutions above that enabled good recovery of [^{18}F]fluoride, reaction with xenon difluoride was investigated (Table 20). TBAOTs with carbonate and oxalate cartridges, and [$(NpNMe_3)_2C_2O_4$] with a carbonate cartridge each afforded similar results.

Table 20: Effect of elution salt and cartridge anion on preparing [^{18}F]xenon difluoride. [a]Analysis of these experiments was run using a mobile phase of water / acetonitrile. These experiments should be repeated using a buffered mobile phase to ensure RCCs are not overestimated.

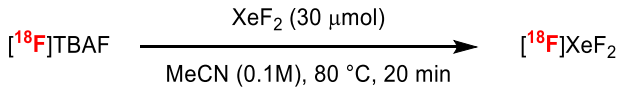


Entry	Elution (2.5 μmol)	Cartridge	% RCC
1	TBAOTs	carbonate	25-33 (*n=3*)
2[a]	TBAOTs	oxalate	22-28 (*n=3*)
3	$[(NpNMe_3)_2C_2O_4]$	carbonate	27-35
4[a]	$[(Bu_4N)_2C_2O_4]$	oxalate	8
5[a]	$[(Bu_4N)_2C_2O_4]$	bicarbonate	18

3.2.4.4 Optimisation of Conditions for Preparing [^{18}F]Xenon Difluoride

Conditions for the reaction of [^{18}F]fluoride with xenon difluoride were investigated (Table 21). These conditions were screened using aliquots of an [^{18}F]fluoride elution, and so the absolute RCC values cannot be compared with those in Table 18 and Table 19. However the trends observed should be consistent with when a full elution of [^{18}F]fluoride is used. Decreasing the temperature from 80 °C to 60 °C resulted in a decrease in RCC from 65% to 44% (Entry 2, Table 21). At temperatures above 80 °C, loss of solvent and radioactivity was observed. Decreasing the duration to 10 minutes resulted in a decrease in RCC to 50% (Entry 3). Reducing the concentration of xenon difluoride to 0.033 M resulted in a decrease in RCC to 40% (Entry 4). However, care must be taking drawing conclusions from this data, as the RCC of [^{18}F]xenon difluoride was found to vary between repeats of the same conditions, and reactions in Table 21 were only run once.

Table 21: Effect of temperature, duration and concentration on synthesis of [^{18}F]xenon difluoride.



Entry	Deviation from above conditions	% RCC
1	none	65
2	60 °C	44
3	10 min	50
4	0.033 M	40

3.2.4.5 Conclusions on preparing [^{18}F]xenon difluoride

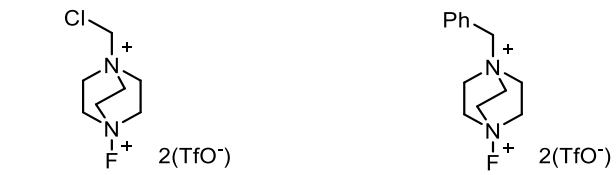
The results discussed above show that use of [$(NpNMe_3)_2C_2O_4$] for eluting [^{18}F]fluoride enables a lower loading of xenon difluoride to be used for the synthesis of [^{18}F]xenon difluoride than when Krytofix-222 and K_2CO_3 are used. This appears at least in part due to reduced decomposition of xenon difluoride when [^{18}F]fluoride is eluted with [$(NpNMe_3)_2C_2O_4$]. The loading of xenon difluoride has been shown to effect the molar activity of [^{18}F]xenon difluoride; preliminary data shows a higher molar activity is obtained using a lower loading of xenon difluoride. However, reducing the xenon difluoride loading below 5 µmol results in no formation of [^{18}F]xenon difluoride, due to complete degradation of xenon difluoride. Use of a large quantity of starting radioactivity of [^{18}F]fluoride did increase the molar activity of [^{18}F]xenon difluoride, but only somewhat. The maximum molar activity measured for [^{18}F]xenon difluoride was low, at 9.4 MBq µmol^{-1}

3.2.5 Preparation of [^{18}F]F-TEDA reagents

3.2.5.1 Model Reaction: [^{18}F]*N*-Benzyl F-TEDA [^{18}F]**3.25**

To facilitate characterisation and reaction monitoring by HPLC in the radiosynthesis of ^{18}F-labelled F-TEDA reagents, *N*-benzylated reagent **3.25** was chosen as the model target

instead of Selectfluor bis(triflate) (Figure 21). This was for three reasons; i) In contrast to Selectfluor bis(triflate), **3.25** has good UV absorbance at 220 nm, enabling the HPLC retention time to be measured by UV detection. This provided a retention time reference to prove formation of the ^{18}F-labelled reagent. ii) The UV absorbance of **3.25** enabled determination of the molar activity, and iii) separation of [^{18}F]Selectfluor from [^{18}F]fluoride by analytic HPLC was not possible due to the poor retention of [^{18}F]Selectfluor on C18 columns. However, *N*-benzyl F-TEDA reagent **3.25** had significantly greater retention, enabling separation from [^{18}F]fluoride for reaction quantification (discussed in detail below). As shown in Scheme 48, **3.25** can be prepared from xenon difluoride in a similar manner to Selectfluor bis(triflate), albeit in lower yield.



Selectfluor bis(triflate) **3.25**

*Figure 21: N-Benzylated reagent **3.25** as a model target enabled more facile characterisation.*

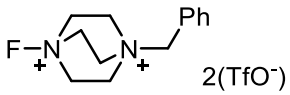
3.2.5.2 HPLC Analysis of F-TEDA Reagents

In previous work from the Gouverneur group on preparing [^{18}F]**3.25** from [^{18}F]F_2 gas, [^{18}F]fluoride co-eluted with [^{18}F]**3.25**, so quantification by radioHPLC was not possible.[69] We investigated various mobile phase compositions for the HPLC analysis of **3.25**, with a Phenomenex Gemini C18 stationary phase. Using mixtures of water and acetonitrile, multiple low intensity UV peak were observed for **3.25** (Entry 1, Table 22). However, when 25 mM aqueous ammonium formate was used as mobile phase, a single UV peak with retention of 4.82 minutes was observed (Entry 2). The precursor *N*-benzyl DABCOnium triflate **3.37** displayed significantly higher retention, eluting at 8.55 minutes

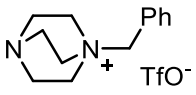
with 5:95 acetonitrile / 25 mM ammonium formate. We aimed to achieve a retention of over 6 minutes to enable separation from xenon difluoride, which eluted between 3.5 and 5 minutes regardless of the additive in the mobile phase. Other mobile phase additives were tested to increase the retention of **3.25**. Use of 25mM ammonium acetate afforded similar retention times to ammonium formate (Entry 3). However, using 13 mM aqueous trifluoroacetic acid, a retention time of 9.85 minutes was observed for *N*-benzylated F-TEDA **3.25**, with the *N*-benzyl DABCOnium triflate **3.37** eluting at 15.80 minutes (Entry 4). Even greater retention was observed using 11 mM aqueous triflic acid, with **3.25** eluting at 39.6 minutes (Entry 5). These mobile phases were acidic (pH < 2.5) and would therefore result in retention of [^{18}F]fluoride on the stationary phase, leading to overestimated RCCs when used for analysing reactions (see Section 3.2.4.2). Alternative less acidic options were found to be aqueous ammonium trifluoroacetate and aqueous sodium triflate, which both resulted in retention times of over 6 minutes for **3.25** (Entries 6 and 7). Enhanced retention of cationic analytes in RP-HPLC using ion-pairing / chaotropic agents such as TFA is widely documented. Triflic acid / sodium triflate is less common, but has been shown to result in even greater retention of cationic analytes on C18 columns than TFA.[191] The cationic analyte pairs with the anionic ion-pairing agent, which has a hydrophobic tail resulting in increased retention. Alternatively, the ion-pairing agent can adsorb to the stationary phase, and its anionic group then increases retention of the cationic analyte in the mobile phase. The retention times were highly sensitive to the solvent that the *N*-benzyl F-TEDA **3.25** sample was prepared in; with a mobile of 0.1% aqueous TFA, a retention time of under 4 minutes was observed

when the sample was injected in acetonitrile, while a retention time of between 8 and 10 minutes was observed when the sample was injected in water.

*Table 22: Effect of mobile phase composition on the retention of **3.25** and **3.37** in RP-HPLC.*



3.25

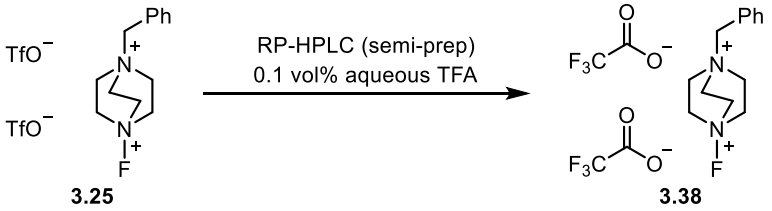


3.37

Entry	Mobile Phase	pH	3.25 RT (min)	3.37 RT (min)
1	H_2O		-	-
2	95% 25 mM ammonium formate, 5% MeCN	6.37	4.82	8.55
3	25 mM ammonium acetate	6.40	4.95	
4	13 mM/0.1 vol% TFA	2.10	9.85	15.80
5	11 mM triflic acid	2.01	39.58	53.97
6	95% 25 mM ammonium trifluoroacetate, 5% MeCN	5.70	16.49	15.67
7	85% 10 mM sodium triflate, 15% MeCN	7.07	7.69	8.79

To confirm that *N*-benzyl F-TEDA **3.25** was not degrading under the HPLC conditions using 13 mM aqueous TFA, the identity of the UV peak at 9.85 minutes was confirmed by ESI+ mass spectroscopy detection. A mass peak at 335 m/z was observed, corresponding to **3.25** paired with a single trifluoroacetate anion. To further confirm the identity of this peak, semi-preparative HPLC was run using a 10 x 250 mm Gemini C18 column eluted with 0.1 vol% aqueous TFA, and the peak was collected. ^{1}H and ^{19}F NMR confirmed the collected species to be **3.25**. ^{19}F NMR revealed that the counteranions had exchanged from triflates pre-HPLC (-78.4 ppm, **3.25**), to trifluoroacetates (-75.6 ppm, **3.38**) post-

HPLC (Scheme 53).[g] This is an important consideration if [^{18}F]Selectfluor is to be purified by HPLC.



*Scheme 53: Counteranion exchange during HPLC analysis of N-benzyl F-TEDA **3.25**.*

HPLC analysis of Selectfluor bis(triflate) was tested using mobile phases of 0.1 vol% aqueous TFA and 0.1 vol% aqueous triflic acid, with detection using mass spectrometry due to lack of a UV chromophore. Under both conditions only poor retention was observed, with Selectfluor eluting under 4 minutes. Indeed, Selectfluor is less lipophilic than *N*-benzyl F-TEDA **3.25** due to the absence of the aromatic ring, accounting for the reduced retention. This retention is insufficient for separation from xenon difluoride and fluoride. *N*-Benzyl F-TEDA **3.25** was therefore used for reaction optimisation and quantification instead. For future work, it is probable that a stationary phase with a higher cation selectivity, such as the Phenomenex Kinetex PFP or Phenomenex Luna CN, would enable separation of Selectfluor from xenon difluoride and fluoride, simplifying reaction analysis. [192]

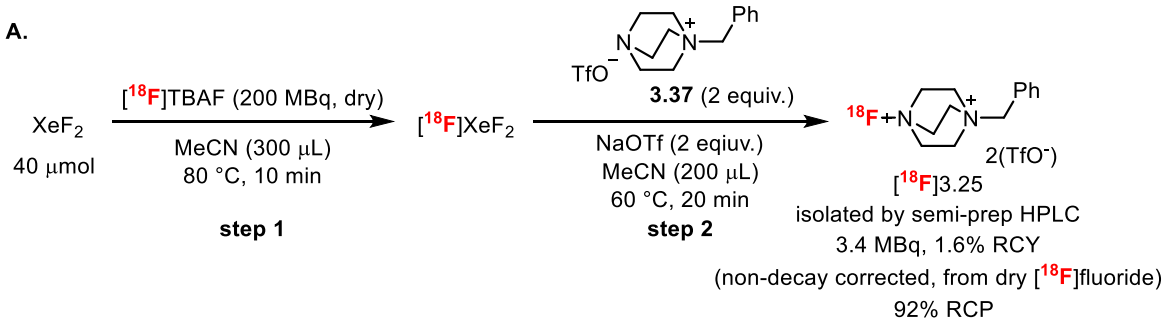
3.2.5.3 Proof of Principle – Synthesis and Isolation of *N*-Benzyl F-TEDA [^{18}F]3.25

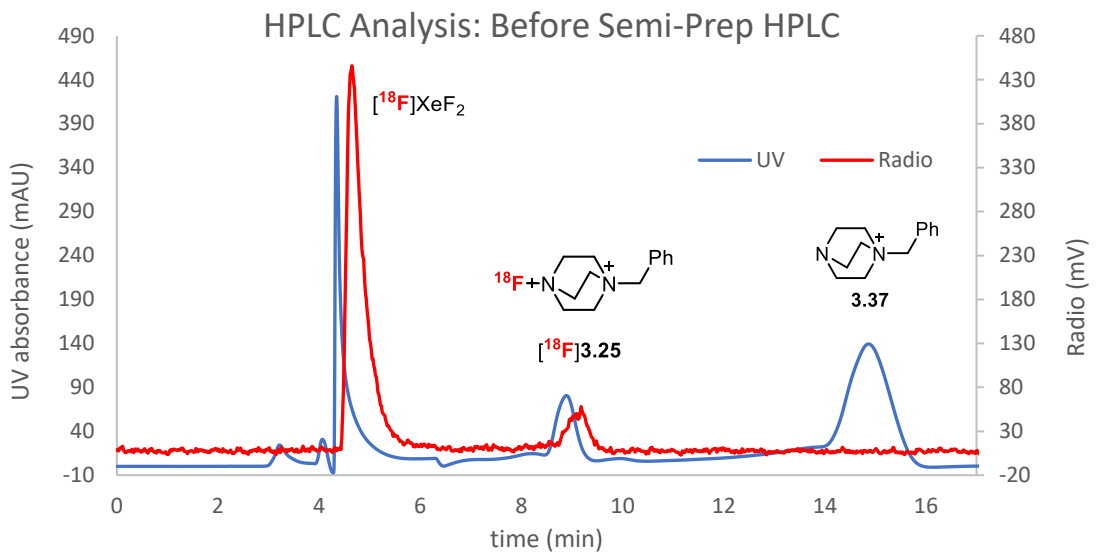
The labelling of [^{18}F]xenon difluoride from [^{18}F]fluoride, and the reaction of xenon difluoride with DABCOnium precursors to prepare F-TEDA reagents both proceed in acetonitrile. An operationally simple two-step one-pot synthesis of *N*-benzyl F-TEDA

[g] Minor traces of triflate were observed in the collected product at -78.8 ppm in ^{19}F NMR.

[^{18}F]**3.25** was therefore investigated. This comprised of first heating [^{18}F]fluoride with xenon difluoride in acetonitrile, forming [^{18}F]xenon difluoride in situ, followed by addition of *N*-benzyl DABCOnium triflate **3.37** and sodium triflate and heating further (Figure 22A).[h] While the experiments presented previously showed that [^{18}F]xenon difluoride can be labelled using as little as 5.0 μmol of xenon difluoride (Table 19), 40 μmol was used for proof of principle to ensure higher RCCs to *N*-benzyl F-TEDA [^{18}F]**3.25**. Starting from a full QMA cartridge elution of 200 MBq of [^{18}]fluoride, [^{18}F]**3.25** was observed in the crude reaction mixture by radioHPLC following the 2-step sequence (Figure 22B). However a significant amount of [^{18}F]xenon difluoride remained unconsumed; the ratio of [^{18}F]**3.25** to [^{18}F]xenon difluoride measured by radioHPLC under these conditions was 11 : 89 (in a repeat radiosynthesis a similar ratio of 8 : 92 was obtained). Excess *N*-benzyl DABCOnium triflate **3.37** was observed by UV. As analysis was run with a mobile phase of 0.1% aqueous TFA, [^{18}F]fluoride was not detected. The crude reaction mixture was purified by semi-prep HPLC, also using a mobile phase of 0.1% aqueous TFA. [^{18}F]**3.25** was separated from xenon difluoride and *N*-benzyl DABCOnium triflate, and was obtained with an RCP of 92% and a chemical purity also of 92% (by UV). Co-injection of [^{18}F]**3.25** with a reference sample of **3.25** confirmed the identity of the isolated product. The RCY was 1.6%, non-decay corrected, from dry [^{18}F]fluoride. A higher RCY may be expected for the synthesis of [^{18}F]Selectfluor, as experiments with xenon difluoride showed Selectfluor to form in significantly higher yields than *N*-benzyl F-TEDA **3.25** (38% vs 20% yield).

[h] The experiments in Figure 22A were conducted before [$(NpNMe_3)_2C_2O_4$] was identified as the optimal base for eluting [^{18}F]fluoride. TBAOTs was used in these experiments.





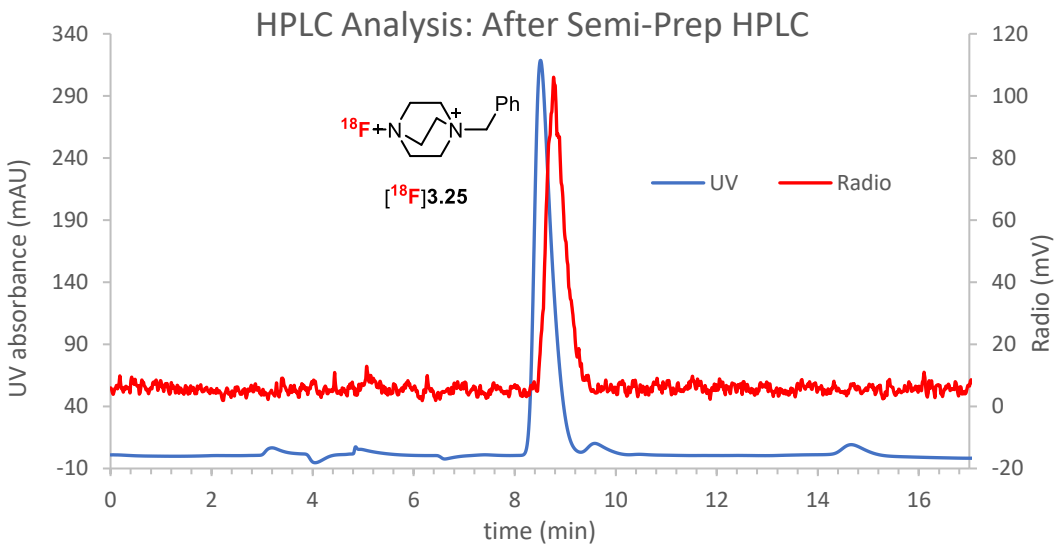
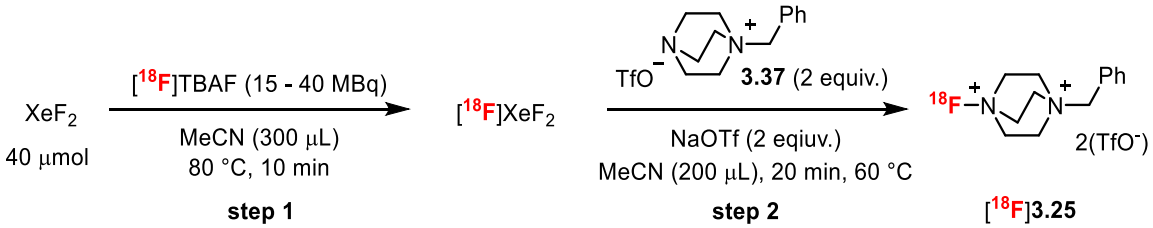


*Figure 22: A: Synthesis of [^{18}F]N-benzyl F-TEDA [^{18}F]**3.25** and isolation by semi-prep HPLC. B. HPLC analysis of the crude [^{18}F]**3.25**, using a mobile phase of 0.1% aqueous TFA. C. HPLC analysis of [^{18}F]**3.25** after purification by semi-Prep HPLC.*

3.2.5.4 Optimisation of *N*-Benzyl F-TEDA [^{18}F]**3.25** Synthesis

Under the conditions detailed in Figure 22A, significant quantities of [^{18}F]xenon difluoride remained unconsumed in the crude product mixture. Optimisation of the reaction between [^{18}F]xenon difluoride and *N*-benzyl DABCOnium triflate **3.37** was therefore investigated (Table 23). Aqueous ammonium trifluoroacetate was used as the HPLC mobile phase for analysis, to enable separation of [^{18}F]*N*-benzyl F-TEDA [^{18}F]**3.25** from other species, and also enable detection of [^{18}F]fluoride for RCC quantification. The same trends observed for preparing Selectfluor bis(triflate) from xenon difluoride (Table 12 and Table 13) were also observed in the synthesis of *N*-benzyl F-TEDA [^{18}F]**3.25** from [^{18}F]xenon difluoride. The RCC (over two-steps) increased with the equivalents of *N*-benzyl DABCOnium triflate **3.37**; 0.5 equivalents afforded 3% RCC (Entry 1, Table 23) while 2 equivalents afforded 11% RCC (Entry 3). Increasing the duration of step 2 from 20 to 30 minutes had no effect on the RCC (Entry 4), however increasing the reaction concentration, by halving the solvent volumes used in step 1 and step 2, resulted in an increase to 16% RCC (Entry 5). Indeed a strong dependence on concentration was also observed in the reaction with F-19 xenon difluoride. Finally, increasing the temperature of step 2 to 80 °C resulted in an increase in RCC to 15% (Entry 6 vs Entry 3). However, conclusions must be drawn carefully form this data, as each condition was run only once. In addition, it is possible that RCCs are overestimated even when using ammonium trifluoroacetate rather than trifluoroacetic acid as the mobile phase additive, due to some retention of [^{18}F]fluoride as discussed previously.

*Table 23: Optimisation of the preparation of [^{18}F]**3.25** from [^{18}F]fluoride. Experiments performed using aliquots of [^{18}F]fluoride eluted with TBAOTs in EtOH.[i] [XeF_2] is the concentration of the reaction with respect to XeF_2 and is quoted for step 2, assuming no decomposition of XeF_2 during step 1.*

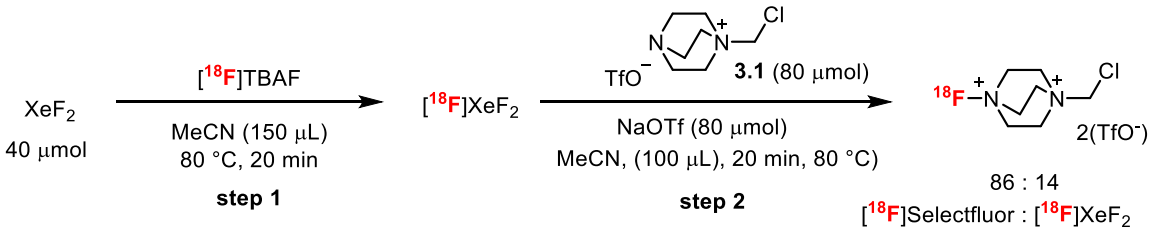


Entry	3.37 (equiv.)	[XeF_2] (M)	Temp (°C)	Step 2 duration (min)	% RCC over 2 steps
1	0.5	0.08	60	20	3
2	1	0.08	60	20	5
3	2	0.08	60	20	11
4	2	0.08	60	30	11
5	2	0.16	60	20	16
6	2	0.08	80	20	15

3.2.5.5 Preparation of [^{18}F]Selectfluor Bis(triflate): Purification

Having optimised the synthesis of model substrate *N*-benzyl F-TEDA [^{18}F]**3.25** from [^{18}F]fluoride, attention was turned to the synthesis of [^{18}F]Selectfluor bis(triflate) (Scheme 54). Purification of [^{18}F]Selectfluor bis(triflate) by HPLC was not attempted due to poor retention on C18 columns resulting in similar retention times to [^{18}F]fluoride, [^{18}F]xenon difluoride, and *N*-chloromethyl DABCOnium triflate **3.1**. Avoidance of HPLC purification is also preferable for operational simplicity and to minimise synthesis time. Nonetheless, purification of [^{18}F]Selectfluor bis(triflate) was required to remove [^{18}F]fluoride and unconsumed [^{18}F]xenon difluoride.

[i] The experiments in Table 23*Table 23* were conducted before [$(NpNMe_3)_2C_2O_4$] was identified as the optimal base for eluting [^{18}F]fluoride. TBAOTs was used in these experiments.



Scheme 54: [^{18}F]Selectfluor bis(triflate) synthesis under optimised conditions.

3.2.5.5.1 Removal of [^{18}F]Xenon Difluoride

Using the conditions optimised in Table 23, a ratio of 86:14 of [^{18}F]Selectfluor bis(triflate) to [^{18}F]xenon difluoride was obtained at the end of synthesis (Figure 23A, [^{18}F]fluoride not observed due to TFA in mobile phase). Solid xenon difluoride has a relatively high vapor pressure of 600 Pa at 298 K, suggesting it is prone to sublimation.[193] Indeed after heating the crude product solution to dryness at 80 °C under a flow of nitrogen, the [^{18}F]xenon difluoride was no longer observed by radioHPLC; only [^{18}F]Selectfluor bis(triflate) remained (Figure 23B). A 17% loss of radioactivity (decay-corrected) was observed after the sublimation process.

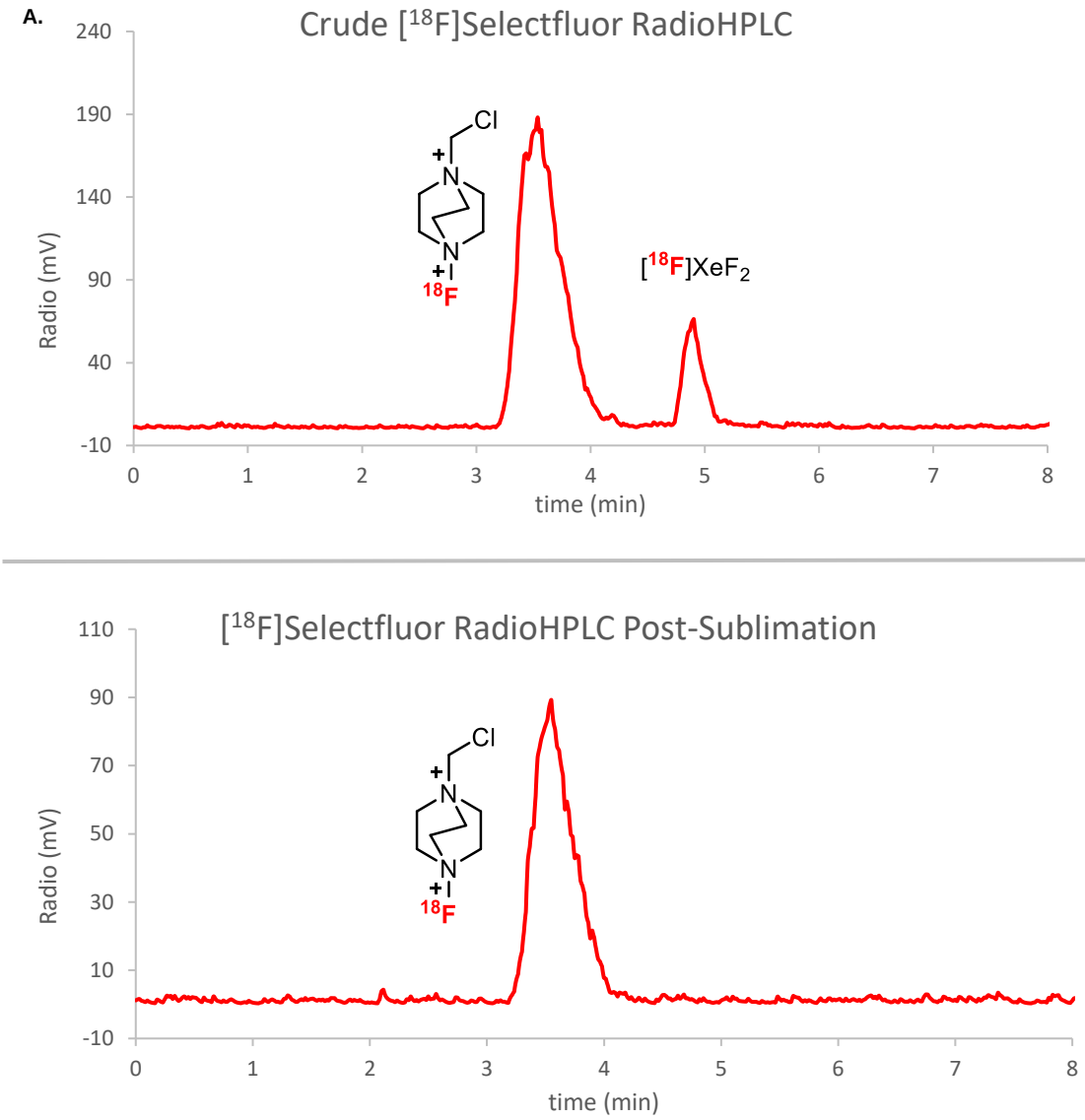


Figure 23: A: Crude reaction mixture containing [18F]Selectfluor bis(triflate) and [18F]xenon difluoride. B: Reaction mixture containing only [18F]Selectfluor bis(triflate) after sublimation of [18F]xenon difluoride. RadioHPLCs run using 0.1 vol% aqueous TFA.

3.2.5.5.2 Removal of [18F]Fluoride

Absolute quantification of the RCP of [18F]Selectfluor was complicated. The relative quantities of [18F]Selectfluor and [18F]xenon difluoride could be measured by radioHPLC, however quantification of [18F]fluoride content was difficult. Using TFA in the mobile phase, [18F]fluoride was retained on the column. Using other less acidic additives such as ammonium formate or ammonium trifluoroacetate in the mobile phase, [18F]fluoride

could be observed however co-eluted with [^{18}F]Selectfluor. Instead, the RCP of [^{18}F]Selectfluor bis(triflate) was measured via HPLC using TFA in the mobile phase to ensure separation from [^{18}F]fluoride; the total radioactivity of crude product injected into the HPLC was measured, and compared with the radioactivity of the collected pure [^{18}F]Selectfluor bis(triflate) (see Chapter 5 for experimental details). The RCP of [^{18}F]Selectfluor bis(triflate) from the crude product mixture after sublimation was approximately 5% (Figure 24). No [^{18}F]xenon difluoride was observed. The radioactivity of the crude mixture post-sublimation is therefore largely accounted for by [^{18}F]fluoride. To increase the RCP of the product, removal of [^{18}F]fluoride using a QMA cartridge was considered; the dicationic [^{18}F]Selectfluor bis(triflate) should not be retained on the cationic stationary phase of the cartridge, while [^{18}F]fluoride should be retained. This was first tested using Selectfluor bis(triflate); a solution of Selectfluor bis(triflate) in 1 mL of 1:1 deuterium oxide/acetonitrile was filtered through a Sep-Pak Accell Plus QMA Plus Light 130 mg cartridge, which was preactivated with 10 mL of 0.1 M aqueous sodium triflate, followed by 10 mL of water. After passing through Selectfluor bis(triflate), the cartridge was washed with a further 2 mL of 1:1 deuterium oxide/acetonitrile. In the collected eluate, 87% of the Selectfluor bis(triflate) was recovered, with no degradation observed by ^{1}H NMR confirming that Selectfluor has little retention on the QMA stationary phase. This was then trialled with crude [^{18}F]Selectfluor bis(triflate); at the end of the radiosynthesis, the reaction mixture was diluted with 2 mL of 8:2 acetonitrile/water and filtered through a QMA cartridge, activated as described above. A substantial reduction in radioactivity was observed, from 711 MBq pre-QMA to 132 MBq post-QMA (decay-corrected). A further 20% decrease in activity was observed upon

drying of the filtrate to afford the final purified product. A higher RCP of 29% was measured post-QMA. The remaining radiochemical impurities were [^{18}F]fluoride / [^{18}F]hydrogen fluoride.

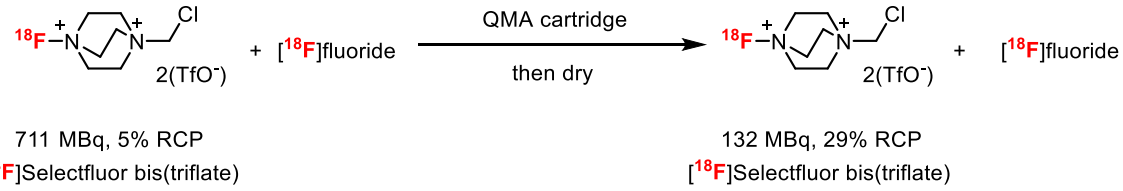
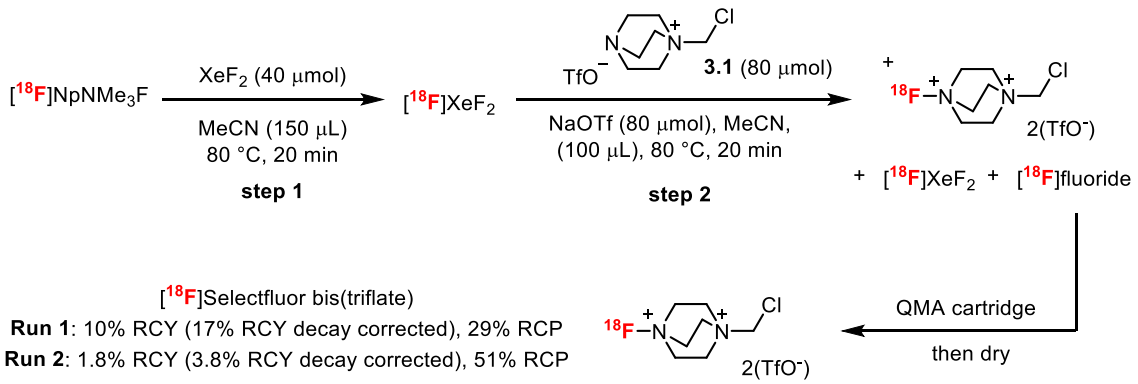


Figure 24: Purification of [^{18}F]Selectfluor bis(triflate) by filtration through a QMA cartridge. RCP = radiochemical purity. The radioactivity post-filtration and drying was decay-corrected to the time the radioactivity of the crude was measured.

3.2.5.6 Summary of [^{18}F]Selectfluor Synthesis

Using the reaction conditions and purification protocols described above, [^{18}F]Selectfluor bis(triflate) was synthesised twice, once in 10% RCY (17% RCY decay corrected) and 29% RCP, and a second time in 1.8% RCY (3.8% RCY decay corrected) and 51% RCP. The radiochemical impurity both times was [^{18}F]fluoride / [^{18}F]hydrogen fluoride. The synthesis could be completed in approximately 70 minutes, including elution and drying of [^{18}F]fluoride.



Scheme 55: Summary of [^{18}F]Selectfluor synthesis from [^{18}F]fluoride.

3.2.5.7 Optimised Synthesis of *N*-Benzyl F-TEDA [^{18}F]**3.25** and Molar Activity

The molar activity was measured for *N*-benzyl F-TEDA [^{18}F]**3.25**. The radiosynthesis was run using the optimised conditions and purification protocol described above (Figure 25). *N*-Benzyl F-TEDA [^{18}F]**3.25** was obtained in 4.5% RCY (6.6% RCY decay corrected), with an RCP of 47% with a synthesis time of approximately 70 minutes. The molar activity, decay-corrected to the end of the synthesis, was 0.017 GBq μmol^{-1}, starting from 1.04 GBq of dried [^{18}F]fluoride. It should be noted that on various occasions, synthesis of [^{18}F]**3.25** failed; only small quantities of [^{18}F]**3.25** were observed, and unreacted [^{18}F]xenon difluoride was detected as the major product. The reason for this is unknown.

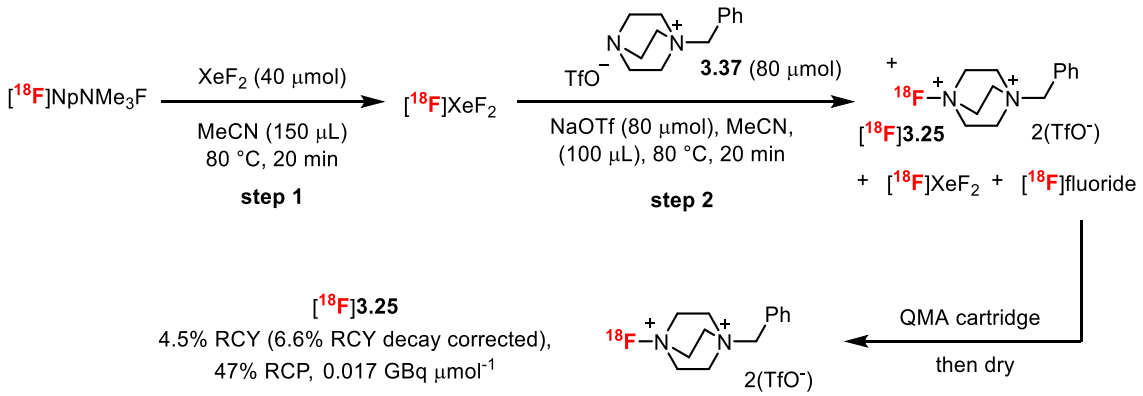
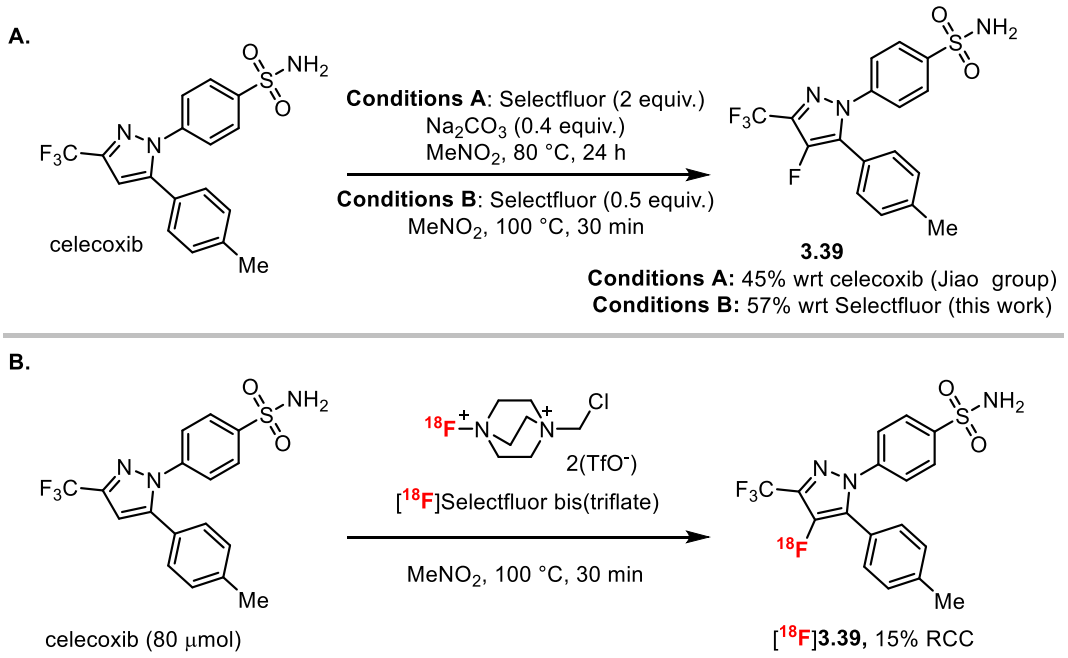


*Figure 25: Synthesis of [^{18}F]N-benzyl F-TEDA [^{18}F]**3.25** and molar activity.*

3.2.6 Applications of [^{18}F]Selectfluor Bis(triflate)

The Jiao group have shown that Selectfluor can directly fluorinate heteroaromatic C–H bonds when nitromethane is used as solvent.[194] The Jiao group demonstrated that this can be applied for selective fluorination of the pyrazole ring of celecoxib to afford **3.39** (Conditions A, Scheme 56A). We optimised the conditions for translation to radiochemistry by increasing the temperature so the duration could be reduced, and by increasing the equivalents of celecoxib to maximise Selectfluor consumption. Under these conditions (Conditions B), **3.39** was obtained in 57% NMR yield with respect to

Selectfluor. Fluorination at other aryl positions occurred only to a minor extent (<5%), determined by ^{19}F NMR. These conditions were applied for the direct radiofluorination of celecoxib with [^{18}F]Selectfluor bis(triflate) (Scheme 56B). [^{18}F]**3.39** was obtained in 15% RCC (from [^{18}F]Selectfluor bis(triflate)), with a selectivity of greater than 95%. ^{18}F-Labelled celecoxib analogues have previously been investigated for PET imaging of COX-2 expression.[195]



Scheme 56: A. Selective C–H fluorination of celecoxib using Selectfluor, reported by the Jiao group (Conditions A),[194] and optimised in this work for translation to ^{18}F-radiolabelling (Conditions B). Yield for Conditions B determined using quantitative ^{19}F NMR with α,α,α-trifluorotoluene as an internal standard. B. This work, using [^{18}F]Selectfluor for the selective radiofluorination of celecoxib. wrt = with respect to.

3.3 Conclusions and Future Work

In this work, an operationally simple, one-pot synthesis of [^{18}F]Selectfluor bis(triflate) from [^{18}F]fluoride has been developed. This synthesis is advantageous as it avoids the use of [^{18}F]F_2 gas. By optimisation of the [^{18}F]fluoride elution, a lower loading of xenon difluoride could be used, which appeared to increase the molar activity of the

intermediate [^{18}F]xenon difluoride slightly. [^{18}F]Selectfluor bis(triflate) was obtained in 10% and 1.8% RCY, with 29% and 51% RCP respectively. Under the same conditions, *N*-benzyl F-TEDA [^{18}F]**3.25** was prepared with a molar activity of 0.017 GBq μmol^{-1}. The current synthesis is limited in affording [^{18}F]Selectfluor bis(triflate) in low RCY and with low molar activity. Further optimisation of the [^{18}F]xenon difluoride labelling, to enable use of a lower quantity of xenon difluoride and thus minimise isotopic dilution, is likely to increase the molar activity. Further work also needs to be done to increase the reproducibility of the RCY of [^{18}F]Selectfluor using this synthesis. The utility of [^{18}F]Selectfluor bis(triflate) has been demonstrated in the synthesis of the radiotracer [^{18}F]**3.39**, previously used for imaging of COX-2 expression.[195]

Chapter 4

^{18}F-Fluorodecarboxylation for Preparing ^{18}F-Labelled Geminal-Difluoro Compounds

This chapter presents work screening [^{18}F]Selectfluor and [^{18}F]xenon difluoride for the ^{18}F-fluorodecarboxylation of α-fluorocarboxylic acids to prepare ^{18}F-labelled geminal-difluoro compounds. The development of a more efficient method using [^{18}F]fluoride and a manganese mediator is then presented, along with a preliminary reaction scope. Synthesis of α-fluorinated carboxylic acid substrates was carried out by R. Szpera, J. Ford, A. W. J. Poh, and Dr. J. Sap (detailed contributions provided in Chapter 5). All other non-radioactive experiments were carried out by R. Szpera. Radiochemical experiments were conducted by R. Szpera with the assistance of Dr. J. Sap and A. W. J. Poh.

4.1 Introduction

4.1.1 The Geminal-Difluoro Motif

With optimised radiosyntheses of [^{18}F]Selectfluor and [^{18}F]xenon difluoride in hand, we investigated applying these reagents for radiolabelling the geminal-difluoro motif. This motif (both RCF_2R and RCF_2H) is prevalent in pharmaceuticals (Figure 26), yet methods for ^{18}F-labelling the motif are highly limited. The geminal-difluoro group has been incorporated into biologically active molecules to increase metabolic stability[196,197] and to fine-tune lipophilicity.[198]

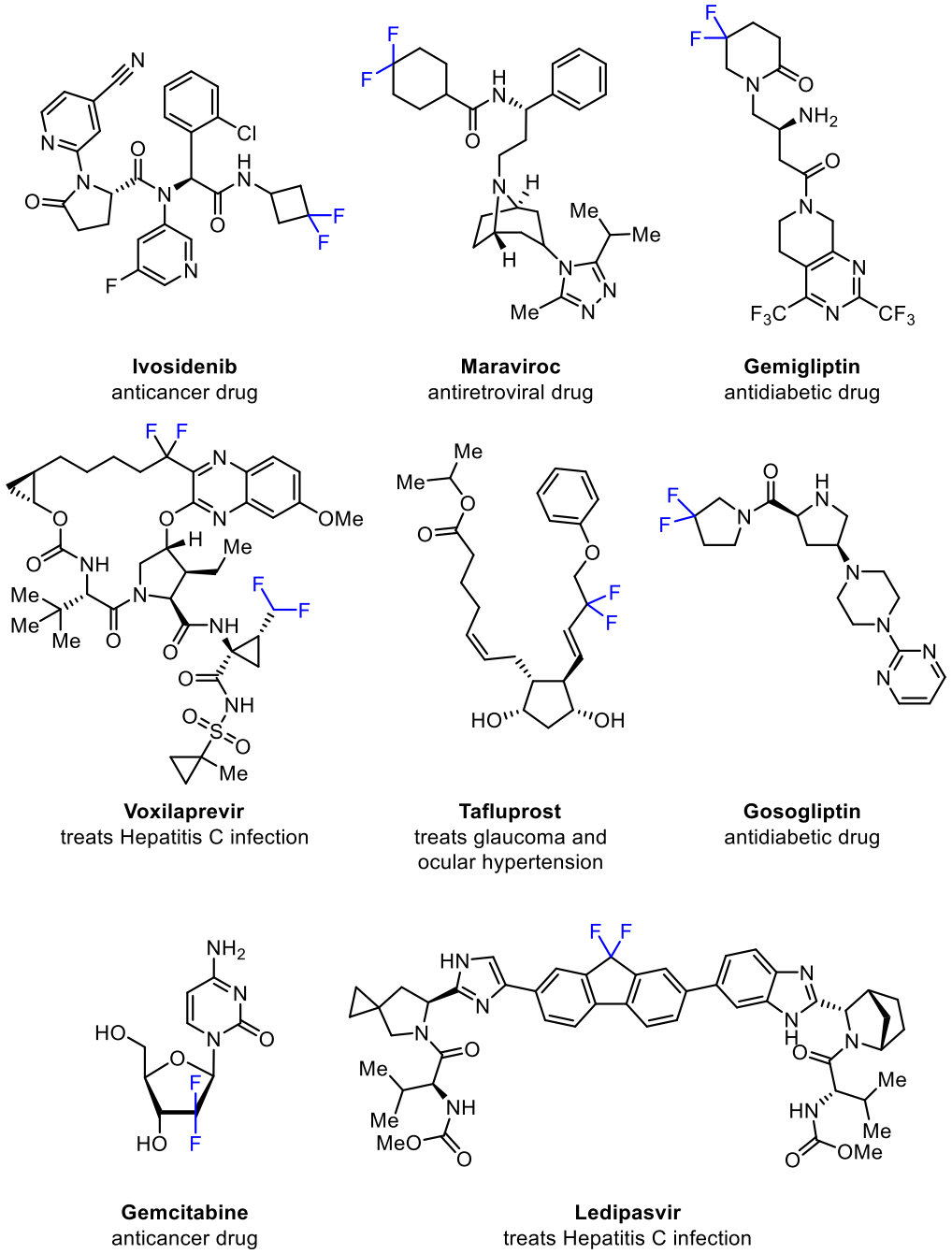
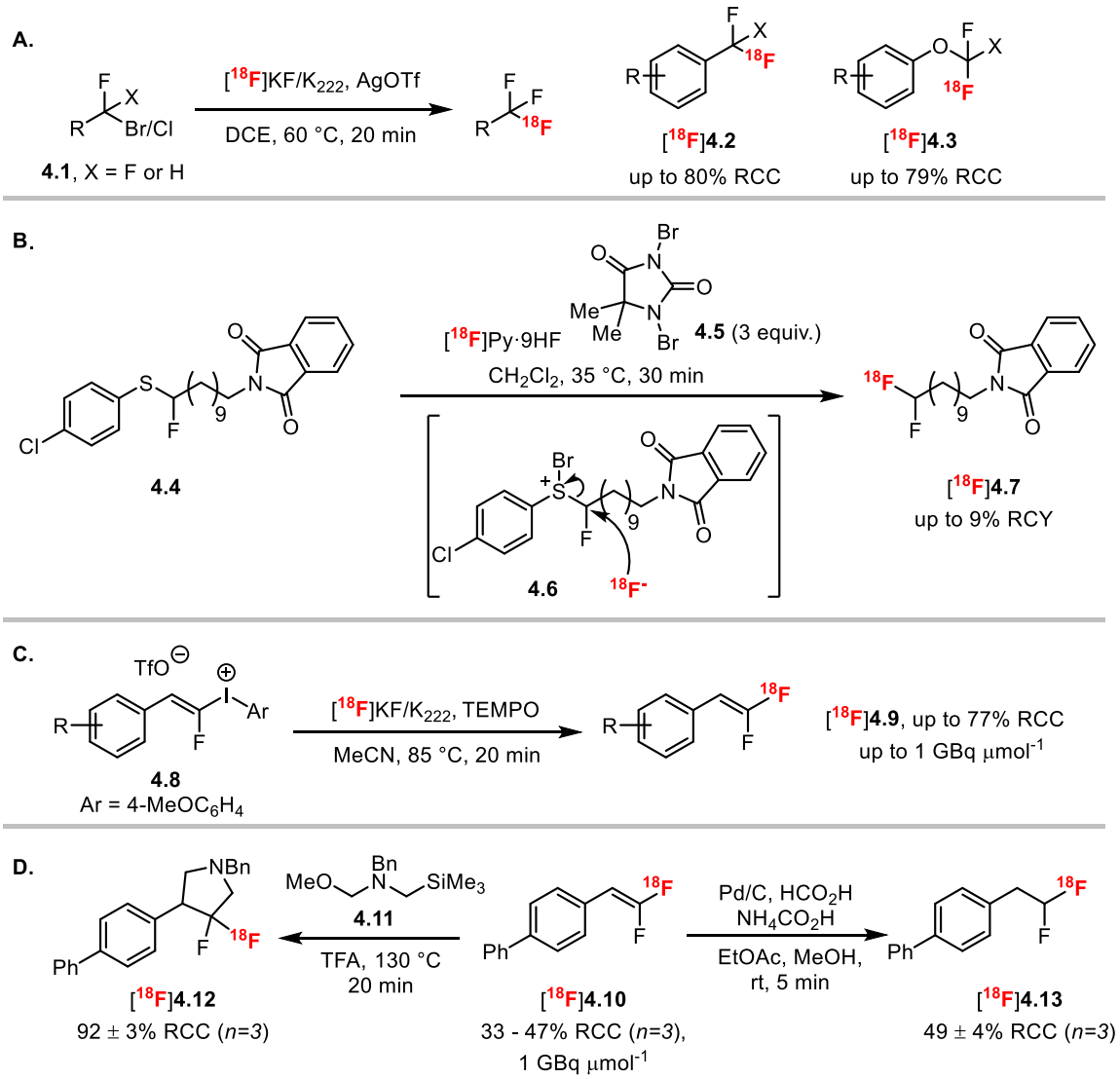


Figure 26: Approved drugs containing the geminal-difluoro motif.

4.1.2 Methods for ^{18}F-Radiolabelling the Geminal-difluoroalkanes

^{18}F-Labelling of di- and trifluoromethyl groups adjacent to activating groups such as arenes ([^{18}F]**4.2**, Scheme 57A) and heteroatoms ([^{18}F]**4.3**) is known, and can be achieved by nucleophilic displacement of a leaving group at a fluorinated carbon (**4.1**).[127,128] However, there is a distinct absence of methods for ^{18}F-radiolabelling geminal-difluoro

groups and other polyfluorinated alkyl motifs which are not adjacent to activating groups, despite their prevalence in medicinal chemistry. The Haufe group have report the ^{18}F-labelling of the geminal-difluoro group of [^{18}F]**4.7** by reacting α-fluorinated thioether **4.4** with [^{18}F]Py·9HF and 1,3-dibromo-5,5-dimethylhydantoin **4.5** (Scheme 57B). Under these conditions the thioether of **4.4** is brominated by **4.5** to form **4.6**, which then undergoes substitution at carbon by [^{18}F]fluoride to afford geminal-difluoro compound [^{18}F]**4.7**. However only a single example is reported, in low RCY and under carrier-added conditions. The molar activity is therefore expected to be low. The Tredwell group have reported preparing 1,1-[^{18}F]difluorinated alkenes [^{18}F]**4.9** by reaction of the corresponding aryliodonium salts **4.8** with [^{18}F]KF/K_{222} (Scheme 57C). Under these conditions, [^{18}F]**4.10** was obtained with a molar activity of 1 GBq μmol^{-1}. Geminal-difluoro pyrrolidine [^{18}F]**4.12** could be obtained via post-labelling 1,3-dipolar cycloaddition with **4.11**, and the reduced difluoroethyl compound [^{18}F]**4.13**. could be obtained by palladium catalysed hydrogenation (Scheme 57D). The scope of the ^{18}F-labelling reaction was largely limited to β,β-difluorostyrenes.



*Scheme 57: A. Synthesis of ^{18}F-labelled di- and trifluoromethyl arenes [^{18}F]**4.2**, and di- and trifluoromethoxy arenes [^{18}F]**4.3** by silver-mediated nucleophilic substitution, reported by the Gouverneur group.[128,127] B. Radiosynthesis of the geminal-difluoro compound [^{18}F]**4.7** using carrier-added [^{18}F]Py·9HF, reported by the Haufe group.[199] C. Synthesis of ^{18}F-labelled 1,1-difluoroalkenes [^{18}F]**4.9** by reaction of fluoroalkenyl(aryl)iodonium triflates **4.8** with [^{18}F]fluoride, reported by the Tredwell group.[200] D. Post-labelling reactions of ^{18}F-labelled 1,1-difluoroalkene [^{18}F]**4.10** to prepare ^{18}F-labelled geminal-difluoro compounds [^{18}F]**4.12** and [^{18}F]**4.13**.*

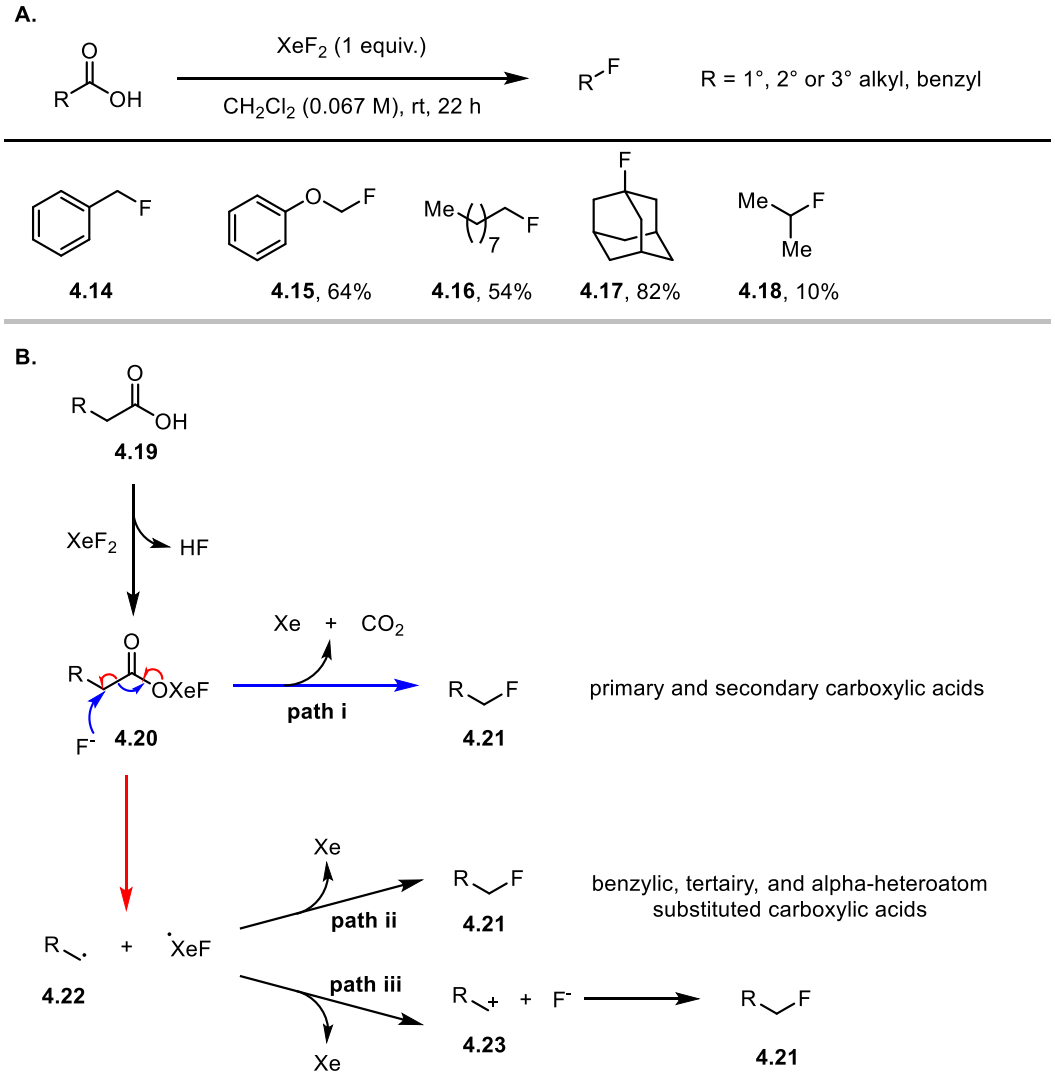
4.1.3 Fluorodecarboxylation Reactions

Fluorodecarboxylation has emerged as a powerful tool for the synthesis of alkyl fluorides from carboxylic acids. Three distinct conditions have emerged for fluorodecarboxylation reactions; i) use of xenon difluoride,[201,202] ii) use of Selectfluor with catalytic silver

nitrate,[203] and iii) use of a fluoride source in combination with stoichiometric iodosobenzene and catalytic manganese.[36]

4.1.3.1 Fluorodecarboxylation with Xenon Difluoride

The Patrick group have reported that treating carboxylic acids with xenon difluoride at room temperature in dichloromethane results in fluorodecarboxylation (Scheme 58A).[201] The scope is broad, enabling access to benzylic (**4.14**), α-heteroatom substituted (**4.15**), primary (**4.16**) and tertiary alkyl fluorides (**4.17**). Secondary alkyl fluorides are formed in low yield (**4.18**). Three distinct mechanisms can operate depending on the substrate (Scheme 58B).[204] Reaction of the carboxylic acid **4.19** with xenon difluoride forms xenon ester **4.20**. For primary and secondary aliphatic carboxylic acids, the xenon ester is displaced in a nucleophilic attack by fluoride (path i) to afford the fluorodecarboxylated product **4.21**. Tertiary, benzylic, and α-heteroatom substituted carboxylic acids undergo radical decarboxylation affording carbon centred radical **4.22**. This can either undergo fluorine atom transfer from FXe· or xenon difluoride (path ii), or can be oxidized to the cation **4.23** and then be trapped by fluoride (path iii). However, broad mechanistic conclusions for substrate classes are hard to draw, as experiments have shown radicals to also be implicated in the fluorination of some primary aliphatic carboxylic acids.[204]

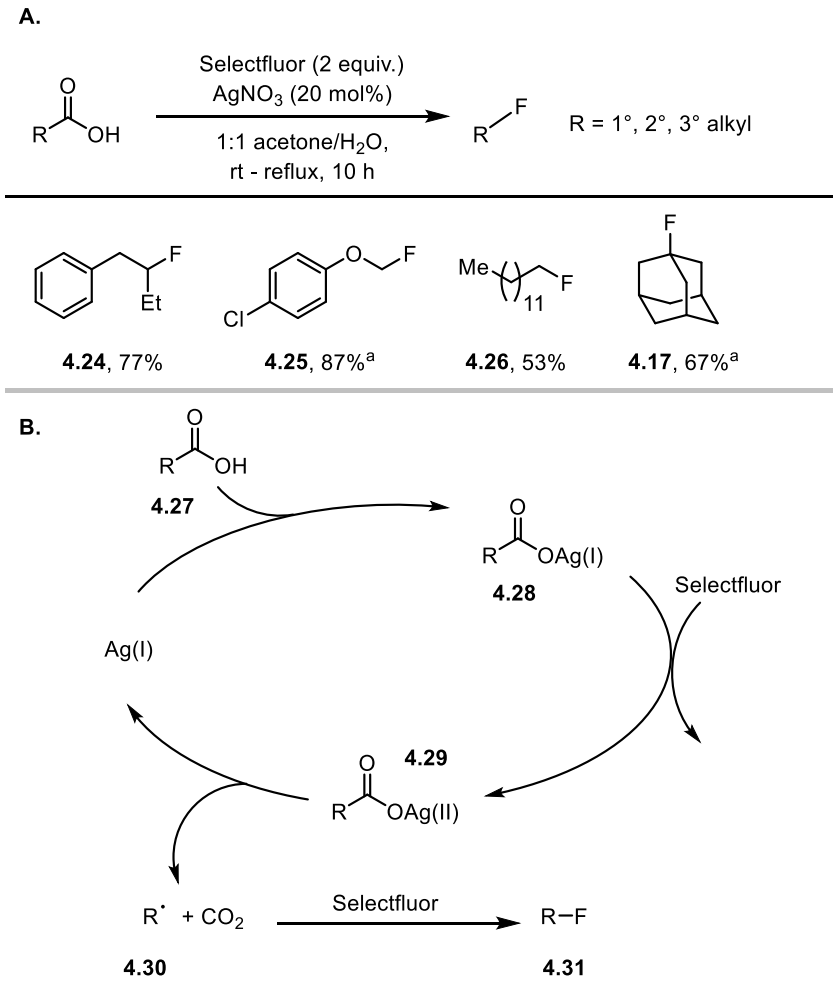


Scheme 58: A. Fluorodecarboxylation of carboxylic acids with xenon difluoride, for preparing primary, tertiary, and α-heteroatom substituted alkyl fluorides and benzyl fluorides, reported by the Patrick group.[201] B. Proposed reaction mechanisms.

4.1.3.2 Fluorodecarboxylation with Selectfluor and Silver Nitrate

Seminal work from the Sammis group in 2012 reported that alkyl radicals (generated from peresters) react with NFSI and Selectfluor via F-atom transfer to generate alkyl fluorides.[205] Following this, the scope of radical fluorination with N-F reagents was extended to carboxylic acid substrates, using Selectfluor and catalytic silver nitrate under aqueous conditions (Scheme 59A).[203] The scope is broader than that using xenon difluoride, enabling access to secondary alkyl fluorides (**4.24**), in addition to α-

heteroatom substituted (**4.25**), primary (**4.26**) and tertiary alkyl fluorides (**4.17**). The mechanism proceeds as follows; reaction of the carboxylic acid **4.27** with silver(I) forms silver(I) carboxylate **4.28**, followed by single electron oxidation by Selectfluor to afford silver(II) species **4.29**. Decarboxylation regenerates the silver(I) catalyst, and affords alkyl radical **4.30**, which undergoes F-atom transfer with Selectfluor to form the fluorinated product **4.31** (Scheme 59B).[206] The MacMillan group have reported photocatalytic fluorodecarboxylation with Selectfluor. An iridium photocatalyst and blue LED irradiation is used in place of silver nitrate to promote generation of the intermediate alkyl radical **4.30** from the carboxylic acid **4.27**.[207]

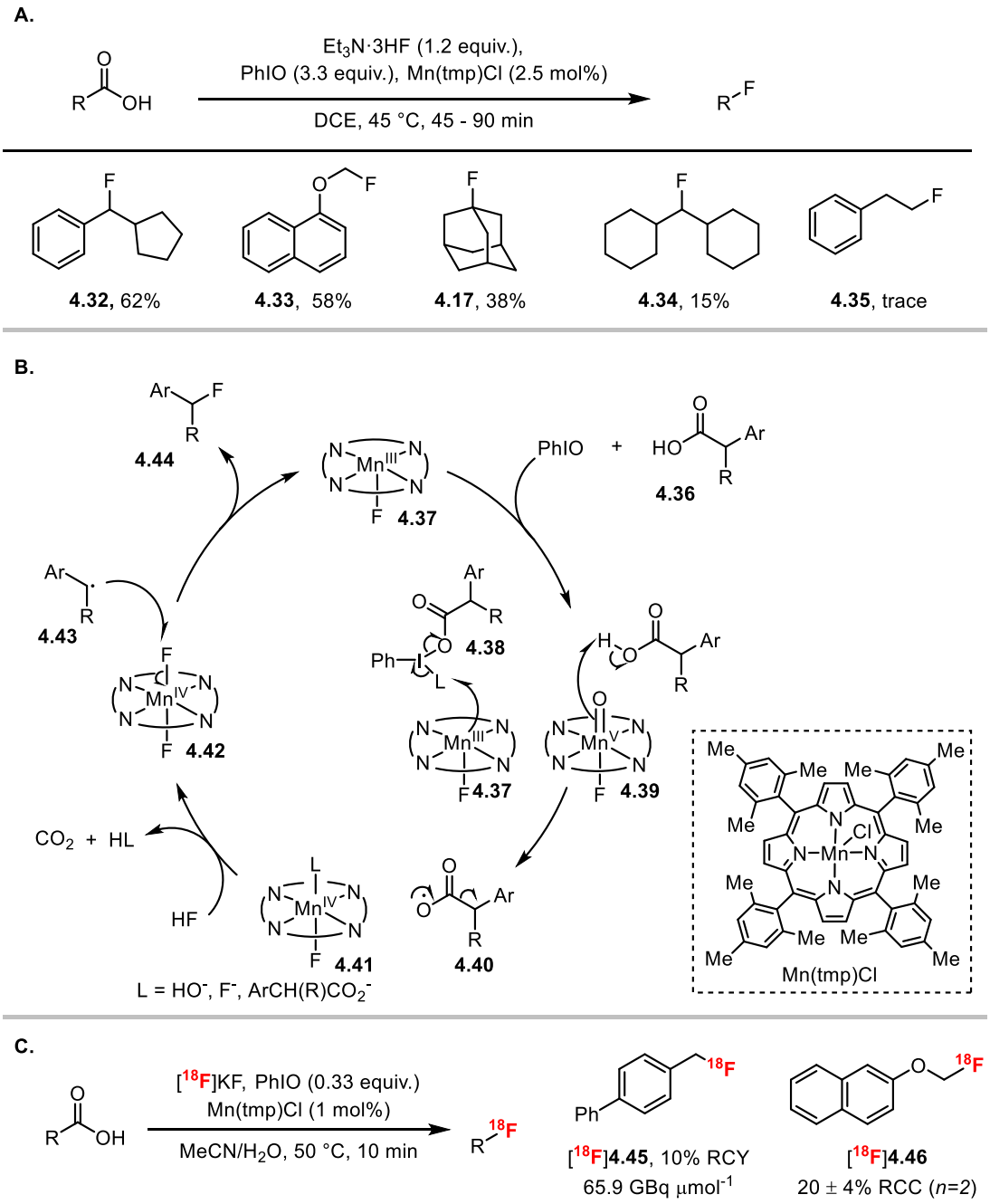


Scheme 59: A. Fluorodecarboxylation with Selectfluor and silver nitrate, for preparing primary, secondary, tertiary, and α-heteroatom substituted alkyl fluorides, reported by the Li group.[203] B. Reaction mechanism proposed by the Flowers group.[206] [a]H_2O used as solvent without acetone.

4.1.3.3 Fluorodecarboxylation with Fluoride and a Manganese Porphyrin

The Groves group have reported that fluorodecarboxylation can be achieved using fluoride in the presence of a stoichiometric oxidant and a manganese catalyst (Scheme 60A).[36] The scope of the reaction is limited to preparing benzyl fluorides such as **4.32** and fluoromethoxy arenes such as **4.33**. The method affords low yields of tertiary alkyl fluorides (**4.17**), very low yields of secondary alkyl fluorides (**4.34**), and only traces of primary alkyl fluorides (**4.35**). This is in contrast to fluorodecarboxylations with Selectfluor which work well with each primary, secondary, tertiary and α-heteroatom substituted carboxylic acids. The reaction is proposed to proceed by the same general

mechanism as when an electrophilic fluorinating agent is used, i.e. generation of a carbon centred radical, followed by fluorine atom transfer (Scheme 60B). However, in this approach the F-atom transfer agent is generated in situ from fluoride and a stoichiometric oxidant. Fluoride ligation to Mn(tmp)Cl forms **4.37**, which followed by oxidation with iodosobenzene affords manganese(V) species **4.39**. H-atom transfer from the carboxylic acid **4.36** generates manganese(IV) species **4.41** and oxygen centred radical **4.40**, which decarboxylates to afford carbon radical **4.43**. This then abstracts a fluorine from manganese(IV) fluoride **4.42** to form the final product **4.44**. Another potential mechanism is reaction of carboxylic acid **4.36** with iodosobenzene to afford iodine(III) species **4.38**, which can react with manganese(III) fluoride **4.37** to afford manganese(IV) fluoride **4.41** and oxygen centred radical **4.40**. While the scope of this method is limited in comparison to that using Selectfluor, the ability to use fluoride to perform a transformation that is typically carried out with an electrophilic fluorinating agent makes the method attractive for use in F-18 radiochemistry. Indeed, the Groves group developed a modified procedure for ^{18}F-fluorodecarboxylation, affording ^{18}F-labelled benzyl fluoride [^{18}F]**4.45** in 10% RCY with molar activity of 65.9 GBq μmol^{-1}, and affording fluoromethoxy arene [^{18}F]**4.46** in 20% RCC (Scheme 60C).

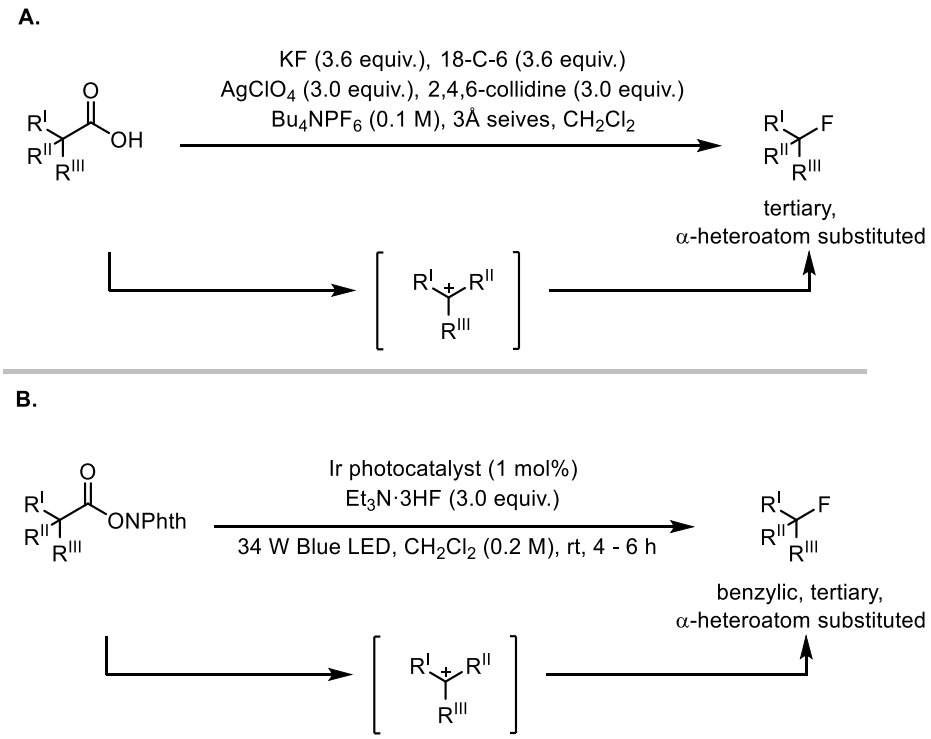


*Scheme 60: A. Fluorodecarboxylation with fluoride and a manganese porphyrin to prepare benzyl fluorides (**4.32**) and fluoromethoxy arenes (**4.33**), reported by the Groves group.[36] B. Proposed mechanism. C. Application for ^{18}F-fluorodecarboxylation.*

4.1.3.4 Other Methods

In addition to the methods discussed above, the Baran group have reported fluorodecarboxylation of carboxylic acids via trapping of electrochemically generated carbocations with fluoride (Scheme 61A).[208] This method is however limited to formation

of tertiary and α-heteroatom substituted alkyl fluorides which are derived from stabilised carbocations. The Doyle group have reported that redox-active *N*-hydroxyphthalimide esters undergo nucleophilic fluorination in the presence of an iridium photocatalyst and visible light (Scheme 61B).[209] Similar to the method reported by the Baran group, the reaction proceeds via the generation of a carbocation. The method is therefore also limited to formation of fluorinated products derived from stabilised carbocations. The Doyle group have shown that the method can be adapted for ^{18}F-radiolabeling.

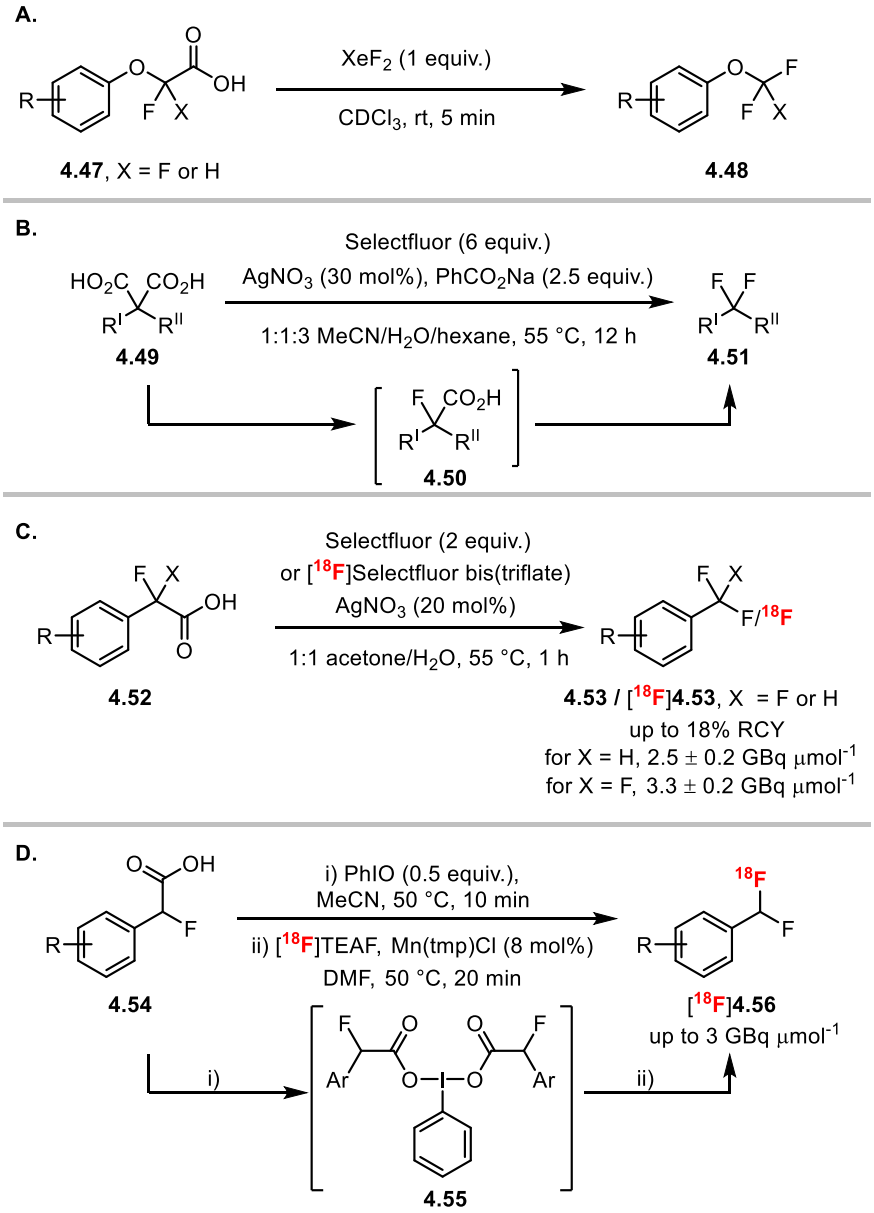


Scheme 61: A. Nucleophilic fluorination of carbocations electrochemically generated from carboxylic acids, reported by the Baran group.[208] B. Nucleophilic fluorination of carbocations generated from redox-active esters via photoredox catalysis, reported by the Doyle group.[209]

4.1.3.5 Fluorodecarboxylation Reactions for Preparing Polyfluorinated Motifs

Fluorodecarboxylation has been applied for the synthesis of polyfluorinated motifs, by employing α-fluorocarboxylic acids as substrates. The Sammis group have shown that di- and trifluoromethoxy arenes **4.48** can be prepared by fluorodecarboxylation of mono-

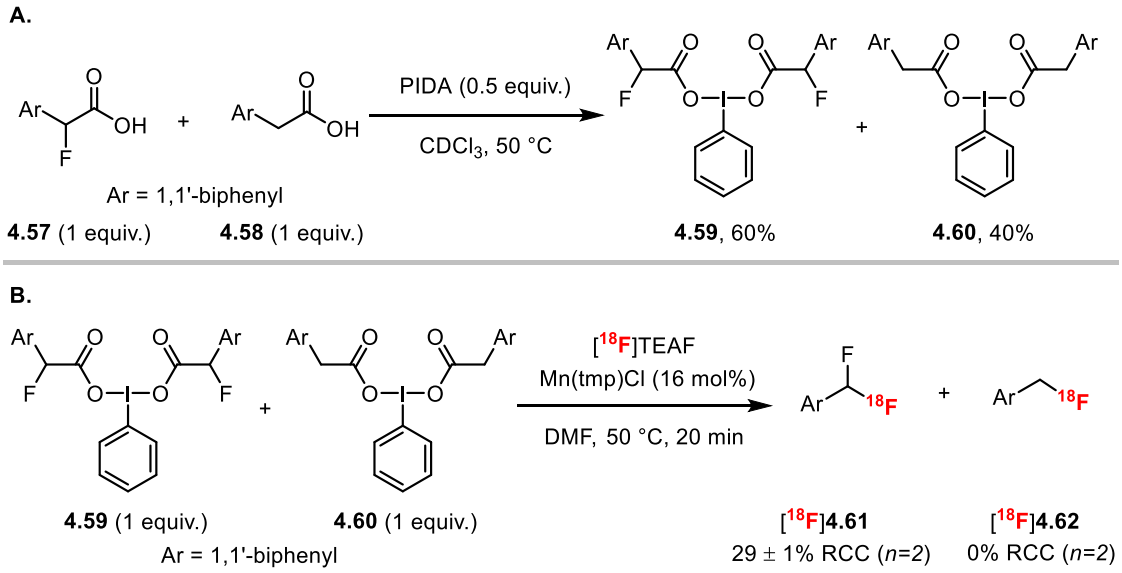
and difluoroaryloxy acetic acids **4.47** with xenon difluoride (Scheme 62A). The Chen group have applied silver nitrate catalysed fluorodecarboxylation with Selectfluor for the synthesis of geminal-difluoroalkanes **4.51** from malonic acid derivatives **4.49** (Scheme 62B).[210] The reaction proceeds via two consecutive decarboxylative radical fluorinations via α-fluorocarboxylic acid **4.50**. This method enables formation of geminal-difluorinated compounds without requiring an adjacent activating aromatic ring or heteroatom. The concept of preparing polyfluorinated motifs via fluorodecarboxylation of α-fluorocarboxylic acids has also been applied for radiolabelling. The Gouverneur and Solin groups have shown that di- and trifluoromethyl arenes **4.53** can be prepared using Selectfluor with silver nitrate (Scheme 62C).[137] Use of [^{18}F]Selectfluor bis(triflate), prepared from high molar activity [^{18}F]F_2 gas produced post-target,[23] enabled access to the corresponding ^{18}F-labelled compounds [^{18}F]**4.53** with molar activities of up to 3.3 GBq μmol^{-1}. The Gouverneur group have applied the manganese porphyrin chemistry developed by Groves for preparing ^{18}F-difluoromethyl arenes [^{18}F]**4.56** directly from [^{18}F]fluoride and α-fluorophenylacetic acids **4.54** (Scheme 62D).[211] Molar activities of up to 3 GBq μmol^{-1} were recorded. RCCs were highest when the substrate **4.54** and iodosobenzene were premixed to form the corresponding iodine(III) species **4.55**, before treatment with [^{18}F]fluoride and the manganese porphyrin.



*Scheme 62: A. Fluorodecarboxylation with xenon difluoride for preparing di- and trifluoromethoxy arenes **4.48**, reported by the Sammis group.[212] B. Fluorodecarboxylation of malonic acids **4.49** with Selectfluor and silver nitrate for preparing geminal-difluoro compounds **4.51**, reported by the Chen group.[210] C. Fluorodecarboxylation with Selectfluor /[^{18}F]Selectfluor bis(triflate) and silver nitrate for preparing di- and trifluoromethyl arenes **4.53** and F-18 isotopologues [^{18}F]**4.53**, reported by the Gouverneur group.[137] D. ^{18}F-Fluorodecarboxylation with [^{18}F]fluoride and a manganese porphyrin for preparing [^{18}F]difluoromethyl arenes [^{18}F]**4.56**, reported by the Gouverneur group.[211]*

The Gouverneur group investigated the effect of fluorine substitution in fluorodecarboxylation substrates.[211] In a competition experiment reacting PIDA with equimolar quantities of non-fluorinated carboxylic acid **4.58** and α-fluorocarboxylic acid

4.57, the iodine(III) species **4.59** of the α-fluorocarboxylic acid formed preferentially (Scheme 63A). In another competition experiment, equimolar quantities of iodine(III) species **4.59** and **4.60** were subjected to the ^{18}F-labelling conditions (Scheme 63B). Only the difluoromethyl arene [^{18}F]**4.61** was observed, with no formation of the fluoromethyl arene [^{18}F]**4.62**. Fluorine substitution therefore facilitates both formation of the intermediate iodine(III) species and fluorodecarboxylation.

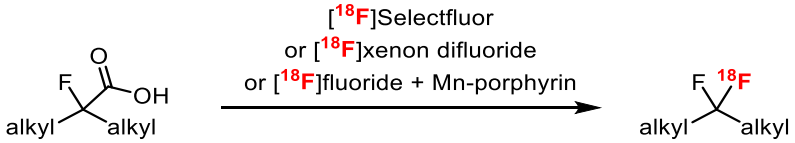


*Scheme 63: A. Competition experiment between non-fluorinated carboxylic acid **4.58** and α-fluorocarboxylic acid **4.57** in reacting with PIDA, reported by the Gouverneur group.[211] B. Competition experiment between non-fluorinated substrate **4.60** and α-fluorinated substrate **4.59** in the ^{18}F-fluorodecarboxylation reaction.*

The methods discussed above enable ^{18}F-radiolabelling of di- and trifluoromethyl groups directly attached to aromatic rings. However, no ^{18}F-radiolabelling method has been reported for preparing geminal-difluoro alkanes which are not adjacent to an activating group, by ^{18}F-fluorodecarboxylation. The only means for ^{18}F-labelling geminal-difluoroalkanes are the limited methods presented in Scheme 57.

4.2 Aims of This Work

The geminal-difluoroalkane motif is prevalent in medicinal chemistry, however there are a distinct lack of methods for preparing ^{18}F-labelled geminal-difluoroalkanes. We aimed to develop an ^{18}F-fluorodecarboxyaltion of α-fluorocarboxylic acids, for preparing ^{18}F-labelled geminal-difluoroalkanes (Scheme 64). For this purpose, we aimed to test [^{18}F]Selectfluor and [^{18}F]xenon difluoride, prepared under the conditions optimised in Chapter 3, as well as manganese porphyrin mediated chemistry. The requisite α-fluorocarboxylic acids were accessible via α-fluorination of the parent carboxylic esters/acids (see Chapter 5 for full experimental details).



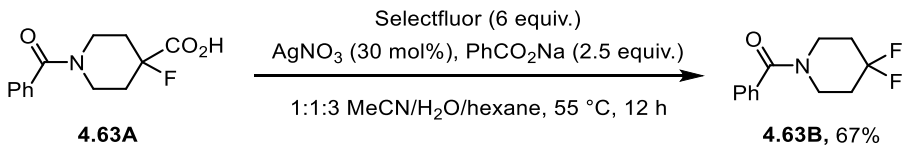
Scheme 64: Aim of this work; to prepare ^{18}F-labelled geminal-difluoroalkanes by ^{18}F-fluorodecarboxylation of α-fluorocarboxylic acids.

4.3 Results and Discussion

4.3.1 Reaction Optimisation

4.3.1.1 ^{18}F-Fluorodecarboxylation with [^{18}F]Selectfluor bis(triflate)

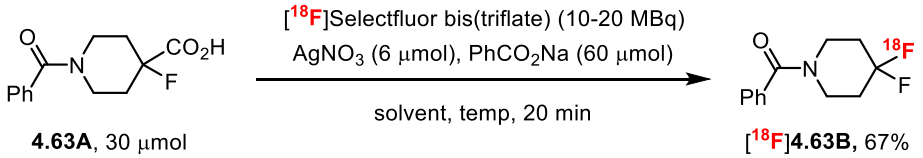
As discussed previously, the Chen group have shown that malonic acid derivatives afford geminal-difluoroalkanes when treated with Selectfluor and silver nitrate.[210] To support the mechanistic proposal that the reaction proceeds via two consecutive fluorodecarboxylations, the Chen group submitted α-fluorocarboxylic acid **4.63A** to the reaction conditions, and indeed **4.63B** was formed (Scheme 65).



*Scheme 65: Fluorodecarboxylation of α-fluorocarboxylic acid **3.91**, reported by the Chen group.*[210]

We therefore tested whether the same reaction could be carried out using [^{18}F]Selectfluor, synthesised from [^{18}F]fluoride as discussed in Chapter 4. The [^{18}F]Selectfluor was used crude (without removal of [^{18}F]fluoride by QMA filtration) and so the RCCs quoted are from [^{18}F]fluoride, and not from radiochemically pure [^{18}F]Selectfluor. Using conditions similar to those reported by the Chen group,[210] traces of [^{18}F]**4.63B** were obtained (Entry 1, Table 24); the product was detected by radioHPLC but the conversion measured by radioTLC was very low. The low RCC from [^{18}F]fluoride is in part due to the very low RCP of the crude [^{18}F]Selectfluor (~5% RCP when not filtered through a QMA cartridge). We speculated that the biphasic reaction conditions also may be problematic; in the radiochemical lab, V-vials are used with low solvent volumes (~300 µL) and we speculated this may result in poor mixing of the phases. Monophasic solvent systems were therefore trialled. Use of water/acetone (as reported for other Selectfluor/silver nitrate fluorodecarboxylations)[137,203] at 50 °C resulted in no product formation (Entry 2). Similarly, acetonitrile/water resulted in no product formation (Entry 3). Using water/acetone and heating at 80 °C resulted in traces of product formation (Entry 4). Doubling the reaction concentration also resulted in formation of just traces of the product (Entry 6). The reactions should be repeated with [^{18}F]Selectfluor purified by QMA filtration to remove [^{18}F]fluoride, to enable more accurate quantification of RCCs from [^{18}F]Selectfluor.

*Table 24: Screening conditions for fluorodecarboxylation of **4.63A** with [^{18}F]Selectfluor bis(triflate). RCCs quoted from [^{18}F]fluoride ([^{18}F]Selectfluor bis(triflate) used crude). [a]No $PhCO_2Na$.*



4.63A, 30 μmol

[^{18}F]**4.63B**, 67%

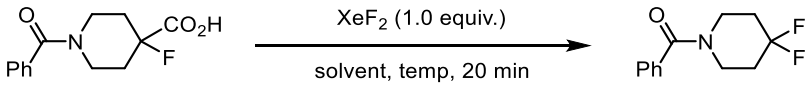
Entry	Solvent	Temp (°C)	% RCC
1	1:1:3 MeCN/ H_2O/cyclohexane	50	trace
2	1:1 Acetone/H_2O	50	0
3	1:1 MeCN/H_2O	50	0
4[a]	1:1 Acetone/H_2O	80	trace
5	1:1 MeCN/H_2O	80	0
6[a]	1:1 Acetone/H_2O (double concentration)	80	trace

4.3.1.2 Fluorodecarboxylation with Xenon Difluoride

The feasibility of fluorodecarboxylation of **4.63A** with xenon difluoride was assessed, before attempting the reaction with [^{18}F]xenon difluoride (Table 25). Yields are quoted with respect to xenon difluoride, and were measured using quantitative ^{19}F NMR with α,α,α-trifluorotoluene as an internal standard. Heating xenon difluoride with 2 equivalents of α-fluorocarboxylic acid **4.63A** at 60 °C in acetonitrile resulted in formation of 11% of the desired difluorinated product **4.63B** after 20 minutes (Entry 1). Screening of other solvents revealed that each dichloromethane, 1,2-dichloroethane (DCE), chloroform, and ethyl acetate afforded higher yields of between 17% and 20% (Entries 2 to 5). Increasing the temperature to 80 °C using DCE resulted in no change in yield (Entry 6). Running the reaction at room temperature resulted in no product formation (Entry 7). Decreasing the concentration from 0.25 M to 0.125 M resulted in little change in yield (Entry 8). Decreasing the equivalents of the substrate **4.63A** also had little effect on the

yield (Entry 9). Reactions in ethyl acetate and DCE resulted in significant fluorination of the solvent. Reactions with xenon difluoride are known to be sensitive to the material of the reaction vessel.[173,212] The reaction was therefore tested in a polyethylene plastic vessel rather than a borosilicate vial, however little in change in the yield was observed (Entry 10). In most of the reactions, a significant quantity of unconsumed α-fluorocarboxylic acid **4.63A** remained at the end (37 – 81%, Table 25).

*Table 25: Optimisation of fluorodecarboxylation of **4.63A** with xenon difluoride. [a]Reaction run in polyethylene vessel. Yields determined by quantitative ^{19}F NMR using α,α,α-trifluorotoluene as internal standard.*



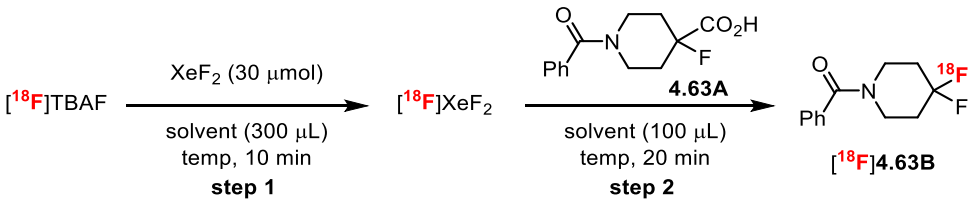
4.63A **4.63B**

Entry	Solvent	Temp (°C)	Equiv. 3.91	[XeF_2] (mM)	% 4.63A remaining	% Yield
1	MeCN	60	2	0.25	48	11
2	CH_2Cl_2	60	2	0.25	53	20
3	DCE	60	2	0.25	59	19
4	$CHCl_3$	60	2	0.25	59	19
5	EtOAc	60	2	0.25	56	17
6	DCE	80	2	0.25	61	20
7	DCE	rt	2	0.25	81	2
8	DCE	60	2	0.125	65	22
9	DCE	60	1	0.25	37	19
10[a]	DCE	60	1	0.25		20

A one-pot two-step procedure for preparing [^{18}F]**4.63B** from [^{18}F]fluoride via [^{18}F]xenon difluoride was tested (Table 26). A solution of xenon difluoride was added to [^{18}F]TBAF and the mixture was heated for 10 minutes (step 1). A solution of α-fluorocarboxylic acid **4.63A** was then added, and the reaction mixture was heated for a further 20 minutes

(step 2). While acetonitrile was typically the solvent used for preparing [^{18}F]xenon difluoride in the synthesis of [^{18}F]Selectfluor, fluorodecarboxylation of **4.63A** with xenon difluoride was shown to be higher yielding in other solvents (Table 25). Changing solvent by evaporation and redissolving after step 1 would be difficult due to the low vapour pressure of xenon difluoride.[193] Therefore either the same solvent was used in both steps 1 and 2, or a solvent mixture was used in step 2. Reactions were analysed using a combination of RadioTLC and RadioHPLC. Using dichloromethane, 2% RCC of [^{18}F]**4.63B** from [^{18}F]fluoride was obtained (Entry 1). The RCC increased to 6% when DCE was used (Entry 2). Chloroform afforded less than 1% RCC (Entry 3). Using acetonitrile for step 1, and then adding substrate **4.63A** in dichloromethane for step 2 (3:1 acetonitrile / dichloromethane) afforded [^{18}F]**4.63B** in 9% RCC (Entry 4). Adjusting the stoichiometry of the carboxylic acid substrate **4.63A** failed to improve the yield (Entries 5 and 6), neither did changing the reaction concentration (Entry 7). Addition of silver nitrate, which catalyses fluorodecarboxylation with Selectfluor,[206] did not increase the yield (Entry 8). Most reactions had small F-18 impurities. These may form by reaction of [^{18}F]xenon difluoride with the solvents, as was observed by ^{19}F NMR for the reactions in Table 25.

*Table 26: Optimisation of ^{18}F-fluorodecarboxylation of **4.63A** with [^{18}F]xenon difluoride. RCCs calculated using a combination of radioTLC and radioHPLC. [a]$AgNO_3$ (11 µmol) added.*



Entry	Solvent	Temp (°C)	4.63A (µmol)	Total Volume (µL)	% RCC [^{18}F]4.63B
1	CH_2Cl_2	40	30	400	2
2	DCE	50	30	400	6
3	$CHCl_3$	50	30	400	<1
4	MeCN (S1), CH_2Cl_2 (S2)	80	30	400	9
5	DCE	50	15	400	3
6	DCE	50	60	400	8
7	DCE	50	30	200	6
8[a]	DCE	50	30	400	2

4.3.1.3 ^{18}F-Fluorodecarboxylation with [^{18}F]Fluoride and Manganese

Fluorodecarboxylation of **4.63A** was tested under the conditions developed by the Groves group using the manganese porphyrin Mn(tmp)Cl.[36] The geminal-difluoro product **4.63B** was obtained in 5% yield by quantitative ^{19}F NMR (Figure 27A). In contrast, when the corresponding non-fluorinated carboxylic acid **4.64A** was submitted to the same conditions, no formation of the fluorodecarboxylation product **4.46B** was observed by ^{19}F NMR (Figure 27B).

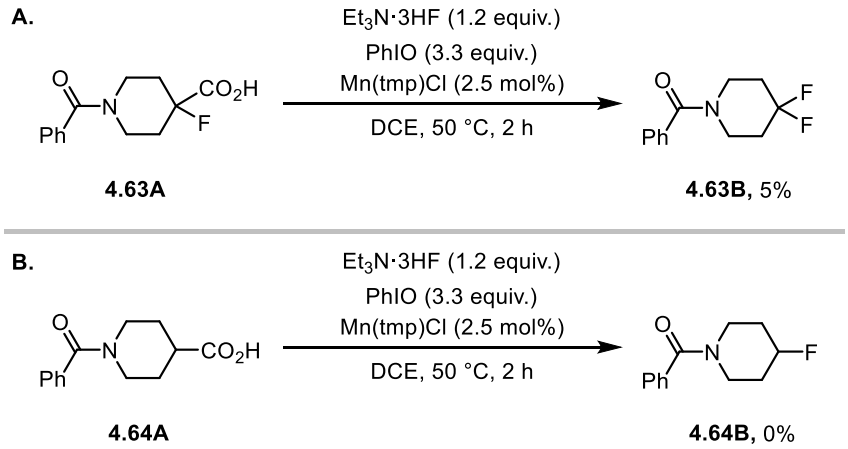
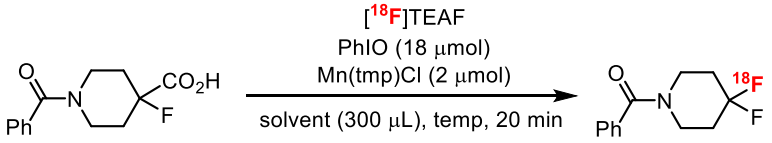


*Figure 27: Fluorodecarboxylation of α-fluorocarboxylic acid **4.63A** and non-fluorinated carboxylic acid **4.64A** under the conditions reported by the Groves Group.*[36]

^{18}F-Fluorodecarboxylation of **4.63A** was trialled next (Table 27). The desired ^{18}F-labelled product [^{18}F]**4.63B** was formed in 16% RCC when **4.63A** was heated with [^{18}F]TEAF, iodosobenzene, and Mn(tmp)Cl in acetonitrile for 20 minutes at 50 °C. Solvent screening revealed DCE afforded a higher RCC of 27% (Entry 2). Increasing the reaction duration from 20 to 40 minutes did not increase the RCC (Entry 5). Increasing the temperature to 80 °C resulted in an increase in RCC to 33% (Entry 6). Doubling the loading of Mn(tmp)Cl did not increase the yield (Entry 7). Increasing the loading of substrate **4.63A** resulted in a decrease in RCC (Entries 8 and 9). However, lowering the substrate loading from 60 µmol to 30 µmol resulted in a significant increase in RCC to 72% (Entry 10). Further reducing the loading of **4.63A** to 16 µmol resulted in a large reduction in RCC to 5% (Entry 11).

Table 27: Optimisation of ^{18}F-fluorodecarboxylation with [^{18}F]fluoride. [a]Reaction left for 40 minutes. [b]4 µmol of Mn(tmp)Cl used rather than 2 µmol. [c]27 µmol of PhIO used. [d]55 µmol of PhIO used.



4.63A **[^{18}F]4.63B**

Entry	Solvent	Temp (°C)	4.63A (µmol)	% RCC
1	MeCN	50	60	16
2	DCE	50	60	27
3	DMF	50	60	5
4	diglyme	80	60	4
5[a]	DCE	50	60	19 (*n=2*)
6	DCE	80	60	33
7[b]	DCE	80	60	23
8[c]	DCE	80	90	1
9[d]	DCE	80	150	29
10	DCE	80	30	72 (*n=4*)
11	DCE	80	16	5

Under the optimised conditions (Entry 10), a single product was observed in the radioHPLC analysis (Figure 28).

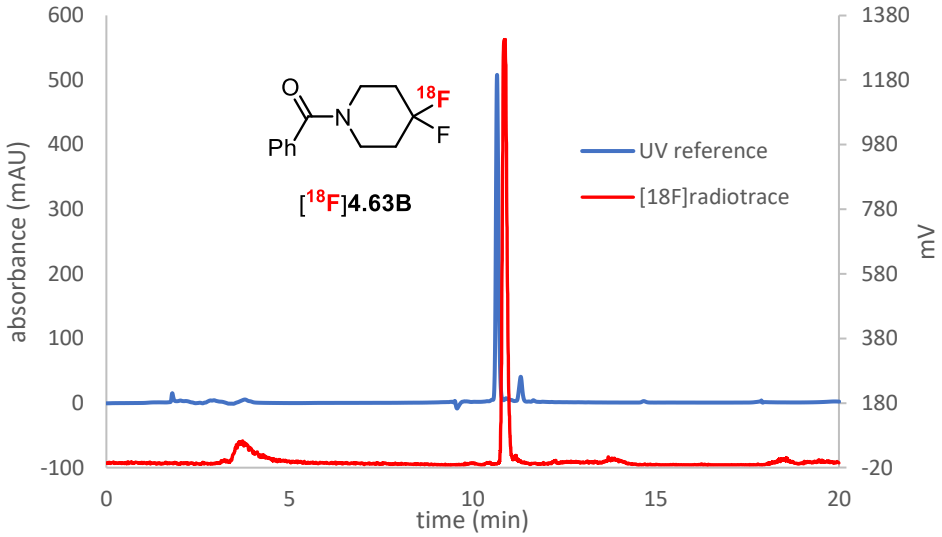


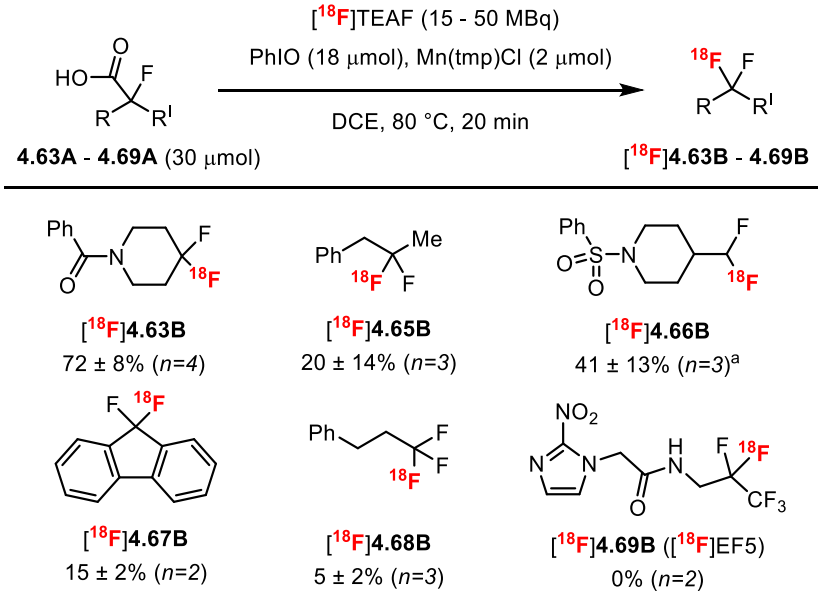
*Figure 28: RadioHPLC trace for reaction of **4.63A** under conditions in Entry 11, Table 27, overlaid with the UV trace of an authentic reference of **4.63B**.*

The RCCs for ^{18}F-fluorodecarboxylation of **4.63A** were far superior using Mn(tmp)Cl and [^{18}F]fluoride, compared to using [^{18}F]Selectfluor or [^{18}F]xenon difluoride. The procedure is also much simpler requiring a single step. Finally, the manganese porphyrin mediated ^{18}F-fluorodecarboxylation does not require the addition of an exogenous fluorine source as is the case for [^{18}F]xenon difluoride and [^{18}F]Selectfluor, which require use of xenon difluoride for their synthesis. The molar activity for the manganese porphyrin mediated method is therefore expected to be higher. We therefore continued to investigate the synthesis of ^{18}F-labelled geminal-difluoro compounds using this method.

4.3.2 Preliminary Substrate Scope

A selection of α-fluorinated carboxylic acids were submitted to the ^{18}F-fluorodecarboxylation conditions (Scheme 66). The model substrate **4.63A** afforded

the ^{18}F-labelled product [^{18}F]**4.63B** in over 70% RCC. Acyclic geminal-difluoro compound [^{18}F]**4.65B** was also labelled, albeit in reduced RCC. In addition to dialkyl substituted CF_2 groups, the ^{18}F-difluoromethyl group of [^{18}F]**4.66B** could be labelled. The method also enabled formation of ^{18}F-labelled benzylic geminal-difluoro compound [^{18}F]**4.67B**. Labelling of the ^{18}F-trifluoromethyl group of [^{18}F]**4.68B** by fluorodecarboxylation of the corresponding α,α-difluorocarboxylic acid afforded the desired product albeit with a low RCC. Further optimisation of the reaction conditions for this substrate failed to improve the RCC. Synthesis of [^{18}F]EF5 using this method was also tested, however proved unsuccessful.



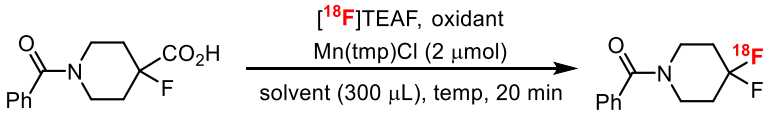
Scheme 66: Preliminary substrate scope for ^{18}F-fluorodecarboxylation for preparing geminal-difluoro compounds. RCCs Determined by a combination of radioHPLC and RadioTLC. [a]MeCN used instead of DCE.

4.3.3 Further Optimisation

In general, adding reagents as stock solutions is more practical in the radiochemistry lab, and results in more reproducible results. Further, when using automated synthesis platforms, reagents are typically manipulated as solutions. However, iodosobenzene is

insoluble in DCE and most other solvents. We therefore aimed to identify an alternative oxidant that is soluble in DCE. Use of the oxidant PIDA under the optimised reaction conditions resulted in an RCC of 67%, only slightly less than that obtained with iodosobenzene (Entry 2, Table 28). However, using PIDA a 69% loss of radioactivity beyond that of decay was measured between dispensing the [^{18}F]fluoride and the end of the reaction. In contrast, only 7% loss was observed with iodosobenzene (Entry 1). This could be resolved by changing the order of addition of reagents. In the standard procedure, [^{18}F]TEAF in acetonitrile was dispensed into a V-vial containing the α-fluorocarboxylic acid **4.63A**, iodosobenzene/PIDA and Mn(tmp)Cl. The acetonitrile was then removed by heating under a flow of nitrogen, before addition of DCE and heating the reaction at 80 °C. The radioactivity was predominantly lost during the removal of acetonitrile before addition of DCE, presumably as volatile [^{18}F]hydrogen fluoride. In the modified procedure, [^{18}F]TEAF was dispensed into a V-vial containing only Mn(tmp)Cl. The acetonitrile was removed, a premixed solution of PIDA and α-fluorocarboxylic acid **4.63A** in DCE was added, and then the reaction was heated at 80 °C. Using this procedure, 0% radioactivity loss beyond decay was observed, and the product was obtained in 60% RCC (Entry 3). Use of PIDA with this order of addition should facilitate translation of the method to automated synthesis platforms.

Table 28: Effect of oxidant and order of addition on radioactivity loss and RCC.



4.63A **[^{18}F]4.63B**

Entry	Oxidant	4.63A/[ox] addition	% Radioactivity loss	% RCC
1	PhIO (18 μmol)	before drying	7	72 ± 8% (n=4)
2	PIDA (15 μmol)	before drying	69	67
3	PIDA (15 μmol)	after drying	0	60

4.3.4 Conclusions and Future work

There are currently very few methods to prepare ^{18}F-labelled geminal-difluoroalkanes compounds despite the prevalence of the motif in pharmaceuticals. This work presents two different operationally simple conditions for ^{18}F-labelling the motif using [^{18}F]fluoride, by ^{18}F-fluorodecarboxylation of α-fluorocarboxylic acids. One approach is a two-step one-pot procedure via [^{18}F]xenon difluoride, and the other is by use of [^{18}F]fluoride directly in combination with a manganese porphyrin catalyst and an oxidant. The latter approach is advantageous in affording higher RCCs and not requiring addition of an F-19 carrier. A small preliminary scope using the latter approach has demonstrated that the reaction works for ^{18}F-labelling cyclic, acyclic, benzylic, and terminal (CF_2H) geminal-difluoro groups. To the best of our knowledge, this is the first direct, non-carrier added method for preparing ^{18}F-labelled geminal-difluoroalkanes. Future work will focus on expanding the substrate scope and applying the method for radiolabelling pharmaceutically relevant molecules.

Chapter 5

Experimental Procedures and Characterisation Data

Unless stated otherwise, the work detailed in this chapter was conducted by R. Szpera.

5.1 General Information

5.1.1 Solvents, Chemicals and Analytical Instruments

All reagents were purchased from commercial suppliers (Sigma-Aldrich, Alfa Aesar, Fluorochem and Apollo Scientific) and used without further purification. Dry solvents were obtained from the MBRAUN-SPS solvent purification system (CH_2Cl_2, THF, 1,4-dioxane, toluene, DMF, MeCN, Et_3N, diisopropylamine) or bottled from commercial suppliers (DMI, MeCN, 1,4-dioxane, DME and EtOH from Sigma-Aldrich) . Reactions were monitored by thin layer chromatography (TLC) on silica gel pre-coated aluminium sheets (Merck Kieselgel 60 F_{254} plates). Visualisation was accomplished by irradiation with UV light at 254 nm. Flash column chromatography (FCC) was performed on Merck silica gel (60, particle size 0.040-0.063 mm). All NMR spectra were recorded on Bruker AVIIIHD 400, AVIIIHD 500 or VII 500. ^{1}H and ^{13}C NMR spectral data are reported as chemical shifts (δ) in parts per million (ppm) relative to the solvent peak using the Bruker internal referencing procedure (edlock). ^{19}F NMR spectra are referenced relative to $CFCl_3$. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, pent = pentet, sept = septet, br = broad, m = multiplet), coupling constants (Hz) and integration. NMR spectra were processed with MestReNova 11.0 or higher. High resolution mass spectra (HRMS, m/z) were recorded on a Thermo Exactive High-Resolution Orbitrap FTMS instrument equipped with Waters Acquity liquid chromatography system using either the heated electrospray (HESI-II) probe for positive and negative electrospray ionization (ESI+) or the atmospheric pressure chemical ionization (APCI) probe. Infrared spectra were recorded as the neat compound or in solution using a Bruker tensor 27 FT-IR spectrometer. Absorptions are reported in

wavenumber (cm^{-1}). Melting points of solids were measured on a Griffin apparatus and are uncorrected.

5.1.2 Radiochemistry

^{18}F-Fluoride was produced by Alliance Medical (UK) or Wales Research and Diagnostic Positron Emission Tomography Imaging Centre (UK) via the $^{18}O(p,n)^{18}F$ reaction, and delivered as [^{18}F]fluoride in [^{18}O]water. HPLC analysis was performed with a Dionex Ultimate 3000 dual channel HPLC system equipped with shared autosampler, parallel UV-detectors and LabLogic NaI/PMT-radiodetectors with Flowram analog output. Due to the separation of the modules the radio-signal is offset by 0.1-0.3 min from the UV signal. Radio-TLC was performed on Merck Kiesegel 60 F254 plates. Analysis was performed using a plastic scintillator/PMT detector.

^{18}F-Labelled compounds were characterised by comparing the radioHPLC trace with the HPLC UV-trace of an authentic reference sample. Unless otherwise stated, RCCs were determined using a combination of radioTLC and radioHPLC as follows:

$$\%\ \mathrm{RCC} = \frac{\%\ \text{purity by radioHPLC (excluding fluoride)} \times \%\ \text{conversion by radioTLC}}{100}$$

RCYs were calculated as the radioactivity of the isolated product as a percentage of the radioactivity of dry [^{18}F]fluoride after elution from the QMA cartridge and azeotropic drying. Unless stated otherwise, RCYs are reported non-decay corrected.

$$\%\ \mathrm{RCY} = \frac{\text{radioactivity of isolated final product}}{\text{starting radioactivity}} \times 100$$

5.2 Experimental Procedures and Characterisation Data for Chapter 2

5.2.1 General Information

Toluene used for the C–O cross-coupling scope was dried using the MBRAUN-SPS solvent purification system and stored under N_2 over 3 Å molecular sieves. However, when toluene was used directly from the MBRAUN-SPS solvent purification system without storing over sieves, no reduction in yield was observed. Phenyl 2,2,2-trifluoroacetate and benzyl 2,2,2-trifluoroacetate were purchased from commercial suppliers.

5.2.2 General Procedures

Screening C–O cross-coupling conditions using $Pd_2(dba)_3$ and a ligand

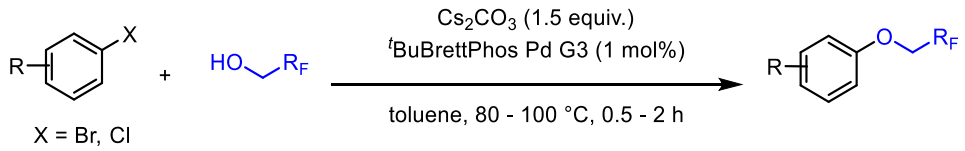
To an oven dried Schlenk tube was added Cs_2CO_3 (244 mg, 0.75 mmol, 1.5 equiv.). The Schlenk tube was placed under vacuum and heated at 450 °C with a heat gun for around 3 minutes, or until the Cs_2CO_3 stopped 'jumping'. After the tube had cooled to room temperature, it was placed under an N_2 atmosphere, and then ligand (6.25 µmol, 1.25 mol%) was added followed by a solution of $Pd_2(dba)_3$ (2.3 mg, 2.5 µmol, 0.5 mol%) in dry toluene (1.5 mL), prepared under N_2. The mixture was stirred at room temperature for 20 minutes. Then 1-(4-bromophenyl)propan-2-one (107 mg, 0.50 mmol, 1.0 equiv.) was added, followed by trifluoroethanol (54 µL, 0.75 mmol, 1.5 equiv.). The Schlenk tube was sealed under N_2, and heated in a preheated oil bath at the specified temperature for the specified duration. The reaction mixture was allowed to cool, diluted with CH_2Cl_2, and filtered through Celite. The filter cake was washed with additional CH_2Cl_2, and then α,α,α-trifluorotoluene (25 µL, 0.204 mmol) was added to the filtrate. A sample of the filtrate was taken, diluted with $CDCl_3$, and analysed by quantitative fluorine NMR.

Screening C–O cross-coupling conditions using ^{t}BuBrettPhos Pd G3

The base (0.75 mmol, 1.5 equiv.) was added to an oven dried Schlenk tube. The Schlenk tube was placed under vacuum and heated with a heat gun for around 3 minutes. *Note*

that NaO^{t}Bu was weighed into a pre-dried Schlenk tube in an N_2 filled glove box, and used directly without heating with a heat gun. After the tube had cooled to room temperature, it was placed under an N_2 atmosphere, and ^{t}BuBrettPhos Pd G3 (4.2 mg, 4.9 µmol, 1 mol%) was added, followed by 1-(4-bromophenyl)propan-2-one (107 mg, 0.50 mmol, 1 equiv.), trifluoroethanol (54 µL, 0.75 mmol, 1.5 equiv.), and finally dry solvent (1.5 mL). The Schlenk tube was sealed under N_2, and heated in a preheated oil bath at the specified temperature for the specified duration. The reaction mixture was allowed to cool, diluted with CH_2Cl_2, and filtered through Celite. The filter cake was washed with additional CH_2Cl_2, and then α,α,α-trifluorotoluene (25 µL, 0.204 mmol) was added to the filtrate. A sample of the filtrate was taken, diluted with $CDCl_3$, and analysed by quantitative fluorine NMR.

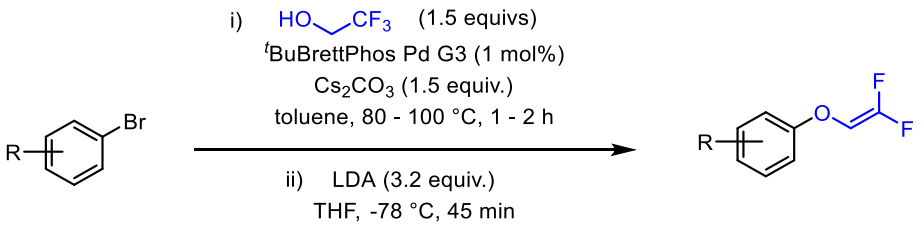
General procedure A: palladium-catalysed C–O cross-coupling



To an oven dried Schlenk tube was added Cs_2CO_3 (488 mg, 1.50 mmol, 1.5 equiv.). The Schlenk tube was placed under vacuum and heated at 450 °C with a heat gun for around 3 minutes, or until the Cs_2CO_3 stopped 'jumping'. After the tube had cooled to room temperature it was placed under an N_2 atmosphere, then aryl halide (1.00 mmol, 1.0 equiv.) and ^{t}BuBrettPhos Pd G3 (8.5 mg, 0.01 mmol, 1 mol%) were added. Dry, degassed toluene (3 mL) was added, followed by the fluorinated alcohol (1.50 mmol, 1.5 equiv.). The Schlenk tube was sealed and heated at 80 °C or 100 °C in a preheated oil bath for the specified time. After completion, the reaction mixture was cooled to room temperature, and then diluted with CH_2Cl_2 (5 mL). The mixture was filtered through a Celite pad. The

Schlenk tube was washed out through the Celite pad with additional CH_2Cl_2 (2 x 5 mL). The filtrate was concentrated *in vacuo* and purified by flash column chromatography.

General procedure B: preparation of geminal-difluorovinyl ethers

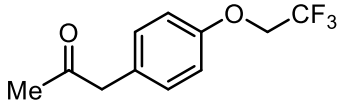


To an oven dried Schlenk tube was added Cs_2CO_3 (488 mg, 1.50 mmol, 1.5 equiv.). The Schlenk was placed under vacuum and heated at 450 °C for 5 minutes. After the tube had cooled to room temperature it was placed under an N_2 atmosphere, and aryl bromide (1.00 mmol, 1.0 equiv.) and ^{t}BuBrettPhos Pd G3 (8.5 mg, 0.01 mmol, 1 mol%) were added. Dry, degassed toluene (3 mL) was added, followed by 2,2,2-trifluoroethanol (108 µL, 1.50 mmol, 1.5 equiv.). The Schlenk was sealed and heated at between 80 and 100°C for between 1 and 2 hours, stirring at 900 RPM. The reaction mixture was cooled to room temperature, and then diluted with CH_2Cl_2 (5 mL). The mixture was filtered through a Celite pad. The Schlenk was washed out through the Celite pad with additional CH_2Cl_2 (2 x 5 mL). The filtrate was concentrated under vacuum, and then taken up in dry THF (2 mL). To a separate 25 mL RBF under N_2 was added dry diisopropylamine (494 µL, 3.5 mmol, 3.5 equiv.) and dry THF (5.6 mL), and the solution was cooled to -78 °C. *n*-BuLi (1.6 M in hexane, 2 mL, 3.2 mmol, 3.2 equiv.) was added dropwise, and the reaction was stirred at -78 °C for 15 minutes, and then 0 °C for 15 minutes. The mixture was then cooled back down to -78 °C, and the solution of the trifluoroethyl ether was added dropwise. Stirring was continued for 45 minutes at -78 °C, and then saturated aqueous NH_4Cl (10 mL) was added at -78 °C and the mixture was allowed to warm to room

temperature. The mixture was then extracted with diethyl ether (3 x 20 mL). The combined organic extracts were dried over $MgSO_4$ and then concentrated under vacuum. The crude was purified by flash chromatography.

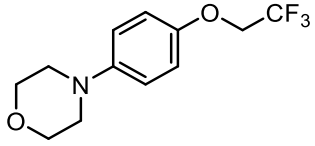
5.2.3 Experimental and Characterisation Data: Fluorinated Alkyl Aryl Ethers

2.40B 1-(4-(2,2,2-trifluoroethoxy)phenyl)propan-2-one



Prepared according to general procedure A (0.50 mmol aryl bromide), heated at 100 °C for 1 hour. Flash column chromatography (15-20% ethyl acetate in pentane) afforded the product as a colourless oil, which solidified to a white solid upon scratching (76 mg, 66% yield). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.19 – 7.11 (m, 2H), 6.95 – 6.87 (m, 2H), 4.33 (q, *J* = 8.2 Hz, 2H), 3.65 (s, 2H), 2.15 (s, 3H). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 206.4, 156.6, 130.8, 128.4, 123.5 (q, *J* = 278.0 Hz), 115.4, 66.0 (q, *J* = 35.7 Hz), 50.0, 29.3. **^{19}F NMR** (377 MHz, Chloroform-*d*) δ -74.0 (t, *J* = 8.1 Hz, 3F). **HRMS** (APCI+) m/z: $[M+H]^+$ Calcd for $C_{11}H_{12}O_2F_3$ 233.0784; Found 233.0790.

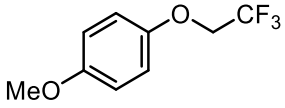
2.41B 4-(4-(2,2,2-trifluoroethoxy)phenyl)morpholine



Prepared according to general procedure A (0.25 mmol aryl bromide), heated at 100 °C for 2 hours. Flash column chromatography (20% ethyl acetate in pentane) afforded the product as an off-white solid (52 mg, 80% yield). **^{1}H NMR** (500 MHz, Chloroform-d) δ 6.94 – 6.85 (m, 4H), 4.30 (q, *J* = 8.2 Hz, 2H), 3.91 – 3.82 (m, 4H), 3.13 – 3.04 (m, 4H). **^{13}C NMR**

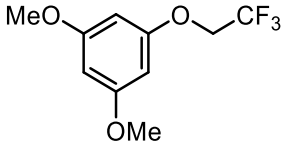
(126 MHz, Chloroform-d) δ 151.8, 147.2, 123.6 (q, *J* = 278.2 Hz), 117.6, 116.2, 67.1, 66.9 (q, *J* = 35.3 Hz), 50.5. **^{19}F NMR** (470 MHz, Chloroform-d) δ -74.1 (t, *J* = 8.3 Hz, 3F). **IR** 2963 (w), 2857 (w), 1512 (s), 1452 (w), 1284 (m), 1233 (s), 1164 (s), 1121 (m), 929 (w), 823 (w). **HRMS** (ESI+) m/z: $[M+H]^+$ Calcd for $C_{12}H_{15}O_2NF_3$ 262.1049; Found 262.1051.

2.42B 1-methoxy-4-(2,2,2-trifluoroethoxy)benzene



Prepared according to general procedure A (1.00 mmol aryl bromide), heated at 100 °C for 2 hours. Flash column chromatography (3% ethyl acetate in pentane) afforded the product as a colourless oil (176 mg, 85% yield). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 6.96 – 6.79 (m, 4H), 4.30 (q, *J* = 8.3 Hz, 2H), 3.78 (s, 3H). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 155.2, 151.8, 123.6 (q, *J* = 278.3 Hz), 116.5, 114.9, 67.0 (q, *J* = 35.2 Hz), 55.8. **^{19}F NMR** (377 MHz, Chloroform-*d*) δ -74.1 (t, *J* = 8.3 Hz, 3F). Analytical data consistent with that previously reported.[85]

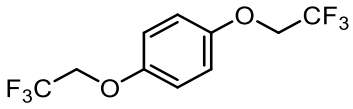
2.43B 1,3-dimethoxy-5-(2,2,2-trifluoroethoxy)benzene



Prepared according to general procedure A (1.00 mmol aryl bromide), heated at 100 °C for 1 hour. Flash column chromatography (20% CH_2Cl_2 in pentane) afforded the product as a colourless oil (211 mg, 89% yield). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 6.17 (t, *J* = 2.1 Hz, 1H), 6.11 (d, *J* = 2.2 Hz, 2H), 4.30 (q, *J* = 8.2 Hz, 2H), 3.77 (s, 6H). **^{13}C NMR** (101 MHz,

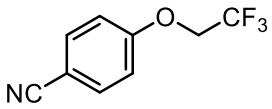
Chloroform-*d*) δ 161.8, 159.3, 123.4 (q, *J* = 277.7 Hz), 94.6, 93.8, 65.8 (q, *J* = 35.7 Hz), 55.6. **^{19}F NMR** (377 MHz, Chloroform-*d*) δ -74.0 (t, *J* = 8.1 Hz, 3F). Analytical data consistent with that previously reported.[106]

2.44B 1,4-bis(2,2,2-trifluoroethoxy)benzene



Prepared according to general procedure A (1.00 mmol aryl bromide), heated at 100 °C for 2 hours. Flash column chromatography (3-5% ethyl acetate in pentane) afforded the product as a white solid (208 mg, 76% yield). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 6.91 (s, 4H), 4.31 (q, *J* = 8.1 Hz, 4H). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 153.0, 123.5 (q, *J* = 278.1 Hz), 116.5, 66.8 (q, *J* = 35.5 Hz). **^{19}F NMR** (377 MHz, Chloroform-*d*) δ -74.0 (t, *J* = 8.2 Hz, 6F). Analytical data consistent with that previously reported.[85]

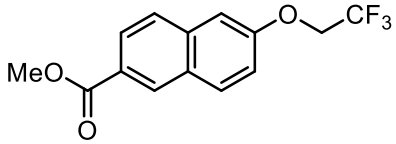
2.45B 4-(2,2,2-trifluoroethoxy)benzonitrile



Prepared according to general procedure A (0.25 mmol aryl bromide), heated at 85 °C for 1.5 hours (93% yield, determined by quantitative ^{19}F NMR yield). Flash chromatography (10% ethyl acetate in pentane) afforded the product as a clear oil. **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 7.64 (m, 2H), 7.02 (m, 2H), 4.41 (q, *J* = 7.9 Hz, 2H). **^{13}C NMR** (126 MHz, Chloroform-*d*) δ 160.4, 134.4, 123.0 (q, *J* = 278.0 Hz), 118.7, 115.6, 106.3, 65.7 (q, *J* = 36.4 Hz). **^{19}F NMR** (470 MHz, Chloroform-*d*) δ -73.8 (t, *J* = 7.8 Hz). **IR** 2228 (w), 1607 (m), 1509

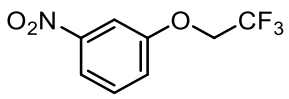
(m), 1284 (m), 1244 (s), 1160 (s), 1069 (m), 975 (m), 833 (m). Analytical data consistent with that previously reported.[90]

2.46B methyl 6-(2,2,2-trifluoroethoxy)-2-naphthoate



Prepared according to general procedure A (1.00 mmol aryl bromide), heated at 80°C for 1.5 hours. Flash column chromatography (33-50% CH_2Cl_2 in pentane) afforded the product as a white solid (232 mg, 93% yield). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.55 – 8.50 (m, 1H), 8.04 (dd, *J* = 8.6, 1.7 Hz, 1H), 7.92 – 7.83 (m, 1H), 7.74 (d, *J* = 8.6 Hz, 1H), 7.29 – 7.21 (m, 1H), 7.14 (d, *J* = 2.6 Hz, 1H), 4.48 (q, *J* = 8.0 Hz, 2H), 3.97 (s, 3H). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 167.2, 157.1, 136.7, 131.6, 130.9, 128.7, 127.2, 126.4, 126.3, 123.4 (q, *J* = 277.8 Hz), 119.2, 107.3, 65.7 (q, *J* = 36.0 Hz), 52.3. **^{19}F NMR** (377 MHz, Chloroform-*d*) δ -73.7 (t, *J* = 8.1 Hz, 3F). **IR** 2952 (w), 1704 (s), 1628 (m), 1509 (m), 1393 (s), 1292 (s), 1164 (s), 971 (m), 666 (w). **HRMS** (ESI+) m/z: $[M+H]^+$ Calcd for $C_{14}H_{12}O_3F_3$ 285.0733; Found 285.0734. **MP** =78-81 °C.

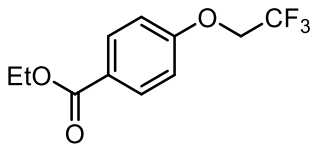
2.47B 1-nitro-3-(2,2,2-trifluoroethoxy)benzene



Prepared according to general procedure A (0.50 mmol aryl bromide), heated at 80 °C for 1.5 hours. Flash column chromatography (7% ethyl acetate in pentane) afforded the product as an off-white solid (96 mg, 87% yield). **^{1}H NMR** (400 MHz, Chloroform-d) δ 7.94

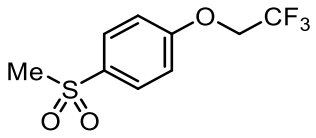
(ddd, *J* = 8.2, 2.1, 0.9 Hz, 1H), 7.78 (t, *J* = 2.3 Hz, 1H), 7.51 (t, *J* = 8.2 Hz, 1H), 7.31 (ddd, *J* = 8.3, 2.6, 0.9 Hz, 1H), 4.45 (q, *J* = 7.9 Hz, 2H). **^{13}C NMR** (101 MHz, Chloroform-d) δ 157.8, 149.3, 130.6, 123.0 (q, *J* = 278.0 Hz), 122.0, 117.7, 109.4, 66.2 (q, *J* = 36.3 Hz). **^{19}F NMR** (377 MHz, Chloroform-d) δ -73.8 (t, *J* = 8.0 Hz, 3F). Analytical data consistent with that previously reported.[90]

2.48B ethyl 4-(2,2,2-trifluoroethoxy)benzoate



Prepared according to general procedure A (0.500 mmol aryl bromide), heated at 80 °C for 1 hour. Flash column chromatography (4-6% ethyl acetate in pentane) afforded the product as a white solid (241 mg, 97% yield). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.07 – 8.00 (m, 2H), 7.00 – 6.93 (m, 2H), 4.41 (q, *J* = 8.0 Hz, 2H), 4.36 (q, *J* = 7.1 Hz, 2H), 1.39 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 166.1, 160.8, 131.9, 125.0, 123.2 (q, *J* = 278.0 Hz), 114.5, 65.7 (q, *J* = 36.0 Hz), 61.0, 14.5. **^{19}F NMR** (376 MHz, Chloroform-*d*) δ -73.8 (t, *J* = 8.0 Hz, 3F). Analytical data consistent with that previously reported.[108]

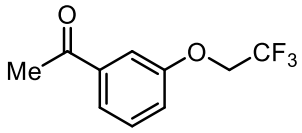
2.49B 1-(methylsulfonyl)-4-(2,2,2-trifluoroethoxy)benzene



Prepared according to general procedure A (0.25 mmol aryl bromide), heated at 80 °C for 2 hours. Flash column chromatography (35% ethyl acetate in pentane) afforded the

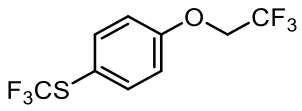
product as a white solid (55 mg, 87% yield). **^{1}H NMR** (400 MHz, Chloroform-d) δ 7.99 – 7.88 (m, 2H), 7.15 – 7.06 (m, 2H), 4.44 (q, *J* = 7.9 Hz, 2H), 3.05 (s, 3H). **^{13}C NMR** (126 MHz, Chloroform-d) δ 161.2, 134.5, 129.9, 123.0 (q, *J* = 278.0 Hz), 115.4, 65.8 (q, *J* = 36.3 Hz), 44.9. **^{19}F NMR** (377 MHz, Chloroform-d) δ -73.7 (t, *J* = 7.8 Hz, 3F). **IR** 2932 (w), 2361 (m), 1286(s), 1149 (s), 968 (m), 913 (s), 745 (s). **HRMS** (ESI+) m/z: $[M+Na]^+$ Calcd for $C_9H_9O_3F_3{}^{23}Na^{32}S$ 277.0117; Found 277.0115. **MP** = 111-113 °C.

2.50B 1-(3-(2,2,2-trifluoroethoxy)phenyl)ethan-1-one



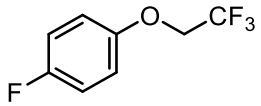
Prepared according to general procedure A (0.50 mmol aryl bromide), heated at 80°C for 2 hours. Flash column chromatography (8-10% ethyl acetate in pentane) afforded the product as a white solid (55 mg, 50% yield). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.63 (dt, *J* = 7.7, 1.2 Hz, 1H), 7.51 (dd, *J* = 2.8, 1.5 Hz, 1H), 7.42 (t, *J* = 7.9 Hz, 1H), 7.17 (ddd, *J* = 8.3, 2.7, 1.0 Hz, 1H), 4.40 (q, *J* = 8.0 Hz, 2H), 2.60 (s, 3H). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 197.5, 157.7, 138.8, 130.1, 123.3 (q, *J* = 278.0 Hz), 123.0, 120.6, 66.0 (q, *J* = 35.8 Hz), 26.8. **^{19}F NMR** (377 MHz, Chloroform-*d*) δ -73.9 (t, *J* = 8.0 Hz, 3F). **HRMS** (APCI+) m/z: $[M+H]^+$ Calcd for $C_{10}H_{10}O_2F_3$ 219.0627; Found 219.0628.

2.51B (4-(2,2,2-trifluoroethoxy)phenyl)(trifluoromethyl)sulfane



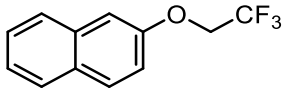
Prepared according to general procedure A (0.50 mmol aryl bromide), heated at 80 °C for 1 hour. Flash column chromatography (pentane) afforded the product as a colourless oil (114 mg, 83% yield). **^{1}H NMR** (500 MHz, Chloroform-d) δ 7.69 – 7.57 (m, 2H), 7.11 – 6.90 (m, 2H), 4.38 (q, *J* = 8.0 Hz, 2H). **^{13}C NMR** (126 MHz, Chloroform-d) δ 159.6, 138.6, 129.7 (q, *J* = 308.2 Hz), 123.2 (q, *J* = 277.9 Hz), 117.5 (q, *J* = 2.4 Hz), 115.9, 65.8 (q, *J* = 36.2 Hz).**^{19}F NMR** (470 MHz, Chloroform-d) δ -43.7 (s, 3F), -73.9 (t, *J* = 8.2 Hz, 3F). **IR** 2361 (w), 913 (s), 745 (s). **HRMS** (APCI+) m/z: $[M]^{\cdot+}$ Calcd for $C_9H_6OF_6S^{\cdot}$ 276.0038; Found 276.0039.

2.52B 1-fluoro-4-(2,2,2-trifluoroethoxy)benzene



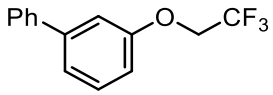
CAUTION: volatile product. Prepared according to general procedure A (0.50 mmol aryl bromide), heated at 85 °C for 1.5 hours. Flash column chromatography (pentane) followed by very careful removal of solvent afforded the product as a clear oil (45 mg, 46% yield). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.06 – 6.97 (m, 2H), 6.94 – 6.87 (m, 2H), 4.32 (q, *J* = 8.1 Hz, 2H). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 158.4 (d, *J* = 240.8 Hz), 153.7 (d, *J* = 2.3 Hz), 116.6 (d, *J* = 8.2 Hz), 116.4 (d, *J* = 23.5 Hz), 66.9 (q, *J* = 35.6 Hz). CF_3 group too low intensity to assign. **^{19}F NMR** (377 MHz, Chloroform-d) δ -74.0 (t, *J* = 8.1 Hz, 3F), -121.3 (tt, *J* = 8.4, 4.3 Hz, 1F). **HRMS** Not observed in ESI, APCI, or EI.

2.53B 2-(2,2,2-trifluoroethoxy)naphthalene



Prepared according to general procedure A (0.25 mmol aryl bromide), heated at 80 °C for 2 hours. Flash column chromatography (pentane) afforded the target product as a white solid (48 mg, 85% yield). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.83 – 7.78 (m, 2H), 7.75 (dd, *J* = 8.2, 1.1 Hz, 1H), 7.48 (ddd, *J* = 8.2, 6.9, 1.3 Hz, 1H), 7.40 (ddd, *J* = 8.1, 6.9, 1.3 Hz, 1H), 7.22 (dd, *J* = 8.9, 2.6 Hz, 1H), 7.16 (d, *J* = 2.6 Hz, 1H), 4.48 (q, *J* = 8.1 Hz, 2H). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 155.4, 134.2, 130.1, 129.8, 127.9, 127.1, 126.9, 123.5 (q, *J* = 277.9 Hz), 118.4, 107.6, 65.9 (q, *J* = 35.8 Hz). **^{19}F NMR** (377 MHz, Chloroform-*d*) δ -73.8 (t, *J* = 8.0 Hz, 3F). Analytical data consistent with that previously reported.[89]

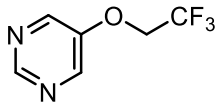
2.54B 3-(2,2,2-trifluoroethoxy)-1,1'-biphenyl



Prepared according to general procedure A (1.00 mmol aryl bromide), heated at 80 °C for 75 minutes. Flash column chromatography (0-3% ethyl acetate in pentane) afforded the target product as a colourless oil (0.240 mg, 95% yield). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.68 – 7.61 (m, 2H), 7.55 – 7.47 (m, 2H), 7.47 – 7.40 (m, 2H), 7.35 (dt, *J* = 7.7, 1.3 Hz, 1H), 7.24 (dd, *J* = 2.6, 1.6 Hz, 1H), 6.97 (ddd, *J* = 8.2, 2.6, 1.0 Hz, 1H), 4.44 (q, *J* = 8.2 Hz, 2H). **^{13}C NMR** (101 MHz, Chloroform-d) δ 157.9, 143.3, 140.6, 130.2, 129.0, 127.8, 127.3, 123.5 (q, *J* = 278.9 Hz), 121.6, 114.2, 113.6, 66.1 (q, *J* = 35.5 Hz). **^{19}F NMR** (377 MHz, Chloroform-*d*) δ -74.1 (t, *J* = 8.3 Hz, 3F). **IR** 1598 (w), 1573 (w), 1478 (m), 1458 (w), 1421

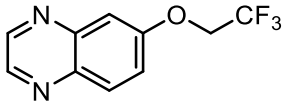
(w), 1274 (m), 1205 (m), 1162 (s), 1078 (w), 975 (m), 882 (w), 756 (s), 673 (s). Analytical data consistent with that previously reported.[89]

2.55B 5-(2,2,2-trifluoroethoxy)pyrimidine



Prepared according to general procedure A (1.00 mmol aryl bromide), heated at 100 °C for 2 hours. Flash column chromatography (35% ethyl acetate in pentane) afforded the product as a pale-yellow oil (160 mg, 90% yield). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.93 (s, 1H), 8.47 (s, 2H), 4.46 (q, *J* = 7.8 Hz, 2H). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 153.3, 151.9, 144.3, 122.8 (q, *J* = 278.2 Hz), 66.2 (q, *J* = 36.5 Hz). **^{19}F NMR** (377 MHz, Chloroform-*d*) δ -73.9 (t, *J* = 7.8 Hz, 3F). Analytical data consistent with that previously reported.[89]

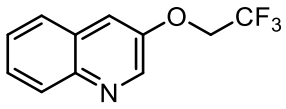
2.56B 6-(2,2,2-trifluoroethoxy)quinoxaline



Prepared according to general procedure A (1.00 mmol aryl bromide), heated at 80 °C for 2 hours (>99% yield, determined by quantitative ^{19}F NMR). Flash column chromatography (15% ethyl acetate in pentane) afforded the product as an off-white solid**. ^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.79 (d, *J* = 1.9 Hz, 1H), 8.75 (d, *J* = 1.9 Hz, 1H), 8.04 (d, *J* = 9.2 Hz, 1H), 7.50 (dd, *J* = 9.3, 2.9 Hz, 1H), 7.37 (d, *J* = 2.8 Hz, 1H), 4.52 (q, *J* = 8.0 Hz, 2H). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 158.18, 145.46, 144.26, 143.52, 139.85, 131.29, 123.16 (q, *J* = 277.8 Hz), 123.07, 108.18, 65.82 (q, *J* = 36.0 Hz). **^{19}F NMR** (377 MHz, Chloroform-*d*) δ -

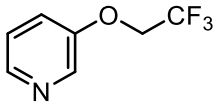
73.6 (t, *J* = 8.0 Hz, 3F). **IR** 2981 (w), 2361 (s), 2341 (m), 1301 (w), 1162 (s), 1066 (m), 913 (s). **HRMS** (ESI+) m/z: $[M+H]^+$ Calcd for $C_{10}H_8ON_2F_3$ 229.0583; Found 229.0585. Analytical data consistent with that previously reported.[104]

2.57B 3-(2,2,2-trifluoroethoxy)quinoline



Prepared according to general procedure A (1.00 mmol aryl bromide), heated at 80 °C for 1 hour. Flash column chromatography (7% ethyl acetate in pentane) afforded the product as a white crystalline solid (204 mg, 90% yield). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.73 (d, *J* = 2.9 Hz, 1H), 8.07 (d, *J* = 8.3 Hz, 1H), 7.71 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.61 (ddd, *J* = 8.4, 6.9, 1.5 Hz, 1H), 7.53 (ddd, *J* = 8.2, 6.9, 1.3 Hz, 1H), 7.39 (d, *J* = 2.8 Hz, 1H), 4.47 (q, *J* = 8.0 Hz, 2H). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 150.8, 144.4, 144.0, 129.4, 128.3, 127.8, 127.7, 127.0, 123.2 (q, *J* = 277.9 Hz), 114.3, 65.9 (q, *J* = 36.2 Hz). **^{19}F NMR** (377 MHz, Chloroform-*d*) δ -73.6 (t, *J* = 8.0 Hz, 3F). Analytical data consistent with that previously reported.[90]

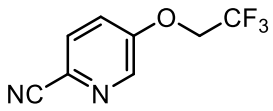
2.58B 3-(2,2,2-trifluoroethoxy)pyridine



Prepared according to general procedure A (1.00 mmol aryl bromide), heated at 100 °C for 4 hours. Flash column chromatography (75% diethyl ether in pentane) with careful evaporation of the solvent (40 °C, 400 mbar) afforded the product as a pale-yellow oil (75

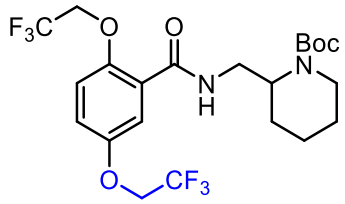
mg, 43% yield). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.37 (dd, *J* = 2.3, 1.4 Hz, 1H), 8.33 (dd, *J* = 3.8, 2.2 Hz, 1H), 7.31 – 7.24 (m, 2H), 4.41 (q, *J* = 8.0 Hz, 2H). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 153.8, 144.2, 138.3, 124.2, 123.2 (q, *J* = 278.4 Hz), 122.1, 66.2 (q, *J* = 35.8 Hz). **^{19}F NMR** (377 MHz, Chloroform-*d*) δ -73.9 (t, *J* = 8.0 Hz, 3F). Analytical data consistent with that previously reported.[85]

2.59B 5-(2,2,2-trifluoroethoxy)picolinonitrile



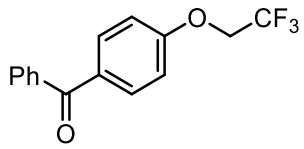
Prepared according to general procedure A (0.25 mmol aryl bromide), heated at 80 °C for 2 hours. Flash column chromatography (20-30% ethyl acetate in pentane) afforded the product as a colourless oil (47 mg, 93% yield). **^{1}H NMR** (400 MHz, Chloroform-d) δ 8.46 (dd, *J* = 2.9, 0.6 Hz, 1H), 7.71 (dd, *J* = 8.7, 0.7 Hz, 1H), 7.33 (dd, *J* = 8.7, 3.0 Hz, 1H), 4.49 (q, *J* = 7.7 Hz, 2H). **^{13}C NMR** (126 MHz, Chloroform-d) δ 155.6, 140.3, 129.7, 127.4, 122.7 (q, *J* = 278.1 Hz), 121.4, 117.1, 65.9 (q, *J* = 36.7 Hz). **^{19}F NMR** (377 MHz, Chloroform-d) δ -73.6 (t, *J* = 7.8 Hz, 3F). **IR** 2237 (w), 1578 (m), 1468 (m), 1243 (s), 1162 (s), 1065 (s), 973 (m), 839 (m). **HRMS** (ESI+) m/z: $[M+H]^+$ Calcd for $C_8H_6ON_2F_3$ 203.0427; Found 203.0429.

N-Boc-flecainide



Prepared according to general procedure A (0.25 mmol aryl bromide), heated at 100 °C for 2 hours. Flash column chromatography (25% ethyl acetate in pentane) afforded the product as a white solid (41 mg, 38% yield). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.72 (d, *J* = 3.3 Hz, 1H), 7.60 (s, 1H), 7.07 (dd, *J* = 8.9, 3.3 Hz, 1H), 6.91 (d, *J* = 9.0 Hz, 1H), 4.53 – 4.41 (m, 2H), 4.37 (q, *J* = 8.1 Hz, 2H), 4.11 – 3.36 (m, 4H), 2.88 (t, *J* = 13.0 Hz, 1H), 1.90 – 1.36 (m, 6H), 1.31 (s, 9H). **^{13}C NMR** (126 MHz, Chloroform-*d*) δ 164.1, 155.6, 153.2, 150.5, 124.5, 123.3 (q, *J* = 278.5 Hz), 123.2 (q, *J* = 280.6 Hz), 120.7, 117.1, 115.7, 77.5, 68.31 – 67.14 (m), 66.5 (q, *J* = 36.8 Hz), 50.0, 39.4, 28.7, 28.4, 26.4, 25.5, 19.4. **^{19}F NMR** (377 MHz, Chloroform-*d*) δ -73.6 (br s, 3F), -74.0 (t, *J* = 8.2 Hz, 3F). **HRMS** (ESI+) m/z: $[M+H]^+$ Calcd for $C_{22}H_{29}O_5N_2F_6$ 515.1975; Found 515.1977.

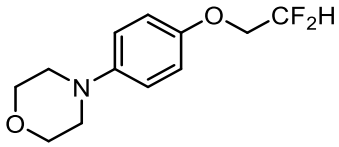
2.101 phenyl(4-(2,2,2-trifluoroethoxy)phenyl)methanone



Prepared according to general procedure A (>99% yield, determined by quantitative ^{19}F NMR). Flash chromatography (5% ethyl acetate in pentane) afforded the target product as white solid. **^{1}H NMR** (400 MHz, Chloroform-d) δ 7.85 (m, 2H), 7.76 (m, 2H), 7.58 (m, 1H), 7.49 (m, 2H), 7.02 (m, 2H), 4.44 (q, J = 8.0 Hz, 2H). **^{13}C NMR** (101 MHz, Chloroform-d) δ 195.4, 160.6, 137.9, 132.7, 132.3, 132.0, 129.9, 128.4, 123.2 (q, J = 278.0 Hz), 114.4,

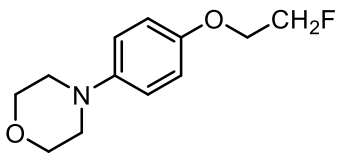
65.7 (q, J = 36.1 Hz). **^{19}F NMR** (377 MHz, Chloroform-d) δ -73.8 (t, J = 8.0 Hz). **IR** 2924 (w), 2364 (w), 1654 (m), 1601 (m), 1282 (s), 1242 (s), 1167 (s), 1074 (m), 634 (m). Analytical data consistent with that reported previously.[108]

2.41C 4-(4-(2,2-difluoroethoxy)phenyl)morpholine



Prepared according to general procedure A (1.00 mmol aryl bromide), heated at 80 °C for 105 minutes. Flash column chromatography (25% ethyl acetate in pentane) afforded the product as an off-white powder (212 mg, 87% yield). **^{1}H NMR** (500 MHz, Chloroform-d) δ 6.88 (m, 4H), 6.06 (tt, *J* = 55.2, 4.1 Hz, 1H), 4.14 (td, *J* = 13.2, 4.1 Hz, 2H), 3.90 – 3.81 (m, 4H), 3.11 – 3.01 (m, 4H). **^{13}C NMR** (101 MHz, Chloroform-d) δ 152.1, 146.8, 117.7, 115.7, 114.0 (t, *J* = 241.1 Hz), 68.1 (t, *J* = 29.3 Hz), 67.1, 50.6. **^{19}F NMR** (376 MHz, Chloroform-d) δ -125.3 (dt, *J* = 55.1, 13.3 Hz, 2F). **IR** 2963 (w), 2361 (w), 1502 (s), 1452 (m), 1231 (m), 1120 (m), 914 (m), 745 (m). **HRMS** (ESI+) m/z: $[M+H]^+$ Calcd for $C_{12}H_{16}O_2NF_2$ 244.1144; Found 244.1143. **MP** = 71-73 °C.

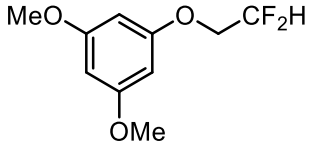
2.41D 4-(4-(2-fluoroethoxy)phenyl)morpholine



CAUTION! 2-fluoroethanol is HIGHLY TOXIC

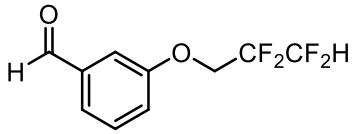
Prepared according to general procedure A (1.00 mmol aryl bromide), heated at 80 °C for 105 minutes. Flash column chromatography (25% ethyl acetate in pentane) afforded the product as an off-white solid (190 mg, 84%). **^{1}H NMR** (500 MHz, Chloroform-d) δ 6.88 (s, 4H), 4.73 (ddd, *J* = 47.5, 4.9, 3.5 Hz, 2H), 4.26 – 4.09 (m, 2H), 3.90 – 3.82 (m, 4H), 3.11 – 3.03 (m, 4H). **^{13}C NMR** (126 MHz, Chloroform-d) δ 152.8, 146.3, 117.8, 115.7, 82.2 (d, *J* = 170.4 Hz), 67.8 (d, *J* = 20.4 Hz), 67.1, 50.7. **^{19}F NMR** (471 MHz, Chloroform-d) δ -223.83 (tt, *J* = 47.7, 28.2 Hz, 1F). **IR** 2858 (w), 2361 (w), 1506 (s), 1370 (m), 1246 (s), 1052 (m), 926 (s), 825 (m). **HRMS** (ESI+) m/z: $[M+H]^+$ Calcd for $C_{12}H_{17}O_2NF$ 226.1238; Found 226.1237. **MP** = 89-91 °C.

2.43C 1-(2,2-difluoroethoxy)-3,5-dimethoxybenzene



Prepared according to general procedure A (1.00 mmol aryl bromide), heated at 80 °C for 2 hours. Flash column chromatography (30% CH_2Cl_2 in pentane) afforded the product as a colourless oil (181 mg, 83%). **^{1}H NMR** (400 MHz, Chloroform-d) δ 6.14 (t, *J* = 2.2 Hz, 1H), 6.09 (d, *J* = 2.2 Hz, 2H), 6.07 (tt, *J* = 55.2, 4.1 Hz, 1H), 4.14 (td, *J* = 13.1, 4.1 Hz, 2H), 3.77 (s, 6H). **^{13}C NMR** (101 MHz, Chloroform-d) δ 161.8, 159.7, 113.7 (t, *J* = 241.1 Hz), 94.2, 93.6, 67.4 (t, *J* = 29.6 Hz), 55.5. **^{19}F NMR** (376 MHz, Chloroform-d) δ -125.3 (dt, *J* = 55.3, 13.1 Hz, 2F). **IR** 2943 (w), 1600 (m), 1478 (w), 1154 (m), 913 (s), 820 (w), 745 (s). **HRMS** (ESI+) m/z: $[M+H]^+$ Calcd for $C_{10}H_{13}O_3F_2$ 219.0827; Found 219.0828.

2.63C 3-(2,2,3,3-tetrafluoropropoxy)benzaldehyde



Gram-scale using Cs_2CO_3:

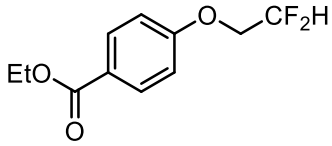
Cs_2CO_3 (3.42 g, 10.5 mmol, 1.5 equiv.) was added to a 2-neck 100 mL round-bottom flask equipped with a stirring bar. The flask was placed under vacuum and heated at 550 °C for 5 – 10 minutes to dry the Cs_2CO_3. After cooling to room temperature, the flask was placed under an N_2 atmosphere, and then equipped with an air condenser. The flask was placed under vacuum again, and all the glassware was dried again at 450 °C. After cooling to room temperature, the setup was placed under an N_2 atmosphere, and 3-bromobenzaldehyde (816 µL, 7.00 mmol, 1.0 equiv.) and ^{t}BuBrettPhos Pd G3 (30 mg, 0.035 mmol, 0.5 mol%) were added. Dry, degassed toluene (20 mL) was added, followed by 2,2,3,3-tetrafluoropropan-1-ol (936 µL, 10.5 mmol, 1.5 equiv.). The reaction mixture was heated at 80 °C in a pre-heated oil bath for 2 hours, stirring at 700 RPM. The reaction progress was monitored by ^{19}F NMR. The reaction mixture was cooled to room temperature and filtered through a Celite pad. The Celite was washed with CH_2Cl_2 (100 mL). The filtrate was washed with water (100 mL), brine (100 mL), dried over $MgSO_4$, and then concentrated *in vacuo*. The crude product was purified by flash column chromatography (10% ethyl acetate in pentane) to afford to the desired compound as a pale-yellow oil (1.53g, 92%).

Gram-scale using K_3PO_4

K_3PO_4 (2.23 g, 10.5 mmol, 1.5 equiv.) was added to a 50 mL round-bottom flask equipped with a stirring bar. The flask was placed under vacuum and heated at 450 °C for 5 minutes

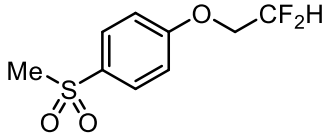
to dry the K_3PO_4. After cooling to room temperature, the setup was placed under an N_2 atmosphere, and ^{t}BuBrettPhos Pd G3 (30 mg, 0.035 mmol, 0.5 mol%), 3-bromobenzaldehyde (816 µL, 7.00 mmol, 1.0 equiv.) and 2,2,3,3-tetrafluoropropan-1-ol (936 µL, 10.5 mmol, 1.5 equiv.) were added, and the flask was equipped with an oven dried refluxed condenser. The setup was evacuated (briefly) and refilled with N_2 three times, and then dry toluene (14 mL, non-degassed) was added. The reaction mixture was heated at 80 °C for 3 hours in a pre-heated oil bath, stirring at 1000 RPM. The reaction mixture was cooled to room temperature, diluted with CH_2Cl_2, and filtered through a Celite pad. The filter cake was washed with additional CH_2Cl_2. The filtrate was concentrated *in vacuo*, and purified by flash column chromatography (3-15% ethyl acetate in pentane) to afford to the desired compound as a colourless oil (1.08 g, 65%). **^{1}H NMR** (400 MHz, Chloroform-d) δ 9.97 (s, 1H), 7.58 – 7.46 (m, 2H), 7.41 (dd, *J* = 2.8, 1.4 Hz, 1H), 7.22 (ddd, *J* = 8.0, 2.8, 1.2 Hz, 1H), 6.07 (tt, *J* = 53.1, 4.7 Hz, 1H), 4.41 (tt, *J* = 11.9, 1.5 Hz, 2H).**^{13}C NMR** (101 MHz, Chloroform-d) δ 191.6, 157.9, 138.0, 130.6, 125.2, 121.9 (s), 114.5 (tt, *J* = 249.5, 27.2 Hz), 112.9, 109.2 (tt, *J* = 248.0, 34.6 Hz), 66.04 – 64.69 (m). **^{19}F{^{1}H} NMR** (377 MHz, Chloroform-d) δ -124.8 (t, *J* = 4.1 Hz, 2F), -139.1 (t, *J* = 4.0 Hz, 2F). **IR** 2361 (w), 1696 (m), 1592 (w), 1452 (w), 1267 (m), 1101 (s), 913 (s), 746 (s), 680 (s). **HRMS** (ESI+) m/z: $[M+H]^+$ Calcd for $C_{10}H_9O_2F_4$ 237.0533; Found 237.0535.

2.48C ethyl 4-(2,2-difluoroethoxy)benzoate



Prepared according to general procedure A (1.00 mmol aryl bromide), heated at 80 °C for 1 hour. Flash column chromatography (10% ethyl acetate in pentane) afforded the product as a white solid (226 mg, 98% yield). **^{1}H NMR** (400 MHz, Chloroform-d) δ 8.02 (m, 2H), 6.94 (m, 2H), 6.11 (tt, *J* = 55.0, 4.1 Hz, 1H), 4.36 (q, *J* = 7.1 Hz, 2H), 4.24 (td, *J* = 12.9, 4.1 Hz, 2H), 1.38 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (126 MHz, Chloroform-*d*) δ 166.2, 161.3, 131.8, 124.4, 114.2, 113.5 (t, *J* = 241.3 Hz), 67.2 (t, *J* = 29.8 Hz), 60.9, 14.5. **^{19}F NMR** (376 MHz, Chloroform-d) δ -125.3 (dt, 54.8, 13.1 Hz, 2F). **IR** = 2991 (w), 1702 (s), 1609 (w), 1515 (w), 1296 (m), 1070 (m), 769 (m). **HRMS** (ESI+) m/z: $[M+H]^+$ Calcd for $C_{11}H_{13}O_3F_2$ 231.0827; Found 231.0830. **MP** = 43-45 °C.

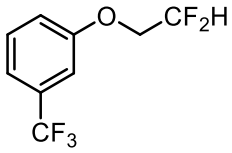
2.49C 1-(2,2-difluoroethoxy)-4-(methylsulfonyl)benzene



Prepared according to general procedure A (1.00 mmol aryl bromide), heated at 80 °C for 1.5 hours. Flash column chromatography (35% ethyl acetate in pentane) afforded the product as an off-white solid (211 mg, 90% yield). **^{1}H NMR** (400 MHz, Chloroform-d) δ 7.96 – 7.81 (m, 2H), 7.10 – 6.97 (m, 2H), 6.11 (tt, *J* = 54.8, 4.0 Hz, 1H), 4.25 (td, *J* = 12.9, 4.0 Hz, 2H), 3.02 (s, 3H). **^{13}C NMR** (126 MHz, Chloroform-d) δ 161.7, 133.8, 129.8, 115.2, 113.3 (t, *J* = 240.1 Hz), 67.3 (t, *J* = 29.7 Hz), 44.8. **^{19}F NMR** (377 MHz, Chloroform-d) δ -125.4 (dt, *J* = 55.0, 12.8 Hz, 2F). **IR** 1595 (m), 1499 (w), 1413 (w), 1295 (s), 1142 (s), 1091

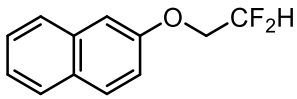
(s), 959 (m), 767 (m). **HRMS** (ESI+) m/z: $[M+H]^+$ Calcd for $C_9H_{11}O_3F_2{}^{32}S$ 237.0392; Found 237.0394. **MP** = 79-81 °C.

2.64C 1-(2,2-difluoroethoxy)-3-(trifluoromethyl)benzene



Prepared according to general procedure A (1.00 mmol aryl bromide), heated at 80 °C for 30 minutes. Flash column chromatography (3% diethyl ether in pentane) afforded the product as a colourless oil (180 mg, 80% yield). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.43 (t, *J* = 7.8 Hz, 1H), 7.29 (d, *J* = 7.7 Hz, 1H), 7.18 – 7.15 (m, 1H), 7.10 (dd, *J* = 8.3, 2.6 Hz, 1H), 6.11 (tt, *J* = 55.0, 4.1 Hz, 1H), 4.22 (td, *J* = 13.0, 4.0 Hz, 2H). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 157.9, 132.3 (q, *J* = 32.5 Hz), 130.4, 123.9 (q, *J* = 272.3 Hz), 118.8 (q, *J* = 3.9 Hz), 118.2, 113.6 (t, *J* = 241.2 Hz), 111.7 (q, *J* = 3.9 Hz), 67.5 (t, *J* = 29.7 Hz). **^{19}F NMR** (377 MHz, Chloroform-*d*) δ -62.9 (s, 3F), -125.74 (dt, *J* = 54.9, 13.1 Hz, 2F). **IR** 2919 (w), 2360 (s), 2341 (s). **HRMS** Not observed in ESI, APCI, or EI.

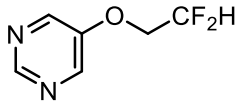
2.53C 2-(2,2-difluoroethoxy)naphthalene



Prepared according to general procedure A (0.50 mmol aryl bromide), heated at 80 °C for 1.5 hours. Flash column chromatography (pentane) afforded the product as a white solid (96 mg, 92% yield). **^{1}H NMR** (500 MHz, Chloroform-d) δ 7.82 – 7.77 (m, 2H), 7.75 (d, *J* =

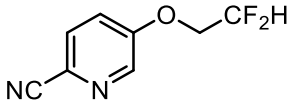
8.3 Hz, 1H), 7.48 (t, *J* = 7.5 Hz, 1H), 7.39 (t, *J* = 7.5 Hz, 1H), 7.19 (d, *J* = 9.0, 2.2 Hz, 1H), 7.14 (d, *J* = 2.5 Hz, 1H), 6.17 (tt, *J* = 55.2, 3.5 Hz, 1H), 4.31 (td, *J* = 13.1, 3.5 Hz, 2H). **^{13}C NMR** (126 MHz, Chloroform-d) δ 155.8, 134.4, 130.0, 129.6, 127.9, 127.0, 126.8, 124.4, 118.5, 113.9 (t, *J* = 241.0 Hz), 107.2, 67.4 (t, *J* = 29.7 Hz). **^{19}F NMR** (471 MHz, Chloroform-d) δ -125.1 (dt, *J* = 55.4, 13.1 Hz, 2F). **IR** 3060 (w), 2361 (w), 1360 (w), 1220 (m), 913 (s), 837 (m). **HRMS** (APCI+) m/z: $[M+H]^+$ Calcd for $C_{12}H_{11}OF_2$ 209.0773; Found 209.0776. **MP** = 48-50 °C.

2.55C 5-(2,2-difluoroethoxy)pyrimidine



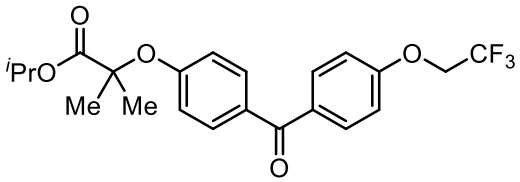
Prepared according to general procedure A (1.00 mmol aryl bromide), heated at 80 °C for 75 minutes. Flash column chromatography (40-50% ethyl acetate in pentane) afforded the product as a pale-yellow oil (163 mg, 92% yield). **^{1}H NMR** (500 MHz, Chloroform-d) δ 8.92 (s, 1H), 8.45 (s, 2H), 6.12 (tt, *J* = 54.6, 4.0 Hz, 1H), 4.30 (td, *J* = 12.8, 4.0 Hz, 2H). **^{13}C NMR** (126 MHz, Chloroform-d) δ 152.8, 152.2, 144.0, 113.1 (t, *J* = 242.0 Hz), 67.7 (t, *J* = 29.7 Hz). **^{19}F NMR** (377 MHz, Chloroform-d) δ -125.5 (dt, *J* = 54.7, 12.8 Hz, 2F). Data consistent with that previously reported.[89] **IR** 1563 (m), 1416 (s), 1279 (s), 1249 (m), 1076 (s), 912 (m), 744 (w), 617 (m). **HRMS** (ESI+) m/z: $[M+H]^+$ Calcd for $C_6H_7ON_2F_2$ 161.0521; Found 161.0521.

2.59C 5-(2,2-difluoroethoxy)picolinonitrile



Prepared according to general procedure A (1.00 mmol aryl bromide), heated at 80 °C for 1.5 hours. Flash column chromatography (20-30% ethyl acetate in pentane) afforded the product as an off-white solid (135 mg, 73% yield). **^{1}H NMR** (500 MHz, Chloroform-d) δ 8.41 (d, *J* = 2.9 Hz, 1H), 7.68 (d, *J* = 8.6 Hz, 1H), 7.30 (dd, *J* = 8.6, 3.0 Hz, 1H), 6.13 (tt, *J* = 54.5, 3.9 Hz, 1H), 4.31 (td, *J* = 12.8, 3.9 Hz, 2H). **^{13}C NMR** (126 MHz, Chloroform-d) δ 156.1, 140.3, 129.7, 126.8, 120.9, 117.2, 112.9 (t, *J* = 242.1 Hz), 67.5 (t, *J* = 29.8 Hz). **^{19}F NMR** (470 MHz, Chloroform-d) δ -125.4 (dt, *J* = 54.6, 13.0 Hz, 2F). **IR** 2962 (w), 2361 (w), 1572 (m), 1457 (m), 1255 (m), 1079 (m), 837 (m), 745 (s). **HRMS** (ESI+) m/z: $[M+H]^+$ Calcd for $C_8H_7ON_2F_2$ 185.0521; Found 185.0522. **MP** = 57-59 °C.

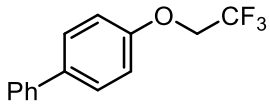
2.65B isopropyl 2-methyl-2-(4-(4-(2,2,2-trifluoroethoxy)benzoyl)phenoxy)propanoate



Prepared according to general procedure A from the corresponding aryl chloride (0.5 mmol), heated at 100 °C for 2 hours. Flash column chromatography (10-12% ethyl acetate in pentane) afforded the product as a colourless oil (197 mg, 93% yield). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.83 – 7.75 (m, 2H), 7.75 – 7.67 (m, 2H), 7.05 – 6.95 (m, 2H), 6.92 – 6.79 (m, 2H), 5.08 (hept, *J* = 6.2 Hz, 1H), 4.43 (q, *J* = 8.1 Hz, 2H), 1.65 (s, 6H), 1.20 (d, *J* = 6.3 Hz, 6H). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 194.3, 173.3, 160.3, 159.5, 132.5, 132.3, 131.9, 130.9, 123.2 (q, *J* = 278.0 Hz), 117.4, 114.4, 79.5, 69.4, 65.7 (q, *J* = 36.0 Hz),

25.5, 21.6. **^{19}F NMR** (377 MHz, Chloroform-*d*) δ -73.8 (t, *J* = 8.0 Hz, 3F). **HRMS** (ESI+) m/z: $[M+H]^+$ Calcd for $C_{22}H_{24}O_5F_3$ 425.1570; Found 425.1568.

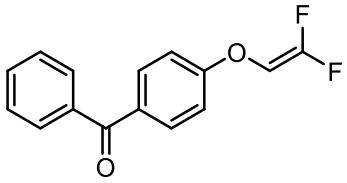
2.66B 4-(2,2,2-trifluoroethoxy)-1,1'-biphenyl



Prepared according to general procedure A from the corresponding aryl chloride (1.0 mmol), heated at 100 °C for 2 hours. Flash column chromatography (2% ethyl acetate in pentane) afford the product as a white solid (243 mg, 96% yield). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.60 – 7.53 (m, 4H), 7.48 – 7.41 (m, 2H), 7.38 – 7.31 (m, 1H), 7.06 – 7.00 (m, 2H), 4.40 (q, *J* = 8.1 Hz, 2H). **^{19}F NMR** (377 MHz, Chloroform-*d*) δ -73.9 (t, *J* = 8.2 Hz). Analytical data consistent with that previously reported.[87]

5.2.4 Experimental and Characterisation Data: Geminal-Difluorovinyl Ethers

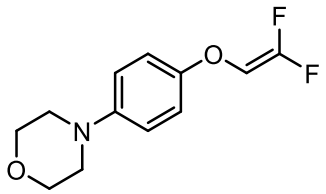
2.95 (4-((2,2-difluorovinyl)oxy)phenyl)(phenyl)methanone



Prepared according to general procedure B. Flash chromatography (45-66% CH_2Cl_2 in pentane) afforded the product as a white solid (50% yield). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.85 (m, 2H), 7.76 (m, 2H), 7.58 (m, 1H), 7.48 (t, *J* = 7.7 Hz, 2H), 7.10 (m, 2H), 6.16 (dd, *J* = 14.8, 3.6 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 195.5, 160.4 (t, J = 1.7 Hz), 157.0 (dd, J = 292.2, 280.2 Hz), 137.9, 132.6, 132.6, 132.5, 132.4, 130.0, 128.4, 115.0,

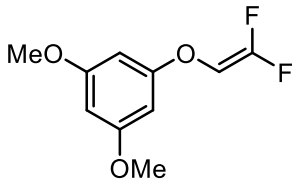
104.1 (dd, J = 56.5, 15.6 Hz). **^{19}F NMR** (376 MHz, Chloroform-*d*) δ -95.4 (dd, *J* = 63.7, 15.0 Hz), -113.8 (dd, *J* = 63.7, 3.7 Hz). **IR** 1768 (w), 1655 (m), 1599 (m), 1504 (w), 1244 (s), 1171 (m), 926 (m), 698 (m). **HRMS** (APCI+) *m/z*: 261.0724 ($M+H^+$); calc. 261.0722 ($C_{15}H_{11}O_2F_2$).

2.96 4-(4-((2,2-difluorovinyl)oxy)phenyl)morpholine



Prepared according to general procedure B. Flash chromatography (20% ethyl acetate in pentane) afforded the product as a pale-yellow oil (92%). **^{1}H NMR** (400 MHz, Chloroform-d) δ 6.98 – 6.92 (m, 2H), 6.91 – 6.84 (m, 2H), 6.01 (dd, *J* = 15.3, 3.3 Hz, 1H), 3.92 – 3.79 (m, 4H), 3.15 – 3.00 (m, 4H). **^{13}C NMR** (101 MHz, Chloroform-d) δ 156.7 (dd, *J* = 290.5, 277.7 Hz), 151.3 (t, *J* = 1.7 Hz), 147.6, 117.5, 116.3, 105.3 (dd, *J* = 55.5, 15.2 Hz), 67.0, 50.4. **^{19}F NMR** (376 MHz, Chloroform-d) δ -98.3 (dd, *J* = 70.7, 15.3 Hz), -116.9 (dd, *J* = 70.7, 3.4 Hz). **IR** 2856 (w), 1768 (m), 1508 (s), 1346 (m), 1229 (s), 1121 (m), 926 (s), 822 (m). **HRMS** (ESI+) *m/z*: 242.0988 ($M+H^+$); calc. 242.0987 ($C_{12}H_{14}O_2NF_2$).

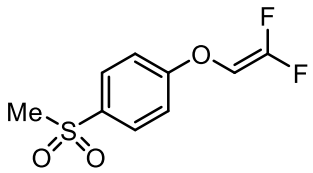
2.97 1-((2,2-difluorovinyl)oxy)-3,5-dimethoxybenzene



Prepared according to general procedure B. Flash chromatography (0-6% ethyl acetate in pentane) afforded the product as a pale-yellow oil (87% yield). **^{1}H NMR** (400 MHz,

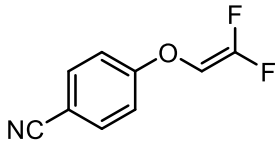
Chloroform-d) δ 6.19 (m, 3H), 6.05 (dd, *J* = 15.1, 3.4 Hz, 1H), 3.78 (s, 6H). **^{13}C NMR** (101 MHz, Chloroform-d) δ 161.8, 159.1 (t, *J* = 1.7 Hz), 156.7 (dd, *J* = 291.1, 278.7 Hz), 104.5 (dd, *J* = 56.1, 15.2 Hz), 95.2, 94.2, 55.6. **^{19}F NMR** (376 MHz, Chloroform-d) δ -97.2 (dd, *J* = 67.8, 15.1 Hz), -115.5 (dd, *J* = 67.9, 3.4 Hz). **IR** 2946 (w), 2842 (w), 1769 (m), 1599 (s), 1477 (m), 1347 (m), 1195 (s), 1154 (s), 928 (m). **HRMS** (APCI+) *m/z*: 217.0671 ($M+H^+$); calc. 217.0671 ($C_{10}H_{11}O_3F_2$).

2.98 1-((2,2-difluorovinyl)oxy)-4-(methylsulfonyl)benzene



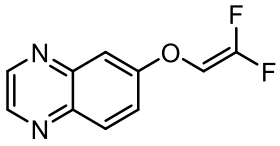
Prepared according to general procedure B. Flash chromatography (25-35% ethyl acetate in pentane) afforded the product as an off-white solid (93% yield). **^{1}H NMR** (400 MHz, Chloroform-d) δ 7.98 – 7.87 (m, 2H), 7.20 – 7.10 (m, 2H), 6.15 (dd, *J* = 14.7, 3.7 Hz, 1H), 3.04 (s, 3H). **^{13}C NMR** (101 MHz, Chloroform-d) δ 161.1 (t, *J* = 1.7 Hz), 157.0 (dd, *J* = 292.8, 281.2 Hz), 135.0, 130.0, 115.9, 103.8 (dd, *J* = 56.7, 15.6 Hz), 44.9. **^{19}F NMR** (377 MHz, Chloroform-d) δ -94.3 (dd, *J* = 61.2, 15.0 Hz), -112.6 (dd, *J* = 61.4, 3.7 Hz). **IR** 3069 (w), 1769 (w), 1593 (w), 1494 (w), 1314 (m), 1295 (m), 1246 (s), 1147 (s), 1092 (m), 930 (m), 766 (m). **HRMS** (ESI+) *m/z*: 257.0057 ($M+Na^+$); calc. 257.0054 ($C_9H_8O_3F_2{}^{23}Na^{32}S$).

2.99 4-((2,2-difluorovinyl)oxy)benzonitrile



Prepared according to general procedure B. Flash chromatography (5-10% ethyl acetate in pentane) afforded the product as a colourless oil (78% yield). **^{1}H NMR** (400 MHz, Chloroform-d) δ 7.65 (m, 2H), 7.10 (m, 2H), 6.11 (dd, *J* = 14.6, 3.7 Hz, 1H). **^{13}C NMR** (101 MHz, Chloroform-d) δ 160.3 (t, *J* = 1.7 Hz), 157.0 (dd, *J* = 292.8, 281.3 Hz), 134.4, 118.7, 116.1, 106.8, 103.7 (dd, *J* = 56.7, 15.7 Hz). **^{19}F NMR** (377 MHz, Chloroform-d) δ -94.3 (dd, *J* = 61.3, 14.6 Hz), -112.6 (dd, *J* = 61.3, 3.6 Hz). **IR** 2230 (w), 1769 (w), 1604 (m), 1505 (m), 1350 (w), 1248 (s), 1174 (s), 1129 (w), 932 (w), 837 (w). **HRMS** (APCI+) *m/z*: 182.0414 ($M+H^+$); calc. 182.0412 ($C_9H_6ONF_2$).

2.100 6-((2,2-difluorovinyl)oxy)quinoxaline

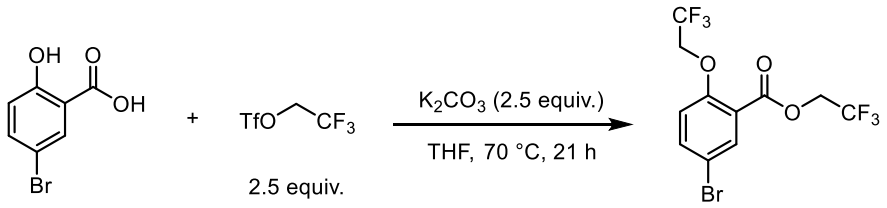


Prepared according to general procedure B. Flash chromatography (35% ethyl acetate in pentane) afforded the product as an off-white solid (81% yield). **^{1}H NMR** (400 MHz, Chloroform-d) δ 8.81 (d, J = 1.9 Hz, 1H), 8.77 (d, *J* = 1.9 Hz, 1H), 8.17 – 7.99 (m, 1H), 7.57 – 7.52 (m, 2H), 6.27 (dd, *J* = 14.8, 3.6 Hz, 1H). **^{13}C NMR** (101 MHz, Chloroform-d) δ 158.1 (t, *J* = 1.9 Hz), 157.1 (dd, *J* = 292.3, 280.6 Hz), 145.6, 144.2, 143.7, 140.1, 131.3, 122.3, 110.1, 104.1 (dd, *J* = 56.7, 15.6 Hz). **^{19}F NMR** (376 MHz, Chloroform-d) δ -94.9 (dd, *J* = 62.5, 14.6 Hz), -113.3 (dd, *J* = 62.7, 3.8 Hz). **IR** 3045 (w), 1772 (m), 1617 (m), 1500 (m),

1357 (s), 1303 (s), 1225 (s), 1109 (m), 871 (m). **HRMS** (ESI+) *m/z*: 209.0522 ($M+H^+$); calc. 209.0521 ($C_{10}H_7ON_2F_2$).

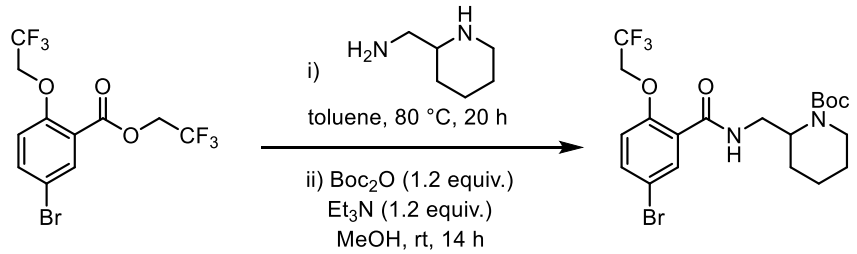
5.2.5 Experimental and Characterisation Data: Other Compounds

2.61 2,2,2-trifluoroethyl 5-bromo-2-(2,2,2-trifluoroethoxy)benzoate



Trifluoroethyl triflate (360 µL, 2.5 mmol, 2.5 equiv.) was added to a mixture of 5-bromo-2-hydroxybenzoic acid (217 mg, 1.00 mmol, 1.0 equiv.) and K_2CO_3 (346 mg, 2.50 mmol, 1.0 equiv.) in dry THF (2 mL) under N_2. The mixture was heated in a sealed vial for 21 hours at 70 °C, then diluted with CH_2Cl_2 and filtered to remove solids. The filtrate was concentrated to a dark oil, which was purified by flash column chromatography (5-10% ethyl acetate in pentane) to afford the product as a colourless oil (0.330 g, 87%). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.02 (d, *J* = 2.6 Hz, 1H), 7.65 (dd, *J* = 8.8, 2.6 Hz, 1H), 6.90 (d, *J* = 8.9 Hz, 1H), 4.68 (q, *J* = 8.4 Hz, 2H), 4.40 (q, *J* = 7.9 Hz, 2H). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 162.8, 156.5, 137.5, 135.3, 123.0 (q, *J* = 276.7 Hz, 2C), 121.5, 117.1, 115.4, 67.6 (q, *J* = 36.3 Hz), 61.2 (q, *J* = 37.0 Hz). **^{19}F NMR** (376 MHz, Chloroform-*d*) δ -73.51 – -73.68 (m, 3F), -73.90 – -74.02 (m, 3F). **HRMS** (ESI+) m/z: $[M+Na]^+$ Calcd for $C_{11}H_7O_{31}{}^{79}BrF_6Na$ 402.9375; Found 402.3975.

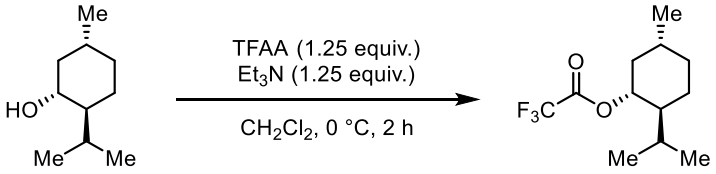
2.62 *tert*-butyl 2-((5-bromo-2-(2,2,2-trifluoroethoxy)benzamido)methyl)piperidine-1-carboxylate



Piperidin-2-ylmethanamine (114 µL, 0.93 mmol, 1.15 equiv.) was added to a solution of *tert*-butyl 2-((5-bromo-2-(2,2,2-trifluoroethoxy)benzamido)methyl)piperidine-1-carboxylate (309 mg, 0.81 mmol, 1.0 equiv.) in dry toluene (1.5 mL) under N_2, and the mixture was heated for 20 hours at 80 °C. While still hot, the reaction mixture was washed with water (3 mL), and then the aqueous was reextracted with toluene (1.5 mL). The combined organic phases were dried over $MgSO_4$ and concentrated under vacuum to afford the benzamide as a white solid that was used without further purification (323 mg, >99% yield). Et_3N (105 µL, 0.76 mmol, 1.21 equiv.) and then Boc_2O (175 µL, 0.76 mmol, 1.21 equiv.) were added to a solution of the crude benzamide (0.250 g, 0.63 mmol, 1 equiv.) in MeOH (7 mL), and the mixture was stirred at room temperature for 14 hours. Water (20 mL) was added and the mixture was extracted with ethyl acetate (2 x 20 mL). The combined organic phases were dried over $MgSO_4$ and concentrated to a viscous oil under vacuum. This crude was purified by flash column chromatography (20% ethyl acetate in pentane) to afford the desired product as a colourless viscous oil (0.248 g, 80% yield), which solidified slowly upon standing. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.19 (d, *J* = 2.6 Hz, 1H), 7.48 (dd, *J* = 8.7, 2.6 Hz, 1H), 7.45 – 7.35 (m, 1H), 6.79 (d, *J* = 8.7 Hz, 1H), 4.61 – 4.28 (m, 3H), 4.13 – 3.22 (m, 3H), 2.97 – 2.73 (m, 1H), 1.70 – 1.46 (m, 6H), 1.28 (s, 9H). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 163.4, 155.5, 154.0, 135.3, 135.2, 125.1, 123.0

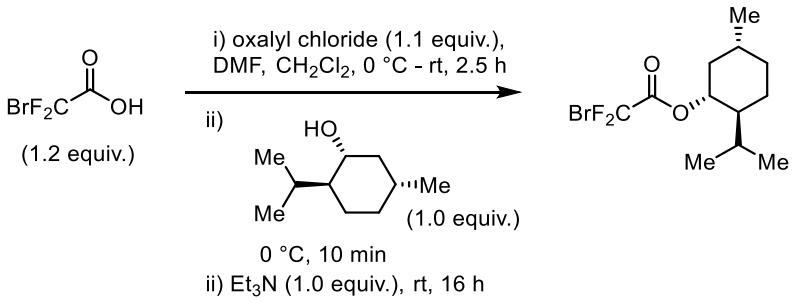
(q, *J* = 278.3 Hz), 116.0, 115.1, 79.5, 66.8 (q, *J* = 36.1 Hz), 49.8, 39.3, 28.2, 26.3, 25.3, 19.2. **^{19}F NMR** (377 MHz, Chloroform-*d*) δ -73.5 (br s, 3F). **HRMS** (ESI+) m/z: $[M+Na]^+$ Calcd for $C_{20}H_{26}O_4N_2{}^{79}BrF_3Na$ 517.0920; Found 517.0919.

2.82 (1*R*,2*S*,5*R*)-menthol trifluoroacetate



A solution of (1*R*, 2*S*, 5*R*)-menthol (1.25 g, 8.0 mmol, 1.0 equiv.) and dry Et_3N (1.4 mL, 10.0 mmol, 1.25 equiv.) in dry CH_2Cl_2 (15 mL) under an N_2 atmosphere was cooled to 0 °C, and then trifluoroacetic anhydride (1.4 mL, 10.0 mmol, 1.25 equiv.) was added dropwise. The reaction mixture was stirred at 0 °C for 2 hours, and then 1 M aqueous HCl (30 mL) was added. The organic phase was retained, further washed with 1 M aqueous HCl (2 x 30 mL), dried over Na_2SO_4 and then concentrated *in vacuo* to afford the crude product as an oil. Flash column chromatography (0-2% ethyl acetate in pentane) afforded the product as a colourless oil (1.923 g, 7.62 mmol, 95% yield). **^{1}H NMR** (500 MHz, Chloroform-d) δ 4.87 (td, *J* = 11.0, 4.5 Hz, 1H), 2.09 – 2.01 (m, 1H), 1.92 – 1.66 (m, 3H), 1.58 – 1.46 (m, 2H), 1.19 – 1.02 (m, 2H), 0.95 – 0.86 (m, 1H), 0.94 (d, *J* = 6.6 Hz, 3H), 0.91 (d, *J* = 7.0 Hz, 3H), 0.78 (d, *J* = 7.0 Hz, 3H). **^{13}C NMR** (126 MHz, Chloroform-d) δ 157.3 (q, *J* = 41.7 Hz), 114.8 (q, *J* = 286.1 Hz), 79.5, 46.9, 40.2, 34.0, 31.6, 26.4, 23.6, 21.9, 20.6, 16.3. **^{19}F NMR** (470 MHz, Chloroform-d) δ -75.41. (s, 3F). Analytical data consistent with that previously reported.[131]

2.83 (1*R*,2*S*,5*R*)-menthol bromodifluoroacetate



A solution of bromodifluoroacetic acid (4.20 g, 24.0 mmol, 1.2 equiv.) in dry CH_2Cl_2 (45 mL) under an N_2 atmosphere was cooled at 0 °C, and then oxalyl chloride (1.86 mL, 22.0 mmol, 1.1 equiv.) was added, followed by dry DMF (~200 µL). The reaction mixture was stirred at 0 °C for 1 hour, and then stirred for a further 90 minutes whilst warming to room temperature. The reaction mixture was then cooled back to 0 °C, and then solid (1*R*, 2*S*, 5*R*)-menthol (3.130 g, 20.0 mmol, 1.0 equiv.) was added all at once. Stirring was continued at 0 °C for 10 minutes, and then dry Et_3N (3.4 mL, 24 mmol) was added dropwise. The reaction was stirred for 16 hours whilst warming to room temperature, and then 1 M aqueous HCl (30 mL) was added. The organic phase was retained, further washed with 1 M aqueous HCl (2 x 30 mL), dried over Na_2SO_4 and then concentrated *in vacuo* to afford the crude product as an oil. Flash column chromatography (0-1% ethyl acetate in pentane) afforded the product as a colourless oil (5.719 g, 18.3 mmol, 91% yield). **^{1}H NMR** (400 MHz, Chloroform-d) δ 4.84 (td, *J* = 11.0, 4.5 Hz, 1H), 2.11 – 2.02 (m, 1H), 1.92 (heptd, *J* = 7.0, 2.8 Hz, 1H), 1.79 – 1.67 (m, 2H), 1.62 – 1.44 (m, 2H), 1.20 – 1.02 (m, 2H), 1.00-0.88 (m, 1H), 0.94 (d, *J* = 6.6 Hz, 3H), 0.91 (d, *J* = 7.0 Hz, 3H), 0.79 (d, *J* = 7.0 Hz, 3H). **^{13}C NMR** (126 MHz, Chloroform-d) δ 159.3 (t, *J* = 30.8 Hz), 109.1 (t, *J* = 314.8 Hz), 79.6, 47.0, 40.0, 34.1, 31.6, 26.3, 23.5, 22.0, 20.7, 16.2. **^{19}F NMR** (377 MHz, Chloroform-

d) δ -60.61 (d, *J* = 154.3 Hz, 1F), -60.94 (d, *J* = 154.3 Hz, 1F). Analytical data consistent with that previously reported.[131]

5.2.6 Other Experimental Procedures

C–O Cross-coupling competition experiment

To an oven dried Schlenk tube was added Cs_2CO_3 (244 mg, 0.75 mmol, 1.5 equiv.). The Schlenk tube was placed under vacuum and heated at 450 °C with a heat gun for around 3 minutes, or until the Cs_2CO_3 stopped 'jumping'. After the tube had cooled to room temperature it was placed under an N_2 atmosphere, and 2-bromonaphthalene (104 mg, 0.500 mmol, 1 equiv.) and ^{t}BuBrettPhos Pd G3 (4.2 mg, 0.005 mmol, 1 mol%) were added. Then 2,2,2-trifluoroethanol (54 µL, 0.75 mmol, 1.5 equiv.) was added, followed by either 2,2-difluoroethanol (47 µL, 0.75 mmol, 1.5 equiv.) or ethanol (44 µL, 0.75 mmol, 1.5 equiv.). Finally, dry, degassed toluene (1.5 mL) was added, and the Schlenk tube was sealed under an N_2 atmosphere and heated at 80 °C in a preheated oil bath for 1 hour. The reaction mixture was cooled to room temperature, and then diluted with CH_2Cl_2. The mixture was filtered through a Celite pad, and the pad was washed with addition CH_2Cl_2. For 2,2,2-trifluoroethanol vs 2,2-difluoroethanol: α,α,α-trifluorotoluene was added to filtrate as an internal standard, and an aliquot was taken, diluted with $CDCl_3$, and analysed by quantitative ^{19}F NMR. For 2,2,2-trifluoroethanol vs ethanol: the filtrate was concentrated to dryness, taken up in $CDCl_3$, and then mesitylene was added as an internal standard. The mixture was analysed by ^{1}H NMR.

(1*R*,2*S*,5*R*)-menthol bromodifluoroacetate **2.83** stability test

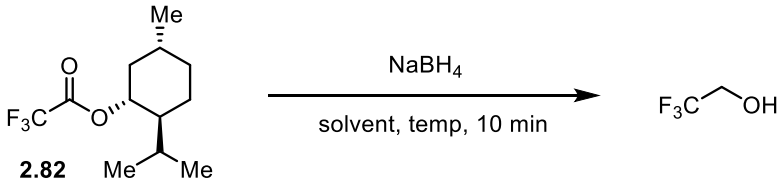
(1*R*,2*S*,5*R*)-menthol bromodifluoroacetate **2.83** (50 mg, 0.16 mmol, 1 equiv.) and dry DMI (0.3 mL) were added to a 1.75 mL vial, followed by DBU (15 µL, 0.10 mmol, 0.63 equiv.).

The vial was sealed and heated at 100 °C in a pre-heated oil bath for 10 minutes. The reaction mixture was then diluted with $CDCl_3$. α,α,α-trifluorotoluene was added as an internal standard, and the mixture was analysed by quantitative ^{19}F NMR.

Water tolerance of C–O cross-coupling

To an oven dried Schlenk tube was added Cs_2CO_3 (244 mg, 0.75 mmol, 1.5 equiv.). The Schlenk tube was placed under vacuum and heated at 450 °C with a heat gun for around 3 minutes, or until the Cs_2CO_3 stopped 'jumping'. After the tube had cooled to room temperature it was placed under an N_2 atmosphere, then 2-bromonapthalene (104 mg, 0.50 mmol, 1.0 equiv.) and ^{t}BuBrettPhos Pd G3 (4.2 mg, 0.005 mmol, 1 mol%) were added. Premixed 1,4-dioxane/water (1.5 mL) was then added (solvent mixture not degassed). The Schlenk tube was very briefly placed under vacuum and then refilled with nitrogen, three times. 2,2,2-Trifluoroethanol (54 µL) was then added, and the Schlenk tube was sealed and heated at 80 °C in a preheated oil bath for 1 hour. The reaction mixture was cooled to room temperature, and then diluted with CH_2Cl_2. The mixture was then filtered through a Celite pad and the filter cake was washed with additional CH_2Cl_2. α,α,α-trifluorotoluene was added to the filtrate, then a sample was removed and diluted with $CDCl_3$ and analysed by quantitative ^{19}F NMR.

(-)-Menthol trifluoroacetate **2.82** reduction



The specified amount of $NaBH_4$ was weighed into a 7 mL vial, then a stock solution of (-)-menthol trifluoroacetate (25 mg, 0.10 mmol, 1.0 equiv.) **2.82** in the specified solvent (1 mL) was added, and the reaction mixture was stirred at the specified temperature for 10

minutes. The reaction mixture was then passed through a syringe filter to remove insolubles, and then $CDCl_3$ (0.5 mL) was added. α,α,α-Trifluorotoluene was added as an internal standard, and the sample was analysed by quantitative ^{19}F NMR.

5.2.7 Radiochemistry

5.2.7.1 HPLC Methods

Method A

Column: Phenomenex Synergi 4µm Hydro-RP 80 Å LC column, 150 x 4.6 mm

Detection: UV (220 nm) and radio

Flow Rate: 1 mL min^{-1}

Mobile Phase: MeCN / water

0 – 1 min (5% MeCN, isocratic), 1 – 10 min (5% – 95% MeCN, linear increase), 10 – 14 min (95% MeCN, isocratic), 14 – 16 min (95% - 5% MeCN, linear decrease), 16 – 18 min (5% MeCN, isocratic).

Method B

Column: Phenomenex Gemini 5µm C18 110 Å LC column, 250 x 10 mm

Detection: UV (254 nm) and radio

Flow Rate: 5 mL min^{-1}

Mobile Phase: MeCN / 25 mM aqueous ammonium formate

0 – 30 mins (75% MeCN, isocratic)

Method C

Column: Phenomenex Synergi 4µm Hydro-RP 80 Å LC column, 150 x 4.6 mm

Detection: UV (220 nm) and radio

Flow Rate: 1 mL min^{-1}

Mobile Phase: MeCN / water

0 - 2 min (20% MeCN, isocratic), 2 – 19 min (20% – 65% MeCN, Chromeleon non-linear gradient ramp, curve = 2), 19 – 20 min (65% -20 % MeCN, linear decrease).

5.2.7.2 Procedures

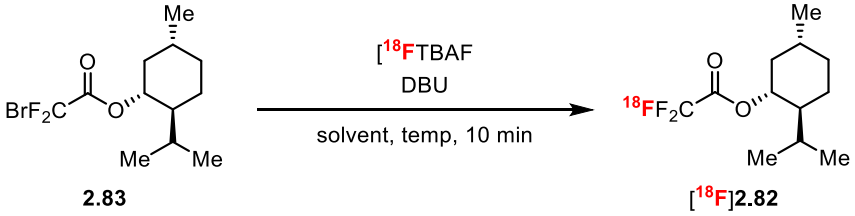
Preparation of [^{18}F]TEAF

Formulation and azeotropic drying of [^{18}F]fluoride was performed using a NanoTek® automated microfluidic device (Advion). A Sep-Pak Accell Plus QMA Carbonate Plus Light Cartridge, 46 mg Sorbent per Cartridge, 40 µm (SKU 186004540) was activated with 10 mL of water. Then [^{18}F]fluoride in [^{18}O]H_2O (3.0 – 5.0 GBq) was trapped on the cartridge. The [^{18}F]fluoride was eluted with a solution of Et_4NHCO_3 (8.0 mg, 42 µmol) in H_2O (200 µL) and MeCN (800 µL). The resulting [^{18}F]TEAF was dried with 4 rounds of azeotropic drying with MeCN under a flow of N_2 at 105 °C. The dry activity was then diluted with MeCN and dispensed in small quantities (20-30 MBq) for screening reactions.

Preparation of [^{18}F]TBAF

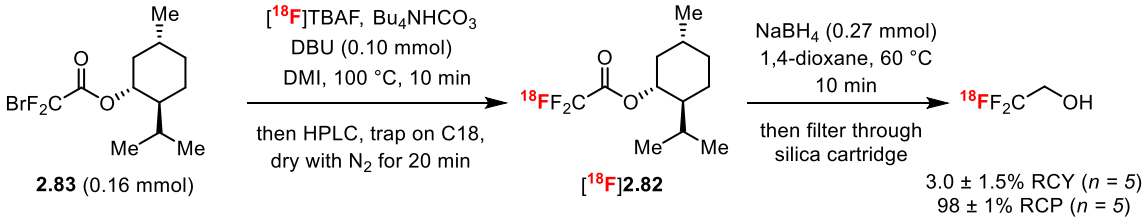
Formulation and azeotropic drying of [^{18}F]fluoride was performed using a NanoTek® automated microfluidic device (Advion). A Sep-Pak Accell Plus QMA Carbonate Plus Light Cartridge, 46 mg Sorbent per Cartridge, 40 µm (SKU 186004540) was activated with 10 mL of water. Then [^{18}F]fluoride in [^{18}O]H_2O (3.0 – 5.0 GBq) was trapped on the cartridge. The [^{18}F]fluoride was eluted with a solution of Bu_4NHCO_3 (6.8 mg, 22 µmol) in H_2O (500 µL) and MeCN (500 µL). The resulting [^{18}F]TBAF was dried with 4 rounds of azeotropic drying with MeCN under a flow of N_2 at 105 °C. The dry activity was then either used directly for a large scale reaction, or diluted with MeCN and dispensed in small quantities (20-30 MBq) for screening reactions.

Screening ^{18}F-labelling of (-)-menthol [^{18}F]trifluoroacetate [^{18}F]2.82



An aliquot of 20-30 MBq of [^{18}F]fluoride was dispensed into a 3.5 mL V-vial equipped with a lid and septum. Then a solution of (1*R*,2*S*,5*R*)-menthol bromodifluoroacetate **2.83** and DBU in dry solvent (300 µL) was added, and the reaction mixture was heated at the specified temperature for 10 minutes. The reaction mixture was diluted with EtOH (200 µL) and then analysed by radioHPLC using HPLC method A.

[^{18}F]Trifluoroethanol



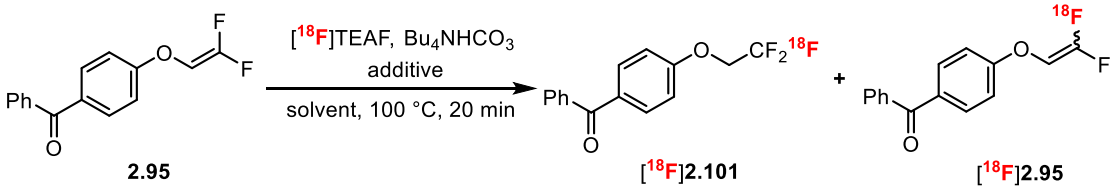
To dry [^{18}F]TBAF was added a freshly prepared solution of (1*R*,2*S*,5*R*)-menthol bromodifluoroacetate (50 mg, 0.16 mmol) and DBU (16 µL, 0.10 mmol) in anhydrous DMI (300 µL). The reaction mixture was stirred at 100 °C for 10 minutes. The mixture was then diluted with MeCN (1 mL), and purified by semi-prep HPLC using HPLC method B. The product [^{18}F]**2.82** (eluting between 22.9 – 24.1 mins) was collected into H_2O (25 mL). The resulting mixture was passed over a Waters Sep-Pak C18 Plus Short cartridge (WAT020515). After trapping, the cartridge was washed with H_2O (2 mL), and then blow dried under a flow N_2 (1.6 – 1.8 L min^{-1}) for approximately 20 minutes. The radioactivity of the cartridge was monitored using a radio-detector attached to the cartridge. If the radioactivity began to drop sharply before 20 minutes, the drying was stopped. The

cartridge was then eluted with anhydrous 1,4-dioxane (2 mL) into a 5 mL V-vial containing $NaBH_4$ (10 mg, 0.265 mmol). Residual solvent on the cartridge was blown into the reaction vial using a flow of N_2. The resulting reaction mixture was heated at 60 °C for 10 minutes. The mixture was then taken up in a syringe filtered through a Sep-Pak Silica Light cartridge (WAT023537) pre-activated with anhydrous dioxane (5 mL), into a dry 5 mL V-vial. Remaining solvent on the cartridge was blown into the V-vial using a flow of N_2. The RCP was measured using HPLC method A.

General procedure C: cross-coupling of [^{18}F]trifluoroethanol with aryl bromides

To a 3.5mL V-vial was added ^{t}BuBrettPhos Pd G3 (2-3 mg, ~3 µmol), then aryl bromide (30 µmol), and then dry Cs_2CO_3 (13 mg, 40 µmol, pre-dried at 450 °C under vacuum in a Schlenk tube). The V-vial sealed with a stir bar and septum. A vent needle was added and then the V-vial was flushed with N_2 for approximately 1 minute. Then [^{18}F]trifluoroethanol solution in 1,4-dioxane was added (15-20 MBq). The resulting reaction mixture was heated at the specified temperature for 20 minutes. The reaction was then diluted with MeCN (100 µL) and analysed by radioHPLC using HPLC method A. The RCC was determined using radioHPLC alone. NOTE: no significant loss in activity, beyond that due to decay, was observed after 20 minutes. This indicates that loss of [^{18}F]trifluoroethanol due to evaporation was insignificant.

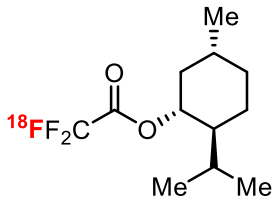
General procedure D: screening of [^{18}F]fluoride addition to geminal-difluorovinyl ether 2.95



An aliquot of [^{18}F]TEAF (approx. 25 MBq) in MeCN was added to a V-vial (containing an additive where applicable). Substrate (0.03 mmol) in solvent (300 µL) was added and the vial was heated at the specified temperature for 20 minutes. The crude mixture was quenched by the addition of 9:1 ethanol/water (300 µL). An aliquot of the crude mixture was analysed by radioTLC and radio HPLC using HPLC method C.

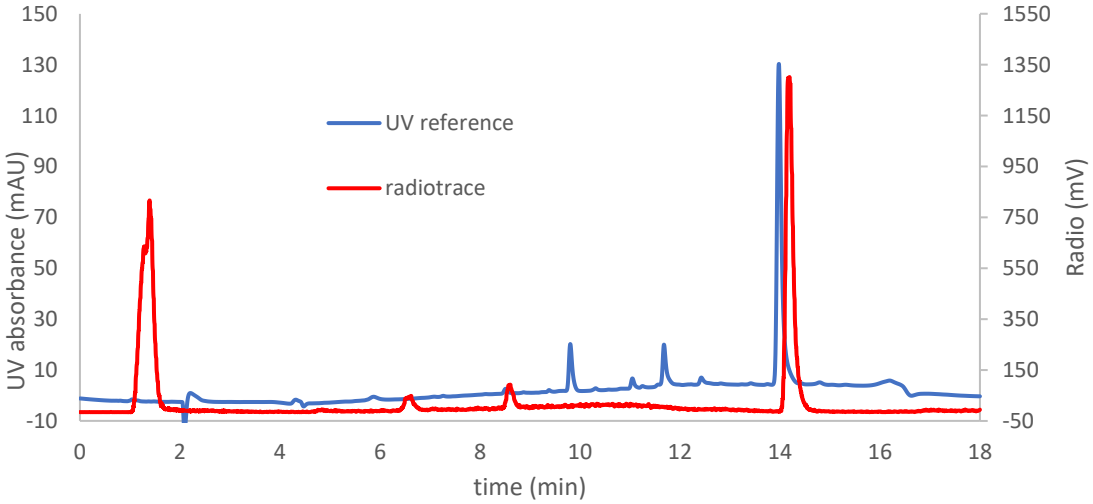
5.2.7.3 Product Characterisation

[^{18}F]**2.82** (-)-menthol [^{18}F]trifluoroacetate

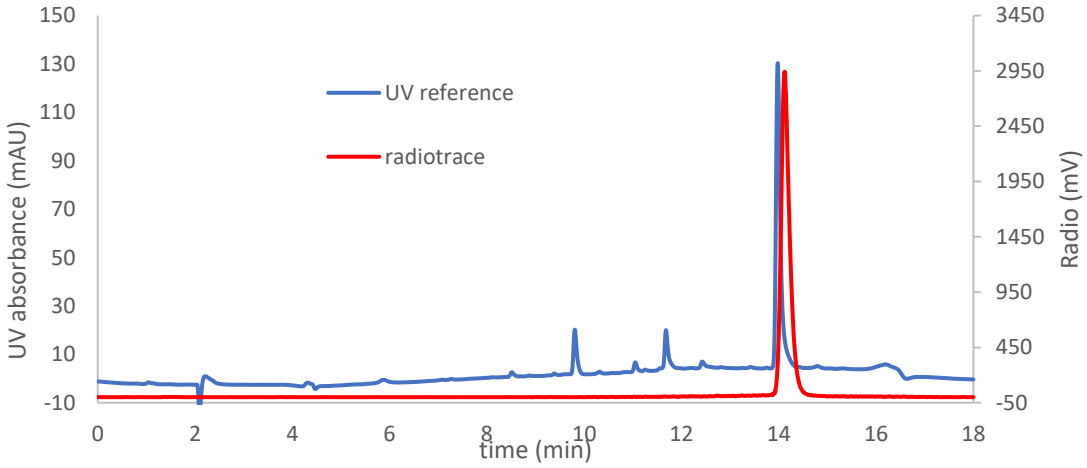


Prepared following the procedure detailed above, on route to [^{18}F]trifluoroethanol.

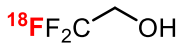
Crude reaction mixture:



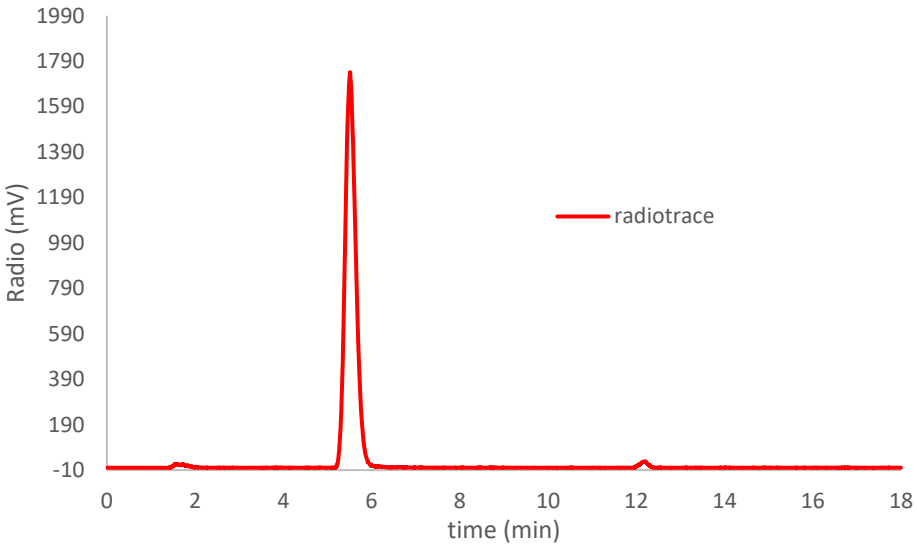
After semi-prep HPLC purification:



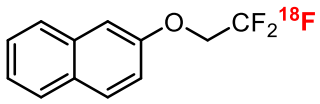
[^{18}F]Trifluoroethanol



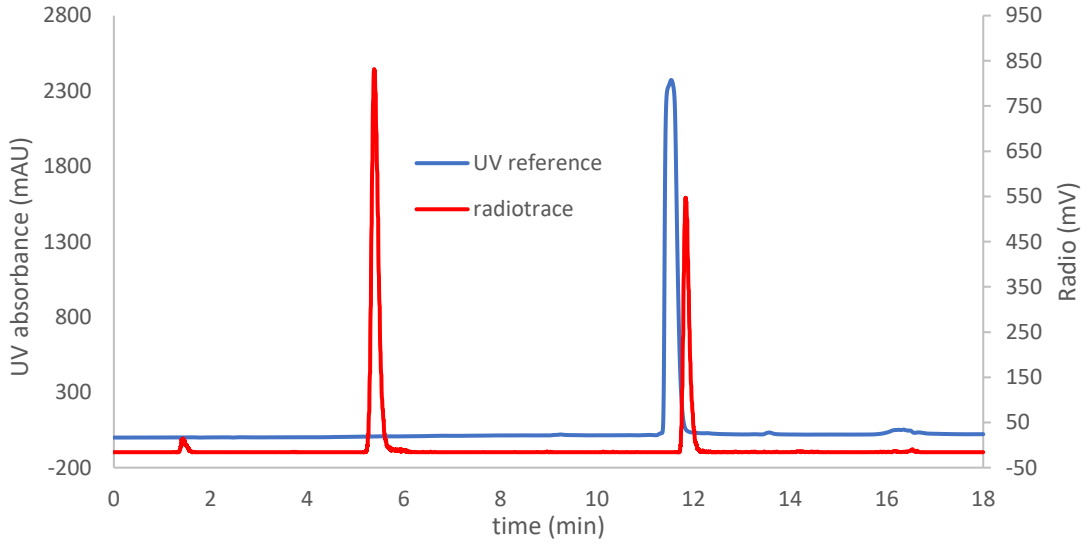
Prepared following the procedure detailed above.



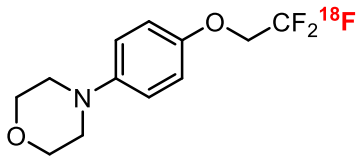
[^{18}F]2.53B 2-(2,2,2-trifluoroethoxy)naphthalene



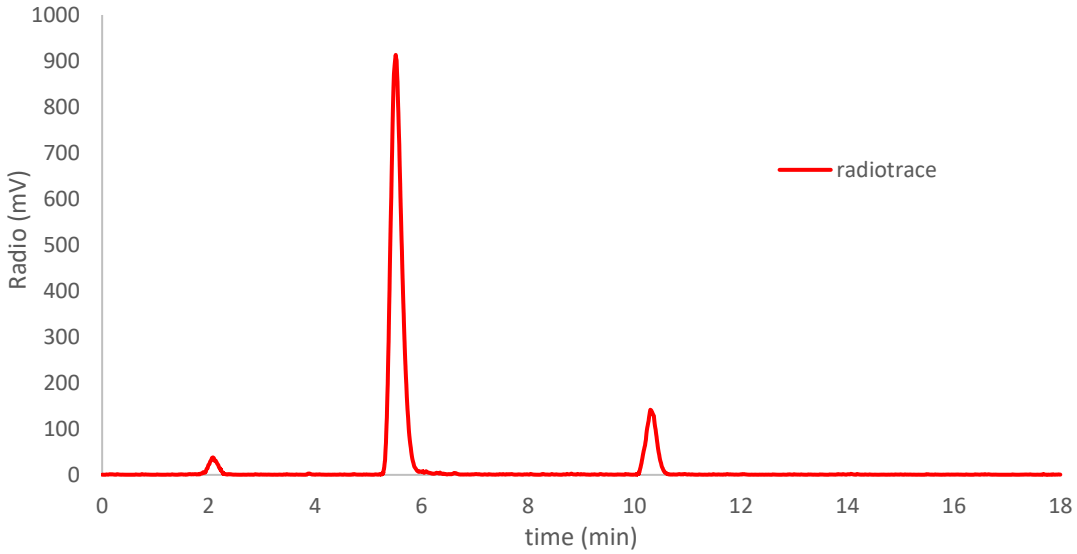
Prepared according to general procedure C, heating at 80 °C.



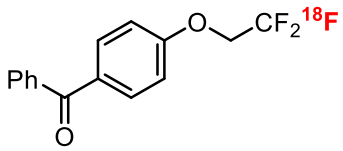
[^{18}F]2.41B 4-(4-(2,2,2-trifluoroethoxy)phenyl)morpholine



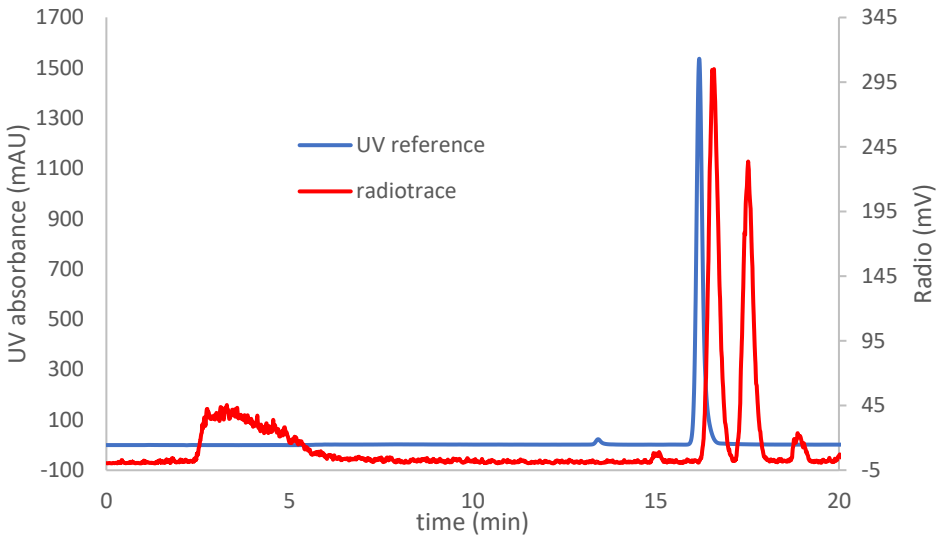
Prepared according to general procedure C, heating at 100 °C.



[^{18}F]2.101 [^{18}F]phenyl(4-(2,2,2-trifluoroethoxy)phenyl)methanone



Prepared according to general procedure D, using 1vol% water in DME as solvent and heating at 100 °C.



Entry	RadioTLC	RadioHPLC	% RCC
1	73	43	31
2	55	57	31

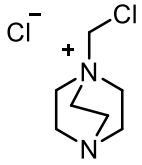
5.3 Experimental Procedures and Characterisation Data for Chapter 3

5.3.1 General Information:

Stock solutions of xenon difluoride were prepared in polypropylene Falcon tubes using dry acetonitrile (non-degassed) and were wrapped in tin foil. Despite NMR experiments showing xenon difluoride was stable in acetonitrile, stock solutions were used within 24 hours of being prepared. Xenon difluoride was purchased from Apollo Scientific. $[(NpNMe_3)_2C_2O_4]$ (CAS 2247698-66-2) was purchased from Sigma Aldrich.

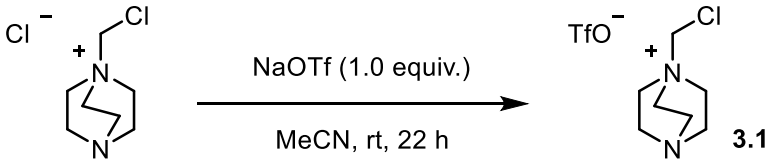
5.3.2 Experimental and Characterisation Data: DABCOnium Salts and F-TEDA Salts

1-(chloromethyl)-1,4-diazabicyclo[2.2.2]octan-1-ium chloride



Prepared according to the literature procedure.[213]

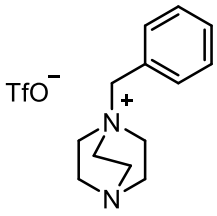
3.1 1-(chloromethyl)-1,4-diazabicyclo[2.2.2]octan-1-ium triflate



1-(chloromethyl)-1,4-diazabicyclo[2.2.2]octan-1-ium chloride (15.77 g, 80 mmol, 1 equiv.) and sodium triflate (13.76 g, 80 mmol, 1.0 equiv.) were added to a dry 500 mL round bottomed flask, then the flask was evacuated and backfilled with N_2 3 times. Dry acetonitrile (160 mL) was added and the mixture was stirred at room temperature under N_2 for 22 hours. The mixture was then filtered through celite, and the filtrate concentrated and dried under high vacuum to afford the product as a white powder (24.25 g, 98%). **^{1}H NMR** (400 MHz, Deuterium Oxide) δ 5.14 (s, 2H), 3.58 (t, *J* = 7.6 Hz,

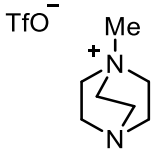
6H), 3.29 (t, *J* = 7.3 Hz, 6H). **^{19}F NMR** (377 MHz, Deuterium Oxide) δ -78.8. Analytical data consistent with that previously reported.[214]

3.37 1-benzyl-1,4-diazabicyclo[2.2.2]octan-1-ium triflate



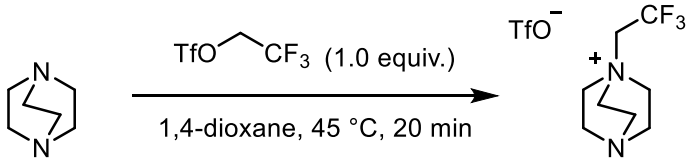
Prepared according to the literature procedure.[69]

1-methyl-1,4-diazabicyclo[2.2.2]octan-1-ium triflate



Prepared according to the literature procedure.[215]

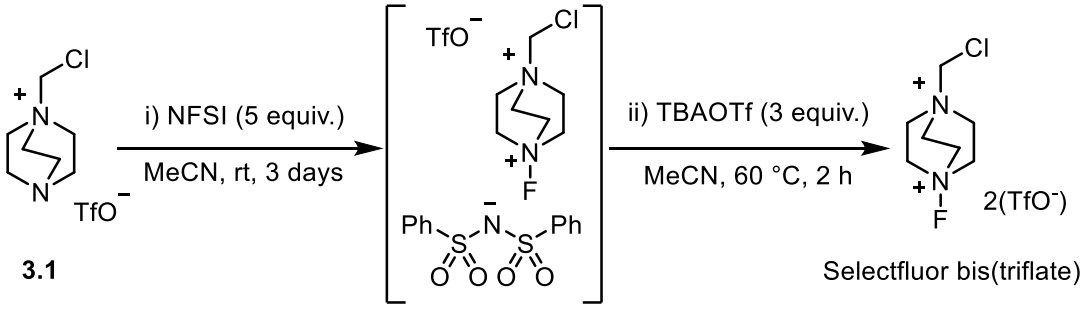
1-(2,2,2-trifluoroethyl)-1,4-diazabicyclo[2.2.2]octan-1-ium



Trifluoroethyl triflate (2.88 mL, 20 mmol) was added dropwise to a solution of 1,4-diazabicyclo[2.2.2]octane (2.244 g, 20.0 mmol) in dry 1,4-dioxane (20 mL) at room temperature under N_2. The mixture was stirred at 45 °C for 20 minutes. Upon cooling back to room temperature a precipitate formed, which was collected by filtration and

washed with copious 1,4-dioxane, diethyl ether and finally pentane to give a free-flowing powder, which was dried under high vacuum to afford the product as a white powder (6.582 g, 96%). **^{1}H NMR** (400 MHz, Acetonitrile-d_3) δ 4.13 (q, J = 8.8 Hz, 2H), 3.55 – 3.42 (m, 6H), 3.21 – 3.11 (m, 6H). **^{19}F NMR** (377 MHz, Acetonitrile-d_3) δ -61.3 (t, J = 8.9 Hz), -79.4. Analytical data consistent with that previously reported.[214]

Selectfluor bis(triflate)



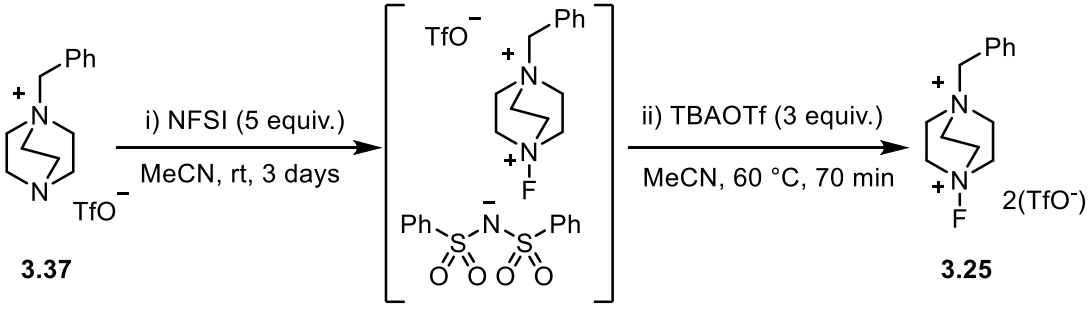
3.1

Selectfluor bis(triflate)

Synthesis of Selectfluor bis(triflate) was based on a reported synthesis of Selectfluor II by the Hu group.[216] 1-(chloromethyl)-1,4-diazabicyclo[2.2.2]octan-1-ium triflate (18.64 g, 60 mmol, 1 equiv.) and NFSI (94.50 g, 300 mmol, 5 equiv.) were added to a dry 1 L round bottomed flask, then the flask was evacuated and backfilled with N_2 3 times. Dry acetonitrile (600 mL) was added, and the mixture was stirred at room temperature under N_2 for 3 days. The precipitated pure product was collected by filtration and dried to afford a white powder. Diethyl ether (100 mL) was added to the filtrate to afford more precipitate which was collected by filtration. This second crop contained NFSI, and so was washed thoroughly with CH_2Cl_2 to afford a second crop of pure product as white powder. The combined first and second crop (11.70 g, 18.7 mmol) was added to a 250 mL round bottomed flask, then the flask was evacuated and backfilled with N_2 3 times. Dry acetonitrile (60 mL) was added, and then the mixture was heated at 60 °C for 15 minutes.

Then tetrabutylammonium triflate (23.49 g, 60 mmol, ~3 equiv.) was added and the heterogenous mixture was heated at 60 °C for 2 hours. Ethyl acetate (100 mL) was added, and the resulting precipitate was collected by filtration, washed with ethyl acetate and dried to afford the product as a white powder (7.787 g, 27% over 2 steps). **^{1}H NMR** (400 MHz, Acetonitrile-d_3) δ 5.35 (s, 2H), 4.76 (q, *J* = 7.4 Hz, 6H), 4.31 (t, *J* = 7.6 Hz, 6H). **^{19}F NMR** (377 MHz, Acetonitrile-d_3) δ 48.0, -79.3. **^{1}H NMR** (500 MHz, Deuterium Oxide) δ 5.57 (s, 2H), 5.04 (q, *J* = 7.4 Hz, 6H), 4.58 (t, *J* = 7.6 Hz, 6H). **^{1}H{^{19}F} NMR** (500 MHz, Deuterium Oxide) δ 5.57 (s, 2H), 5.04 (t, *J* = 7.6 Hz, 6H), 4.58 (t, *J* = 7.6 Hz, 6H). Analytical data consistent with that previously reported.[169]

3.25 1-benzyl-1,4-diazabicyclo[2.2.2]octan-1-ium bis(triflate)



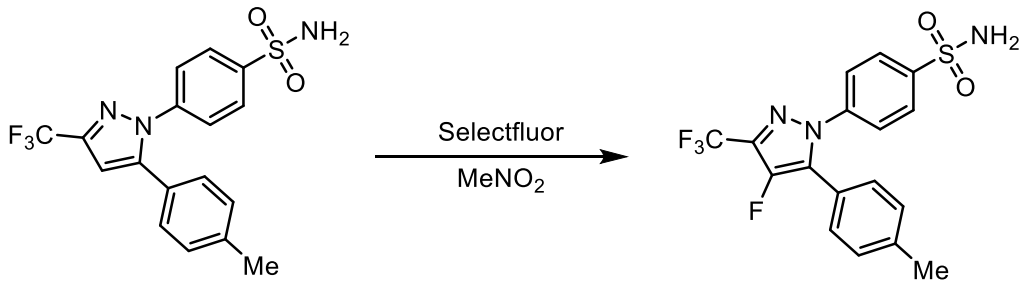
3.37 **3.25**

Synthesis of *N*-benzyl F-TEDA **3.25** was based on a reported synthesis of Selectfluor II by the Hu group.[216] 1-benzyl-1,4-diazabicyclo[2.2.2]octan-1-ium triflate (1.41 g, 4.0 mmol, 1.0 equiv.) and NFSI (6.30 g, 20.0 mmol, 5.0 equiv.) were added to a 250 mL round bottomed flask, then the flask was evacuated and backfilled with N_2 3 times. Dry acetonitrile (15 mL) was added, and the mixture was stirred at room temperature under N_2 for 3 days. The solvent was removed under vacuum and then a mixture of 1:1 $CHCl_3$/Et_2O (80 mL) was added and the mixture was stirred for 10 minutes and then filtered. The solid was washed with Et_2O (30 mL) and then pentane (100 mL) to afford a

free-flowing white powder. This was dissolved in dry MeCN (8.0 mL), then tetrabutylammonium triflate (4.70 g, 12.0 mmol, 3 equiv.) was added and the solution was heated at 60 °C for 70 minutes. The mixture was then concentrated under vacuum and redissolved in CH_2Cl_2 (30 mL). Et_2O was then added until the mixture became very cloudy, and the mixture was filtered. The solid was washed with Et_2O, then pentane, and then CH_2Cl_2 (note that significant material loss occurred during the CH_2Cl_2 wash), to afford the desired product as an off-white powder. Note: In some cases this synthesis afforded the product contaminated with an unidentified DABCO derived by-product (0-20%). **^{1}H NMR** (400 MHz, Acetonitrile-d_3) δ 7.70 – 7.46 (m, 6H), 4.75 (s, 2H), 4.63 (m, 6H), 4.17 (m, 6H). **^{19}F NMR** (377 MHz, Acetonitrile-d_3) δ 49.8, -79.4. Analytical data consistent with that previously reported.[69]

5.3.3 Experimental and Characterisation Data: Other Compounds

3.39 4-(4-fluoro-5-(p-tolyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)benzenesulfonamide



celecoxib **3.39**

Procedure for isolating a sample as a reference for HPLC :

Modified version of the literature procedure.[194] Celecoxib (190 mg, 0.5 mmol, 1.0 equiv.) and Selectfluor (710 mg, 2.0 mmol, 4.0 equiv.) were heated at 100 °C in nitromethane (2 mL) for 45 minutes. The reaction mixture was diluted with water and extracted three

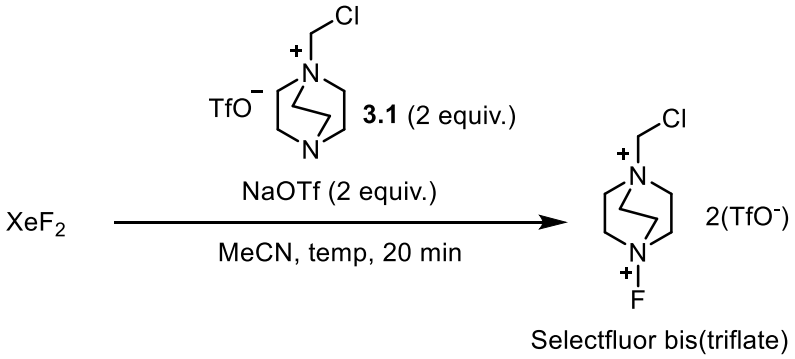
times with ethyl acetate. The combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated under vacuum. The crude was purified by flash chromatography (20-30% ethyl acetate in pentane) to afford a mixture of approximately 2.5:1 celecoxib and **3.39** as an off-white powder (70 mg). **^{19}F NMR** (377 MHz, Methanol-d_4) δ -63.4 (d, *J* = 7.1 Hz), -173.5 (q, *J* = 7.1 Hz). **LRMS** (ESI+) m/z: $[M+H]^+$ Calcd for $C_{17}H_{14}F_4N_3O_2S$ 400.1; Found 400.1. Analytical data consistent with that previously reported.[194]

Procedure optimised for Selectfluor consumption and short duration, for translation to ^{18}F-radiolabelling:

Celecoxib (38 mg, 0.1 mmol, 2.0 equiv.) and Selectfluor bis(triflate) (24 mg, 0.05 mmol, 1.0 equiv.) were heated at 100 °C in nitromethane (0.2 mL) for 30 minutes. The mixture was then diluted with deuterated acetonitrile, α,α,α-trifluorotoluene (20 µL) was added as an internal standard, and the mixture was analysed by quantitative ^{19}F NMR.

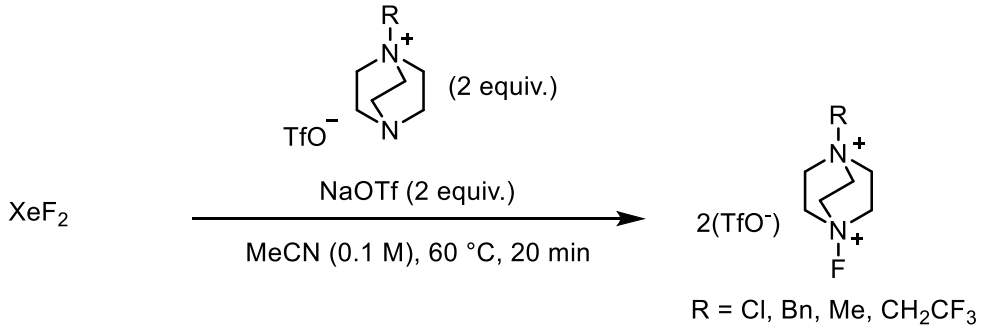
5.3.4 Experimental and Characterisation Data: N-F Compounds from Xenon Difluoride

General procedure for screening Selectfluor bis(triflate) synthesis from xenon difluoride



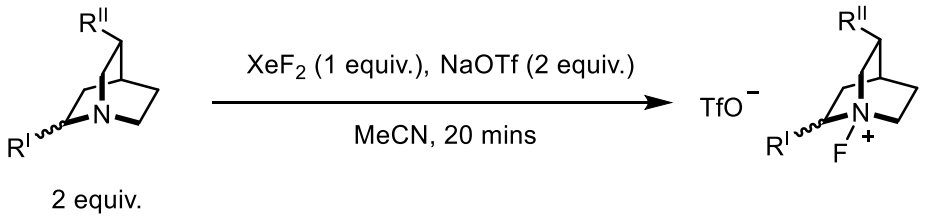
A solution of sodium triflate in dry acetonitrile (0.4 M, 250 µL, 0.10 mmol, 2.0 equiv.) was added to 1-(chloromethyl)-1,4-diazabicyclo[2.2.2]octan-1-ium triflate **3.1** (31.1 mg, 0.10 mmol, 2.0 equiv.) in a 3.5 mL borosilicate glass vial. The mixture was stirred for approximately 1 minute, and then a solution of xenon difluoride in dry acetonitrile (0.2 M, 250 µL, 0.05 mmol, 1 equiv.) was added. The vial lid was screwed on, and the reaction was stirred at 600 RPM for the specified duration in a pre-heated oil bath at the specified temperature. The reaction mixture was then diluted with a solution of α,α,α-trifluorotoluene (5 µL) in MeCN (2 mL total volume). The yield was then determined using quantitative ^{19}F NMR with CHORUS, comparing the integration of the Selectfluor **F**-N resonance with the CF_3 resonance of α,α,α-trifluorotoluene. Some reactions were also repeated and diluted with deuterated acetonitrile, so that the ^{1}H NMR was clearer and could be interpreted.

General procedure E: preparing F-TEDA reagents from xenon difluoride



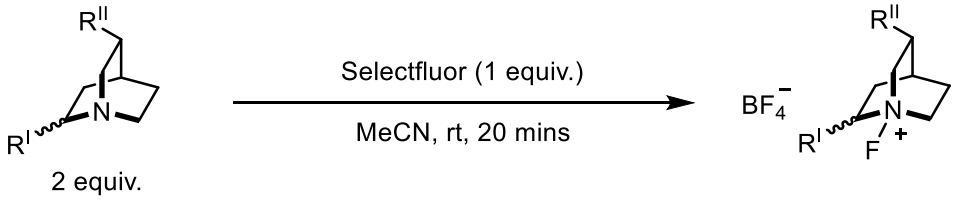
A solution of sodium triflate in dry acetonitrile (0.4 M, 250 µL, 0.10 mmol, 2.0 equiv.) was added to DABCOnium triflate **3.1** (0.10 mmol, 2.0 equiv.) in a 3.5 mL borosilicate glass vial. The mixture was stirred for approximately 1 minute, and then a solution of xenon difluoride in dry acetonitrile (0.2 M, 250 µL, 0.05 mmol, 1 equiv.) was added. The vial lid was screwed on, and the reaction was stirred at 600 RPM for 20 minutes in a pre-heated oil bath at 60 °C. The reaction mixture was then diluted with a solution of α,α,α-trifluorotoluene (internal standard) in MeCN (2 mL total volume). The yield was then determined using quantitative ^{19}F NMR with CHORUS, comparing the integration of the F-TEDA **F**-N resonance with the CF_3 resonance of α,α,α-trifluorotoluene. The products were characterised in the crude mixture, and had ^{1}H and ^{19}F NMR spectra consistent with those reported in the literature. ^{1}H NMR spectra were referenced to acetonitrile at 1.96 ppm. ^{1}H NMR shifts were slightly different to those reported in the literature due to different NMR solvent compositions. The diagnostic ^{1}H NMR shift for each F-TEDA product is the quartet between 4.5 to 5.0 ppm (quartet due to 1 x $^{3}J_{H\text{-}F}$ and 2 x $^{3}J_{H\text{-}H}$). The diagnostic ^{19}F NMR shift is that for **F**-N at approximately 50 ppm.

General procedure F: fluorination of quinuclidine and cinchona alkaloid derivatives with xenon difluoride



A solution of xenon difluoride in dry acetonitrile (0.2 M, 250 µL, 0.05 mmol, 1 equiv.) was added to a suspension/solution of quinuclidine/cinchona alkaloid derivative (0.10 mmol, 2 equiv.) and sodium triflate (17.2 mg, 0.10 mmol, 2 equiv.) in dry acetonitrile (250 µL) in a 3.5 mL glass vial. The vial lid was screwed on, and the reaction was stirred at 600 RPM for 20 minutes at either room temperature or 60 °C in a preheated oil bath. The mixture was then diluted with deuterated acetonitrile (and CH_2Cl_2 to homogenise if necessary), and then α,α,α-trifluorotoluene was added as internal standard and the reaction was analysed by quantitative ^{19}F NMR and mass spectroscopy (ESI+).

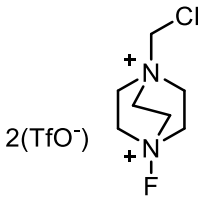
General procedure G: fluorination of quinuclidine and cinchona alkaloid derivatives with Selectfluor



A solution of Selectfluor in 24:1 acetonitrile/water (0.2 M, 250 µL, 0.05 mmol, 1 equiv.) was added to a suspension/solution of quinuclidine/cinchona alkaloid derivative (0.10 mmol, 2 equiv.) in acetonitrile (250 µL) in a 3.5 mL glass vial. The vial lid was screwed on, and the reaction was stirred at 600 RPM for 20 minutes at room temperature. The mixture was then diluted with deuterated acetonitrile (and CH_2Cl_2 to homogenise if

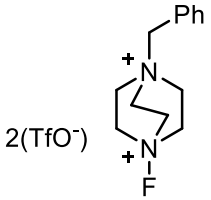
necessary), and then α,α,α-trifluorotoluene was added as internal standard and the reaction was analysed by quantitative ^{19}F NMR and mass spectroscopy (ESI+).

Selectfluor Bis(triflate)



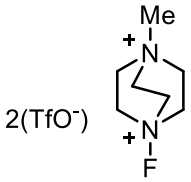
Prepared according to general procedure E. **^{1}H NMR** (400 MHz, non-deuterated acetonitrile) δ 5.35 (s, 2H), 4.76 (q, *J* = 7.4 Hz, 6H), 4.32 (t, *J* = 7.6 Hz, 6H). **^{19}F NMR** (376 MHz, non-deuterated acetonitrile) δ 48.2, -79.2. Analytical data consistent with that previously reported.[169]

3.25 1-benzyl-4-fluoro-1,4-diazabicyclo[2.2.2]octane-1,4-diium bis(triflate)



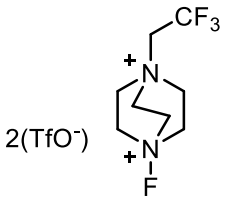
Prepared according to general procedure E. **^{1}H NMR** (400 MHz, non-deuterated acetonitrile) δ 4.75 (s, 2H), 4.63 (q, *J* = 7.4 Hz, 6H), 4.18 (t, *J* = 7.6 Hz, 6H). Aromatic protons overlap with those of the starting material and so are not reported. **^{19}F NMR** (376 MHz, non-deuterated acetonitrile) δ 50.6, -78.5. Analytical data consistent with that previously reported.[69]

Selectfluor II Bis(triflate)



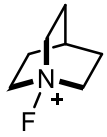
Prepared according to general procedure E. **^{1}H NMR** (400 MHz, non-deuterated acetonitrile) δ 4.69 (q, *J* = 7.7 Hz, 6H), 4.24 (t, *J* = 7.5 Hz, 6H). The protons of the Me group overlap with other resonances. ^{19}F NMR (376 MHz, non-deuterated acetonitrile) δ 47.8, -78.5. Analytical data consistent with that previously reported.[169]

3.26 1-fluoro-4-(2,2,2-trifluoroethyl)-1,4-diazabicyclo[2.2.2]octane-1,4-diium Bis(triflate)



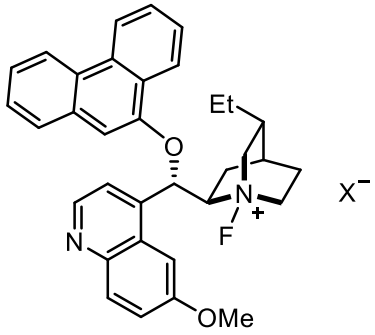
Prepared according to general procedure E. **^{1}H NMR** (400 MHz, non-deuterated acetonitrile) δ 4.81 (q, *J* = 7.4 Hz, 6H), 4.61 (q, *J* = 8.3 Hz, 2H), 4.49 (t, *J* = 7.5 Hz, 6H). **^{19}F NMR** (376 MHz, non-deuterated acetonitrile) δ 49.5, -62.0 (t, *J* = 8.3 Hz), -78.5. Analytical data consistent with that previously reported.[169]

3.31 *N*-fluoroquinuclidinium



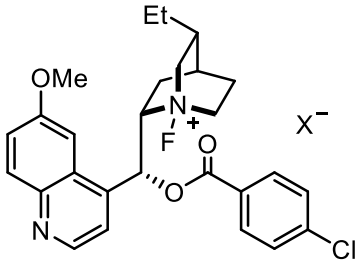
Prepared according to general procedure G. **^{19}F NMR** (376 MHz, Acetonitrile-d_3) δ 56.7. **LRMS** ESI+ m/z: [M^+] Calcd for $C_7H_{13}FN$ 130.2; Found 130.2. NMR data consistent with that previously reported.[185]

3.33 *N*-fluorohydroquinidin-9-phenanthryl ether



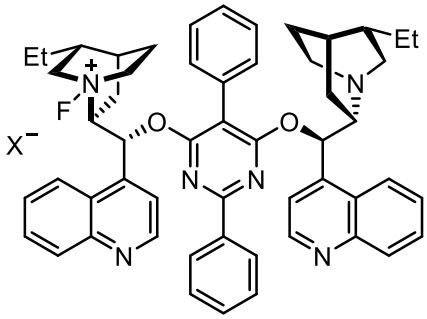
Prepared according to general procedure F (X = TfO^-) or G (X = BF_4^-). Analytical data of title compound provided after following general procedure F, with reaction performed at room temperature; **^{19}F NMR** (376 MHz, Acetonitrile-d_3) δ 37.4. **LRMS** ESI+ m/z: [M^+] Calcd for $C_{34}H_{34}FN_2O_2$ 521.3; Found 521.2.

3.34 *N*-fluorohydroquinine-4-chlorobenzoate



Prepared according to general procedure F (X = TfO^-) or G (X = BF_4^-). Analytical data of title compound provided after following general procedure F, with reaction performed at room temperature; **^{19}F NMR** (376 MHz, Acetonitrile-d_3) δ 43.0. **LRMS** ESI+ m/z: [M^+] Calcd for $C_{27}H_{29}{}^{35}ClFN_2O_3$ 483.2; Found 482.2. NMR data consistent with that previously reported.[180]

3.35 *N*-fluoro(DHQ)$_2$Pyr



Prepared according to general procedure F (X = TfO^-) or G (X = BF_4^-). The substrate was suspended in 500 µL of acetonitrile prior to addition of the fluorinating agent rather than 250 µL due to the large mass. Analytical data of title compound provided after following general procedure F, with reaction performed at room temperature; **^{19}F NMR** (376 MHz, Acetonitrile-d_3) δ 42.6. **LRMS** ESI+ m/z: [M^+] Calcd for $C_{56}H_{60}FN_6O_4$ 899.5; Found 899.4.

5.3.5 Other Experimental Procedures

General procedure for assessing the stability of xenon difluoride to [^{18}F]fluoride eluting agents

A solution of xenon difluoride in dry acetonitrile (0.2 M, 250 µL, 0.05 mmol, 1 equiv.) was added to a solution/suspension of the additive in dry acetonitrile (250 µL) in a 3.5 mL borosilicate glass vial. NOTE: For tests with Kryptofix-222 + potassium carbonate and dicyclohexano-18-crown-6 + potassium carbonate, the two additives were pre-stirred at 80 °C for 5 minutes before addition of the xenon difluoride solution. The vial was sealed and stirred at 600 RPM for 20 minutes in a pre-heated oil bath at 80 °C. Then a stock solution containing α,α,α-trifluorotoluene as an internal standard in deuterated acetonitrile (250 µL) was added and quantitative ^{19}F NMR was run immediately.

Procedure for monitoring xenon difluoride hydrolysis by ^{19}F NMR

A 2 mL stock solution of 25 mM xenon difluoride + 20 µL of α,α,α-trifluorotoluene (internal standard) in dry acetonitrile was prepared. This was used in all the following experiments.

12.5 mM Xenon Difluoride in Acetonitrile / Deuterated Acetonitrile:

To a borosilicate NMR tube was added the 25 mM xenon difluoride stock solution (0.25 mL) followed by deuterated acetonitrile (0.25 mL). The mixture was left unstirred in the NMR tube at room temperature. Quantitative ^{19}F NMR was acquired at 16, 129, and 473 minutes (time between addition of deuterated acetonitrile and end of NMR acquisition).

12.5 mM Xenon Difluoride in Acetonitrile / Deuterium Oxide:

To a borosilicate NMR tube was added the 25 mM xenon difluoride stock solution (0.25 mL) followed by deuterium oxide (0.25 mL). The mixture was left unstirred in the NMR tube at room temperature. Quantitative ^{19}F NMR was acquired at 16, 34, 54, 102, 162,

223, 282, 342 and 463 minutes (time between addition of deuterium oxide and end of NMR acquisition).

12.5 mM Xenon Difluoride and 12.5 mM Ammonium Formate in Acetonitrile / Deuterium Oxide:

To a borosilicate NMR tube was added the 25 mM xenon difluoride stock solution (0.25 mL) followed by 25 mM ammonium formate in deuterium oxide (0.25 mL). The mixture was left unstirred in the NMR tube at room temperature. Quantitative ^{19}F NMR was acquired at 15, 42, 70, 127, 133, 174, 227, 297 and 478 minutes (time between addition of 25 mM ammonium formate in deuterium oxide and end of NMR acquisition).

Comparison of the integrations of the internal standard and that of xenon difluoride in the quantitative ^{19}F NMR enabled calculation of % decomposition.

Titration of 3.1 with hydrogen fluoride

A 0.5 M stock solution of hydrogen fluoride was prepared by diluting 48% aqueous hydrogen fluoride (100 µL, 2.76 mmol) with dry acetonitrile (5.46 mL). 1 mL of this solution was diluted with 3 mL of dry acetonitrile, to afford a 0.125 M solution of hydrogen fluoride in acetonitrile. A solution of **3.1** (7.8 mg, 25 µmol) in deuterated acetonitrile (400 µL) and acetonitrile (100 µL) was prepared and added to a borosilicate NMR tube, and ^{1}H NMR was acquired. The solution of **3.1** was then titrated with the 0.125 M hydrogen fluoride. ^{1}H NMR was acquired after addition (total volume added) of 50 µL (6.25 µmol, 0.25 equiv.), 100 µL (12.5 µmol, 0.50 equiv.), 150 µL (18.75 µmol, 0.75 equiv.), 200 µL (25 µmol, 1.0 equiv.) and 400 µL (50 µmol, 2.0 equiv.) of the 0.125 M hydrogen fluoride. ^{1}H NMR spectra were referenced to acetonitrile at 1.96 ppm.[217]

Anion Exchange of TBAOTs on a QMA carbonate cartridge

A Sep-Pak Accell Plus QMA Carbonate Plus Light Cartridge, 46 mg Sorbent per Cartridge, 40 µm (SKU 186004540) was activated with 10 mL of water, then 2 mL of methanol, and the 1 mL of deuterated methanol. A solution of TBAOTs (1.6 mg, 3.75 µmol) in deuterated methanol (0.75 mL) was passed over the cartridge followed by 1 mL of air. The eluate was collected and analysed by ^{1}H NMR and IR.

5.3.6 Radiochemistry

5.3.6.1 General Information

Xenon difluoride and [$(NpNMe_3)_2C_2O_4$] were added used as stock solutions in dry acetonitrile, and ethanol respectively. The stock solutions were prepared fresh on the day polypropylene in Falcon tubes. RCCs of [^{18}F]XeF_2 and [^{18}F]3.25 were determined using radioHPLC alone.

Elution Efficiency:

Unless states otherwise, the elution efficiency was calculated as the eluted and dried radioactivity (decay-corrected to when the radioactivity trapped on the cartridge was measured) as a fraction of the radioactivity initially trapped on the QMA cartridge.

$$\%\ \text{elution efficiency} = \frac{\text{eluted and dried radioactivity (decay corrected)}}{\text{radioactivity initially on QMA cartridge}} \times 100$$

[^{18}F]Selectfluor bis(triflate) RCP

A sample of [^{18}F]Selectfluor bis(triflate) was injected into the analytical HPLC. The radioactivity of the sample vial before and after injection was measured, enabling the radioactivity injected to the HPLC to be calculated. The radioHPLC peak for the product was collected, and the radioactivity measured. All radioactivities were decay-corrected to when the radioactivity of the sample vial was measured prior to HPLC injection. The ratio of collected radioactivity to injected radioactivity was then calculated. Typically,

over 5 MBq was injected into the HPLC, so that the radioactivity collected could be measured with reasonable accuracy.

$$\%\ \mathrm{RCP} = \frac{\text{radioactivity collect from HPLC (decay corrected)}}{\text{radioactivity injected into HPLC}} \times 100$$

5.3.6.2 HPLC Methods

Method D:

Column: Phenomenex Gemini 5 µm C-18 110 Å 250 x 4.6 mm

Detection: UV (220 nm, 254 nm) and radio

Flow Rate: 1 mL min^{-1}

Mobile Phase: MeCN / 25 mM aqueous ammonium formate

0 - 12 min (45% MeCN, isocratic)

Method E:

Column: Phenomenex Gemini 5 µm C-18 110 Å 250 x 4.6 mm

Detection: UV (220 nm, 254 nm) and radio

Flow Rate: 1 mL min^{-1}

Mobile Phase: MeCN / water

0 - 12 min (45% MeCN, isocratic)

Method F:

Column: Phenomenex Gemini 5 µm C-18 110 Å 250 x 4.6 mm

Detection: UV (220 nm, 254 nm) and radio

Flow Rate: 1 mL min^{-1}

Mobile Phase: 0.1 vol% aqueous TFA

0 - 20 min (100% 0.1 vol% aqueous TFA, isocratic)

Method G:

Column: Phenomenex Gemini 5 µm C-18 110 Å 250 x 4.6 mm

Detection: UV (220 nm, 254 nm) and radio

Flow Rate: 1 mL min^{-1}

Mobile Phase: MeCN / 25 mM aqueous ammonium trifluoroacetate

0 - 20 min (5% MeCN, isocratic)

Method H:

Column: Phenomenex Gemini 5µm C18 110 Å LC column, 250 x 10 mm

Detection: UV (254 nm) and radio

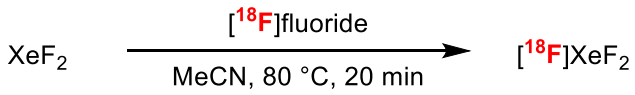
Flow Rate: 4 mL min^{-1}

Mobile Phase: 0.1 vol% aqueous TFA

0 - 20 min (100% 0.1 vol% aqueous TFA, isocratic)

5.3.6.3 Procedures

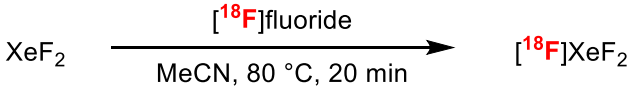
Screening of [^{18}F]fluoride elutions for preparing [^{18}F]xenon difluoride



A Sep-Pak Accell Plus QMA Carbonate Plus Light Cartridge, 46 mg Sorbent per Cartridge, 40 µm (SKU 186004540) was activated with 10 mL of water. Then 100-250 MBq of [^{18}F]fluoride in [^{18}O]H_2O was trapped on the cartridge, and then the cartridge was washed with 2 mL of water. The radioactivity on the cartridge was measured. Then the elution

solution (5 mM, 500 µL, 2.5 µmol) was passed through the cartridge into a 5 mL Wheaton V-vial. Note that for elution solutions containing a base and a solubilising agent (e.g. Kryptofix-222), a 1:2.5 ratio of base to solubilising agent was used, and the solution was 5 mM with respect to base. The eluted radioactivity was measured. If necessary, more elution solution was passed through the cartridge until a sufficient amount of the trapped radioactivity was eluted. The [^{18}F]fluoride was then dried under a flow of N_2 (at 90 °C for ethanolic solutions and 100 °C for acetonitrile / water solutions), and before the [^{18}F]fluoride was dry an additional 1 mL of solvent was added to aid azeotropic drying (ethanol or acetonitrile respectively). Once the [^{18}F]fluoride was dry, the radioactivity was measured. Then a stock solution of xenon difluoride in dry acetonitrile (0.1 M, 0.3 mL, 30 µmol) was added and the reaction was stirred at 80 °C for 20 minutes. The radioactivity was measured, and then the reaction mixture was diluted with water (100 µL) and shaken. A sample (~20 µL) was removed and diluted with 1:1 acetonitrile / water in a plastic HPLC vial. The sample was analysed immediately using HPLC method D.

Testing the effect of xenon difluoride loading



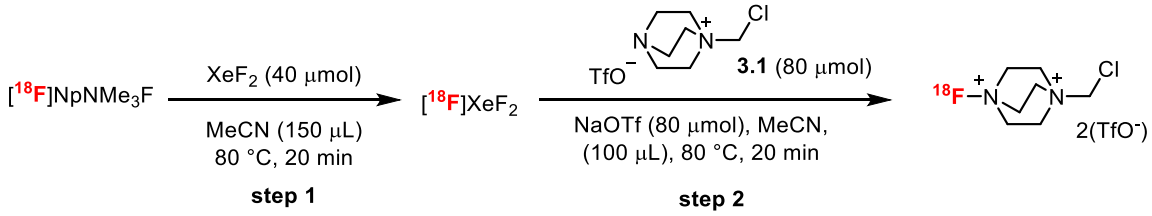
A Sep-Pak Accell Plus QMA Carbonate Plus Light Cartridge, 46 mg Sorbent per Cartridge, 40 µm (SKU 186004540) was activated with 10 mL of water. Then 70-120 MBq of [^{18}F]fluoride in [^{18}O]H_2O was trapped on the cartridge, and then the cartridge was washed with 2 mL of water. The radioactivity on the cartridge was measured. The [^{18}F]fluoride was then eluted with either TBAOTs in ethanol (5 mM, 750 µL, 3.75 µmol) or [$(Me_3NNp)_2C_2O_4$] in ethanol (5 mM, 500 µL, 2.5 µmol) into a 5 mL Wheaton V-vial. The eluted radioactivity was measured. The [^{18}F]fluoride was then dried under a flow of N_2 at

90 °C and before the [^{18}F]fluoride was dry an additional 1 mL of EtOH was added to aid azeotropic drying. Once the fluoride was dry, the radioactivity was measured. Then a stock solution of xenon difluoride in dry acetonitrile (either 0.1 M, 0.05 M, 0.025 M, 0.0167 M or 0.0125 M, 300 µL) was added and the reaction was stirred at 80 °C for 20 minutes. The radioactivity was measured, and then the reaction mixture was diluted with water (100 µL) and shaken. A sample (~20 µL) was removed and diluted with 1:1 acetonitrile / water in a plastic HPLC vial. The sample was analysed immediately using HPLC method D.

Testing the effect of the QMA cartridge counteranion

A Sep-Pak Accell Plus QMA Carbonate Plus Light Cartridge, 46 mg Sorbent per Cartridge, 40 µm (SKU 186004540) was equilibrated with 10 mL of a 0.1 M aqueous solution of the specified base, followed by 10 mL of water. The same procedure as described above for the labelling of [^{18}F]xenon difluoride was then followed.

*Synthesis of [^{18}F]Selectfluor bis(triflate) and [^{18}F]**3.25***



A Sep-Pak Accell Plus QMA Carbonate Plus Light Cartridge, 46 mg Sorbent per Cartridge, 40 µm (SKU 186004540) was activated with 10 mL of water. Then [^{18}F]fluoride in [^{18}O]H_2O was trapped on the cartridge, and then the cartridge was washed with 2 mL of ethanol. The [^{18}F]fluoride was then eluted with [$(Me_3NNp)_2C_2O_4$] in ethanol (5 mM, 500 µL, 2.5 µmol) in a 5 mL Wheaton V-vial. The cartridge was flushed into the V-vial with 1 mL of air, and then the [^{18}F]fluoride was dried at 85 °C under a flow of nitrogen N_2. An additional

1 mL ethanol was added before the [^{18}F]fluoride was dry, and then heating was continued until the [^{18}F]fluoride was dry. Then xenon difluoride (6.8 mg, 40 µmol) in dry acetonitrile (150 µmol) was added (from larger stock solution). The resulting solution was heated at 80 °C for 20 minutes. Then a suspension of DABCOnium triflate (80 µmol) and sodium triflate (14 mg, 80 µmol) in dry acetonitrile (100 µL) was added, and the mixture was heated at 80 °C for 20 minutes. The mixture was then concentrated under a flow of N_2 at 80 °C, then diluted with 2mL of 8:2 MeCN/H_2O and passed over QMA chloride (SKU: WAT023525**,** preactivated with 10 mL 0.1 M aqueous NaOTf followed by 10 mL water). The resulting solution was analysed using HPLC method F.

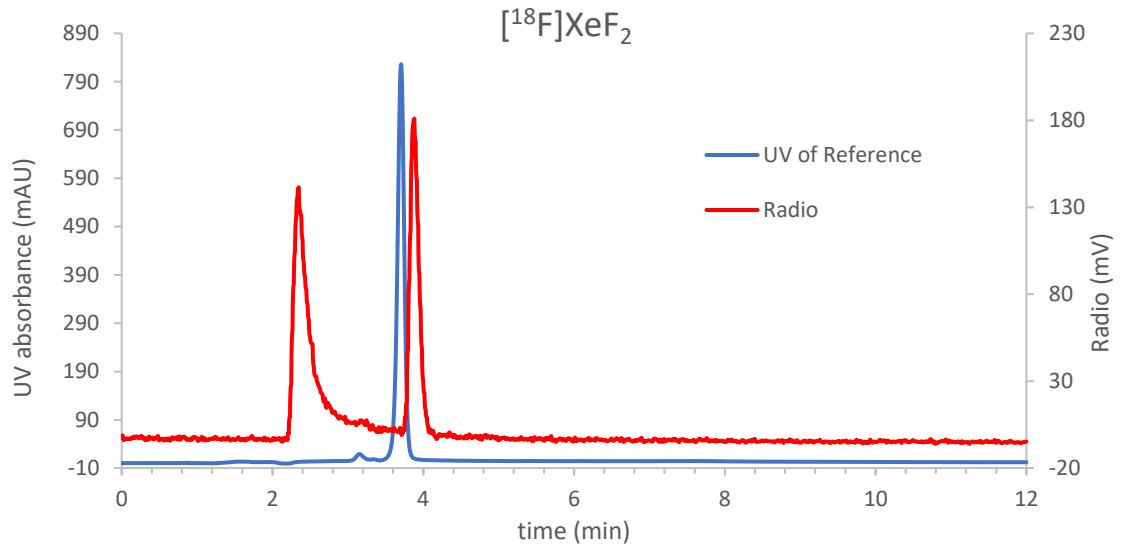
*Preparation of [^{18}F]**3.39***

[^{18}F]Selectfluor bis(triflate), prepared as described above, was dried at 100 °C under a flow of N_2. To 46 MBq of dried [^{18}F]Selectfluor bis(triflate) was added celecoxib (32 mg, 80 µmol) in $MeNO_2$ (160 uL). The reaction mixture was heated at 100 °C for 30 mins, and then analysed using HPLC method D.

5.3.6.4 Product Characterisation

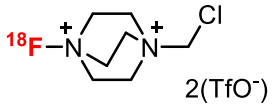
[^{18}F]Xenon difluoride

Representative HPLC trace of crude [^{18}F]xenon difluoride from optimisation reactions in Table 18, acquired using HPLC method D.

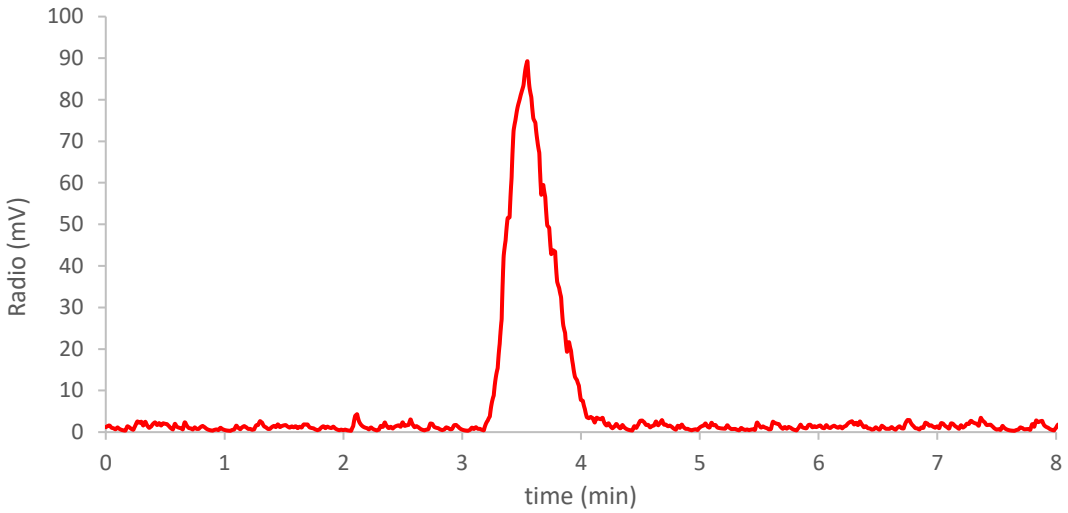


Note: HPLC method D or F was used for determining the molar activity of [^{18}F]xenon difluoride.

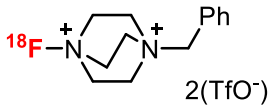
[^{18}F]Selectfluor bis(triflate)



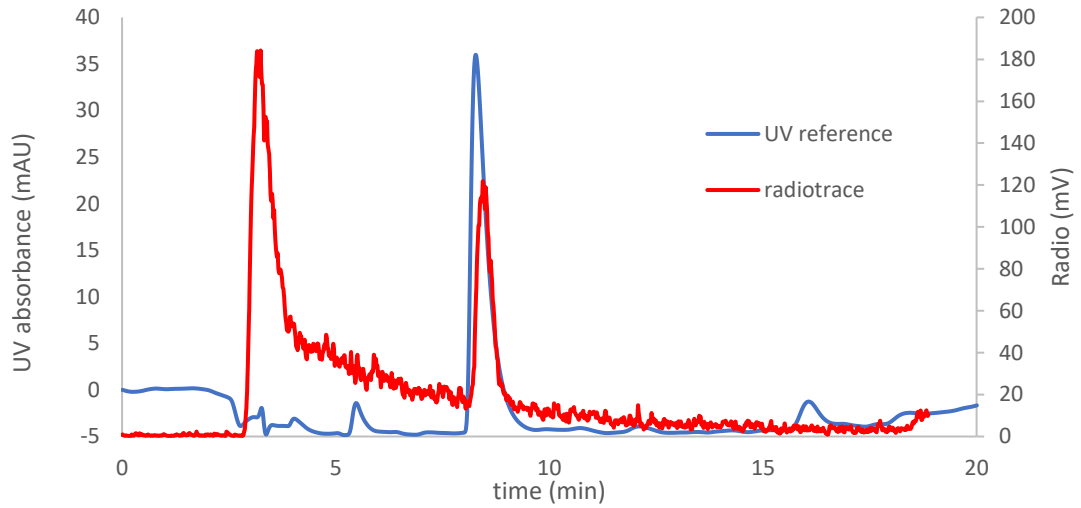
Representative HPLC trace of [^{18}F]Selectfluor prepared as described above, acquired using HPLC method F.



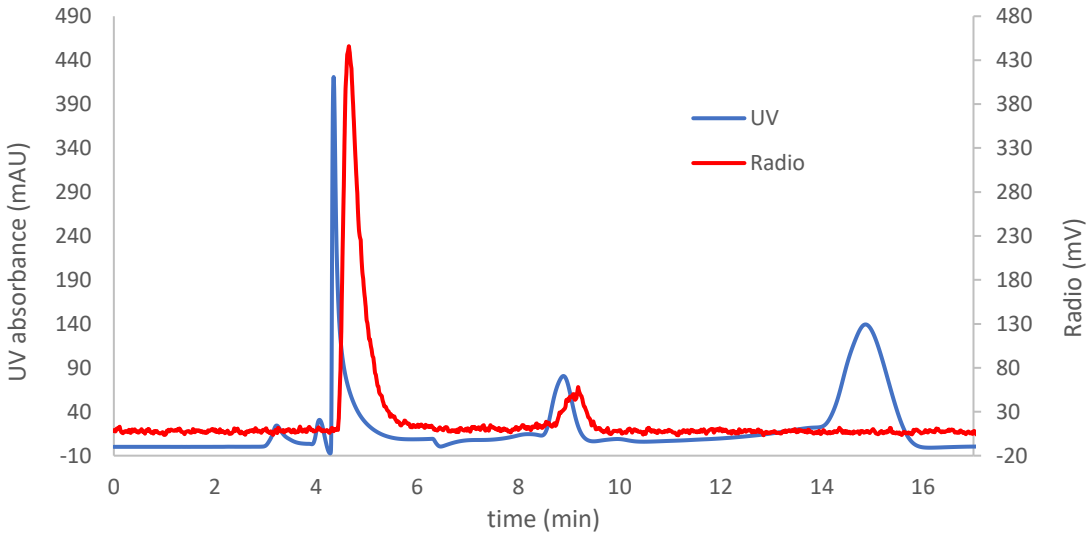
[^{18}F]3.25 1-benzyl-4-fluoro-1,4-diazabicyclo[2.2.2]octane-1,4-diium bis(triflate)



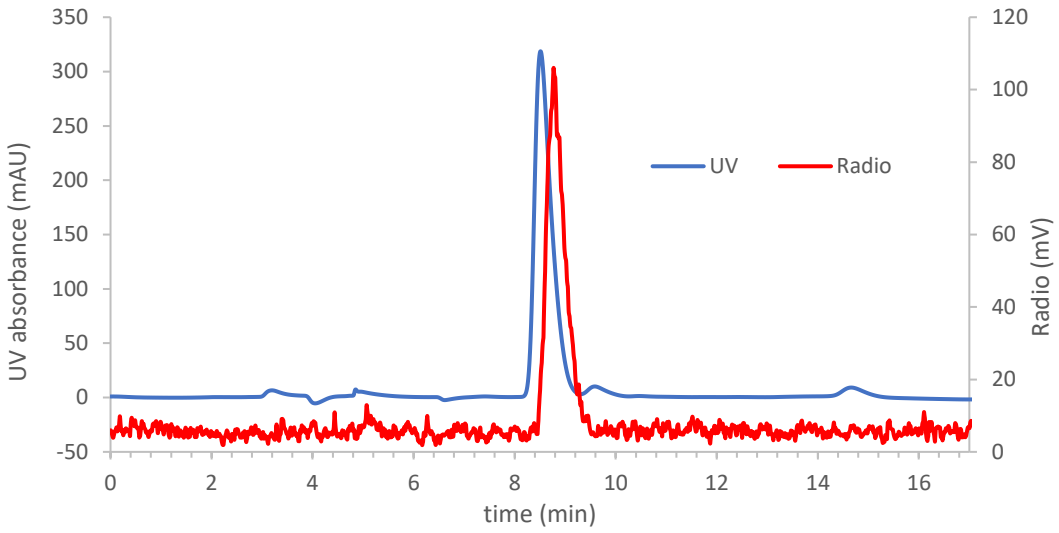
Representative HPLC trace of crude [^{18}F]**3.25** acquired using HPLC method G. This HPLC method was used for quantifying the RCC of [^{18}F]**3.25** in the optimisation reactions in Table 23.



Representative HPLC of crude [^{18}F]**3.25** using HPLC method F

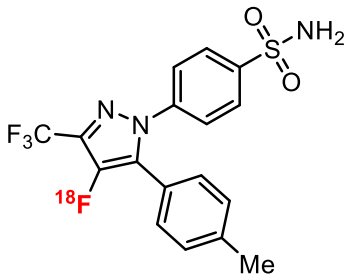


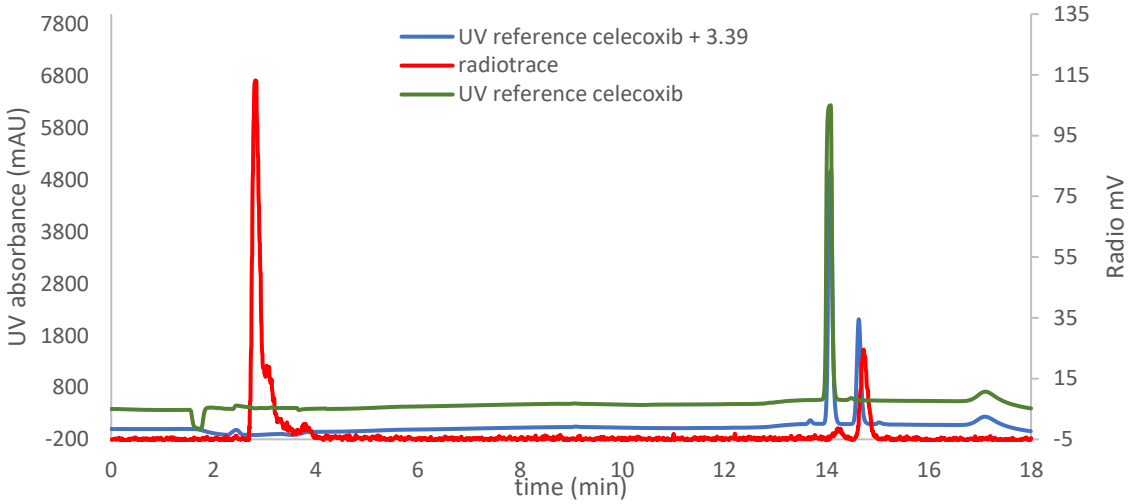
HPLC trace of [^{18}F]**3.25** using HPLC method F, following isolation by HPLC method H. Co-injected with a reference sample of **3.25.**



Note: HPLC method F was used for determining the molar activity of [^{18}F]**3.25**.

[^{18}F]3.39 4-(4-fluoro-5-(p-tolyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)benzenesulfonamide

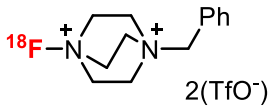


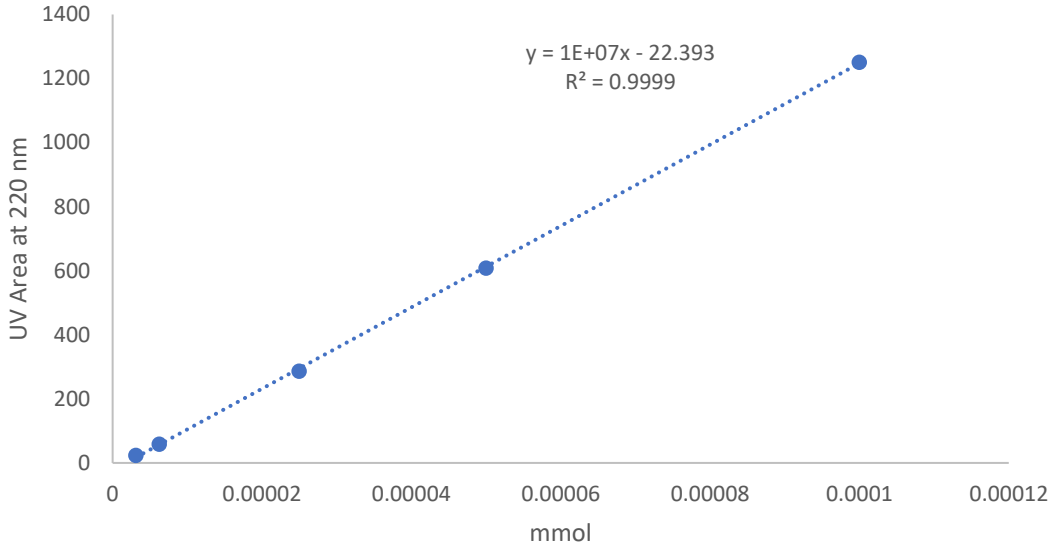


Note: two peaks are visible in the UV reference (blue trace), as **3.39** could not be separated from celecoxib by flash chromatography. To determine which of the two peaks in the UV reference was celecoxib and which was **3.39**, a sample of pure celecoxib was run separately (green trace). This confirmed that the later UV peak was for **3.39**, and hence that the peak in the radiotrace was due to [^{18}F]**3.39**.

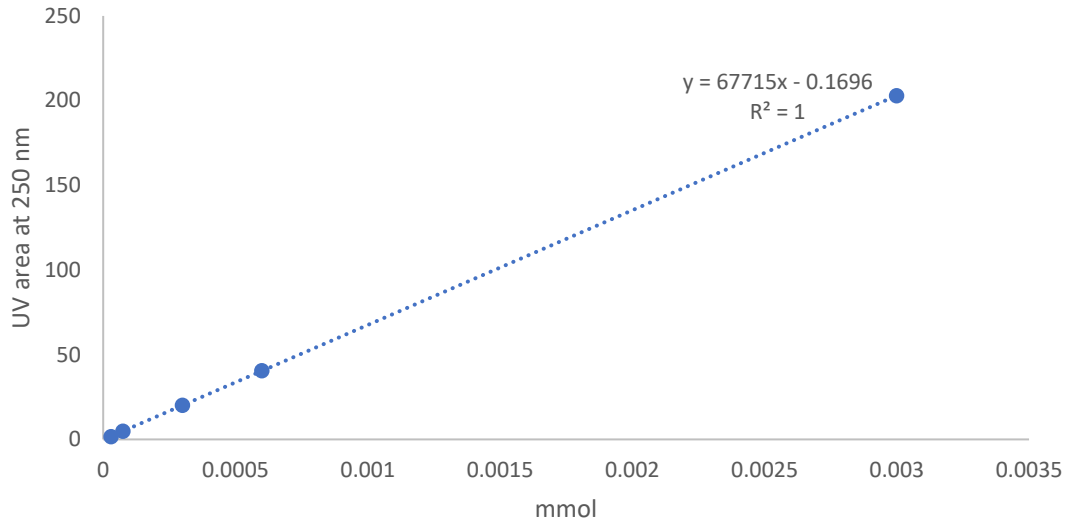
5.3.6.5 Molar activity UV calibration curves

3.25 molar activity UV calibration – HPLC method F, 220 nm



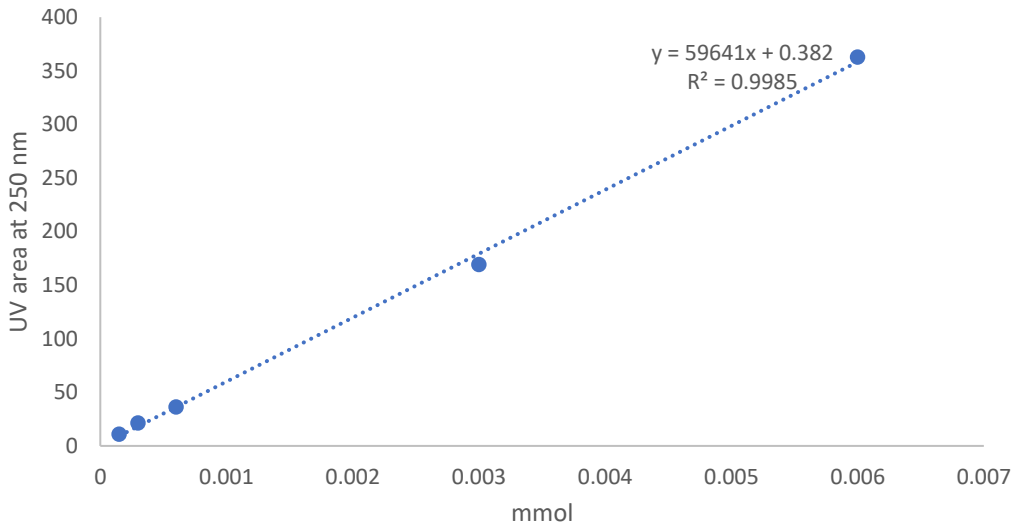


Xenon difluoride molar activity UV calibration – HPLC method E, 250 nm



Note: The calibration curve was measured using HPLC method E, but molar activity data from [^{18}F]xenon difluoride was collected using HPLC method D. Negligible difference in UV peak area was observed when the same quantity of xenon difluoride was injected using either method.

Xenon difluoride molar activity UV calibration – HPLC method F, 250 nm



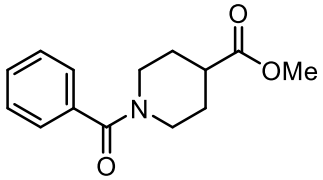
Note: The UV calibration curve for xenon difluoride using HPLC method F was different to when HPLC method D or E was used. In general, HPLC method D and the associated UV calibration curve were used for measuring molar activity of [^{18}F]xenon difluoride, but HPLC method F was used on occasion.

5.4 Experimental Procedures and Characterisation Data for Chapter 4

5.4.1 Experimental and Characterisation Data: Substrates

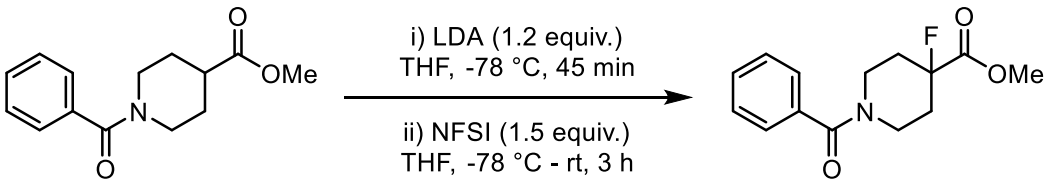
Note: Formic acid was used as a mobile phase additive in the purification of some carboxylic acids by flash chromatography. To remove traces of formic acid, the final product was azeotroped with toluene.

methyl 1-benzoylpiperidine-4-carboxylate



Prepared according to the literature procedure.[218]

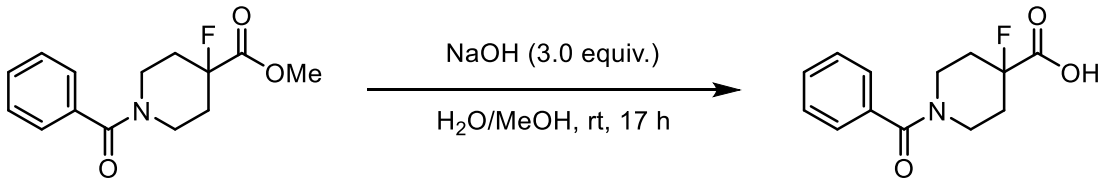
methyl 1-benzoyl-4-fluoropiperidine-4-carboxylate



2.5 M *n*-BuLi (5.2 mL, 13.1 mmol, 1.2 equiv.) was added to a solution of $^{i}Pr_2NH$ (2.0 mL, 14.2 mmol, 1.3 equiv.) in dry THF (10 mL) at –78 °C under N_2. The mixture was stirred at –78 °C for 15 minutes, then at 0 °C for 20 minutes, then cooled back to -78 °C. A solution of methyl 1-benzoylpiperidine-4-carboxylate (2.70 g, 10.9 mmol, 1.0 equiv.) in dry THF (10 mL) was added dropwise, and the mixture was then stirred at -78 °C for 45 minutes. A solution of NFSI (5.17 g, 16.4 mmol, 1.5 equiv.) in dry THF was then added dropwise at -78 °C. After complete addition, the mixture was stirred at 0 °C for 20 minutes, and then at room temperature for 3 hours. The mixture was then quenched by addition of 1 M HCl,

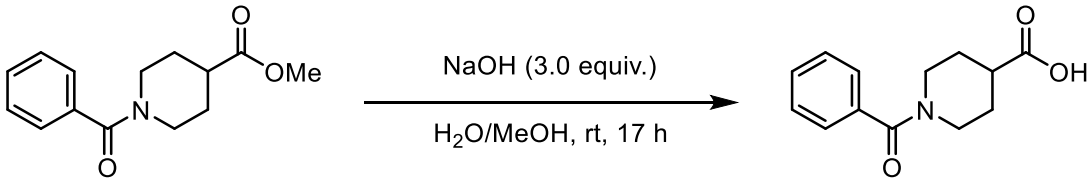
and extracted 3 times with ethyl acetate. Combined organic phases were washed with water, then brine, then dried over Na_2SO_4 and concentrated in vacuo. Flash column chromatography (50-60% ethyl acetate in pentane) afforded the product as a pale-yellow powder (2.10 g, 73% yield). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.49 – 7.37 (m, 5H), 4.63 (s, 1H), 3.81 (s, 3H), 3.78 – 3.63 (m, 1H), 3.53 – 3.09 (m, 2H), 2.35 – 1.81 (m, 4H). **^{19}F NMR** (377 MHz, Chloroform-*d*) δ -167.6 – -168.0 (m). Analytical data consistent with that previously reported.[210]

4.63A 1-benzoyl-4-fluoropiperidine-4-carboxylic acid



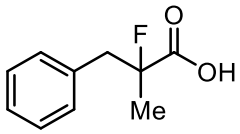
3 M aqueous NaOH (7.5 mL, 22.5 mmol, 3 equiv.) was added to a solution of methyl 1-benzoyl-4-fluoropiperidine-4-carboxylate (2.00 g, 7.5 mmol, 1 equiv.) in MeOH, and the resulting mixture was stirred at room temperature for 17 hours. The mixture was concentrated *in vacuo* to ~20 mL, then 1 M aqueous HCl (50 mL) was added, and the mixture was extracted three times with ethyl acetate. The combined organic phases were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. Flash column chromatography (5-7% MeOH in CH_2Cl_2) afforded the product as a fluffy white powder (1.25 g, 66% yield). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 10.58 (s, 1H), 7.48 – 7.36 (m, 5H), 4.85 – 4.26 (m, 1H), 3.88 – 3.55 (m, 1H), 3.51 – 2.95 (m, 2H), 2.41 – 1.74 (m, 4H). **^{19}F NMR** (377 MHz, Chloroform-*d*) δ -167.6 (td, *J* = 35.2, 17.9 Hz). Analytical data consistent with that previously reported.[210]

4.64A 1-benzoylpiperidine-4-carboxylic acid



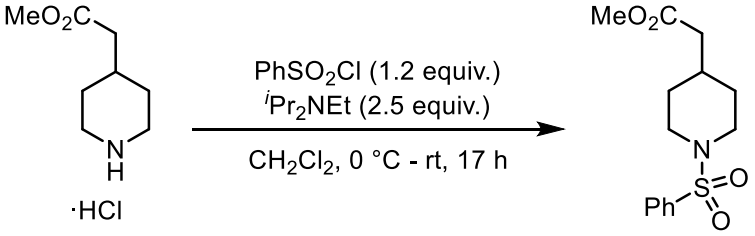
3 M Aqueous NaOH (7.5 mL, 22.5 mmol, 3.0 equiv.) was added to a solution of methyl 1-benzoylpiperidine-4-carboxylate (1.96 g, 7.5 mmol, 1.0 equiv.) in MeOH (75 mL), and the mixture was stirred at room temperature for 16 hours. The mixture was then concentrated under vacuum to a volume of approximately 10 mL, and was then diluted with water. The mixture was then washed 3 times with ethyl acetate, acidified to pH 1 with concentrated HCl, and then extracted 3 times with ethyl acetate. The combined organic extracts were dried over Na_2SO_4 and concentrated under vacuum. The product was dissolved in toluene and dried under vacuum twice to remove residual water by azeotropic drying. This afforded the crude product as a fluffy white powder. The product was further purified by flash chromatography (6-8% MeOH in CH_2Cl_2), to afford the desired product as a white powder (1.22 g, 70% yield). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 9.31 (s, 1H), 7.53 – 7.29 (m, 5H), 4.51 (s, 1H), 3.74 (s, 1H), 3.24 – 2.96 (m, 2H), 2.61 (tt, *J* = 10.6, 4.0 Hz, 1H), 2.18 – 1.56 (m, 4H). **LRMS** (ESI+) m/z: $[M+Na]^+$ Calcd for $C_{13}H_{15}NNaO_3$ 256.1; Found 256.1. Analytical data consistent with that previously reported.[219]

4.65A 2-fluoro-2-methyl-3-phenylpropanoic acid



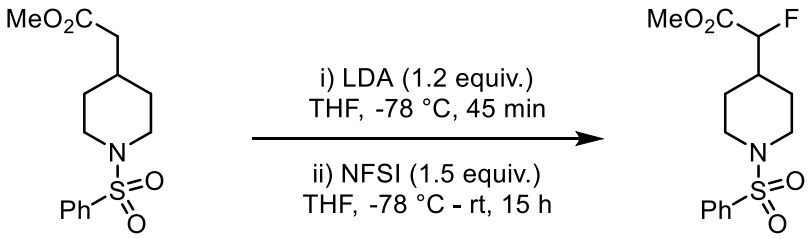
Prepared according to the literature procedure by J. Ford.[210]

methyl 2-(1-(phenylsulfonyl)piperidin-4-yl)acetate



Prepared by J. Ford. Characterised by R. Szpera. A solution of benzene sulphonyl chloride (0.77 mL, 6 mmol, 1.2 equiv.) was added to a mixture of methyl 2-(piperidin-4-yl)acetate hydrochloride (968 mg, 5 mmol, 1 equiv.) and $^{i}Pr_2NEt$ (2.17 mL, 12.5 mmol, 2.5 equiv.) in dry CH_2Cl_2 (15 mL) at 0 °C. The reaction was then stirred at room temperature for 3 hours. Following aqueous work up, the product was purified by flash chromatography (ethyl acetate/pentane) to afford the product as a white powder (0.869 g, 58% yield). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.79 – 7.71 (m, 2H), 7.63 – 7.56 (m, 1H), 7.56 – 7.48 (m, 2H), 3.82 – 3.73 (m, 2H), 3.63 (s, 3H), 2.27 (td, *J* = 12.0, 2.5 Hz, 2H), 2.21 (d, *J* = 6.8 Hz, 2H), 1.83 – 1.64 (m, 3H), 1.42 – 1.27 (m, 2H). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 172.6, 136.3, 132.8, 129.1, 127.8, 51.7, 46.3, 40.4, 32.2, 31.3. **IR** 2922 (w), 2846 (w), 1734 (s), 1339 (m), 1167 (s), 935 (w), 740 (s). **MP** 135-138 °C. **HRMS** (ESI+) m/z: $[M+Na]^+$ Calcd for $C_{14}H_{19}O_4NNaS$ 320.0927; Found 320.0928.

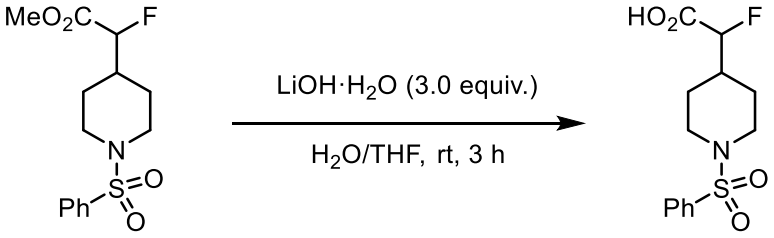
methyl 2-fluoro-2-(1-(phenylsulfonyl)piperidin-4-yl)acetate



2.5 M *n*-BuLi (1.1 mL, 2.76 mmol, 1.2 equiv.) was added to a solution of $^{i}Pr_2NH$ (422 µL, 2.99 mmol, 1.3 equiv.) in dry THF (2 mL) at -78 °C under N_2. The mixture was stirred at -78 °C for 20 minutes, then at 0 °C for 20 minutes, then cooled back to -78 °C. A solution of methyl 2-(1-(phenylsulfonyl)piperidin-4-yl)acetate (683 mg, 2.3 mmol, 1.0 equiv.) in dry THF (8 mL) was added dropwise (NOTE: this mixture had to be heated to solubilise the substrate), and the mixture was then stirred at -78 °C for 20 minutes, then at 0 °C for 30 minutes, then cooled back to -78 °C. A solution of NFSI (942 mg, 2.99 mmol, 1.3 equiv.) in dry THF (5 mL) was then added dropwise at -78 °C. After complete addition, the mixture was stirred at -78 °C for 30 minutes, and then at room temperature for 15 hours. The mixture was diluted with water and extracted 3 times with CH_2Cl_2. Combined organic phases were washed with brine then dried over Na_2SO_4 and concentrated in vacuo. Flash column chromatography (25-33% ethyl acetate in pentane) afforded the product as a pale-yellow oil (163 mg, 22% yield). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.80 – 7.72 (m, 2H), 7.60 (ddt, *J* = 8.3, 6.5, 1.4 Hz, 1H), 7.57 – 7.49 (m, 2H), 4.71 (dd, *J* = 48.6, 4.6 Hz, 1H), 3.91 – 3.82 (m, 2H), 3.77 (s, 3H), 2.38 – 2.17 (m, 2H), 1.95 – 1.55 (m, 5H). **^{19}F NMR** (377 MHz, Chloroform-*d*) δ -198.4 (dd, *J* = 48.7, 21.9 Hz). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 169.0 (d, *J* = 24.0 Hz), 136.2, 132.8, 129.1, 127.6, 91.2 (d, *J* = 188.0 Hz), 52.4, 45.8 (d, *J* = 5.0 Hz), 38.1 (d, *J* = 20.6 Hz), 26.9 (d, *J* = 3.5 Hz), 25.4 (d, *J* = 4.8 Hz). **IR** 2953 (w), 1759 (m),

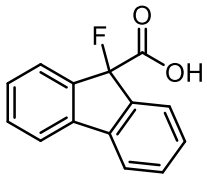
1338 (m), 1219 (w), 1168 (s), 1093 (m), 740 (s). **MP** 80–82 °C. **HRMS** (ESI+) m/z: $[M+H]^+$ Calcd for $C_{14}H_{19}O_4NFS$ 316.1013; Found 316.1016.

4.66A 2-fluoro-2-(1-(phenylsulfonyl)piperidin-4-yl)acetic acid



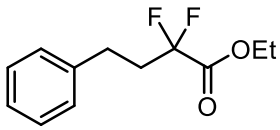
Prepared by J. Ford. Characterised by R. Szpera. A solution of lithium hydroxide monohydrate (126 mg, 1.40 mmol, 3.0 equiv.) in water (1.2 mL) was added to a solution of methyl 2-fluoro-2-(1-(phenylsulfonyl)piperidin-4-yl)acetate (148 mg, 0.47 mmol, 1 equiv.) in THF (1.2 mL). The mixture was stirred for 3 hours at room temperature. The reaction mixture was then acidified to pH 1 with 6 M aqueous HCl, and was then extracted three times with ethyl acetate. The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by flash chromatography (1% formic acid, 5% CH_2Cl_2 94% ethyl acetate) to afford the product as a white powder (0.118 g, 83% yield). **^{1}H NMR** (400 MHz, Methanol-d_4) δ 7.81 – 7.74 (m, 2H), 7.70 – 7.64 (m, 1H), 7.63 – 7.57 (m, 2H), 4.89 (s, 3H), 4.79 (dd, *J* = 48.9, 3.9 Hz, 1H), 3.88 – 3.78 (m, 2H), 2.37 – 2.23 (m, 2H), 1.95 – 1.75 (m, 2H), 1.73 – 1.64 (m, 1H), 1.63 – 1.49 (m, 2H). **^{13}C NMR** (101 MHz, Methanol-*d*4) δ 172.2 (d, *J* = 24.4 Hz), 137.7, 134.1, 130.3, 128.7, 92.2 (d, *J* = 184.2 Hz), 47.1 (d, *J* = 7.3 Hz), 39.1 (d, *J* = 20.3 Hz), 28.2 (d, *J* = 3.2 Hz), 26.4 (d, *J* = 4.7 Hz). **^{19}F NMR** (377 MHz, Methanol-d_4) δ -200.2 (dd, *J* = 49.0, 23.9 Hz). **IR** 2363 (w), 1742 (br, m), 1468 (m), 1336 (s), 1168 (s), 1093 (m), 932 (m), 740 (s). **MP** 143-145 °C. **HRMS** (ESI+) m/z: $[M+H]^+$ Calcd for $C_{13}H_{17}O_4NFS$ 302.0857; Found 302.0858.

4.67A 9-fluoro-9H-fluorene-9-carboxylic acid



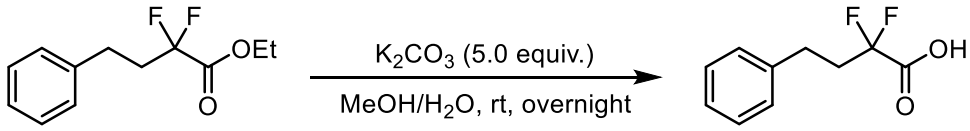
Prepared according to the literature procedure by J. Sap.[209]

ethyl 2,2-difluoro-4-phenylbutanoate



Prepared according to the literature procedure.[220] **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.30 (m, *J* = 7.1, 1.0 Hz, 2H), 7.25 – 7.16 (m, 3H), 4.28 (q, *J* = 7.2 Hz, 2H), 2.85 – 2.76 (m, 2H), 2.49 – 2.29 (m, 2H), 1.34 (t, *J* = 7.1 Hz, 3H). **^{19}F NMR** (377 MHz, Chloroform-*d*) δ -106.37 (t, *J* = 16.5 Hz).

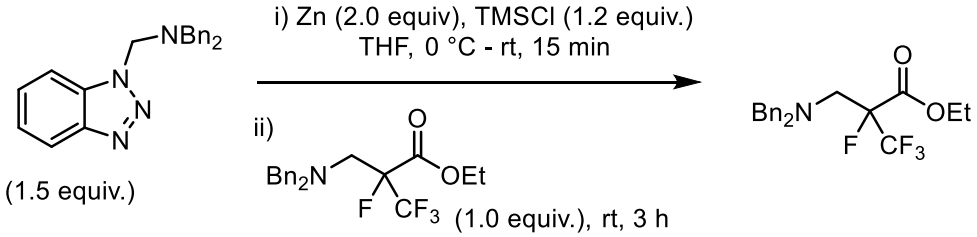
4.68A 2,2-difluoro-4-phenylbutanoic acid



A solution of K_2CO_3 (2.76 g, 20.0 mmol, 5.0 equiv.) in water (7 mL) was added to a solution of ethyl 2,2-difluoro-4-phenylbutanoate (913 mg, 4.0 mmol, 1.0 equiv.) in MeOH (14 mL). The mixture was stirred overnight at room temperature, and was then diluted with water, and washed 2 times with ethyl acetate. The mixture was then acidified to pH 1 with 6 M aqueous HCl, and extracted 3 times with ethyl acetate. The combined organic phases were dried over Na_2SO_4 and concentrated under vacuum. The crude was purified by flash

chromatography (1% formic acid, 30% ethyl acetate, 69% pentane) to afford the product as a beige solid (517 mg, 64% yield). Traces of formic acid left from flash chromatography were removed by azeotroping with toluene. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.34 – 7.27 (m, 2H), 7.25 – 7.18 (m, 3H), 6.97 (br s, 1H), 2.92 – 2.77 (m, 2H), 2.55 – 2.33 (m, 2H). **^{19}F NMR** (377 MHz, Chloroform-*d*) δ -106.9 (t, *J* = 16.6Hz, 2F). Analytical data consistent with that previously reported.[221]

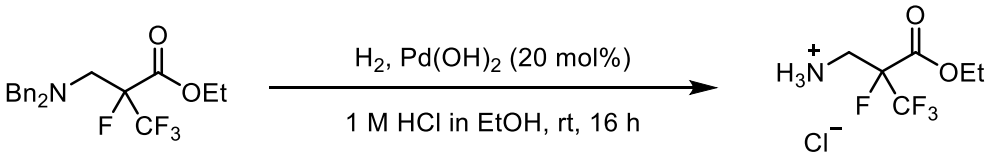
ethyl 2-((dibenzylamino)methyl)-2,3,3,3-tetrafluoropropanoate



Zinc powder (327 mg, 5.0 mmol, 2 equiv.) was added to a dry RBF, and then the flask was evacuated and refilled with nitrogen three times. Dry THF (7.5 mL, 0.33 M) was then added, followed by trimethylsilyl chloride (0.38 mL, 3.0 mmol, 1.2 equiv.). The suspension was stirred at RT under nitrogen for 15 minutes. The suspension was then cooled to 0 °C, and 1-(Dibenzylaminomethyl)benzotriazole (1.23 g, 3.75 mmol, 1.5 equiv.) was added all at once. Then ethyl 2-bromo-2,3,3,3-tetrafluoropropanoate (633 mg, 2.5 mmol, 1 equiv.) was added dropwise, and the mixture was then stirred for 3 hours at room temperature. The mixture was then diluted with ethyl acetate and filtered through celite to remove zinc salts. The filtrate was washed with 1 M aqueous HCl (the product remains in the organic phase), then saturated aqueous sodium bicarbonate, then brine, and then dried over Na_2SO_4 and concentrated in vacuo. Purification by flash chromatography (0-2% ethyl

acetate in pentane) afford the product as a colourless oil (605 mg, 63% yield). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.47 – 7.27 (m, 10H), 4.43 (dq, *J* = 10.7, 7.1 Hz, 1H), 4.11 (dq, *J* = 10.7, 7.1 Hz, 1H), 4.00 (d, *J* = 13.7 Hz, 2H), 3.52 (d, *J* = 13.7 Hz, 2H), 3.46 (dd, *J* = 35.5, 14.7 Hz, 1H), 3.20 (dd, *J* = 14.7, 12.9 Hz, 1H), 1.27 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 163.6 (d, *J* = 26.4 Hz), 138.0, 129.3, 128.4, 127.4, 121.3 (qd, *J* = 286.0, 28.6 Hz), 95.9 (dq, *J* = 201.6, 29.5 Hz), 62.9, 59.0 (d, *J* = 3.2 Hz), 52.9 (d, *J* = 18.0 Hz), 13.8. **^{19}F NMR** (376 MHz, Chloroform-*d*) δ -76.7 (d, *J* = 7.0 Hz), -176.1 (ddq, *J* = 34.6, 13.8, 7.1 Hz). **IR** 2811 (w), 1772 (s), 1496 (w), 1454 (w), 1252 (s), 1203 (s), 1062 (m), 971 (w), 699 (s). **HRMS** (ESI+) m/z: $[M+H]^+$ Calcd for $C_{20}H_{22}O_2NF_4$ 384.1581; Found 384.1581.

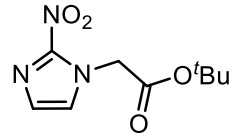
ethyl 2-(aminomethyl)-2,3,3,3-tetrafluoropropanoate hydrochloride



A solution of ethyl 2-((dibenzylamino)methyl)-2,3,3,3-tetrafluoropropanoate (575 mg, 1.5 mmol, 1 equiv.) in 1 M HCl in EtOH (7.5 mL, prepared by diluting concentrated aqueous HCl with EtOH) was added to an RBF containing 20% $Pd(OH)_2$ on carbon (210 mg, 0.30 mmol, 20 mol%). The flask was evacuated and backfilled the hydrogen gas 6 times, and then left stirring under hydrogen at room temperature for 16 hours. The mixture was then filtered through celite and concentrated under vacuum to afford a yellow residue that was triturated with diethyl ether to afford the product as a white powder (286 mg, 80% yield). **^{1}H NMR** (400 MHz, Methanol-d_4) δ 4.46 (m, 2H), 3.91 (dd, *J* = 26.1, 14.5 Hz, 1H), 3.78 (dd, *J* = 14.5, 12.6 Hz, 1H), 1.37 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR** (101

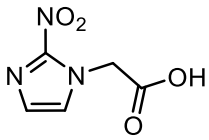
MHz, Methanol-d_4) δ 162.7 (d, *J* = 24.3 Hz), 122.0 (qd, *J* = 285.3, 27.4 Hz), 91.6 (dq, *J* = 206.6, 32.5 Hz), 65.9, 40.2 (dq, *J* = 19.9, 1.9 Hz), 14.0. **^{19}F NMR** (376 MHz, Methanol-d_4) δ -78.7 (d, *J* = 7.9 Hz), -181.5 (ddq, *J* = 26.2, 12.8, 7.9 Hz). **IR** 3502 (br, w), 2859 (br, w), 1760 (s), 1518 (w), 1283 (s), 1185 (s), 1022 (m), 854 (w). **MP** 132-135 °C. **HRMS** (ESI+) m/z: [M-Cl]$^+$ Calcd for $C_6H_{10}O_2NF_4$ 204.0642; Found 204.0644.

tert-butyl 2-(2-nitro-1H-imidazol-1-yl)acetate



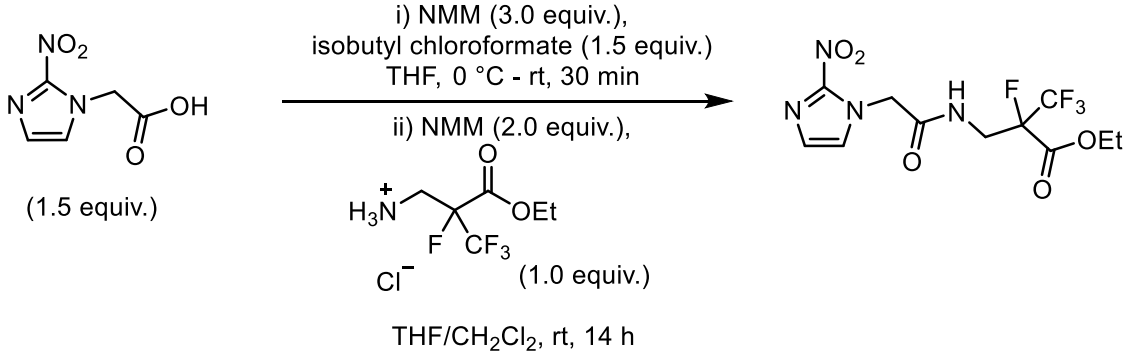
Prepared according to the literature procedure.[222]

2-(2-nitro-1H-imidazol-1-yl)acetic acid



Prepared according to the literature procedure from *tert*-butyl 2-(2-nitro-1H-imidazol-1-yl)acetate, however the reaction was left for 4 hours rather than 1 hour to ensure so the reaction could run to completion.[222]

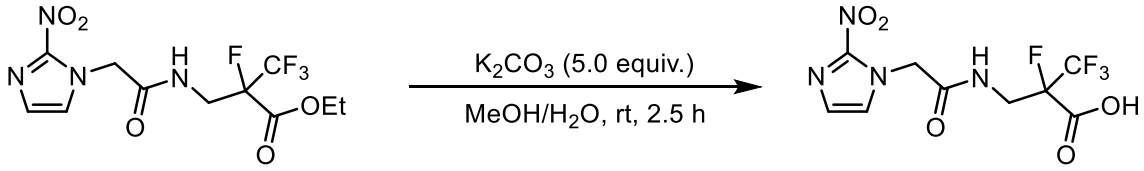
ethyl 2,3,3,3-tetrafluoro-2-((2-(2-nitro-1H-imidazol-1-yl)acetamido)methyl)propanoate



A solution of 2-(2-nitro-1H-imidazol-1-yl)acetic acid (213 mg, 1.35 mmol, 1.5 equiv.) and *N*-methylmorpholine (296 µL, 2.7 mmol, 3.0 equiv.) in dry THF (1 mL) was added over 10 minutes to a solution of isobutyl chloroformate (176 µL, 1.35 mmol, 1.5 equiv.) in dry THF (1 mL) under N_2 at 0 °C. The mixture was stirred at room temperature for 30 minutes. A solution/suspension of ethyl 2-(aminomethyl)-2,3,3,3-tetrafluoropropanoate hydrochloride (216 mg, 0.90 mmol, 1.0 equiv.) and *N*-methylmorpholine (200 µL, 1.8 mmol, 2.0 equiv.) in dry THF (5 mL) and dry CH_2Cl_2 (5 mL) was then added, and the resulting mixture was stirred at room temperature under N_2 for 14 hours. The reaction mixture was then diluted with CH_2Cl_2, washed 2 times with 1 M aqueous HCl, then with saturated aqueous $NaHCO_3$, then with brine, then dried over Na_2SO_4 and concentrated under vacuum. The crude product was purified by flash chromatography (2-4% MeOH in CH_2Cl_2) to afford the desired product as an orange residue (194 mg, 61% yield). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.19 (d, *J* = 1.1 Hz, 1H), 7.15 (d, *J* = 1.1 Hz, 1H), 6.91 (dd, *J* = 8.0, 4.7 Hz, 1H), 5.18 – 5.00 (m, 2H), 4.47 – 4.23 (m, 3H), 3.75 (ddd, *J* = 14.8, 12.5, 4.6 Hz, 1H), 1.30 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (126 MHz, Methanol-d_4) δ 168.5, 163.9 (d, *J* = 25.5 Hz), 146.4, 129.3, 128.4, 122.5 (qd, *J* = 284.8, 27.9 Hz), 93.5 (dq, *J* = 201.5, 30.8 Hz), 64.8, 50.6 (d, *J* = 521.9 Hz), 40.8 (d, *J* = 20.7 Hz), 14.1. **^{19}F NMR** (377 MHz, Chloroform-*d*) δ -

76.7 (d, *J* = 8.0 Hz, 3F), -178.5 (q, *J* = 7.9 Hz, 1F). **IR** 3299 (w, br), 2923 (w), 1755 (m), 1694 (m), 1544 (m), 1494 (m), 1371 (s), 1159 (s), 842 (w). **HRMS** (ESI-) m/z: $[M-H]^-$ Calcd for $C_{11}H_{11}O_5N_4F_4$ 355.0671; Found 355.0662.

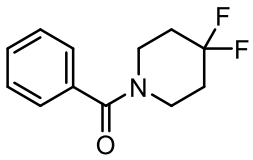
4.69A 2,3,3,3-tetrafluoro-2-((2-(2-nitro-1H-imidazol-1-yl)acetamido)methyl)propanoic acid



A solution of the ester (107 mg, 0.30 mmol, 1 equiv.) in MeOH (1 mL) was added to a solution of K_2CO_3 (207 mg, 1.50 mmol, 5 equiv.) in water (0.5 mL), and the resulting mixture was stirred vigorously at room temperature for 2.5 hours (TLC showed complete consumption of the starting material). The reaction mixture was then diluted with water (5 mL) and washed with ethyl acetate. The reaction mixture was acidified to pH 1 with 6 M aqueous HCl, and was then extracted three times with ethyl acetate. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo to afford the product as a white powder (90 mg, 91% yield). **^{1}H NMR** (400 MHz, Methanol-*d*$_4$) δ 7.43 (d, *J* = 1.2 Hz, 1H), 7.16 (d, *J* = 1.2 Hz, 1H), 5.20 (s, 2H), 4.25 – 4.06 (m, 1H), 3.89 (t, *J* = 14.7 Hz, 1H). **^{13}C NMR** (126 MHz, Methanol-*d*$_4$) δ 168.6, 165.5 (d, *J* = 25.1 Hz), 146.3, 129.3, 128.4, 122.7 (qd, *J* = 284.8, 28.3 Hz), 93.3 (dq, *J* = 200.5, 30.3 Hz), 52.6, 40.8 (dd, *J* = 20.8, 2.1 Hz). **^{19}F NMR** (377 MHz, Methanol-*d*$_4$) δ -78.3 (d, *J* = 7.5 Hz), -179.6 (ddt, *J* = 27.7, 14.7, 7.3 Hz). **IR** 3309 (w, br), 1750 (m), 1694 (m), 1499 (m), 1372 (s), 1205 (m), 1157 (m), 778 (m). **MP** 188-191 °C. **HRMS** (ESI+) m/z: $[M-+H]^+$ Calcd for $C_9H_9O_5N_4F_4$ 329.0504; Found 329.0505.

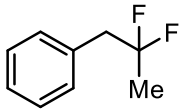
5.4.2 Experimental and Characterisation Data: References

4.64B (4,4-difluoropiperidin-1-yl)(phenyl)methanone



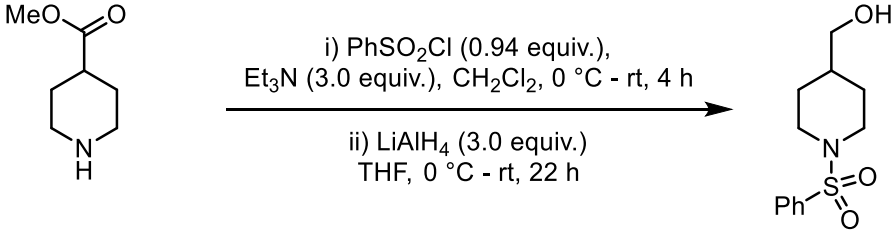
Prepared from 1-benzoyl-4-fluoropiperidine-4-carboxylic acid **4.63A** according to the literature procedure.[210]

4.65B (2,2-difluoropropyl)benzene



Prepared according to the literature procedure.[210]

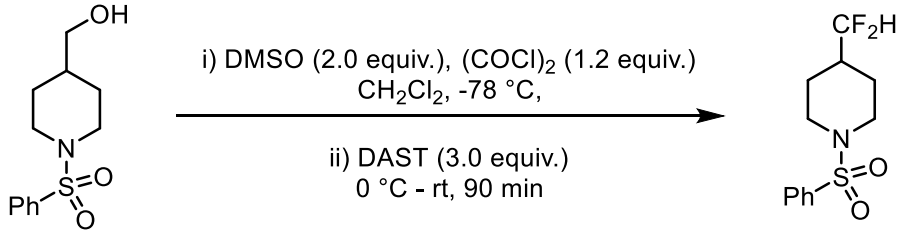
(1-(phenylsulfonyl)piperidin-4-yl)methanol



Benzene sulphonyl chloride (1.8 mL, 14 mmol, 0.94 equiv.) was added to a solution of methyl piperidine-4-carboxylate (2.03 mL, 15 mmol, 1.0 equiv.) and dry triethylamine (6.27 mL, 45 mmol, 3.0 equiv.) in dry CH_2Cl_2 (30 mL) at 0 °C. The mixture was stirred at 0 °C for 2 hours then at room temperature for 2 hours. The reaction mixture was diluted with CH_2Cl_2 and washed twice with 1 M aqueous HCl, and then washed with brine. The organic phase was dried over Na_2SO_4 and concentrated under vacuum. The resulting

material was dissolved in dry THF (15 mL), and added to a suspension of lithium aluminium hydride (1.71 g, 45 mmol, 3.0 equiv.) in dry THF (45 mL) under N_2 at 0 °C. The mixture was allowed to warm to room temperature and stirred for 22 hours. The mixture was then cooled to 0 °C, and then water (2 mL) was added slowly, followed by 15% aqueous NaOH (2 mL), and then finally more water (6 mL). The mixture was stirred at room temperature for a further 15 minutes, then $MgSO_4$ was added to form a slurry, which was stirred for 15 minutes. The mixture was then filtered, and the filter cake was washed with THF. The filtrate was concentrated under vacuum, and the resulting crude product was purified by flash chromatography (75-100% ethyl acetate in pentane) to afford the product as a white powder (1.39 g, 36% yield over 2 steps). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.81 – 7.72 (m, 2H), 7.64 – 7.57 (m, 1H), 7.56 – 7.51 (m, 2H), 3.90 – 3.79 (m, 2H), 3.47 (d, *J* = 6.0 Hz, 2H), 2.36 – 2.20 (m, 2H), 1.85 – 1.72 (m, 2H), 1.51 – 1.21 (m, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 136.4, 132.8, 129.1, 127.7, 67.1, 46.2, 37.9, 28.2. **IR** 3408 (br, w), 2920 (w), 2851 (w), 1466 (w), 1336 (m), 1167 (s), 1095 (m), 932 (m), 740 (s). **MP** 82-85 °C. **HRMS** (ESI+) m/z: $[M+H]^+$ Calcd for $C_{12}H_{18}O_3NS$ 256.1002; Found 256.1002.

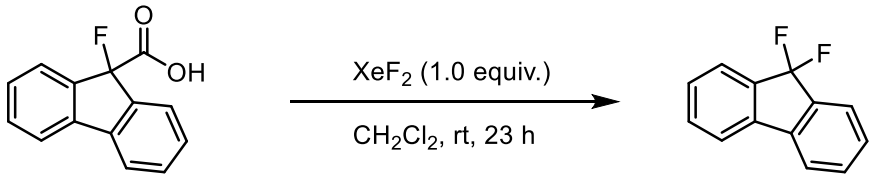
4.66B 4-(difluoromethyl)-1-(phenylsulfonyl)piperidine



DMSO (710 µL, 10.0 mmol, 2.0 equiv.) was added dropwise to a solution of oxalyl chloride (515 µL, 6.0 mmol, 1.2 equiv.) in dry CH_2Cl_2 (10 mL) at -78 °C under nitrogen. The mixture was stirred for 10 minutes at -78 °C and then a solution of (1-(phenylsulfonyl)piperidin-

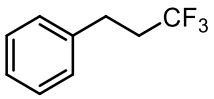
4-yl)methanol (1.275 g, 5.0 mmol, 1.0 equiv.) in CH_2Cl_2 (10 mL) was added dropwise. Stirring was continued at -78 °C for 20 minutes, over which time the reaction mixture solidified. The reaction mixture was diluted with dry CH_2Cl_2 (10 mL) and warmed to 0 °C. As the reaction mixture was warming, triethylamine was added, and the mixture was stirred at 0 °C for 30 minutes. Saturated aqueous sodium bicarbonate was then added, and the reaction mixture was extracted with CH_2Cl_2 three times. The combined organic phases were dried over Na_2SO_4 and concentrated under vacuum. The crude aldehyde was dissolved in dry CH_2Cl_2 (2 mL) and added dropwise to DAST (1.98 mL, 15.0 mmol, 3.0 equiv.) at 0 °C under nitrogen. The mixture was stirred at room temperature for 90 minutes, and was then diluted with CH_2Cl_2, cooled to 0 °C, and quenched by addition of saturated aqueous sodium bicarbonate. The organic phase was separated, and the aqueous phase was extracted twice with CH_2Cl_2. The combined organic phases were dried over Na_2SO_4 and concentrated under vacuum. The resulting crude product was purified by flash chromatography (20% ethyl acetate in pentane) to afford the desired product as a white solid (866 mg, 63% yield over 2 steps). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.78 – 7.71 (m, 2H), 7.63 – 7.57 (m, 1H), 7.56 – 7.50 (m, 2H), 5.55 (td, *J* = 56.4, 4.5 Hz, 1H), 3.93 – 3.81 (m, 2H), 2.26 (td, *J* = 12.0, 2.6 Hz, 2H), 1.86 – 1.75 (m, 2H), 1.76 – 1.59 (m, 1H), 1.59 – 1.45 (m, 2H). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 136.2, 133.0, 129.2, 127.7, 117.9 (t, *J* = 242.0 Hz), 45.4, 39.4 (t, *J* = 20.6 Hz), 24.4 (t, *J* = 4.9 Hz). **^{19}F NMR** (377 MHz, Chloroform-*d*) δ -123.3 (dd, *J* = 56.7, 12.5 Hz). **IR** 2963 (w), 1447 (w), 1336 (s), 1165 (s), 1096 (w), 1050 (s), 927 (m), 691 (m). **MP** 90-93 °C. **HRMS** (ESI+) m/z: $[M+H]^+$ Calcd for $C_{12}H_{16}O_2NF_2S$ 276.0864; Found 276.0866.

4.67B 9,9-difluoro-9H-fluorene



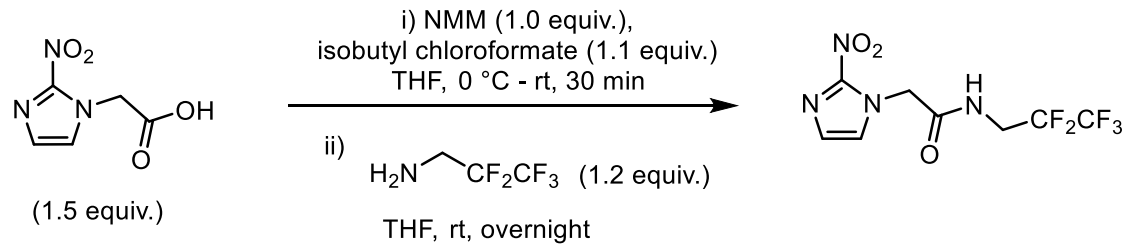
Xenon difluoride (0.12 g, 0.70 mmol, 1.0 equiv.) was added to a solution of 9-fluoro-9H-fluorene-9-carboxylic acid (0.16 g, 0.70 mmol, 1.0 equiv.) in dry CH_2Cl_2 (10 mL) in a polypropylene Falcon tube. The mixture was stirred at room temperature for 23 hours with the lid loosely screwed on to allow gasses to vent. The mixture was then diluted with pentane and washed 2 times with saturated aqueous $NaHCO_3$. The organic was then dried over Na_2SO_4 and concentrated under vacuum to afford a yellow solid. This crude product was purified by flash chromatography (10% CH_2Cl_2 in pentane) to afford the desired product as a white solid (29 mg, 21% yield). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.66 – 7.61 (m, 2H), 7.58 (dt, *J* = 7.6, 1.1 Hz, 2H), 7.47 (tq, *J* = 7.5, 1.0 Hz, 2H), 7.34 (td, *J* = 7.5, 1.1 Hz, 2H). **^{19}F NMR** (377 MHz, Chloroform-*d*) δ -111.5 (2F). Analytical data consistent with that previously reported.[209]

4.68B (3,3,3-trifluoropropyl)benzene



Purchased from Fluorochem.

4.69B EF5



N-methylmorpholine (330 µL, 3.0 mmol, 1.0 equiv.) was added to a solution of 2-(2-nitro-1H-imidazol-1-yl)acetic acid (513 mg, 3.0 mmol, 1.0 equiv.) in dry THF (60 mL) under N_2 at 0 °C, at the mixture was stirred for 10 minutes at 0 °C. Then isobutyl chloroformate (428 µL, 3.3 mmol, 1.1 equiv.) was added, and stirring was continued at 0 °C for 30 minutes. A solution of 2,2,3,3,3-pentafluoropropylamine (383 µL, 3.6 mmol, 1.2 equiv.) in dry THF (6 mL) was then added, and the mixture was stirred at room temperature under N_2 overnight. The reaction mixture was then diluted with CH_2Cl_2, washed 2 times with 1 M aqueous HCl, then with saturated aqueous $NaHCO_3$, then with brine, then dried over Na_2SO_4 and concentrated under vacuum. The crude product was purified by flash chromatography (5% MeOH in CH_2Cl_2) to afford the desired product as an off-white powder (297 mg, 33% yield). **^{1}H NMR** (400 MHz, DMSO-d_6) δ 9.05 (t, *J* = 6.3 Hz, 1H), 7.65 (s, 1H), 7.20 (s, 1H), 5.21 (s, 2H), 4.03 (td, *J* = 15.8, 6.3 Hz, 2H). **^{19}F NMR** (377 MHz, DMSO-d_6) δ -83.5, -120.4 (t, *J* = 15.8 Hz). Analytical data consistent with that previously reported.[223]

5.4.3 Radiochemistry

5.4.3.1 HPLC and TLC Methods

Method I:

Stationary Phase: Phenomenex Gemini 5 µm C-18 110 Å 250 x 4.6 mm

Mobile Phase: 0 - 5 min (5% MeCN in water, isocratic), 5 – 7.5 min (5% – 95% MeCN in water, linear increase), 7.5 – 14.5 min (95% MeCN in water, isocratic), 14.5 – 15.5 min (95% - 5% MeCN in water, linear decrease), 15.5 – 18 min (5% MeCN in water, isocratic)

Flow Rate: 1 mL min^{-1}

Detection: Radio and UV (220 nm or 254 nm)

RadioTLC

RadioTLC run in either 10% EtOH in CH_2Cl_2, or 20% EtOH in CH_2Cl_2

5.4.3.2 Procedures

Preparation of [^{18}F]TEAF

A Sep-Pak Accell Plus QMA Carbonate Plus Light Cartridge, 46 mg Sorbent per Cartridge, 40 µm (SKU 186004540) was activated with 10 mL of water. Then [^{18}F]fluoride in [^{18}O]H_2O (2-5 GBq) was trapped on the cartridge, and then the cartridge was washed with 2 mL of water. The [^{18}F]fluoride was eluted using a solution of Et_4NHCO_3 (9 mg, 47 µmol) in MeCN (800 µL) and water (200 µL). The eluted [^{18}F]TEAF was dried at 110 °C under a flow of N_2. Before the [^{18}F]fluoride was dry, MeCN (1.5 mL) was added, and drying was continued (for azeotropic removal of water). The dry [^{18}F]TEAF was dissolved in 3 mL of MeCN for dispensing.

General procedure E: ^{18}F-fluorodecaboxylation using Mn(tmp)Cl and PhIO

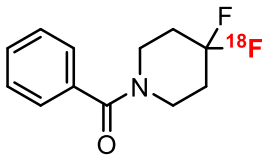
Mn(tmp)Cl (1.8 mg, 2 µmol), PhIO (4 mg, 18 µmol), and carboxylic acid substrate (30 µmol) were added to a 3.5 mL V-vial with stir bar. Then [^{18}F]TEAF in MeCN was added (20-50 MBq), and the MeCN removed at 80 °C under a flow of N_2. Then DCE (300 µL) added, and the reaction was stirred at 80 °C for 20 minutes. The mixture was then diluted with EtOH (300 µL) and analysed using HPLC method I and RadioTLC (sample prepared in a filter vial).

General procedure F: ^{18}F-fluorodecaboxylation using Mn(tmp)Cl and PIDA

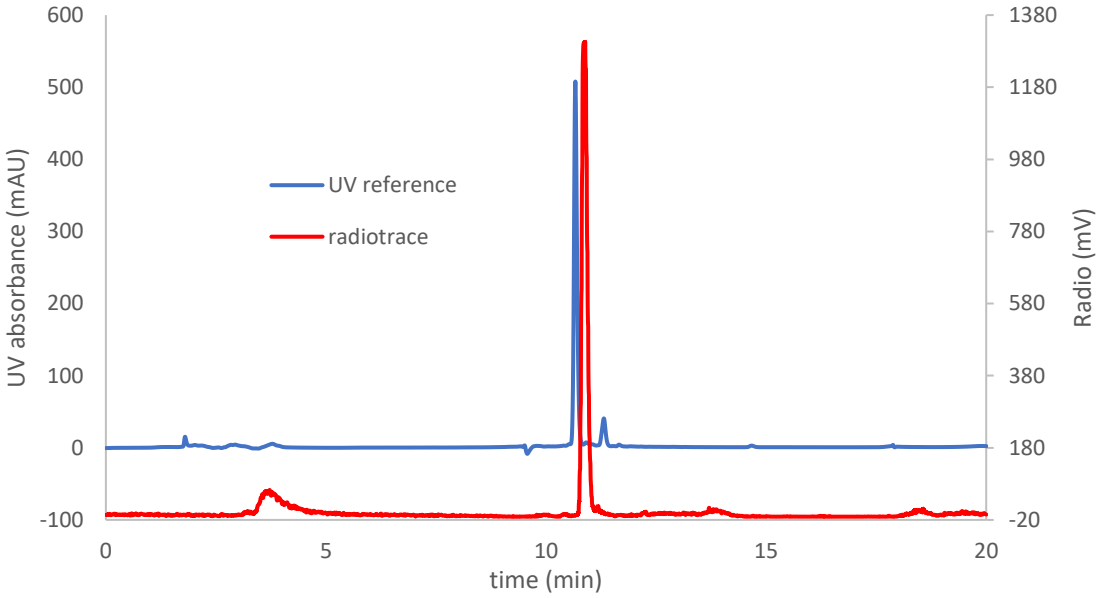
Mn(tmp)Cl (1.8 mg, 2 µmol) was added to a 3.5 mL V-vial with stir bar. Then [^{18}F]TEAF in MeCN was added (20-50 MBq), and the MeCN removed at 80 °C under a flow of N_2. The carboxylic acid substrate (30 µmol) and PIDA (4.8 mg, 15 µmol) were sonicated together in DCE (300 µL) and this mixture was then added to the V-vial, and the reaction was stirred at 80 °C for 20 minutes. The mixture was then diluted with EtOH (300 µL) and analysed using HPLC method I and RadioTLC (sample prepared in a filter vial).

5.4.3.3 Product Characterisation

[^{18}F]4.63B [^{18}F](4,4-difluoropiperidin-1-yl)(phenyl)methanone

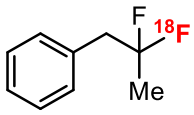


Prepared according to general procedure E.

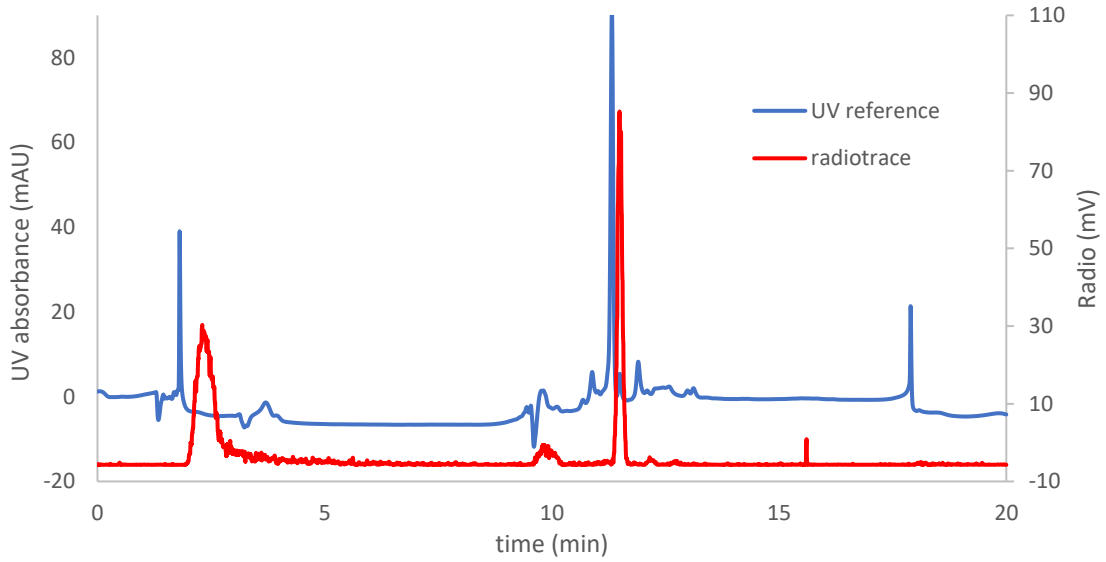


Entry	RadioTLC	RadioHPLC	% RCC
1	60	97	58
2	79	99	78
3	80	99	79
4	72	98	71

[^{18}F]4.65B [^{18}F](2,2-difluoropropyl)benzene

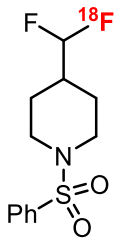


Prepared according to general procedure E.

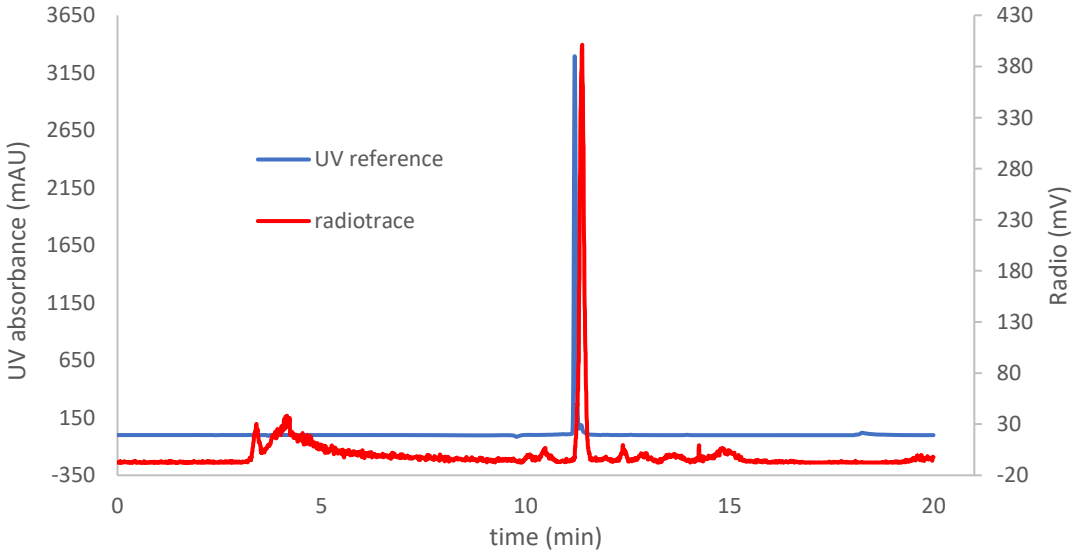


Entry	RadioTLC	RadioHPLC	% RCC
1	12	62	7
2	45	87	39
3	15	89	13

[^{18}F]4.66B [^{18}F]4-(difluoromethyl)-1-(phenylsulfonyl)piperidine

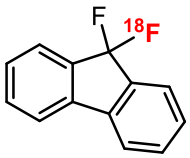


Prepared according to general procedure E, but with MeCN as the reaction solvent rather than DCE, as MeCN afforded a higher RCC (however only based on *n*=1 with DCE).

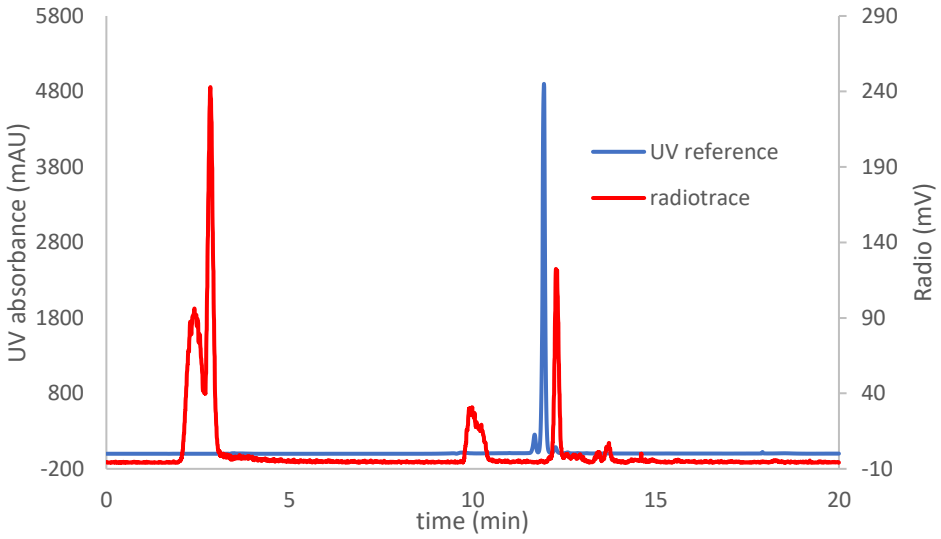


Entry	RadioTLC	RadioHPLC	% RCC
1	58	97	56
2	32	78	25
3	50	84	42

[^{18}F]4.67B [^{18}F]9,9-difluoro-9H-fluorene

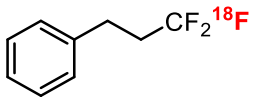


Prepared according to general procedure E.

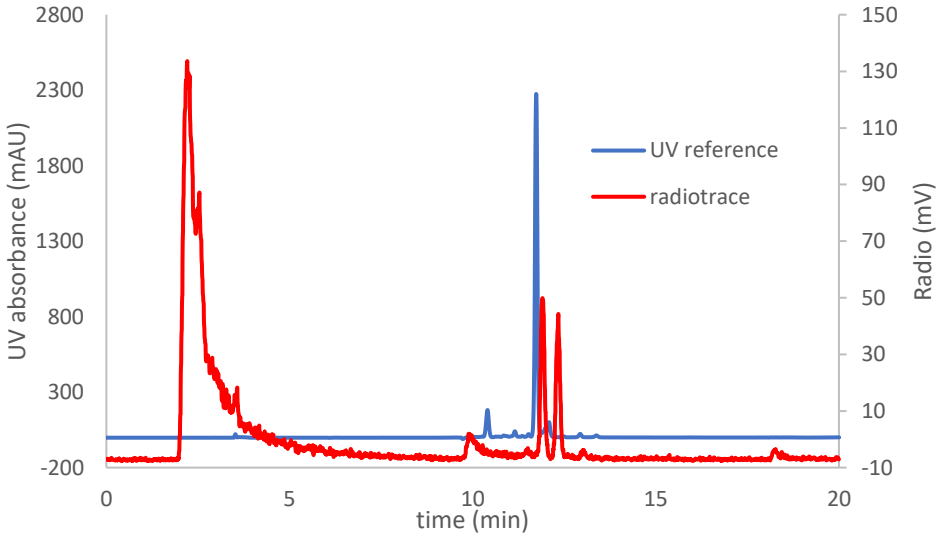


Entry	RadioTLC	RadioHPLC	% RCC
1	36	49	18
2	36	32	12

[^{18}F]4.68B [^{18}F](3,3,3-trifluoropropyl)benzene



Prepared according to general procedure E.



Entry	RadioTLC	RadioHPLC	% RCC
1	17	43	7
2	12	56	7
3	19	13	2

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