

Novel Methods for ^{18}F -Radiolabelling

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



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Author's Declaration

The work presented in this thesis was conducted under the supervision of Prof. Véronique Gouverneur and carried out at the Chemistry Research Laboratory, University of Oxford, unless otherwise specified. 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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Acknowledgements

To my family; I am incredibly lucky to have you as my mother, father and sister. You are all inspirations to me and I would not be where I am without your support each and every day. I don't know where life is leading me from here, but I know that you will be standing beside me and I hope that I will be making you proud.

To the friends I have made and who have been there through my years at Oxford, from the first day in 2008 to the day I write this in 2016. Words on a page would barely begin to convey the appreciation I have and I hope that one day I can thank you all personally.

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Abstract - Novel Methods for ^{18}F -Radiolabelling

The expansion of [^{18}F]-radiolabelling methodologies is vital for the advancement of Positron Emission Tomography (PET) as a medical imaging tool. Novel protocols will simplify access to current PET tracers and allow development of original tracers, potentially enhancing the imaging quality or permit imaging of a wider range of clinical problems. A general introduction is presented in **Chapter 1**, covering PET, application of fluorine-19 in the pharmaceutical industry, the production of fluorine-18 and the current state-of-art for [^{18}F]-radiolabelling.

The results chapters are divided in to two parts; **Part I (Chapters 2 - 4)** concern the synthesis of [^{18}F]fluoroarenes and **Part II (Chapters 5 and 6)** discuss diversity oriented radiofluorination techniques, targeting novel [^{18}F]motifs.

In **Part I, Chapter 2** describes the use of hypervalent iodine reagents to mediate an umpolung approach for fluorination and radiofluorination of *N*-arylsulfonamides and anilides. **Chapter 3** again utilises hypervalent iodine reagents, but as spirocyclic iodonium(III) ylide precursors, being applied to semi-automated and automated microfluidic conditions. **Chapter 4** discusses the development of conditions for the production and isolation of radiopharmaceuticals employing Cu(II)-mediated radiofluorination of aryl boronic pinacol esters.

In **Part II, Chapter 5** discusses the applicability of halogen exchange reactions to reach polyfluorinated motifs and **Chapter 6** focuses on the application of a single diazo precursor to access three polyfluorinated motifs with single-step reactions.

Finally, **Chapter 7** provides experimental data for compounds discussed in this thesis.

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Abbreviations

α	Alpha, alpha particle	EoB	End of bombardment
β^+	Positron	EoS	End of synthesis
γ	Gamma	eq.	Equivalents
δ	Chemical shift (ppm)	ESI	Electrospray ionisation
Δ	Heat	Et	Ethyl
λ	Wavelength	eV	Electron volt
ν	Wavenumbers (cm ⁻¹)	EWOD	Electrowetting-on-dielectric
χ_F	Pauling electronegativity	FI	Field ionisation
°C	Celsius	g	Gram(s)
Å	Angström (10 ⁻¹⁰ m)	<i>gem</i> -	Geminal
aq.	Aqueous	GLC	Gas-liquid chromatography
Ar	Aryl	GP	General Procedure
Boc	<i>tert</i> -Butyloxycarbonyl	GSH	Glutathione
Bq	Becquerel	h	Hour(s)
c.a.	Carrier added	Het	Heteroatom
cat.	catalytic/catalyst	HF·pyr	HF·pyridine
CI	Chemical ionisation	HFIP	1,1,1,3,3,3-Hexafluoro-2-propanol
COD	1,5-cyclooctadiene	HMDS	Hexamethyldisilazane
cond.	Conditions	HPLC	High performance liquid chromatography
CT	Computed tomography	HRMS	High-resolution mass spectroscopy
<i>d</i>	Deuteron	Hz	Hertz
d.c.	Decay corrected	h ν	Light energy
d.r.	Diastereomeric ratio	i.d.	Internal diameter
DABCO	(1,4-diazabicyclo[2.2.2]octane)	<i>i</i> Pr	<i>iso</i> -Propyl
DAST	Diethylaminosulfur trifluoride	IR	Infrared spectroscopy
dba	dibenzylideneacetone	J	Scalar coupling constant
DCE	1,2-Dichloroethane	K _{2,2,2}	Kryptofix 2.2.2, 4,7,13,16,21,24-hexaoxa-1,10-diaza-bicyclo[8.8.8]-hexacosane
DCM	Dichloromethane	kcal	Kilocalorie
DIBAL	Diisobutylaluminium hydride	kDa	KiloDalton
DMAP	4-Dimethylaminopyridine	L	Ligand; litre(s)
DMF	<i>N,N</i> -Dimethylformamide	L-Men	L-Menthyl
DMSO	Dimethylsulfoxide	LG	Leaving group
DMT	Dimethoxytrityl	M	Moles per cubic decimetre (mol dm ⁻³)
DOD	Dose on demand	<i>m</i> CPBA	<i>meta</i> -Chloroperoxybenzoic acid
E	Electrophile	MCS	Micro-channel system
ee	Enantiomeric excess	MCS	Micro-channel system
EI	Electrospray ionization	Me	Methyl

MeCN	Acetonitrile	RCY	Radiochemical yield
mGluR5	Metabotropic glutamate receptor subtype-5	RDS	Rate-determining step
min	Minute(s)	rt	Room temperature
mm	Milimeters	s	Seconds
mol	Mole(s)	SA	Specific activity
MP	Melting point	salen	<i>N,N'</i> -Ethylenebis(salicylimine)
MRI	Magnetic resonance imaging	sat.	Saturated
MS	Molecular sieves	SERT	Serotonin reuptake transporter
MTBE	Methyl <i>tert</i> -butyl ether	SET	Single electron transfer
MVS	Micro-vessel system	SM	Starting material
n	Number of runs	S_N2	Bimolecular nucleophilic substitution
n.c.a.	Non-carrier added	S_NAr	Nucleophilic aromatic substitution
NBS	<i>N</i> -Bromosuccinimide	SPE	Solid phase extraction
<i>n</i>Bu	<i>normal</i> -Butyl	SVR	Surface to volume ratio
NCS	<i>N</i> -Chlorosuccinimide	t_{1/2}	Half-life
NET	Norepinephrine reuptake transporter	TBAF	Tetrabutylammonium fluoride
NFSI	<i>N</i> -fluorobenzenesulfonimide	TBAT	Tetrabutylammonium difluorotriphenylsilicate
nm	nanometer(s)	<i>t</i>Bu	<i>tert</i> -Butyl
NMR	Nuclear magnetic resonance	TCA	Trichloroacetic acid
Nu	Nucleophile	TEAB	Tetraethylammonium bicarbonate
OAc	Acetate	TEAF	Tetraethylammonium fluoride
OTf	Triflate, trifluoromethanesulfonate	TEMPO	(2,2,6,6-Tetramethylpiperidin-1-yl)oxyl
P	Proton	TFA	Trifluoroacetic acid
PET	Positron emission tomography	THF	Tetrahydrofuran
Ph	Phenyl	TLC	Thin layer chromatography
PIDA	(Diacetoxyiodo)benzene	TMEDA	Tetramethylenediamine
PIFA	(bis(trifluoroacetoxy)iodo)benzene	TMS	Tetramethylsilyl
pin	Pinacol ester	t_R	Residence time
pK_a	Acid dissociation constant	TREAT.HF	Triethylamine trihydrofluoride
ppm	Parts per million	TSPO	Translocator protein
pyr	Pyridine	UV/vis	Ultraviolet-visible light
QMA	Anion exchange cartridge	xs.	Excess
quant.	Quantitative	18-crown-6	1,4,7,10,13,16-Hexaoxacyclo-octadecane
R	Alkyl group		
RCC	Radiochemical conversion		

INTRODUCTION

I. Introduction – PET and Radiochemistry

I.I. Positron Emission Tomography

Positron emission tomography (PET) is a potent, non-invasive functional imaging technique that utilises positron-emitting radioisotopes as labels on tracer compounds. It is typically used for clinical diagnosis and treatment analysis, as well as for drug discovery and development. PET imaging can provide information not only on human physiology, but also metabolism and molecular level events that cannot be generated by structural imaging techniques, such as X-ray or ultrasound. The use of PET imaging in conjunction with complimentary structural imaging techniques, mainly X-ray computed tomography (X-ray CT)¹ and magnetic resonance imaging (MRI),² is especially valuable as it provides both physiological and anatomical details which cannot be found using either method alone.

The radioisotopes that are most commonly exploited for PET tracers are short-lived and decay almost exclusively by positron emission (β^+). Carbon-11, nitrogen-13, oxygen-15 and fluorine-18 (Table 1.1) are examples of typical radionuclides, which can be used to replace their stable counterparts (^{12}C , ^{14}N , ^{16}O , ^{19}F) without affecting the biological activity of the tracer compound. This differentiates them from other techniques in which an imaging ‘handle’ is attached to a specific targeting section. As these ‘handles’ can be relatively large structures used for ligating the radionuclide, this can result in changing the bioactivity of the targeting section and complicating the overall tracer design.

The radioisotopes used for PET are produced in cyclotrons – compact particle accelerators capable of producing proton and deuteron beams – by bombardment of a specific target. Due to the relative short half-lives ($t_{1/2}$) of these isotopes, the preparation

of tracers typically involves the radioisotope being installed in the final steps of the synthesis, preferentially at the same site as the isotope production and final imaging use. As ^{18}F has a longer half-life, this enables greater flexibility with the transport of activity, either as [^{18}F]fluoride from the cyclotron for use, or as the final tracer product, prepared for injection. A timeframe of three isotope half-lives is used as a guide for the maximum time that can be completed between end-of-bombardment (EoB) to injection, and as such there is need for the development of rapid radiosynthetic methods that are able to cope with the relatively sensitive nature of the bioactive tracer structures.³

Radionuclide	Production	Half-life ($t_{1/2}$, min)	Decay Process	Decay Product	Maximum β^+ energy (keV)	Range (in H_2O)
Carbon-11	$^{14}\text{N}(p,\alpha)^{11}\text{C}$	20.4	99.8% β^+	^{11}B	960	4.1
Nitrogen-13	$^{16}\text{O}(p,\alpha)^{13}\text{N}$	9.97	100% β^+	^{13}C	1190	5.4
Oxygen-15	$^{15}\text{N}(d,n)^{15}\text{O}$	2.04	99.9% β^+	^{15}N	1720	8.2
Fluorine-18	$^{18}\text{O}(p,n)^{18}\text{F}^a$	109.8	97% β^+	^{18}O	635	2.4

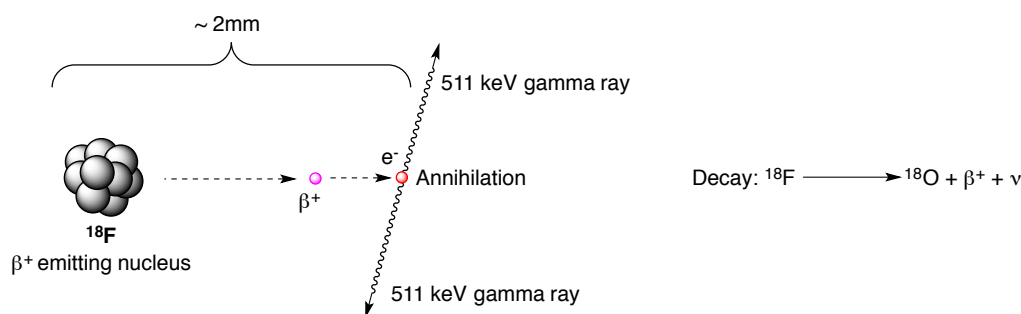
a) For production of [^{18}F]fluoride, other productions discussed in Section 1.3.1..

Table 1.1: Production and decay of common PET radionuclides.³

The positron emitted during the decay process is not detected directly, but undergoes annihilation with an electron from the surrounding material, producing two gamma (γ) rays emitted at 180° from each other (Scheme 1.1). A ring of highly sensitive detectors picks up these coincidental γ -rays, initially converting them into light and then electrical impulses using a photo-multiplier. These impulses are consequently processed into a 2D or 3D image of the subject.

The distance travelled by the positron before annihilation, which is controlled by the energy of emission, dictates the resolution of the image. The shorter the range, the closer the annihilation is to the actual decay site and therefore the higher the resolution of the final image. Fluorine-18 has the lowest mean emission energy of the

commonly used radioisotopes (511 keV) and thus has the lowest range (2.4 mm in water), resulting in the highest resolution images.³



Scheme 1.1: Decay of ^{18}F and annihilation, producing emitted photons.

PET is a very sensitive technique, especially when the tracer is prepared under non-carrier added (n.c.a.) methods, requiring sub-nanomolar quantities of the tracer to generate enough annihilation events for an image.⁴ This means that the *in vivo* system is not perturbed by the introduction of the tracer, and so accurate information can be gathered. Additionally, very potent or toxic compounds can be studied at subpharmacological or subtoxicological doses.

PET has been adopted across a wide range of medical disciplines; in oncology for the detection and monitoring of tumours, in cardiology for the imaging of myocardial perfusion and in neurology for the early detection and monitoring of debilitating disorders, such as Alzheimer's and Parkinson's disease. PET tracers are also monitored over time as physiological and biochemical aspects that change the distribution and concentration of the tracer over time, can yield important clinical information.

1.2. Use of Fluorine and Fluorine-18 in Bioactive Structures

The incorporation of fluorine is important in the pharmaceutical and agrochemical industry due to the pharmacological properties that it can impart on the parent molecule. Whilst fluorine is the most abundant halogen in the Earth's crust, it is notable that there are very few organofluorine compounds found as natural products,⁵

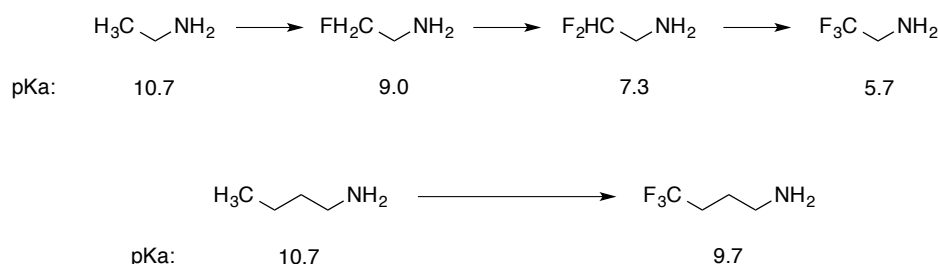
⁶ yet 20-25%⁷ of approved drugs contain at least one fluorine atom, increasing to around 30% when considering the best selling.⁸ These fluorine containing drugs include some blockbuster pharmaceuticals, such as; Lipitor (dyslipidemia), Januvia (diabetes), Arcoxia, Celebrex (both arthritis), Sustiva (anti-HIV) and Prozac (depression).⁹ The use of fluorine in pharmaceuticals has a long history¹⁰ though the most notable increase in use was during the early 1980s due to the introduction of diethylaminosulfur trifluoride (DAST) as a selective fluorinating reagent, an increase mirrored in the agrochemical industry.¹¹

Although fluorine occurs in very few naturally occurring biological molecules, due to its size, it can often be substituted in place of a proton or hydroxyl group without considerably modifying the molecular structure in solution.¹² Whilst protons are most commonly replaced with fluorine, the Van der Waal's radius and bond lengths are closer to those of C-O (Table 1.2).

X	Van der Waal's Radius (Å)	Bond Length (C-X) (Å)
H	1.20	1.09
O	1.40 - 1.52	1.43
F	1.35 - 1.47	1.35 - 1.41

Table 1.2: Comparison between steric influences of substitution of fluorine.¹²

The incorporation of fluorine can have several beneficial effects on the *in vivo* interactions of the drug molecule, stemming from fluorine being the most electronegative element ($\chi_p = 3.98$);¹³ this electronegativity leads to a highly polarised C-F bond, resulting in significant ionic character and a strong effect on the acidity or basicity of the proximal functional groups.¹⁴ Acids are typically made more acidic and the basicity of bases is decreased with increasing fluoride incorporation (Scheme 1.2).⁹ Modification of the pKa of these functional groups can fine tune the binding affinity to specific sites and the pharmacokinetic properties of pharmaceutical molecules.¹⁵



Scheme 1.2: pKa variation on increasing incorporation of fluorine.¹⁶

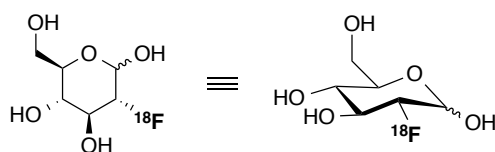
The lipophilicity of drug molecules can also be modulated by strategic inclusion of fluorine. A drug must be lipophilic enough to pass through the lipid bilayer of a cell, but if it is too lipophilic than it can become trapped inside the cell. Lipinski's rule of 5 suggests that a $\log P < 5$ will give good adsorption.¹⁷ It is commonly misconstrued that the incorporation of fluorine will increase the lipophilicity of a molecule, which is true for aromatic fluorination, per/polyfluorination and fluorination adjacent to π -bonds. However, with saturated alkyl chains, mono-, di- or trifluorination can decrease the lipophilicity due to fluorine's strong electron-withdrawing capability.

Fluorine is also frequently used to increase the metabolic stability of molecules, owing to the higher dissociation energy of C-F bond compared to C-H (105.4 vs. 98.8 kcal/mol)⁷ as well as increase binding affinity by means of structural conformation,¹⁸ direct site contact or indirect contact mediated by H_2O molecules.¹⁹

There are three possible routes for use of PET imaging in drug discovery; via the radiolabelling of potential drug candidates and analysis of *in vivo* activity and distribution, via occupancy studies to determine the displacement of known radioligands on administration of new candidates and finally by monitoring of the pharmacological response to administration of novel drug candidates, by tracking the system with known radiotracers such as [^{18}F]FDG.

2- [^{18}F]Fluoro-2-deoxy-D-glucose ([^{18}F]FDG) (Scheme 1.3) is the most widely applied tracer in use. This radiofluorinated analogue of glucose, typically labelled by

substitution of a mannose triflate or tosylate precursor, tracks increased metabolism in cells and, as such, is used in oncology²⁰ for diagnosis and disease mapping due to the up-regulation of aerobic glycolysis in cancerous cells. Once taken up by a cell, there is an initial phosphorylation reaction, though further metabolism is prevented by the presence of the ^{18}F in place of a hydroxyl at the C2-position.²¹ This results in the phosphorylated [^{18}F]FDG being trapped in the cell for visualisation.



Scheme 1.3: 2- ^{18}F Fluoro-2-deoxy-D-glucose ([^{18}F]FDG).

As PET imaging only requires the administration of small quantities of the drug, this usually falls below toxicity levels and so studies can take place in rodent, non-human primate²² and human subjects before Phase I clinical trials.²³ In this way, information on the pharmacodynamics and pharmacokinetic properties of a compound can be established to a higher degree than from *in vitro* analysis alone, before the clinical trial stage. Consequently, the use of PET imaging to screen potential drug candidates eliminates poor candidates prior to the expensive and long clinical trials, saving both time and money. As the current drug discovery pipeline through clinical development and approval typically lasts 5 – 10 years²⁴ costing up to \$2.6 billion²⁵ per drug, the ultimate savings by the use of PET imaging can be very significant.

1.3. [^{18}F]Fluorination

The scale of fluorine-18 present in reactions, for both research and radiosynthesis of PET tracers, typically lies in the pico- to nanomolar range, well below that achievable in traditional fluorine-19 chemistry.³ This leads to vast stoichiometric excesses of the precursor and other reagents, which results in pseudo-first-order reaction kinetics with

respect to the radioisotope concentration. Consequently, some reactions that take hours or days to reach completion in the 'cold' fluorine-19 lab can be completed in minutes in the 'hot' fluorine-18 radiolab.

There are, however, disadvantages to the low amounts of fluorine-18 present in these reactions. It can be difficult to directly translate 'cold' chemistry into the 'hot' radiolab, especially when metal catalysts are used, and minor impurities in reagents or solvents can become significant.

There are two sources of fluorine-18 for radiofluorination; nucleophilic [^{18}F]fluoride and [^{18}F]F₂ (and derived reagents) for electrophilic fluorination. These can be utilised under two strategies; either to directly label the target compound, or to label an intermediate prosthetic group which is then linked to the remaining structure. As discussed earlier, the favoured option is for the [^{18}F]fluorination to occur as late as possible, however due to the longer half-life of fluorine-18, post-fluorination reactions are possible, which are not always possible with other PET radioisotopes. Of the two sources, nucleophilic [^{18}F]fluoride is favoured as it offers greater selectivity in the reaction, easier to handle (very few facilities are equipped to handle [^{18}F]F₂ gas required for electrophilic radiofluorination) and [^{18}F]fluoride is capable of giving tracers with much higher specific activity (SA).

SA of the final product is an important consideration for radiosynthesis. It is defined as a measure of activity per unit mass of the labelled compound, commonly quoted as gigaBecquerel per micromole (GBq/ μmol). This is a measure of the activity over the total amount of the compound present, including that bearing fluorine-19. Presence of the ^{19}F -analogue is unavoidable due to fluorine-19 being present in the reaction, whether introduced deliberately or unintentionally by absorption, isotope exchange or from trace quantities in reagents and solvents used. The theoretical maximum values

are never reached, due to isotopic dilution, but SA can be maximised by application of non-carrier added procedures. The use of a carrier (the fluorine-19 reagent analogous to the fluorine-18 source being used) can be useful to force a reaction, or unavoidable as in the case of $[^{18}\text{F}]\text{F}_2$, however these carrier added (c.a.) reactions lead to much lower SA due to the increased ^{19}F -analogue formed.

Radiochemical reaction efficiency can either be measured by radiochemical conversion (RCC) or radiochemical yield (RCY). Radiochemical conversion, typically measured by combination of radioTLC and radioHPLC, is a measure of radiofluorinated product against remaining $[^{18}\text{F}]$ reagent and is inherently decay corrected [d.c.]. Radiochemical yield is the collected product activity at the end of synthesis (EoS) against the activity at the start of the synthesis. This can be decay corrected to time at start of synthesis, which negates total synthesis time, or non-decay corrected [n.d.c.], which takes into account synthesis time. For this thesis, only isolated activities will be denoted as RCY, even though this is regularly used in literature to denote RCC.

After the production of the PET tracer there are strict pharmacological quality controls when considering administration of a PET tracer that are in place to protect the imaging subject, however these will not be discussed in detail in this thesis.

1.3.1. Production of Fluorine-18

The type of fluorine-18 desired dictates the cyclotron target and method of bombardment, as shown in Table 1.3.

^{18}F source	Target	Nuclear Reaction	SA (GBq/ μmol)
$[^{18}\text{F}]\text{F}^-$	$^{18}\text{OH}_2$	$^{18}\text{O}(p,n)^{18}\text{F}$	5000
$[^{18}\text{F}]\text{F}_2$	$\text{Ne} + \text{F}_2$	$^{20}\text{Ne}(d,\alpha)^{18}\text{F}$	0.37 - 0.74
$[^{18}\text{F}]\text{F}_2$	$^{18}\text{O}_2 + \text{F}_2$	$^{18}\text{O}(p,n)^{18}\text{F}$	1
$[^{18}\text{F}]\text{F}_2^{\text{a}}$	$^{18}\text{OH}_2$	$^{18}\text{O}(p,n)^{18}\text{F}$	55

a) 'Post-target' method.

Table 1.3: Production methods for ^{18}F sources.

$[^{18}\text{F}]\text{Fluoride}$ is produced by proton bombardment of ^{18}O -enriched water, under the $^{18}\text{O}(p,n)^{18}\text{F}$ nuclear reaction, and is delivered from the cyclotron as $[^{18}\text{F}]\text{fluoride}$ in ^{18}O -enriched water. The counter-ion to the $[^{18}\text{F}]\text{fluoride}$ is unknown, though is believed to come from the metal used to construct the target container. This method of production produces the highest SA source of fluorine-18, which permits the radiosynthesis of high SA radiotracers allowing for smaller amounts of tracer compound to be injected for the same amount of activity. This is vital for tracers targeting scarce receptor sites, which may become saturated with unlabelled compound if a lower SA tracer is used.

As the $[^{18}\text{F}]\text{fluoride}$ is delivered as an aqueous solution, this results in a species that is highly solvated and weakly nucleophilic; a poor reagent for radiofluorination. Consequently it requires separation from the ^{18}O -enriched water and activation before use. This is achieved by use of an anion exchange cartridge (QMA) to trap the $[^{18}\text{F}]\text{fluoride}$, which then can be eluted with a basic solution containing an appropriate cation. This is most commonly accomplished by use of potassium carbonate in a mixture of acetonitrile and water, before heating with further additions of anhydrous acetonitrile azeotropically dries this solution. A cryptand, usually Kryptofix 2.2.2 ($\text{K}_{2.2.2}$), is included in the elution solution to assist the resolution of the $[^{18}\text{F}]\text{KF}$ in the reaction solvent as $[^{18}\text{F}]\text{KF}/\text{K}_{2.2.2}$. Other commonly used cations for elution are tetraalkylammonium ions (tetraethylammonium and tetrabutylammonium) from their bicarbonate salts, which do not require further cryptands.

An important note on the elution of [^{18}F]fluoride is that an excess of eluting cation is always used, which results in a quantity of base being carried through the QMA cartridge into the azeotropic drying and resulting resolution of [^{18}F]fluoride. Consequently, when radiofluorination reagents such as [^{18}F]KF/ $\text{K}_{2.2.2}$ and tetraethylammonium [^{18}F]fluoride ([^{18}F]TEAF) are used, it must be remembered that significant amounts of potassium carbonate and tetraethylammonium bicarbonate (TEAB), respectively, remain in solution. This remaining base can have serious effects on the radiofluorination reaction itself, as will be discussed later.

Electrophilic fluorine-18, as [^{18}F]F $_2$, can be produced directly by two nuclear reactions; irradiation of a Ne/F $_2$ gas mixture with deuterium ($^{20}\text{Ne}(d,\alpha)^{18}\text{F}$) or irradiation of [^{18}O]O $_2$ gas with protons ($^{18}\text{O}(p,n)^{18}\text{F}$) in a manner similar to production of [^{18}F]fluoride. The former procedure is rarely used as it is low yielding and produces very low SA [^{18}F]F $_2$ due to the high amount of F $_2$ used as carrier.²⁶ An illustration of this is a 1 – 2 hour bombardment with 8 – 9 MeV deuterons results in < 37 MBq with SA of 0.37 – 0.74 GBq/ μmol .²⁷

The latter procedure is much more frequently utilised, with the excited $^{18}\text{F}^*$ atoms produced from the initial bombardment adhering to the nickel walls of the target. The carrier F $_2$ gas (~0.1% in Ne or Kr) is then introduced, accompanied with a second irradiation of the target that incites the isotopic exchange to form the [^{18}F]F $_2$ gas. In this ‘double-shoot’ method a lower amount of carrier is required resulting in higher SA, though these are still limited to ~1 GBq/ μmol .²⁸

An alternative, indirect, route has been reported by Bergman and Solin from the Turku PET Centre. This ‘post-target’ method uses [^{18}F]fluoride, produced by the $^{18}\text{O}(p,n)^{18}\text{F}$ nuclear reaction, which is azeotropically dried and reacted with methyl iodide to produce [^{18}F]fluoromethane, purified by gas chromatography. This is transferred to an

electrical discharge chamber with a small amount of carrier F₂ gas. The electrical discharge results in atomisation and ¹⁸F/¹⁹F isotope exchange to form [¹⁸F]F₂ gas with SA up to 55 GBq/μmol.²⁹

[¹⁸F]F₂ produced by these methods can be used to access further electrophilic radiofluorination reagents, to be discussed in Section 1.3.3..

1.3.2. Nucleophilic [¹⁸F]Fluorination

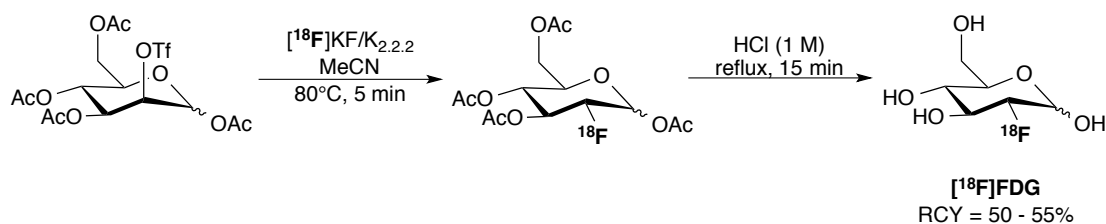
[¹⁸F]Fluoride is the most commonly used source of fluorine-18 for radiofluorination as it can be produced in higher SA, and is much easier to transport and handle. Following azeotropic drying to produce the reactive [¹⁸F]fluoride species, the most commonly utilised reaction pathways are aliphatic or aromatic substitutions on appropriately activated precursors.

Precursor design for radiofluorination reactions has a high dependence on the stability of the precursor, minimisation of side reactions and ease of separation of final products, not just the final attainable incorporation of [¹⁸F]fluoride. Furthermore, the presence of protic functional groups (acid, alcohol, amide etc.) tends to reduce the reactivity of the [¹⁸F]fluoride. It is generally beneficial to protect these functionalities, however this introduces the requirement for post-fluorination deprotection steps, increasing the synthesis time.

1.3.2.1. Nucleophilic Aliphatic [¹⁸F]Fluorination

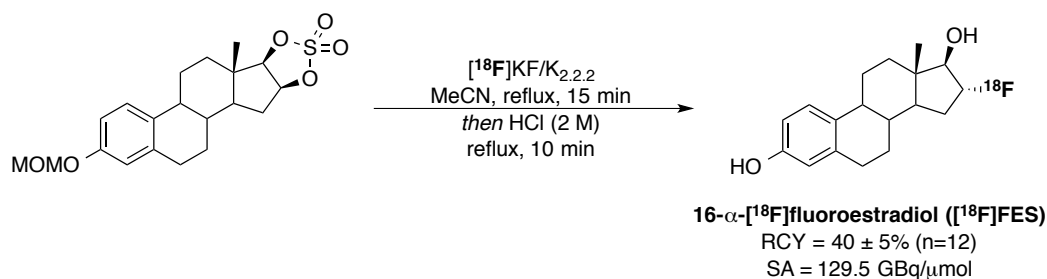
Thermally induced direct S_N2 mechanisms are most commonly applied for the radiofluorination of aliphatic motifs with high SA (> 100 GBq/μmol). Precursors are designed with appropriate leaving groups, most commonly sulfonates (tosyl, triflyl, mesyl, nosyl) or halides (I, Br).

As described in Section 1.2., [^{18}F]FDG is the most prominent radiotracer to date and is the most commonly prepared tracer in PET facilities. It is routinely produced from a globally acetate protected D-glucose precursor with a triflate leaving group (Scheme 1.4). Substitution with [^{18}F]KF/K_{2.2.2} and deprotection under acidic conditions gives [^{18}F]FDG in 50 - 55% RCY [n.d.c.].³⁰



Scheme 1.4: Nucleophilic production of [^{18}F]FDG.³⁰

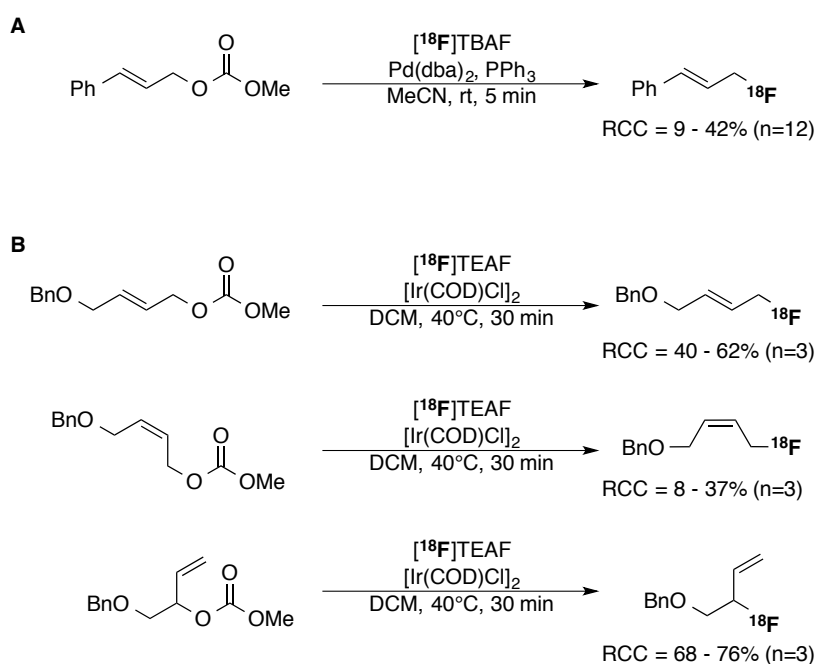
More complex cyclic sulfones have also been successfully adopted as precursors for aliphatic radiolabelling by S_N2, exemplified by the radiofluorination of 16- α -[^{18}F]fluoroestradiol (Scheme 1.5),^{31, 32} a tracer used for the imaging of primary and metastatic breast cancer.³³



Scheme 1.5: Cyclic sulfone precursor for 16- α -[^{18}F]fluoroestradiol ([^{18}F]FES).³²

The use of transition metal complexes to mediate the radiofluorination of aliphatic centres has also been reported. These procedures typically require lower temperatures and are more selective, an important consideration when an enantio-enriched tracer is required.

The Gouverneur group has presented two routes for allylic fluorination by use of $\text{Pd}(\text{dba})_2$ ⁱ or $[\text{Ir}(\text{COD})\text{Cl}]_2$ ⁱⁱ that were demonstrated to be applicable to radiofluorination. The use of the $\text{Pd}(\text{o})$ complex³⁴ allowed for the radiofluorination of cinnamyl [^{18}F]fluoride in good RCC (9 - 42% (n=12)) at room temperature in 5 minutes (Scheme 1.6, A). Comparatively, cinnamyl chloride and cinnamyl bromide required heating to 110°C for 20 minutes to return RCCs of 40% and 42% respectively. Excellent incorporation could be obtained by adoption of the Ir(II) complex,³⁵ with retention of regiochemistry when the reaction was heated to 40°C for 30 minutes (B). For both of these procedures, use of tetraalkylammonium salts as the [^{18}F]fluoride source was found to be beneficial to the incorporation, over the use of [^{18}F]KF/ $\text{K}_{2,2,2}$.



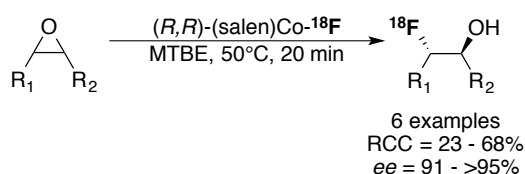
Scheme 1.6: $\text{Pd}(\text{o})$ (A)³⁴ and Ir(II) (B)³⁵ mediated routes to allylic- ^{18}F .

Building on the work of Bruns³⁶ and Haufe,³⁷ Doyle developed an enantioselective fluorination by $\text{Co}(\text{II})$ -catalysed ring opening of epoxides.^{38, 39} Shortly after reports of adaption of this methodology for radiofluorination from Revunov and Zhuravlev, including the radiosynthesis of enantioenriched [^{18}F]FMISO (55% ee),⁴⁰ Doyle and

ⁱ dba = dibenzylideneacetone

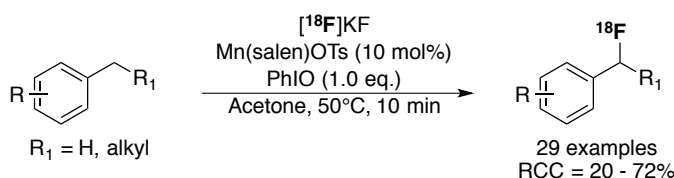
ⁱⁱ COD = 1,5-cyclooctadiene

Kung presented their conversion of this approach (Scheme 1.7).⁴¹ By use of a solution of (R,R)-(salen)Co(III)OTs to elute the trapped [¹⁸F]fluoride, they were able to form a (R,R)-(salen)Co(III)-¹⁸F species which was able to undergo the same epoxide opening reaction, giving an excellent level of incorporation and enantioselectivity. Furthermore, by use of a (R,R,R,R)-(linked salen)(CoOTs)₂ complex to elute, they were able to demonstrate the radiofluorination of five radiotracers, including [¹⁸F]FMISO in 67 ± 4% RCC (n=3) with 90% ee.



Scheme 1.7: Doyle's Co(II)-mediated enantioselective epoxide opening radiofluorination.⁴¹

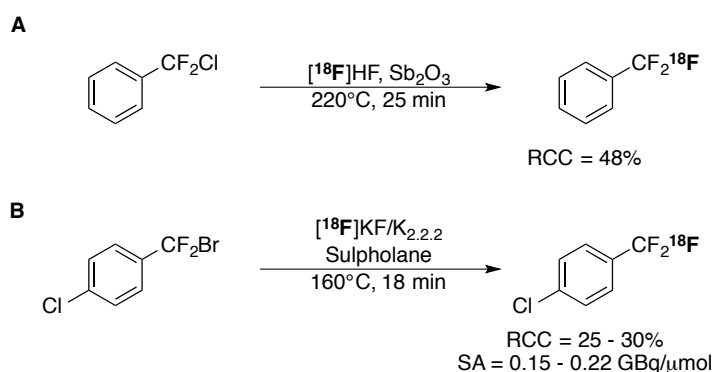
Groves and Hooker removed the necessity for prefunctionalisation with a suitable leaving group by the development of benzylic C-H radiofluorination mediated by a Mn(III) complex, Mn(salen)OTs (Scheme 1.8).⁴² They were able to demonstrate the wide applicability of this procedure on 20 small molecule model substrates and a further nine bioactive molecules with RCC = 20 - 72% (n>3). Additionally, they demonstrated a dry-down free procedure by use of an acetone solution of the Mn(III) complex to elute the [¹⁸F]fluoride (further discussion on base-free elution is covered in Chapter 4). Carroll *et al.* were able to extend this methodology to [¹⁸F]trifluoromethyl functionalities by utilising the difluoromethyl precursors.⁴³



Scheme 1.8: Groves and Hooker's Mn(III)-mediated benzylic C-H radiofluorination.⁴²

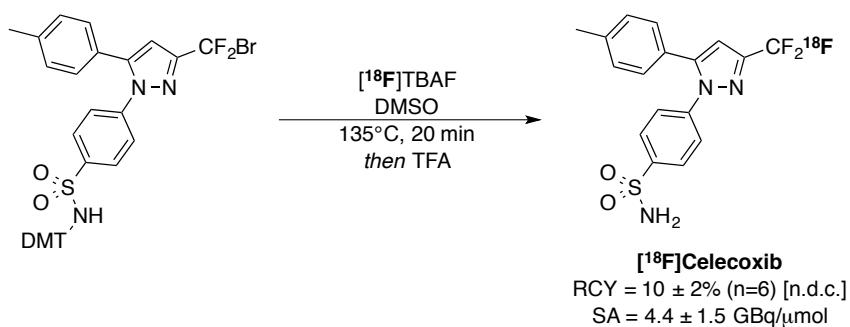
Radiolabelling of polyfluorinated benzylic functionalities, such as aryl-CF₃, -CF₂H and -CF₂R, is an area that is much less developed than for monofluorinated motifs. The

first example of a [^{18}F]trifluoromethyl arene was by isotope exchange on α,α,α -trifluorotoluene with [^{18}F]KF/18-crown-6.⁴⁴ Halogen exchange reactions with the chloro- or bromodifluoromethylarene precursors with various [^{18}F]fluoride sources have also been developed, though harsh reaction conditions are required. Chlorodifluoromethylarene precursors require heating up to 220°C for 25 minutes in the presence of [^{18}F]HF and antimony trioxide, with the incorporation rapidly decreasing with reduced temperature or time (Scheme 1.9, A).⁴⁵ Bromodifluoromethylarene precursors do not require such harsh conditions, though conditions of [^{18}F]KF/ $\text{K}_{2.2.2}$ in sulfolane at 160°C are fairly representative for good incorporation (B).⁴⁶ Unfortunately it was found that the precursors decomposed under the reaction conditions, releasing fluoride that results in very low SA.



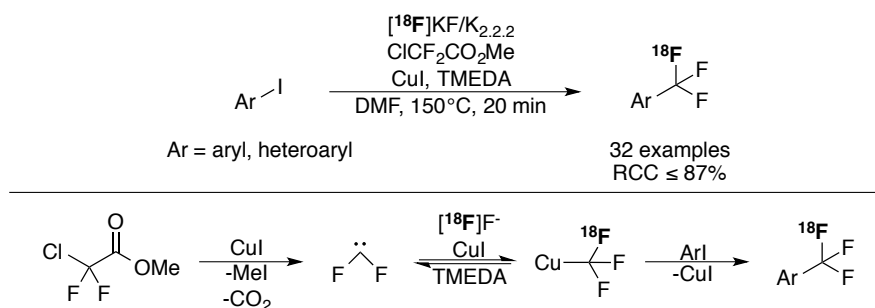
Scheme 1.9: Radiosynthesis of [^{18}F]trifluoromethylarenes by halogen exchange from chloro- (A)⁴⁵ and bromodifluoromethylarenes (B).⁴⁶

Despite the harsh conditions required, radiopharmaceuticals have been prepared by halogen exchange, with indirect radiofluorination and post-fluorination steps used for (S)-[^{18}F]Fluoxetine⁴⁷ and direct radiofluorination for [^{18}F]Celecoxib (Scheme 1.10),⁴⁸ both utilising bromodifluoromethylarene precursors.



Scheme 1.IO: Direct radiofluorination of [¹⁸F]Celecoxib by halogen exchange.⁴⁸

Conventional routes for introduction of trifluoromethyl functionality is by copper(I)-catalysed cross-coupling with F_3C^- sources. Huiban *et al.* were able to generate ' $[\text{F}] \text{Cu(I)-CF}_3$ ' from difluorocarbenes, generated from methyl chlorodifluoroacetate, and $[\text{F}]\text{KF}/\text{K}_{2.2.2}$ (Scheme 1.II).⁴⁹ As the $:\text{CF}_2$ to $[\text{F}]\text{F}_3\text{C}^-$ step is an equilibrium, ^{19}F -fluoride is released and can then be abstracted by to give 'cold' F_3C^- , ultimately diluting the SA of the final product. An illustrative SA, measured from the synthesis of 4-([¹⁸F]trifluoromethyl)nitrobenzene, was 0.1 GBq/μmol. While the conditions required were similar to that seen with the halogen exchange reactions (DMF, 150°C), the substrate scope and overall incorporation was improved.

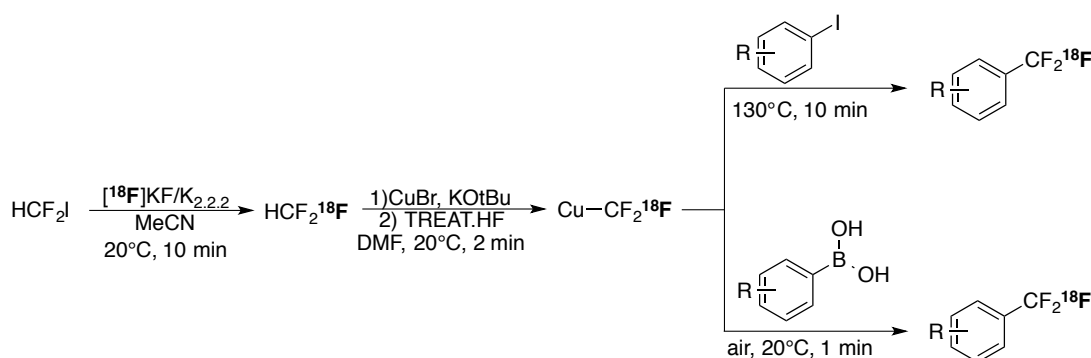


Scheme 1.II: Cu(I)-mediated [¹⁸F]trifluoromethylation or aryl iodides.⁴⁹

Riss⁵⁰ presented an alternative method for $[\text{F}]\text{Cu(I)-CF}_3$ generation, utilising Vugts'⁵¹ radiosynthesis of [¹⁸F]trifluoromethane from difluoroiodomethane and consequent deprotonation by potassium *tert*-butoxide in the presence of CuBr. This one-pot procedure was demonstrated on a range of electron rich, neutral and deficient arenes,

the SA remained problematic, with 0.139 GBq/ μ mol found for 4-([18 F]trifluoromethyl)benzonitrile.

Further extensions to this methodology by Vugts⁵² expanded the precursor scope to arylboronic acids by purging air through the reaction. This was proposed to oxidise [18 F]Cu(I)-CF₃, prepared in a similar manner to Riss, to [18 F]Cu(II)-CF₃, which is able to undergo the trifluoromethylation in 1 minute at room temperature. Furthermore, decreasing the loading of difluoroiodomethane and introducing the use of triethylammonium trihydrofluoride (TREAT.HF) to stabilise the [18 F]Cu(I)-CF₃ species, lead to a rather counter-intuitive increase in SA to 22 - 32 GBq/ μ mol for the [18 F]trifluoromethylation of aryl iodides.

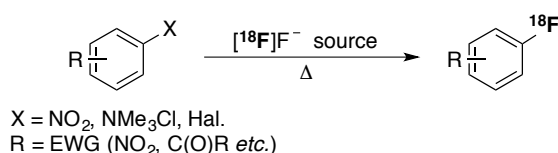


Scheme 1.12: General reaction methodology for Cu-mediated [18 F]trifluoromethylation of aryl iodides and arylboronic acids from [18 F]trifluoromethane.

1.3.2.2. Nucleophilic Aromatic [18 F]Fluorination

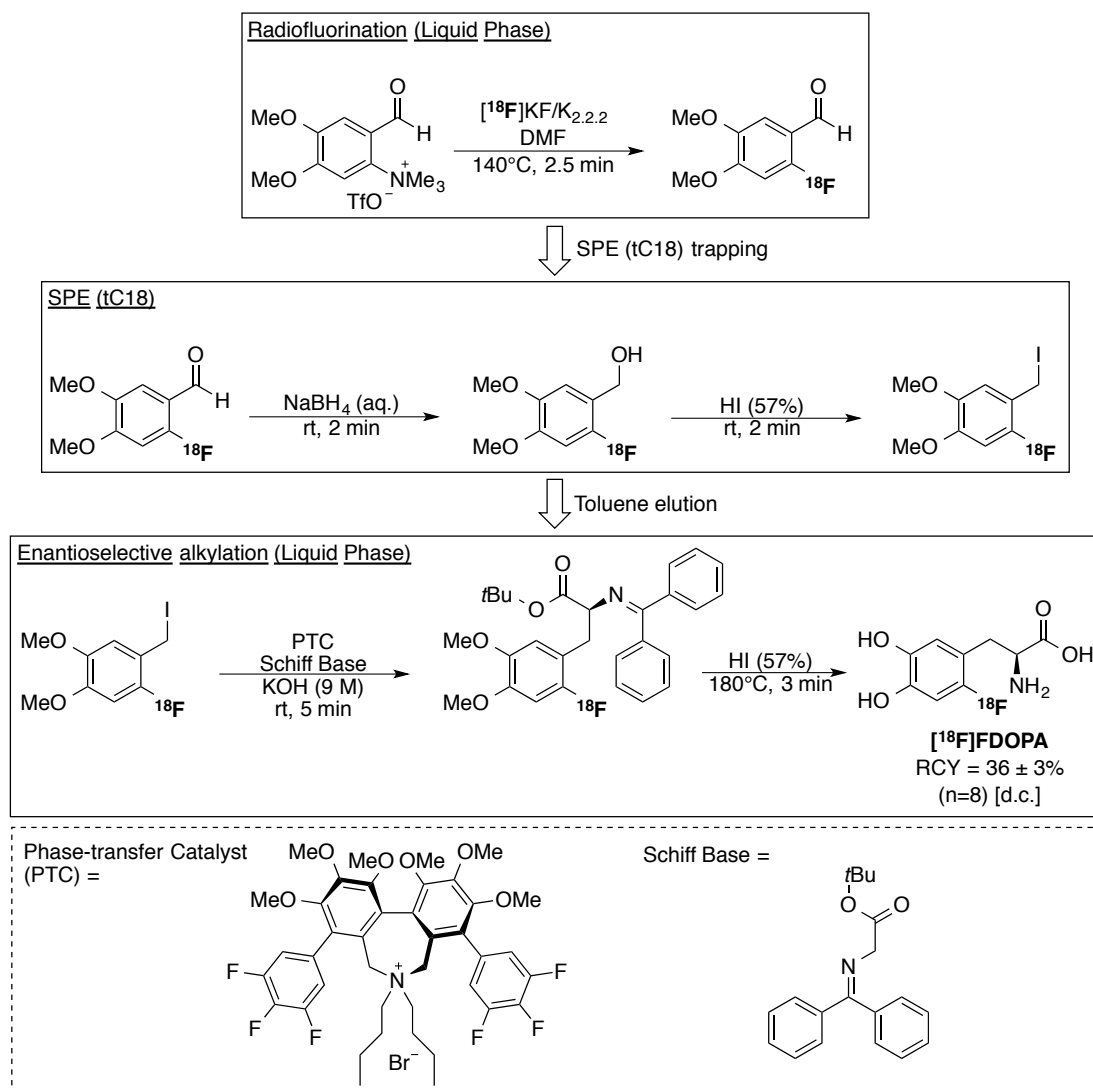
Despite being a relatively strong bond, C(sp³)-F (BDE = 109.9 kcal/mol) are susceptible to metabolism, leading to in vivo radiodefluorination.⁷ This release is problematic as [18 F]fluoride binds strongly with skeletal systems, increasing the background ‘noise’ in PET scans. The metabolic effect can be minimised by the use of aryl fluorine-18 labelling.

The most common⁵³ method for radiofluorination of arenes is by nucleophilic aromatic substitution (S_NAr), a route which is relatively simple regarding precursor preparation and can give good [¹⁸F]fluoride incorporation (Scheme 1.13). It is limited to suitably activated precursors, bearing electron withdrawing groups situated *ortho* or *para* to the leaving group. Nitro- and trimethylammonium salt groups are most commonly employed as the leaving group, though there are examples of haloarenes but these are not typically as effective. Trimethylammonium salt based precursors have an additional advantage that they are much easier to separate from the radiofluorinated products than the nitro- or haloarene based precursors, which tend to have similar chromatographic properties.



Scheme 1.13: General reaction scheme for radiofluorination by S_NAr.

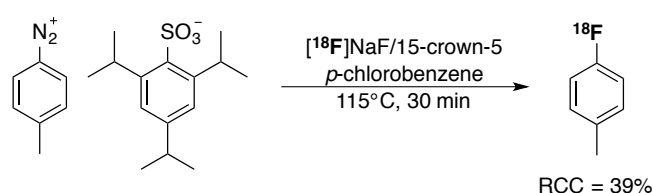
Harsh conditions are normally required, with reactions run at high temperatures in polar aprotic solvents such as DMF or DMSO. Molten salts have also been used as the reaction medium, though to a much lesser degree.⁵⁴ Due to the required conditions, functional groups carried by substrates radiofluorinated in this manner are required to have significant thermal stability. There are examples of S_NAr radiofluorination reactions being run with milder conditions, however the precursors require very favourable substitution patterns. Indeed, 2-chloro-1-[¹⁸F]fluoro-4-nitrobenzene can be prepared with 71 - 76% RCC from the trimethylammonium triflate precursor at room temperature.⁵⁵



Scheme 1.14: S_NAr radiofluorination in synthesis of [¹⁸F]FDOPA by Luxen and Lemaire.^{56, 57}

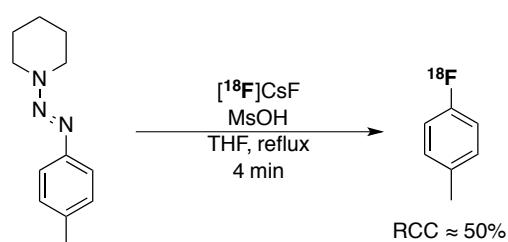
Despite the conditions required, the relative ease of preparation and stability of these precursors compared to those required for alternative syntheses of [¹⁸F]arenes mean that the S_NAr approach has been applied to a large number of radiopharmaceuticals. In cases where the target compound does not bear the necessary electron deficient ring, rapid and efficient post-fluorination strategies have been devised. This can be demonstrated by the radiofluorination of 6-[¹⁸F]fluoro-L-dihydroxy-phenylalanine ([¹⁸F]FDOPA) from Luxen and Lemaire (Scheme 1.14), which involves four post-fluorination steps, though remains the highest yielding routes in literature.^{56, 57}

The earliest routes to electron neutral and electron rich arenes were thermal fluorodediazonations,⁵⁸ based on the Balz-Schiemann reaction from aryldiazonium [¹⁸F]tetrafluoroborates though, due to competing incorporation of fluorine-19, the maximum theoretical incorporation would be 25% with very low SA. The incorporation and SA could both be increased by use of modified Balz-Schiemann reactions with use of counter-ions that would not undergo isotopic exchange, such as the diazonium 2,4,6-triisopropylbenzenesulfonate precursor (Scheme 1.15).⁵⁹



Scheme 1.15: Radiosynthesis of 4-[¹⁸F]fluorotoluene via a modified Balz-Schiemann reaction.⁵⁹

An alternative route to the diazonium precursor is to form it *in situ* by means of a Wallach reaction; protonation of a 1-aryl-3,3-dialkyl triazene substrate promotes decomposition to the corresponding amine and diazonium (Scheme 1.16).⁶⁰ Thermal decomposition of this diazonium in the presence of [¹⁸F]fluoride gives the [¹⁸F]fluoroarene.

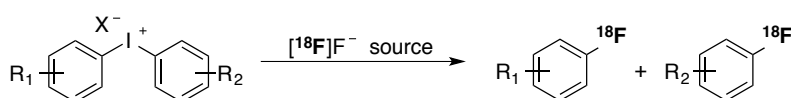


Scheme 1.16: Radiosynthesis of 4-[¹⁸F]fluorotoluene via a Wallach reaction.⁶⁰

Neither of these routes found much application in light of other protocols that involve more stable precursors. Triarylsulfonium salts⁶¹ and diaryl sulfoxides⁶² can be used for electron deficient and neutral arenes, though radiofluorination of diaryliodonium salts is one of the most favoured modern routes to [¹⁸F]arenes as electron rich, neutral and deficient arenes can be labelled (Scheme 1.17).⁶³ When reacted with [¹⁸F]fluoride,

[^{18}F]fluoroarene and the corresponding iodoarene are produced; the regioselectivity is dictated primarily by the comparative electron density on the two arenes. For unsymmetrical diaryliodonium salts, the radiofluorination favours the more electron deficient arene, though in almost all reactions there is a degree of the secondary [^{18}F]arene formed. Consequently, *para* methoxy substitution is often utilised on one arene to direct the radiofluorination toward the other aromatic.

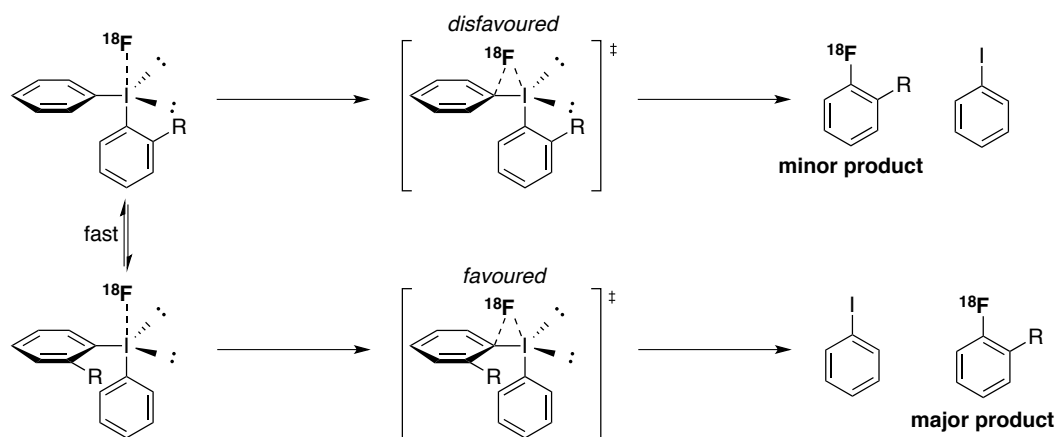
There have been attempts to find non-participating aromatic substituents, with 2-thienyl⁶⁴ being proposed as a promising candidate for regiospecific [^{18}F]labelling, though the lack of 2-[^{18}F]fluorothiophene was later acknowledged to be more likely due to problematic identification under radiofluorination conditions.⁶⁵



Scheme 1.17: General reaction scheme for radiofluorination of diaryliodonium salts.

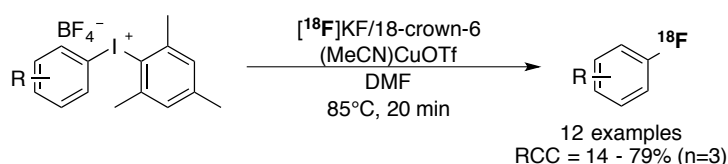
A study by Coenen suggests that the counter-ion also plays a significant role in the reactivity of the substrate.⁶⁴ When considering a series of (2-methoxyphenyl)(2-thienyl)iodonium salts the counter-ion effect on the RCC is tosylate < iodide < triflate < bromide and for reaction rates is tosylate < bromides < iodides < triflates.

Furthermore, substitution at the *ortho* position on one aromatic ring has a profound effect in shifting the selectivity toward that arene. This ‘*ortho* effect’ is attributed to mechanistic considerations; starting from a trigonal bipyrimidal complex⁶⁶ the transition state in which the *ortho* substituent lies in an equatorial position is favoured (Scheme 1.18). Pike conducted a study on this effect,⁶⁷ determining that the capacity of the *ortho* substituent to direct the radiofluorination toward its aromatic ring progresses 2-methoxy < hydrogen < 2-iso-propyl $\approx$ 2-ethyl < 2-methyl < 2-bromo < 2,4,6-trimethyl < 2,6-dimethyl. The appearance of the 2-methoxy at the lower end of that series suggests that the ‘*ortho* effect’ is not solely a steric effect.



Scheme 1.18: Mechanism of radiofluorination of diaryliodonium salts, demonstrating the 'ortho' effect'.⁶⁶

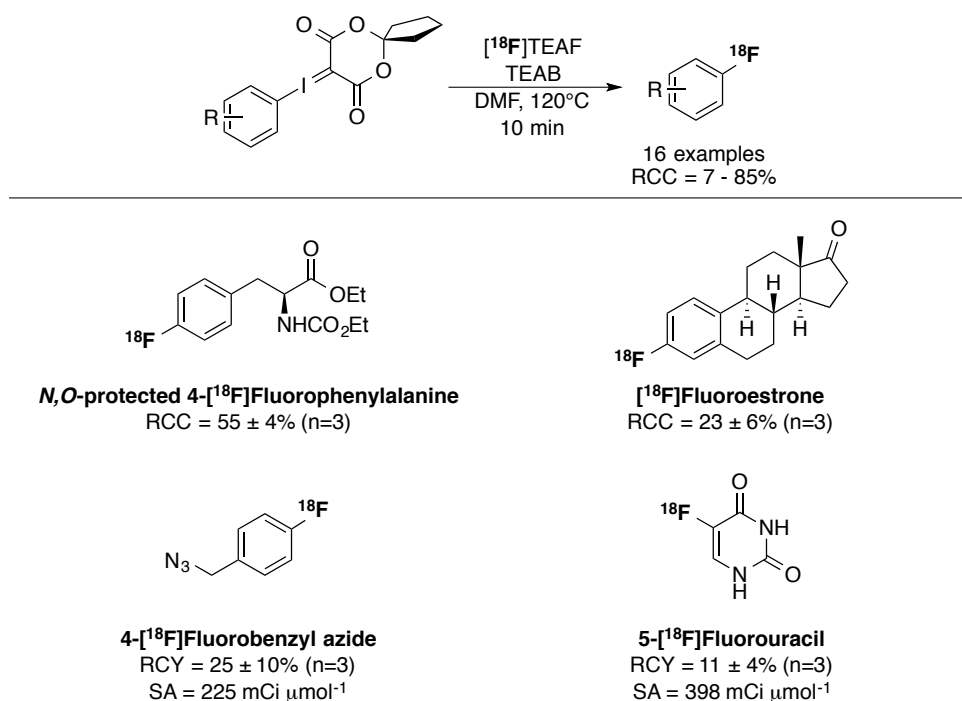
The use of Cu(I) and Cu(II) salts to mediate the fluorination of diaryliodonium salts was pioneered by Sanford, a protocol that effectively eliminates the regioselectivity determined by the relative electron densities and any 'ortho effect' in favour of a strong steric bias for the smaller aryl group during oxidative addition at the copper centre.⁶⁸ Sanford, in collaboration with Scott, was able to translate this for radiofluorination, during which they found that the Cu(I) source $(\text{MeCN})_4\text{CuOTf}$ gave the best incorporation and reproducibility (Scheme 1.19).⁶⁹



Scheme 1.19: Cu(I)-mediated radiofluorination of diaryliodonium tetrafluoroborates.⁶⁹

A similar set of precursors, iodonium ylides, have recently emerged as a promising alternative to the diaryliodonium salts, giving complete regioselectivity for the radiofluorination on the arene. The earliest report of their use for radiofluorination of arenes was in a patent by Satyamurthy and Barrio in 2010,⁷⁰ an approach that was taken forward by Coenen for the radiosynthesis of two serotonin and norepinephrine reuptake transporter (SERT and NET) ligands, 4-((3- and 4-fluorophenoxy)phenylmethyl)piperidine.⁷¹

Optimisation studies on the iodonium ylide by Vasdev first introduced the spirocyclic auxiliary, with the cyclopentyl found to increase precursor stability and incorporation of [^{18}F]fluoride during radiofluorination.⁷² They were able to demonstrate applicability to a series of substrates bearing electron donating and withdrawing functionalities, as well as four compounds with radiopharmaceutical interest, including the first radiosynthesis (SPE isolation) of 5- ^{18}F fluorouracil from nucleophilic [^{18}F]fluoride with $\text{RCY} = 11 \pm 4\%$ ($n=3$) [n.d.c.] (Scheme 1.20). A series of azido click reagents were later synthesised using this methodology by the same group.⁷³

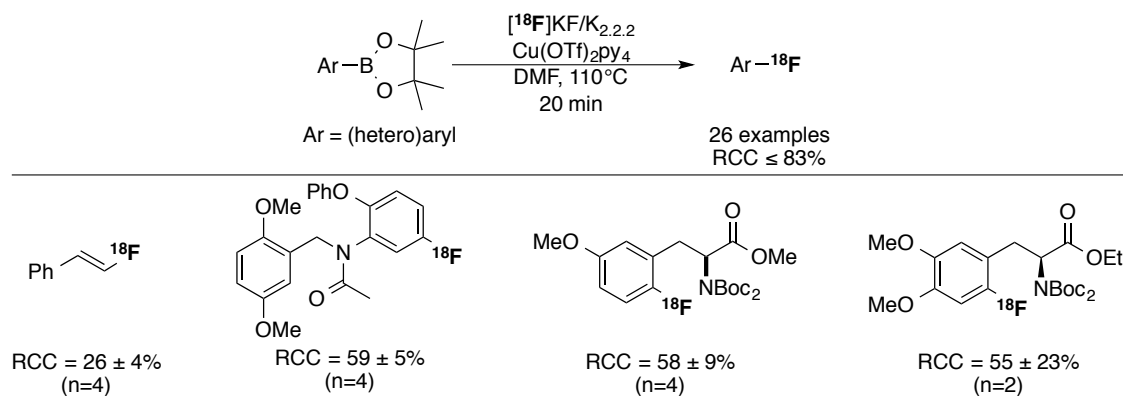


Scheme 1.20: Radiofluorination of spirocyclic iodonium ylides.⁷²

Aside from use with diaryliodonium salts, copper has also been shown to promote the fluorination of arylboronate esters. The first example of this was disclosed by Hartwig, using an electrophilic fluorine source, 1-fluoro-2,4,6-trimethylpyridinium hexafluorophosphate in conjunction with silver fluoride.⁷⁴ Sanford was later able to build from this to a purely nucleophilic approach, using potassium fluoride and $\text{Cu}(\text{OTf})_2$.⁷⁵

In 2014, Tredwell, Preshlock, Taylor *et al.*, from the Gouverneur group, established the first protocol for [^{18}F]fluoride radiolabelling of pinacolyl arylboronates mediated by $\text{Cu}(\text{OTf})_2\text{py}_4$ (Scheme 1.21).⁷⁶ This procedure was able to demonstrate effectiveness on a wide range of arenes, substituted *ortho*, *meta* and *para* with electron withdrawing and donating groups, and heteroarenes in the form of 5-[^{18}F]fluoro-1-tosyl-1H-indole and 6-[^{18}F]fluoroquinoline. Furthermore, they were able to access three radiopharmaceuticals, (*N*-5-[^{18}F]fluoro-2-phenoxyphenyl)-*N*-(2,5-dimethoxybenzyl)acetamide ([^{18}F]DAA1106), 6-[^{18}F]fluoro-*m*-D,L-tyrosine and [^{18}F]FDOPA in good radiochemical conversions. [^{18}F]DAA1106, a very potent translocator protein (18 kDa) (TSPO) PET ligand,⁷⁷ was labelled in $\text{RCC} = 59 \pm 5\%$ ($n=4$) and a *N,N*-diBoc protected 6-[^{18}F]fluoro-*m*-D,L-tyrosine methyl ester was found to give $\text{RCC} = 58 \pm 9\%$ ($n=4$), which included 16% of the partially deprotected *N*-Boc analogue. The deprotection could be completed by treatment with HI (57%) at 130°C.

Similarly, a *N,N*-diBoc protected ethyl ester precursor for [^{18}F]FDOPA could be radiofluorinated in $\text{RCC} = 55 \pm 23\%$ ($n=2$), with quantitative deprotection by HI (57%). Industrial collaborators, Imanova, were able to isolate 609 MBq of [^{18}F]FDOPA from 13 GBq ($\text{RCY} = 12\%$ ($n=1$) [d.c.]) of starting [^{18}F]fluoride by this protocol, which met the European Pharmacopoeial standards with radiochemical purity and enantiomeric excess both exceeding 98%.

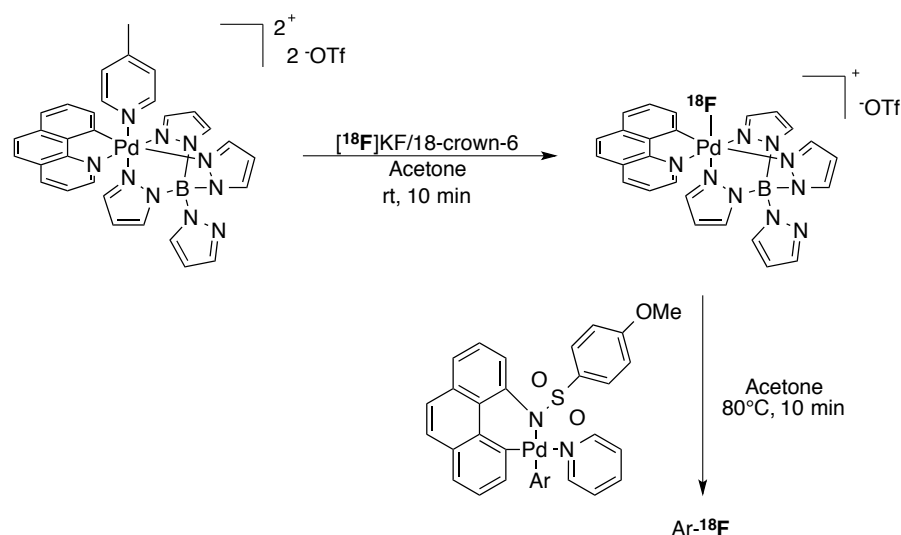


Scheme 1.21: $\text{Cu}(\text{OTf})_2\text{py}_4$ mediated radiofluorination of pinacolyl arylboronates.⁷⁶

Recently Sanford and Scott have reported a similar protocol for the radiofluorination of arylboronic acids, with similar functional group tolerance shown by the Gouverneur approach.⁷⁸

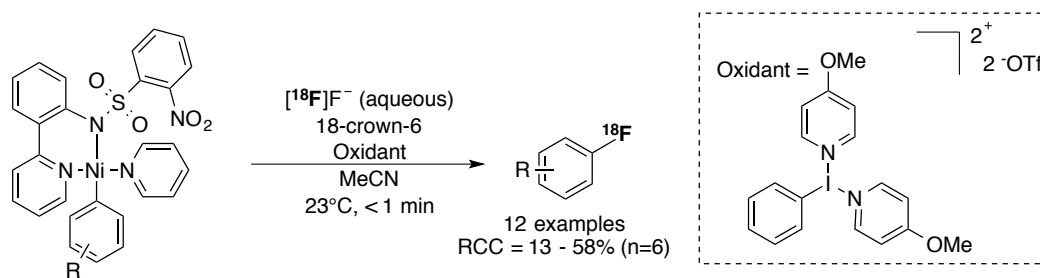
Ritter approached the radiofluorination of electron rich arenes with a [¹⁸F]fluoride umpolung approach (Scheme 1.22).⁷⁹ Reaction of [¹⁸F]KF/18-crown-6 with a highly fluorophilic Pd(IV) complex gave 90% incorporation as a Pd(IV)-¹⁸F complex. This new complex is now considered an electrophilic [¹⁸F]fluorine reagent, produced from nucleophilic [¹⁸F]fluoride. This removes the low SA and handling issues found when producing electrophilic radiofluorination reagents from [¹⁸F]F₂. A second preformed Pd(II)-aryl complex is then introduced, and following an initial single electron transfer (SET), the [¹⁸F]fluoride is transferred from the Pd(III)-¹⁸F complex to the Pd(III)-aryl complex. A second SET precedes the reductive elimination to form the ¹⁸F-aryl bond.⁸⁰

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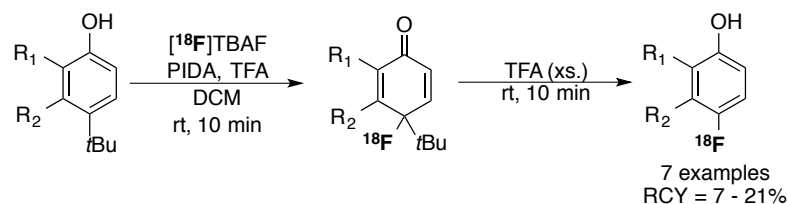
Scheme 1.22: Radiosynthesis of [¹⁸F]arenes utilising preformed Pd(IV) and Pd(II) complexes.⁷⁹

Ritter has also reported that Ni(II)-aryl complexes can undergo a similar mechanism, but rather than two preformed Pd complexes being required, a single complex can achieve the [¹⁸F]fluoride capture and subsequent reductive elimination (Scheme 1.23).⁸²



Scheme 1.23: Ni(II)-mediated radiofluorination of arenes.⁸²

An alternative, metal-free, umpolung approach was developed in the Gouverneur group, in which the reactivity of the precursor was switched, rather than of the [¹⁸F]fluoride (Scheme 1.24).⁸³ Targeting the *para* radiofluorination of phenolic structures, a commercial hypervalent iodine reagent was used to oxidatively dearomatise a precursor bearing a *para tert*-butyl functionality. This activated the ring toward nucleophilic attack by [¹⁸F]fluoride, with *para* selectivity directed by inductive stabilisation of the intermediate cation on this position by *tert*-butyl. Acid mediated rearomatisation furnished the corresponding 4-[¹⁸F]fluorophenol.



Scheme 1.24: Oxidative radiofluorination of phenols by Gao *et al.*⁸³

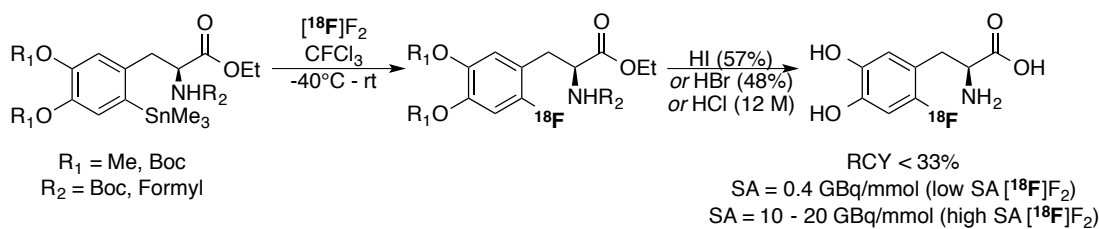
The reaction was demonstrated on a small number of model substrates, though a palladium-mediated post-fluorination Suzuki-Miyaura cross coupling of phenylboronic acid and 2-bromo-4-[¹⁸F]fluorophenol synthesised by this procedure was also established. While the 4-fluorophenol motif is present in several important radiotracers, this protocol has yet to be successfully applied to the radiofluorination of these.

1.3.3 Electrophilic [^{18}F]Fluorination

Electrophilic [^{18}F]fluorination does enable access to some systems that are difficult to access by nucleophilic routes, though its use is becoming less common especially with the development of new nucleophilic radiofluorination routes. The reasons centre on four main areas: 1) few facilities are equipped to produce and handle [^{18}F]F₂ gas used for electrophilic radiofluorination or preparation of other electrophilic [^{18}F]sources. 2) Reactions that use [^{18}F]F₂ often suffer from low regioselectivity resulting in a mixture of [^{18}F]labelled products, leading to more complex and longer purification requirements. 3) The radiochemical yield is inherently limited to a maximum of 50%. 4) Due to the use of F₂ as a carrier, the SA of the final products is low.

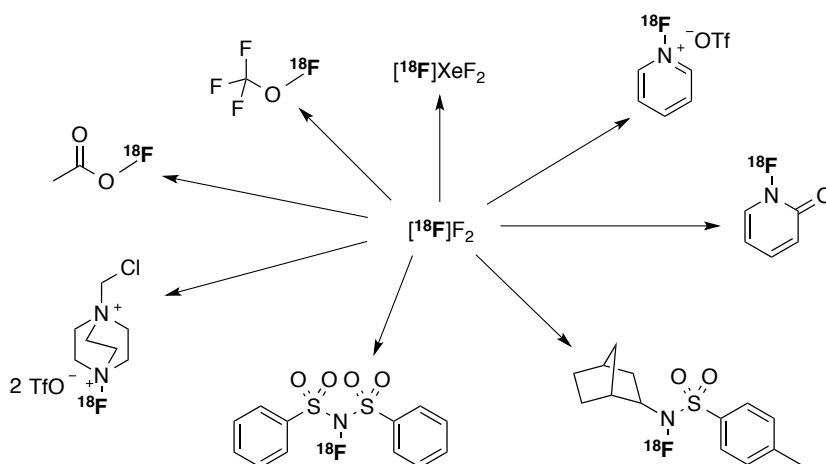
Notwithstanding these limitations, electrophilic routes in radiofluorination are well established and [^{18}F]F₂ has been used to prepare several imaging agents. Routes to aliphatic compounds are limited due to the highly reactive nature of [^{18}F]F₂ leading to non-regiospecific labelling, though include the direct [^{18}F]fluorination of alkenes, used for the radiosynthesis of nucleoside analogues,⁸⁴ and addition of [^{18}F]F₂ across a perfluorinated olefin to access [^{18}F]EF5.⁸⁵

Aromatically [^{18}F]labelled compounds are prepared via radiofluorodemetalation, most commonly on precursors bearing trialkyltin substitution exemplified by the synthesis of [^{18}F]FDOPA⁸⁶ (Scheme 1.25) and related structures 3-O-methyl-6-[^{18}F]fluoro-L-DOPA⁸⁷ and 2-[^{18}F]fluoro-L-tyrosine.⁸⁸ This radiosynthesis demonstrates the improvements to SA offered by the high SA protocols reported by Bergman and Solin, with SA increasing from 0.4 GBq/ μmol to 10 GBq/ μmol .⁸⁹



Scheme 1.25: General electrophilic route to $[^{18}\text{F}]\text{FDOPA}$.

$[^{18}\text{F}]\text{F}_2$ can also be used to prepare secondary radiofluorination reagents, designed to limit the reactive nature of this gas and increase selectivity and functional group tolerance (Scheme 1.26). These secondary reagents include O- $[^{18}\text{F}]\text{fluorinated}$ hypofluorides, perchloryl $[^{18}\text{F}]\text{fluoride}$, $[^{18}\text{F}]\text{XeF}_2$ and N- $[^{18}\text{F}]\text{F}$ reagents.



Scheme 1.26: Secondary electrophilic $[^{18}\text{F}]\text{fluorination}$ reagents derived from $[^{18}\text{F}]\text{F}_2$.

Acetyl $[^{18}\text{F}]\text{hypofluorite}$ ($[^{18}\text{F}]\text{AcOF}$) and more reactive trifluoromethyl $[^{18}\text{F}]\text{hypofluorite}$ ($[^{18}\text{F}]\text{F}_3\text{COF}$) have both been prepared, though via differing routes. The trifluoromethyl $[^{18}\text{F}]\text{hypofluorite}$ species is prepared by reacting cesium fluoride, F_2 and carbonyl fluoride with target bound ^{18}F in the target chamber at 100°C for 35 minutes.⁹⁰

Acetyl $[^{18}\text{F}]\text{hypofluorite}$, which is the most widely used electrophilic radiofluorination reagent after $[^{18}\text{F}]\text{F}_2$, is prepared in a gas-solid phase reaction from $[^{18}\text{F}]\text{F}_2$ being passed through a column containing acetic acid and alkali metal acetate as the stationary phase. This reaction is quantitative and the column is consequently flushed to release

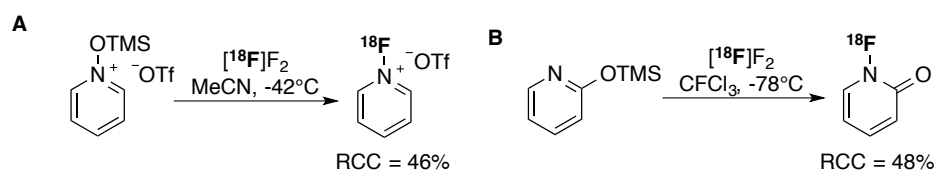
half of the activity as [^{18}F]AcOF and the remaining activity as [^{18}F]HF.AcOK.⁹¹ This secondary reagent has been used to label a phenylalanine residue of a cyclic Arg-Gly-Asp (RDG) peptide for imaging of tumors.⁹² This reaction did yield mono- and difluorinated products, which could be purified by chromatography and used to image integrin receptors, a family of transmembrane glycoproteins that mediate cell adhesion to extracellular matrix proteins and other cells.

Perchoryl [^{18}F]fluoride ([^{18}F]FClO₃) can be prepared in a manner similar to that of [^{18}F]AcOF, with a stationary phase of KClO₃ utilised and half of the activity forming the desired [^{18}F]FClO₃, with the remaining 50% forming [^{18}F]KF.⁹³ There have been attempts to prepare this reagent from [^{18}F]fluoride in n.c.a. procedure by addition of fuming sulfuric acid to [^{18}F]fluoride (as [^{18}F]HF or [^{18}F]KF) in the presence of HClO₄, though this approach is very low yielding (1 – 6%).⁹⁴

XeF₂ is a powerful fluorination reagent, and the [^{18}F]analogue can be prepared from [^{18}F]F₂ by the direct reaction of xenon at high pressure and high temperature in a sealed nickel reactor, with the solid reagent isolated by vacuum sublimation.⁹⁵ More recent routes to [^{18}F]XeF₂ tend to use [^{18}F]fluoride in acetonitrile with heating or in DCM at room temperature.⁹⁶⁻⁹⁸ [^{18}F]XeF₂ formed from [^{18}F]F₂ has been used to label [^{18}F]FDG^{99,100} and [^{18}F]FDOPA, though only with poor incorporation overall.¹⁰¹

N-F reagents are the most commonly used research laboratory sources of electrophilic fluorine,¹⁰² and accordingly several *N*-[^{18}F]F reagents have been prepared from [^{18}F]F₂. The earliest reports of one of these reagents was from Oberdorfer *et al.* in 1988, by the reaction of [^{18}F]F₂ on *N*-trimethylsilylpyridinium triflate in MeCN to give *N*-[^{18}F]fluoropyridinium triflate (Scheme 1.27, A)¹⁰³ and reaction on 2-(trimethylsiloxy)pyridine in CFCl₃, to give 1-[^{18}F]fluoro-2-pyridone (B).¹⁰⁴ Both of these

reactions gave RCY = 40 – 49%, with significant quantities of [^{18}F]FSiMe₃ formed as a by-product.

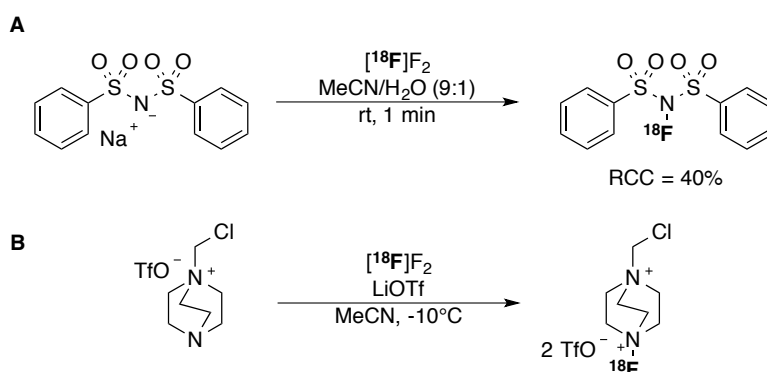


Scheme 1.27: Radiosynthesis of *N*-[^{18}F]fluoropyridinium triflate (A)¹⁰³ and 1-[^{18}F]fluoro-2-pyridone (B).¹⁰⁴

These reports were shortly followed by Satyamurthy *et al.*, who prepared a range of *N*-[^{18}F]fluoro-*N*-alkylsulfonamides from the parent *N*-alkylsulfonamides with [^{18}F]F₂ in RCY < 45%, which were shown to be efficient reagents for the radiofluorination of arylmagnesium bromide precursors.¹⁰⁵ These three original *N*-[^{18}F]F reagents were presented to have promise as secondary electrophilic [^{18}F]fluorination reagents, however there have been no further reports beyond their initial preparation and application.

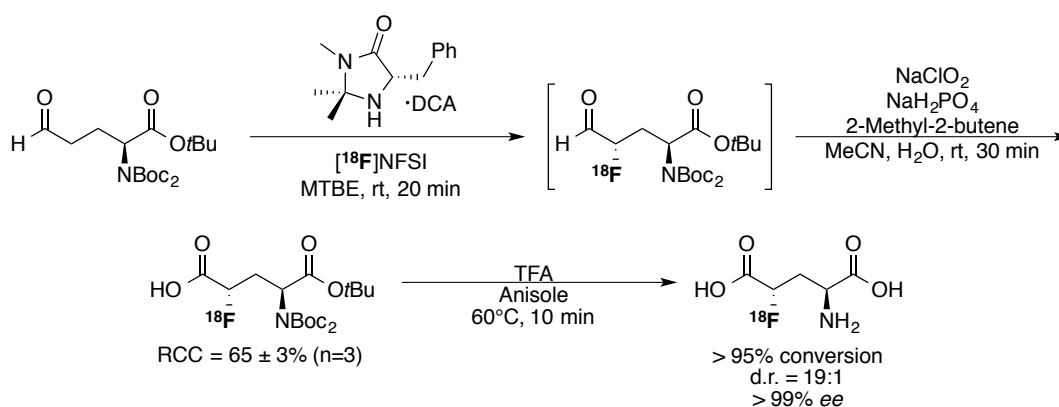
More recently, two of the most commonly utilised *N*-F reagents, *N*-fluorobenzenesulfonimide (NFSI) and 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (Selectfluor) have been prepared as [^{18}F]analogues. [^{18}F]NFSI^{106, 107} is synthesized by bubbling [^{18}F]F₂ through a MeCN/H₂O solution containing the sodium salt precursor (Scheme 1.28, A) and [^{18}F]Selectfluor bis(triflate)¹⁰⁸ is prepared similarly from the DABCO derived precursor in MeCN at -10°C or acetone at room temperature in the presence of lithium triflate (B). This procedure utilised high SA [^{18}F]F₂ and the triflate counter ion was chosen in preference to the tetrafluoroborate used with Selectfluor to eliminate isotopic exchange and consequent loss of SA, with studies further suggesting the bis(triflate) is the more reactive analogue.¹⁰⁹ For both of these synthesis, one equivalent of [^{18}F]NaF and [^{18}F]LiF, respectively, was formed. The radiochemical incorporation could be

determined for [^{18}F]NFSI, but not for [^{18}F]Selectfluor as it could not be identified by HPLC as it lacked a chromophore and co-elutes with [^{18}F]LiF.



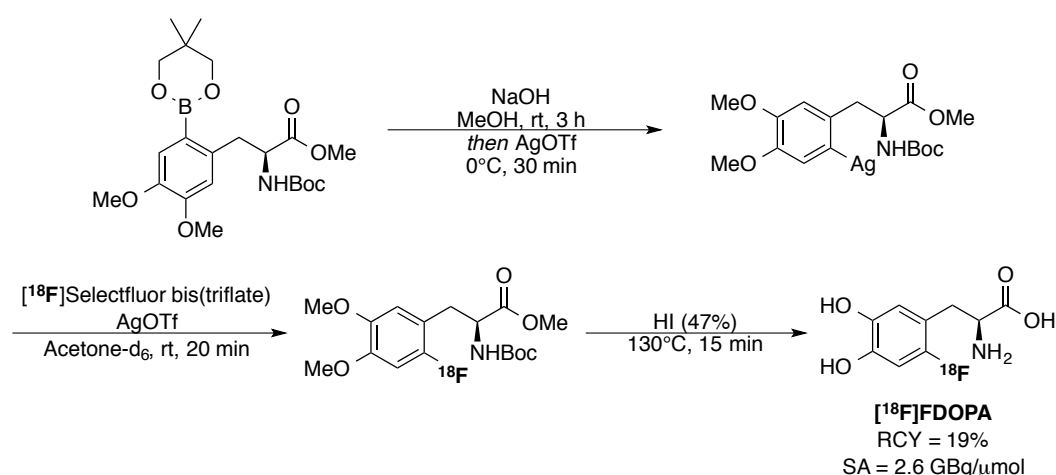
Scheme 1.28: Radiosynthesis of [^{18}F]NFSI (A)^{106, 107} and [^{18}F]Selectfluor (B).¹⁰⁸

[^{18}F]NFSI can be identified by radioHPLC and can be obtained in up to 40% RCY [n.d.c.], indicating the reaction almost matched the maximum theoretical yield ($\text{RCY}_{\text{max}} = 50\%$ due to formation of [^{18}F]NaF) and is azeotropically dried before use. It has been applied to the radiofluorination of allyl silanes and silyl enol ethers with excellent conversion. A recent report from Buckingham *et al.* has further established the importance of [^{18}F]NFSI with the first examples of organomediated asymmetric [^{18}F]fluorination to give enantioenriched α -[^{18}F]fluoroaldehydes ($ee > 90\%$), exemplified by the radiosynthesis of (2*S*,4*S*)-4-[^{18}F]fluoroglutamic acid (Scheme 1.29) which has shown potential for imaging lung and breast tumours¹¹⁰ or as an alternative to [^{18}F]FDG in [^{18}F]FDG negative tumours.¹¹¹



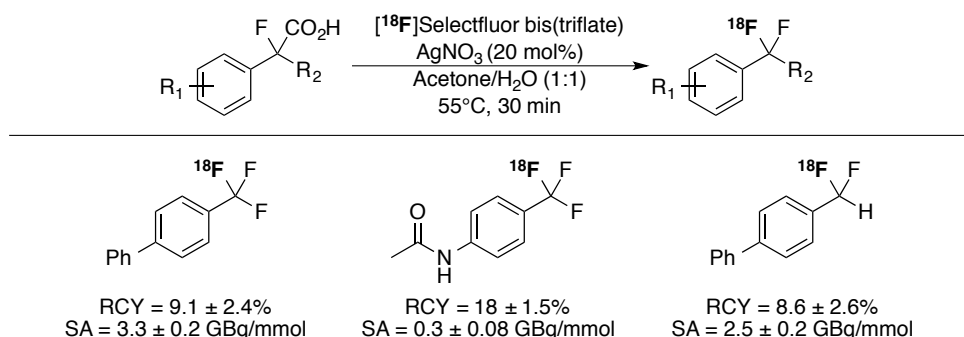
Scheme 1.29: Radiosynthesis of (2*S*,4*S*)-4-[^{18}F]fluoroglutamic acid.¹⁰⁷

$[^{18}\text{F}]$ Selectfluor bis(triflate), which was unsuccessful when applied to the enantioselective organomediated radiofluorination of Buckingham *et al.*, has been successfully applied to the radiofluorination of electron-rich aryl stannane precursors in the presence of 2 equivalents of AgOTf in acetone.¹⁰⁸ Furthermore, it has been used for the radiosynthesis of $[^{18}\text{F}]$ FDOPA in a 19% RCY (SA = 2.6 GBq/ μmol), from an arylboronate ester precursor via an aryl silver species (Scheme 1.30).¹¹²



Scheme 1.30: Radiosynthesis of $[^{18}\text{F}]$ FDOPA with $[^{18}\text{F}]$ Selectfluor (bis)triflate.¹¹²

$[^{18}\text{F}]$ Selectfluor bis(triflate) has also been used in silver-mediated decarboxyfluorination of α,α -difluoro- and α -fluoroarylacetic acids to give the corresponding $[^{18}\text{F}]$ tri- and $[^{18}\text{F}]$ difluoromethylarenes (Scheme 1.31), which are not accessible from $[^{18}\text{F}]\text{F}_2$.¹¹³



Scheme 1.31: Ag(I)-mediated decarboxyradiofluorination with $[^{18}\text{F}]$ Selectfluor bis(triflate).¹¹³

1.4. Thesis Outline

This thesis is concerned with expanding the field of radiofluorination chemistry, utilising [^{18}F]fluoride. Following this general introduction (**Chapter 1**) to PET, fluorine-18, its production and radiofluorination, it is split into two distinct parts; **Part I** (**Chapters 2 - 4**) details work toward the synthesis of [^{18}F]fluoroarenes and **Part II** (**Chapters 5 and 6**) is focused on diversity oriented radiofluorination, regarding development of novel [^{18}F]motifs and using single precursors as the foundation to access several radiolabelled substructures.

Part I, Chapter 2 examines the use of an umpolung approach to fluorination and radiofluorination of *N*-arylsulfonamides and anilides, mediated by hypervalent iodine reagents.

Chapter 3 explores the application of microfluidic technology to the radiofluorination of spirocyclic iodonium(III) ylides, with rapid optimisation and application to radiopharmaceuticals, including the fully automated synthesis of 4-[^{18}F]fluorobenzyl azide.

In **Chapter 4**, the use of copper-mediated radiofluorination of aryl boronic pinacol esters, developed in the Gouverneur group, is applied to the isolation of [^{18}F]labelled radiopharmaceuticals, providing a generally-applicable route to diverse range of important tracers.

Part II, Chapter 5 contains several projects focused on the preparation of *geminal* difluorinated motifs, by both electrophilic and nucleophilic fluorination methods. The core of the work centres on the use of halogen exchange reactions by [^{18}F]fluoride to prepare these motifs with aims toward post-fluorination functionalization of [^{18}F]ArOCF₂CO₂H and [^{18}F]ArCF₂CO₂H. Finally, the application of similar

methodology for the assembly of three novel [^{18}F]labelled motifs, [^{18}F]ArOCF₃, [^{18}F]ArOCF₂H and [^{18}F]ArSCF₃, as well as [^{18}F]ArCF₃ and [^{18}F]ArCF₂H is discussed.

The use of a single diazo precursor is described in **Chapter 6** for the synthesis of three [^{18}F]motifs; the first example of using [^{18}F]fluoride to label CF₂CF₃, and the first examples of ArC¹⁸FHCF₃ and ArC¹⁸FBrCF₃.

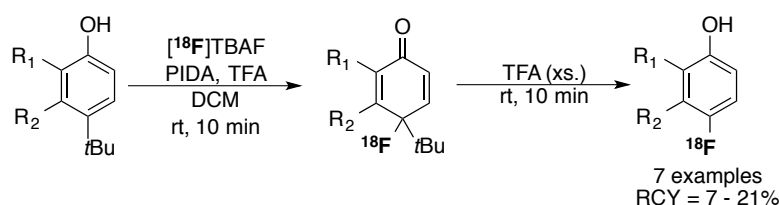
Finally, **Chapter 7** provides the experimental procedures and characterisation of substrates presented in this thesis, as well as the thesis references.

PART I

Synthesis of [^{18}F]Arenes

2. Oxidative Fluorination and Radiofluorination of *N*-Protected Anilines

As discussed in Chapter 1, most applicable routes to the (radio)fluorination of electron-rich arenes require transition metal activation^{79, 82, 114, 115} or the preparation of hypervalent iodine(III) precursors.⁶³ One of the alternative strategies followed an umpolung approach, utilised by the Gouverneur group for the radiofluorination of phenols (see Section 1.3.2.2. for full discussion).⁸³



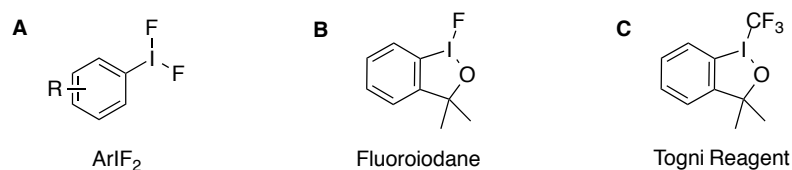
Scheme 2.1: Oxidative radiofluorination of phenols by Gao *et al.*⁸³

While hypervalent iodine reagents have been shown to mediate a wide range of oxidative transformations,¹¹⁶⁻¹²⁰ at the start of this project, this remained the only example of its use in [¹⁸F]radiochemistry. This project targeted this umpolung approach, with an aim to expand the breadth of its application in this field.

2.1. Introduction

Oxidative fluorinations, using hypervalent iodine(III), can either utilise separate oxidising and fluorinating reagents, such as diacetoxyiodobenzene (PIDA) with an external fluoride source, or involve a single oxidising and fluorinating substance which carries the fluorine on an iodine(III) centre (an I-F reagent). There are two forms of I-F reagent, with the earliest forms and most common being difluoroiodoarenes (ArIF₂) (Scheme 2.2, A). The other category takes the form of monofluoro species, as 1-fluoro-3,3-dimethyl-1,2-benziodoxazole (fluoroiodoane) (B), with a structure similar to that

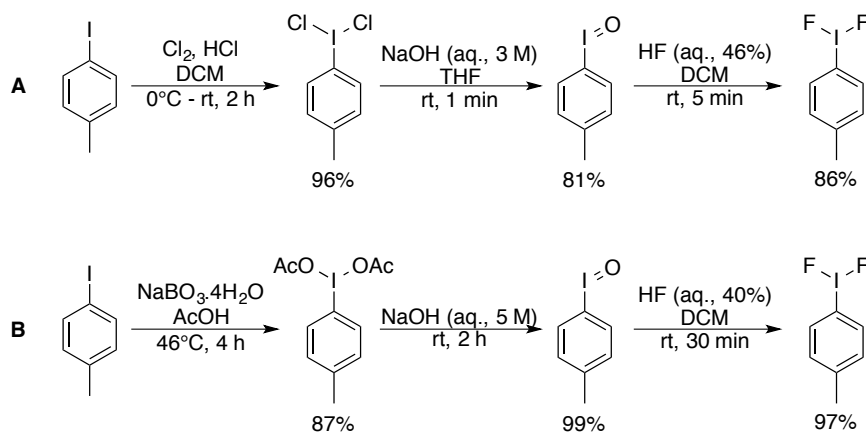
found with the Togni's trifluoromethylation reagent, 3,3-dimethyl-1-(trifluoromethyl)-1,2-benziodoxole (C).



Scheme 2.2: Structures of difluoroiodoarenes (ArIF_2) (A), 1-fluoro-3,3-dimethyl-1,2-benziodoxole (fluoriodane) (B) and 3,3-dimethyl-1-(trifluoromethyl)-1,2-benziodoxole (Togni Reagent) (C).

2.1.1. Difluoroiodoarenes

ArIF_2 reagents have been synthesised by several different methods, however the most commonly used routes are via oxidation of the parent aryl iodide to corresponding dichloro-¹²¹ (Scheme 2.3, A) or (diacetoxy)iodoarenes¹²² (B), followed by the base hydrolysis to the iodosoarene and consequent treatment with aqueous HF. The use of the diacetoxyiodoarene, and furthermore the use of (diacetoxy)iodotoluene to afford difluoroiodotoluene (TolIF_2) is favoured due to the increased stability of this compound when compared to the corresponding unsubstituted arenes.



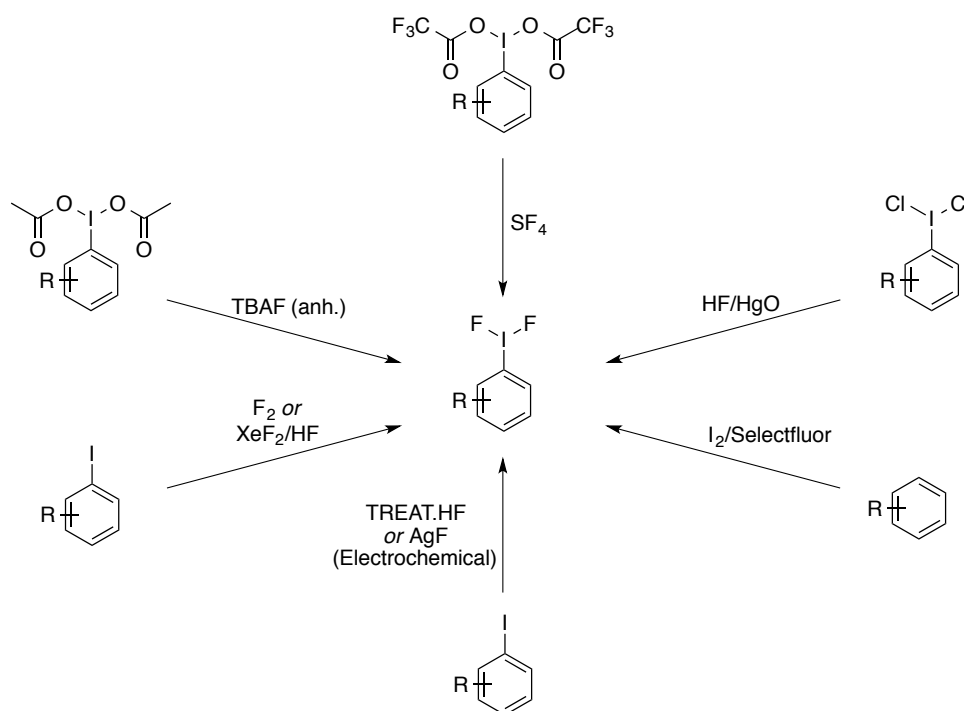
Scheme 2.3: Difluoroiodotoluene (TolIF_2) synthesis scheme via dichloroiodotoluene (A)¹²¹ or (diacetoxy)iodotoluene (B)¹²² with the common iodosoarene intermediate.

These routes are preferred due to the starting materials being relatively cheap and easy to handle, meaning the synthesis can be applied on a large scale.

Other routes from aryl iodine(III) compounds involve reaction with various fluoride sources; reaction of (diacetoxy)iodoarenes with strictly anhydrous TBAF;¹²³ (di-trifluoroacetoxy)iodoarenes with SF₄;¹²⁴ or dichloriodoarenes with aqueous HF in the presence of mercury oxide (Scheme 2.4).¹²⁵

Oxidative difluorination reactions have been described from iodoarenes; via direct fluorination of iodoarenes with F₂ at very low temperature,^{126, 127} with XeF₂ in the presence of anhydrous HF;¹²⁸ electrochemical reactions in the presence of triethylammonium trihydrofluoride (TREAT.HF);^{129, 130} or silver(I) fluoride in acetonitrile.¹³¹

A direct oxidative iododifluorination from the parent arene with elemental iodine and Selectfluor had also been published.¹³²

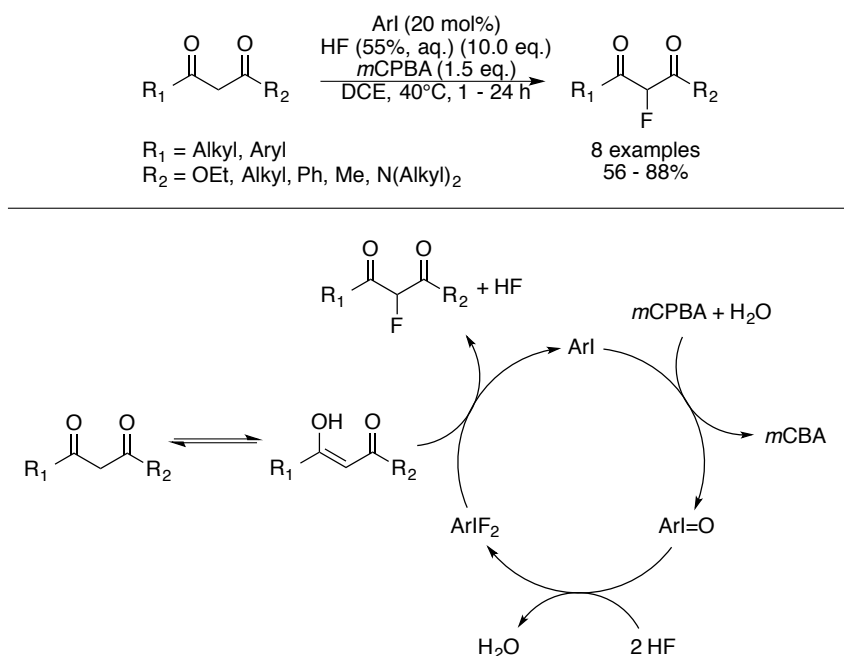


Scheme 2.4: General conditions for synthesis of ArIF₂ reagents.

The use of ArIF₂ reagents has been applied to a wide range of fluorination reactions; fluorination of alkenes and alkynes,¹³³⁻¹³⁶ fluorocyclisations,¹³⁷⁻¹⁴⁰ ring expansion fluorination,^{141, 142} ring contraction fluorination¹⁴³ as well as α-fluorination of carbonyls

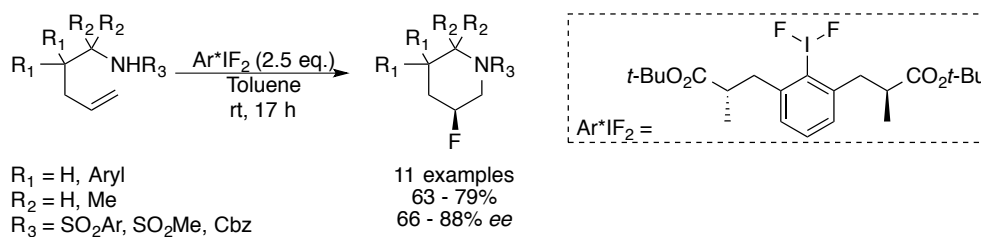
(including 1,3-diketones, β -ketoesters, amides, silyl enol ethers and monocarbonyl compounds).^{130, 140, 144-149} The α -fluorination of α -selenoesters and amides,¹²² and α -phenylthioesters and amides¹⁵⁰⁻¹⁵³ have also been described, via a Fluoro-Pummerer mechanism.

In situ formation of these difluoroiodoarenes has also been reported, in which it is used as a catalyst for oxidative fluorination of 1,3-diketones, β -ketoesters and β -ketoamides (Scheme 2.5).¹⁵⁴ Kitamura *et al.* used *m*CPBA and aqueous HF to regenerate an iodosoarene.



Scheme 2.5: *In situ* generation of catalytic ArIF_2 .¹⁵⁴

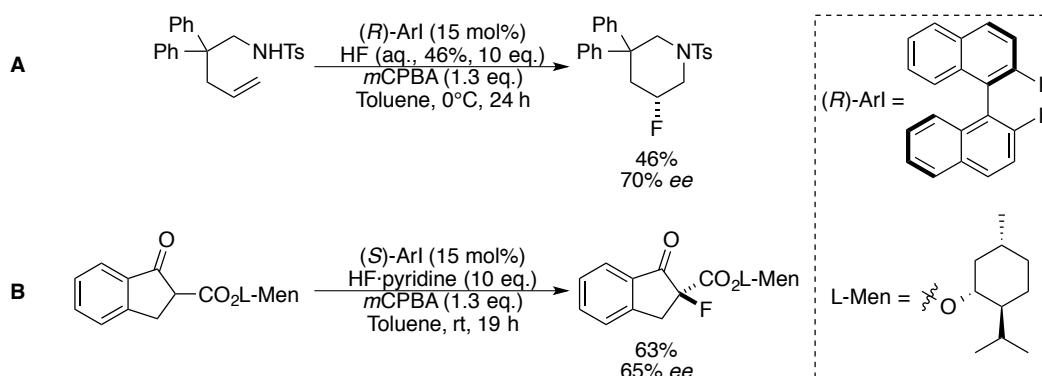
Enantioselective fluorination reactions have also been described, utilising chiral difluoroiodoarenes, synthesised from a chiral iodoarene with Selectfluor and TREAT-HF in MeCN.¹³⁹ Using this reagent for aminofluorination, Nevado *et al.*, could achieve moderate *ee* values for 2-fluoropiperidine and azepane products (Scheme 2.6). Notably, the optimum results, in terms of enantioselectivity, were found when toluene was utilised as the reaction solvent, though the use of DCM gave better yields, in line with other hypervalent iodine-mediated fluorinations.



Scheme 2.6: Enantioselective fluorination using chiral ArIF_2 .¹³⁹

A combination of the two previous routes was investigated by Shibata, Kita *et al.*, to give a catalytic, asymmetric aminofluorination of alkenes.¹⁴⁰ Use of *m*CPBA was used in conjunction with HF·pyridine, allowed the *in situ* formation of chiral difluoroiodoarene from a chiral binaphthyldiiodide precursor. This methodology was also applied to the asymmetric fluorination of β -ketoesters (Scheme 2.7, B) and the aminofluorination of alkenes (A), however only moderate *ee* values could be produced, even with the presence of adamantyl or menthyl esters. The regeneration of the catalytic ArIF_2 species follows the cycle in Scheme 2.5, via the iodosoarene.

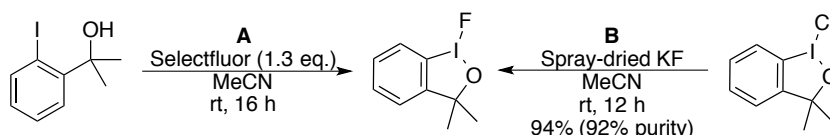
Despite the *ee* values for these procedures remaining moderate, these two reports are notable as the first examples of nucleophilic fluoride being employed in metal-free catalytic enantioselective fluorination reactions.



Scheme 2.7: Enantioselective fluorination using chiral catalytic ArIF_2 .¹⁴⁰

2.1.2. 1-Fluoro-3,3-dimethyl-1,2-benziodoxoles (Fluoroiodane)

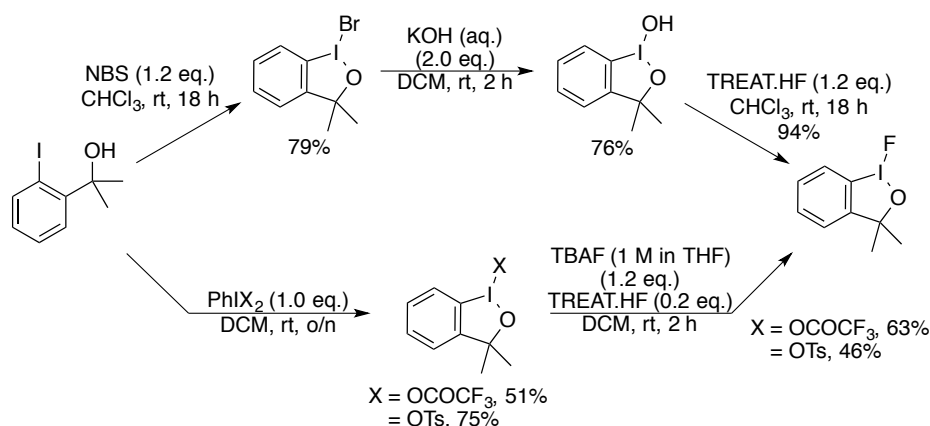
The earliest route to 1-fluoro-3,3-dimethyl-1,2-benziodoxole was described by Legault *et al.*, in 2012, via the oxidative fluorination of 2-(2-iodophenyl)propan-2-ol with an excess of Selectfluor (Scheme 2.8, A).¹⁵⁵ The yield was not specified in the publication, and this route is limited to small scale due to the high cost of Selectfluor.



Scheme 2.8: Synthesis of fluoroiodane by Legault (A)¹⁵⁵ and Togni (B).¹⁵⁶

The Togni group was able to split the oxidation and fluorination steps, while investigating fluoroiodane as an intermediate in the synthesis of the Togni trifluoromethylation reagent. They employed a halogen exchange on the chloro-analogue with spray-dried KF (B),¹⁵⁶ and whilst this route was able to give excellent yields, it required strictly anhydrous conditions, and so, like the Legault procedure, is impractical to apply to large scale production of fluoroiodane.

Shortly after the report by Togni, the Stuart group presented a 3-step protocol starting from the same 2-(2-iodophenyl)propan-2-ol as Legault; oxidative bromination with NBS (79%), substitution with hydroxide (76%) and then fluoride (94%) gave the desired fluoroiodane in a 56% yield over the 3 steps (Scheme 2.9).¹⁵⁷ As the fluorination step engages TREAT.HF as the fluoride source, this protocol would be much more applicable to large scale syntheses. Moreover, this fluoride source can be replaced with TBAF (1.0 M in THF) if the hydroxide group was substituted with a superior leaving group, such as a triflate or tosylate (installed directly from 2-(2-iodophenyl)propan-2-ol), with only 0.2 equivalents of TREAT.HF required.



Scheme 2.9: Stuart group routes to fluoroiodane.¹⁵⁷

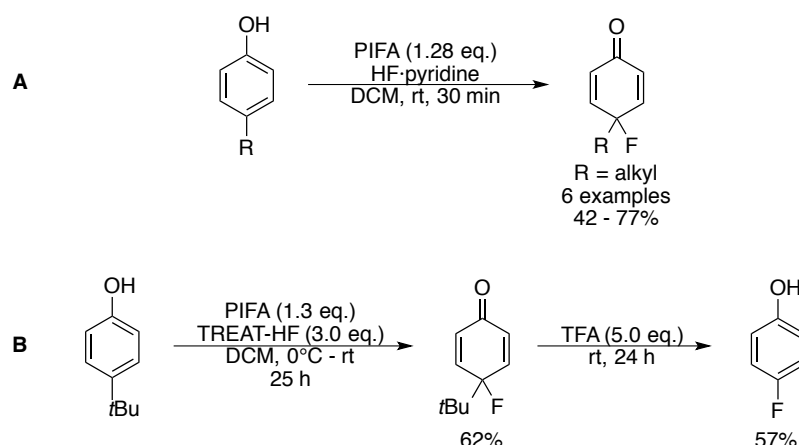
Geary *et al.*, from the Stuart group, were able to show its application to the mono α -fluorination of β -ketoesters and to the difluorination of 1,3-diketones,^{157, 158} as well as intramolecular fluorocyclisation of unsaturated carboxylic acids mediated by silver tetrafluoroborate.¹⁵⁹

Furthermore, the Szabó group have expanded its application to geminal difluorination of styrenes, mediated by silver tetrafluoroborate,¹⁶⁰ Pd(II) catalysed iodofluorination of alkenes,¹⁶¹ Zn(II) catalysed amino- and oxyfluorocyclisations and Cu(I) catalysed carbofluorocyclisation reactions.¹⁶²

2.1.3. Use of Hypervalent Iodine(III) Reagents for the Fluorination of Aromatics

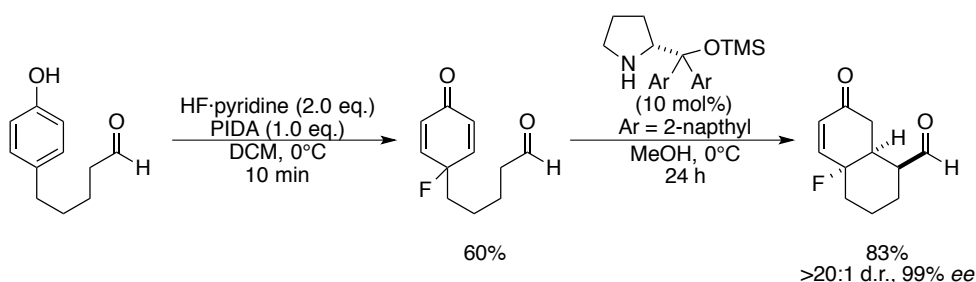
The earliest report of an oxidative fluorination of arenes was by Feiring in 1979, developed with either lead dioxide or cobalt trifluoride in neat HF on acetophenone or nitrobenzene,¹⁶³ however it was not until much later that Jouannetaud, Jacquesy *et al.* published the first oxidative fluorination of phenols, mediated by a hypervalent iodine oxidant, with a slight excess (1.28 equivalents) of oxidant (bis(trifluoroacetoxy)iodo)benzene (PIFA) in HF·pyridine to afford 4-fluorocyclohexa-2,5-dienones (Scheme 2.10, A).¹⁶⁴

Langlois *et al.* introduced the concept of 4-*tert*-butyl substitution to provide a leaving group, enabling site-selective acid mediated rearomatisation of the dienone to give 4-fluorophenol (**B**).¹⁶⁵ In this seminal report, PIFA was again applied as the oxidant, however the fluoride source was changed to TREAT-HF to give 4-*tert*-butyl-4-fluorocyclohexa-2,5-dienone from the first step, which was then treated with TFA to afford the rearomatised 4-fluorophenol.



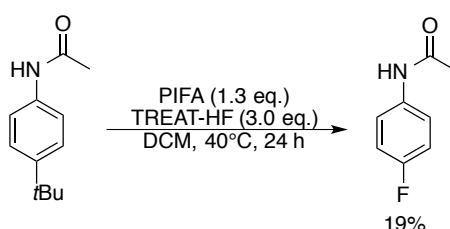
Scheme 2.10: Oxidative fluorination of phenols by Jouannetaud, Jacquesy *et al.* (A)¹⁶⁴ and Langlois *et al.* (B).¹⁶⁵

Oxidative fluorination/cyclisation reactions have also been described, utilising these hypervalent iodine(III) protocols, leading to desymmetrisation of the phenols. The use of pendant *para* amine nucleophiles was reported by Jouannetaud, Jacquesy *et al.* with the cyclisation reaction being promoted by addition of acid or base.¹⁶⁶ The Gaunt group was able to combine this with organocatalysis, developing a chiral amine catalysed desymmetrising, asymmetric intramolecular Michael addition following a oxidative dearomatisation, mediated by PIDA.¹⁶⁷ In this account was a single example of the use of HF-pyridine as a fluoride nucleophile source, resulting in the formation of a quaternary C-F bond with excellent diastereo- and enantioselectivity.



Scheme 2.11: Organocatalytic, enantioselective oxidative dearomatisation of phenols by Gaunt.¹⁶⁷

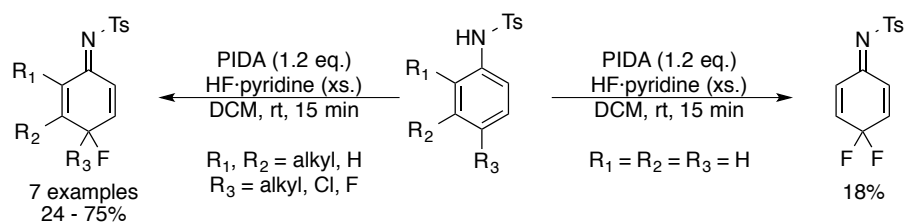
Oxidative fluorination to give fluorinated aromatics is not limited to phenols, and there is precedent for its use on aniline based substrates. In the same publication as the introductions of the *tert*-butyl leaving group, Langlois reported that the same reaction conditions for the oxidative fluorination of phenols on an unprotected 4-*tert*-butylaniline yielded no fluorinated product, though the use of an acetamide protecting group did lead to some success, with a 19% yield of the desired product (Scheme 2.12).¹⁶⁵ Contrasting to the phenols, it was found that the rearomatisation occurred directly without the need for TFA and without the isolation of the 4-*tert*-butyl-4-fluorocyclohexa-2,5-dienimine intermediate.



Scheme 2.12: Oxidative fluorination of 4-*tert*-butylacetanilide by Langlois *et al.*¹⁶⁵

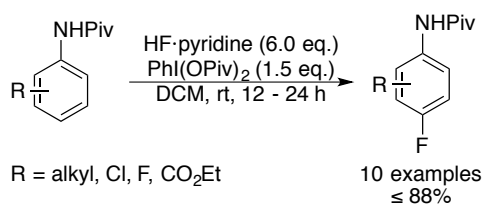
Jouannetaud, Jacquesy and *et al.* were able to expand from this and reported the oxidative fluorination of *N*-tosyl anilines, with PIDA and HF·pyridine.¹⁶⁸ This enabled the isolation of the corresponding 4-fluoro-4-substituted cyclohexa-2,5-dienimines (Scheme 2.13). Di-*ortho* methyl substitution and electron withdrawing groups *para* to the C-N bond lead to high *para* regioselectivity, though removal of the *para*

substituents lead to over oxidation and formation of the difluorinated product, 4,4-difluorocyclohexa-2,5-dienimine.



Scheme 2.13: Oxidative fluorination of *N*-tosyl protected anilines to give mono- or difluorinated products.¹⁶⁸

During the course of this project, a report by Meng and Li described the hypervalent iodine-mediated oxidative *para* fluorination of *N*-pivaloyl protected anilines (Scheme 2.14).¹⁶⁹ As with Langlois, there was no requirement for the addition of an acidic rearomatisation step, or for the presence of a dedicated *tert*-butyl leaving group.



Scheme 2.14: Oxidative fluorination of *N*-pivaloyl protected, *para* unsubstituted anilines.¹⁶⁹

bis(*tert*-Butylcarbonyloxy)iodobenzene ($\text{PhI}(\text{OPiv})_2$) was found to be the oxidant of choice for this reaction, leading to greater yields than PIDA or PIFA; however this procedure, on the contrary to Jouannetaud, Jacquesy *et al.*, was unable to be applied to *N*-sulfonyl protected anilines, leading only to complex mixtures of products.

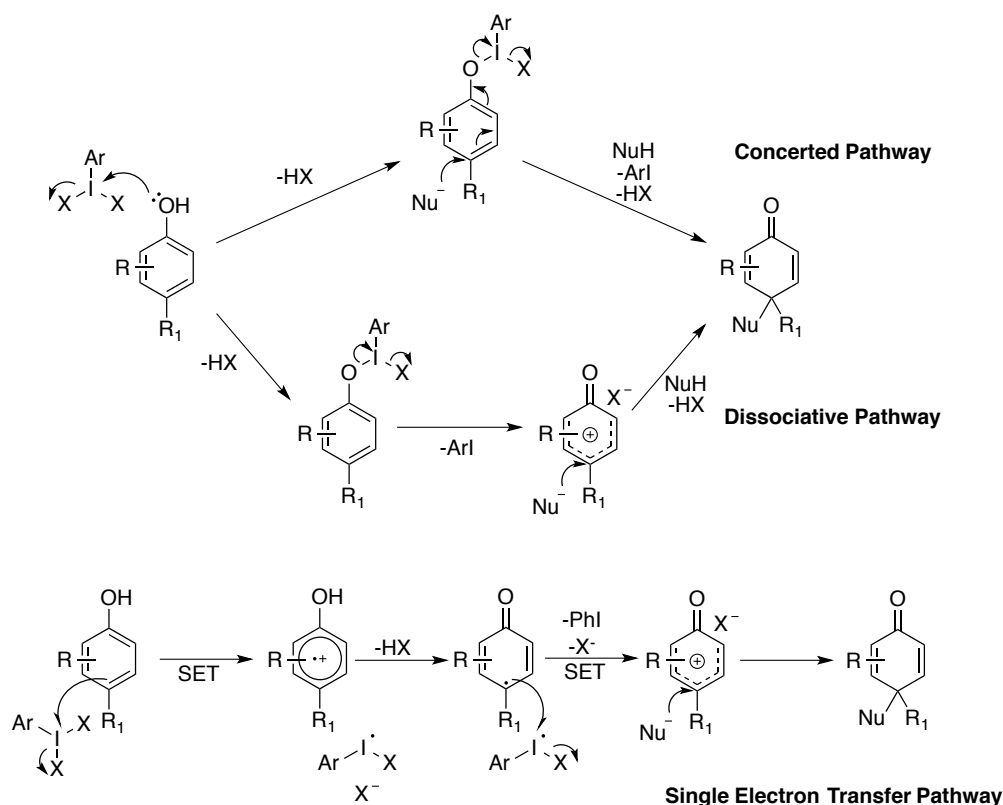
2.1.4. Mechanism of Oxidative Fluorination of Aromatics

There are two proposed mechanisms for the oxidative fluorination of phenols: via a concerted process or a dissociative pathway via a phenoxenium ion (Scheme 2.15). In the former, ligand exchange on the hypervalent iodine(III) reagent by the phenol precedes a combined nucleophilic attack, oxidation of the phenol and reduction of the

iodine centre. In the latter, the phenol is oxidised by the hypervalent iodine(III), which is reduced to the iodoarene. The phenoxenium ion is then trapped by the nucleophile to give the dienone.^{170, 171}

While definitive proof of either mechanism has not been experimentally established, frontier molecular orbital analysis and the electronic effects leading to high regioselectivity support the presence of a phenoxenium ion.^{172, 173}

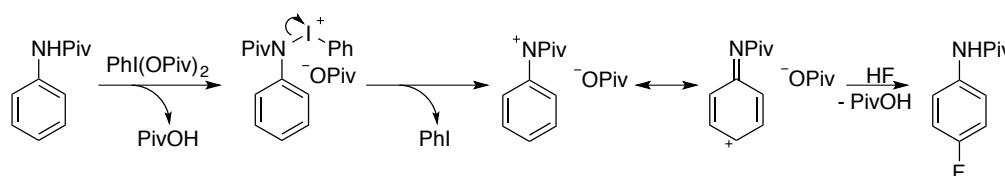
A third, alternative, mechanism has been discounted. This proposed mechanism, involved two consecutive SETs to the oxidant from the substrate, to give a radical and then cation in turn. This was disproved as the use of other oxidants, which are known to oxidise phenols through SET, was unsuccessful for this reaction.¹⁶⁵



Scheme 2.15: Possible concerted and dissociative mechanisms for the hypervalent iodine(III)-mediated oxidation of phenols. The SET pathway has been disproved by Langois.¹⁶⁵

For the oxidative fluorination of *N*-pivaloyl protected anilines, Meng and Li proposed a mechanism similar to the dissociative mechanism on the phenols (Scheme 2.16).¹⁶⁹ The

anilide is oxidised by the hypervalent iodine, transforming the nitrogen to a nitrenium ion, before a nucleophilic fluoride attack on the *para* position. This is again supported by the strong electronic effect leading to high regioselectivity. This proposed mechanism was based on the literature precedent for *para* hydroxy-,¹⁷⁴ acetoxy-¹⁷⁵ and tosyloxylation,¹⁷⁶ each of which report no incorporation of the respective nucleophile *ortho* to the C-N.



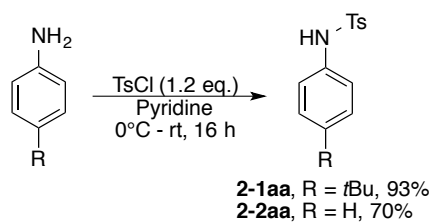
Scheme 2.16: Proposed mechanism for the hypervalent iodine(III)-mediated oxidation of anilide by Meng and Li¹⁶⁹

2.2. Results and Discussion

Protecting group investigations, substrate scope and [¹⁸F]labelling reactions were carried out in conjunction with Faye Buckingham.¹⁷⁷

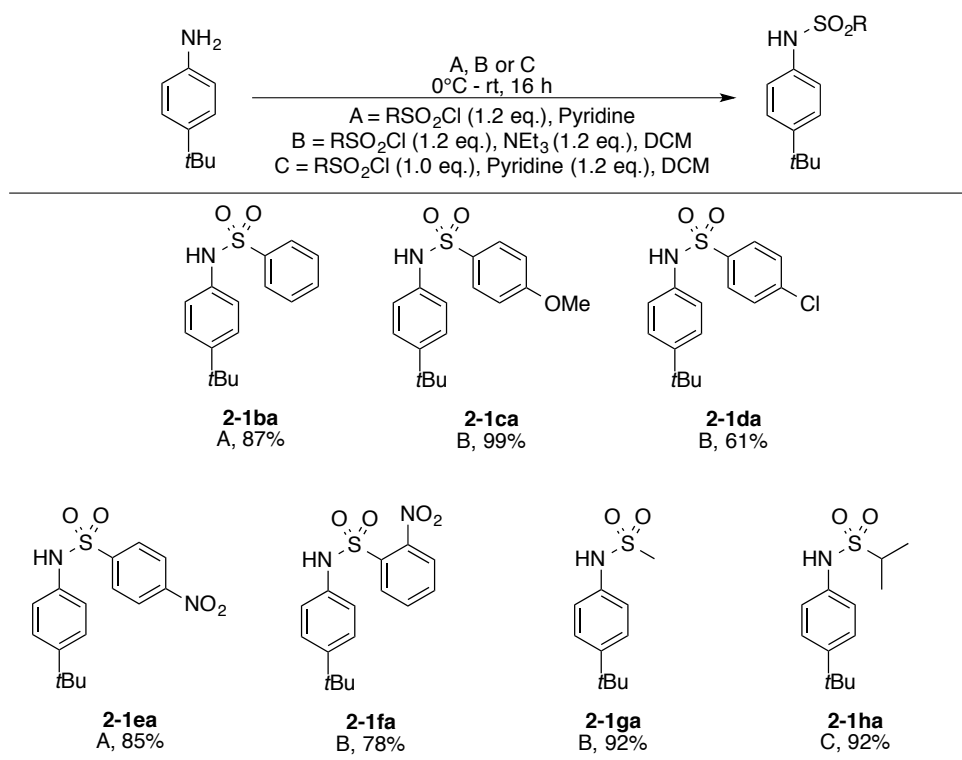
2.2.1. Precursor Synthesis

Preliminary reactions and initial optimizations were carried out using *N*-tosyl protected aniline with (**2-1aa**) and without (**2-2aa**) the *para tert*-butyl group (Scheme 2.17). Both of these substrates could be synthesized from the parent aniline with tosyl chloride (1.2 equivalents) in pyridine in very good yields (**2-1aa** - 93%, **2-2aa** - 70%). The use of catalytic DMAP was investigated, however this was found to promote the *bis*-tosylations and was consequently discontinued.



Scheme 2.17: Synthesis of *N*-tosyl protected anilines for preliminary investigation.

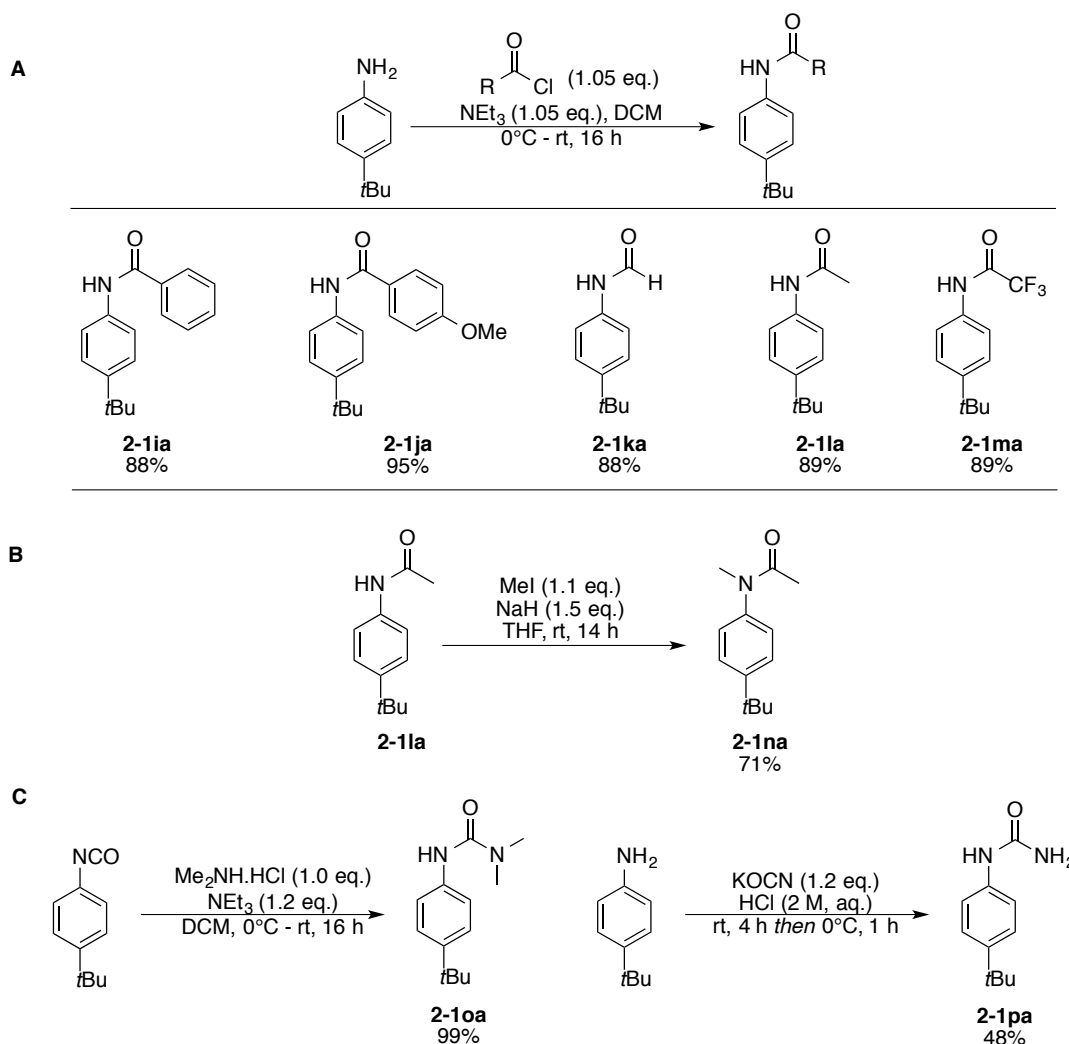
Once the optimized conditions had been established, other sulfonamide and anilides, based on the 4-*tert*-butylaniline, were synthesized to determine the tolerance of the reaction for protecting group variation. The sulfonyl protecting groups were installed by use of the sulfonyl chloride in the presence of pyridine or triethylamine, though the use of pyridine was preferred to avoid the formation of the *bis*-sulfonated by-product. Under these conditions, seven further *N*-arylsulfonamides (**2-1ba** - **2-1ha**) were synthesized in 78 – 92% yield (Scheme 2.18).



Scheme 2.18: Synthesis of *N*-arylsulfonamide substrate scope.

The range of anilide substrates was synthesized in a manner similar to the *N*-arylsulfonamides, using the commercially available acid chlorides with triethylamine

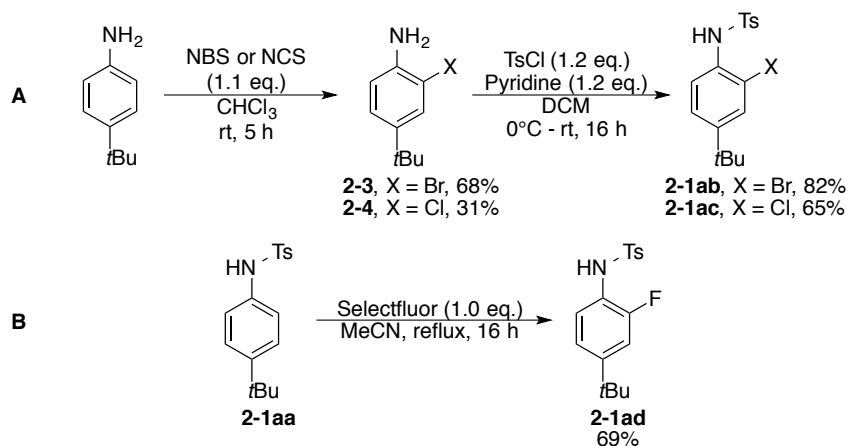
in DCM (Scheme 2.19, A). This route was applied to the synthesis of five anilides (**2-1ia** - **2-1ma**) in excellent yields (88 – 95%) and **2-1la** was carried onto the bis-protected aniline (**2-1na**) via methylation in a 71% yield (B). Two ureas (**2-1oa** and **2-1pa**) were also synthesized from the appropriate amines and isocyanates, in 99% and 48% yields respectively (C).



Scheme 2.19: Synthesis of anilide (A), bis-protected anilide (B) and urea substrates (C).

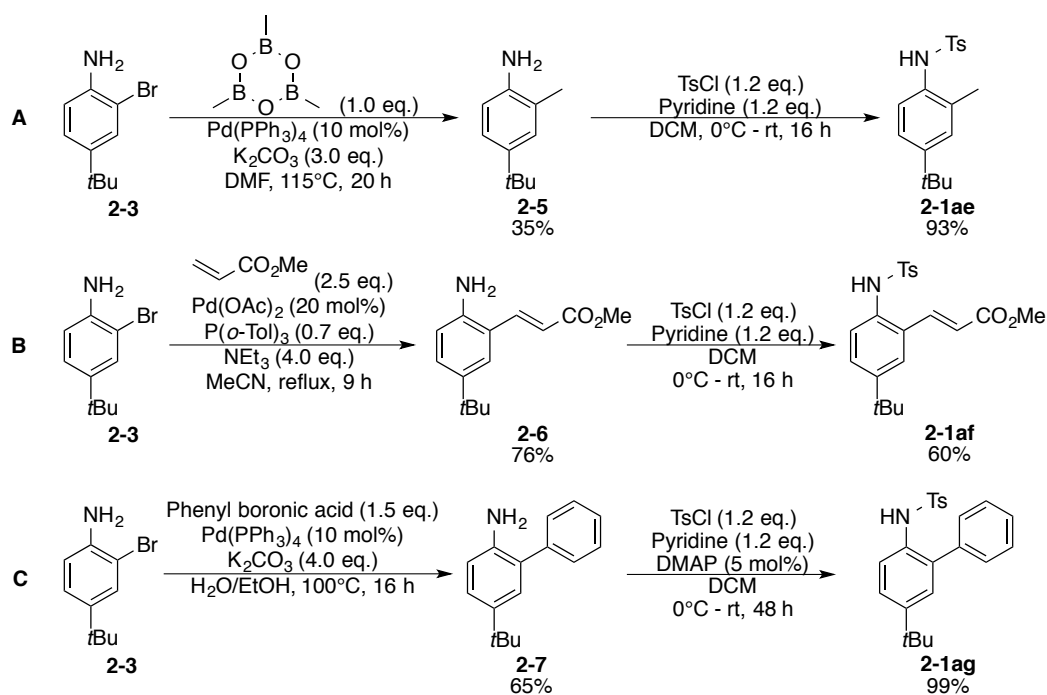
To examine the scope of the *N*-aryl portion of the substrates, a series of *N*-tosyl protected anilines were synthesized starting with *ortho*-halogen substrates. 2-Bromo- and 2-chloro-4-(*tert*-butyl)aniline (**2-3** and **2-4**) were both synthesized in 68% and 31%, respectively, from 4-*tert*-butylaniline with *N*-bromosuccinimide (NBS) and *N*-chlorosuccinimide (NCS) in chloroform. Tosyl protection was achieved in 82% and 65%

to give precursors **2-1ab** and **2-1ac** (Scheme 2.20, A). The corresponding 2-fluoro analogue **2-1ad** could be obtained from **2-1aa** in 69% by refluxing in MeCN with Selectfluor (B).



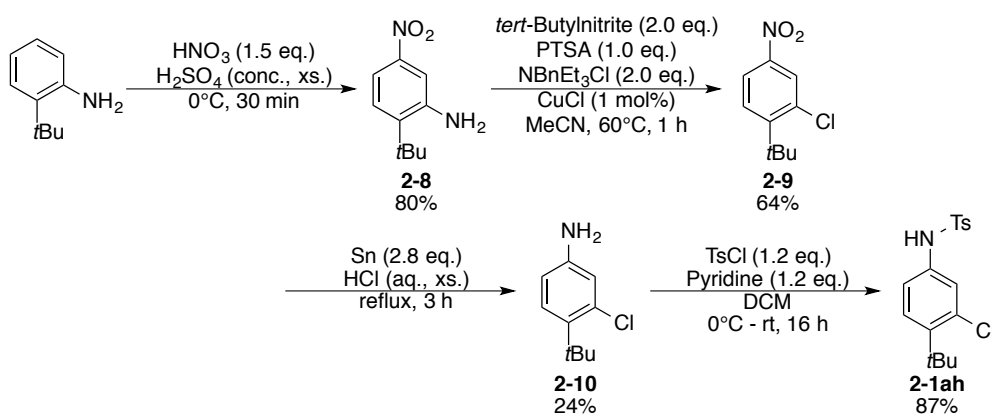
Scheme 2.20: *ortho*-Halo substituted precursor synthesis.

2-3 was used in the synthesis of three further substrates via Pd(o) catalyzed couplings. A Suzuki reaction (Scheme 2.21, A) with trimethylboroxine gave low conversion to the 2-methyl substituted aniline **2-5** and a Heck reaction with an excess of methyl acrylate gave the α,β -unsaturated methyl ester **2-6** in 76% (B). Standard tosylation conditions on these intermediates gave 93% and 60% of **2-1ae** and **2-1af**, respectively. Another Suzuki coupling (C) with phenyl boronic acid, followed by a modified tosylation gave the 2-phenyl substrate **2-1ag** in 64% over two steps. DMAP was required due to the *ortho* phenyl.



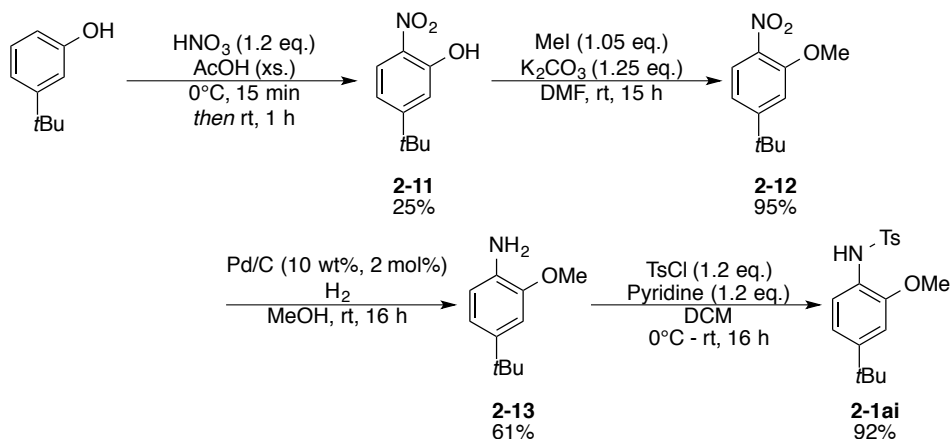
Scheme 2.21: Pd(0) catalyzed couplings from intermediate **2-3**.

Synthesis of the *meta* halogen substituted compounds proved to be more complex, with the 3-chloro precursor (**2-1ah**) requiring 4 steps, from 2-*tert*-butylaniline (Scheme 2.22). This was nitrated via electrophilic aromatic substitution with a nitronium ion formed by combination of nitric acid and sulfuric acid at 0°C. Under these conditions, the free amine is protonated and, therefore, becomes *meta* directing, leading to a good yield of **2-8** (80%). A copper(I) chloride catalyzed Sandmeyer reaction was followed by a low-yielding reduction of the nitro-group to give 15% of **2-10** over the two steps. Finally, protection by tosyl chloride under the standard conditions in an excellent yield gave the desired precursor **2-1ah**.



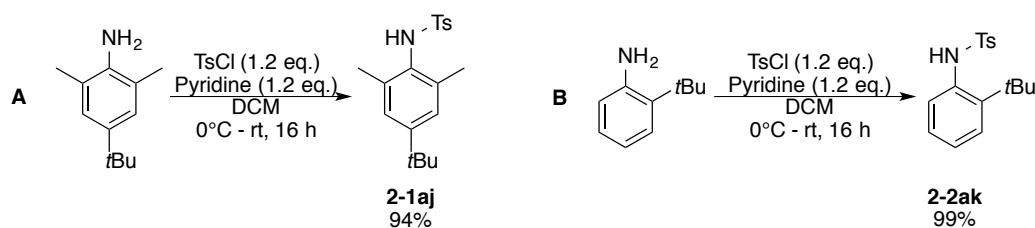
Scheme 2.22: *meta*-Chloro precursor synthesis.

A 2-methoxy substituted substrate (**2-1ai**) was also produced, in a four-step procedure from 3-*tert*-butylphenol (Scheme 2.23). A nitration was again carried out, using acetic acid rather than sulfuric in an attempt to limit over nitration of the substrate, though only a low yield (**2-11**, 25%) could be isolated. Methylation (**2-12**, 95%) and hydrogenation (**2-13**, 61%) gave the desired parent aniline, which was then tosyl protected under the standard conditions to give **2-1ai** in a 92% yield or 13% over the four steps.



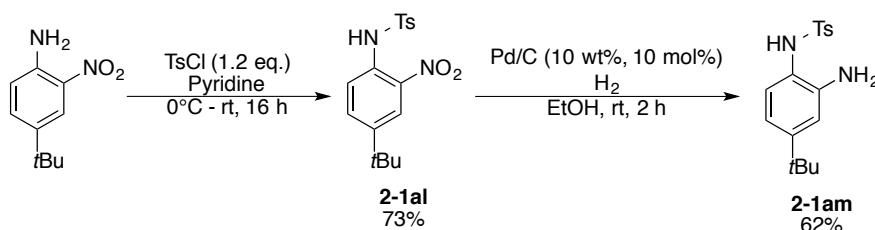
Scheme 2.23: *ortho*-Methoxy substrate synthesis.

The 2,6-dimethyl precursor (**2-1aj**) was more simply synthesized, from commercially available 2,6-dimethyl-4-*tert*-butylaniline, with tosyl chloride and pyridine in DCM in an excellent yield (99%) (Scheme 2.24, A). Similarly, a 2-*tert*-butyl precursor (**2-2ak**), which contains no leaving group *para* to the sulfonamide, was synthesized from its parent aniline in a 94% yield (**B**).



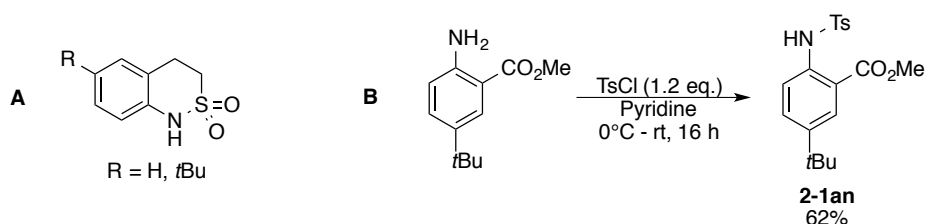
Scheme 2.24: Tosyl protection of commercially available anilines.

Slight modification of these conditions, running the reaction in pyridine as the solvent, allowed the tosylation of 2-nitro-4-*tert*-butylaniline to give the precursor **2-1al** (Scheme 2.25), and this could be carried forward through hydrogenation with palladium on carbon to give the free amine precursor **2-1am**.



Scheme 2.25: Tosylation to give precursor **2-1al** and reduction to **2-1am**.

Two further benzosultams were synthesizedⁱⁱⁱ for this project (Scheme 2.26).¹⁷⁸ During this synthesis, methyl 2-amino-5-*tert*-butyl benzoate ester was formed as an intermediate and this was tosylated to give methyl 5-(*tert*-butyl)-2-(4-methylphenylsulfonamido)benzoate (**2-1an**) as the final substrate.



Scheme 2.26: Benzosultams synthesized by Dr B. Checa (A). Tosylation of benzosultam synthesis intermediate to give **2-1an** (B).

ⁱⁱⁱ Synthesis carried out by Dr B. Checa

2.2.2. ¹⁹F-Reaction Development

As this project aimed to develop a hypervalent iodine(III)-mediated oxidative fluorination of aniline based substrates, ultimately to be applicable to use with [¹⁸F]fluoride, it was decided at the start of the project that the reaction time should be limited to 15 minutes, with a further 5 minutes for the acid mediated rearomatisation. The initial conditions adopted were those previously published by Gao *et al.*, with 1.0 equivalent of PIDA and 4.0 equivalents of HF-pyridine in DCM, and the reactions were carried out in Falcon tubes (polypropylene) to avoid the HF reacting with the borosilicate glassware. On reaction completion, sodium bicarbonate (sat., aq.) was used to neutralise the excess acid present before an aqueous extraction was carried out. For reaction optimisation, yields were primarily found by ¹⁹F NMR analysis relative to 1-fluoro-3-nitrobenzene (¹⁹F NMR: δ = -109.7 ppm) as an internal standard. As with all ¹⁹F NMR yields in this thesis, the relaxation time (D_1) was increased to 10 s to increase accuracy.

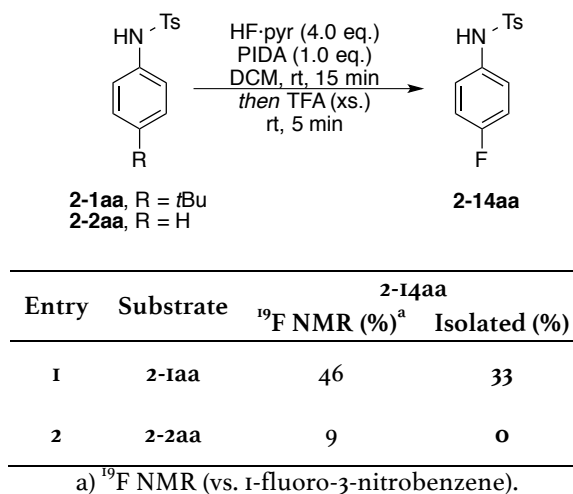
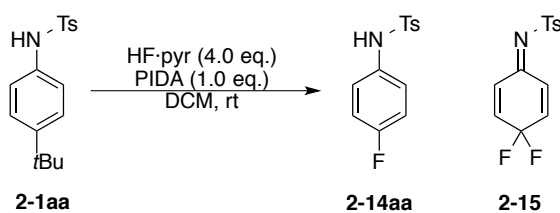


Table 2.1: Preliminary reaction investigation

Gratifyingly, it was found that exposing the 4-*tert*-butyl (**2-1aa**) and unsubstituted (**2-2aa**), tosyl protected anilines to these conditions (Table 2.1), gave the desired *N*-tosyl-4-fluoroaniline, **2-14aa** (¹⁹F NMR: δ = -116.6 ppm). It was found, in line with literature

precedent, that the presence of the *tert*-butyl leaving group led to a five-fold increase in the conversion. Furthermore, the isolation of **2-14aa** formed from **2-2aa** (^{19}F NMR = 9%) proved to be very difficult under standard silica gel chromatography conditions due to the product eluting with both the starting material and other unidentified side products (Entry 2). Conversely, the presence of the *tert*-butyl on the starting material lead to separation of the product and starting material under similar chromatography conditions giving an isolated yield of 33% (^{19}F NMR = 46%) (Entry 1). Additionally, it was found that this reaction afforded fewer unidentified fluorinated side products than for the unsubstituted precursor. This can be attributed to a stabilising effect of the *tert*-butyl on the nitrenium intermediate, via inductive electron donation, which directs the fluorination toward the *para* selectivity.

With the application to [^{18}F]radiochemistry in mind, a time study was carried out to investigate whether further cuts to the reaction time could be afforded (Table 2.2). Rather remarkably, after only 1 minute (Entry 1), the reaction gave a 32% ^{19}F NMR yield of **2-14aa**, which increased to 37% after 5 minutes and 44% after 15 minutes (Entries 2 and 3). This lessening increase in yield was simultaneous with an increase in the yield of the difluorinated side-product **2-15** (^{19}F NMR: δ = -96.6 ppm), arising from a second oxidation of **2-14aa** and subsequent fluorination. From these results it was decided that the reaction time would remain as 15 minutes, at least for the ^{19}F optimisation, and could be readdressed in the radiofluorination section if necessary.



Entry	Time (min)	2-14aa (%) ^a	2-15 (%) ^a
1	1	32	7
2	5	37	10
3	15	44	20

a) ¹⁹F NMR (vs. 1-fluoro-3-nitrobenzene).

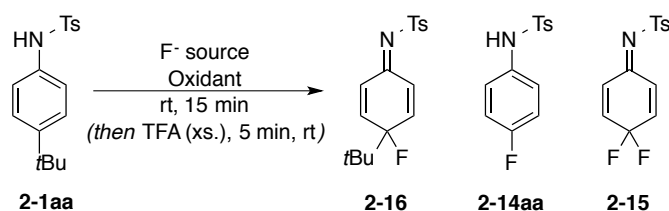
Table 2.2: Time study for the oxidative fluorination.

Consequently, an optimisation of this procedure was carried out, using **2-1aa**, with variation in oxidant, solvent and fluoride source examined. Reactions were analysed by ¹⁹F NMR, with yields of the desired product **2-14aa**, the over-oxidised difluorinated by-product **2-15** and the un-rearomatised dienamine intermediate **2-16** (¹⁹F NMR: $\delta = -160.4$ ppm) all measured.

As shown in Table 2.1, the presence of the *tert*-butyl leaving group enabled a 46% ¹⁹F NMR yield of **2-14aa**. In addition, 6% of difluorinated product **2-15** was identified, with no trace of the un-rearomatised intermediate **2-16** (Table 2.3, Entry 1).

Interestingly, **2-14aa** could be obtained in a 44% yield even when no TFA quench was carried out (Entry 2). This is likely due to the presence of excess HF·pyridine providing an environment acidic enough to promote the rearomatisation, negating the need for the quench. However, under these conditions, an increase in the over oxidised product to 20% was observed, which was less prominent after the TFA quench, suggesting that the rearomatisation or decomposition of this by-product is affected by the presence by TFA. Variation of the oxidant to PhI(OPiv)₂, as used by Meng and Li¹⁶⁹ gave a slight increase in yield of **2-14aa** (52%) while the use of PIFA reduced it to 34% (Entries 3 and

4). As PIDA is much cheaper^{iv} and more commonly available than PhI(OPiv)₂, it was chosen as the preferential oxidant.



Entry	F ⁻ Source (eq.)	Oxidant (eq.)	Solvent	TFA	2-16 (%) ^a	2-14aa (%) ^a	2-15 (%) ^a
1 ^b	HF·pyr (4.0)	PIDA (1.0)	DCM	✓	0	46	6
2 ^c	HF·pyr (4.0)	PIDA (1.0)	DCM	-	0	44	20
3	HF·pyr (4.0)	PhI(OPiv) ₂ (1.0)	DCM	✓	0	52	0
4	HF·pyr (4.0)	PIFA (1.0)	DCM	-	0	34	6
5	HF·pyr (4.0)	PIDA (1.0)	DCE	-	0	43	13
6	HF·pyr (4.0)	PIDA (1.0)	THF	-	0	0	0
7	HF·pyr (4.0)	PIDA (1.0)	Et ₂ O	-	8	0	0
8	TREAT.HF (4.0)	PIDA (1.0)	DCM	-	85	0	0
9	TREAT.HF (4.0)	PIDA (1.0)	DCM	✓	0	42	9
10	TBAF·3H ₂ O (1.0)	PIDA (1.0)	DCM	✓	0	12	0
11	HF·pyr (1.0)	PIDA (1.0)	DCM	-	68	19	6
12	HF·pyr (1.0)	PIDA (1.0)	DCM	✓	0	94	2
13	HF·pyr (1.0)	PhI(OPiv) ₂ (1.0)	DCM	✓	0	92	3
14	HF·pyr (1.0)	PIDA (2.0)	DCM	✓	0	0	43

a) ¹⁹F NMR (vs. 1-fluoro-3-nitrobenzene); b) Table 2.1, Entry 1; c) Table 2.2, Entry 3.

Table 2.3: Reaction optimization.

The use of DCE gave 43% **2-14aa** (Entry 5), in line with the result with DCM and the literature precedent using these two solvents. Application of THF and Et₂O both effectively shut the reaction down, giving none of the desired product in either case (Entries 6 and 7).

^{iv} PIDA: £0.58/mmol; PhI(OPiv)₂: £2.97/mmol [Sigma Aldrich, 23/03/2016]

Variation of fluoride source gave some interesting results; TBAF·3H₂O only gave 12% of **2-14aa**, after a TFA quench, assumed to be due to the reduced nucleophilicity of the fluoride (Entry 10). Use of TREAT.HF gave a ¹⁹F NMR yield of 42% of **2-14aa** after the TFA quench (Entry 9), a result comparable to that with HF·pyridine, however when the quench was not carried out 85% of the dienamine intermediate **2-16** was identified. This confirms that the HF·pyridine is accountable for the rearomatisation seen previously when no TFA quench was needed. Furthermore, there is obviously not a complete conversion from **2-16** to **2-14aa** by quenching, as only 42% **2-14aa** was found, suggesting that there are other pathways that this intermediate can follow.

Reduction in HF·pyridine to 1.0 equivalent (Entry 12) unexpectedly lead to an increase in the yield to 94%, though the TFA quench was now essential to promote the rearomatisation. Without the quench, 68% of intermediate **2-16** remained, with the yield of **2-14aa** dropping to 19% (Entry 11). Under the reduced fluoride conditions PhI(OPiv)₂ performed similarly to PIDA, giving 92% of **2-14aa** (Entry 13). As expected, increase of oxidant to 2.0 equivalents lead to exclusively over oxidised dienamine **2-15** (43%) (Entry 14).

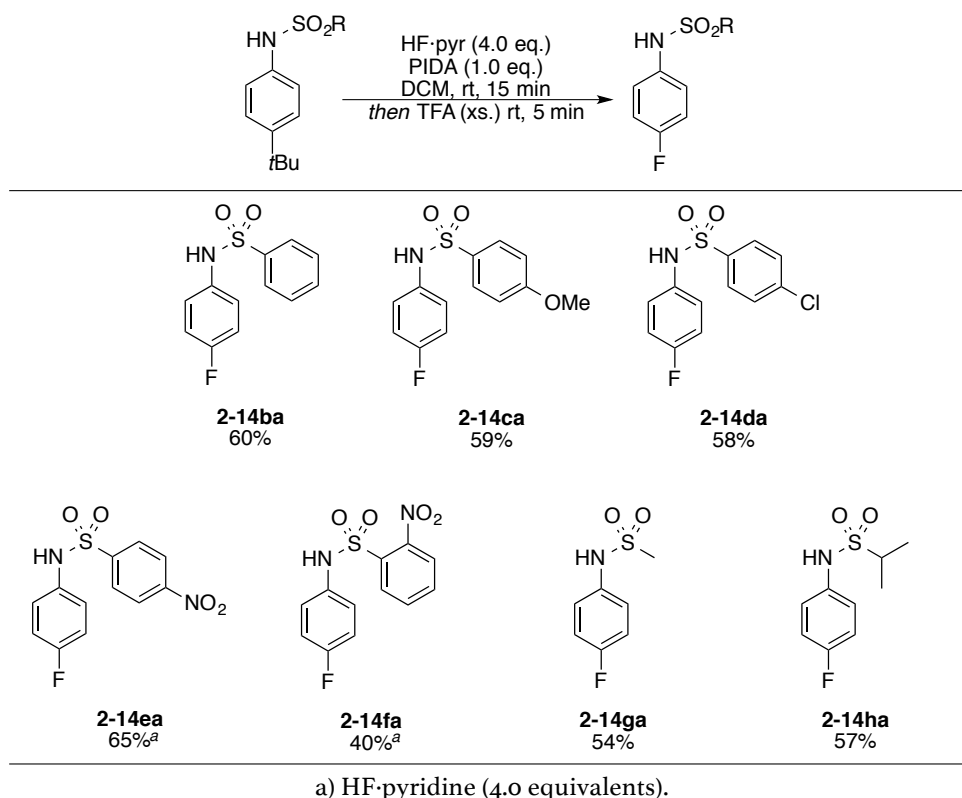
Accordingly, the optimised conditions for the fluorination of *N*-tosyl-4-*tert*-butylaniline (**2-1aa**) are 1.0 equivalent HF·pyridine with 1.0 equivalent PIDA in DCM at room temperature for 15 min before addition of excess TFA for 5 min to promote the rearomatisation. These conditions give a 94% ¹⁹F NMR yield of *N*-tosyl-4-fluoroaniline (**2-14aa**), with 2% of the over oxidised dienamine **2-15**. Isolated product could, however, only be isolated by silica column chromatography in 61% yield. The losses in yield from the ¹⁹F NMR to isolation were due to the product eluting closely with other unidentified compounds resulting in losses due to fraction overlap. Variation of the elution conditions was attempted, however no greater separation could be achieved.

2.2.2.1. Protecting Group Variation

Influence of the sulfonyl protecting group was first examined, by applying the optimised conditions to five aryl and two alkyl substituted variations (synthesised in Section 2.2.1.) with yields found as the isolated product following silica column chromatography.

The reaction was found to be generally applicable to all sulfonyl protecting groups investigated, with isolated yields of 40 – 65% (Scheme 2.27). Removal of the 4-methyl from the tosyl group lead to essentially no change in yield (**2-14ba**, 60%), nor did its replacement with electron-donating 4-methoxy (**2-14ca**, 59%) and weakly electron-withdrawing 4-chloro (**2-14da**, 58%). Use of strongly electron-withdrawing nitro substituents meant that comparable yields could only be achieved when an excess (4.0 equivalents) of HF·pyridine was used, with 2- (**2-14fa**) and 4-nitro (**2-14ea**) giving 40% and 65% respectively.

A similar need to use excess HF·pyridine was found with the *iso*-propyl substituted *N*-arylsulfonamide **2-1ha** to give **2-14ha** (57%), but use of a nosyl protecting group could give a 54% yield **2-14ga** with 1.0 equivalent. This result is of note as, although the sulfonyl derivatives are useful as such, the removal of nosyl groups may be advantageous in certain circumstances due to the milder conditions required for its deprotection.¹⁷⁹

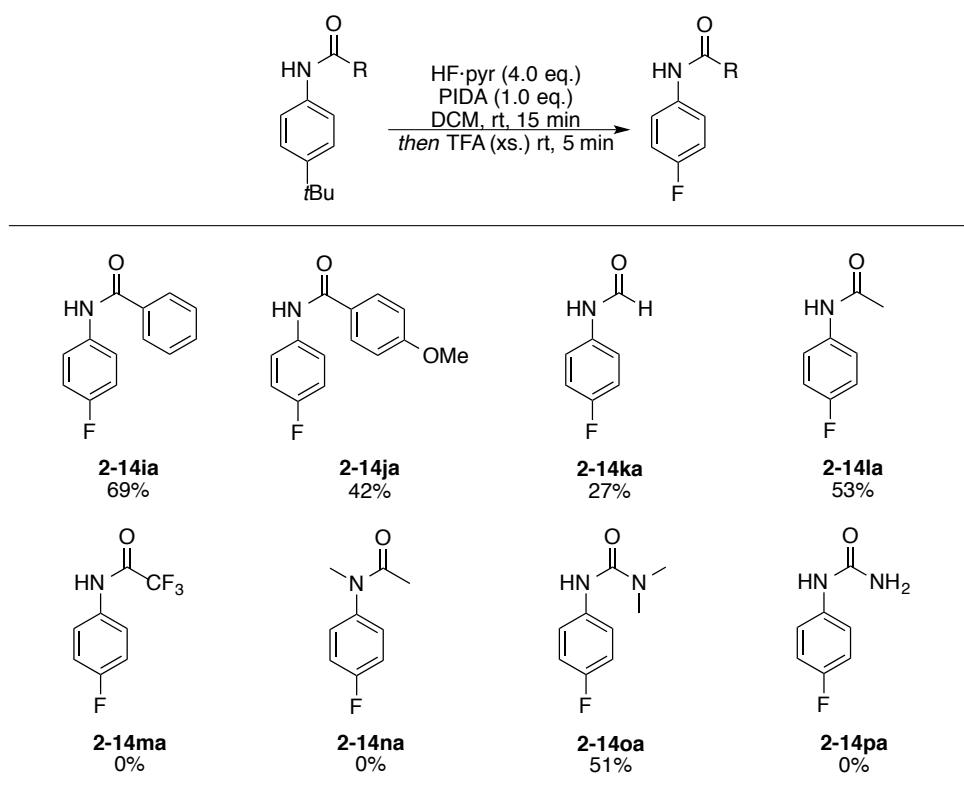


Scheme 2.27: *N*-Arylsulfonamide protecting group study.

Considering the work by Meng and Li, a series of anilide substrates was also assessed (synthesised in Section 2.2.1.). Across all anilide (**2-1ia** - **2-1ma**), bis-protected (**2-1na**) and urea precursors (**2-1oa** and **2-1pa**), it was found that the use of excess HF·pyridine was required and a much greater variation in yields was observed with variation of the carbonyl protecting group (Scheme 2.28).

Benzoyl groups gave the best yields, with the unsubstituted parent carbonyl **2-1ia** leading to an isolation of fluorinated product **2-14ia** in a 69% yield, while substitution by 4-methoxy (**2-1ja**) resulted in a drop to 42% of **2-14ja**. Replacement of the benzoyl with formyl and acetyl gave 27% **2-14ka** and 53% **2-14la** respectively, though trifluoroacetyl shut the reaction down, giving no yield of **2-14ma** even under the excess HF·pyridine conditions. No product (**2-14na**) was also observed when the bis-protected aniline precursor **2-1na** was subjected to the reaction. Use of dimethyl urea **2-1oa** did

lead to a good yield of the fluorinated product **2-14oa**, though removal of the two methyl groups lead to product (**2-14pa**).



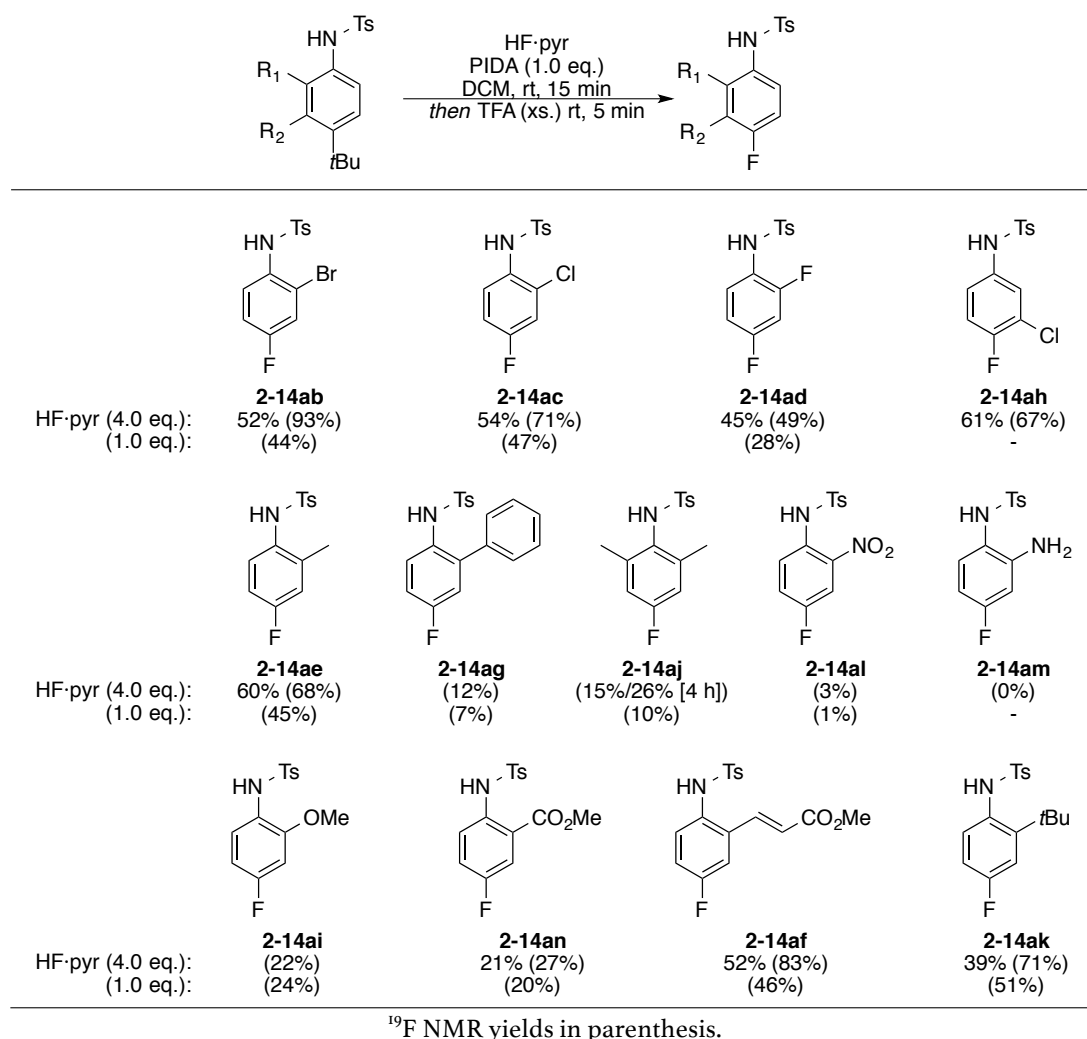
Scheme 2.28: Anilide protecting group study.

The increased variation in the yields with these anilide substrates can be attributed to the larger effect on the electron-withdrawing character of the carbonyl on the nitrogen lone pair that is required for proposed mechanism (see Scheme 2.30). The stronger the electron-withdrawing capability, the less available the electrons are to attack the hypervalent iodine centre to allow the oxidation of the aromatic ring.

2.2.2.2. *N*-Aryl Substitution Variation

The effect of the *N*-aryl sub-motif was assessed by subjecting a series of substrates, synthesized in Section 2.2.1., to the reaction conditions with both 1.0 and 4.0 equivalents of HF·pyridine (Scheme 2.29). This showed that a range of *ortho* and *meta* substituents were compatible with the reaction, including halogens, alkyl groups and ester

functionalities. Conversely to the unsubstituted model substrate, in almost all cases the use of excess (4.0 equivalents) HF·pyridine proved to give the better yields.



Scheme 2.29: Substrate scope study.

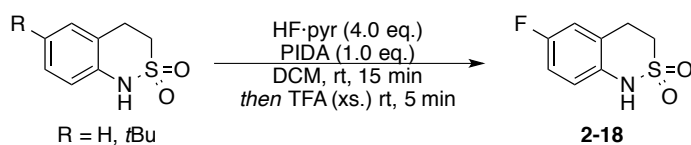
The reaction can tolerate the presence of a single methyl group *ortho* to the sulfonamide, with a 60% isolated yield (68% ¹⁹F NMR) of **2-14ae**, however when this was replaced by a phenyl group (**2-14ag**) or a second methyl group was situated at the 6-position (**2-14aj**) (¹⁹F NMR: $\delta = -114.6$ ppm), the reaction only gave 12% or 15%, respectively, by ¹⁹F NMR, with the increased sterics hindering attack on the PIDA. The yield could be increased to 26% of **2-14aj** by increasing the reaction time to 4 hours. Remarkably, when the *tert*-butyl was moved from *para* to *ortho*, the reaction was still selective for the *para*-fluorinated product, **2-14ak** (¹⁹F NMR: $\delta = -115.7$ ppm), with no

trace of either the 2-fluoro (**2-17**) (^{19}F NMR: $\delta = -129.7$ ppm) or 2,4-difluoro **2-14ad** (^{19}F NMR: $\delta = -112.0, 123.4$ ppm) detected in the crude reaction mixture. Reference for the 2-fluoro analogue **2-17** was synthesized in the same manner as the precursors, from 2-fluoroaniline and *p*-toluenesulfonyl chloride in an 84% yield. This preference for *para* selectivity is likely due the steric hinderance to the fluorination at the *ortho* position in the nitrenium intermediate.

The presence of halogen substituents either *ortho* or *meta* lead to isolated yields of 45 – 61% (**2-14ab** - **2-14ad**, **2-14ah**), which suggests that the halogens do not have a major effect on the reaction, but strong variation is observed on examination of the ^{19}F NMR yields with 2-Br (**2-14ab**) > 2-Cl (**2-14ac**) $\approx$ 3-Cl (**2-14ad**) > F (**2-14ah**). Placing a more strongly electron-withdrawing ester functionality at the *ortho* position does reduce the yield to 21% of the isolated fluorinated product (**2-14an**), however when the ester is separated from the ring using an olefin, then the yield recovered to 52% **2-14af** showing the effect on the reaction is due to electronic effects rather than the ester taking part in side reactions. It could be envisioned that the use of an electron-donating group would help stabilize the intermediate and so increase the yield, but the yield of the 2-methoxy substrate **2-14ai** (^{19}F NMR: $\delta = -113.8$ ppm) was 24% (1.0 eq. HF·pyridine). This is believed to be due to fluoride attack on the methoxy to form methyl fluoride.

Compounds with free amines (**2-1am**) cannot be used in this reaction, in line with the literature precedent,¹⁶⁵ and a 2-nitro substituent only lead to a 3% ^{19}F NMR yield of the desired product **2-14al** (^{19}F NMR: $\delta = -114.8$ ppm).

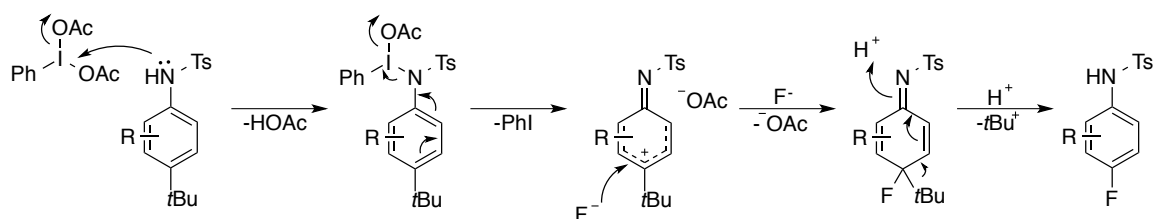
Pleasingly, this fluorination reaction was also successful on the benzosultam substrate (Table 2.4). While the *tert*-butyl group was still necessary, its presence enabled the isolation of **2-18** in a 52% yield (Entry 2). A control experiment (Entry 1) on the unsubstituted benzosultam, only yielded 10% **2-18** by ^{19}F NMR (^{19}F NMR: $\delta = -122.8$).



Entry	R	¹⁹ F NMR (%)	2-18 Isolated (%)
1	H	10	-
2	<i>t</i> Bu	83	52

Table 2.4: Oxidative fluorination of benzosultams.

Mechanistically, the dissociative route proposed by Meng and Li fits with the results that have been found in this project, supported by the exclusively *para* fluorination observed. Following an initial attack on the iodine(III) centre by a lone pair from the nitrogen, reduction of the iodine centre results in loss of formation of the iodobenzene and formation of a nitrenium ion. This would be stabilised by dissociation of the positive charge onto the *para* position of the arene, bearing the *tert*-butyl functionality, and ensuing site-selectivity for the fluorination. Acid mediated rearomatisation would enable the *tert*-butyl group to leave, which likely loses a proton to give 2-methylprop-1-ene.



Scheme 2.30: Proposed mechanism for fluorination.

This theoretical mechanism is supported by the substrate scope; strongly electron-withdrawing groups on either the *N*-aryl ring or the protecting group negatively affect the yield, with this effect reduced with reducing withdrawing potential. Increasing the steric influence of *ortho* substituting groups reduces the yields observed, due to having a destabilising influence on the nitrenium ion intermediate, which would likely hold a relatively planar conformation.

2.2.3. Oxidative Radiofluorination of *N*-Arylsulfonamides

The ultimate aim for this project was its application toward radiofluorination. The use of [^{18}F]HF is not possible due to the need for highly specialised apparatus¹⁸⁰ however Gao *et al.* were able to mimic the actions of [^{18}F]HF by using tetra-*n*-butylammonium [^{18}F]fluoride, [^{18}F]TBAF, with TFA.⁸³ **2-1aa** was used as the model substrate, initially under the literature conditions, but [^{18}F]TEAF was used instead of [^{18}F]TBAF. [^{18}F]TEAF and [^{18}F]TBAF show similar reactivity but the bicarbonate precursor is commercially available and therefore would be more easily adopted by other research centres.

These modified literature conditions utilised [^{18}F]TEAF, PIDA (1.0 equivalent) and TFA (4.0 equivalent) in DCM for 15 minutes, then a further 10 min with excess TFA (Table 2.5). Unfortunately, application to **2-1aa** only gave RCC = $2 \pm 1\%$ ($n=4$) of 4-[^{18}F]fluoro-*N*-tosylaniline ([^{18}F]2-14aa) which is significantly lower than that found for the phenolic substrates (Entry 1). Change in solvent to MeCN, or change of oxidant to iodosotoluene or $\text{PhI}(\text{OPiv})_2$ did not lead to any product formation, with RCC = 0% ($n=2$) in all instances (Entries 2 - 4).

As the conditions used were trying to imitate the presence of [^{18}F]HF, change of the additive from TFA ($\text{pK}_a = -0.3$, H_2O) to acetic acid ($\text{pK}_a = 4.8$, H_2O) or trichloroacetic acid (TCA) ($\text{pK}_a = 0.7$, H_2O) was explored with the intention of more closely mimicking HF ($\text{pK}_a = 3.2$, H_2O). This approach was unsuccessful; acetic acid showed no reactivity and TCA only gave trace product ($< 1\%$) (Entries 5 and 6).

Finally, the use of silver triflate, which had been reported as effective in a hypervalent iodine-mediated C-H fluorination with [^{18}F]CsF by Sanford *et al.*, was investigated. Use of 1.0 equivalent (with respect to substrate) did give RCC = $3 \pm 1\%$ ($n=2$), but increasing

to 4.0 equivalent, or addition of 4.0 equivalents of TFA, lead to no conversion (Entries 7 - 9).

CC(C)(C)c1ccc(NC(=O)c2ccc(C)cc2)cc1
 $\xrightarrow[\text{then TFA (xs.), 10 min}]{\text{[}^{18}\text{F}\text{]TEAF, Oxidant (1.0 eq.), Additive, DCM, rt, 15 min}}$
CC(C)(C)c1ccc(NC(=O)c2ccc([F-18])cc2)cc1

2-1aa **[¹⁸F]2-14aa**

Entry	Oxidant	Additive (eq.)	[¹⁸ F]2-14aa RCC (%)	n
1	PIDA	TFA (4.0)	2 ± 1	4
2 ^a	PIDA	TFA (4.0)	0	2
3	Toll=O	TFA (4.0)	0	2
4	PhI(OPiv) ₂	TFA (4.0)	0	2
5	PIDA	AcOH (4.0)	0	2
6	PIDA	TCA (4.0)	Trace	2
7	PIDA	AgOTf (1.0)	3 ± 1	2
8	PIDA	AgOTf (4.0)	0	2
9	PIDA	AgOTf (1.0) + TFA (4.0)	0	2

a) MeCN as solvent ([¹⁸F]TEAF dispensed in DCM).

Table 2.5: Initial investigations into oxidative radiofluorination of *N*-arylsulfonamides.

Despite the desire for a high specific activity protocol, these results indicated that this would not be possible under current hypervalent iodine-mediated oxidative fluorination conditions. As the results from the ¹⁹F reactions had produced good yields in short reaction times, a carrier-added approach was considered by which TEAF and HF·pyridine would replace the TFA in the first step. This approach led to significant improvement in the RCC of [¹⁸F]2-14aa, with the use of TEAF (1.0 equivalent) giving RCC = 8 ± 4% (n=4) and HF·pyridine (1.0 equivalent) giving RCC = 52 ± 6% (n=4) (Table 2.6, Entries 1 and 2). Exclusion of the oxidant (Entry 3) led to no incorporation of [¹⁸F]fluoride into [¹⁸F]2-14aa, demonstrating that this radiofluorination follows the same oxidative fluorination mechanism as for the fluorine-19 studies.

Application of these carrier added conditions to *N*-(4-(*tert*-butyl)phenyl)acetamide (**2-1a**) as a model anilide substrate unfortunately showed that these conditions were not transferrable. Only trace (RCC < 1%, n=2) incorporation was detected when HF·pyridine (1.0 equivalent) was used as the carrier.

2-1aa		[¹⁸F]2-14aa		
Entry	F ⁻ Source (eq.)	Additive (eq.)	[¹⁸ F]2-14aa RCC (%)	n
1	TEAF (1.0)	TFA (4.0)	8 ± 4	4
2	HF·pyr (1.0)	-	52 ± 6	4
3 ^a	HF·pyr (1.0)	-	0	2
4	TolIF ₂	-	15	1

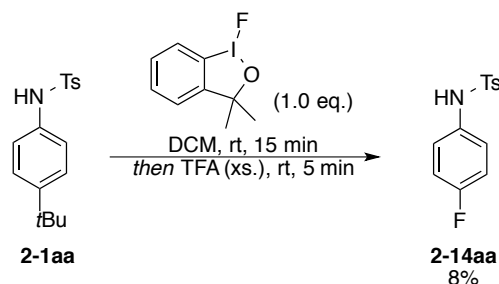
a) No PIDA in reaction

Table 2.6: Carrier-added approach to oxidative radiofluorination of *N*-arylsulfonamides.

As the reaction had worked well with added ¹⁹F⁻, whilst not with TFA, AcOH and TCA, the possibility of an ArIF₂ species being involved in the mechanism was considered. Application of difluoriodotoluene (TolIF₂) (Entry 4) was successful with RCC = 15% (n=1), and although this was again a carrier added route, it suggests the possibility for the use of *in situ* derived I-¹⁸F reagents for radiofluorination. Due to the stoichiometry of [¹⁸F]fluoride in these reactions, it is not feasible to try and form an ArI¹⁸F₂ reagent, however the formation of [¹⁸F]fluoroiodane would be viable, especially considering it's synthesis by the Stuart group using TBAF as the fluorinating reagent.¹⁵⁷

As a proof of concept, that these fluoroiodanes could be used for oxidative fluorination, a reaction using [¹⁹F]fluoride was carried out which gave a ¹⁹F NMR yield of 8% **2-14aa** (Scheme 2.31). Despite the low yield, this supported the hypothesis that this could be

used for the hypervalent iodine-mediated oxidative fluorination of *N*-arylsulfonamides without dilution of SA, if it were possible to form the I-¹⁸F bond *in situ*.



Scheme 2.31: Use of fluoroiodane as oxidant and fluoride source. Yield is by ¹⁹F NMR (vs. 1-fluoro-3-nitrobenzene).

Thus, a series of fluoroiodane precursors were tested under the reaction conditions (Table 2.7), however no reactivity was found in all experiments, even when the leaving group was changed (Entries 1, 3, 6 and 7) or if the [¹⁸F]TEAF and oxidant were pre-stirred to incite the formation of the desired [¹⁸F]fluoroiodane (Entries 2 and 5). Surprisingly, the use of fluoroiodane as the oxidant, in another carrier-added route, lead to no conversion which was unexpected considering the previous success with carrier added routes and the ¹⁹F test reaction result.

Due to the low stability in water and as it cannot be observed by the mass spectrometry analysis capabilities of SOMIL, it was not possible to determine whether [¹⁸F]fluoroiodane was being formed in the reaction and then not successfully fluorinating the *N*-arylsulfonamide precursor.

Entry	R	Pre-stir (10 min)	[¹⁸ F]2-14aa RCC (%)	n
1	CO ₂ CF ₃	-	0	2
2	CO ₂ CF ₃	✓	0	2
3	OTs	-	0	2
4	OTs	-	0	2
5	OTs	✓	0	2
6	Cl	-	0	2
7	Br	-	0	2
8	F	-	0	2

Table 2.7: Attempted *in situ* formation of [¹⁸F]fluoroiodane.

2.3. Summary

This project has established that a series of *N*-arylsulfonamides, bearing a range of sulfonyl protecting groups and *N*-aryl substituents, can be subjected to oxidative fluorination reactions, mediated by hypervalent iodine(III) reagents. This class of substrates had previously been reported to be unsuited with this transformation. The use of anilide substrates was also successfully applied under this umpolung strategy.

The corresponding oxidative radiofluorination was only able to give low conversion under non-carrier added conditions, however RCC = 52 ± 6% (n=4) could be attained when using HF·pyridine as a carrier. Whilst carrier added approaches are disfavoured, these results signify that an umpolung, oxidative fluorination approach to the [¹⁸F]fluorination of *N*-arylsulfonamides is possible. As there are constant improvements in the availability of high SA fluorine-18 sources, such as high SA Selectfluor (up to 20

GBq/ μmol),¹⁰⁸ this route should be reinvestigated if a mild route to high SA [^{18}F]HF is ever established.

Although the development of an I- ^{18}F was unsuccessful, this category of reagents could prove to be extremely useful in radiofluorination chemistry due to the extent of fluorination reactions I-F reagents have been shown to be proficient in. As it will be difficult to prove the formation of these reagents by radioHPLC or other analytical methods, it may be prudent to focus on a reaction that is much more established and efficient, rather than incorporate into new reaction development.

3. Continuous-Flow Microfluidic Radiofluorination of Spirocyclic Iodonium Ylides

Procedures for maximising the conversion and reproducibility of reactions as well as improvements for the safe handling of high levels of radioactivity have evolved over time, not just in reaction methodology, but also in the technology which is used. Moving forward from the original manual methods, the first technological advances used remote-controlled systems¹⁸¹ and then customised robotic systems.¹⁸² Following these was the development of bespoke compact platforms with these designs being shaped into commercial apparatus.^{183, 184} The forefront of clinical production techniques now include disposable cassettes that contain all the required reagents and precursors for a pre-programmed run for a specific tracer.^{57, 185}

The use of automation for the synthesis of radiotracers offers significant advantages over traditional manual techniques, mainly due to increased reproducibility, both in repeated production runs at a single site or for translation of procedures from research sites into clinical production facilities, such as hospitals.^{186, 187}

The ideal solution is for the radiosynthesis of complex tracers to become commonplace at clinical sites without the need for highly trained and specialised radiochemists to be on site for all production runs. This solution can only be foreseen by the development of fully automated tracer production protocols.

3.1. Microfluidic Approaches in Radiochemistry

Several semi- or fully-automated systems have been developed which were renditions of vessel-based reaction procedures, in which millilitres of solvent (0.5 – 5 mL) are used with milligrams of reagents and precursors (10 – 50 mg). However, when considering a

non-carrier added radiofluorination with [^{18}F]fluoride, this scale is many orders of magnitude higher than the concentration of [^{18}F]fluoride, which lies in the femto- to nanomolar range.¹⁸⁸

Therefore these reactions can be considered to have low atom efficiency regarding precursor, additives or reaction mediators, solvent volumes and any post-fluorination reactions that are required. Depending on the radiotracer being studied, the precursors can be very difficult to synthesise or excess materials can have implications for the later stages of the radiofluorination or product isolation and reformulation, due to toxicity (e.g. stannane precursors, metal mediators) or undesired side-reactions.

The use of microfluidic technology offers higher atom efficiency reactions by reducing the volume of solvent and precursor loading, whilst having a higher surface to volume ratio (SVR) in the reaction container. A superior SVR leads to faster heating and more efficient mixing of reagents that can give better RCCs and product selectivity.¹⁸⁹ Furthermore, the digitally controlled nature of microfluidic systems leads to greater reaction control due to the ability to fine-tune the ratio of reagents and residence time (t_R ; total time a single point in the reaction bolus is within the microfluidic reactor).

Aside from the radiochemistry implications, microfluidic platforms require less space and, therefore, the smaller spatial volumes need to be shielded. This is an important consideration when new radiochemical and radiopharmaceutical sites are being set up, with both structural and financial implications.

Wängler *et al.* have divided the microfluidic systems into two broad architecture types: continuous-flow and stop-flow (batch mode).¹⁸⁷ Stop-flow microfluidics uses discontinuous rates of flow and the residence time at stopped flow determines the temperature exposure of the reaction. A high level of integration of different functional

elements into the flow system is seen as a significant advantage of these systems over continuous-flow,¹⁹⁰ as well as potential for further reductions in reagent and solvent use by utilisation of electrowetting-on-dielectric (EWOD) microdevices. Pascali *et al.* have made a similar divide in microfluidic systems, describing stop-flow as micro-vessel systems (MVS), defined as a downscaling of conventional chemistry techniques.¹⁸⁶ There are several examples of stop-flow synthetic platforms, however this thesis will focus on the use of continuous-flow technology, namely on the NanoTek® platform manufactured by Advion, Inc. (Ithica, NY, USA).^{191, 192} Furthermore, discussion will not cover in detail the differences and advantages of platform design, construction material, shielding concepts and fluid movement control, however these topics are covered in detail in reviews by Pascali¹⁸⁶ and Wängler.¹⁸⁷

3.1.1. Continuous-Flow Microfluidics

Continuous-flow microfluidic, defined as micro-channel systems (MCS) by Pascali *et al.*, are composed of a network of fine channels with an internal diameter (i.d.) $\leq 300\ \mu\text{m}$, in which the resolvable [¹⁸F]fluoride and precursors, either neat or in solution, are reacted. Systems that have i.d. $> 300\ \mu\text{m}$ are known as mesofluidic, or more commonly referred to as flow reactors and are mostly used for industrial scale productions. In continuous-flow reactors the whole synthetic process occurs along a pre-defined fluid path, and the t_R is controlled by the flow rate of the reaction bolus through the reactor itself.

The use of channels as reactors, rather than more traditional vessel based systems, results in a much greater SVR even when compared to MVS. This greater ratio holds the advantages that were previously discussed, as well as the removal of radiolysis effects¹⁹³ that can still be observed in MVS. However, the greater SVR also leads to greater surface interactions that can lead to absorption of the radionuclide and

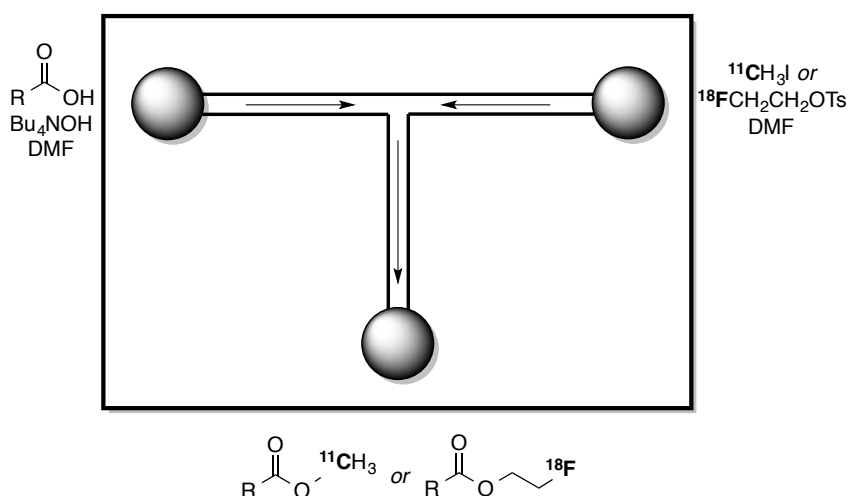
reduction in recovered activity, or nucleation of precipitates due to microscopic surface roughness. Due to the fine nature of the channels, this precipitation can easily lead to blocking of reactors, which can be very difficult, if not impossible, to clear. Consequently the materials used for the construction¹⁹⁴ of the reactors must be carefully considered, as well as any passivation before use and effective cleaning procedures post-reaction. Caution towards avoiding this precipitation generally means that reagent concentrations in the channels are similar to that found in traditional vessel based chemistry, however the volumes used per reaction are much smaller and, therefore, a reduction in the quantities of reagents used is nevertheless achieved.

As these channels are used as the reactor, the mixing of the [¹⁸F]fluoride and precursors is different to that seen in vessels and careful control of this mixing has direct effects for conversion. This can be affected by a number of factors including the flow rate, channel geometry and the solvent viscosity.

A final consideration for continuous-flow systems is that the reactions are conducted under much higher pressures (10 - 30 bar) than seen in MVS and traditional chemistry (< 5 bar). This means the temperatures used can be significantly greater than the boiling point of the reaction solvent resulting in improved reaction rates and consequently improved radiochemical conversions can be achieved in very short synthesis time.

The design of continuous-flow systems is technologically much easier than for stop-flow systems and so many of the early examples of microfluidic radiofluorination utilised this approach. Pike disclosed one of the first syntheses using a simple T-shaped micro-reactor for the radiosynthesis of ¹¹C- and ¹⁸F-labelled esters, with RCCs up to 88% (Scheme 3.1).¹⁹⁵ While Pike used activities of ~37 MBq, Steel *et al.* were able

increase this to up to 37 GBq for the fully automated synthesis of [^{18}F]FDG, with no signs of radiolysis, in $\text{RCY} \leq 40\%$ [d.c.] with a total synthesis time of 10 minutes.¹⁹⁶



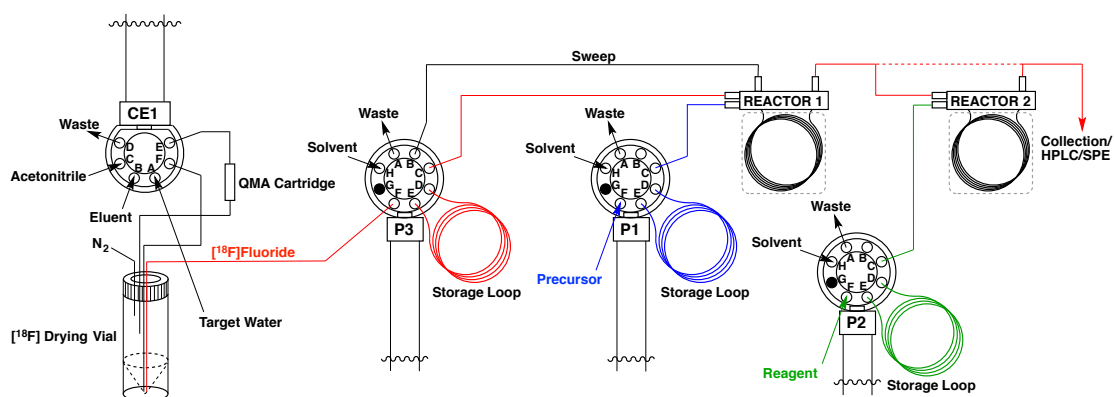
Scheme 3.1: Early development of a simple T-shaped micro-reactor from Pike.¹⁹⁵

This synthesis of [^{18}F]FDG was widely used as a benchmark for continuous-flow systems and Wester *et al.* were able to build on this and obtain a $\text{RCY} = 81 \pm 4\%$ ($n=8$) for eight subsequent production runs from a single loading of the storage reservoirs in a process time of 7 minutes for each run.¹⁹⁷ This was obtained on a commercially available Scintomics platform, with in-house modifications, based on a 7 m flow reactor of 300 μm i.d., and has since been commercialised itself.

3.1.2. NanoTek® (Advion, Inc.)

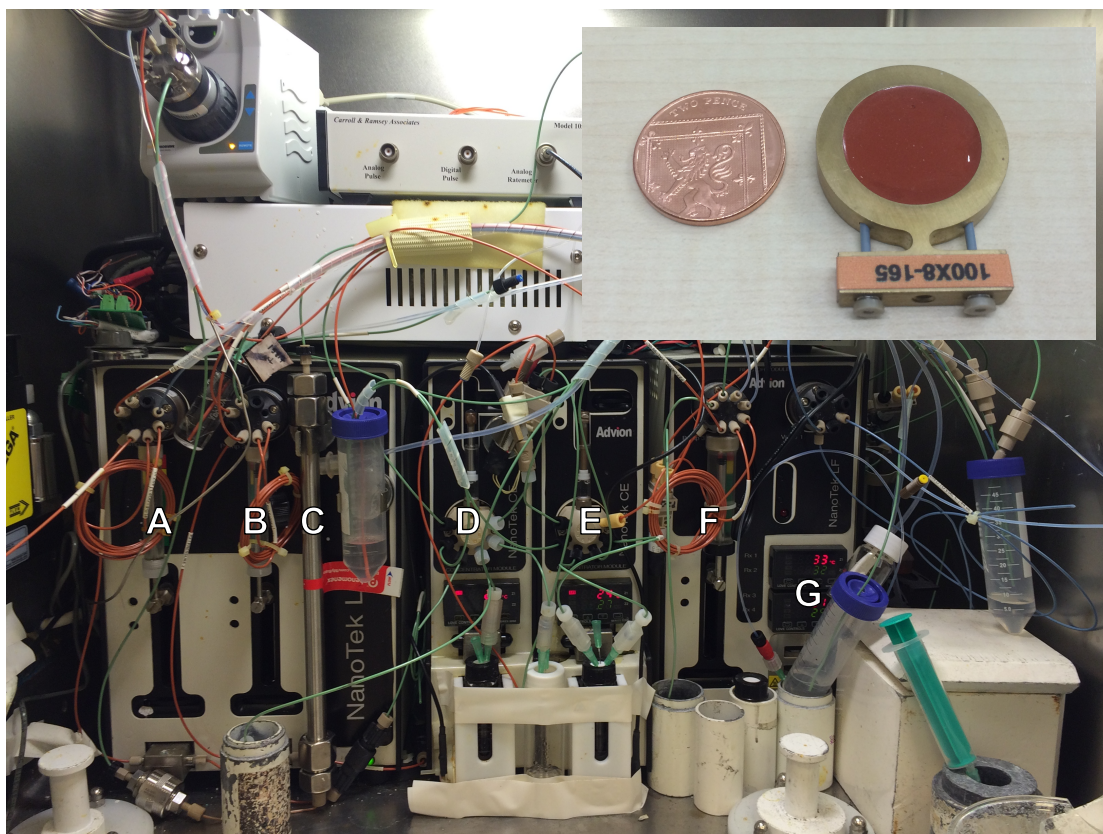
The NanoTek® platform is one of several commercially available continuous-flow microfluidic platforms which have been developed from these early platform designs. It was used for this thesis investigation into microfluidic-assisted radiofluorination. While the NanoTek® system was originally presented solely for radiofluorination reactions, this has expanded to encompass a variety of radionuclides, including carbon-11,^{198, 199} nitrogen-13²⁰⁰ and technetium-99m²⁰¹ however these nuclides and radiosyntheses will not be discussed in this thesis.

The platform (Scheme 3.2) typically consists of one Concentrator module (CE1), used for the azeotropic drying of [^{18}F]fluoride, which is then loaded into a storage loop on Pump 3 (P3), housed on the reactor module, for dispensing into the reactor. There are two further pump modules (P1 and P2), which are used to introduce the precursor (P1) and any further reagents needed if a second step is required. Under this set-up, one or two-step microfluidic procedures are accessible, utilising coiled loop reactors of fused silica capillary tubing of varying lengths and diameters. There are 4 reactor slots which can be connected in series and each reactor can be heated to 220°C and sustain pressures of up to 400 psi. As this is a modular system, additional modules can easily be added in for more complex set-ups if required.



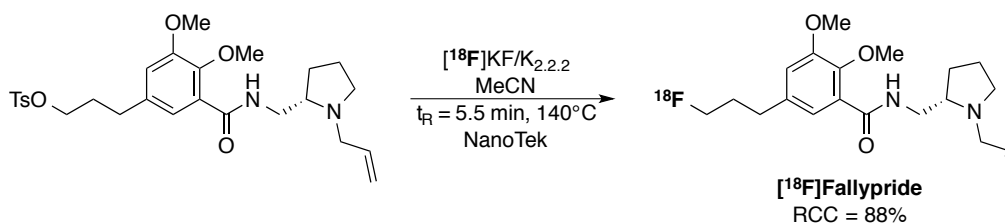
Scheme 3.2: Standard NanoTek® set-up (only 2 reactors shown).

The NanoTek® microfluidic control software, in ‘Discovery Mode’, enables fine tuning of reaction conditions (temperature, flow rate, pump ratio etc.) between radiofluorination runs, while utilising the same batch of [^{18}F]fluoride, precursor and other reagents.²⁰² Each reaction is carried out by the pumps concurrently pushing reaction solvent into the pump storage loops and, therefore, forcing the reagents into the reactor. Once the appropriate volumes of each reagent have been introduced, P3 pushes the reaction solvent through a sweep line, into the reactor and collection line, and so ensuring the entire reaction bolus has been collected and washing the lines in the process, ready for the next run to be carried out.



Scheme 3.3: A NanoTek® platform (main) and a single reactor (8m, 64 μ L) (inset) in the Siemens Organic Molecular Imaging Laboratory (SOMIL), University of Oxford. A - Pump 1, B - Pump 2, C - semi-Prep HPLC, D - Concentrator 1, E - Concentrator 2, F - Pump 3, G - Reactor Module.

The earliest report of a radiopharmaceutical being produced on the NanoTek® platform came from Pike *et al.* for the synthesis of [18 F]fallypride (Scheme 3.4),²⁰³ which is used for the imaging of dopamine subtype 2 receptors in rodent and non-human primates^{204, 205} as well as humans.^{206, 207} Even though this was a simple S_N2 substitution on a tosylate precursor, a noteworthy feature of this procedure was that, when compared to traditional vessel based radiosyntheses, only 1 – 2% of precursor was needed yet incorporation could be more than doubled with RCC = 88%.

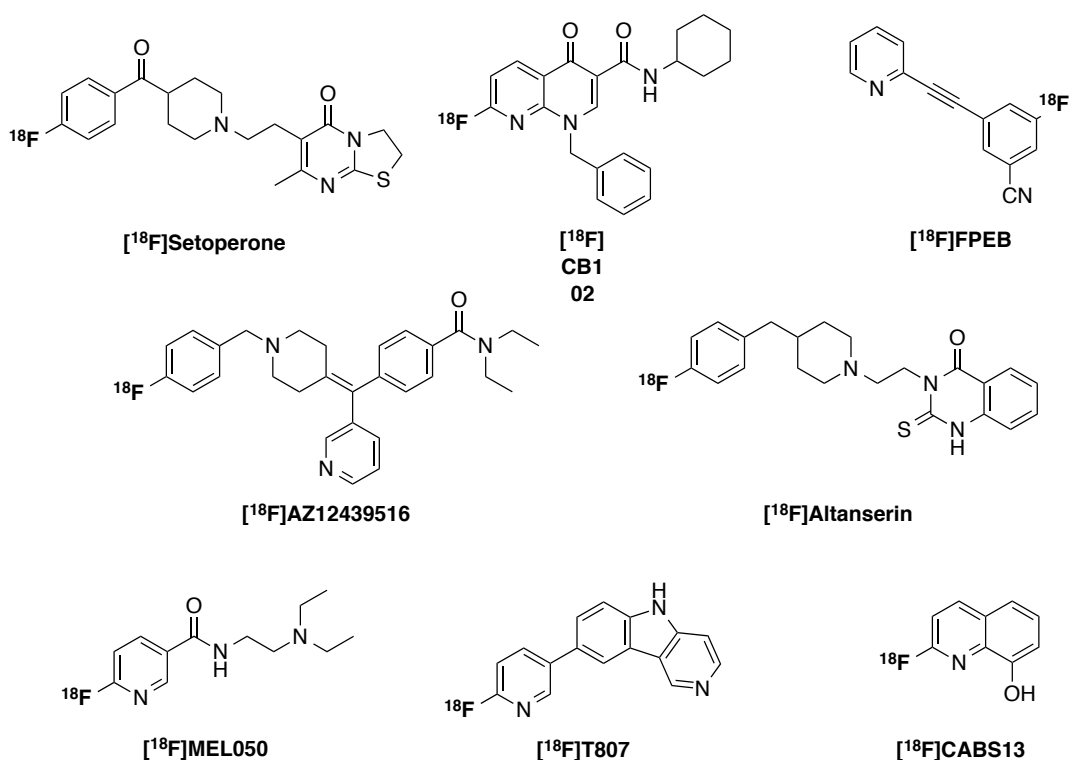


Scheme 3.4: Radiosynthesis of [18 F]fallypride.²⁰³

Following this original report from Pike, there is an ever increasing number of radiopharmaceuticals being synthesised on the NanoTek® platform, and many show the benefits of microfluidic systems; reduced reagent and solvent use, reduced reaction time and increased reproducibility.

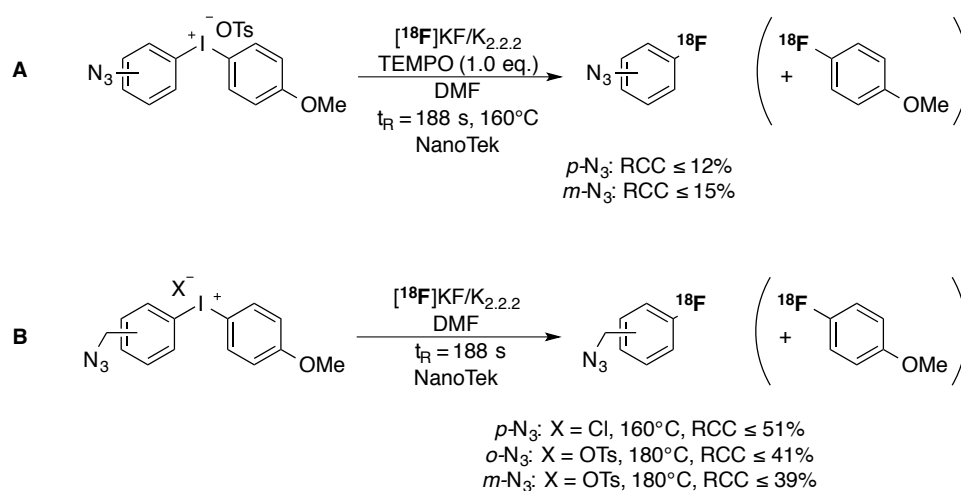
Labelling on non-aromatic positions typically follows simple S_N2 reactions, most commonly utilising the tosylated precursor, and the NanoTek® has been used to label [¹⁸F]*N*-fluoroacetyl-*N*-(2,5-dimethoxybenzyl)-2-phenoxyaniline (bromo- precursor),²⁰⁸ [¹⁸F]FLT,²⁰⁹ [¹⁸F]FIAU (triflate precursor),²¹⁰ [¹⁸F]FE@SUPPY and [¹⁸F]FE@SUPPY:2,²¹¹ [¹⁸F]FMC, [¹⁸F]FEC and [¹⁸F]FPC (via the [¹⁸F]fluoroalkylating reagents [¹⁸F]FMTos,²¹² [¹⁸F]FETos and [¹⁸F]FPTos²¹³), [¹⁸F]FAZA,²¹⁴ [¹⁸F]FPMA ([¹⁸F]ML-Io),²¹⁵ [¹⁸F]FE@SNAP,²¹⁶ [¹⁸F]FET²¹⁷ and [¹⁸F]MISO.²¹⁸

S_NAr remains the most common route for labelling aromatics on the NanoTek, due to improvement to reaction rates and conversions associated with microfluidics and the precursors being relatively simple to synthesise. In this way several radiotracers, using trimethylammonium-, chloro- and nitro- based precursors, have been synthesised, including [¹⁸F]setoperone,²¹⁹ [¹⁸F]CB102,²¹³ [¹⁸F]AZ12439516 (via 4-¹⁸Ffluorobenzaldehyde),²²⁰ [¹⁸F]altanserine,²²¹ [¹⁸F]T807,²²² [¹⁸F]MEL050,²²³ [¹⁸F]FPEB²²⁴ and [¹⁸F]CABS13 (Scheme 3.5).²²⁵ Whilst many of these tracers, both aromatic and aliphatic, have been used in preclinical studies, the report of microfluidic radiofluorination of [¹⁸F]T807 represented the first in human study of a radiopharmaceutical produced via microfluidics.



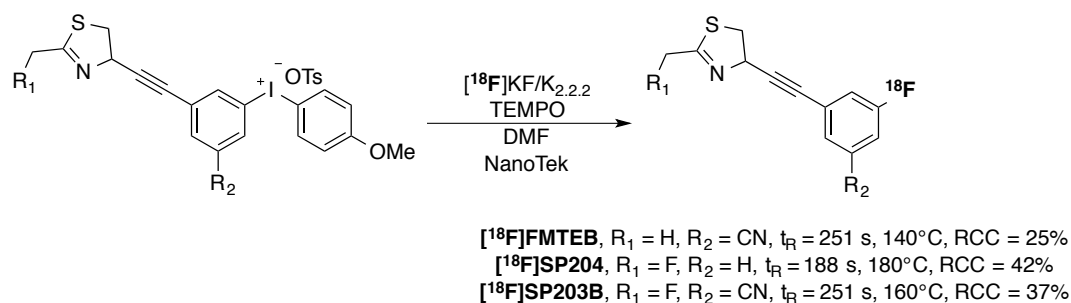
Scheme 3.5: [¹⁸F]Arene radiotracers labelled on the NanoTek® platform by S_NAr.

Aside from nucleophilic aromatic substitution reactions, Pike has reported extensive examples of radiofluorination of arenes from diaryliodonium salt precursors. This includes simple arenes, bearing *ortho*-alkyl substitution,⁶⁷ more highly functionalised arenes as potential labelling synthons,²²⁶ 2- and 3-[¹⁸F]fluorohalopyridines,²²⁷ 3- and 4-[¹⁸F]fluorophenylazides (Scheme 3.6, A) and 2-, 3- and 4-[¹⁸F]fluorobenzylazides (B), which are useful as click synthons for labelling of peptides and proteins.¹⁸⁹



Scheme 3.6: Radiosynthesis of 3- and 4-[¹⁸F]fluorophenylazides (A) and 2-, 3- and 4-[¹⁸F]fluorobenzylazides (B). 0.7 – 2.7% of 4-[¹⁸F]fluoroanisole was found in each case.¹⁸⁹

This methodology was applied to the radiosynthesis of three metabotropic glutamate receptor subtype-5 (mGluR5) antagonist tracers, [^{18}F]FMTEB, [^{18}F]SP204 and [^{18}F]SP203B (Scheme 3.7). The addition of radical scavenger TEMPO was found to improve the incorporation, with the optimised conditions giving conversions in the range 25 – 42 %.²²⁸

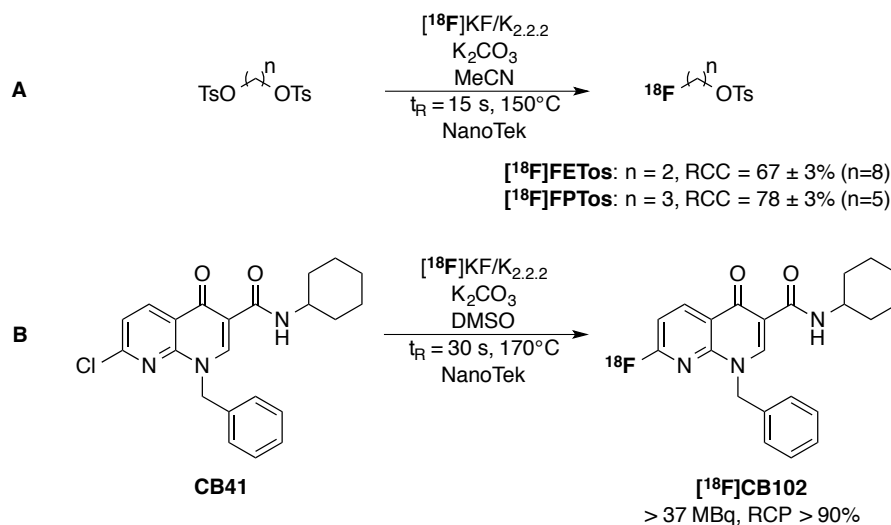


Scheme 3.7: mGluR5 antagonist radiosynthesis via diaryliodonium tosylates.²²⁸

Expanding from hypervalent diaryliodonium salts, Pike has also utilised diarylsulfoxides as precursors.⁶² For symmetrical precursors, high RCCs (> 21%) were only obtained when *para*-nitro, cyano or trifluoromethyl groups were included, or 2- or 4-pyridines were used. Unsymmetrical precursors were highly selective for arenes bearing a *para*-nitro group, however, no incorporation was observed when neither arene carried this functionality.

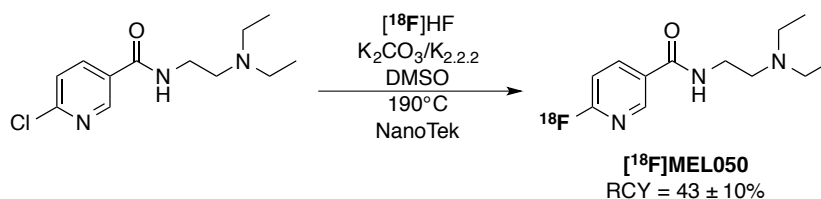
The versatility of this platform for rapid optimisation and labelling²⁰² was comprehensively explored by Pascali *et al.* when they reported the optimisation of two [^{18}F]fluoroalkylating synthons, [^{18}F]fluoroethyltosylate ([^{18}F]FETos) and [^{18}F]fluoropropyltosylate ([^{18}F]FPTos) (Scheme 3.8, A), and were able to demonstrate the theory of dose on demand (DOD) for radiopharmaceuticals on a cannabinoid type 2 receptor agonist, CB4I as [^{18}F]CBio2 (B).²¹³ They were also able to show that [^{18}F]CBio2 could be purified by automated SPE, in preparation for animal studies, and the SPE cartridge could be recycled and preconditioned by automated macros to be ready for

the next production run. The final RCY of these production runs was not given, though the minimum required for animal studies was stated as 37 MBq.



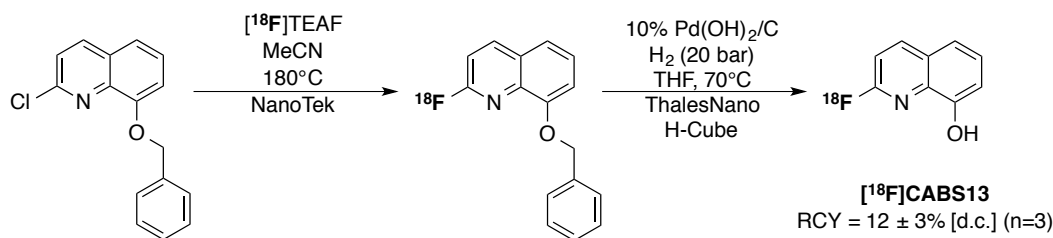
Scheme 3.8: Radiosynthesis of $[^{18}\text{F}]\text{FETos}$, $[^{18}\text{F}]\text{FPTos}$ (A) and $[^{18}\text{F}]\text{CB102}$ (B) on a NanoTek® platform.²¹³

Pascali *et al.* were able to build on these results and successfully incorporate semi-prep HPLC purification and SPE reformulation allowing for in-line purification of radiopharmaceuticals, controlled under the same software as the microfluidic platform itself.²²⁹ Again using $[^{18}\text{F}]\text{CB102}$ as the model, they were able to demonstrate a production level radiosynthesis in a one step procedure ($\text{RCY} = 22 \pm 5\%$ [d.c.], $\text{RCP} > 95\%$, 14 min). A separate two step procedure gave $[^{18}\text{F}]\text{fluoroethyl choline}$ ($[^{18}\text{F}]\text{FEC}$) ($\text{RCY} = 56 \pm 6\%$ [d.c.], $\text{RCP} > 97\%$, 13 min), via $[^{18}\text{F}]\text{FETos}$, with both of these procedures coming under fully automated macros, including HPLC isolation and SPE reformulation. The potential of this combined system was further demonstrated with automated production of $[^{18}\text{F}]\text{MELo50}$ (Scheme 3.9), which is used for the imaging of primary and metastatic melanoma,²³⁰ including HPLC-SPE purification and reformulation in $\text{RCY} = 43 \pm 10\%$ in a total synthesis time of 50 minutes.²²³



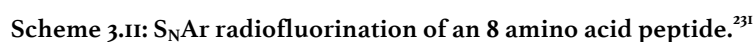
Scheme 3.9: Automated radiofluorination, purification and reformulation of melanoma imaging agent [¹⁸F]MEL050.²²³

Another variation was achieved by Liang *et al.*, who were able to connect the NanoTek[®] platform with a ThalesNano H-Cube, for hydrogenation, and then a GE TRACERlab FX_{FN} for final HPLC purification (Scheme 3.10).²²⁵ This system was developed on the reduction of 4-[¹⁸F]fluoronitrobenzene to 4-[¹⁸F]fluoroaniline and was consequently presented as useful for radiopharmaceuticals by the radiosynthesis of [¹⁸F]CABS13 (RCY = 12 ± 3% [d.c.] (n=3), 45 min).



Scheme 3.10: Liang *et al.* microfluidic radiofluorination and in line hydrogenation of [¹⁸F]CABS13.²²⁵

Aside from small molecule radiotracers, Selivanova *et al.* have used the NanoTek[®] platform for the direct labelling of 7 or 8 amino acid derivatives of Bombesin (Scheme 3.11).²³¹ The radiofluorination step was carried out via a S_NAr mechanism on either a trimethylammonium or diphenylsulfonium leaving group, with the greatest RCY = 43% [d.c.] after SPE C18 isolation. Comparatively, conventional reaction conditions result in 5 – 20% RCY [d.c.] after HPLC isolation.²³²



Fc1cc(F)c(OC(=O)c2ccn([N+](C)(C)C)cc2)c(F)c1.[18F]TBAF>>Fc1cc(F)c(OC(=O)c2ccn([18F])cc2)c(F)c1

Fc1cc(F)c(OC(=O)c2ccn([18F])cc2)c(F)c1.N[C@@H](Cc3ccccc3)C(=O)N[C@@H](C[C@H](C)C)C(=O)N>>Fc1cc(F)c(OC(=O)c2ccn([18F])cc2)c(F)c1.N[C@@H](Cc3ccccc3)C(=O)N[C@@H](C[C@H](C)C)C(=O)N[C@@H](C[C@H](C)C)C(=O)N

[¹⁸F]F-Py-TFP
 RCC ≤ 97%

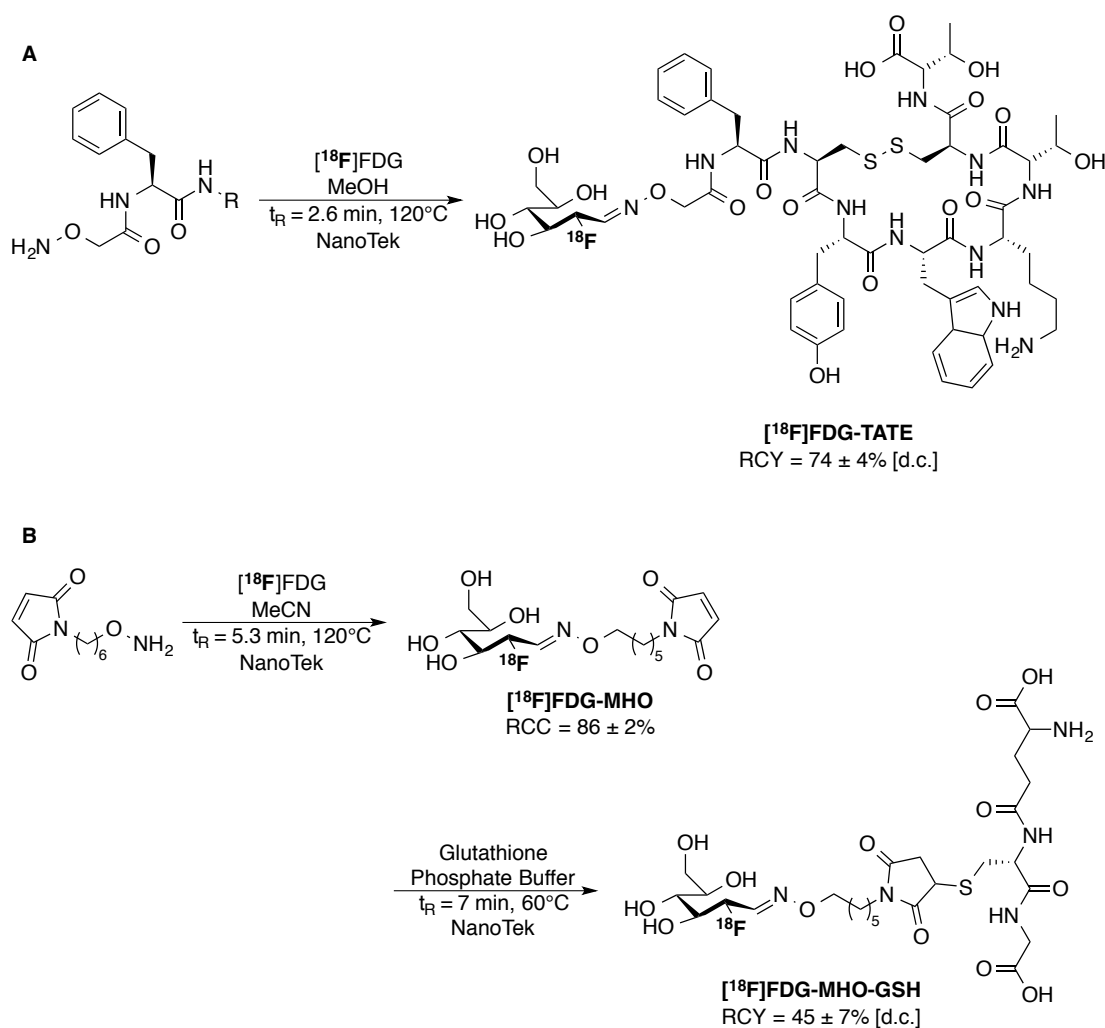
[¹⁸F]F-Py-YGGFL
 RCY = 9% [n.d.c.]

Scheme 3.12: Two reactor radiolabelling of a model peptide via [¹⁸F]F-Py-TFP.²³³

Larger phosphopeptide-cell-penetrating peptide dimers have also been labelled on a NanoTek platform, however the radiofluorination step is actually carried out on a GE TRACERlab FX_{FDG} module to form the prosthetic group *N*-succinimidyl 4-[¹⁸F]fluorobenzoate ([¹⁸F]SFB).²³⁴ This was then incorporated at the *N*-terminal position, using the microfluidic reactor.²³⁵ There was a report in 2014 of the automated radiosynthesis of [¹⁸F]SFB (RCY = 13 ± 8%, RCP > 95%) on a NanoTek®, which was prepare [¹⁸F]fluorobenzoylated human serum albumin ([¹⁸F]FB-HSA) however this is yet to be described in a full paper.²³⁶

Bouvet and Wuest have applied this platform to the post-fluorination labelling of peptide, using [¹⁸F]FDG that had been synthesised at a separate location.²³⁷ [¹⁸F]FDG-TATE, a somatostatin receptor ligand, could be directly labelled in a single reactor and HPLC purified with RCY = 74 ± 4% [d.c.] and RCP > 95% in a total synthesis time of 30 – 50 minutes, depending on the starting activity of [¹⁸F]FDG (Scheme 3.13, A).

[¹⁸F]FDG-maleimide-hexyloxime ([¹⁸F]FDG-MHO) (**B**), a thiol-reactive prosthetic group, could similarly be prepared in a single step from *N*-(6-aminooxy)hexyl maleimide hydrochloride (RCC = 86 ± 2%). This could be isolated by semi-prep HPLC (RCY = 75 ± 2% [d.c.], RCP > 95%) however, by incorporation of reactors 2 and 3, glutathione (GSH) was labelled as [¹⁸F]FDG-MHO-GSH in a two step procedure in a 45 ± 7% [d.c.] RCY after HPLC isolation.

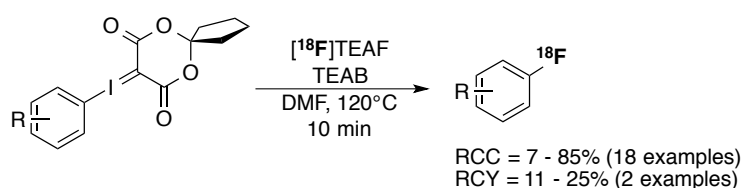


Scheme 3.13: [¹⁸F]FDG radiolabelling of TATE and GSH.²³⁷

3.1.3. Chapter Aims

The potential held by the use of microfluidic technology for the production of radiopharmaceuticals is vast, as has been described in this introduction. Nevertheless, when considering the radiosynthesis of [¹⁸F]arenes, the use of S_NAr protocols and diaryliodonium salt precursors are sub-optimal. Lower yields and non-regiospecific labelling introduce requirements for higher starting activities and longer and more complex purifications. Therefore, there remains scope for elaboration of existing vessel-based chemistry protocols, as well as development of radiolabelling techniques that are not possible under traditional vessel-based systems.

The use of spirocyclic iodonium(III) ylides for the efficient, regioselective radiofluorination of non-activated (hetero)arenes and radiopharmaceuticals (Scheme 3.14) was first developed by the Vasdev group (see Section 1.3.2.2. for full discussion).^{72, 73, 238} It was envisioned that the application of microfluidic technology could be used to improve the RCC of this system, whilst reducing the amount of precursor required and the overall synthesis time.



Scheme 3.14: Radiofluorination of spirocyclic iodonium(III) ylides⁷²

3.2. Application of Microfluidics to the Radiofluorination of Spirocyclic Iodonium(III) Ylides

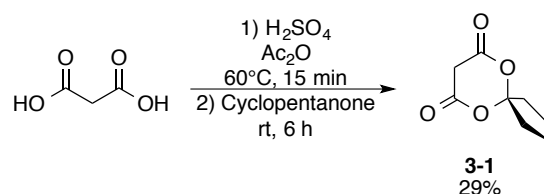
The initial aims of this project were to use 4-^[18F]fluorobiphenyl as a model substrate to validate a translation of spirocyclic iodonium(III) ylide radiofluorination methodology onto a continuous-flow microfluidic platform. Utilisation of the high throughput capabilities of these systems would be exploited to produce optimised conditions on this model substrate, which would then be verified with the synthesis of 2-^[18F]fluoro-1,3,5-trimethylbenzene and 4-bromo-1-^[18F]fluoro-2-methoxybenzene. Once optimised conditions were established, they would be used as primary conditions for radiopharmaceutically relevant compounds ^[18F]fluorobenzyl azide, a building block for click chemistry, 5-^[18F]fluoro-2,4-dimethoxypyrimidine, a precursor to 5-^[18F]fluorouracil (5-^[18F]FU), and 3-^[18F]fluoro-5-(2-pyridinylethynyl)benzonitrile (^[18F]FPEB), a metabotropic glutamate receptor subtype 5 (mGluR5) antagonist.

A NanoTek® (Advion, Inc.), a commercial continuous-flow microfluidic platform, was used for this study. NanoTek® systems are commonly used for research and synthesis

of radiopharmaceuticals (see Section 3.1.2.),²⁰² with the ability for rapid optimisation (up to 48 reactions per day achieved during the course of this project) and synthesis automation. Notably for this project, the NanoTek® has previously been used for the synthesis of [¹⁸F]FPEB ($2.1 \pm 0.4\%$, $n=3$), exploiting a S_NAr reaction and direct comparison between the methods will be able to be made.²²⁴

3.2.1. Synthesis of Spirocyclic Iodonium(III) Ylide Precursors

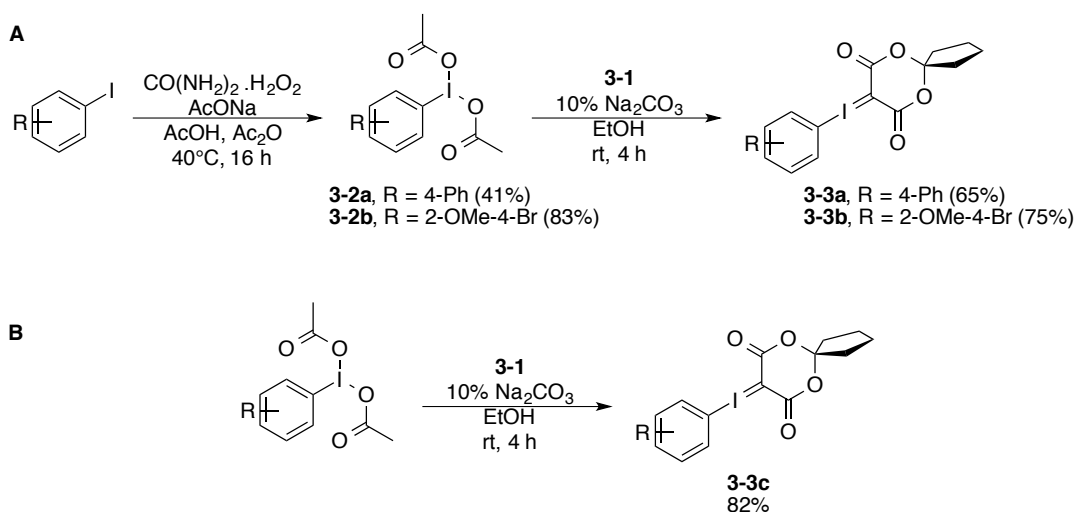
The spirocyclic iodonium(III) ylides are formed from the aryl iodides either via oxidation to the (diacetoxy)iiodoarene and consequent substitution with the spirocyclic auxiliary in two steps or in a direct one step procedure, following the procedures of Rotstein *et al.*⁷² The spirocyclic auxiliary itself, 6,10-dioxaspiro[4.5]decane-7,9-dione (**3-1**) was synthesised from pentanone and malonic acid and purified by recrystallization in a 29% yield (Scheme 3.15).



Scheme 3.15: Synthesis of spirocyclic auxiliary.

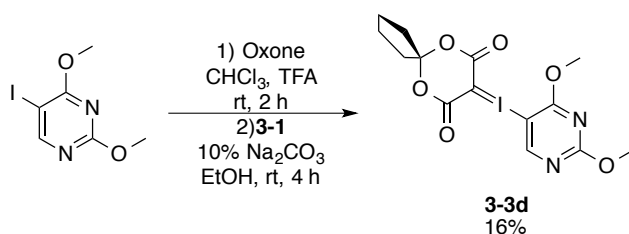
4-(Diacetoxyiodo)-1,1'-biphenyl (**3-2a**) and 4-bromo-1-(diacetoxyiodo)-2-methoxybenzene (**3-2b**) were synthesised from the commercially available aryl iodides using a urea-hydrogen peroxide adduct oxidant, and then carried forward to their respective ylides, 6,10-dioxaspiro[4.5]decane-7,9-dion-[1,1'-biphenyl-4-iodonium] ylide (**3-3a**) and 6,10-dioxaspiro[4.5]decane-7,9-dion-[4-bromo-2-methoxybenzene-1-iodonium] ylide (**3-3b**), via substitution with **3-1**, in 27% and 62% yields respectively, over two steps (Scheme 3.16, A). Iodomesitylene diacetate is commercially available and was subjected to the same substitution conditions to give 6,10-

dioxaspiro[4.5]decane-7,9-dion-[1,3,5-trimethylbenzene-2-iodonium] ylide (**3-3c**) in an 82% yield over a single step (**B**).



Scheme 3.16: Model spirocyclic iodonium(III) ylide synthesis.

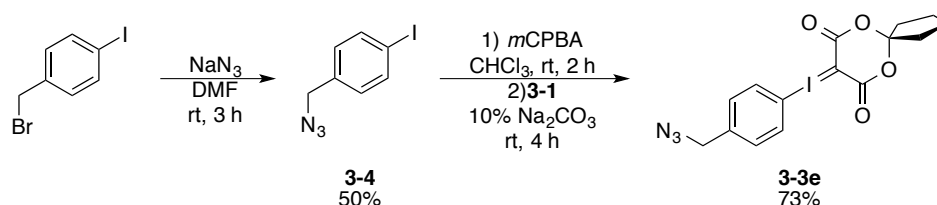
For the more highly functionalised compounds, a single step procedure was used as the (diacetoxiodo)arenes have previously been found to have stability issues. 6,10-Dioxaspiro[4.5]decane-7,9-dion-[2,4-dimethoxypyrimidine-5-iodonium] ylide (**3-3d**) was prepared from commercially available 5-iodo-2,4-dimethoxypyrimidine by oxidation with oxone and consequent coupling with (**3-1**) without isolation of the intermediate (Scheme 3.17). Each step of the reaction was monitored by TLC until loss of starting material was confirmed. Purification by recrystallization gave the desired precursor in a poor yield (16%), however this was more than sufficient for this investigation.



Scheme 3.17: One-step synthesis of 5- ^{18}F fluoro-2,4-dimethoxypyrimidine ylide precursor.

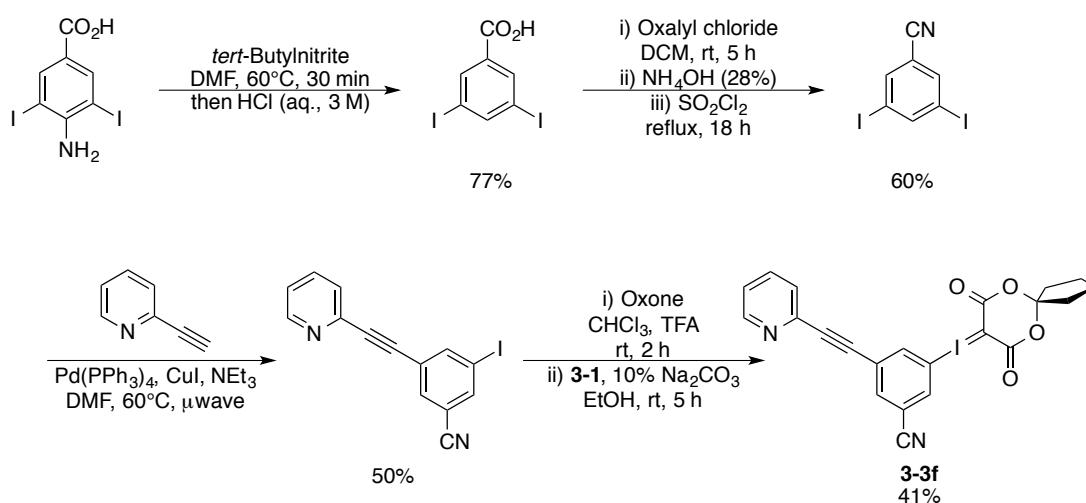
For the formation of 6,10-dioxaspiro[4.5]decane-7,9-dion-[1-(azidomethyl)benzene-4-iodonium] ylide **3-3e** (Scheme 3.18), 4-iodobenzyl bromide was first converted to

iodobenzyl azide (**3-4**) using sodium azide. In a method similar to that used for **3-3d**, this was then oxidised to **3-3e**, using *m*CPBA as the oxidant, and then coupled with the spirocyclic auxiliary in 37% over two steps.



Scheme 3.18: Synthesis of 4-[¹⁸F]fluorobenzyl azide ylide precursor.

The [¹⁸F]FPEB precursor, 3-((7,9-dioxo-6,10-dioxaspiro[4.5]decan-8-ylidene)-λ³-iodanyl)-5-(pyridine-2-ylethynyl)benzonitrile (**3-3f**) required a more complex synthetic route.^{238, v} A Sandmeyer reaction, using *tert*-butyl nitrite on 4-amino-3,5-diiodobenzoic acid, gave 3,5-diiodobenzonitrile which was then converted into the corresponding amide via the formation of an acid chloride, amidation and consequent dehydration. This was coupled with 3-ethynylpyridine under microwave assisted Sonagashira coupling conditions to give 3-iodo-5-(pyridine-2-ylethynyl)benzonitrile. Finally, the ylide **3-3f** was formed under the same conditions as those used for **3-3d** in a 9% yield over the 4 steps.

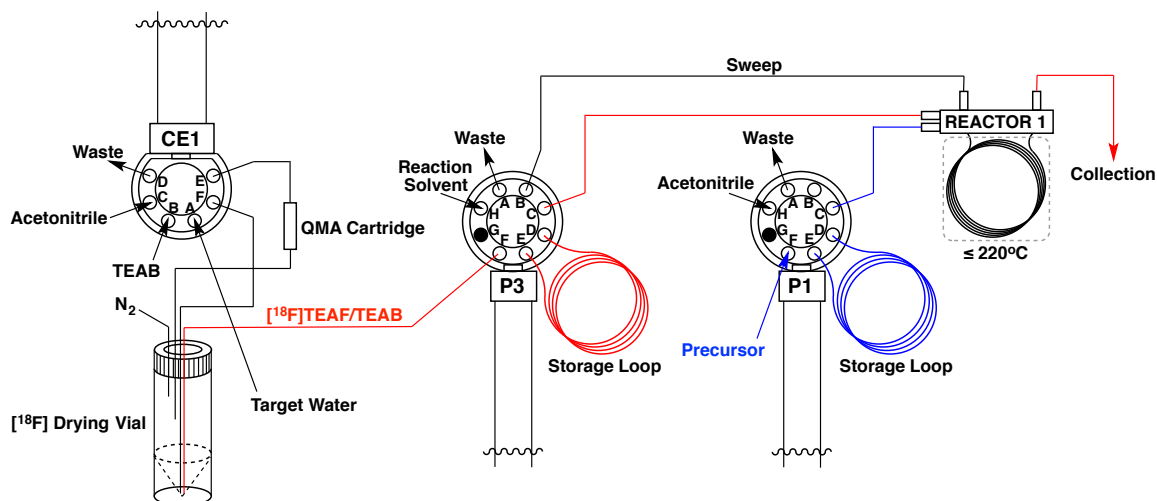


Scheme 3.19: Synthesis of [¹⁸F]FPEB precursor (**3-3f**), carried out by Dr N. Stephenson.²³⁸

^v Synthesis of **3-3f** carried out by Dr N. Stephenson

3.2.2 Reaction Optimisation and Validation

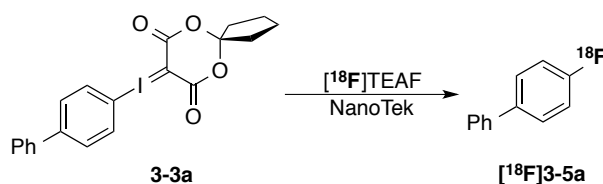
Initial conditions for the validation studies were chosen to closely mirror those developed by the Vasdev group,⁷² run in DMF and using tetraethylammonium [¹⁸F]fluoride ([¹⁸F]TEAF) as the [¹⁸F]fluoride source. This was obtained from a fully automated drying routine using Concentrator 1 (CE1) on the NanoTek® platform by trapping [¹⁸F]fluoride, produced in ¹⁸OH₂, on a QMA anion-exchange cartridge, release with a solution of tetraethylammonium bicarbonate (TEAB) in MeCN:H₂O (1:1) and azeotropically dried with dry MeCN. The dry [¹⁸F]TEAF was taken up in a volume of dry DMF (volume determined by the final [¹⁸F]TEAF concentration desired). As discussed previously, due to the very low amount of ¹⁸F⁻ ions present, an excess of base must be used for the elution and consequently the majority of the tetraethyl ammonium salt will remain in the bicarbonate form. Therefore, when [¹⁸F]TEAF is referred to, it is a [¹⁸F]TEAF/TEAB mixture and so the concentration of the remaining bicarbonate can play a significant role in the radiofluorination reaction.



Scheme 3.20: NanoTek® schematic for validation and optimisation.

The NanoTek® was set up (Scheme 3.20) with two storage loops, one on Pump 3 (P3) for [¹⁸F]TEAF (initially 12 mg/mL) and the other on Pump 1 (P1) for the ylide precursor **3-3a** (initially 8 mg/mL) to give 4-[¹⁸F]fluoro-1,1'-biphenyl (**3-5a**) (Scheme 3.21). These two

pumps were used to introduce the solutions concurrently (P1:P3 = 1) into a single 4 m reactor loop heated to the desired temperature at a total flow rate of 60 $\mu\text{L}/\text{min}$. The reactions were then collected for analysis by radioHPLC and radioTLC. All radioHPLC runs carried out over the course of this investigation indicated a single radiolabelled product being formed, with no other radiolabelled organic material. In each case, product identity was confirmed as being the desired product for that reaction by overlay of a chromatogram of an authentic reference, or by co-injection with authentic reference.



Scheme 3.21: Model reaction for microfluidic application and optimisation.

On examination of these initial conditions across a temperature range of 130 - 220°C, it was pleasing to find that the RCC of [¹⁸F]3-5a from the microfluidic approach ($82 \pm 4\%$, $n=2$, 190°C) was comparable to the optimised manual protocol (85%).⁷² Consequently a more exhaustive optimisation of the reaction conditions was carried out, starting with solvent variation (Figure 3.1). The use of DMSO ($69 \pm 1\%$, $n=2$, 190°C) or MeCN ($72 \pm 9\%$, $n=2$, 190°C) offered no improvement to the best result with DMF, however, notably the use of MeCN offered significant improvements of RCC at both the lower and higher temperatures. Despite not improving the best result with DMF, this result is noteworthy as the use of acetonitrile was dismissed early in the manual protocol due to its low boiling point and low RCC observed ($9 \pm 8\%$, $n=3$). This demonstrates the capacity of MCS to withstand high pressure and push solvents well past their atmospheric boiling points.

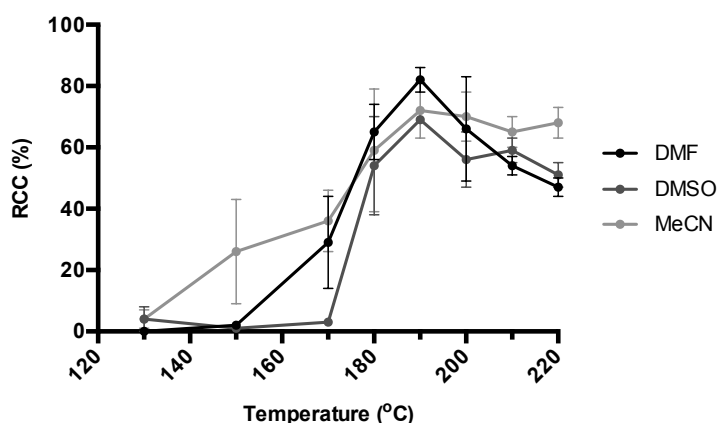


Figure 3.1: Solvent variation plot for the radiosynthesis of $[^{18}\text{F}]3-5a$.

Prior to examining the effects of changing the precursor and $[^{18}\text{F}]$ TEAF loading, the rate and ratio at which the precursor and $[^{18}\text{F}]$ TEAF are introduced was examined. Variation of the ratio of P1:P3 showed that decreasing the ratio of precursor had a detrimental effect on the conversions observed (Figure 3.2). Correspondingly, increasing the ratio of precursor led to slight improvements in the overall conversion, however this was not implemented in the following optimisation due to the limitations that this would impose on full batch reactions. As the P1 and P3 loops used had similar volumes, a ratio of 1:1 would be preferable as then the entire volume of each loop could be used. In increasing the ratio of P1:P3 > 1, the P1 loop would be emptied earlier than the P3 loop and, therefore, not all the $[^{18}\text{F}]$ TEAF in P3 loop would be used. As one of the main reasons for using microfluidic technology was to reduce wastage, an alternative would be to increase the concentration of precursor in P1, which will be discussed later.

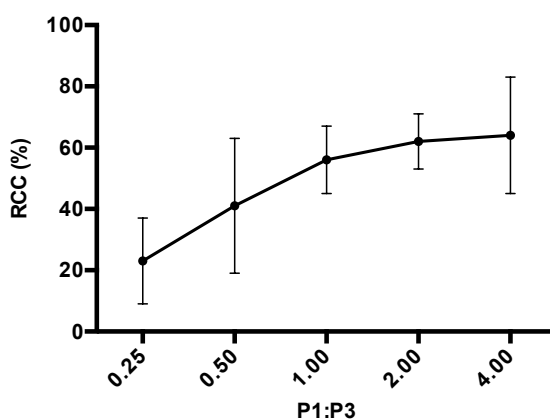


Figure 3.2: P1 (3-3a):P3 ($[^{18}\text{F}]$ TEAF) ratio variation plot for the radiosynthesis of $[^{18}\text{F}]3-5a$.

The rate at which the reaction bolus passes through the reactor can have major effects on the overall conversion, due to the changes in t_R . Decreasing the flow rate, and so increasing t_R , would mean that the reaction is held at the reaction temperature for a longer time, which can have beneficial effects on the conversion (Figure 3.3). Conversely, an increased t_R can also lead to increased by-product formation and much longer overall synthesis times when considering complete batch runs. With the four metre reactor, which has a volume of 32 μL , a rate of 60 $\mu\text{L}/\text{min}$ sets the $t_R = 32$ s. It was found that with this model substrate **3-3a**, that no significant increase or decrease in RCC was found by either increasing or decreasing rate.

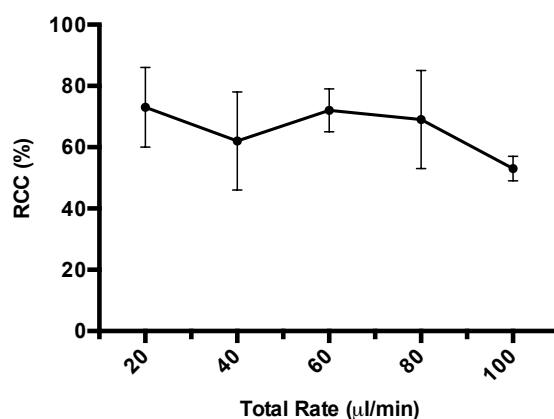


Figure 3.3: Rate variation plot for the radiosynthesis of $[^{18}\text{F}]\mathbf{3-5a}$.

As the variation in $\text{Pr}:\text{P}_3$ ratio had suggested that increased precursor would be beneficial to the reaction, the concentration of **3-3a** was doubled to 16 mg/mL and subjected to the same temperature range as previously examined (Figure 3.4). As expected, the increased concentration lead to increased RCC across the entire range, with the RCC now being found to be effectively quantitative ($95 \pm 1\%$, $n=2$, $190/200^\circ\text{C}$). Furthermore, the drop in RCC observed when $T > 190^\circ\text{C}$ was no longer as apparent. Decreasing the concentration of **3-3a** to 4 mg/mL was significantly detrimental to the incorporation of $[^{18}\text{F}]\text{fluoride}$ with the best $\text{RCC} = 6 \pm 1\%$ ($n=2$, 210°C).

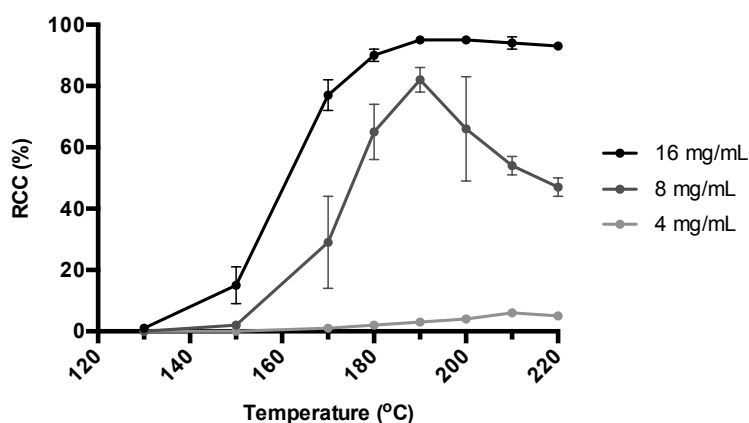


Figure 3.4: Precursor loading variation plot for the radiosynthesis of $[^{18}\text{F}]\mathbf{3-5a}$.

Decreasing the base loading to 6 mg/mL led to slight improvement in conversion at the lowest temperatures, though significant decreases in conversion as the reaction temperature was increased (Figure 3.5). Increasing the base loading to 18 mg/mL decreased the conversion considerably, though not to the same degree at higher temperature as when the base was decreased.

The role of the base in the reaction mechanism has not been proven, though is influential toward $[^{18}\text{F}]$ fluoride incorporation, whilst it can have adverse effects by promoting side reactions.²³⁸ Furthermore, recent studies have shown that the precursors decompose via multiple pathways when heated with tetraethylammonium bicarbonate.²³⁹ Consequently, the base loading in the reaction is an important parameter to control effectively.

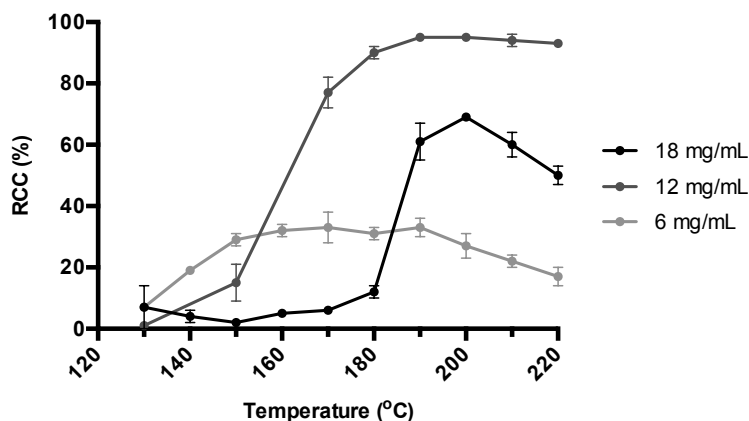
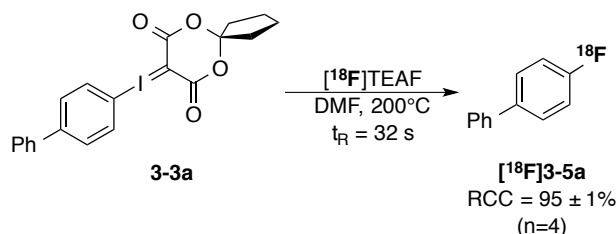


Figure 3.5: $[^{18}\text{F}]\text{TEAF}$ loading variation plot for the radiosynthesis of $[^{18}\text{F}]\mathbf{3-5a}$.

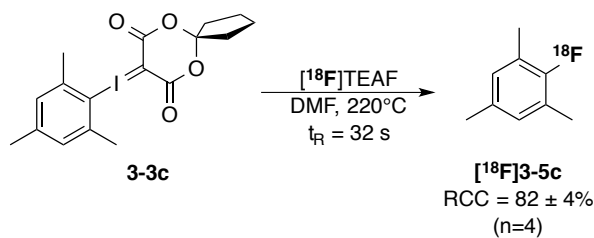
Final optimized conditions (16 mg/mL precursor, 12 mg/mL [^{18}F]TEAF, DMF, 60 $\mu\text{L}/\text{min}$, $\text{P1:P3} = 1, 4$ m reactor) gave excellent conversion to [^{18}F]3-5a ($95 \pm 1\%$, $n=4$, 200°C) (Scheme 3.22), representing an increase in the manual procedure by Rotstein *et al.*⁷²



Scheme 3.22: Optimised conditions for the radiosynthesis of 4-[^{18}F]fluoro-1,1'-biphenyl ([^{18}F]3-5a).

In order to confirm that these conditions would be valid for application to the radiopharmaceutical targets for this study, they were applied to 3-3b and 3-3c to form 4-bromo-1-[^{18}F]fluoro-2-methoxybenzene ([^{18}F]3-5b) and 2-[^{18}F]fluoro-1,3,5-trimethylbenzene ([^{18}F]3-5c).

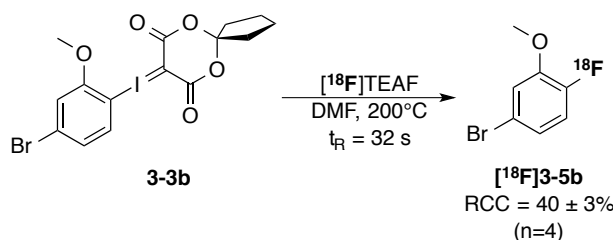
The formation of [^{18}F]3-5c was found to proceed better at 220°C , rather than the 200°C as for [^{18}F]3-5a, giving an excellent $\text{RCC} = 82 \pm 4\%$ ($n=4$) (Scheme 3.23). This represents a significant improvement in yield when compared to that achieved by the original manual protocol ($45 \pm 13\%$, $n=3$).



Scheme 3.23: Radiosynthesis of 2-[^{18}F]fluoro-1,3,5-trimethylbenzene ([^{18}F]3-5c).

Gratifyingly, the reaction on 3-3b also gave a good yield ($40 \pm 3\%$, $n=4$, 200°C) (Scheme 3.24). Variation from 200°C lead to loss of conversion with 190°C and 210°C giving $30 \pm 8\%$ ($n=4$) and $31 \pm 6\%$ ($n=4$), respectively. Unfortunately, the RCCs found using this

microfluidic approach were not as good as those found in the literature precedent ($56 \pm 11\%$, $n=3$).



Scheme 3.24: Radiosynthesis of 4-bromo-1- ^{18}F -fluoro-2-methoxybenzene (^{18}F 3-5b).

Despite the microfluidic approach giving a lower conversion to ^{18}F 3-5b, these results have clearly shown that this reaction can easily be applied to a microfluidic platform to give excellent RCCs. Additionally, adoption of microfluidics and semi-automation of the reaction has led to a decrease in the variation seen between identical runs. Therefore, the optimized conditions were carried forward to radiopharmaceutically relevant compounds.

3.3. Microfluidic Synthesis of Radiopharmaceutically Relevant Compounds

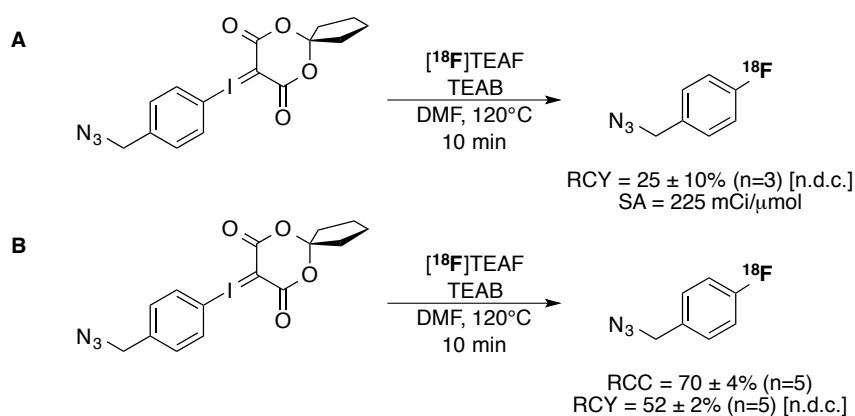
3.3.1 4- ^{18}F -Fluorobenzyl Azide

The first compound selected to be labeled using this new protocol was 4- ^{18}F -fluorobenzyl azide (^{18}F 3-5e), which is used to label larger structures that cannot be directly radiofluorinated. This is typically accomplished via utilization of Huisgen cycloadditions (“click reactions”) in a building-block approach to give a 1,2,3-triazole linker, which is stable *in vivo*.²⁴⁰ It can be considered to be superior to other similar azide synthons containing aliphatic C-F bonds, such as 2- ^{18}F -fluoroethylazide,²⁴¹ as the aromatic C-F bond is known to be less susceptible to *in vivo* radiodefluorination.²⁴²

Hitherto, several approaches have been used to label [^{18}F]**3-5e**. Thonon *et al.* described the first radiosynthesis, via a stepwise protocol, starting with 4-formyl-*N,N,N*-trimethylanilinium triflate which was subjected to nucleophilic aromatic radiofluorination conditions. Reduction to the alcohol, followed by bromination, was carried out on a C18 cartridge, before the benzyl bromide was eluted in DMF and finally an azide exchange resin (Amberlite IRA-400) was used to form [^{18}F]**3-5e**. This four step procedure gave a RCY = 34% [d.c.] in a total synthesis time of 75 minutes.²⁴³ The same group was able to automate this synthesis to give RCY up to 60% [d.c.] in a synthesis time of 40 min.²⁴⁴ A direct $\text{S}_{\text{N}}\text{Ar}$ route, using 4-nitrobenzyl azide, has also been described which was isolated and used for the labeling of Bombesin, a GRP-receptor-specific neuropeptide containing 14 amino acids in a RCY = 31%, however the RCY of the first step is not disclosed.²⁴⁵

A microfluidic synthesis, also on the NanoTek® platform, developed by Pike and Chun used diaryliodonium salt precursors, which gave a RCC = 51% with 3% of the corresponding 4- ^{18}F fluoroanisole.¹⁸⁹

Radiofluorination of spirocyclic iodonium(III) ylides has also been used for the synthesis of [^{18}F]**3-5e**. In the original paper by Rotstein *et al.*, a RCY = $25 \pm 10\%$ (n=3) was obtained after isolation via SPE on a C18 cartridge.⁷² After the completion of this project, the Vasdev group have published an improved synthesis, based on the same methodology giving RCC = $70 \pm 4\%$ (n=5) and RCY = $52 \pm 2\%$, (n=5).⁷³



Scheme 3.25: Spirocyclic iodonium(III) ylide radiofluorination routes to 4- $[^{18}\text{F}]$ fluorobenzyl azide ($[^{18}\text{F}]\mathbf{3-5e}$) published before (A)⁷² and after (B)⁷³ this project by the Vasdev group.

6,10-Dioxaspiro[4.5]decane-7,9-dion-[1-(azidomethyl)benzene-4-iodonium] ylide (**3-3e**) was subjected to the optimised conditions developed for the synthesis of $[^{18}\text{F}]\mathbf{3-5a}$ and gave moderate conversion to the desired azide $[^{18}\text{F}]\mathbf{3-5e}$ ($31 \pm 1\%$, $n=3$, 200°C) with a temperature dependence similar to $[^{18}\text{F}]\mathbf{3-5a}$ (Figure 3.6, A). Unlike $[^{18}\text{F}]\mathbf{3-5a}$, when the total flow rate was dropped from $60 \mu\text{L}/\text{min}$ to $20 \mu\text{L}/\text{min}$ an increase in RCC to 44% ($n=1$) was observed (B). This increase in conversions was considered to be most likely attributed to an increase in t_R , from 32 s to 96 s . However, when considering whole batch production runs, decreasing the rate would unacceptably triple the total run time. Therefore, the reactor was replaced with an 8 m version ($64 \mu\text{L}$) and the rate returned to $60 \mu\text{L}/\text{min}$. In switching to a longer reactor, the t_R could be increased (32 s (4 m) to 64 s (8 m) at $60 \mu\text{L}/\text{min}$) while minimising the rise in total time taken for the run.

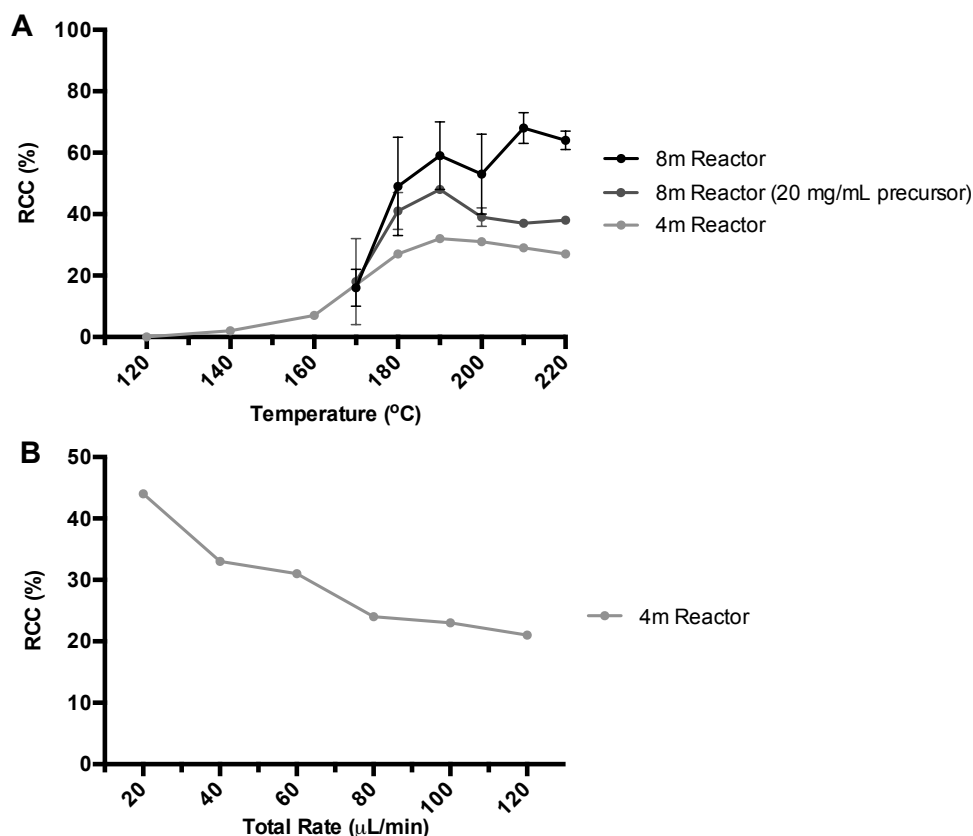
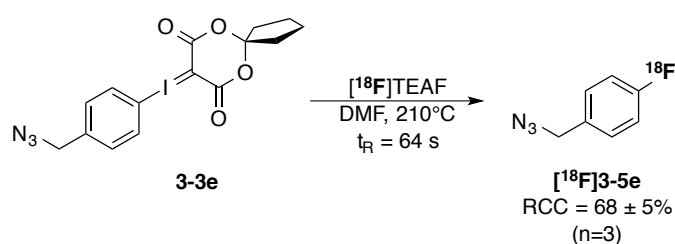


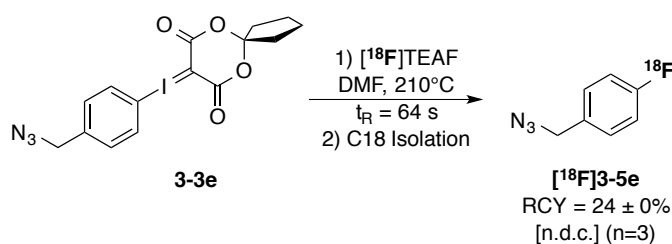
Figure 3.6: Temperature (A) and rate (B) dependence on the radiosynthesis of [^{18}F]3-5e.

Adoption of the 8 m reactor led to increased RCC across the entire temperature range studied, with 210°C being found as the optimum temperature ($68 \pm 5\%$, $n=3$) (Scheme 3.25). This conversion represents a 17% increase on Pike's microfluidic approach, whilst requiring a shorter t_R (64 s compared to 188 s).¹⁸⁹ As an increase in conversion had been observed with increased precursor loading, the PI loop concentration of 3-3e was increased to 20 mg/mL though this unfortunately only led to a fall in conversion across all temperatures.



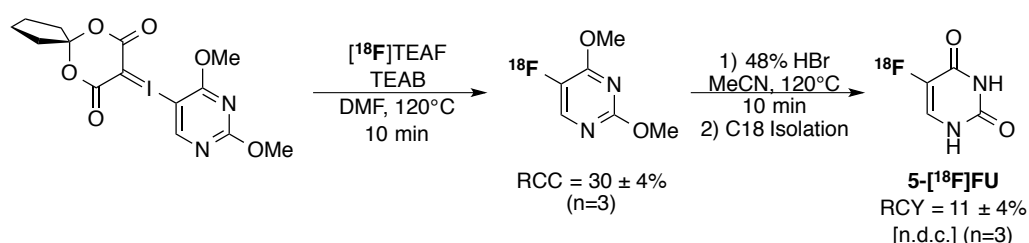
Scheme 3.25: Radiosynthesis of [^{18}F]3-5e.

As one of the aims of this project was to demonstrate a fully automated synthesis on the NanoTek® platform, the optimised conditions were combined with macros written for SPE isolation using a C18 cartridge. Thus, a fully automated synthesis of [¹⁸F]3-5e has been demonstrated, from azeotropic drying to final collection vial giving a RCY = 24 ± 0% (n=3) [n.d.c.] with RCP = 95% in a total synthesis time of 60 minutes from target unload to assay of final product (Scheme 3.26). This yield is comparable to that found in the preliminary spirocyclic iodonium(III) ylide paper,⁷² and demonstrates an increase in reproducibility, however this achievement has since been surpassed by the reoptimisation of this system by the Vasdev group, which gave RCY = 52 ± 2% (n=5) [n.d.c.].⁷³



as the common problems associated with [^{18}F] F_2 , including low yields, low specific activity and several [^{18}F]by-products²⁵⁰ (See Section 1.3.3. for full discussion on [^{18}F] F_2).

Since Visser, there have been few significant advances in the production of 5- ^{18}F FU, until Rotstein *et al.* showed the first nucleophilic route using the spirocyclic iodonium(III) ylide radiochemistry (Scheme 3.27).⁷² 5- ^{18}F Fluoro-2,4-dimethoxypyrimidine was produced from its corresponding ylide in $\text{RCC} = 30 \pm 4\%$ ($n=3$) and deprotection with hydrobromic acid gave 5- ^{18}F FU in $\text{RCC} = 23 \pm 3\%$ ($n=3$) and isolation by SPE gave a $\text{RCY} = 11 \pm 4\%$ [n.d.c.] ($n=3$).



Scheme 3.27: Nucleophilic route to 5- ^{18}F FU using spirocyclic iodonium(III) ylide methodology.⁷²

Resulting from the successes of this project, it was envisioned that the application of this microfluidic technology, with the addition of a second reaction vessel for the deprotection and integration with a semi-prep HPLC system would be able to increase the conversion to 5- ^{18}F fluoro-2,4-dimethoxypyrimidine (^{18}F 3-5d) and provide a platform for the regular production of this important tracer.

Using the optimized conditions from the synthesis of ^{18}F 3-5a, no reactivity was observed below 180°C (Figure 3.7, A). The greatest conversion was found at 190°C (11%, $n=1$), however this result did seem to be anomalous with reference to the previous results. Interestingly, a study into the rate effect at 190°C showed similar conversions as initially found though showed a decrease in RCC when the rate was both increased and decreased (B). As discussed previously, a decrease in conversion associated with an increased rate is expected due to a decrease in t_R ; a decrease in conversion with decreased rate is less common.

It was theorised that at lower temperatures **3-3d** may not have a sufficiently long t_R to undergo the radiofluorination, but conversely by increasing t_R , decomposition may be occurring.

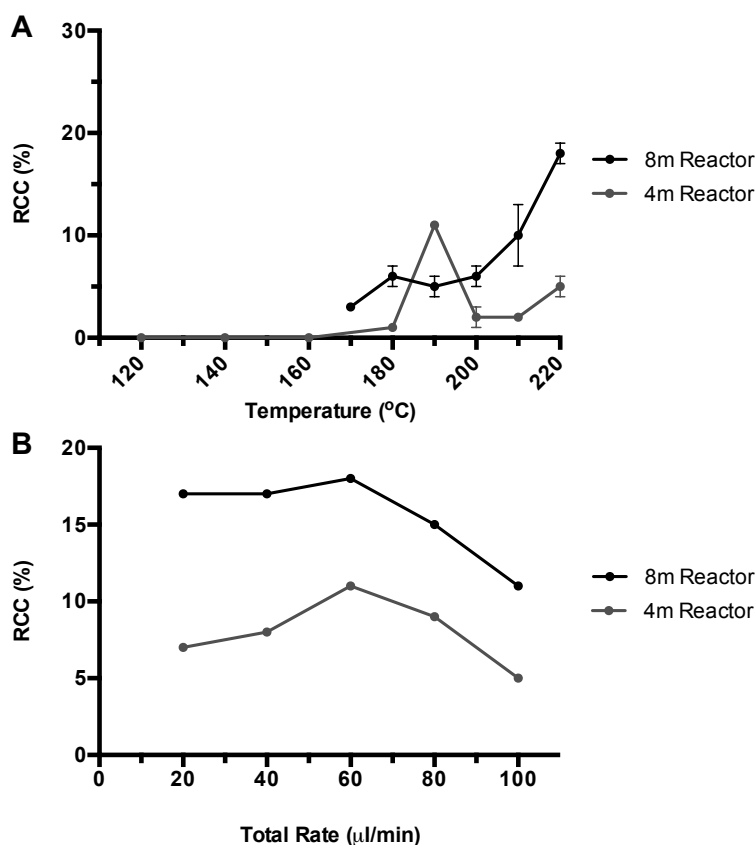
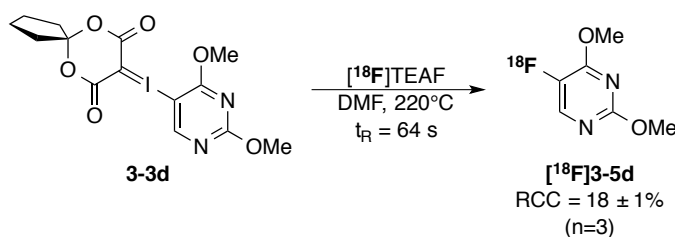


Figure 3.7: Temperature (A) and rate (B) dependence for the radiosynthesis of $[^{18}\text{F}]\mathbf{3-5d}$.

As the use of an 8 m reactor had significantly improved the conversion to $[^{18}\text{F}]\mathbf{3-5e}$, the effects of this change on the radiofluorination of $[^{18}\text{F}]\mathbf{3-5d}$ were probed in the range 170 – 220°C. Pleasingly, the RCC of the reaction did increase ($18 \pm 1\%$, $n=3$, 220°C), though disappointingly it remained below the conversion attained by the original manual protocol. Study of the rate effect showed a similar trend to the 4 m reactor with the conversion decreasing when the rate was either increased or decreased.



Scheme 3.28: Radiofluorination of 5-^[18F]fluoro-2,4-dimethoxypyrimidine (^[18F]3-5d).

Ultimately, the use of microfluidic technology has not offered the desired outcome for this substrate, though satisfyingly a moderate conversion was observed (Scheme 3.28). As this project was looking for a common set of conditions for the radiofluorination of a series of substrates, the radiofluorination of **3-3d** to ^[18F]3-5d was no longer pursued.

This substrate, along with ^[18F]3-5b, both performed poorly under the optimised conditions. It is noteworthy that the optimisation was carried out on a relatively electron neutral substrate in comparison to the electron rich nature of these two substrates. As it has been shown that the base plays a significant role in the reaction,^{238, 239} the use of microfluidics is likely escalating this effect. It would be prudent to readdress this with a complete optimisation on an *ortho* or *para* methoxy substituted precursor and comparing the conditions with those currently used.

3.3.3. 3-^[18F]Fluoro-5-(2-pyridinylethynyl)benzonitrile (^[18F]FPEB)

The inadequate results from the attempts to form 5-^[18F]FU, and the desire to prove that application of microfluidic technology would improve the synthesis of important radiopharmaceuticals, meant that our attention turned to ^[18F]FPEB. ^[18F]FPEB is a metabotropic glutamate receptor subtype-5 (mGluR5) antagonist. mGluR5 is a glutamatergic neural receptor implicated in a number of central nervous system disorders including chronic neurodegenerative disorders, such as Alzheimer's, Huntington's and Parkinson's diseases. The radiolabelled tracer has been subjected to

pre-clinical^{251, 252} and clinical^{253, 254} PET neuroimaging studies and has shown high brain penetration, selectivity and potency²⁵⁵ in rodents, non-human primates and humans.

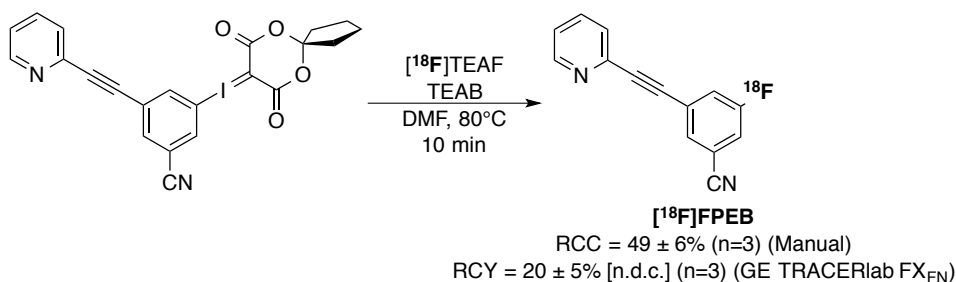
Due to the poorly activated nature of the fluorinated ring, as it lacks an electron-withdrawing group substituted *ortho* or *para* to the substitution position, direct S_NAr radiofluorination is unflavoured. Nevertheless, Hamill *et al.* offered a microwave assisted S_NAr protocol in 2005, using the chloro- precursor to give an isolated RCY = 4 ± 0.6% [n.d.c.] (n=4) for the original production of [¹⁸F]FPEB (Table 3.1, Entry 1).²⁵⁶ Despite the low yield, and the authors declaring that the chloro- substrate was unlikely to be the optimal precursor, they were able to use their route to characterise the *in vitro* and *in vivo* behaviour of [¹⁸F]FPEB. Wong *et al.*,²⁵³ have also described a similar procedure, though used [¹⁸F]CsF as the [¹⁸F]fluoride source, rather than [¹⁸F]KF/K_{2.2.2} (Entry 2).

Two years later, Wang²⁵¹ was able to successfully apply this route using a nitro-precursor. Lim²⁵⁷ and Liang²²⁴ presented automated protocols for this reaction in 2014, on GE TRACERlab FX_{FN} and NanoTek® systems, respectively (Entries 3 - 5). However all of these syntheses were unable to significantly improve on the yield obtained by Hamill with RCYs = 1 – 5% [n.d.c.].

Entry	X	Conditions	RCY [n.d.c.]	Procedure
1	-Cl	$[^{18}\text{F}]\text{KF}/\text{K}_{2.2.2}$ DMSO, MW(45 W) 5 x 15 s	4 ± 0.6 (n=4)	Hamill <i>et al.</i> ²⁵⁶
2	-Cl	$[^{18}\text{F}]\text{CsF}$ DMSO, MW(50 W) 4 min	Not stated	Wong <i>et al.</i> ²⁵³
3	-NO ₂	$[^{18}\text{F}]\text{KF}/\text{K}_{2.2.2}$ DMSO, 115°C 10 min	5%	Wang <i>et al.</i> ²⁵¹
4	-NO ₂	$[^{18}\text{F}]\text{KF}/\text{K}_{2.2.2}$ DMSO, 150°C 15 min GE TRACERlab FX _{FN}	2.6% (n>100)	Lim <i>et al.</i> ²⁵⁷
5	-NO ₂	$[^{18}\text{F}]\text{TEAF}$ DMSO, 215°C t _R = 96 s NanoTek® (Advion)	2.1 ± 0.4 (n=4)	Liang <i>et al.</i> ²²⁴
6	-IAux	$[^{18}\text{F}]\text{TEAF}$ DMF, 80°C GE TRACERlab FX _{FN}	$20 \pm 5\%$ (n = 3)	Stephenson <i>et al.</i> ²³⁸

Table 3.1: Previous radiosyntheses of $[^{18}\text{F}]\text{FPEB}$.

During the course of this work Stephenson *et al.*,²³⁸ from the Vasdev group, were able to apply their spirocyclic iodonium(III) ylide radiochemistry to produce $[^{18}\text{F}]\text{FPEB}$ (Entry 6). Application of their original conditions was only able to give a RCC = 6% with 21% of a by-product that was later identified as the benzamide formed by base mediated hydrolysis of the nitrile group. Optimisation was able to suppress the benzamide formation and ultimately give a RCC = $49 \pm 6\%$ (n=3). Automation of this protocol on a GE TRACERlab FX_{FN}, with in-line HPLC purification and reformulation gave an RCY = $20 \pm 5\%$ (n = 3) which was validated as ready for human injection.



Scheme 3.29: Automated spirocyclic iodonium(III) ylide approach to $[^{18}\text{F}]\text{FPEB}$.²³⁸

The 8 m reactor was immediately applied for the radiofluorination of $[^{18}\text{F}]\text{FPEB}$ ($[^{18}\text{F}]\text{3-5f}$) as it had proved superior to the 4 m, during our work on $[^{18}\text{F}]\text{3-5d}$ and $[^{18}\text{F}]\text{3-5e}$ (Figure 3.8). Concern for the base mediated hydrolysis of the nitrile, which occurred at 120°C in Stephenson's manual procedure, lead to the lower end of the temperature range studied to be reduced to 100°C. However during this optimisation, even at 220°C, the sole radioproduct found by radioHPLC was $[^{18}\text{F}]\text{3-5f}$. The results indicated that this radiofluorination occurred exceptionally at 200°C with an $\text{RCC} = 68 \pm 5\%$ ($n=2$) (Scheme 3.30). It was apparent that this lay in a relatively narrow optimum range as rapid decline in RCC was observed when the temperature was varied from this point.

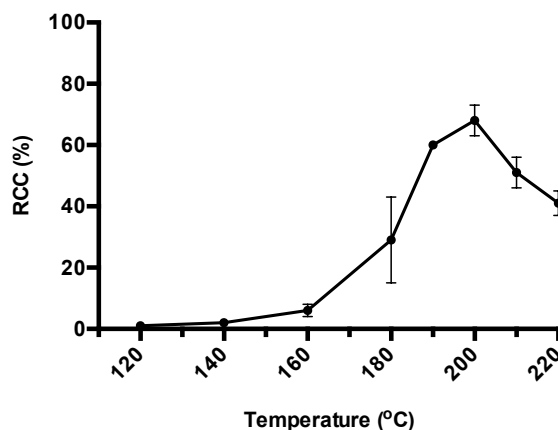
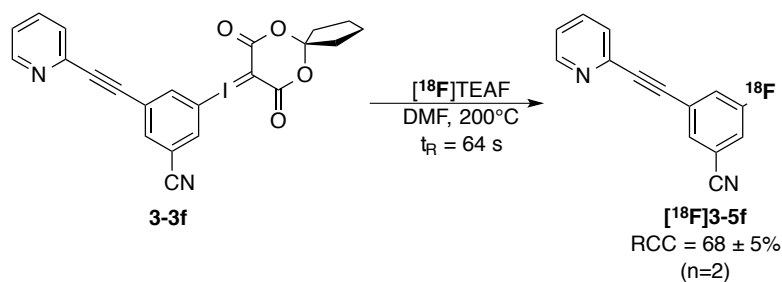


Figure 3.8: Temperature dependence of $[^{18}\text{F}]\text{3-5f}$ radiosynthesis.

The conversion obtained is, to date, significantly higher than all other known routes to $[^{18}\text{F}]\text{3-5f}$. As the NanoTek® platform has previously been used to prepare $[^{18}\text{F}]\text{3-5f}$ for human use,²²⁴ it can be foreseen that its use, in conjunction with spirocyclic iodonium(III) ylide radiofluorination, could be very useful for the preparation of

preclinical and clinical doses of [^{18}F]3-5f from relatively small doses of [^{18}F]fluoride. Isolation of [^{18}F]3-5f produced by this microfluidic route has not been attempted to date, however the appropriate platforms are available for in-line semi-prep HPLC purification to be carried out.



Scheme 3.30: Microfluidic route to [^{18}F]FPEB ([^{18}F]3-5f).

3.4. Summary

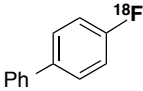
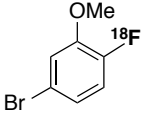
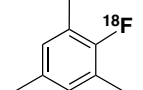
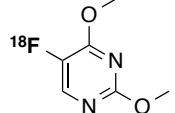
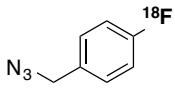
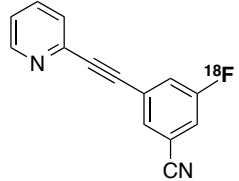
Substrate	Manual ⁷² RCC (%)	Microfluidic RCC (%)
[^{18}F]3-5a 	85%	95 ± 1% (n = 4)
[^{18}F]3-5b 	56 ± 11% (n = 3)	40 ± 3% (n = 4)
[^{18}F]3-5c 	45 ± 13% (n = 3)	82 ± 4% (n = 4)
[^{18}F]3-5d 	30 ± 4% (n = 3)	19 ± 0% (n = 2)
[^{18}F]3-5e 	25 ± 10% (n = 3)	68 ± 5% (n = 3)
[^{18}F]3-5f 	49 ± 6% (n = 3) ²³⁸	68 ± 5% (n = 2)

Table 3.2: Comparative RCC's from manual procedure to microfluidic approach.

Over the course of this project, the radiofluorination of spirocyclic iodonium(III) ylides has been successfully applied to a microfluidic platform. The radiochemical conversions obtained were superior to the preceding manual procedure for the electron neutral and electron deficient precursors, though were reduced for electron rich arenes (Table 3.2).

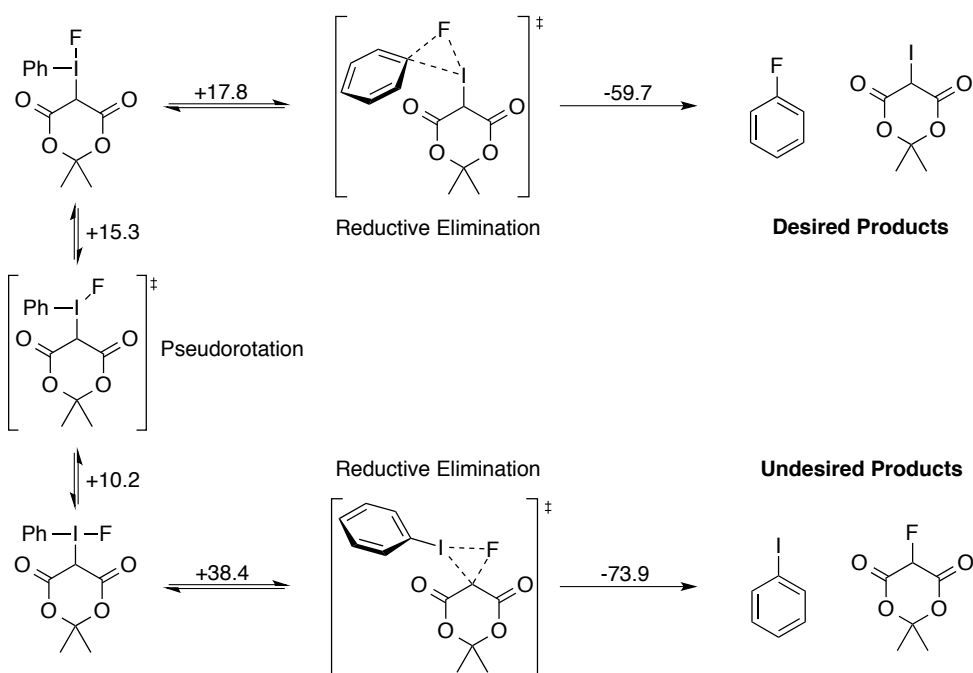
Furthermore, a fully automated protocol has been established for the radiosynthesis of 4-[^{18}F]fluorobenzyl azide, demonstrating the capability for this system to be applied to the radiosynthesis of important [^{18}F]bioconjugation reagents.

3.5. Addendum: Mechanistic Discussion

During the preparation of this thesis, Rotstein, Wang *et al.* reported an expansion of this work, including detailed mechanistic studies through computational analysis. The proposed mechanism infers an initial coordination of [^{18}F]fluoride to the hypervalent iodine centre followed by a reductive elimination to form the aryl- ^{18}F bond, with the latter step being rate limiting. Investigations into other mechanistic pathways, including dimeric or solvent assisted, proved to be futile.

The complete regioselectivity demonstrated by the radiofluorination of spirocyclic iodonium(III) ylides, which is not shown by diaryliodonium(III) salts, is due to the barrier to reductive elimination to the aryl- ^{18}F (17.8 kcal mol $^{-1}$) being much less than that shown for the reductive elimination to give the alkyl- ^{18}F (38.4 kcal mol $^{-1}$). Furthermore, the barrier to reductive elimination to the aryl- ^{18}F from the spirocyclic iodonium(III) ylide is reduced with increasing electron deficiency of the arene, which is consistent with the greater extent of radiofluorination seen on electron deficient substrates. For diaryliodonium(III) salts, which go through a similar

coordination/reductive elimination mechanism, the barrier energies are much more comparable, depending on the electron densities of the arenes.



Scheme 3.31: Computational analysis of the fluorination of spirocyclic iodonium(III) ylides (energies given as kcal/mol).²³⁹

The computational model that they utilised showed that the reductive elimination was little affected by structural changes to the auxiliary, though they theorised that it was instrumental in the rate of precursor decomposition. Through this approach they were able to identify a superior spirocyclic auxiliary, spiroadamantyl-1,3-dioxane-4,6-dione. By subjecting a precursor bearing this new auxiliary, and one bearing Meldrum's acid, to the reaction conditions (DMF- d_7 , 120°C, 10 minutes) without radioactivity, they were able to experimentally prove that the auxiliary did affect the rate of decomposition in the presence of tetraethylammonium bicarbonate, though no decomposition was seen in the absence of base. The corresponding aryl iodide was identified as one of the decomposition products, though it is supposed that there are several decomposition pathways.

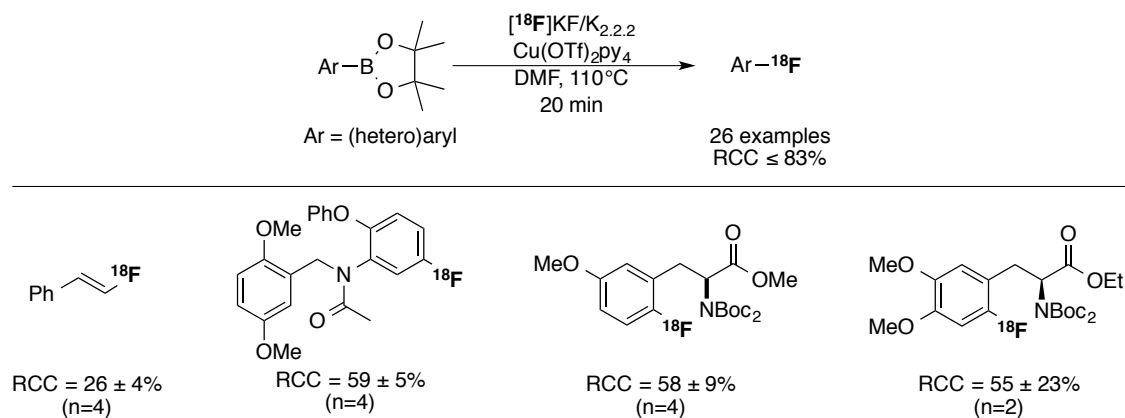
This supports the assertions in this chapter that the amount of base in these reactions plays a significant role in the total [^{18}F]fluoride incorporation, due to influencing the decomposition. Additionally, as the rate of the reductive elimination is reduced with electron rich substrates, it can be implied that the reduced conversions seen in this project for electron rich precursors is due to slower reaction rates being combined with an increased rates of decomposition as the reactions are run at much greater temperatures.

4. Copper-Mediated [^{18}F]Labelling of Radiopharmaceuticals

To date, there is no general procedure what can be simply modified to produce a wide range of [^{18}F]arene bearing radiopharmaceuticals in good yields for clinical application, with easily accessible and stable precursors.⁵³ As discussed in Section 1.3.2., there are several routes available to access [^{18}F]arene bearing radiopharmaceuticals, including $\text{S}_{\text{N}}\text{Ar}$, metal-mediated, diaryliodonium salt and spirocyclic iodonium(III) ylides, however there are several disadvantages associated with these routes including low yields, difficult to synthesise and unstable precursors and non-regioselective labelling.

4.1. Copper-Mediated Radiofluorination of Pinacolyl Arylboronates

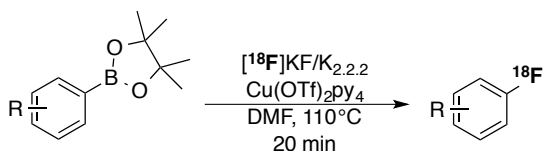
One of the most promising new routes toward [^{18}F]arenes is the Cu(II)-mediated radiofluorination of pinacolyl arylboronates (Scheme 4.1) (see Section 1.3.2.2. for full discussion).⁷⁶ This Chan-Lam cross-coupling reaction, mediated by $\text{Cu}(\text{OTf})_2\text{py}_4$ was able to demonstrate effectiveness on a wide range of arenes, heteroarenes and three radiopharmaceuticals. Despite this methodology proving to be promising in ‘research mode’ reactions, in which a complete batch of [^{18}F]fluoride is dried and then divided into 20 – 30 individual reactions, when it was applied to large scale production runs of radiotracers, the yields began to significantly diminish.



Scheme 4.1: $\text{Cu}(\text{OTf})_2\text{py}_4$ mediated radiofluorination of pinacolyl arylboronates.⁷⁶

This was quickly attributed to the increase in base, used to elute the QMA-trapped [^{18}F]fluoride, in the reaction when a complete batch of [^{18}F]fluoride is carried through to a single reaction rather than being divided into multiple reactions. This theory was confirmed by running the ‘research mode’ conditions with additional $\text{K}_2\text{CO}_3/\text{K}_{2.2.2}$.^{vi}

Zlatopolskiy *et al.* conclusively showed that the base was the cause in the reduced yields by carrying out parallel reactions with diluted [^{18}F]fluoride (‘research mode’), under [^{18}F]fluoride dried under commonly used conditions (‘high base’) and finally under new ‘low base’ conditions (Table 4.1).²⁵⁸ Under the ‘research mode’ conditions, the RCCs for [^{18}F]fluorobenzene, 4-[^{18}F]fluoroanisole and 3-[^{18}F]fluorobenzaldehyde, were found to be 66 – 76%, however this reduced to 5 – 7% under the high base conditions. Fortunately, the use of their new low base conditions (0.06 mg K_2CO_3 , 0.27 mg $\text{K}_{2.2.2}$) allowed the RCCs to increase to 41 – 64%, which, although less than found under research mode, would allow for good yields under isolation conditions.



Entry	R	Research Mode	‘High Base’	‘Low Base’
1	H	67	5	62
2	4-OMe	66	7	42
3	3-CHO	76	7	41

Table 4.1: Low base conditions developed by Zlatopolskiy *et al.*²⁵⁸

There have been other investigations into the use of this procedure for the production of radiotracers, however these have all reported difficulties under the current reaction protocols.^{259, 260} Accordingly, the Gouverneur group focused on developing a new set of

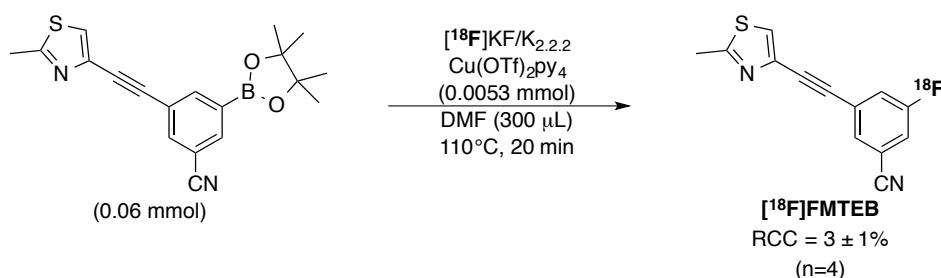
^{vi} Tredwell, Preshlock, Taylor – unpublished results

conditions to allow this promising protocol to be applied to the production of radiotracers.

4.2. Preliminary Investigations on Base Effects

Preliminary investigations were carried out by Dr M. Tredwell, Dr S. Preshlock and S. Verhoog.^{vii}

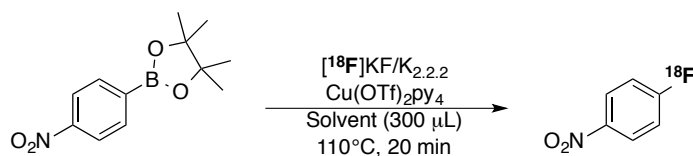
As the spiking experiments had shown that potassium carbonate was detrimental to the incorporation of [¹⁸F]fluoride, a modified elution was required to reduce the levels of potassium carbonate in the radiofluorination itself. Prior to this study, a re-optimisation of the reaction conditions was carried out as the reaction performed poorly on electron deficient arenes. Using [¹⁸F]FMTEB as an illustration (Scheme 4.2), $RCC = 3 \pm 1\%$ ($n=4$) was obtained under the previously published conditions (0.06 mmol precursor, 0.0053 mmol Cu(OTf)₂py₄, DMF, 110°C, 20 min).



Scheme 4.2: Radiofluorination of [¹⁸F]FMTEB under literature conditions.⁷⁶

By using 4-[¹⁸F]fluoronitrobenzene as a model target (Table 4.2), re-optimisation was able to increase the RCC from $14 \pm 2\%$ ($n=4$) to $70 \pm 5\%$ ($n=4$) when the substrate stoichiometry was increased to 0.03 mmol precursor and 0.04 mmol Cu(OTf)₂py₄ in DMF. Changing the solvent to DMA was found to further increase the incorporation of [¹⁸F]fluoride, however DMF was retained as the reaction solvent as it has wider acceptance and general use in industrial and clinical application.

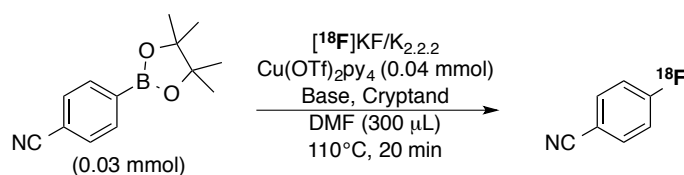
^{vii} Unpublished results.



Entry	Substrate (mmol)	Cu(OTf) ₂ py ₄ (mmol)	Solvent	RCC (%)	n
1	0.0053	0.06	DMF	14 ± 2	4
2	0.0053	0.015	DMF	14 ± 2	4
3	0.02	0.015	DMF	53 ± 3	4
4	0.04	0.015	DMF	62 ± 1	2
5	0.04	0.03	DMF	70 ± 5	5
6	0.04	0.03	DMA	83 ± 2	4
7	0.03	0.02	DMA	81 ± 3	4

Table 4.2: Re-optimisation on 4-[¹⁸F]fluoronitrobenzene by Tredwell, Preshlock and Verhoog.

A series of ‘spiking’ experiments on the radiofluorination of 4-[¹⁸F]fluorobenzonitrile, whereby additional base and cryptand were added to the optimized conditions, were carried out to screen suitable bases for the elution (Table 4.3). As expected, addition of K₂CO₃ and K_{2.2.2} resulted in a significant reduction in the RCC when compared to the unspiked reaction. Use of potassium oxalate (K₂C₂O₄) as a base in place of K₂CO₃ was able to recover a substantial amount of the lost RCC. Testing furthermore showed that [¹⁸F]TEAF was a poor choice of [¹⁸F]fluoride source.



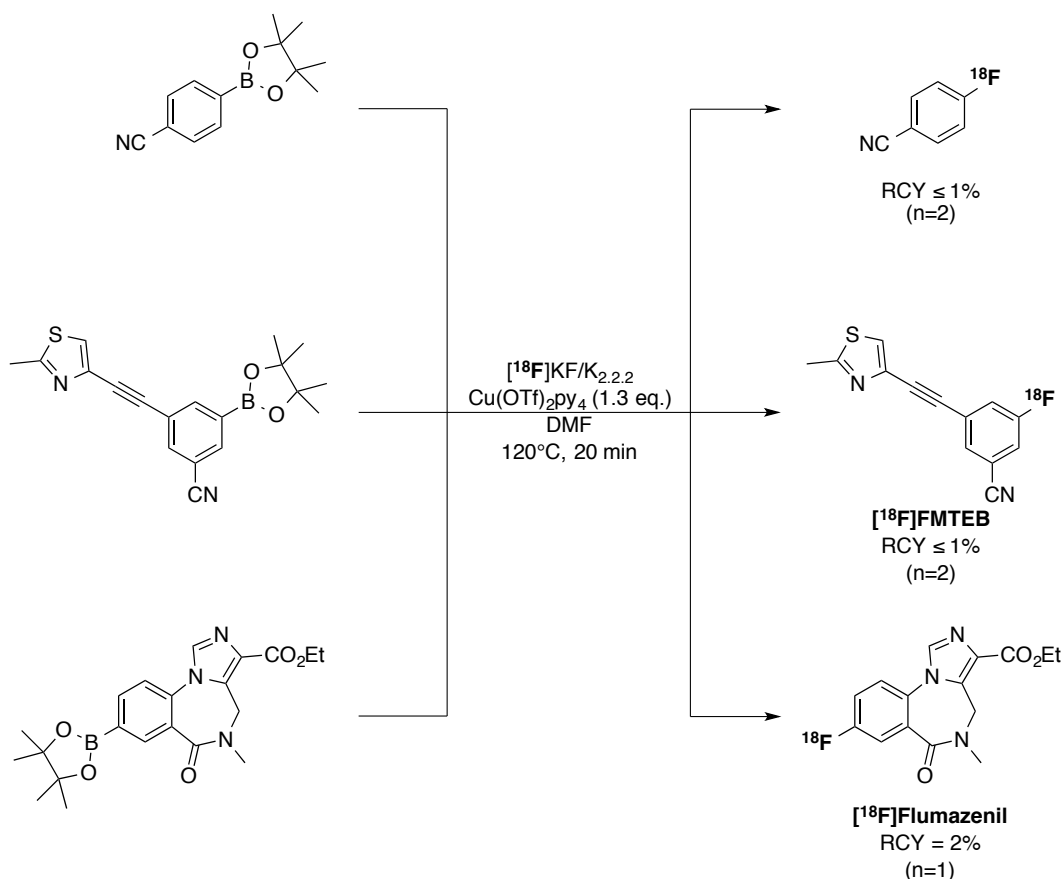
Entry	Base (mmol)	Cryptand (mmol)	RCC (%)	n
1	-	-	62 ± 8	4
2	K ₂ CO ₃ (0.02)	K _{2.2.2} (0.04)	13 ± 1	2
3	K ₂ C ₂ O ₄ (0.02)	18-crown-6 (0.04)	41 ± 6	2
4	K ₂ C ₂ O ₄ (0.02)	K _{2.2.2} (0.04)	41 ± 4	2
5	Et ₄ NHCO ₃ (0.02)	-	2 ± 0	2

Table 4.3: Spiking of radiofluorination reactions to examine base effect.

Potassium oxalate has previously been used as an alternative to potassium carbonate in radiofluorination protocols. Its use has been shown to be vital to achieving good incorporation by preventing precursor decomposition²⁶¹ or substrate racemisation,²⁶² as it is less basic and has essentially no nucleophilic properties. However, as it is less basic, complete substitution of potassium carbonate with potassium oxalate can lead to significant loss of activity as [¹⁸F]HF.²⁶³ Consequently, a small quantity of potassium carbonate is required to prevent these losses.

Application of K₂C₂O₄.H₂O (0.02 mmol), K₂CO₃ (1.5 μmol) and K_{2.2.2} (0.04 mmol) gave excellent elution efficiency from the QMA-trapped [¹⁸F]fluoride, and was basic enough to prevent loss of activity as [¹⁸F]HF. Unfortunately, the [¹⁸F]KF/K_{2.2.2} produced in this manner did not improve the isolated radiochemical yields of the copper-mediated radiofluorination reaction (Scheme 4.3).

Using 4-fluorobenzonitrile as a model substrate yielded ≤ 1% (n=2) while application to two radiotracer compounds, [¹⁸F]FMTEB and [¹⁸F]Flumazenil did not lead to any noteworthy increase in RCY, with ≤ 1% (n=2) and 2% (n=1) found respectively.



Scheme 4.3: Preliminary isolation results using potassium oxalate 'high base' elution conditions.

4.3. Results and Discussion

Despite the spiking experiments suggesting that the use of potassium oxalate would be beneficial to the reactions, the radiochemical yields remained far below acceptable levels for production of radiotracers. As changing the base had not been successful, new protocols whereby the base loading could be reduced, or eliminated entirely, would need to be developed.

The project on Cu(II) elution of QMA-trapped $[^{18}\text{F}]$ fluoride and consequent radiofluorination of pinacolyl arylboronates was carried out with Dr S. Preshlock. The project on low base elution and radiopharmaceutical isolations were carried out with Dr S. Preshlock and S. Verhoog.

Precursor synthesis was carried out by members of the Gouverneur group: Dr S. Preshlock ($[^{18}\text{F}]$ Flumazenil), Dr S. Gruber ($[^{18}\text{F}]$ FMTEB, $[^{18}\text{F}]$ FPEB), Dr T. Cailly ($[^{18}\text{F}]$ MFBG, $[^{18}\text{F}]$ FDA), T. Wilson ($[^{18}\text{F}]$ MFBG, $[^{18}\text{F}]$ FMT, $[^{18}\text{F}]$ FDA) and N. Taylor ($[^{18}\text{F}]$ DAA1106, $[^{18}\text{F}]$ FDOPA).

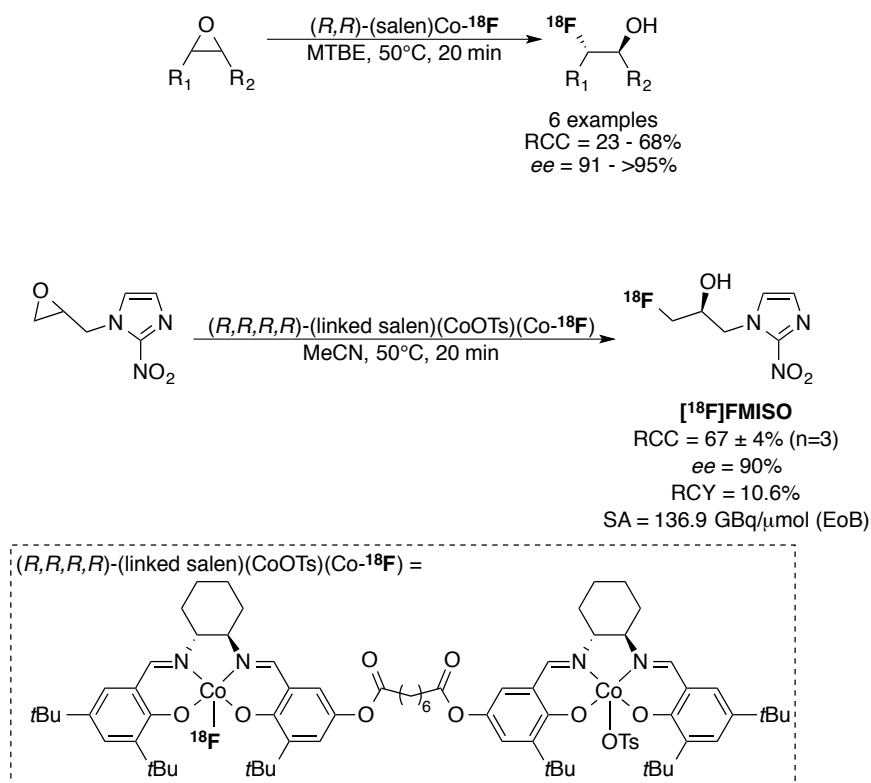
4.3.1. Cu(II) Elution of $[^{18}\text{F}]$ Fluoride

Typically, basic solutions are used to elute $[^{18}\text{F}]$ fluoride trapped on anion exchange cartridges, however there are methods by which the base can be entirely eliminated. There are two examples whereby a solution of the metal complex, used to mediate the respective radiofluorination, has been successfully adopted as the eluent for the QMA-trapped $[^{18}\text{F}]$ fluoride. In this manner, adoption of $\text{Cu}(\text{OTf})_2\text{py}_4$ to elute the $[^{18}\text{F}]$ fluoride would eliminate the problems associated with the presence of base.

4.3.1.1. Literature Precedent

In 2014, Doyle and co-workers reported an asymmetric radiosynthesis of $[^{18}\text{F}]$ fluorohydrins by ring opening of epoxides with chiral mono- and dimeric cobalt catalysts (Scheme 4.4).⁴¹ The (*R,R*)-Co(salen)OTs or (*R,R,R,R*)-(linked salen) $\text{Co}_2(\text{OTs})_2$ complex was dissolved in MeOH for the elution, which had to be rigorously removed under a stream of argon at room temperature for 45 – 60 min, assisted by the addition of methyl *tert*-butyl ether or acetonitrile, respectively. The resulting Co- ^{18}F complexes were shown to successfully radiolabel a complex array of epoxides bearing diverse functional groups with high levels of stereocontrol. Furthermore, the use of a microwave to assist with the removal of MeOH and reaction itself enabled the isolation

of [^{18}F]FMISO with RCY = 11% [n.d.c.] in a synthesis time of 37 min^{viii} with SA = 136.9 GBq/ μmol (EoB) or 33.3 GBq/ μmol (EoS).



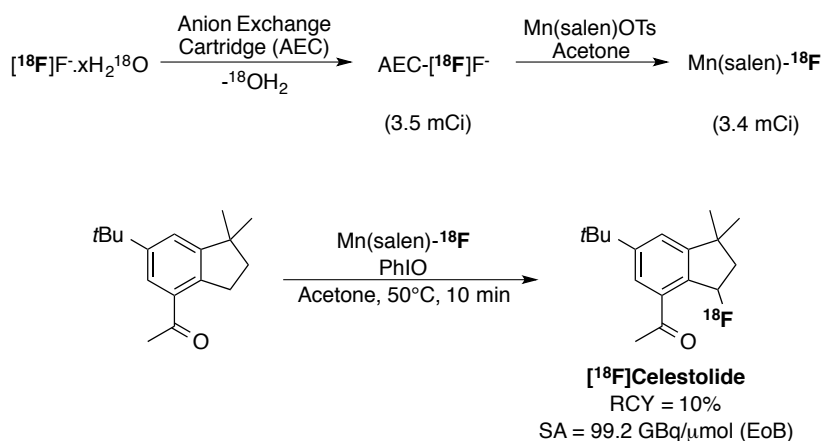
Scheme 4.4: Use of Co(salen)OTs complexes to elute [^{18}F]fluoride, forming Co- ^{18}F reactive species.⁴¹

Shortly after the publication from Doyle, Hooker and Groves were able to demonstrate the use of a Mn(salen)OTs complex in acetone to elute trapped [^{18}F]fluoride with 97% efficiency (Scheme 4.5).⁴² Remarkably, this procedure required no drying after the elution and the following reaction, a benzylic C-H radiofluorination, could be carried out in the elution solution, with no apparent erosion in the RCC of the fluorination step. They applied this protocol to the radiolabelling of [^{18}F]Celestolide, an artificial musk, with RCY = 10% [n.d.c.] in a total synthesis time of 110 min,^{ix} with a SA = 2.68 99.2 GBq/ μmol (EoB).

^{viii} Synthesis time given from start of elution to end of reaction, not including radioHPLC time.

RadioHPLC time: 13.9 – 14.0 min.

^{ix} Time from start of synthesis to injection onto HPLC was 30 min.



Scheme 4.5: ‘Dry-down free’ Mn(salen)OTs elution of [^{18}F]fluoride and C-H benzylic radiofluorination of [^{18}F]Celestolide.⁴²

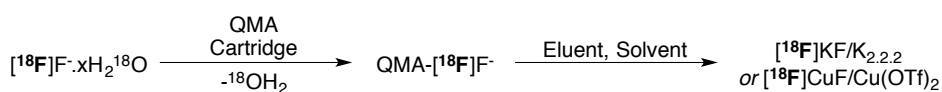
There have been no procedures for metal-mediated radiofluorination of arenes that utilise this approach to elution,^{53, 264} however, as the base was detrimental to the copper-mediated radiofluorination reaction, the use of Cu(II) complexes to elute the cartridge was investigated, with a hope to eliminate the base entirely.

4.3.1.2. Results and Discussion

Initial investigations in this focused on the elution itself, rather than the complete reaction. This was due to ensuring that the majority of the [^{18}F]fluoride was eluted, as poor elution would lead to poor isolated yields, which would not necessarily be shown by analysis of the radiochemical conversions. As a reference, the standard $\text{K}_2\text{CO}_3/\text{K}_{2.2.2}$ conditions were used, which gave 99% elution efficiency (Table 4.3, Entry 1).

Direct replacement of the $\text{K}_2\text{CO}_3/\text{K}_{2.2.2}$ (0.02 mmol) with $\text{Cu}(\text{OTf})_2\text{py}_4$ (0.0053 mmol) in the same solvent (MeCN/ H_2O 4:1) lead to only 2% (Entry 2) elution from the cartridge, which was not improved by the use of pure MeCN (Entry 3) or DMF (Entry 4). The use of alcoholic solvents did slightly improve the elution, with EtOH and MeOH giving 4% (Entry 5) and 12% (Entry 6) respectively. The elution efficiency could be improved significantly by increasing the fraction of water in the solvent; with 50% H_2O in MeCN

giving 42% (Entry 7) efficiency and this could be increased to 56% (Entry 8) by use of EtOH.



Entry	Eluent	mmol	Solvent	Efficiency (%)
1	K ₂ CO ₃ /K _{2.2.2}	0.0200	MeCN:H ₂ O (4:1)	99
2	Cu(OTf) ₂ py ₄	0.0053	MeCN:H ₂ O (4:1)	2
3	Cu(OTf) ₂ py ₄	0.0053	MeCN	<1
4	Cu(OTf) ₂ py ₄	0.0053	DMF	2
5	Cu(OTf) ₂ py ₄	0.0053	EtOH	4
6	Cu(OTf) ₂ py ₄	0.0053	MeOH	12
7	Cu(OTf) ₂ py ₄	0.0053	MeCN:H ₂ O (1:1)	42
8	Cu(OTf) ₂ py ₄	0.0053	EtOH:H ₂ O (1:1)	56
9	Cu(OTf) ₂ py ₄	0.0400	EtOH:H ₂ O (1:1)	92
10	Cu(OTf) ₂ py ₄	0.0400	MeCN:H ₂ O (1:1)	90
11	Cu(OTf) ₂ py ₄	0.0200	EtOH:H ₂ O (4:1)	70
12	Cu(OTf) ₂ py ₄	0.0400	EtOH:H ₂ O (9:1)	60
13	Cu(OTf) ₂ py ₄	0.0400	MeCN:H ₂ O (4:1)	48
14	Cu(OTf) ₂ (H ₂ O) ₄	0.0400	MeCN:H ₂ O (4:1)	45

Elution efficiency was calculated by percentage of activity eluted over sum of activity eluted and QMA post-elution.

Table 4.3: Cu(I) elution efficiency of [¹⁸F]fluoride optimisation.

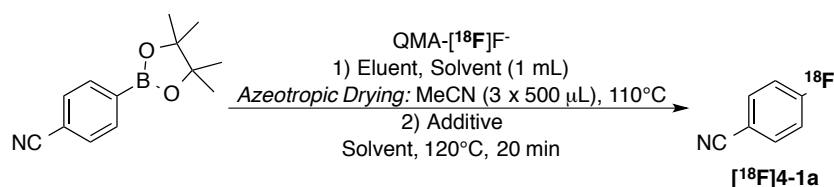
Unfortunately, an efficiency of around 50% would not be acceptable for radiotracer production, as this would immediately be limiting the RCY to 50% [d.c.]. Fortunately, it was found that increasing the loading of Cu(II) in the elution solution to 0.04 mmol did enable the efficiency of the elution up to 92% (Entry 9) when EtOH/H₂O (1:1) was used as the solvent. Replacement of the EtOH with MeCN was almost as successful, with 90% (Entry 10) [¹⁸F]fluoride eluted.

At this Cu(II) loading (0.04 mmol), reduction of the water content of the EtOH/H₂O solution from 50% to 20% and 10% gave elution efficiencies of 70% (Entry 11) and 60% (Entry 12) respectively. A more rapid decline in efficiency was seen with the MeCN system, with a drop of efficiency to 48% (Entry 13) when the water content was reduced to 20%.

It was envisioned that the more active species in this elution may have been a tetra-aqua complex, instead of the tetra-pyridine, though use of Cu(OTf)₂(H₂O)₄ did not lead to any improvement, giving a comparative efficiency (45%) (Entry 14).

On establishing appropriate conditions for the elution of the cartridges, using 0.04 mmol Cu(OTf)₂py₄ in MeCN/H₂O or EtOH/H₂O (1:1), analysis of the consequent reaction was carried out. Initially, a control reaction was carried out using 0.02 mmol K₂CO₃/K_{2.2.2} in MeCN/H₂O (4:1) as the eluent, and 0.04 mmol Cu(OTf)₂py₄ was used for the reaction after the azeotropic drying, to provide a reference point for the radiofluorination to give 4-[¹⁸F]fluorobenzonitrile ([¹⁸F]4-1a), which gave RCC = 10% (Table 4.4, Entry 1). Under the previously published 'research mode' conditions, the RCC = 39 ± 7 (n=4),⁷⁶ for [¹⁸F]4-1a and, therefore, this result confirmed that the amount of base present does have a significant effect on the yield of this reaction.

At this point, it is important to note that the elution efficiency, although noted in Table 4.4, has no significance for the radiochemical conversion for each reaction. The radiochemical conversion is a quantification of the amount of [¹⁸F]fluoride incorporated against the amount remaining, and, with the scales used, the amount of [¹⁸F]fluoride present does not play a significant role in the reaction itself.



Entry	1) Elution			2) Reaction			n
	Eluent (mmol)	Solvent	Efficiency (%)	Additive (mmol)	Solvent	[^{18}F]4-1a RCC (%)	
1	$\text{K}_2\text{CO}_3/\text{K}_{2.2.2}$ (0.02)	MeCN:H ₂ O (4:1)	99	$\text{Cu}(\text{OTf})_2\text{py}_4$ 0.04	DMF	10	1
2	$\text{Cu}(\text{OTf})_2\text{py}_4$ (0.04)	MeCN:H ₂ O (4:1)	54	-	DMF	8	1
3	$\text{Cu}(\text{OTf})_2\text{py}_4$ (0.04)	EtOH:H ₂ O (9:1)	60	-	DMF	17	1
4	$\text{Cu}(\text{OTf})_2\text{py}_4$ (0.02)	EtOH:H ₂ O (4:1)	70	$\text{Cu}(\text{OTf})_2\text{py}_4$ 0.02	DMF	28	1
5	$\text{Cu}(\text{OTf})_2\text{py}_4$ (0.04)	EtOH:H ₂ O (1:1)	95 ± 1	-	DMF/pyridine (9:1)	31 ± 8	2
6	$\text{Cu}(\text{OTf})_2\text{py}_4$ (0.04)	MeCN:H ₂ O (1:1)	93 ± 1	-	DMF/pyridine (9:1)	55 ± 2	3
7	$\text{K}_2\text{CO}_3/\text{K}_{2.2.2}$ (0.02)	MeCN:H ₂ O (4:1)	98 ± 0	$\text{Cu}(\text{OTf})_2\text{py}_4$ 0.04	DMF/pyridine (9:1)	3 ± 1	2
8	$\text{Cu}(\text{OTf})_2\text{py}_4$ (0.04)	EtOH:H ₂ O (1:1)	94	$\text{K}_2\text{CO}_3/\text{K}_{2.2.2}$ 0.02	DMF/pyridine (9:1)	1	1
9	$\text{Cu}(\text{OTf})_2\text{py}_4$ (0.04)	MeCN:H ₂ O (1:1)	95	$\text{K}_2\text{CO}_3/\text{K}_{2.2.2}$ 0.02	DMF/pyridine (9:1)	0	1

Table 4.4: $\text{Cu}(\text{OTf})_2\text{py}_4$ elution efficiency and effect on reactivity study.

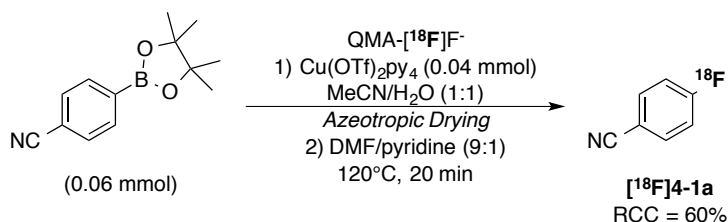
Disappointingly, the initial reactions, run in DMF, using Cu(II) as the eluent gave poor conversion, with RCC = 8% (Entry 2) and 17% (Entry 3) when eluted with MeCN/H₂O (4:1) and EtOH/H₂O (9:1) respectively. When 0.02 mmol $\text{Cu}(\text{OTf})_2\text{py}_4$ was used to elute the cartridge (in EtOH/H₂O (4:1)) and a further 0.02 mmol added after drying, the RCC could be increased to 28% (Entry 4).

As adding catalyst after drying increased the yield, it was hypothesised that the Cu(II) species being formed during the azeotropic drying process may not be as active as $\text{Cu}(\text{OTf})_2\text{py}_4$, with the tetra-pyridine most likely being lost and a tetra-aqua complex forming. Running the reaction (eluted with 0.04 mmol $\text{Cu}(\text{OTf})_2\text{py}_4$ in EtOH/H₂O (1:1)) in DMF/pyridine (9:1) did lead to a slight increase in RCC to 31 ± 8 (n=2) (Entry 5), and it

was found that switching the elution solvent to MeCN/H₂O (1:1) improved the RCC to 55 ± 2 (n=3) (Entry 6).

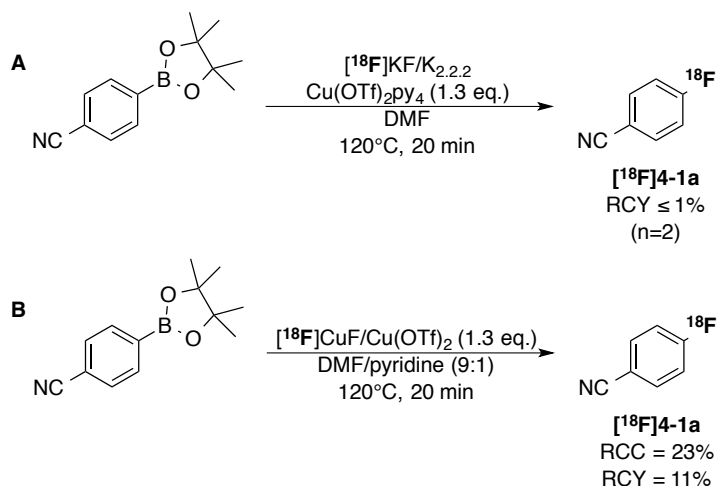
To confirm that this result, which was significantly better than the previously published result,⁵³ was due to the elimination of the base, a series of reactions were carried out using DMF/pyridine (9:1). Using the 0.02 mmol K₂CO₃/K_{2.2.2} elution conditions, the reaction performed worse than when DMF alone was used as the solvent, with RCC = $3 \pm 1\%$ (n=2) found (Entry 7). Using Cu(OTf)₂py₄ in EtOH/H₂O (1:1) or MeCN/H₂O (1:1) as the eluent, and spiking with 0.02 mmol K₂CO₃/K_{2.2.2} gave RCC $\leq 1\%$, therefore corroborating the base was detrimental to the reaction (Entries 8 and 9).

The applicability of these conditions were confirmed by running the reaction through the NanoTek® platform under simulated drying, reaction and isolation conditions, without semi-prep HPLC, which gratifyingly gave RCC = 60% (Scheme 4.6) to [¹⁸F]4-1a.



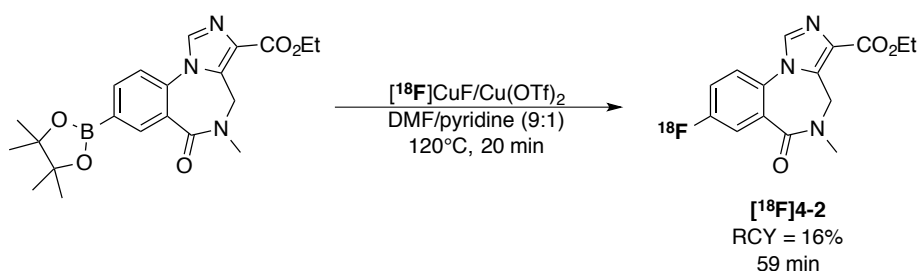
Scheme 4.6: Simulated automated isolation conditions.

Comparison of the original reduced base conditions (K₂CO₃ (1.5 μmol)/K₂C₂O₄.H₂O (0.02 mmol)/K_{2.2.2}(0.04 mmol)), with these optimised Cu(II) elution conditions was carried out under isolation conditions. Using the base elution (Scheme 4.7, A) lead to a radioTLC conversion of 1%, with 33.9 MBq isolated from 3.32 GBq (RCY = 0.3% [n.d.c.]), whilst using the Cu(OTf)₂py₄ elution conditions (B) gave a radioTLC conversion of 23% and 331.1 MBq from 2.95 GBq starting activity (RCY = 11% [n.d.c.]).



Scheme 4.7: Comparison of isolated RCY obtained from potassium oxalate elution (A) or Cu(OTf)₂py₄ elution (B).

As this showed significant improvement over the potassium oxalate procedure, it was applied to the synthesis of radiotracer [¹⁸F]Flumazenil ([¹⁸F]4-2)(Scheme 4.8), of which 650 MBq was isolated in a total synthesis time of 59 min, equating to a RCY = 16% [n.d.c.]. This was significantly better than the 2% RCY (n=1) found under the ‘high base’ potassium oxalate conditions. Flumazenil is a benzodiazepine receptor antagonist, which was initially labelled by carbon-11 to image the distribution of GABA_A receptors in human brains.^{265, 266} Preparation of a fluorine-18 labelled derivative has permitted longer scan time and longer time-distribution studies due to the longer t_{1/2}.



Scheme 4.8: Cu(OTf)₂py₄ eluted [¹⁸F]fluoride for the radiolabelling of [¹⁸F]Flumazenil ([¹⁸F]4-2).

Despite these results being improvements on the best base elution conditions at the time, there was concern over the procedure due the reduced crude radioTLC RCC for [¹⁸F]4-1a when comparing the simulated isolation (RCC = 60%) to the actual isolation conditions (RCC = 23%). Furthermore, when the reaction for [¹⁸F]4-2 was carried out, a

significant amount of activity remained in the reaction vial after it had been emptied and washed as part of the isolation procedure, and the reaction itself was noted to be cloudy light blue rather than the usual clear dark blue. Examination of the protocols showed that the only notable variation between the two procedures was the anion-exchange cartridge was changed from a Waters (Carbonate)^x in the simulated conditions to a Chromafix (Bicarbonate)^{xi}.

A series of elution experiments, without any [¹⁸F]fluoride, was carried out by pushing 0.04 mmol (27 mg) Cu(OTf)₂py₄ in MeCN/H₂O (1:1) through an activated cartridge into a v-vial, which was then azeotropically dried. The mass of the v-vial (containing a stirrer bar) was measured before and after the ‘elution’ and drying to find the variation in mass. The masses shown can be used to suggest a trend, however they cannot be used to quantify how much Cu(II) makes it through the cartridges as there is likely to be multiple species present due to ligand counter ion exchange.

Entry	QMA	Pre-conditioning	Initial (g)	End (g)	Δ (mg)	Resolution (DMF, 120°C)
1	-	-	24.9204	24.9336	13.2	Immediate
2	Chromafix (Bicarbonate)	-	25.5696	25.5762	6.6	Cloudy blue with material remaining on vial
3	Chromafix (Bicarbonate)	0.5 M K ₂ CO ₃	25.5445	25.5589	14.4	Immediate
4	Waters (Carbonate)	-	25.7058	25.7154	9.6	Immediate

Table 4.5: Comparison of effect of QMA counter-ion on resolution.

When no cartridge was used, it can be assumed that almost all the Cu(II) was transferred into the drying vial. A Δ_{mass} of 13 mg was found after drying, supporting the theory that the pyridine ligands are being lost in the drying procedure. Hypothetically, assuming a pure Cu(OTf)₂ species is formed, then this recovered mass equates to 0.036 mmol (Table 4.5, Entry 1).

^x Waters Sep-Pak Accell Plus QMA Carbonate Plus Light Cartridge (46 mg) (Part #186004540)

^{xi} Chromafix PS-HCO¹⁸F separation cartridge (45 mg) (Part #731876)

The reduced Δ_{mass} when the Chromafix (Bicarbonate) cartridge was used (Entry 2), suggests that some Cu(II) is being trapped on the cartridge, which can effectively be negated by preconditioning with carbonate anions (Entry 3). A slightly reduced mass was found for the Waters (Carbonate) cartridge, though this could be due to an increased dead volume as the Waters cartridges fittings are larger than those on the Chromafix (Entry 4).

Most importantly, it was found that using the Chromafix (Bicarbonate) drying cartridge, the dried Cu(II) complex could not be completely resoluted, even if left at 120°C for 15 min. An obvious white solid remained on the vial surface and the solution was cloudy blue. This could explain the high losses that we found due to activity remaining on the glass in the previous isolation procedure. The use of no cartridge or a carbonate form (either preconditioned Chromafix bicarbonate or the Waters carbonate) lead to immediate resolution of all material into a dark blue solution.

Consequently, there is the possibility of increasing the isolated yield of this Cu(II) elution procedure to match or possibly exceed the conditions using the optimised conditions from Section 4.3.2.. This would be the first example of a metal-based elution, using the radiofluorination reaction-mediating complex, being better than the base elution, however these reactions have not been tested.

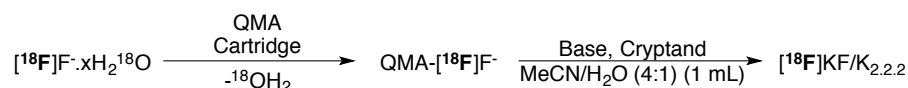
4.3.2. Development of Low Base Conditions

While investigating the Cu(OTf)₂py₄ elution, 'low base' conditions were also being considered. Discussion with The Institute of Cancer Research offered a modification on the elution conditions that had been successfully applied while investigating [¹⁸F]labelling using the arylBPin methodology. It had been found that reducing the base loading to 0.1 mg potassium carbonate (0.7 μmol), 1 mg potassium oxalate

monohydrate (6 μmol) and 6.3 mg Kryptofix-2.2.2 (17 μmol) had enabled good elution of the [^{18}F]fluoride from the cartridge.

4.3.2.1. Reaction Optimisation

Assessment of these conditions under the drying protocols at Siemens Organic Molecular Imaging Laboratory (SOMIL), University of Oxford showed that the base loading was sufficient to give excellent elution of [^{18}F]fluoride from a QMA cartridge, and basic enough to minimise losses as [^{18}F]HF (Table 4.6). When compared to the standard elution conditions ($97 \pm 1\%$, ($n=2$)) (Entry 1), the low base conditions performed identically ($97 \pm 0\%$, ($n=2$)) (Entry 3). As the cartridge itself contains carbonate anions that are eluted along with the [^{18}F]fluoride, pre-treating the cartridge with potassium oxalate was investigated and this made no difference to the elution capability ($97 \pm 0\%$, ($n=2$)) (Entry 4), though did seem to reduce the trapping efficiency of the cartridge of the initial loading of the [^{18}F]fluoride.

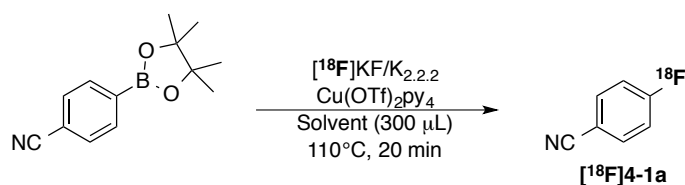


Entry	QMA counter-ion	Base (mmol)	Cryptand (mmol)	Elution Efficiency (%)	n
1	Carbonate	K ₂ CO ₃ (0.014)	K _{2.2.2} (0.024)	97 $\pm$ 1	2
2	Carbonate	K ₂ CO ₃ (0.004)	K _{2.2.2} (0.007)	85 $\pm$ 8	2
3	Carbonate	K ₂ C ₂ O ₄ (0.006)	K _{2.2.2} (0.017)	97 $\pm$ 0	2
4	Oxalate ^a	K ₂ C ₂ O ₄ (0.006)	K _{2.2.2} (0.017)	97 $\pm$ 0	2

a) Cartridge pre-treated with 3 mL of K₂C₂O₄ solution (10 mg/mL).

Table 4.6: Elution efficiency of the low base with and without pre-treating.

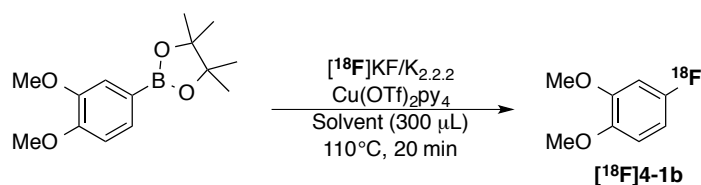
A brief study (Table 4.7) on the effect of changing the stoichiometry of Cu(OTf)₂py₄ and substrate, using 4-[^{18}F]fluorobenzonitrile ([^{18}F]4-1a) as a model substrate indicated that the 0.03 mmol precursor and 0.04 mmol Cu(OTf)₂py₄ in DMA, as found in the preliminary results (see Section 4.2.), was optimal (Entry 4).



Entry	Cu(OTf) ₂ py ₄ (mmol)	Substrate (mmol)	Solvent	[¹⁸ F]4-1a RCC (%)	n
1	0.06	0.0053	DMF	51 ± 2	2
2	0.02	0.04	DMF	82 ± 4	2
3	0.04	0.03	DMF	72 ± 4	2
4	0.04	0.03	DMA	91 ± 0	2

Table 4.7: Re-optimisation on electron deficient substrates.

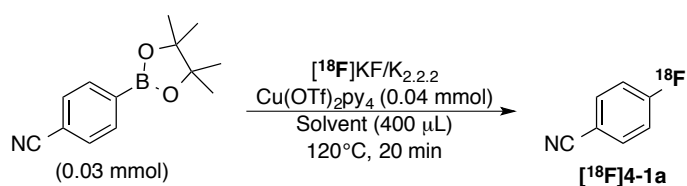
For electron rich arenes, the literature conditions (0.06 mmol precursor, 0.0053 mmol Cu(OTf)₂py₄, DMF, 110°C, 20 min) gave RCC = 54 ± 3% (n=4).⁷⁶ Translation to the low base conditions would not be possible due to the low Cu(II) loading being overwhelmed by the remaining base, so a new optimisation was required (Table 4.8). As previous optimisation had shown that excess Cu(II) to substrate had a detrimental effect on the incorporation with electron rich arenes, it was predicted that the application of the new optimised conditions would perform poorly (Entry 1). Using 4-[¹⁸F]fluoro-1,2-dimethoxybenzene ([¹⁸F]4-1b) as a model substrate, it was found that reversing the stoichiometry to 0.02 mmol Cu(OTf)₂py₄ and 0.04 mmol substrate gave a better incorporation (37 ± 4%, (n=2)) (Entry 2), with a strong improvement again seen with application of DMA (68 ± 5%, (n=2)) (Entry 3).



Entry	Cu(OTf) ₂ py ₄ (mmol)	Substrate (mmol)	Solvent	[¹⁸ F]4-1b RCC (%)	n
1	0.04	0.03	DMF	15 ± 1	2
2	0.02	0.04	DMF	37 ± 4	2
3	0.02	0.04	DMA	68 ± 5	2

Table 4.8: Re-optimisation on electron rich substrates.

By using individual elutions to produce [¹⁸F]KF/K_{2.2.2} with the new low base conditions, using [¹⁸F]4-1a again as a model, the benefits of DMA became more evident (Table 4.9). The incorporation more than doubled (68 ± 2%, (n=2)) (Entry 2) when used in preference over DMF (30 ± 10%, (n=2)) (Entry 1), under the new optimised conditions. Pre-treating the cartridge with oxalate offered no discernable improvement (68 ± 12%, (n=2)) (Entry 3). For these reactions, the solvent volume was increased to 400 µL due to requirements of radiosynthetic platforms that this reaction was to be verified on (see Section 4.3.2.3.).



Entry	QMA counter-ion	Solvent	[¹⁸ F]4-1a RCC (%)	n
1	Carbonate	DMF	30 ± 10	2
2	Carbonate	DMA	68 ± 2	2
3	Oxalate ^a	DMA	68 ± 12	2

a) Cartridge pre-treated with 3 mL of K₂C₂O₄ solution (10 mg/mL).

Table 4.9: Simulated isolation conditions with individual preparation of [¹⁸F]KF/K_{2.2.2}.

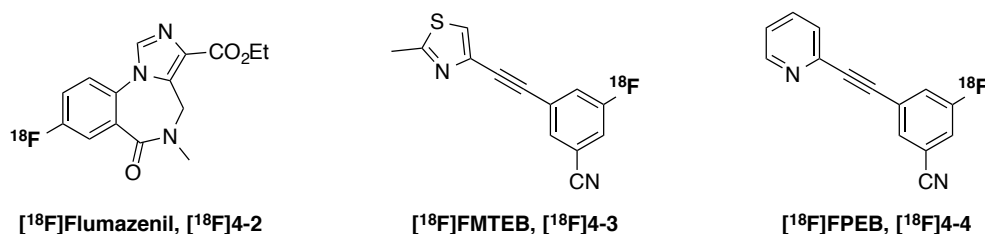
4.3.2.2. Radiofluorination of Radiopharmaceuticals

Aside from the new elution conditions, further changes were made to the previous protocols to increase the effectiveness and efficiency of the purification of the final radiotracers. Previously, under the high base conditions, an isocratic mobile phase of MeCN/H₂O was used for the semi-prep HPLC. However, this required the reaction to be transferred to a second vial to dilute with water, loaded onto a Waters Sep-Pak C18 cartridge, washed with H₂O, eluted with MeCN in to a third vial, diluted with H₂O to match the isocratic HPLC solvent conditions and finally loaded into the HPLC loop for HPLC purification. This protocol resulted in significant losses in activity due to the number of vials used and in transfer lines.

By adoption of 25 mM ammonium formate (AMF) as the aqueous phase, the preparation for substrates that required no deprotection could now be reduced to dilution with 25 mM AMF, followed by loading into the HPLC loop. For the substrates that required deprotection, the Sep-Pak C18 was sometimes still required as the reaction solvent was detrimental to the deprotection step itself. This will be specified for the substrates as each is discussed. When the Sep-Pak C18 cartridge was still required, automated macros were written to automate the loading and washing of the cartridge, increasing the efficiency and reproducibility of this step.

By application of the optimised conditions (Cu(OTf)₂py₄ (0.04 mmol), DMA (400 µL), 120°C, 20 min) to the corresponding precursor (0.03 mmol), [¹⁸F]Flumazenil ([¹⁸F]4-2), [¹⁸F]FMTEB ([¹⁸F]4-3) and [¹⁸F]FPEB ([¹⁸F]4-4) could be directly radiofluorinated and isolated in 35 ± 7% (n=3), 29 ± 6% (n=2) and 13 ± 5% (n=2) RCYs [n.d.c.] respectively (Table 4.10, Entries 1, 2 and 4). [¹⁸F]4-3 and [¹⁸F]4-4 are radiotracers that have been developed for the study of the metabotropic glutamate receptor subtype-5 (mGluR5) (as discussed in Section 3.3.3). For both [¹⁸F]4-3 and [¹⁸F]4-4 it was found that pre-treating

the QMA cartridge with oxalate counter-ions was beneficial to the final RCYs. [^{18}F]4-2 was not tested under reaction conditions when the cartridge was not pre-treated, though it is reasonable to assume that the reaction would respond in a manner similar to that of [^{18}F]4-3 and [^{18}F]4-4.



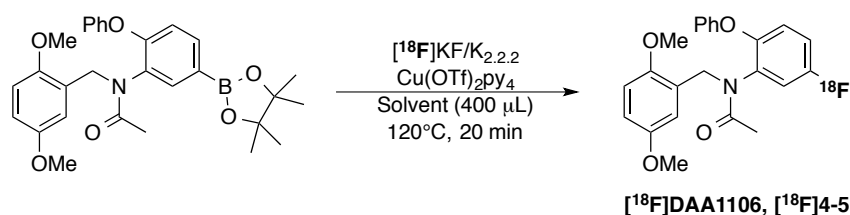
Entry	Radiotracer	QMA counter-ion	RCY (%) [n.d.c]	n
1	[^{18}F]4-2	Oxalate	35 ± 7	3
2	[^{18}F]4-3	Oxalate	29 ± 6	2
3	[^{18}F]4-3	Carbonate	14	1
4	[^{18}F]4-4	Oxalate	13 ± 5	2
5	[^{18}F]4-4	Carbonate	7 ± 3	2

Reaction conditions: precursor (0.03 mmol), Cu(OTf)₂py₄ (0.04 mmol), DMA (400 µL), 120°C, 20 min

Table 4.10: Radiosynthesis of three radiopharmaceuticals; [^{18}F]Flumazenil ([^{18}F]4-2), [^{18}F]FMTEB ([^{18}F]4-3) and [^{18}F]FPEB ([^{18}F]4-4).

[^{18}F]DAA1106 ([^{18}F]4-5) is a potent radioligand for the 18 kDa TSPO, which is a biomarker of brain inflammation and reactive gliosis. Targeting of TSPO with radioligands can provide information for monitoring of neurological and psychiatric disorders.^{267, 268} When the precursor (0.04 mmol) to [^{18}F]4-5 was treated with [^{18}F]KF/K_{2.2.2} and Cu(OTf)₂py₄ (0.02 mmol) in DMF at 120°C using a pre-treated cartridge, 14 ± 3% (n=3) RCY [n.d.c.] was obtained (Table 4.11, Entry 1). In contrast to the electron deficient substrates, not pre-treating the cartridge was found to not adversely affect the reaction (RCY = 14% (n=1) [n.d.c.]) (Entry 2). Reducing the precursor loading by half to 0.02 mmol was found to slightly improve the yield (RCY = 16 ± 2% (n=2) [n.d.c.]) (Entry 3), though it was not until DMA was substituted as the solvent that the

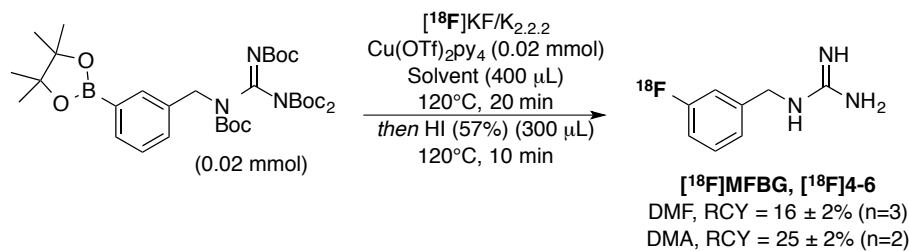
RCY significantly increase. In this way [^{18}F]4-5 could be isolated in $39 \pm 1\%$ ($n=1$) RCY [n.d.c.] (Entry 4).



Entry	QMA counter-ion	Precursor (mmol)	Cu(OTf) ₂ py ₄ (mmol)	Solvent	[^{18}F]4-5 RCY (%) [n.d.c]	n
1	Oxalate	0.02	0.04	DMF	14 ± 3	3
2	Carbonate	0.02	0.04	DMF	14	1
3	Carbonate	0.02	0.02	DMF	16 ± 2	2
4	Carbonate	0.02	0.02	DMA	39 ± 1	2

Table 4.11: Radiosynthesis of [^{18}F]DAA1106 ([^{18}F]4-5).

meta-[^{18}F]-Fluorobenzylguanidine ([^{18}F]MFBG) ([^{18}F]4-6) is a promising radiotracer for the imaging of norepinephrine transporter (NET) protein, which is overexpressed in 90% of neuroblastomas.²⁶⁹ While [^{123}I]MIBG and [^{131}I]MIBG have been successfully used as imaging agents, [^{18}F]MFBG has been developed as a superior tracer²⁷⁰ due to the limitations of low spatial resolution and long lasting residual activity with the iodine-123 and iodine-131 labelled analogues. The precursor for [^{18}F]4-6 had to be tetra-Boc protected for the radiofluorination reaction, though this protection was simply removed by addition of HI (57%) (300 μL) into the reaction vial, which was kept at 120°C for a further 10 minutes. Sodium hydroxide was used to partially neutralise the reaction mixture before the semi-prep HPLC purification. Adoption of the optimised conditions from [^{18}F]4-5, gave $25 \pm 2\%$ ($n=2$) RCY [n.d.c.] of isolated [^{18}F]4-6 (Scheme 4.9). Replacement of DMA with DMF leads to a considerable drop in the RCY ($7 \pm 3\%$ ($n=3$) [n.d.c.]).



Scheme 4.9: Radiosynthesis of $[^{18}\text{F}]\text{MFBG}$ ($[^{18}\text{F}]\text{4-6}$).

For $[^{18}\text{F}]\text{FDOPA}$ ($[^{18}\text{F}]\text{4-7}$), 6- $[^{18}\text{F}]\text{fluoro-L-meta-tyrosine}$ ($[^{18}\text{F}]\text{FMT}$) ($[^{18}\text{F}]\text{4-8}$) and 6- $[^{18}\text{F}]\text{fluorodopamine}$ ($[^{18}\text{F}]\text{FDA}$) ($[^{18}\text{F}]\text{4-9}$), protected precursors again had to be used and a Sep-Pak C₁₈ cartridge was required to remove the reaction solvent before deprotection. After the radiofluorination, the reaction was diluted with water (8 mL) and trapped on the cartridge before being washed with a further 2 mL water. Elution from the cartridge was completed with acetone, which was removed at 120°C under a stream of N₂. The dry residue was directly treated with HI (57%) (400 μL) at 150°C^{xii} for 10 minutes, before partial neutralisation with and semi-prep HPLC purification.

$[^{18}\text{F}]\text{4-7}$ is currently seen as the ‘gold standard’ for studies of the dopaminergic system, neuroendocrine tumours, neuropsychiatric disorders and cognitive behaviour, though has been plagued by poor radiosynthetic routes.²⁷¹ To date, the highest yielding nucleophilic pathway involves an initial aromatic substitution followed by a multi-step post-fluorination reaction pathway.^{56, 57} More recently diaryliodonium triflate precursors have been shown to be amenable to direct radiofluorination, though only in $14 \pm 4\%$ RCY [d.c.] in a synthesis time of 117 ± 4 minutes.²⁷² Electrophilic protocols are also well established, though are limited by use of $[^{18}\text{F}]\text{F}_2$ and low specific activities.

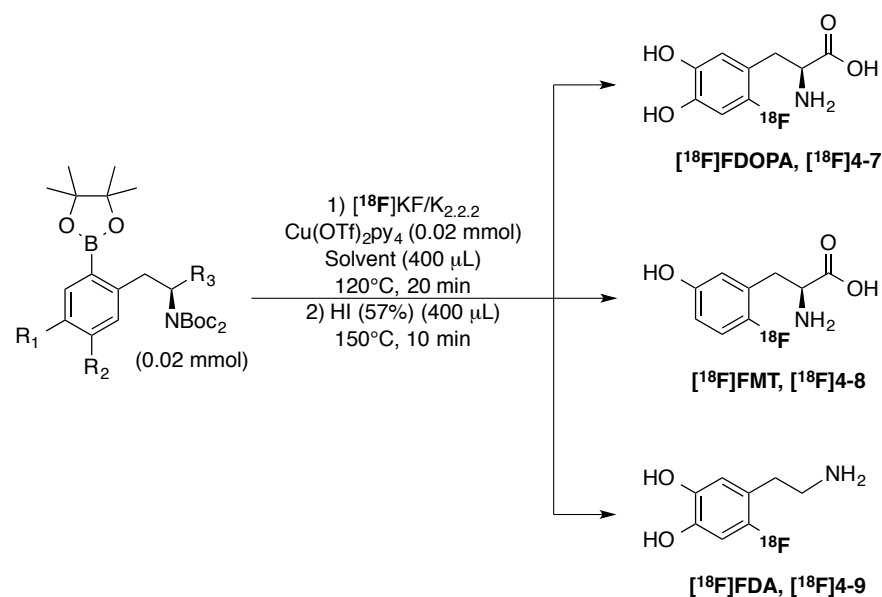
$[^{18}\text{F}]\text{4-8}$ has been reported to have a greater *in vivo* metabolic stability than $[^{18}\text{F}]\text{4-7}$, as it is not a substrate compatible with catechol-O-methyl-transferase, and can be used for imaging in similar clinical aspects as $[^{18}\text{F}]\text{4-7}$.²⁷³ Until recently the only routes to $[^{18}\text{F}]\text{4-8}$

^{xii} $[^{18}\text{F}]\text{FDA}$ run at 130°C

were electrophilic,²⁷⁴⁻²⁷⁶ though in 2015 Meleán *et al.*²⁷⁷ reported a three step procedure from [¹⁸F]fluoride with an initial S_NAr with an overall RCY of 8 - 13%. Rotstein *et al.*²³⁹ have also presented a nucleophilic route, utilising the spirocyclic iodonium methodology in a RCY = 12% (n=3) [n.d.c.] after deprotection and isolation.

[¹⁸F]4-9 has been used for the diagnosis and localisation of pheochromocytoma²⁷⁸ and imaging of paragangliomas.²⁷⁹ As with [¹⁸F]4-7 and [¹⁸F]4-8, the majority of radiosynthetic routes have followed electrophilic pathways²⁸⁰ or multi-step nucleophilic protocols.²⁸¹ Zlatopolskiy *et al.* were able to employ Ichiishi *et al.*'s CuOTf(MeCN)₄ mediated radiofluorination of (mesityl)(aryl)iodonium tetrafluoroborates⁶⁹ to produce [¹⁸F]4-9 in a 23% (n=1) RCY [n.d.c.].²⁵⁸

Application of the Cu(OTf)₂py₄ mediated radiofluorination conditions gave good isolated RCYs of all three radiotracers (Table 4.12). While [¹⁸F]4-9 followed the previous two tracers, with the reaction performing noticeably better when run in DMA (29 ± 5% (n=2) [n.d.c.]) (Entry 6), there was no solvent dependence seen for [¹⁸F]4-7, with both solvents yielding 22 ± 3% (n<2) [n.d.c.] (Entries 1 and 2). Surprisingly, [¹⁸F]4-8 could be isolated in a higher RCY = 15 ± 1% (n=3) [n.d.c.] (Entry 3) when the reaction was run in DMF, contrary to all of the other radiotracers labelled in this project.



Entry	Radiotracer	R_1	R_2	R_3	Solvent	$[^{18}\text{F}]$ 4-7, 8, 9 RCY (%) [n.d.c]	n
1	$[^{18}\text{F}]$ 4-7	OMe	OMe	CO_2Et	DMF	22 ± 3	3
2	$[^{18}\text{F}]$ 4-7	OMe	OMe	CO_2Et	DMA	22 ± 3	2
3	$[^{18}\text{F}]$ 4-8	H	OMe	CO_2Et	DMF	15 ± 1	3
4	$[^{18}\text{F}]$ 4-8	H	OMe	CO_2Et	DMA	11 ± 3	2
5 ^a	$[^{18}\text{F}]$ 4-9	OMe	OMe	H	DMF	20 ± 6	2
6 ^a	$[^{18}\text{F}]$ 4-9	OMe	OMe	H	DMA	29 ± 5	2

a) HI deprotection run at 130°C .

Table 4.12: Radiosynthesis of $[^{18}\text{F}]$ FDOPA ($[^{18}\text{F}]$ 4-7), $[^{18}\text{F}]$ FMT ($[^{18}\text{F}]$ 4-8) and $[^{18}\text{F}]$ FDA ($[^{18}\text{F}]$ 4-9).

Consequently, by adoption of these low base conditions, eight important clinical tracers have been radiofluorinated and isolated in good RCYs. By comparison of the RCYs obtained by this protocol with the literature precedent (Table 4.13) it is apparent that this procedure has the capacity to equal the majority of highest reported RCYs for each radiotracer produced from $[^{18}\text{F}]$ fluoride. $[^{18}\text{F}]$ 4-4 and $[^{18}\text{F}]$ 4-5 do fall behind the literature precedent, though increases are seen for $[^{18}\text{F}]$ 4-3, $[^{18}\text{F}]$ 4-8 and $[^{18}\text{F}]$ 4-9.

Entry	Radiotracer	This Work RCY (%) [n.d.c.] [d.c.]		n	Literature RCY (%)	Methodology (Synthesiser)	Procedure
1	$[^{18}\text{F}]$ Flumazenil $[^{18}\text{F}]$ 4-2	35 ± 7	54 ± 10	3	67 ± 3 [d.c.] (n=3)	Diaryliodonium Tosylate (Manual)	Moon <i>et al.</i> ²⁸²
					53 ± 9 [d.c.] (n=94)	Diaryliodonium Tosylate (GE TRACERlab FX _{FN})	Moon <i>et al.</i> ²⁸³
2	$[^{18}\text{F}]$ FMTEB $[^{18}\text{F}]$ 4-3	29 ± 6	44 ± 9	2	20 ± 1 [n.d.c.] (n = 3)	Microwave/ Diaryliodonium Tosylate (Modified Synthia) ²⁸⁴	Telu <i>et al.</i> ²²⁸
3	$[^{18}\text{F}]$ FPEB $[^{18}\text{F}]$ 4-4	13 ± 5	19 ± 6	2	20 ± 5 [n.d.c.] (n = 3)	Spirocyclic Iodonium Ylide (GE TRACERlab FX _{FN})	Stephenson <i>et al.</i> ²³⁸
4	$[^{18}\text{F}]$ DAA1106 $[^{18}\text{F}]$ 4-5	31 ± 1	61 ± 3	2	50 [n.d.c.] (n=1)	CuOTf(MeCN) ₄ / Diaryliodonium Tetrafluoroborate (Manual)	Zlatopolskiy <i>et al.</i> ²⁵⁸
5	$[^{18}\text{F}]$ MFBG $[^{18}\text{F}]$ 4-6	25 ± 2	41 ± 2	2	22 ± 4 [n.d.c.] 31 [d.c.] (n=9)	Diaryliodonium Triflate (IBA Synthera)	Hu <i>et al.</i> ²⁸⁵
6	$[^{18}\text{F}]$ FDOPA $[^{18}\text{F}]$ 4-7	22 ± 3	40 ± 4	2	24 [n.d.c.] 36 ± 4 [d.c.] (n=8)	S _N Ar Multi-step (GE FASTlab)	Liebert <i>et al.</i> ⁵⁶ Lemaire <i>et al.</i> ^{57, a}
7	$[^{18}\text{F}]$ FMT $[^{18}\text{F}]$ 4-8	15 ± 1	30 ± 2	2	8-13 [n.d.c.]	S _N Ar Multi-step	Meleán <i>et al.</i> ²⁷⁷
					12 [n.d.c.] (n=3)	Spirocyclic Iodonium Ylide (Manual)	Rotstein <i>et al.</i> ²³⁹
8	$[^{18}\text{F}]$ FDA $[^{18}\text{F}]$ 4-9	29 ± 5	53 ± 9	2	23 (n=1) [n.d.c.]	CuOTf(MeCN) ₄ / Diaryliodonium Tetrafluoroborate (Manual)	Zlatopolskiy <i>et al.</i> ²⁵⁸

a) Both reports give same RCY

Table 4.13: Comparison of radiotracer production (with semi-prep HPLC) protocols.

4.3.2.3. Industrial Protocol Validation

A significant hindrance to the widespread application of PET tracers is the protocols for productions are designed manually and are not amenable to automation, or are devised on one platform, but are not amenable to automation on additional synthetic platforms.

The prior radiofluorination optimisation and isolation for this project had been performed using a NanoTek® platform, though not incorporating the microfluidic aspect of this apparatus. Consequently, industrial collaborators were approached to validate this methodology, taking the optimised conditions from the NanoTek® and applying modifications on it to their respective platforms. It is noteworthy that these reactions were not independently optimised for each platform. The modifications that were applied to the procedure were due to mechanical considerations.

Entry	Radiotracer	NanoTek® (Oxford)	Synthra (Imanova)	Neptis (ABX)
1	[¹⁸ F]Flumazenil [¹⁸ F]4-2	35 ± 7 ^a (n=3)	19 ^a (n=1)	16 ± 4 ^c (n=10)
2	[¹⁸ F]FPEB [¹⁸ F]4-4	13 ± 5 ^a (n=2)	5 ^a (n=1)	-
3	[¹⁸ F]FDOPA [¹⁸ F]4-7	22 ± 3 ^b (n=2)	9 ^b (n=1)	-
4	[¹⁸ F]FMT [¹⁸ F]4-8	15 ± 1 ^b (n=2)	10 ^b (n=1)	-

Radiofluorination conditions: a) Precursor (0.03 mmol), Cu(OTf)₂py₄ (0.04 mmol), DMA (400 µL), 120°C, 20 min; b) Precursor (0.02 mmol), Cu(OTf)₂py₄ (0.02 mmol), DMF (400 µL), 120°C, 20 min; c) Precursor (0.036 mmol), Cu(OTf)₂py₄ (0.044 mmol), DMA (1 mL), 130°C, 10 min.

Table 4.14: RCY comparison with synthetic platform.

Gratifyingly, the reaction performed adequately on both the Synthra and Neptis platforms (Table 4.14), with RCYs falling lower than found previously, though this was expected with unoptimised conditions. It is expected that optimisation on each platform would account for this lost yield.

More importantly, these reactions allowed for accurate calculation of SA for these radiotracers. The radiochemistry facilities at the University of Oxford do not have direct access to a cyclotron for [^{18}F]fluoride production and require delivery from commercial production facilities. A consequence of this is that the [^{18}F]fluoride will have undergone several half-lives before delivery and any SA calculations will be negatively affected.

The SA for [^{18}F]4-2 and [^{18}F]4-4, produced on the Synthra platform, were calculated as 124 GBq/ μmol and 121 GBq/ μmol respectively. This falls within the expected region for [^{18}F]fluoride produced radiotracers, indicating that tracers produced in this manner would be acceptable for clinical imaging studies. As a comparison, the SA values calculated for the same tracers produced at Oxford were found to be 27 GBq/ μmol and 43 GBq/ μmol respectively.

4.4. Summary

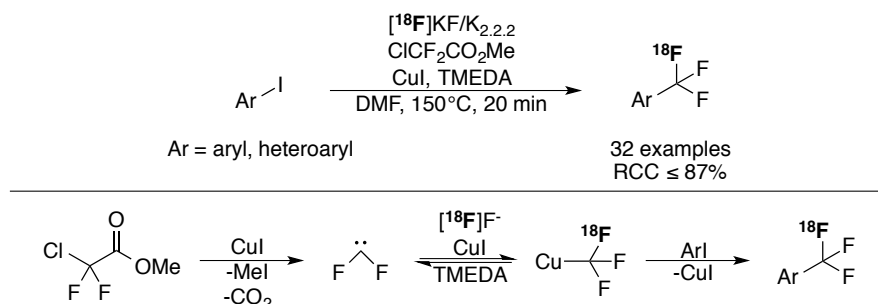
In conclusion, this project has taken a promising approach to radiofluorination, developed under research conditions in the Gouverneur group though unsuitable for production level radiosyntheses, and has successfully adapted it so that eight radiotracers of clinical importance have been labelled. Two sets of conditions have been established for electron rich and electron deficient arenes, which means that a wide range of other radiotracers are within the remit and accessibility of this protocol. Furthermore, this reaction has been validated on two additional synthetic platforms, giving good RCYs under conditions that were not individually optimised. SA calculated for this reaction are good and well within the level requisite for high quality clinical imaging requirements.

PART II

Diversity Oriented Radiofluorination

5. Radiofluorination of *Geminal* Difluorinated Motifs

The nucleophilic [^{18}F]labelling of sites that bear more than one fluorine is more difficult than the monofluorination-type reactions covered in Part 1. Motifs, including *geminal* difluorinated, trifluoromethyl and related structures, are typically labelled by halogen exchange under harsh conditions or incorporation of the entire group as one unit, rather than introduction of a single fluorine-18 radionuclide. This introduces the possibility of isotopic exchange and consequent reduction in SA of the final product. This is exemplified by the trifluoromethylation of aryl iodides by Huiban *et al.* (Scheme 5.1), in which they use copper(I)-mediated decarboxylation of methyl chlorodifluoroacetate, which forms $:\text{CF}_2$ carbene (see Section 1.3.2.1. for full discussion).⁴⁹



Scheme 5.1: Trifluoromethylation of aryl iodides by Huiban *et al.*.⁴⁹

These problems arise from the low amounts of [^{18}F]fluoride present in radiofluorination reactions, as previously discussed. The other reagents, including the precursor, are in vast excesses and so the possibility of introducing more than one fluorine-18 radionuclide is close to nil. As such, there is interest in developing routes toward late-stage introduction of single fluorine atoms into motifs already bearing fluorine atoms, with a view to translating these approaches to radiofluorination protocols.

While there are well-established, if problematic, routes to [^{18}F]trifluoromethylarenes and [^{18}F]monofluorinated aliphatics, the [^{18}F]difluorinated motif is poorly covered (see Sections 1.3.2. and 1.3.3.). When considering fluorine screens of potential drug candidates, being able to finely tune biological activity with incremental fluorine incorporation is essential, and as such, as are routes to radiofluorinating these motifs. Furthermore, there are several pharmaceuticals that bear difluorinated motifs.

One such drug that has attracted much attention in the radiochemistry community is Gemcitabine (Figure 5.1), a nucleoside analogue with two *geminal* fluorine atoms on the 2' carbon of deoxycytidine. Gemcitabine is an anti tumour agent, marketed as Gemzar[®] by Eli Lilly, which is used for treatment of various carcinomas (pancreatic cancer, non-small cell lung cancer, bladder cancer, breast cancer, ovarian cancer (with carboplatin) and bladder cancer (with cisplatin)), where it acts as an antimetabolite, by inhibition of ribonucleotide reductase (RNR) and DNA synthesis.²⁸⁶ This stops cellular replication, therefore tumour growth and results in apoptosis. Unfortunately, Gemcitabine is compromised by high levels of toxicity, rapid metabolism and poor tumor uptake in the majority of patients, resulting in ineffective courses of chemotherapy.^{287,288}

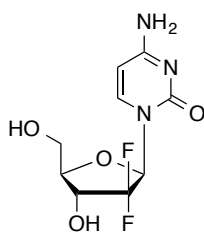
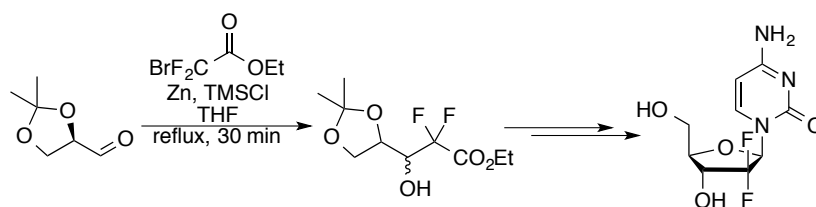


Figure 5.1: Gemcitabine (Gemzar[®], Eli Lilly)

Development of an ^{18}F -labelled Gemcitabine radiotracer would allow detailed studies of the drug uptake into tumors, allowing for patient stratification with a single PET scan, rather than a complete chemotherapy course. It would also facilitate the development of pro-nucleotides and variations to the Gemcitabine motif in order to investigate better alternatives and more personalized medicines.²⁸⁹

As with most fluorinated drugs, the literature syntheses of Gemcitabine are not suitable as approaches that could be modified for ^{18}F -labelling, as the *gem*-difluoro moiety is introduced early in the procedure. In the most common cases (Scheme 5.2), it is introduced via a Reformatskii reaction and then a series of consequent steps are carried out to obtain the final Gemcitabine structure (Hertel²⁹⁰ [9 steps (6.1%)], Shen²⁹¹ [10 steps (10%)], Kim²⁹² [9 steps (20%)]). There are other routes from Sauve²⁹³ and Gong²⁹⁴ which introduce the *gem*-difluoro functionality with LiHMDS/NFSI and DAST respectively, but all these routes could only be completed on a multi-day timetable post-fluorination and so rule them out as a possible routes for [^{18}F]labelling.



Scheme 5.2: General literature synthesis of Gemcitabine.

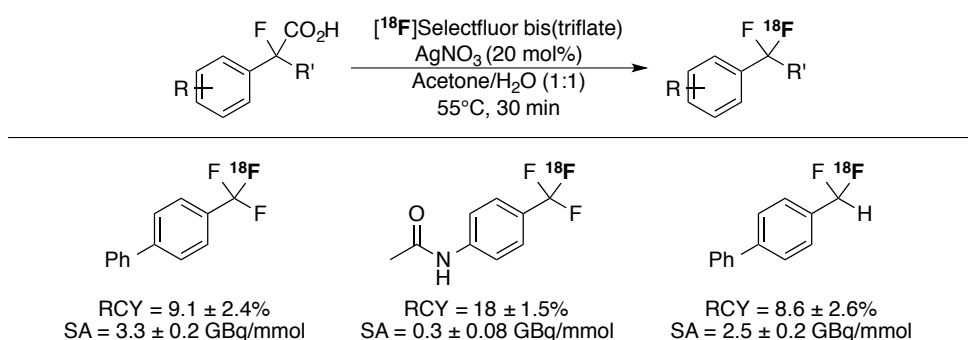
Consequently, development of a method for high SA, late-stage radiofluorination of *geminal* difluorinated compounds is now becoming a necessary advancement for the PET community.

5.1. Electrophilic Decarboxyfluorination

Two routes were initially proposed for development of this late-stage fluorination – an electrophilic decarboxyfluorination and a nucleophilic $\text{S}_{\text{N}}2$ mechanism. The nucleophilic route was based on a paper²⁹⁵ detailing a $\text{S}_{\text{N}}2$ reaction on α,α -chlorofluorocarbonyl compounds and will be discussed in Section 5.2..

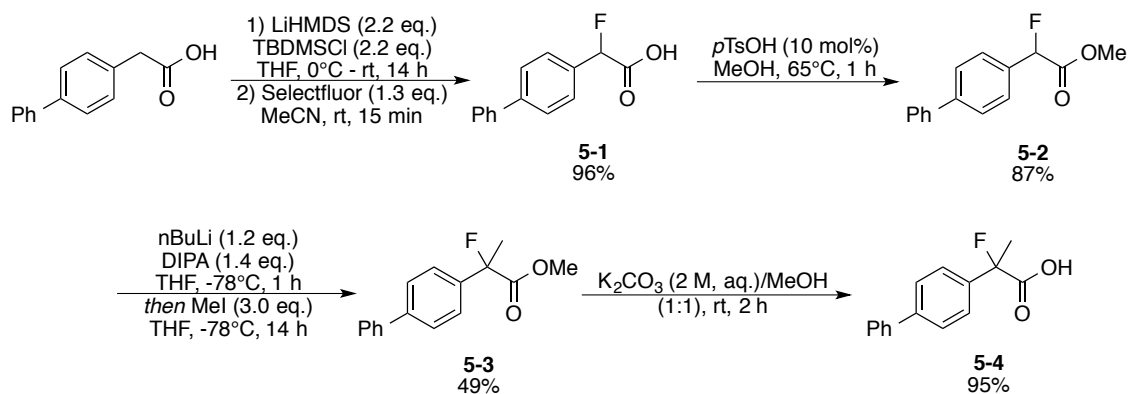
The electrophilic route aimed to build on the silver(I)-mediated [^{18}F]decarboxyfluorination using [^{18}F]Selectfluor bis(triflate) work from Mizuta *et al.* which gave access to di- and trifluoromethyl arenes (Scheme 5.3).¹¹³ In 2012, the Li

group disclosed the use of Selectfluor, in combination with catalytic silver nitrate, for the decarboxyfluorination of carboxylic acids.²⁹⁶ This methodology was adapted by the Gouverneur group for the synthesis of [¹⁸F]labelled di- and trifluoromethyl arenes using high SA [¹⁸F]Selectfluor bis(triflate).¹¹³ However, this decarboxyfluorination methodology was not applied in the synthesis of di-alkyl or aryl-alkyl substituted CF₂ groups, therefore both of these substrate classes have been investigated.



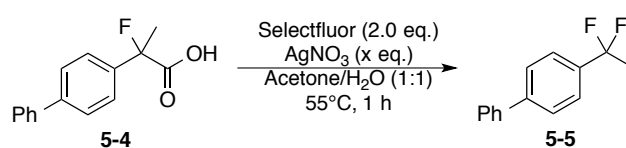
Scheme 5.3: AgNO₃ mediated [¹⁸F]decarboxyfluorination with [¹⁸F]Selectfluor bis(triflate).¹¹³

The first step to take was to show that this decarboxyfluorination is amenable to alkyl substituents to give an aryl-alkyl substituted *gem*-difluoro motif. In keeping with previous work from the Gouverneur group, a biphenyl structure was chosen as the aryl substituent, with a simple methyl group as the alkyl substituent. Consequently, 2-(4-biphenyl)-2-fluoropropanoic acid (**5-4**) was synthesized from 4-biphenylacetic acid via the methylation of methyl biphenyl-4-yl(fluoro)acetate (**5-2**), in a 39% yield over four steps.



Scheme 5.4: Synthesis of 2-(4-biphenyl)-2-fluoropropanoic acid.

When **5-4** (^{19}F NMR: $\delta = -144.4$ ppm) was subjected to 2.0 equivalents of Selectfluor and 0.4 equivalents of silver nitrate in acetone/water (1:1) at 55°C for 1 hour (Table 5.1, Entries 1 and 2), ^{19}F NMR showed a 94% conversion to 4-(1,1-difluoroethyl)biphenyl (**5-5**) (^{19}F NMR: $\delta = -87.2$ ppm) relative to 1-fluoro-3-nitrobenzene (^{19}F NMR: $\delta = -109.7$ ppm) as an internal standard; isolating from these conditions gave a 92% yield. On halving the equivalents of silver nitrate (Entry 3), the yield dropped to 45%. In this way, it was proven that this reaction could tolerate alkyl substituents.

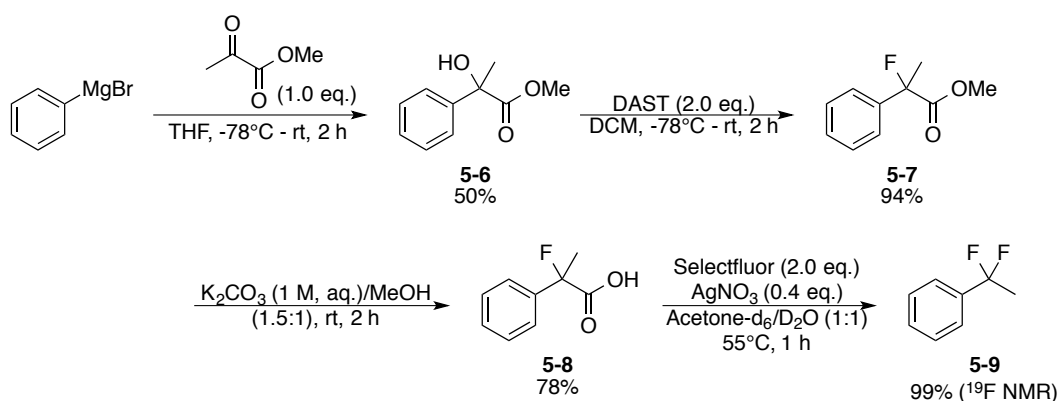


Entry	AgNO ₃ (eq.)	5-5 (^{19}F NMR, %)
1	0.4	94
2	0.4	92 ^a
3	0.2	45

a) Isolated yield.

Table 5.1: Initial investigations toward effects of alkyl substitution on decarboxyfluorination.

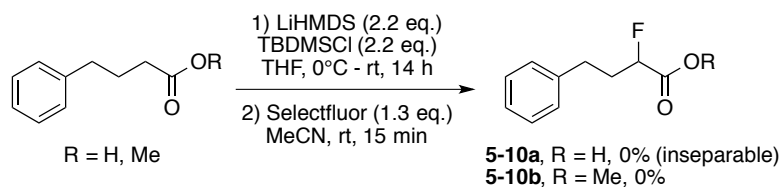
To confirm this result, an unsubstituted arene precursor was synthesized from phenylmagnesium bromide with methyl pyruvate, which was then fluorinated and hydrolysed to give 2-fluoro-2-phenylpropanoic acid (**5-8**) in 37% yield over three steps. **5-8** (^{19}F NMR: $\delta = -151.8$ ppm) was subjected to the same decarboxyfluorination conditions, carried out in deuterated solvent due to volatility of the final product, which gave a 99% yield of (1,1-difluoroethyl)benzene (**5-9**) (^{19}F NMR: $\delta = -83.8$ ppm). Isolation was not attempted due to volatility (BP = 65°C (40 mmHg)).²⁹⁷



Scheme 5.5: Synthesis and decarboxyfluorination of 2-fluoro-2-phenylpropanoic acid.

In this way, two complimentary routes to starting materials have been established, which would enable the synthesis of a diverse range of alkyl-aryl substituted compounds as precursors to the decarboxyfluorination, which has been shown to perform excellently, albeit on two unfunctionalised substrates.

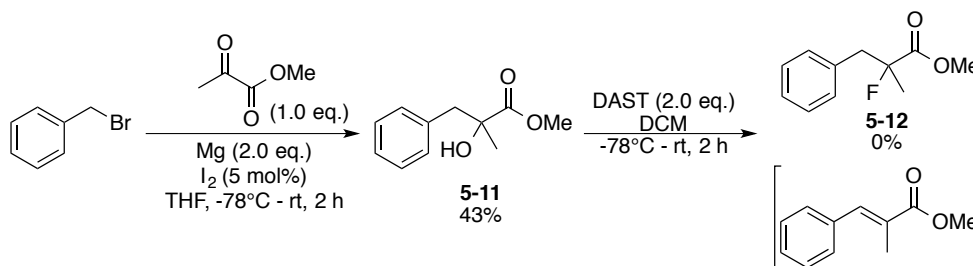
However, as the focus of this project was towards more generic *geminal* difluorinated motifs, studies quickly moved onto the di-alkyl substituted motif. In order to synthesize di-alkyl substrates **5-10a** and **5-10b**, initially similar routes as used for the synthesis of **5-4** were attempted on 4-phenylbutyric acid and methyl 4-phenylbutanoate (Scheme 5.6). Unfortunately, the initial fluorination was not successful in either case due to reaction not proceeding, for methyl 4-phenylbutanoate, or as the starting material being inseparable from the product, for 4-phenylbutyric acid.



Scheme 5.6: Initial fluorination reactions toward the synthesis of alkyl-alkyl substituted precursors.

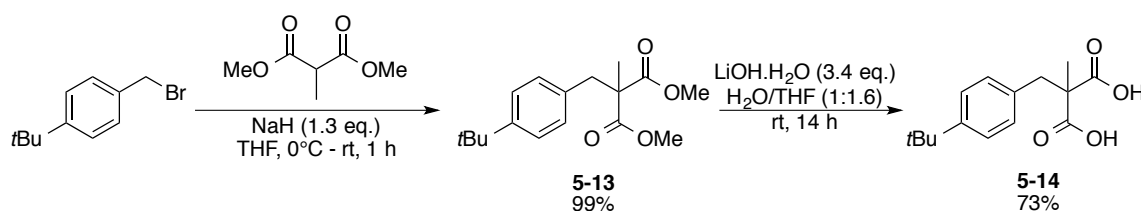
The alternative route was also pursued in an attempt to form an alkyl-alkyl substituted precursor (Scheme 5.7). From benzyl bromide, the Grignard reaction performed adequately, giving 43% of **5-II**, however attempts to fluorinate this with DAST were

unsuccessful. It is believed that, whilst methyl 2-fluoro-2-methyl-3-phenylpropanoate (**5-12**) can be observed by ^{19}F NMR analysis of the crude reaction mixture (^{19}F NMR: $\delta = -155.1$ ppm), attempts to purify by flash column chromatography lead to the elimination of the fluoride to give the conjugated olefin. This was characterized by loss of the signal of the benzylic sp^3 protons in the ^1H NMR spectrum.



Scheme 5.7: Failed synthesis of methyl 2-fluoro-2-methyl-3-phenylpropanoate.

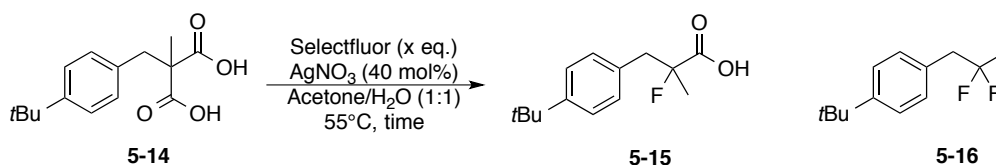
Due to the difficulties in purifying these substrates for proof of principle of decarboxylative fluorination, the concept of a double decarboxyfluorination to form the CF_2 moiety was instead investigated, on (4-*tert*-butylbenzyl)(methyl)propanedioic acid (**5-14**). This precursor was synthesised from 4-*tert*-butylbenzyl bromide and dimethyl methyl malonate followed by hydrolysis of the di-methyl ester intermediate (**5-13**) with lithium hydroxide in 99% and 73% yields, respectively (Scheme 5.8).



Scheme 5.8: Synthesis of (4-*tert*-butylbenzyl)(methyl)propanedioic acid.

On being subjected to same conditions as used previously, 2.0 equivalents of Selectfluor and 40 mol% silver nitrate, 29% of the monofluorinated product (**5-15**) (^{19}F NMR: $\delta = -153.7$ ppm) was found, along with 3% of the difluorinated product (**5-16**) (^{19}F NMR: $\delta = -88.3$ ppm) (Table 5.2, Entry 1) relative to 1-fluoro-3-nitrobenzene as the internal reference. When the stoichiometry of Selectfluor was doubled, to 4.0

equivalents, the amount of the monofluorinated product fell to 5%, accompanied by an increase in the yield of the difluorinated product to 32% (Entry 2).



Entry	Selectfluor (eq.)	Time (h)	5-15 (%) ^a	5-16 (%) ^a
1	2.0	1	29	3
2	4.0	1	5	32
3	4.0	4	2	35

a) ¹⁹F NMR yields.

Table 5.2: Decarboxyfluorination of (4-*tert*-butylbenzyl)(methyl)propanedioic acid.

Logically, it was assumed that the fluorinations occurred consecutively rather than concurrently though this hypothesis was validated with a time dependent study with ¹⁹F NMR yields taken at time splits of 1, 5, 10, 20, 30, 45 and 60 minutes. Shown in Figure 5.2, the two fluorination reactions occur consecutively, with the monofluorinated product **5-15** being formed rapidly from the start of the reaction, followed by sequestration as the difluorinated product **5-16** is formed via the second fluorination step. The final yield found after one hour was only 20%, so notably lower than for the previous experiment with these conditions. This has been attributed to the reaction being very sensitive to oxygen, a small volume of which may have been introduced each time a timepoint was extracted from the reaction vessel. These results also seemed to imply that the reaction has not reached completion after 1 hour, as neither of the lines had plateaued. Consequently the reaction was run over 4 hours (Table 5.2, Entry 3); however this did not lead to any significant increase in yield of **5-16**.

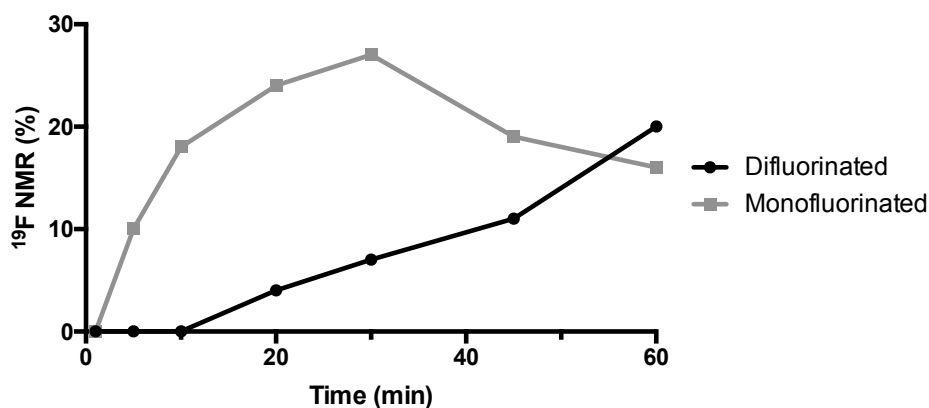
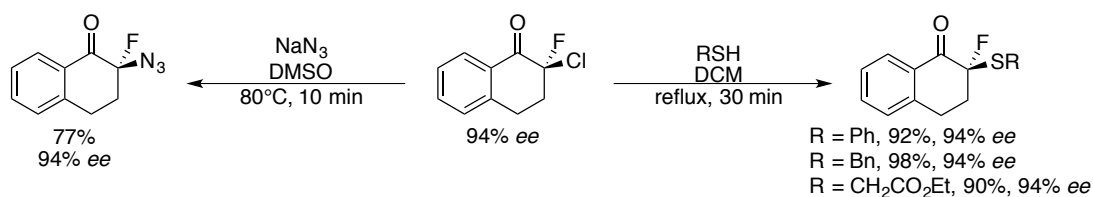


Figure 5.2: Time study on decarboxyfluorination of 5-14.

This route is the first example of a double *geminal* decarboxyfluorination and, more importantly for this project, has shown that a di-alkyl substituted CF_2 group can be made from a $\text{R}_2\text{CFCO}_2\text{H}$ motif. As $[^{18}\text{F}]$ Selectfluor bis(triflate), used for the $[^{18}\text{F}]$ decarboxyfluorination, is generated under carrier added conditions with high SA $[^{18}\text{F}]\text{F}_2$, there is potential for this route to be applied to radiofluorination of *geminal* difluorinated motifs.

5.2. Nucleophilic $\text{S}_{\text{N}}2$ Fluorination by Halogen Exchange

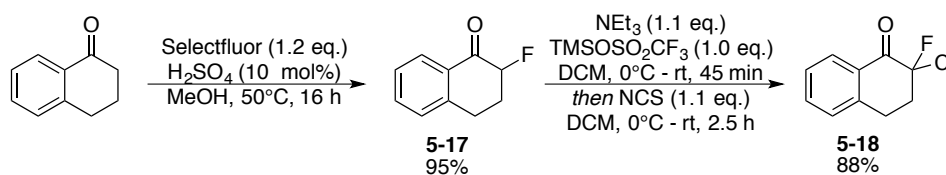
For the nucleophilic approach, the aim was for a halogen exchange (halex) reaction to be developed, building on the work of Shibatomi *et al.*, but utilising a fluoride nucleophile in place of their nitrogen or sulfur-based nucleophiles (Scheme 5.9).²⁹⁵



Scheme 5.9: Substitution on CFCl motif by Shibatomi *et al.*²⁹⁵

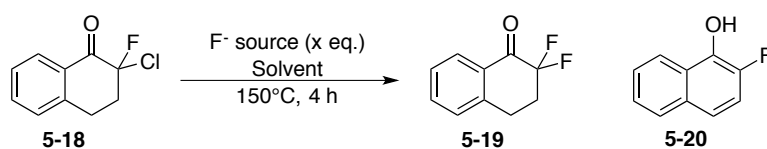
Shibatomi's report centered around the use 2-chloro-2-fluoro-3,4-dihydronaphthalen-1(2H)-one (5-18), which was consequently chosen as the model substrate on which to begin the investigations toward this halex reaction. This precursor was synthesised from the parent 1-tetralone, which was fluorinated with Selectfluor to give α -

fluorotetralone (**5-17**) and consequently chlorinated with NCS in 84% over the two steps.



Scheme 5.10: Synthesis of 2-chloro-2-fluoro-3,4-dihydronaphthalen-1(2H)-one.

Initially **5-18** was subjected to high temperature reactions, as these are typically required for halox reactions, with a screen for fluoride sources and solvents (Table 5.3). The desired product 2,2-difluoro-3,4-dihydronaphthalen-1(2H)-one (**5-19**) (^{19}F NMR: $\delta = -111.7$ ppm) could be identified by ^{19}F NMR spectroscopy when 1.0 equivalent TBAF $\cdot 3\text{H}_2\text{O}$ was used as the fluoride source in either DMF or DMSO (Entries 5 and 6), though 4.0 equivalents of KF had to be used as 1.0 equivalent gave no yield (Entries 1 - 4). However, alarmingly, it was found that whilst **5-18** (^{19}F NMR: $\delta = -116.3$ ppm) had been completely consumed in the reaction, the yields remained very poor. The greatest yield at this high temperature was 3% when 4.0 equivalents TBAF $\cdot 3\text{H}_2\text{O}$ were used in DMSO (Entry 7) whilst the major product in all cases was an initially unknown species. Purification of this compound enabled identification as 2-fluoro-1-naphthol (**5-20**) (^{19}F NMR: $\delta = -145.4$ ppm), which could be isolated in a 93% yield when KF (1.0 equivalents) was used in DMF (Entry 1).

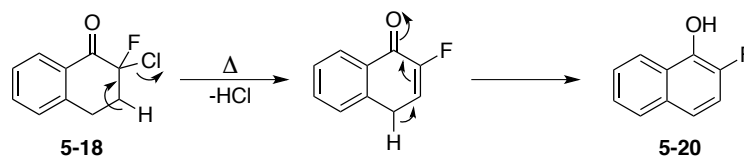


Entry	F ⁻ source (eq.)	Solvent	5-18 (%) ^a	5-19 (%) ^a	5-20 (%) ^a
1	KF (1.0)	DMF	0	0	99 ^b
2	KF (4.0)	DMF	0	2	33
3	KF (1.0)	DMSO	0	0	33
4	KF (4.0)	DMSO	0	2	21
5	TBAF.3H ₂ O (1.0)	DMF	0	2	57
6	TBAF.3H ₂ O (1.0)	DMSO	0	2	36
7	TBAF.3H ₂ O (4.0)	DMSO	0	3	39
8	TBAF bis(pinacol) (1.0)	DMF	0	2	84
9	TBAF bis(pinacol) (1.0)	DMSO	0	<1	21
10	-	DMF	0	0	99

a) ¹⁹F NMR (vs. 1-fluoro-3-nitrobenzene); b) 93% yield after isolation.

Table 5.3: High temperature S_N2 reaction with fluoride nucleophile.

This is presumed to be formed through, initially, an E₂ mechanism with loss of HCl, followed by keto-enol tautomerisation (Scheme 5.11), forced by the aromatic stability of 5-20. Potassium fluoride and TBAF.3H₂O are more basic than the nucleophiles utilised by Shibatomi *et al.*,²⁹⁵ who did not report any naphthol product under their substitution conditions. Consequently it is likely that this mechanism is facilitated by this increased basicity.



Scheme 5.11: Proposed E₂ mechanism for formation of the naphthol product.

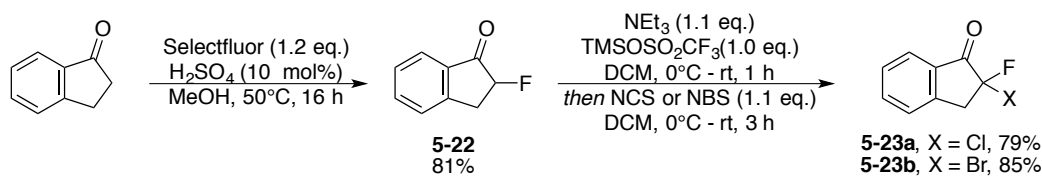
It was considered that a less basic, more nucleophilic version of TBAF,²⁹⁸ TBAF bis(pinacol) (5-21), would be a better fluoride source, which can be synthesised in an 87%

yield by refluxing TBAF. $\cdot$ 3H₂O with 2.0 equivalents of pinacol in hexane for two hours before being allowed to cool to room temperature without stirring.

Unfortunately, with the adoption of **5-21** the yield of the difluorinated product **5-19** did not improve and **5-20** remained as the major product (Table 5.3, Entries 8 and 9). On running the control reactions with no fluoride source in DMF (Entry 10), a 99% yield of **5-20** was found by ¹⁹F NMR spectroscopy, which shows that the decomposition of the starting material occurs independently of fluoride under these high temperature conditions.

Further variations were investigated, including alternative fluoride sources (AgF, TEAF. $\cdot$ H₂O), alternative solvents (MeCN, THF, DCM) under reduced temperature and time, though in all cases the major product was found to be the naphthol (**5-20**) and the yield of the difluorinated product was never greater than 3%.

Attempts to change the structure of the substrate also lead to low yields. Analogous indanone substrates were synthesised, bearing either a chloride (**5-23a**) or bromide (**5-23b**) leaving group. These precursors were synthesised in the same manner as for **5-17**, with the fluorination yielding 81% 2-fluoro-2,3-dihydro-1H-inden-1-one (**5-22**) and the consequent chlorination and bromination steps yielding 79% and 85% respectively.



Scheme 5.12: Substrate synthesis for **5-23a/b**.

As MeCN had, tentatively, been seen as the best solvent from the attempted S_N2 reaction screen on **5-17**, it was first investigated for the fluorination of **5-23b**. The initial conditions showed that the majority of the starting material was being consumed (Entry 1), though only 2% of the desired product **5-24** (¹⁹F NMR: δ = -111.6 ppm) was

found by ^{19}F NMR along with 49% of the elimination product **5-25** (^{19}F NMR: $\delta = -143.8$ ppm). Increasing to 3.0 equivalents of $\text{TBAF}\cdot 3\text{H}_2\text{O}$ lead to loss of all material (Entries 2 and 3). The chlorinated analogue gave similar results.

Entry	$\text{TBAF}\cdot 3\text{H}_2\text{O}$ (eq.)	Solvent	Temperature ($^{\circ}\text{C}$)	Time (min)	5-23b (%) ^a	5-24 (%) ^a	5-25 (%) ^a
1	1.0	MeCN	80	20	13	2	49
2	3.0	MeCN	80	60	0	1	0
3	3.0	MeCN	80	20	0	<1	0

a) ^{19}F NMR (vs. 1-fluoro-3-nitrobenzene).

Table 5.4: Halogen exchange on **5-23b** by fluoride.

Subsequently, no further effort was placed in the investigation of this substrate as a model compound for nucleophilic fluorination to produce *geminal* difluorinated motifs, as it was likely to continue to be plagued by the formation of the elimination product. The result of these studies suggests that a hallex reaction to form these *geminal* difluorinated motifs is possible, however caution must be paid toward any possible elimination pathways.

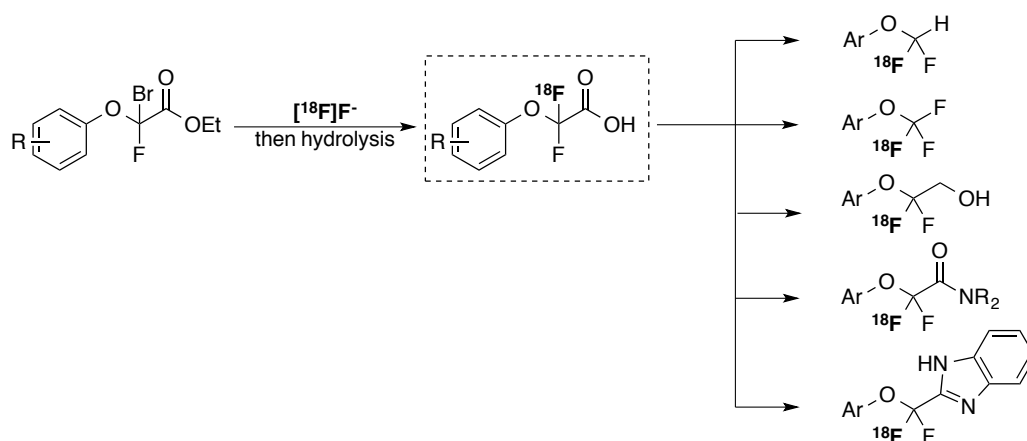
5.3. Radiofluorination by Halogen Exchange on α,α -Fluorobromoesters

In the Gouverneur group, T. Khotavivattana^{xiii} had been working on the synthesis of aryl- OCF_3 and $-\text{OCF}_2\text{H}$ motifs, which are becoming more common in pharmaceutical projects. Consequently, development of ^{18}F labelling strategies for these groups is an important step forward in the development of a wider scope for PET tracers.

Building on the previous hallex reactions, it was envisaged that the incorporation of ^{18}F fluoride could be achieved by $\text{S}_{\text{N}}2$ on a α,α -fluorobromoester precursor, followed

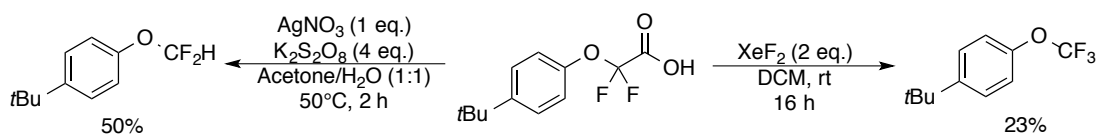
^{xiii} T. Khotavivattana, DPhil Thesis (in preparation)

by hydrolysis to the acid and finally decarboxylative functionalization. Whilst these two routes would be the focus of this investigation, further functionalization reactions can be envisioned, including reduction to the alcohol, amidation or formation of heterocycles such as benzimidazole. (Scheme 5.13). By using a hallex reaction to introduce the [^{18}F]fluoride, it was hoped that the low SA difficulties found with [^{18}F]trifluoromethylation could be addressed.



Scheme 5.13: Theoretical strategy toward [^{18}F]labelled aryl- OCF_3 and OCF_2H , as well as other functionalities.

Initial studies, by T. Khotavivattana, under fluorine-19 conditions were able to show the decarboxylation and decarboxyfluorination working in 50% and 23% yields, respectively. Despite these optimised conditions only giving poor to moderate yields of the desired products, these results were sufficient to justify trials under radiolabelling conditions.



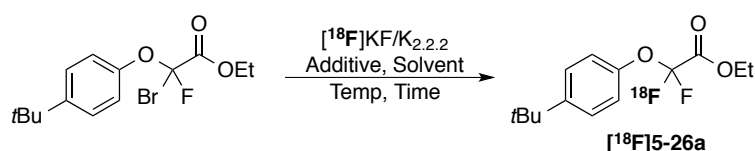
Scheme 5.14: Optimised decarboxylation (A) and decarboxyfluorination (B) by T. Khotavivattana.

5.3.1. Ethyl 2-Bromo-2-fluoro-2-aryloxyacetates

Initial studies in this area focused on the optimisation of the substitution of the bromine with [^{18}F]fluoride. The 4-tert-butyl substituted compound, ethyl bromo(4-tert-

butylphenoxy)fluoroacetate,^{xiv} was chosen as this was the model substrate utilised by T. Khotavivattana. Its use mitigated concerns about the volatility of the final -OCF₃ and -OCF₂H products, as were held for the unsubstituted phenyl substrate.

The preliminary reaction conditions utilised [¹⁸F]KF/K_{2.2.2} in MeCN to form [¹⁸F]5-26a, which immediately returned good RCC, 28 ± 2% (n=2) (Table 5.5, Entry 1), when heated to 80°C after 10 minutes. Extending the reaction time to 20 minutes led to an increase in conversion to 57 ± 10% (n=4) though no further incorporation was observed with further extensions, suggesting the reaction was complete after this time (Entries 3 and 4). Decreasing the temperature to 50°C lead to a slight increase in RCC, giving 64 ± 8% (n=4) (Entry 7).



Entry	Solvent	Concentration (M)	Additive (eq.)	Temp (°C)	Time (min)	[¹⁸ F]5-26a RCC (%)	n
1	MeCN	0.100	-	80	10	28 ± 2	2
2	MeCN	0.100	-	80	20	57 ± 10	4
3	MeCN	0.100	-	80	30	56 ± 16	2
4	MeCN	0.200	-	80	20	53 ± 4	2
5	MeCN	0.033	-	80	20	64 ± 6	2
6	MeCN	0.017	-	80	20	70 ± 6	4
7	MeCN	0.100	-	50	20	64 ± 8	4
8	MeCN	0.033	-	50	20	69 ± 8	2
9	MeCN	0.017	-	50	20	30 ± 3	2
10	<i>t</i> BuOH	0.100	-	80	20	32 ± 10	2
11	MeCN	0.100	AgNO ₃ (1.0)	80	20	<1 ± 0	2
12	MeCN	0.100	NaI (1.0)	80	20	1 ± 0	2

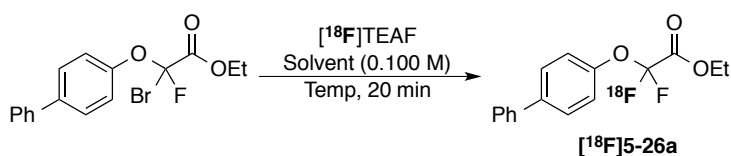
Table 5.5: Preliminary S_N2 optimisation.

^{xiv} Precursors for this project synthesised by T. Khotavivattana (DPhil, thesis in preparation).

The reaction was shown to have a slight concentration dependence, with RCC increasing to $64 \pm 6\%$ ($n=2$) and $70 \pm 6\%$ ($n=2$) when the concentration was decreased to 0.033 M and 0.017 M respectively. When the concentration was increased to 0.200 M, the RCC dropped slightly to $53 \pm 4\%$ ($n=2$) (Entries 4 - 6). The concentration effect was seemingly mirrored when the temperature was decreased to 50°C, with RCC increasing to $69 \pm 8\%$ ($n=2$) at 0.033 M, though unexpectedly decreased to $30 \pm 3\%$ ($n=2$) at 0.017 M (Entries 7 - 9).

Even though these conditions were already giving excellent conversion, routes toward accelerating the S_N2 reaction were investigated. As this procedure was to include post-fluorination steps, it was important to reduce the time taken for each step as far as possible, while maximising RCC.

In view of this, the solvent was changed to *tert*-butanol but this only lead to a decrease in RCC to $32 \pm 10\%$ ($n=2$) after 20 minutes (Entry 10). Further attempts to accelerate the reaction, with the addition of silver nitrate (Entry 11) or sodium iodide (Entry 11), as an attempted Finkelstein catalyst, both lead to only trace incorporation being observed ($RCC \leq 1\%$).

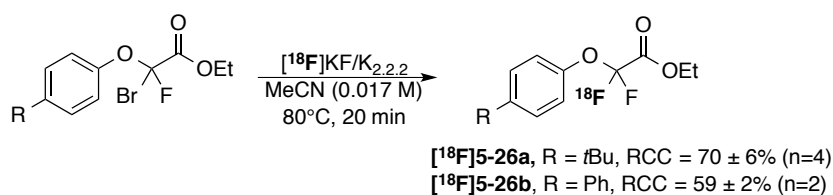


Entry	Solvent	Temp (°C)	[¹⁸ F]5-26a RCC (%)	n
1	MeCN	80	1 ± 0	2
2	<i>t</i> BuOH	80	4 ± 0	2
3	DMF	150	0	2

Table 5.6: Attempted halox reaction with [¹⁸F]TEAF.

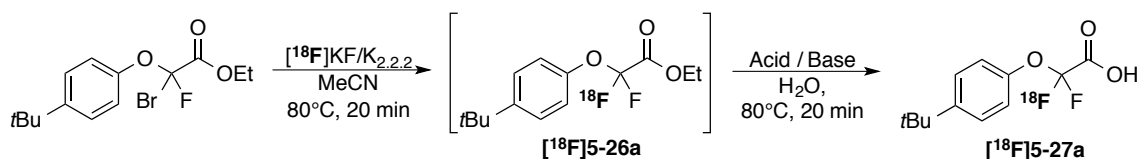
The use of [^{18}F]TEAF was also investigated, under the influence of solvent system on the *para*-phenyl substrate. When MeCN and *tert*-butanol were used, the reaction only gave $1 \pm 0\%$ and $4 \pm 0\%$ RCC, respectively (Table 5.6, Entries 1 and 2). In an attempt to increase the incorporation, the solvent was changed to DMF and the temperature increased to 150°C , though no desired product was observed and an apparent decomposition of the starting material as suggested by loss of UV-HPLC peak (Entry 3).

Therefore the best conditions found, initially, for the fluorination of ethyl 2-bromo-2-(4-(*tert*-butyl)phenoxy)-2-fluoroacetate, were [^{18}F]KF/ $\text{K}_{2.2.2}$ in MeCN at 80°C , with a concentration of 0.017 M. These conditions gave a $\text{RCC} = 70 \pm 6\%$ ($n=4$) and application to the *para*-phenyl substituted compound gave $\text{RCC} = 59 \pm 2\%$ ($n=2$) (Scheme 5.15).



Scheme 5.15: Optimised conditions for radiosynthesis of [^{18}F]5-26a/b.

The next step to be addressed would be the hydrolysis of the acid from the ester. Originally, the intention was to use simple acid or base hydrolysis, following which the reaction would be neutralised before the functionalization step.



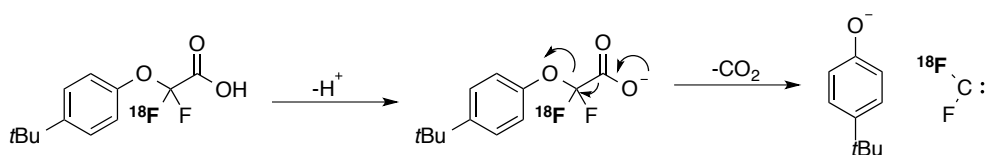
Entry	Acid/Base (eq.)	[^{18}F]5-26a RCC (%) ^a	[^{18}F]5-27a RCC (%)	n
1	1 M HNO_3 (10 eq.)	19 ± 18	22 ± 14	2
2	1 M NaOH (5 eq.)	-	26 ± 0	2

a) Post-hydrolysis.

Table 5.7: Preliminary investigations into a one-pot, two-step hydrolysis.

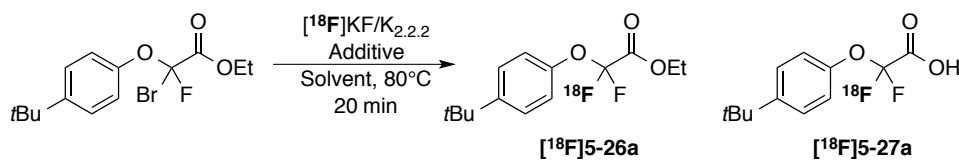
Under acidic hydrolysis conditions, $\text{RCC} = 22 \pm 14\%$ ($n=2$) of the acid was found following the hydrolysis step, along with $19 \pm 18\%$ ($n=2$) of the ester intermediate (Table 5.7, Entry 1). This shows that the hydrolysis was not complete and furthermore that reactions would be unreliable for repetitions due to the high error observed. In the case of the basic hydrolysis (Entry 2), $\text{RCC} = 26 \pm 0\%$ ($n=2$) of the acid was found, with no ester recovered. Assuming that the first step performed as in the initial radiofluorination optimisation ($\text{RCC} \approx 70\%$), for both of these hydrolysis procedures only around one third of the ester formed was converted into the acid, with considerable loss of radiolabelled substrate.

The complete loss of other radiofluorinated product, especially under the basic hydrolysis conditions, is thought to be due to an instability in the carboxylate intermediate, which would then collapse to evolve carbon dioxide, alongside a $[\text{F}^{18}]\text{F}_2\text{C}:$ carbene and the phenolate (Scheme 5.16). Decarboxylative formation of $\text{F}_2\text{C}:$ carbenes is a known mechanism and was applied for the $[\text{F}^{18}]$ trifluoromethylation of aryl iodides discussed as the start of this chapter.⁴⁹



Scheme 5.16: Proposed base-induced decarboxylative decomposition.

In light of these results, the second-step hydrolysis was deemed not to be an appropriate route to the acid, resulting in other routes being considered. One of these was the *in situ* deprotection, during the radiofluorination step. During the drying of the $[\text{F}^{18}]$ fluoride, K_2CO_3 is used as the source of potassium, for the counter-ion to the $[\text{F}^{18}]$ fluoride, and therefore was considered as the starting point, for an *in situ* base hydrolysis.



Entry	Solvent	Conc. (M)	Additive	[¹⁸ F]5-26a RCC (%)	[¹⁸ F]5-27a RCC (%)	n
1	MeCN	0.017	K ₂ CO ₃ (1.4 eq.)	24 ± 20	40 ± 18	2
2	MeCN	0.017	K ₂ CO ₃ (2.8 eq.)	22 ± 6	14 ± 2	2
3	MeCN	0.017	K ₂ CO ₃ (1.4 eq.) K _{2.2.2} (2.4 eq.)	1 ± 1	82 ± 4	4
4	MeCN	0.017	K ₂ CO ₃ (1.4 eq.) 18-crown-6 (2.4 eq.)	34 ± 13	37 ± 18	2
5	MeCN	0.033	K ₂ CO ₃ (1.4 eq.) K _{2.2.2} (2.4 eq.)	-	73 ± 10	2
6	DMF	0.017	K ₂ CO ₃ (1.4 eq.) K _{2.2.2} (2.4 eq.)	-	60 ± 11	2
7 ^a	DMSO	0.017	K ₂ CO ₃ (1.4 eq.) K _{2.2.2} (2.4 eq.)	<1 ± 0	2 ± 1	2
8 ^a	tBuOH	0.017	K ₂ CO ₃ (1.4 eq.) K _{2.2.2} (1.4 eq.)	-	45 ± 10	2
9 ^a	MeCN	0.017	K ₂ CO ₃ (1.4 eq.) K _{2.2.2} (2.4 eq.)	<1 ± 0	80 ± 4	4
10 ^b	MeCN	0.017	K ₂ CO ₃ (1.4 eq.) K _{2.2.2} (2.4 eq.)	1 ± 1	80 ± 8	2
11 ^a	MeCN	0.017	K ₂ CO ₃ (1.4 eq.) K _{2.2.2} (1.4 eq.)	4 ± 3	70 ± 13	2
12 ^a	MeCN	0.017	TEAHCO ₃ (1.4 eq.)	38 ± 8	6 ± 2	2
13 ^a	MeCN	0.017	TBAOH (1.4 eq.)	20 ± 0	1 ± 0	2
14	MeCN	0.017	Cs ₂ CO ₃ (1.4 eq.)	15 ± 1	36 ± 0	2
15	MeCN	0.017	LiOH (1.4 eq.)	9 ± 4	22 ± 1	2
16	MeCN	0.017	CsOH.H ₂ O (1.4 eq.)	31 ± 22	16 ± 6	2
17	MeCN/H ₂ O (59:1)	0.017	Cs ₂ CO ₃ (1.4 eq.)	40 ± 2	7 ± 4	2
18	MeCN/H ₂ O (59:1)	0.017	LiOH (1.4 eq.)	15 ± 2	43 ± 1	2
19	MeCN/H ₂ O (59:1)	0.017	CsOH.H ₂ O (1.4 eq.)	5 ± 3	18 ± 8	2

a) 10 min reaction; b) 5 min reaction.

Table 5.8: Investigations toward *in situ* hydrolysis of [¹⁸F]5-26a.

Gratifyingly the first reaction, where 1.4 equivalents of K_2CO_3 was used as the additive, showed the feasibility of this method, giving $40 \pm 18\%$ ($n=2$) RCC of the desired acid product ($[^{18}\text{F}]\text{5-27a}$) though the conversion was not complete as $24 \pm 20\%$ ($n=2$) of the ester product ($[^{18}\text{F}]\text{5-26a}$) remained (Table 5.8, Entry 1). On doubling the amount of K_2CO_3 to 2.8 equivalents (Entry 2), the amount of ester product remaining did not reduce appreciably and the RCC of the desired acid fell to 14%, possibly due to the mechanism proposed for the instability of the carboxylate.

As increasing the amount of base had been shown to decrease the yield of the significant product, it was hoped that increasing the solubility – by use of cryptands – of the base would increase the rate of reaction. Both 2.2.2-cryptand (Kryptofix-2.2.2/ $\text{K}_{2.2.2}$) (Entry 3) and 18-crown-6 (Entry 4) were used in excess (2.4 equivalents) in the reaction and both lead to increases in the yield of the acid product, with $\text{K}_{2.2.2}$ being noticeably better, giving $82 \pm 4\%$ ($n=4$) RCC with only $1 \pm 1\%$ of the ester remaining.

Despite this system giving an excellent yield of the anticipated acid, the effect of the solvent was tested (Entries 6 - 8), with DMF and *t*BuOH giving clean conversion to the acid, though in reduced yields compared to MeCN, and DMSO performing poorly with very little incorporation of $[^{18}\text{F}]\text{fluoride}$ observed.

Decreasing the reaction time (Entries 9 and 10) did not have a significant effect on the RCC of the acid, with $80 \pm 8\%$ ($n=2$) found even after the time was reduced from 20 minutes to 5 minutes. Decreasing the amount of $\text{K}_{2.2.2}$ to 1.4 equivalents (Entry 11) lead to a decrease in the yield of the acid (RCC = $70 \pm 13\%$ ($n=2$)), as well as a small increase in the ester remaining, and increasing the concentration of the reaction reduced the RCC to $73 \pm 10\%$ ($n=2$) (Entry 5).

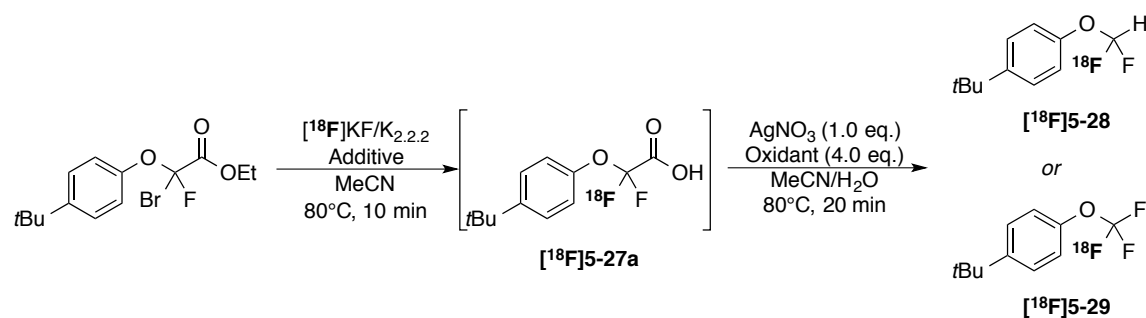
The use of alternative bases was also considered though tetraethylammonium bicarbonate and tetrabutylammonium hydroxide did not give good conversion to the acid (Entries 12 and 13), with moderate overall incorporation into [^{18}F]5-26a. Use of cesium carbonate, lithium hydroxide and cesium hydroxide monohydrate (Entries 14 - 16) were able to give a greater ratio of [^{18}F]5-27a:[^{18}F]5-26a, though could not match the overall incorporation seen with potassium carbonate and $\text{K}_{2.2.2}$. As there was a noticeable lack of solvation of these three bases, 5% H_2O (10 μL) was added to the reaction solvent (Entries 17 - 19), though this was found to be beneficial for the lithium hydroxide example alone.

Consequently it was found, contrary to initial expectations, that the best procedure involved a one-step fluorination/hydrolysis. This then led to the examination of the functionalization of the difluorocarboxylic acid. It was hoped that this could be achieved in a second step without the need for isolation of the acid.

As MeCN had been found to be optimal, it was believed that the use of MeCN/ H_2O as the solvent for the decarboxyfunctionalisation would be acceptable. This would not be in line with the acetone/ H_2O system, which was found to be superior on the ^{19}F substrate, though MeCN/ H_2O has also been shown to be acceptable for silver-mediated decarboxylation of these substrates.^{xv} To achieve this, the second step would be added directly to the reaction vessel itself, as a solution of the oxidant (4.0 equivalents) and AgNO_3 (1.0 equivalent) in H_2O . A series of conditions were screened (Table 5.9), utilising potassium persulfate ($\text{K}_2\text{S}_2\text{O}_8$) and Selectfluor to effect the proto- and fluorodecarboxylation reactions, to give [^{18}F]5-28 and [^{18}F]5-29, respectively. Unfortunately, $\leq 2\%$ RCC ($n=2$) of either of the desired products could be obtained.

^{xv} T. Khotavivattana, DPhil Thesis (in preparation)

What became evident from these reactions was a massive loss of incorporation of [^{18}F]fluoride from organic materials, shown by a reduction in the radioTLC yield.

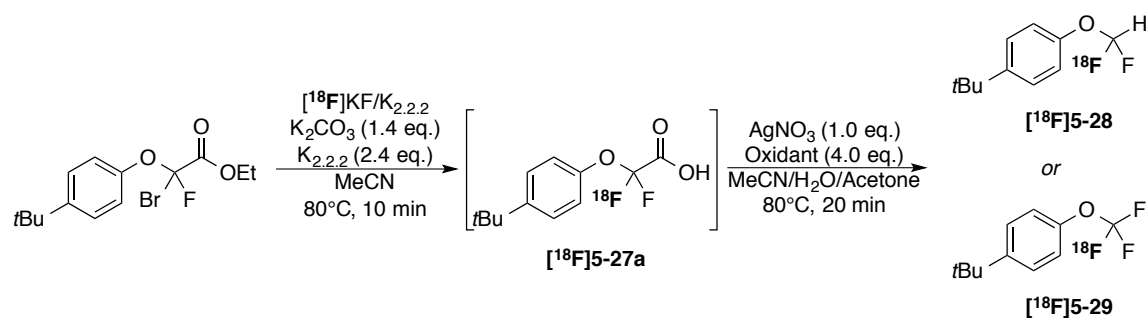


Entry	Additive	Oxidant	[^{18}F]5-28 RCC (%) ^a	[^{18}F]5-29 RCC (%)	n
1	K_2CO_3 (1.4 eq.) $\text{K}_{2.2.2}$ (1.4 eq.)	$\text{K}_2\text{S}_2\text{O}_8$	-	-	2
2	K_2CO_3 (1.4 eq.) $\text{K}_{2.2.2}$ (1.4 eq.)	Selectfluor	-	1 ± 1	2
3	K_2CO_3 (1.4 eq.)	$\text{K}_2\text{S}_2\text{O}_8$	2 ± 0	-	2
4	K_2CO_3 (1.4 eq.)	Selectfluor	-	-	2
5	K_2CO_3 (1.4 eq.) $\text{K}_{2.2.2}$ (2.4 eq.)	$\text{K}_2\text{S}_2\text{O}_8^a$	1 ± 0	-	2
6	K_2CO_3 (1.4 eq.) $\text{K}_{2.2.2}$ (2.4 eq.)	Selectfluor ^a	$<1 \pm 0$	$<1 \pm 0$	2

^a) 4 eq. AgNO_3

Table 5.9: Initial examination of one-pot, two-step decarboxyfunctionalisation.

As the MeCN/ H_2O system had shown trace of the desired product, it was hoped that running the second step in acetone/ H_2O could improve yield of the decarboxylation step.



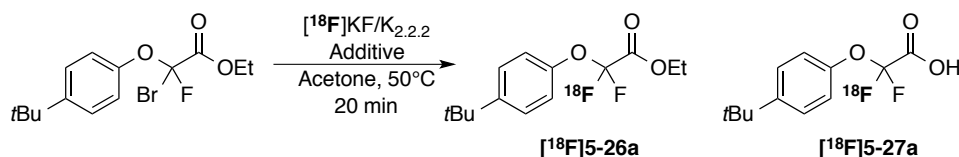
Entry	Oxidant	[¹⁸ F]5-28 RCC (%) ^a	[¹⁸ F]5-29 RCC (%)	n
1	K ₂ S ₂ O ₈	-	-	2
2	Selectfluor	-	-	2
3	Sep-Pak purification then K ₂ S ₂ O ₈	18 ^a	-	1

a) HPLC conversion from purified acid.

Table 5.10: Initial examination of one-pot and two-pot, two-step decarboxyfunctionalisation.

Initially the second step was added as an acetone/H₂O solution to the MeCN in the reaction vessel (Table 5.10, Entries 1 and 2), but there was no sign of either product forming via this route. These reactions showed the same loss of incorporation of ¹⁸F as shown in the initial decarboxylation screen. The product was found in a better yield, after the reaction was subjected to a Sep-Pak purification before the second step was added (Entry 3), which led to the belief that the decomposition pathway could be being compounded by the MeCN remaining in the reaction vessel.

Hence, the use of acetone as the reaction solvent for the entire process was considered. This had not been covered in the initial solvent screen, as it is an unusual solvent for use in [¹⁸F]radiolabelling though it has some favourable qualities such as a high volatility so it can easily be removed if solvent changes are required. It also required the temperature to be dropped to 50°C, which was not too great a concern as this had previously been shown not to significantly reduce RCC for the initial radiofluorination step.



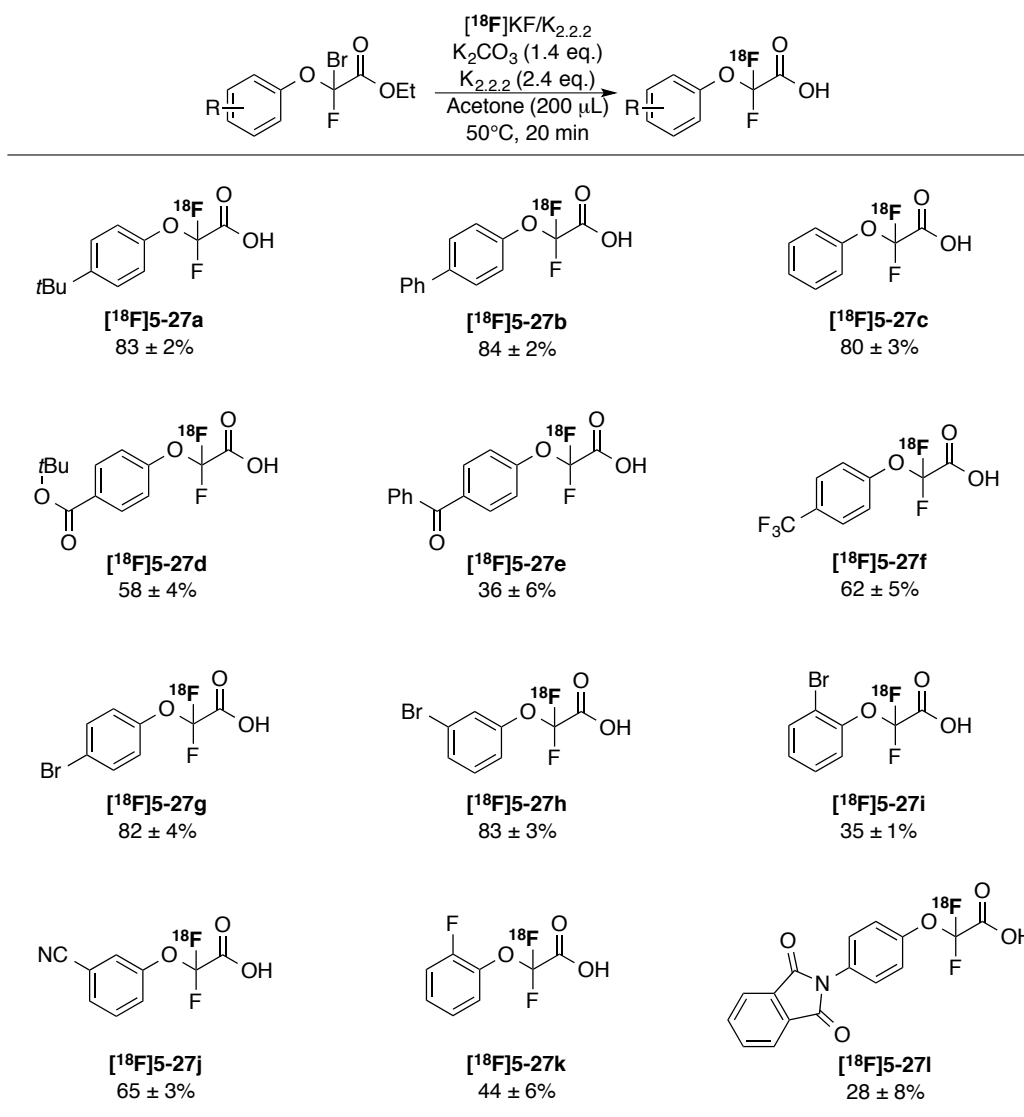
Entry	Concentration (M)	Additive	[¹⁸ F]5-26a RCC (%)	[¹⁸ F]5-27a RCC (%)	n
1	0.017	-	4 ± 4	-	2
2	0.017	K ₂ CO ₃ (1.4 eq.) K _{2.2.2} (2.4 eq.)	-	81 ± 6	2
3	0.033	K ₂ CO ₃ (1.4 eq.) K _{2.2.2} (2.4 eq.)	<1 ± 0	74 ± 0	2
4	0.05	K ₂ CO ₃ (1.4 eq.) K _{2.2.2} (2.4 eq.)	-	83 ± 2	4
5 ^a	0.017	K ₂ CO ₃ (1.4 eq.) K _{2.2.2} (2.4 eq.)	2 ± 1	79 ± 5	6
6 ^a	0.017	K ₂ CO ₃ (1.4 eq.) K _{2.2.2} (1.4 eq.)	4 ± 2	72 ± 1	2
7 ^a	0.017	K ₂ CO ₃ (1.4 eq.)	20 ± 10	6 ± 1	2

a) 10 min reaction.

Table 5.11: Study of the effect of solvent exchange to acetone.

The first reaction examined the formation of the difluorinated ester alone, with no base additive, and gave only 4 ± 4% RCC (n=2) (Table 5.11, Entry 1). On addition of K₂CO₃/K_{2.2.2} (Entries 2 - 7) the incorporation increased dramatically to parallel that seen with MeCN. Use of 1.4 equivalents potassium carbonate and 2.4 equivalents K_{2.2.2} gave RCC = 81 ± 6% (n=2) under the same concentration as for MeCN (0.017 M). There was no significant concentration dependence observed (Entries 2 - 4), with the best RCC observed when the concentration was increased from 0.017 M to 0.05 M (83 ± 2% (n=4)) (Entry 5), though this variation is all within experimental error. There was not a significant reduction in conversion when the reaction time was reduced to 10 minutes (RCC = 75 ± 7% (n=4)) (Entry 5). Reduction of K_{2.2.2} to 1.4 equivalents gave a slightly lower RCC (72 ± 1% (n=2)) (Entry 6), though complete removal of the K_{2.2.2} (Entry 7) did lead to a much lower overall yield (6 ± 1% (n=2)), with the major product being the ester (20 ± 10% (n=2)).

These optimised conditions, run at 0.05 M, were used to show the expansion of the substrate scope of this reaction.

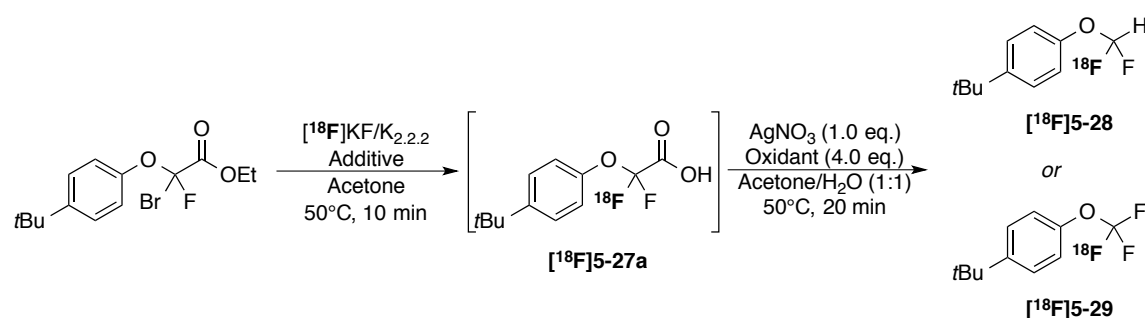


Scheme 5.17: Substrate scope for radiofluorination of ethyl 2-bromo-2-fluoro-2-aryloxyacetates. RCC, $n=4$ for all substrates.

Substrates that are electron neutral, or with weakly electron donating groups, such as the phenyl, *para*-*tert*-butyl and *para*-phenyl substrates all reacted well to give excellent RCCs. The *ortho*-bromo substrate did not give as high a yield as the *meta*- and *para*-analogues, which is theorised to be due to the large steric bulk of the bromine hindering the nucleophilic attack of the [¹⁸F]fluoride. *Para* substituted electron withdrawing groups ([¹⁸F]5-27d - f) did lead to a reduced yield compared to the majority

of other substrates, as did *ortho* substituents ($[^{18}\text{F}]5\text{-27i/k}$), however the RCCs obtained are still very good in radiochemical terms. Presently, the substrate table does not show any electron-rich aromatic rings, which is due to difficulties arising from the radical bromination in the presence of these motifs, but that is required for the synthesis of the precursors.

Despite changing the solvent to acetone for the initial step, the problematic proto- and fluorodecarboxylation reactions remained futile (Table 5.12). The second step was added as a solution of the oxidant and silver nitrate in H_2O to give 1:1 acetone/ H_2O , though only trace yields were ever found, even when the $\text{K}_{2.2.2}$ loading was dropped to 1.4 equivalents and removed entirely. These negative results were again accompanied by a low radioTLC yields, suggesting a loss in ^{18}F incorporation during the second step.



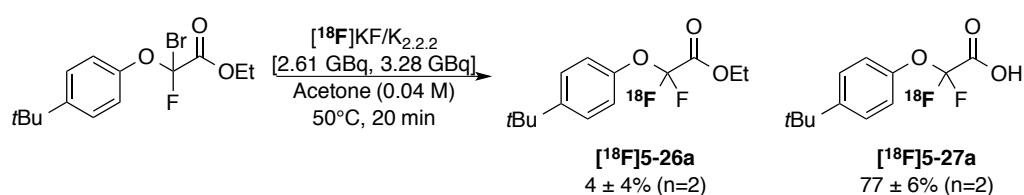
Entry	Additive	Oxidant	$[^{18}\text{F}]5\text{-28}$ RCC (%)	$[^{18}\text{F}]5\text{-29}$ RCC (%)	n
1 ^a	K_2CO_3 (1.4 eq.) $\text{K}_{2.2.2}$ (2.4 eq.)	$\text{K}_2\text{S}_2\text{O}_8$	0	-	2
2 ^a	K_2CO_3 (1.4 eq.) $\text{K}_{2.2.2}$ (2.4 eq.)	Selectfluor	0	$<1 \pm 0$	2
3	K_2CO_3 (1.4 eq.) $\text{K}_{2.2.2}$ (1.4 eq.)	$\text{K}_2\text{S}_2\text{O}_8$	0	-	2
4	K_2CO_3 (1.4 eq.) $\text{K}_{2.2.2}$ (1.4 eq.)	Selectfluor	1 ± 0	2 ± 0	2
5	K_2CO_3 (1.4 eq.)	$\text{K}_2\text{S}_2\text{O}_8$	0	-	2
6	K_2CO_3 (1.4 eq.)	Selectfluor	0	0	2
7 ^b	K_2CO_3 (1.4 eq.) $\text{K}_{2.2.2}$ (2.4 eq.)	$\text{K}_2\text{S}_2\text{O}_8$	6	-	1

a) First step run for 20 minutes; b) Sep-Pak Silica cartridge purification.

Table 5.12: Study into the effect of acetone on one-pot and two-pot, two-step decarboxyfluorinations.

Interestingly, when a Sep-Pak Silica cartridge purification of the acid was carried out before the second step, an increase in the conversion to [^{18}F]5-28 could be observed (RCC = 6% (n=1)). This result suggested that the remaining potassium carbonate could be detrimental to this reaction.

Whilst all these reactions were run under 'research conditions', where a single azeotropic drying procedure was run to produce [^{18}F]KF/K_{2.2.2}, which was then dispensed as 20 - 30 MBq aliquots to be used in the reaction, one method for reducing the potassium carbonate would be to run the reactions on a large scale basis. Under this protocol, the initial radiofluorination reaction would be run on a higher level of activity, which would then be dispensed in small aliquots of 20 - 30 MBq for the decarboxylation. This would mean that instead of having the entire potassium carbonate loading in each decarboxylation reaction, a single loading of potassium carbonate would be split into many decarboxylation reactions. Scaling up the activity (run at 2.61 GBq and 3.28 GBq) showed similar incorporation into [^{18}F]5-27a (RCC = 77 $\pm$ 6% (n=2)) to the research mode results, though some of [^{18}F]5-26a was found (4 $\pm$ 4%(n=2)).

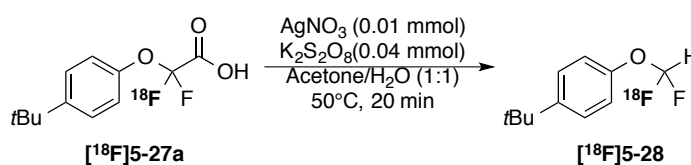


Scheme 5.18: Large scale synthesis of [^{18}F]5-27a.

For these reactions the solvent volume was increased from 200 μL to 250 μL , changing the concentration from 0.05 M to 0.04 M, though previous results have shown that there is no strong concentration effect evident under these conditions. Furthermore, it must be noted that no additional potassium carbonate and K_{2.2.2} was added to this reaction other than that which was used in the azeotropic drying procedure, which

equates to 1.4 equivalents potassium carbonate and 2.4 equivalent $K_{2.2.2}$, as was added to the smaller scale reactions.

On completion of the radiofluorination step, the reaction was diluted with acetone and dispensed into reaction vials for investigations into the protodecarboxylation.



Entry	Concentration (M)	$[^{18}\text{F}]\text{5-27a}$ Recovered (%)	$[^{18}\text{F}]\text{5-28}$ RCC (%)	n
1	0.025	5 ± 3	10 ± 6	3
2	0.05	7 ± 0	7 ± 7	2

Table 5.13: Decarboxyprotonation of $[^{18}\text{F}]\text{5-27a}$ produced by large scale synthesis. Recovered $[^{18}\text{F}]\text{5-27a}$ is given as radioTLC corrected by radioHPLC.

Under this large scale protocol, the final incorporation of ^{18}F into $[^{18}\text{F}]\text{5-28}$ could be increased to $10 \pm 6\%$ ($n=3$), though only $5 \pm 3\%$ ($n=3$) of $[^{18}\text{F}]\text{5-27a}$ could be recovered. As it is known that the majority of the $[^{18}\text{F}]\text{fluoride}$ is incorporated into $[^{18}\text{F}]\text{5-27a}$ in the first step, this exemplifies the massive losses in incorporation of ^{18}F from organic material following the decarboxyfluorination reaction as inorganic $[^{18}\text{F}]\text{fluoride}$ (Figure 5.3).

The mechanism by which the ^{18}F is lost is unknown, though running the decarboxyfluorination reaction while eliminating either the silver nitrate or the potassium persulfate did not show the same losses, with the majority of $[^{18}\text{F}]\text{5-27a}$ starting material being recovered.

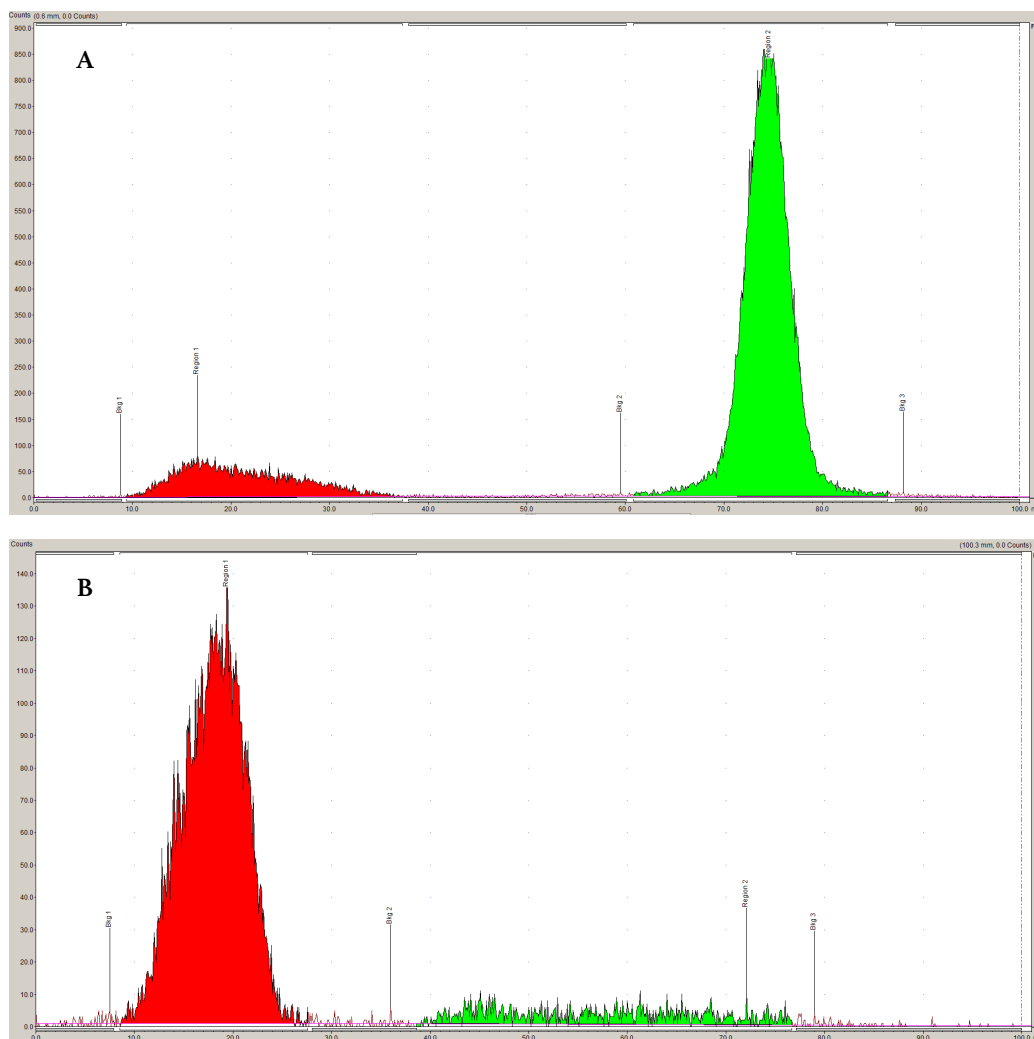


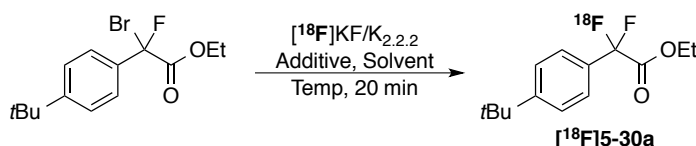
Figure 5.3: RadioTLC of before (A) and after (B) protodecarboxylation reaction, showing losses in incorporated ^{18}F fluoride. Green region represents all activity incorporated into organics (^{18}F 5-26a and ^{18}F 5-27a in A, ^{18}F 5-26a, ^{18}F 5-27a and ^{18}F 5-28 in B); A - 84%, B - 10%. RadioTLC run in MeOH.

Despite very promising results from the halogen exchange to form the *geminal* difluorinated motif, results toward post-fluorination reactions have so far remained poor. The reason behind the extensive losses of incorporated ^{18}F fluoride has been discussed, though not proven. Further investigations into the purification of the ^{18}F 5-27a prior to the decarboxylation and the effect that this will have on the post-fluorination reactions are being pursued.

5.3.2. Ethyl 2-Bromo-2-fluoro-2-arylacetaes (ArCFBrCO₂Et)

In a similar manner to the ArOCF₃/ArOCF₂H work, the concept of decarboxyfunctionalization of aryl-CF₂CO₂H has been explored. This is due to it having the potential to lead to a synthetic route to high specific activity di- and trifluoromethyl groups, as well prospective decarboxylative C-C bond formation.

However, this project has not progressed in line with the ArOCF₃/ArOCF₂H work as there have been issues arising from the initial fluorination step, which lead to an unidentified impurity and noticeably depreciating yields depending on the age and storage of the starting ester, complicating achieving definitive conclusions.^{xvi}



Entry	Solvent	Concentration (M)	Additive (eq.)	Temp (°C)	Time (min)	[¹⁸ F]5-30a RCC (%)	n
1	DMF (300 μL)	0.100	-	150	10	23 ± 1	2
2	DMSO (300 μL)	0.100	-	150	20	2 ± 2	2
3	<i>t</i> BuOH (300 μL)	0.100	-	80	30	6 ± 2	4
4	MeCN (300 μL)	0.100	-	80	20	22 ± 8	8
5	MeCN (300 μL)	0.033	-	80	20	60 ± 8	2
6	MeCN (600 μL)	0.017	-	80	20	46 ± 8	12 ^a
7	MeCN (600 μL)	0.050	-	50	20	60 ± 7	2
8	MeCN (300 μL)	0.100	-	50	20	22 ± 7	4
9	MeCN (600 μL)	0.017	-	50	20	38 ± 13	6
10	Acetone (600 μL)	0.017	-	50	20	<1 ± 0	2
11	MeCN (300 μL)	0.100	AgOTf (1.0)	80	20	0 ± 0	2

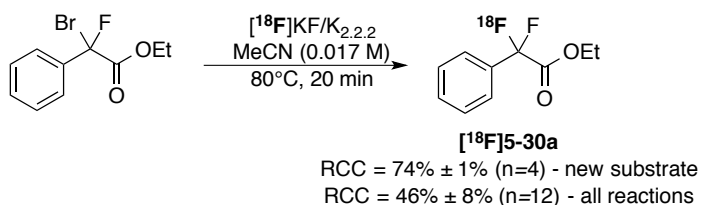
a) See Scheme 5.19.

Table 5.14: Introductory S_N2 optimisation.

^{xvi} Ethyl bromo(4-*tert*-butylphenyl)fluoroacetate and related precursors synthesised by A. Bajjon (MChem, 2014).

The primary reactions were run at high temperature (Table 5.14, Entries 1 and 2), though only relatively low levels of incorporation were observed, with DMF ($\text{RCC} = 23 \pm 1\%$ ($n=2$)) performing better than DMSO ($\text{RCC} = 2 \pm 2\%$ ($n=2$)). The low incorporation levels observed is believed to be due to decomposition of the starting material, rather than due to the reaction performing poorly in these solvents, suggested by UV-HPLC analysis. Reducing the temperature to 80°C , and changing the solvent to *t*BuOH did not improve the RCC (Entry 3), however when the reaction was run in MeCN, the RCC increased to $43 \pm 10\%$ ($n=4$). It must be noted that it was at this point that we first observed the variability in the RCC, which decreased with increasing age of the starting material. This result was found when newly synthesised substrate was used (purified within 24 hours of reaction), though four subsequent runs were carried out on material that had not been purified within 24 hours, which dropped the mean RCC value to 22 ± 8 ($n=8$).

All of these reactions were found to have a radiochemical impurity, which has not been identified, which increases in share of total incorporation with age of substrate. It was found that decreasing the concentration of the reaction (Entries 5 and 6) decreased the amount of impurity formed, and further increased the RCC of the desired ester product. Scheme 5.19 shows the correlation between using a new batch of substrate, in comparison to the collective RCC when all runs are combined.



Scheme 5.19: Effect of substrate age on radiofluorination incorporation.

Reducing the temperature further did not increase the yield of the reaction (Entries 7 - 9), and the use of acetone shut down the reaction almost entirely (Entry 10). As with the

ArOCF₂CO₂H work, the use of a silver salt to accelerate the reaction did not proceed as hoped and stopped the reaction completely (Entry 11).

The use of [¹⁸F]TEAF was also investigated though this [¹⁸F]fluoride source was not followed up as majority of the activity was incorporated into unidentified side products. The radiochemical purity of the desired product of the reaction in MeCN was 31 ± 4% (n=2), which is appreciably less than that found with [¹⁸F]KF/K_{2.2.2} under identical reaction conditions (RCP = 70 ± 15% (n=4)). RCC to [¹⁸F]5-30a with [¹⁸F]TEAF was 21 ± 3% (n=4), which is half of that found with [¹⁸F]KF/K_{2.2.2}.

As the impurity being formed had not been identified, a screen of ester groups was performed in order to ascertain whether it was exclusive to the ethyl ester functionality, or pertained a separate aspect of the reaction. The methyl ([¹⁸F]5-30b) (Table 5.15, Entry 2), *tert*-butyl ([¹⁸F]5-30c) (Entry 3) and allyl ([¹⁸F]5-30d) (Entry 4) ester functionalities were all tested, with all giving the same impurity, to differing degrees. Noticeably, the substrate bearing an allyl group performed better than the corresponding ethyl ester, both in terms of the yield of the desired product and in limiting the formation of the impurity.

[¹⁸F]5-30a - d

Entry	R	RCC (%)	Impurity (%)	n
1	Et ([¹⁸ F]5-30a)	55 ± 3	6 ± 1	2
2	Me ([¹⁸ F]5-30b)	32 ± 8	11 ± 0	2
3	<i>t</i> Bu ([¹⁸ F]5-30c)	10 ± 3	23 ± 2	2
4	CH=CH ₂ ([¹⁸ F]5-30d)	63 ± 8	4 ± 0	2

Table 5.15: Study on the effect of ester substitution on the incorporation and impurity formation.

As the fluorination/hydrolysis steps had the ability to be combined in the ArOCF₂CO₂H work, a similar reaction was considered for this system. Regrettably, this arrangement was not as easily implemented; with reduced yields of the ester and only a small conversion to the acid found under the optimised conditions from ArOCF₂CO₂H.

5.3.3. Summary

The nucleophilic [¹⁸F]fluorination of compounds was generally constrained to simple S_N2 reactions to give monofluoroalkyl motifs, though this reaction has been widely and very successfully applied. Over the course of this project, it has been demonstrated that this reaction can be effectively applied to the fluorination of *geminal* difluorinated motifs on appropriately activated structures bearing α-ester functionality. In this manner, arylOCF₂CO₂Et, arylOCF₂CO₂H and arylCF₂CO₂Et motifs have all been [¹⁸F]labelled with good to excellent radiochemical conversion.

This has opened up avenues of investigation toward the post-fluorination decarboxylative functionalization, and to product diversification – a very useful tool in drug discovery programs. Whilst initial attempts toward this have been promising, the yields obtained to date have unfortunately been poor.

5.4. Silver(I) Triflate Mediated Radiofluorination

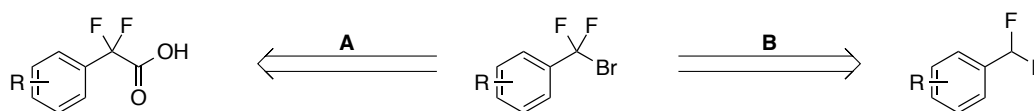
Inspired by the successes shown by revisiting the hallex reaction on activated systems, the Gouverneur group also addressed its utility for the radiofluorination of aryl-X systems, where X = -CF₃, -CF₂H,²⁹⁹ -OCF₃, -OCF₂H and -SCF₃³⁰⁰ systems. It was found that transition metal based activation of the -CF₂Br or -CFHCl precursors, enabled the radiofluorination of these motifs under mild conditions, which allows access to

clinically important motifs, some of which were not previously within reach of [^{18}F]labelling.

This project was completed in collaboration with L. Pfeifer (substrate synthesis), T. Khotavivattana, S. Verhoog (substrate synthesis and radiochemistry) and Dr M. Tredwell (radiochemistry).

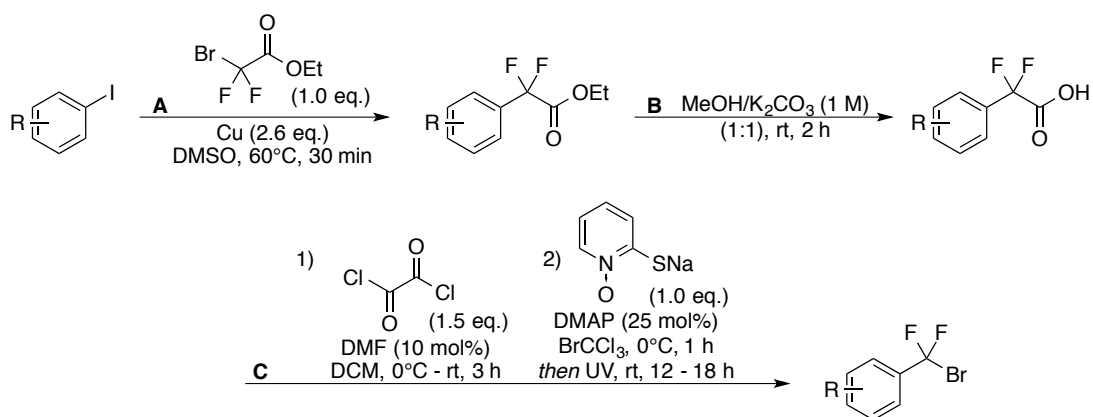
5.4.1. Synthesis of Aryl- CF_2Br Precursors

The synthesis of the aryl- CF_2Br precursors was achieved by means of two routes; decarboxylative radical bromination (Scheme 5.20, **A**) and radical bromination of difluoromethyl precursors (**B**). As both of these follow radical pathways, there are typically several side products arising from bromination on the aromatic ring itself.



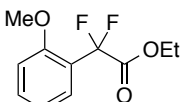
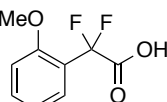
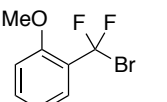
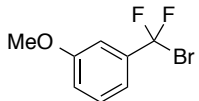
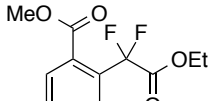
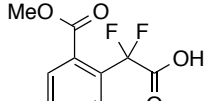
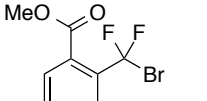
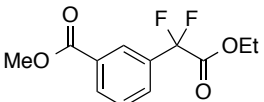
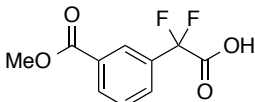
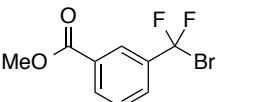
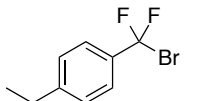
Scheme 5.20: Retrosynthesis of aryl- CF_2Br precursors.

The decarboxylative radical bromination pathway (Scheme 5.21, **C**) initially forms an acyl chloride from the 2,2-difluoro-2-arylacetic acid precursor with oxalyl chloride, which is then treated with 2-mercaptopyridine *N*-oxide sodium salt in bromotrichloromethane under UV irradiation to induce the radical bromination. The 2,2-difluoro-2-arylacetic acid precursor can itself be synthesised from the parent aryl iodide by copper-coupling with ethyl bromodifluoroacetate (**A**) and consequent base hydrolysis of the ester (**B**).



Scheme 5.21: General mechanism for decarboxylative bromination methodology.

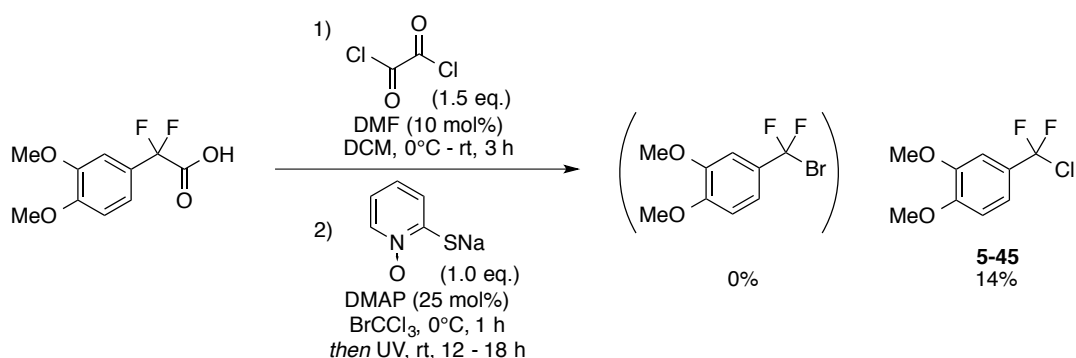
Five substrates were successfully brominated in this manner; 1-[bromo(difluoro)methyl]-2-methoxybenzene (**5-33**), 1-[bromo(difluoro)methyl]-3-methoxybenzene (**5-34**), methyl 2-[bromo(difluoro)methyl]benzoate (**5-38**), methyl 3-[bromo(difluoro)methyl]benzoate (**5-43**) and 1-(4-[bromo(difluoro)methyl]phenyl)ethanone (**5-44**), with isolated yields of 43 - 60%. Purification of these compounds was difficult due to co-elution of by-products in close proximity with the desired compounds. These by-products are believed to be due to bromination of the aromatic ring under the final decarboxylative radical bromination conditions. Due to this, it must be acknowledged that the 2-methoxy (**5-33**) and 4-acetophenone (**5-44**) products could only be isolated in >91% and >97% purity, respectively.

Entry	Step A (%)	Step B (%)	Step C (%)
1	 5-31, 96%	 5-32, 66%	 5-33, 60%
2	-	- ^a	 5-34, 55%
3	 5-36, 41% ^b	 5-37, 82%	 5-38, 56%
4	 5-41, 46% ^c	 5-42, 71%	 5-43, 44%
5	-	- ^a	 5-44, 43%

a) 2,2-Difluoro-2-arylacetic acid precursor synthesised by M O'Duill (DPhil, 2015);¹¹³ b) Methyl 2-iodobenzoate precursor (5-35) synthesised from 2-iodobenzoic acid in 70%; c) Methyl 3-iodobenzoate precursor (5-40) synthesised from ethyl 3-iodobenzoate via 3-iodobenzoic acid (5-39) in 86% over 2 steps.

Table 5.16: Yields for copper coupling (Scheme 5.21, A), ester hydrolysis (B) and decarboxylative bromination reactions (C).

Whilst this decarboxylative radical bromination pathway did lead to isolation of these five precursors for the radiofluorination, there were several other structures that were not amenable to this procedure. Application to 3-cyano or 2,4,6-trimethyl substrates lead to multiple side products due to bromination of the arene substituents. Interestingly, when these conditions were applied to a 3,4-dimethoxy precursor, instead of forming the ArCF₂Br substrate, as was desired, it was found to form the ArCF₂Cl (5-45) analogue (Scheme 5.22).



Scheme 5.22: Attempted decarboxylative radical bromination of (3,4-dimethoxyphenyl)(difluoro)acetic acid.^{xvii}

Initially it was presumed that the major product, as shown by crude ^{19}F NMR (^{19}F NMR: $\delta = -46.7$ ppm), was the desired brominated product, however after isolation HRMS analysis proved that the 5-45 had instead formed (Figure 5.4). As with the previous compounds, co-elution with other by-products complicated purification, resulting in an isolated yield of only 14% of 5-45.

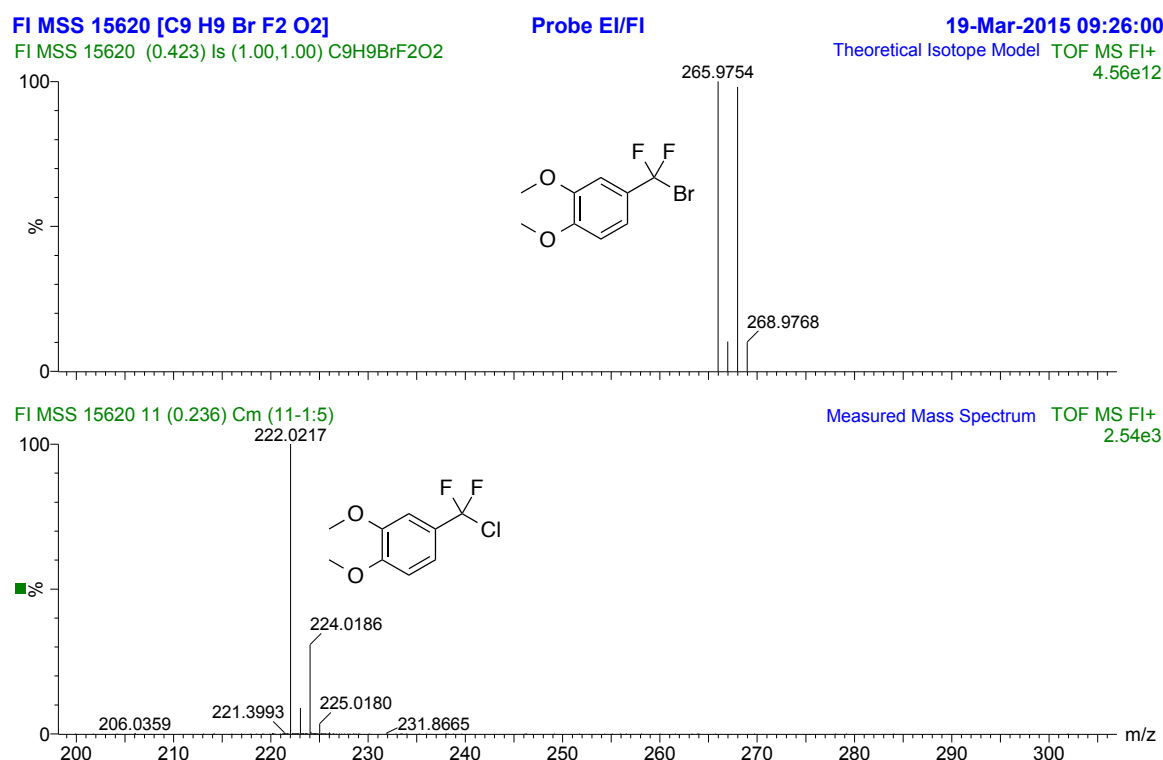
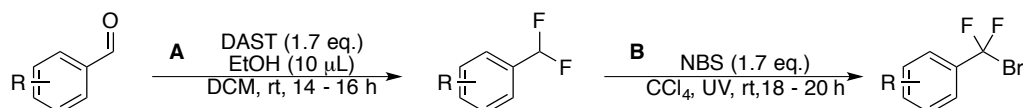


Figure 5.4: HRMS analysis of 4-[chloro(difluoro)methyl]-1,2-dimethoxybenzene (5-45); Calculated mass ($\text{C}_9\text{H}_9^{35}\text{ClF}_2\text{O}_2$) = 222.0259.

^{xvii} (3,4-Dimethoxyphenyl)(difluoro)acetic acid precursor synthesised by M. O'Duill (DPhil, 2015).

The alternative route employed during this project involved the radical bromination of difluoromethylarenes by NBS in tetrachloromethane under UV irradiation (Scheme 5.23, B). The difluoromethylarene precursors could simply be made by electrophilic *geminal* difluorination of the aryl aldehyde with DAST (A).



Scheme 5.23: General mechanism and yields for radical bromination route.

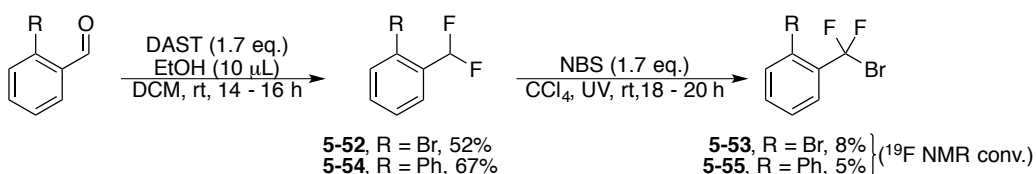
In this manner, three further substrates could be prepared for the radiofluorination studies; 1-[bromo(difluoro)methyl]naphthalene (5-47), 1-bromo-3-[bromo(difluoro)methyl]benzene (5-49) and 1-[bromo(difluoro)methyl]-3-*tert*-butylbenzene (5-51) in 9%, 23% and 24% yields over the two steps, respectively (Table 5.17).

Entry	Step A (%)	Step B (%)
1	 5-46, 59%	 5-47, 16%
2	 5-48, 58%	 5-49, 39%
3	 5-50, 54%	 5-51, 45%

Table 5.17: Yields for geminal difluorination (Scheme 5.23, A) and radical bromination (B).

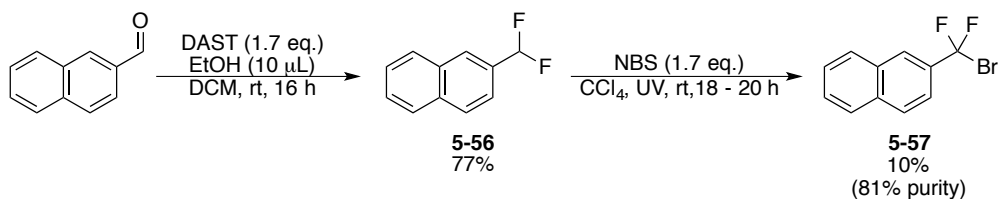
As with the decarboxylative radical bromination procedure, this methodology was attempted on other substrates with limited success, yielding no substrates of sufficient quality to take forward to the radiolabelling study.

When substituents were placed *ortho* to the difluoromethyl functionality, the radical bromination reaction gave very poor conversion to the difluorobromomethyl substrate. This can be illustrated by two examples (Scheme 5.24); 1-bromo-2-(difluoromethyl)benzene (5-52) and 2-(difluoromethyl)biphenyl (5-54), on being subjected to the radical bromination conditions, only gave 8% and 5% conversion compared to the remaining starting material. From these low conversions, isolating 1-bromo-2-[bromo(difluoro)methyl]benzene (5-53) (^{19}F NMR: $\delta = -45.4$ ppm) and 2-[bromo(difluoro)methyl]biphenyl (5-55) (^{19}F NMR: $\delta = -38.6$ ppm) was unrealizable.



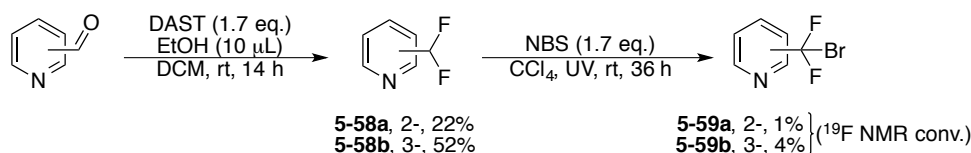
Scheme 5.24: Low conversion for radical bromination on *ortho*-substituted compounds.

This methodology also leads to side products that co-elute with the desired material. During attempts to synthesise 2-[bromo(difluoro)methyl]naphthalene (5-57), 2-(difluoromethyl)naphthalene (5-56) was subjected to the radical bromination conditions, and on purification by flash column chromatography (pentane), could be obtained in a 10% yield, though with only 81% purity. 5-57 (^{19}F NMR: $\delta = -43.5$ ppm) was contaminated with two further products, one arising at ^{19}F NMR: $\delta = -44.2$ ppm (11%) and the other at -44.1 ppm (8%). Due to the nature of these ^{19}F NMR peaks arising so close to that of the desired product, it is assumed that the $-\text{CF}_2\text{Br}$ motif has been formed though during the reaction bromination on the aromatic rings also occurred.



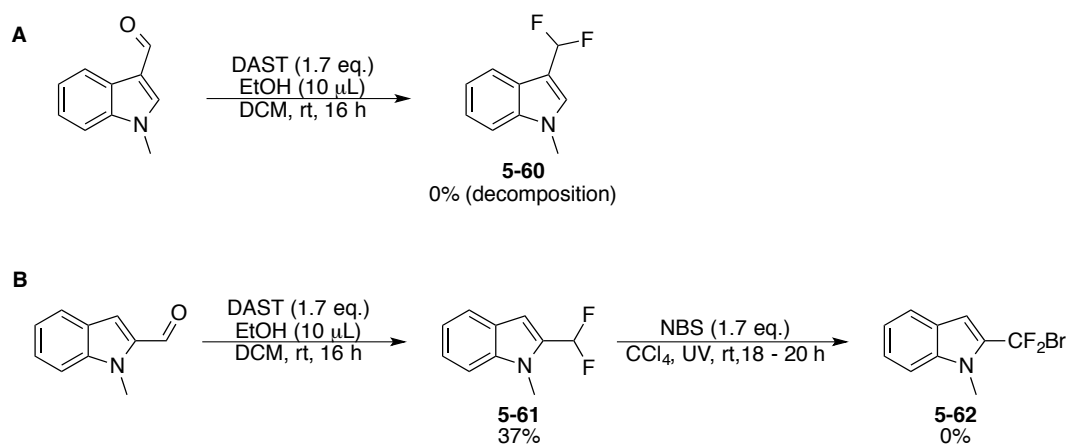
Scheme 5.25: Attempted isolation of 2-[bromo(difluoro)methyl]naphthalene.

In order to expand the scope, the synthesis of heteroarene-based substrates was also investigated. Pyridine-2-carboxaldehyde and pyridine-3-carboxaldehyde were both *geminally* difluorinated with DAST in 22% and 52% respectively, before being subjected to the radical bromination conditions. On completion of the reaction, crude ^{19}F NMR showed poor conversion for both substrates with 2-[bromo(difluoro)methyl]pyridine (**5-59a**) being found in 1% (^{19}F NMR: $\delta = -50.9$ ppm) and 3-[bromo(difluoro)methyl]pyridine (**5-59b**) in 4% (^{19}F NMR: $\delta = -44.8$ ppm), compared to their respective starting materials, even when run for extended reaction times (36 hours).



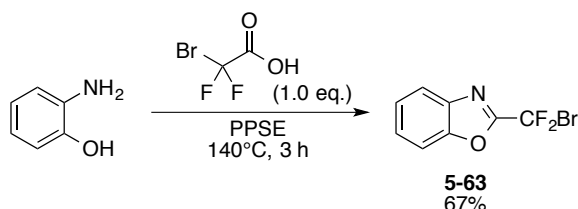
Scheme 5.26: Attempted synthesis of 2- and 3-[bromo(difluoro)methyl]pyridine.

Methyl-protected indole structures were also investigated (Scheme 5.27). Attempts toward the synthesis of 3-(difluoromethyl)-1-methyl-1H-indole (**5-60**) were unsuccessful as the product (^{19}F NMR: $\delta = -106.0$ ppm) decomposed on loading onto silica for flash column chromatography (Scheme 5.27, A). 2-(Difluoromethyl)-1-methyl-1H-indole (**5-61**) was found to be more stable and could be isolated in a 37% yield, however the radical bromination of this substrate gave no conversion to **5-62** (B).



Scheme 5.27: Attempted synthesis of *N*-methyl indoles via radical bromination.

As the radical bromination reactions were not amenable to substrates bearing heteroarenes, a different approach was required. Gratifyingly, use of trimethylsilyl polyphosphate (PPSE) as a dehydrating reagent enabled the synthesis of 2-[bromo(difluoro)methyl]-1,3-benzoxazole (**5-63**), isolated in a 67%.



Scheme 5.28: Synthesis of 2-[bromo(difluoro)methyl]-1,3-benzoxazole.

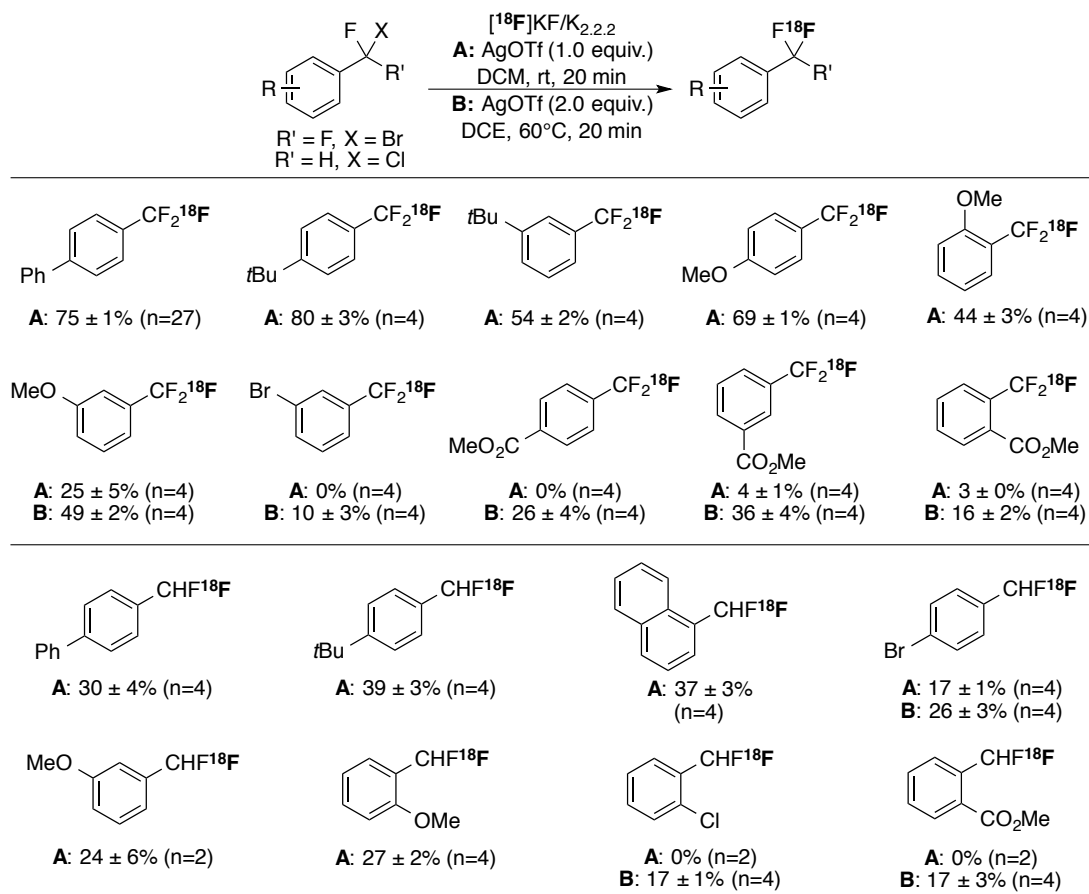
5.4.2. Radiofluorination of Aryl-CF₃, -CF₂H, -OCF₃, -OCF₂H and -SCF₃

Dr M. Tredwell, T. Khotavivattana and S. Verhoog carried out the radiofluorination phase of this project.

As discussed, the presence of α -fluorine severely inhibits the substitution reaction on aryl-CF₂Br, and analogous motifs. Significant thermal activation is required and, even under such forcing conditions, the reaction only performs poorly. Incorporation can be achieved without any additives,³⁰¹ though this requires considerable thermal activation; up to 135°C in DMSO with [¹⁸F]TBAF.⁴⁸ When considering an aryl-CF₂Br precursor, no incorporation of [¹⁸F]fluoride is observed at room temperature.

The previous work in this chapter had, however, suggested that with appropriate activation, the halox reaction on these motifs was possible and so transition metal-based activation was explored. The applicability of silver(I) salts in radiofluorination is well known, with [¹⁸F]fluorination of arylstannanes¹⁰⁸ and arylboronic acids¹¹² as well as the [¹⁸F]decarboxyfluorination of 2,2-difluoro-2-arylacetic acids¹¹³ having been presented by the Gouverneur group alone. These reactions reflect the diverse chemistry associated with silver(I);³⁰²⁻³⁰⁴ acting as a Lewis acid in the first instance,

together with being a strong I^- oxidant for the decarboxyfluorination reaction. Silver(I) also is known to have strong halide affinity, and it was hypothesised that this could facilitate the halex reaction under radiofluorination conditions.



Scheme 5.29: [^{18}F]Labelling of tri- and difluoromethylarenes by silver triflate mediated halex.

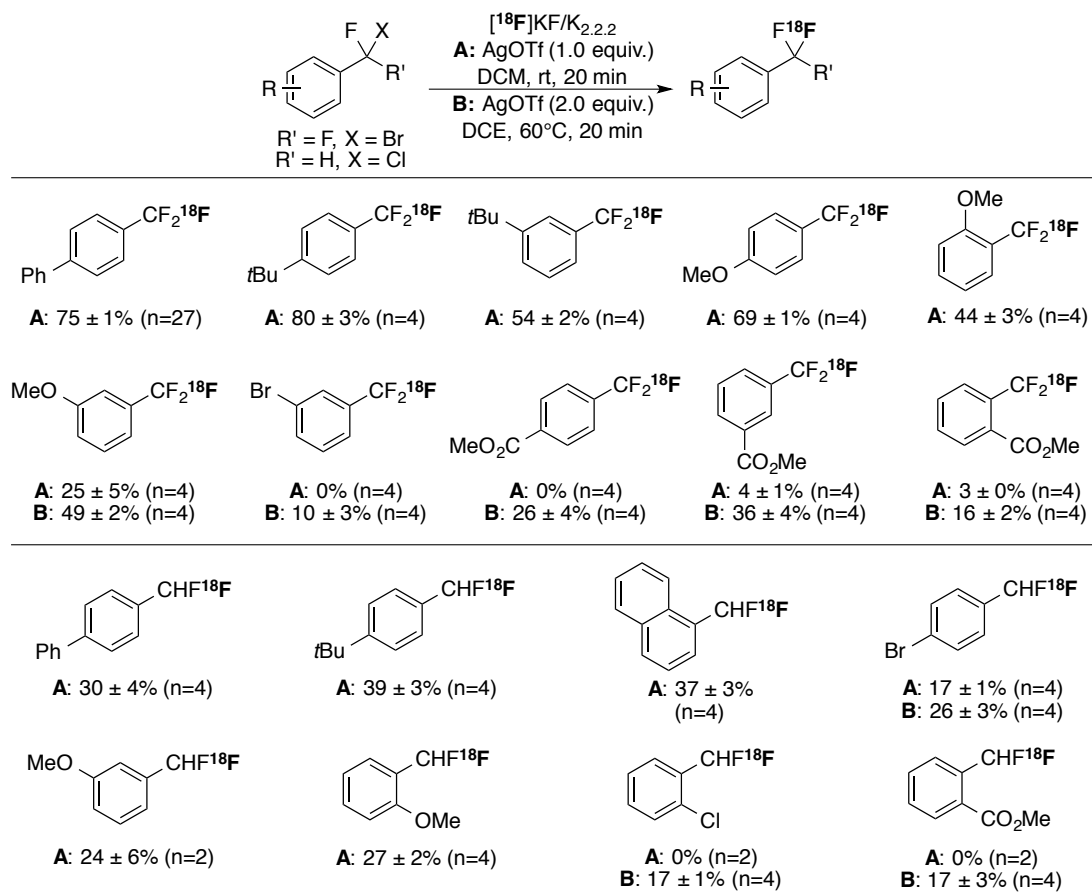
The treatment of the aryl- CF_2Br , - CHFCl ,^{xviii} - OCF_2Br , - OCHFCl ^{xix} and - SCF_2Br ^{xx} precursors with silver triflate enabled the incorporation of [^{18}F]fluoride under much milder conditions than previously possible. Two sets of conditions were established, using [^{18}F]KF/ $\text{K}_{2.2.2}$ as the [^{18}F]fluoride source. The majority of the substrates could be successfully radiofluorinated at room temperature in DCM for 20 minutes, with 1.0 equivalent AgOTf. For the substrates that performed poorly under these conditions,

^{xviii} Aryl- CF_2^{18}F precursors bearing *para* substitution synthesised by S Verhoog (DPhil, thesis in preparation). Aryl- CHF^{18}F precursors synthesised by L Pfeifer (DPhil, thesis in preparation).

^{xix} Aryl- OCHF^{18}F and Aryl- $\text{OCF}_2^{18}\text{F}$ precursors synthesised by T Khotavivattana (DPhil, thesis in preparation).

^{xx} Aryl- $\text{SCF}_2^{18}\text{F}$ precursors synthesised by S Verhoog (DPhil, thesis in preparation).

heating to 60°C in DCE for 20 minutes with 2.0 equivalents of AgOTf typically gave greater conversion. Unfortunately the reaction did not proceed on any heteroarene substrates, under either set of conditions.

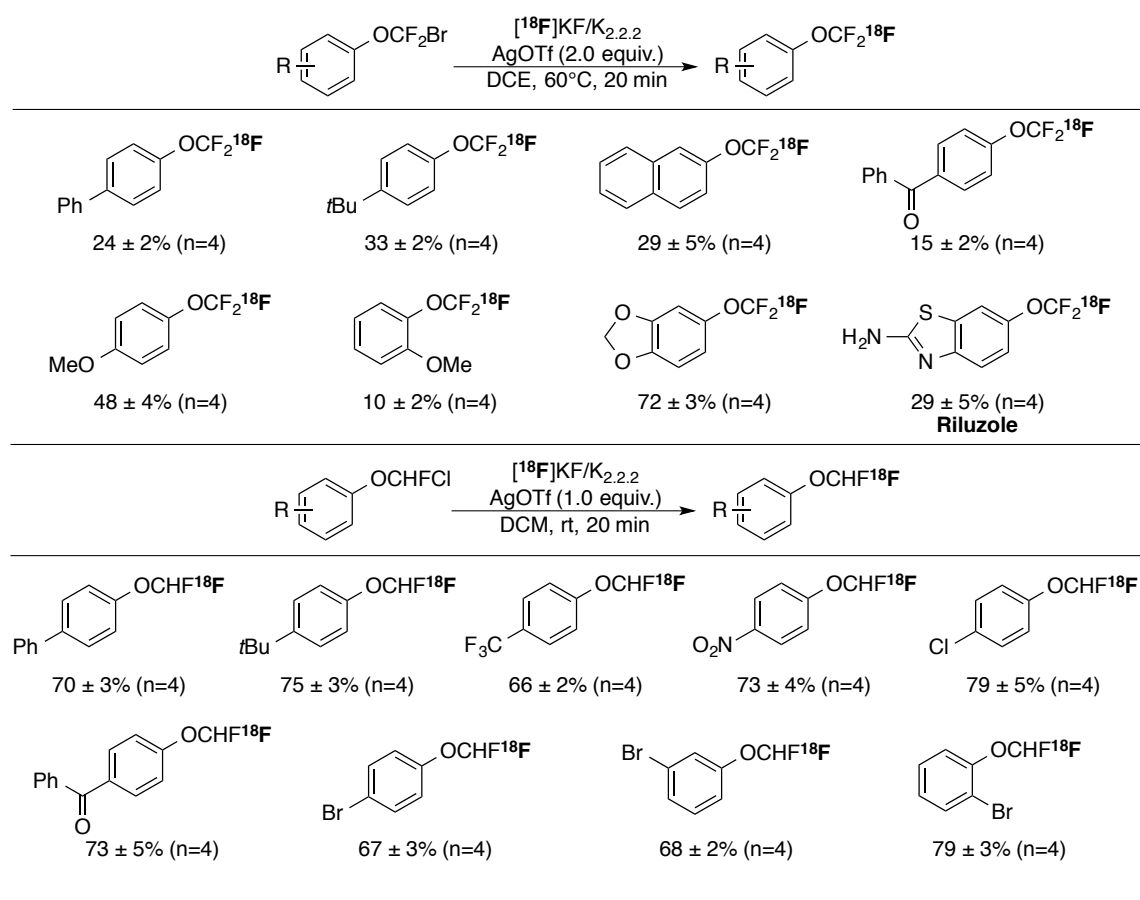


Scheme 5.30: [¹⁸F]Labelling of tri- and difluoromethoxyarenes by silver triflate mediated hallex.

Under these conditions, a wide range of *para*, *meta* and *ortho* substituted aryl-CF₃, -CF₂H (Scheme 5.29), -OCF₃, -OCF₂H (Scheme 5.30) and -SCF₃ (Scheme 5.31) were radiofluorinated. This represents the first [¹⁸F]labelling of aryl-OCF₃, -OCF₂H and -SCF₃ motifs, which is an important step forward for the development of new drugs and PET tracers.

Competition experiments indicated a reactivity series toward [¹⁸F]fluoride of: ArOCHFCl > ArCF₂Br ≈ ArCHFCl > ArSCF₂Br > ArOCF₂Br. Unfortunately, the SA of these compounds was found to be in the range of 0.25 - 0.03 GBq/μmol, which is very

low for a nucleophilic [^{18}F]fluoride approach, though this is comparable to other trifluoromethylation routes.⁴⁹ The low SA has been postulated to be due to formation of the acyl fluoride, an effect of low amounts of water remaining in the system, possibly assisted by the base remaining from the QMA elution. During this side reaction, fluorine-19 is released, which can then undergo the $\text{S}_{\text{N}}2$ reaction and therefore diluting the SA of the final product.

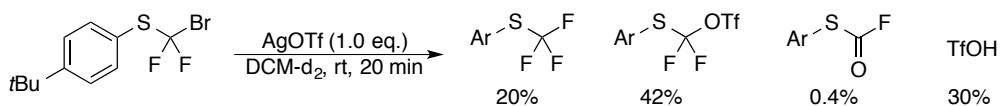


Scheme 5.31: [^{18}F]Labelling of trifluoromethylthioarenes by silver triflate mediated halox.

This theory was supported by subjecting the unlabelled final product reference to the reaction conditions, which lead to no incorporation of [^{18}F]fluoride, thus eliminating an isotopic exchange reaction diluting the SA.³⁰⁰

Furthermore, treating the starting materials with 1.0 equivalent of silver triflate in deuterated DCM at room temperature for 20 minutes showed complete consumption

of the bromodifluoromethyl- motif and 20% ^{19}F NMR yield of the trifluoromethyl- motif, proving that there is release of fluoride from the starting material under these reaction conditions.



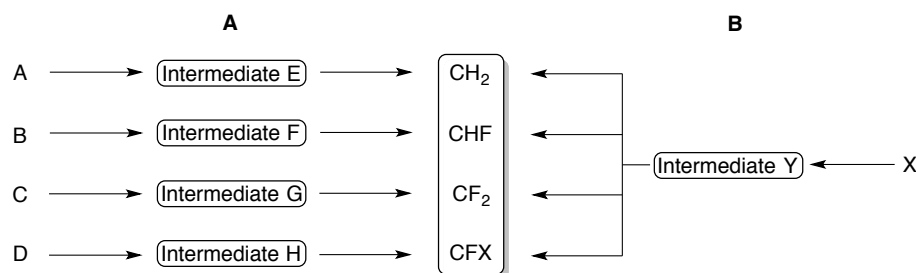
Scheme 5.32: Acyl fluoride formation and release of fluorine-19 (yields by ^{19}F NMR).^{xxi}

^{xxi} Reaction run by S Verhoog (DPhil, thesis in preparation).

6. [^{18}F]Fluorination of 1-(Diazo-2,2,2-trifluoroethyl)arenes

When studying compounds in systematic fluorine screens, the synthesis of poly/perfluoroalkylated compounds with incrementally varying fluorine content is protracted and inefficient, requiring parallel synthesis to take place with minor changes in the starting material (Scheme 6.1, A).

A more efficient approach to this would be late-stage fluorination/diversification of a common precursor to access several related structures which represent a series of poly/perfluoroalkylated compounds (B). In this way, only a single synthesis to a common precursor (Intermediate Y) would be required and furthermore, the late-stage nature of the fluorination would make it amenable to [^{18}F]labelling.

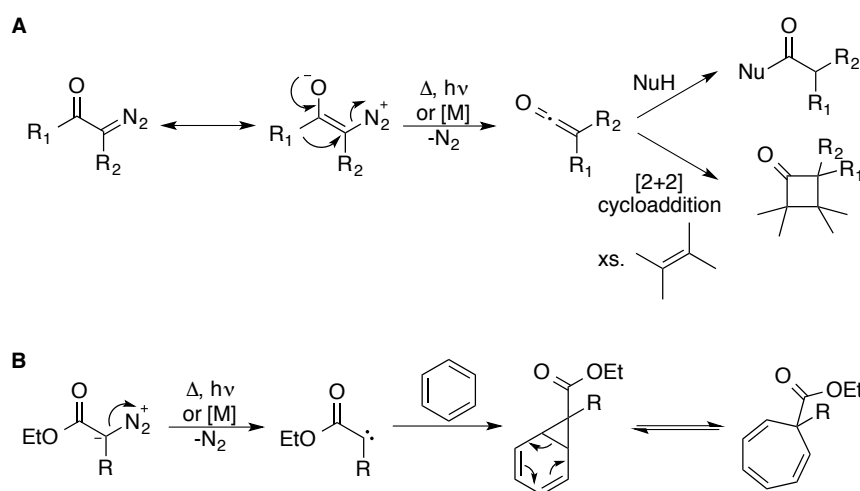


Scheme 6.1: Individual synthetic routes to poly/perfluorinated compounds (A) compared to late-stage fluorination/diversification (B). X = Hal., CF₃, OCF₃, SCF₃ etc.

6.1. Diazo Compounds

Diazo compounds have a long history in literature, since the first reports from Griess on the influence of nitrous acid on aminonitro- and aminodinitrophenol in 1858.³⁰⁵ Only more recently have these motifs been frequently used to access complex molecular structures.³⁰⁶ The common mechanistic pathway is via a carbene or metal-carbenoid species, driven by loss of N₂ on heating, irradiation or treatment with an activating species, which is then used as the reactive species in the reaction mechanism.

α -Diazo carbonyl compounds³⁰⁷ are by far the most favoured family of diazo compounds, due to their ease of preparation and relatively stable nature, along with the wide scope of transformations. These include Wolff rearrangements (Scheme 6.2, A),³⁰⁸ Büchner ring expansions^{309, 310} (B) as well as the reactions typically associated with diazo compounds;³¹¹ C-H insertions, α,α -substitution and carbene dimerization, as well as being an intermediate in the Bamford-Stevens reaction.



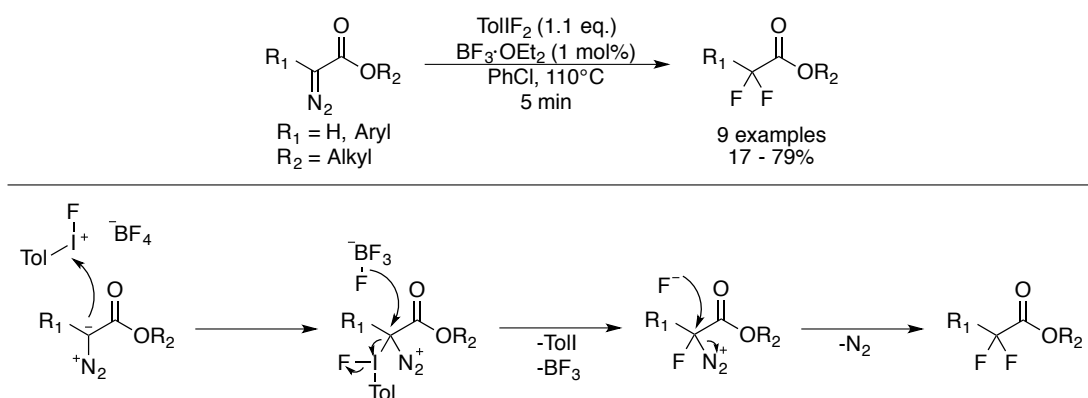
Scheme 6.2: Wolff rearrangement (A)³⁰⁸ and Büchner ring expansion (B)³¹² mechanisms.

6.1.1. α,α -Substitution and Fluorination

Treatment of diazo compounds with elemental halogens (chlorine, bromine, iodine) give the corresponding α,α -dihalogenated product in good yield.³⁰⁷ Unlike Cl_2 , Br_2 and I_2 , the reaction with elemental fluorine under normal conditions is not simple. A complex mixture of products is obtained after a violently exothermic reaction unless the reaction is conducted at -70°C in CFCl_3 with very dilute conditions,³¹³ or trifluoromethyl hypofluorite, a milder electrophilic reagent, is employed.³¹⁴

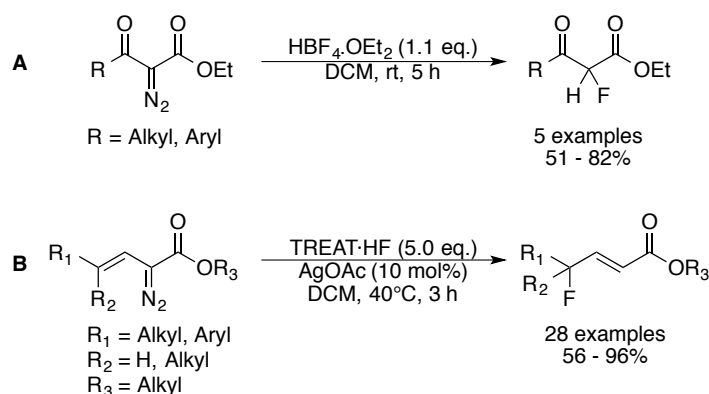
Murphy *et al.* have recently found that application of difluoroiodotoluene (ToIIF_2) with heating in the presence of $\text{BF}_3\cdot\text{OEt}_2$ (1 mol%), a Lewis acid catalyst, can give the α,α -difluorinated product in moderate to good yields (Scheme 6.3).³¹⁵ The authors proposed

that ToIF_2 and the Lewis acid form a reactive $[\text{ToIF}]^+\text{BF}_4^-$ species, with no free carbene intermediate formed during the reaction, despite the high temperatures used. This was verified by addition of $\text{Rh}_2(\text{OAc})_4$ or $\text{Cu}(\text{OTf})_2$ to the diazo precursor with ToIF_2 , which resulted in precursor decomposition without the formation of the difluorinated product. Additionally, this synthesis was also shown to proceed with the analogous dichloroiodoarene, to yield the α,α -dichlorinated product.



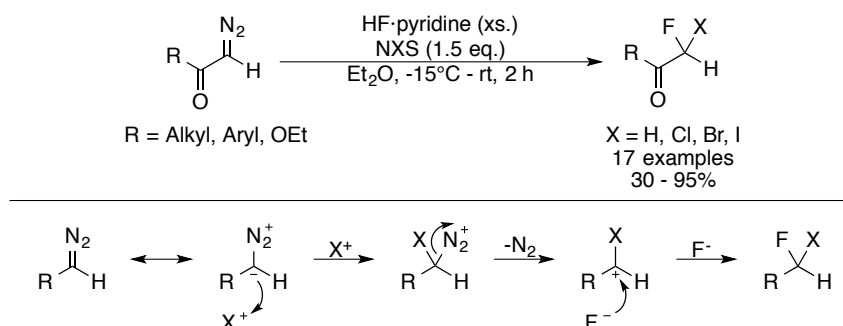
Scheme 6.3: Lewis acid catalysed α,α -difluorination of α -diazo carbonyl compounds.³¹⁵

The reaction of diazo compounds with anhydrous HF ^{316, 317} to give the hydrofluorinated products has been known for over 100 years. Whilst anhydrous HF is difficult to handle and extremely toxic, requiring specialist equipment, $\text{HF}\cdot\text{pyridine}$ (Olah's reagent)³¹⁸ is a tempered source of fluoride that is much easier to handle. Application to simple diazo ketone systems gives moderate yields of the hydrofluorinated product. The stronger tetrafluoroboric acid ($\text{HBF}_4\cdot\text{OEt}_2$)³¹⁹ is required for β -ketoesters (Scheme 6.4, A), which do not undergo the hydrofluorination with Olah's reagent, and $\text{TREAT}\cdot\text{HF}$, catalysed by silver acetate (10 mol%), has been reported to regioselectively hydrofluorinate allyl diazo esters with migration of the double bond (B).³²⁰



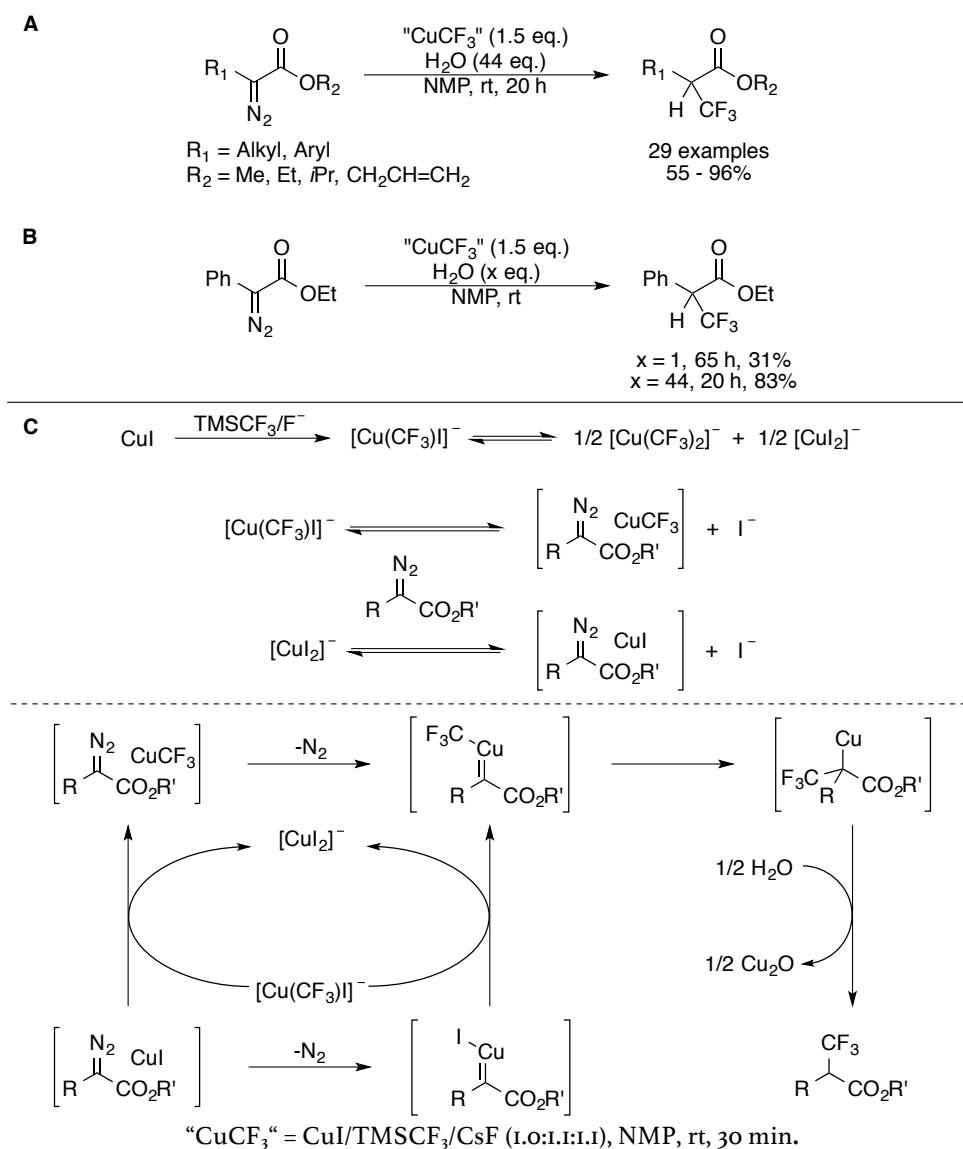
Scheme 6.4: Hydrofluorination of β -ketoesters (A)³¹⁹ and allyl diazo esters (B).³²⁰

In the same report as the hydrofluorination with HF·pyridine, Olah *et al.* reported that the addition of *N*-halosuccinimides (NCS, NBS, NIS) as electrophilic sources of halogens gave the corresponding halofluorinated motifs (Scheme 6.5).³¹⁸ The reactions mechanism is postulated to proceed by electrophilic attack on the diazoalkane by X⁺ (X = H, Cl, Br, I), followed by loss of N₂ and nucleophilic attack on the carbocation by fluoride.



Scheme 6.5: Olah's hydro- and halofluorination.³¹⁸

In addition to direct fluorination, α -diazo esters have been hydrotrifluoromethylated with the application of CuCF₃ reagents, generated *in situ* (Scheme 6.6, A). These reagents undergo a migratory insertion step, followed by protodecupration to give the trifluoromethylated product (C). The addition of excess H₂O was found to increase the yield of this reaction, believed to be due to assisting the migratory insertion step³²¹ and the elimination of water was found to promote the difluoromethylenation (B).³²²



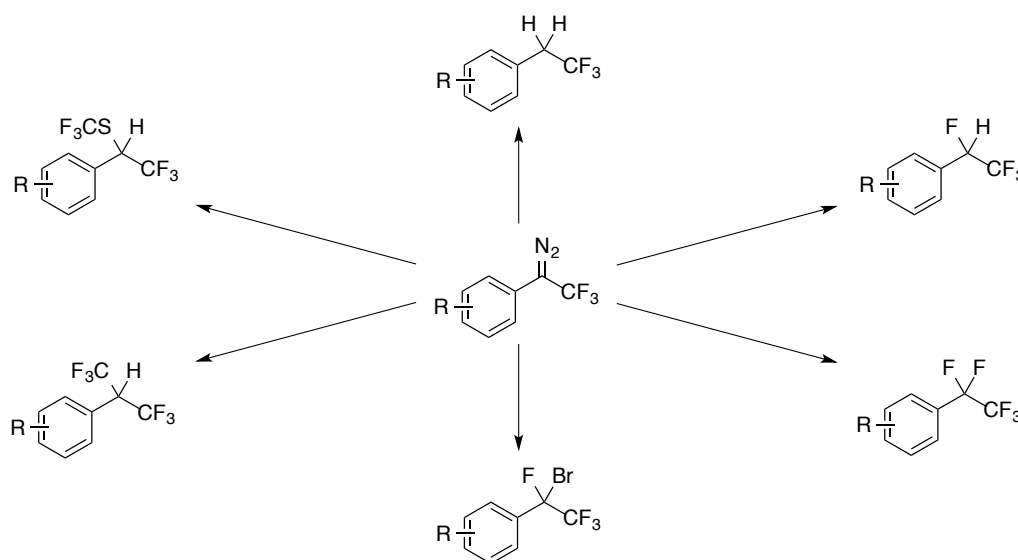
Scheme 6.6: "CuCF₃" mediated hydrotrifluoromethylation.^{321, 322}

The proposed mechanism (C) involves a $[\text{Cu}(\text{CF}_3)\text{I}]^-$ species being formed when CuI is treated with TMSCF₃ and CsF, which reversibly forms two further species; $[\text{Cu}(\text{CF}_3)_2]^-$ and $[\text{CuI}_2]^-$. The $[\text{Cu}(\text{CF}_3)_2]^-$ was considered to be unreactive toward the diazo compound, however $[\text{Cu}(\text{CF}_3)\text{I}]^-$ and $[\text{CuI}_2]^-$ can form complexes with the substrate, with loss of I⁻, promoted by the solvation of the iodine in the water. Loss of N₂ from either complex gives the copper-carbene species. In the case of the CuI/substate complex, ligand exchange with $[\text{Cu}(\text{CF}_3)\text{I}]^-$, either before or after extrusion of N₂, ultimately gives the trifluoromethylcopper-carbene species which undergoes migration of the CF₃ before hydrolysis gives the trifluoromethylated product along with

unreactive Cu_2O . The existence of $[\text{Cu}(\text{CF}_3)\text{I}]^-$ and $[\text{Cu}(\text{CF}_3)_2]^-$ species was supported by ^{19}F NMR analysis.

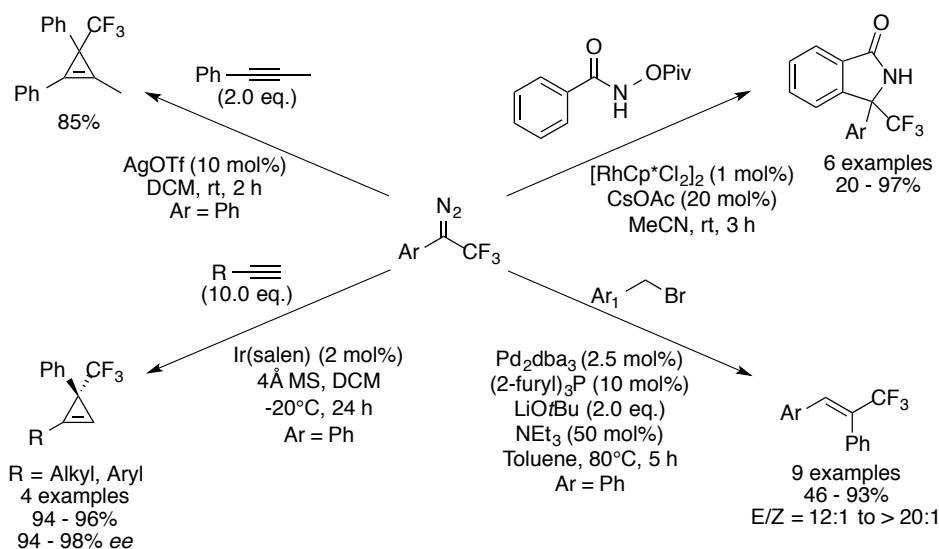
6.2. Preliminary Results from the Gouverneur Group

Dr E. Emer and J. Twilton, working within the Gouverneur group, initially developed this approach with fluorine-19. They were able to harness the reactivity of diazo systems and have developed an alternative diversity-oriented approach, where CF_3CH_2^- , CF_3CFH^- , CF_3CF_2^- , CF_3CFBr^- , $(\text{CF}_3)(\text{SCF}_3)\text{CH}^-$ and $(\text{CF}_3)_2\text{CH}^-$ -arenes can all be synthesised from a common 1-(diazo-2,2,2-trifluoroethyl)arene precursors (Scheme 6.7).^{323, 324}



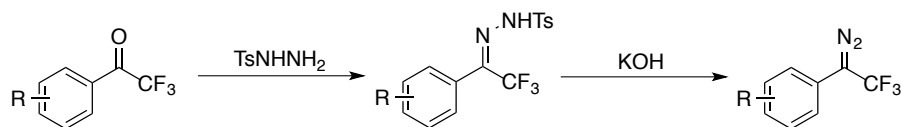
Scheme 6.7: Emer and Twilton's fluorination/diversification of 1-(diazo-2,2,2-trifluoroethyl)arenes³²³

This family of precursors was chosen as they have been employed in a range of transformations (Scheme 6.8), though these have focused on the use of transition metals to form reactive metal carbenoid species and consequent formation of cyclopropanes (as intermediates from tosylhydrazones),³²⁵ cyclopropenes,^{326, 327} olefins³²⁸ and γ -lactams.³²⁹ Remarkably, this literature does not cover α,α -substitution reactions on these precursors.



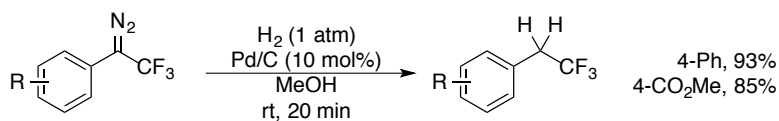
Scheme 6.8: Representative known reactions of 1-(diazo-2,2,2-trifluoroethyl)arenes; cyclopropenation,^{326, 327} olefination³²⁸ and γ -lactams formation.³²⁹

These precursors are readily accessible from the aryl trifluoromethylketones (Scheme 6.9),³³⁰ which give the tosylhydrazones on treatment with tosylhydrazide. An interrupted Bamford-Stevens reaction then gives access to the 1-(diazo-2,2,2-trifluoroethyl)arene precursor. The final precursors were found to be stable for months in a freezer under air.



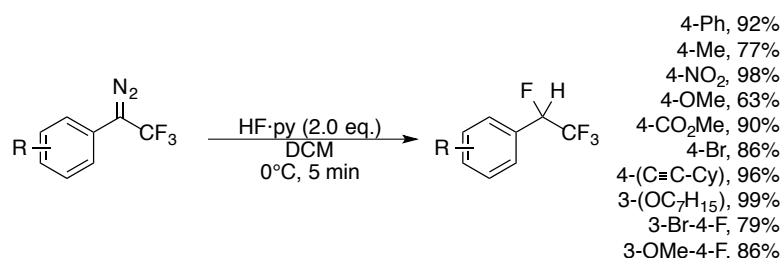
Scheme 6.9: Preparation of 1-(diazo-2,2,2-trifluoroethyl)arene precursors.³²³

Considering the complete spectrum of poly/perfluoroethylarenes ($\text{CF}_3\text{CF}_n\text{H}_{2-n}$ -arenes), they demonstrated that the precursor could be simply hydrogenated with palladium on carbon (10 mol%) under a H_2 atmosphere in 20 minutes, to give the CF_3CH_2 -arene in excellent yield (Scheme 6.10).



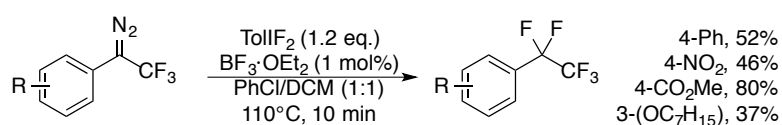
Scheme 6.10: Pd/C catalysed hydrogenation of 1-(diazo-2,2,2-trifluoroethyl)arenes.³²³

Treatment of the precursor with excess HF·pyridine (2.0 equivalents) in DCM at 0°C enabled the formal HF addition to give the CF₃CFH-arene (Scheme 6.11). This was demonstrated on a series of ten *para* and *meta* substituted arenes, which all gave good to excellent yields. The unsubstituted arene yield was lower than for the functionalised examples, with a ¹⁹F NMR yield of 52%, due to the volatility of the product.



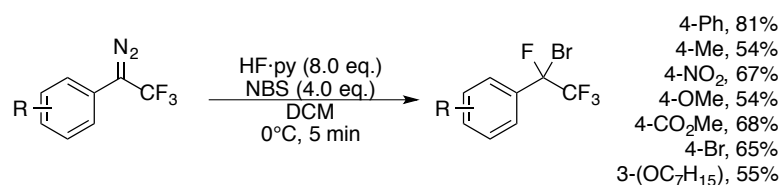
Scheme 6.11: Hydrofluorination of 1-(diazo-2,2,2-trifluoroethyl)arenes.

The *geminal* difluorination of these precursors was carried out using conditions modified from Murphy *et al.*,³¹⁵ in chlorobenzene/DCM (1:1) with TolIF₂ and BF₃·OEt₂ (1 mol%) to give the perfluoroethylarene (CF₃CF₂-) in moderate to good yields (Scheme 6.12). This methodology required elevated temperature (110°C), though was complete in 10 minutes, and was demonstrated on four substrates bearing electron-donating and electron-withdrawing groups.



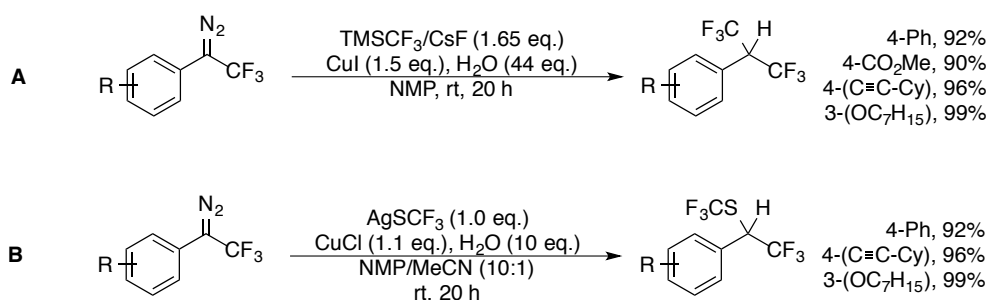
Scheme 6.12: Difluorination of 1-(diazo-2,2,2-trifluoroethyl)arenes.

The bromofluorination reaction, to give CF₃CFBr-arenes, was completed in a manner similar to that of Olah *et al.*,³¹⁸ with the addition of NBS (4.0 equivalents) as a bromine source (Scheme 6.13). In this manner, with 8.0 equivalents HF·pyridine, good yields (54 – 81%) could be obtained, again with a 5 minute reaction time. Surprisingly, unlike the conditions used by Olah, the reaction was found to perform better in DCM, with only 50% ¹⁹F NMR yield found after 24 h in Et₂O on the biphenyl compound.



Scheme 6.13: Bromofluorination of 1-(diazo-2,2,2-trifluoroethyl)arenes.

Hydrotrifluoromethylation (Scheme 6.14, A) and hydrotrifluoromethylthiolation (B) were accomplished under copper(I)-mediated conditions, using TMSCF₃/CsF with CuI and AgSCF₃ with CuCl respectively. An excess of H₂O was required in both reactions, along with a longer reaction time carried out at room temperature. Both of these reactions gave moderate to excellent yields; (1,1,1,3,3,3-hexafluoropropan-2-yl)arenes ((CF₃)₂CH-arenes) were isolated in 39 – 88% (4 examples) and (2,2,2-trifluoro-1-phenylethyl)(trifluoromethyl)sulfanes ((CF₃)(SCF₃)CH-arenes) in 46 – 77% (3 examples).



Scheme 6.14: Hydrotrifluoromethylation (A) and hydrotrifluoromethylthiolation (B) of 1-(diazo-2,2,2-trifluoroethyl)arenes.

6.3. Results and Discussion

The radiofluorination reactions in this chapter were carried out with Dr M. Tredwell. Precursor and reference synthesis was carried out by J. Twilton, as described in Section 6.2.

Following the work by Emer and Twilton,³²³ the potential for a range of similar [¹⁸F]labelled functionalities being obtained from a single precursor was realised. This is an important prospective approach to radiofluorination of tracers for drug discovery, in which fine tuning the lipophilicity, structure and pK_a of compounds is essential to

maximising the effectiveness of a drug or tracer. This investigation only focuses on the formal $X^{18}\text{F}$ ($X = \text{H}, \text{F}, \text{Br}$) addition reactions, and therefore neither the formal fluoroform or trifluoromethane thiol additions have been examined. The monofluorination and fluorobromination reactions were quickly recognised as being suitable for radiofluorination application due to only requiring 5 minutes at 0°C . Whilst the fluorobromination reaction was run at elevated temperature, this still lay well within the potential of radiofluorination reactions.

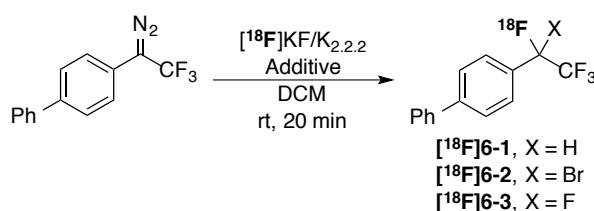
This work would also continue the Gouverneur groups interest in utilising carbene chemistry for $[^{18}\text{F}]$ radiochemistry, following on from the copper-mediated trifluoromethylation of aryl iodides reported in 2013.⁴⁹

6.3.1. Non-Carrier Added $[^{18}\text{F}]$ Fluorination

Primary investigations followed an n.c.a. approach, using $[^{18}\text{F}]\text{KF}/\text{K}_{2.2.2}$ as the $[^{18}\text{F}]$ fluoride source. In this way, only the monofluorination and fluorobromination would be technically possible as a formal F_2 addition is not possible under n.c.a. radiofluorination conditions due to the pico- to nanomolar quantities of $[^{18}\text{F}]$ fluoride present. Under these n.c.a. reaction conditions, double $[^{18}\text{F}]$ fluoride incorporation is widely considered to be unattainable.

Initial conditions paralleled those optimised under ^{19}F -conditions by Emer and Twilton, using DCM as the solvent and 4-(1-diazo-2,2,2-trifluoroethyl)-1,1'-biphenyl as a model substrate. Adjustments were made to the reaction temperature, increased to room temperature for ease of use, and reaction time increased to 20 minutes in the first instance. Unfortunately these conditions gave no incorporation of $[^{18}\text{F}]$ fluoride into the monofluorinated product 4-(1,2,2,2-tetrafluoroethyl)-1,1'-biphenyl ($[^{18}\text{F}]\text{6-1}$), with only $[^{18}\text{F}]$ fluoride being observed by radioTLC (Table 6.1, Entry 1). In an attempt to activate

the substrate toward the [^{18}F]fluorination, two acidic pyridinium reagents, pyridinium trifluoromethanesulfonate and 2,4,6-trimethylpyridinium trifluoromethanesulfonate were added to the reaction. It was predicted that using a pyridinium triflate as an additive would act *in lieu* of the HF-pyridine without having to resort to c.a. conditions, however this approach did not lead to any increase in incorporation (Entries 2 and 3).



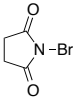
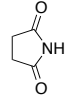
Entry	Additive	RCC (%)			n
		[^{18}F]6-1	[^{18}F]6-2	[^{18}F]6-3	
I	-	0			2
2	 (0.6 eq.)	0			2
3	 (0.5 eq.)	0			2
4	 (1.5 eq.)	0	0		2
5	 (1.7 eq.)	0			2
6	$\text{Sn}(\text{OTf})_2$ (8 mol%) PIDA (0.8 eq.)	1 ± 1		0	2

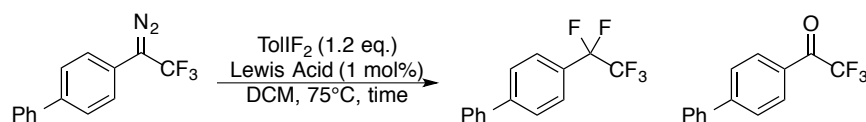
Table 6.1: Initial n.c.a. studies.

As the use of NBS had promoted the bromofluorination reaction with fluorine-19, 1.5 equivalents were used as an additive in an attempt to force the nucleophilic attack of Br^+ from the electron-rich diazo-bearing carbon and, in turn, encourage the loss of N_2 . This too was unsuccessful for the formation of 4-(1-bromo-1,2,2,2-tetrafluoroethyl)-1,1'-

biphenyl ($[^{18}\text{F}]\mathbf{6-2}$) (Entry 4). Furthermore, the use of 1.7 equivalents of succinimide as a proton source was futile (Entry 5).

The only reaction that gave trace $[^{18}\text{F}]\mathbf{6-1}$ (RCC = $1 \pm 1\%$ ($n=2$)) was when $\text{Sn}(\text{OTf})_2$ (8 mol%) was used as an additive in conjunction with PIDA (0.8 equivalents) (Entry 6). These conditions were elected to reflect the difluorination conditions, though use of both PhIF_2 and $\text{BF}_3 \cdot \text{OEt}_2$ as described by Emer and Twilton would have lead to isotopic dilution and, in effect, a carrier added procedure.

During the ^{19}F -bromofluorination reaction optimisation, J. Twilton³²⁴ carried out a screen of Lewis Acid catalysts in provision for this radiofluorination project (Table 6.2). $\text{Sn}(\text{OTf})_2$ (Entry 6) emerged as the best alternative to $\text{BF}_3 \cdot \text{OEt}_2$ (Entry 1), giving a slightly improved ^{19}F NMR yield of the difluorinated product, albeit with an extended reaction time and an increased yield of the ketone by product. Other Lewis Acids screened promoted the formation of the ketone to the detriment of the difluorinated product yield (Entries 2 - 5 and 7 - 9).



Entry	Lewis Acid	Time (h)		
1	BF ₃ ·OEt ₂	0.5	56	29
2	InCl ₃	5	Trace	70
3	Bi(OTf) ₃	0.5	0	60
4	AgOTf	0.5	12	40
5	Zn(OTf) ₂	3	36	34
6	Sn(OTf) ₂	0.75	59	35
7	[Cu(MeCN) ₄]OTf	0.75	8	36
8	Mg(OTf) ₂	5	11	85
9	Sm(OTf) ₃	1	31	53

¹⁹F NMR yields

Table 6.2: Lewis Acid screen carried out by J. Twilton^{324, xxii}

Consequently, as none of these n.c.a. approaches had given appreciable conversions, this investigation was stalled to begin investigations along a c.a. approach as it was now believed that the HF·pyridine was essential to activate the precursor to the radiofluorination reactions.

6.3.2. Carrier Added [¹⁸F]Fluorination

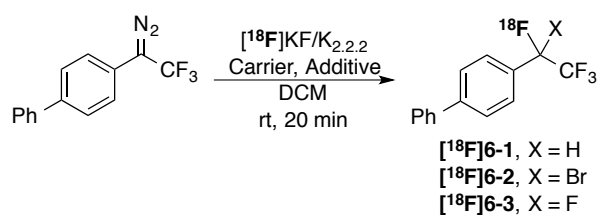
As described in Section 1.3., the use of n.c.a. [¹⁸F]fluoride is favoured over c.a. [¹⁸F]fluoride, due to the reduced SA that is inherent with c.a. approaches. Unfortunately, in this case, the n.c.a. methodologies had failed to give acceptable results and consequently c.a. approaches had to be considered. For these reactions, calculation of the SA was not attempted due to it being a c.a. procedure.

^{xxii} Table reproduced from “The Synthesis and Reactivity of α-Trifluoromethyl Diazo Compounds”, J. Twilton, MChem, University of Oxford, 2014.

As the use of HF·pyridine had been successful for hydrofluorination under the ^{19}F -conditions, 1.0 equivalent (1 μL) was added to the reaction as the carrier in the first instance (Table 6.3, Entry 1). However, the incorporation remained zero for this c.a. approach, which was surprising considering that spiking ^{19}F -reactions with ^{18}F typically gives good isotope exchange and radiochemical conversion. On analysis of the reaction protocol, the use of a glass vial for the dissolution of HF·pyridine in DCM before addition to the reaction was identified as a possible failing point, due to fluoride from HF sources readily reacting with the silicate in glass.

Therefore the reaction protocol was adjusted so that the HF·pyridine was prepared in a Fischerbrand® polypropylene centrifuge tube and this immediately resulted in $71 \pm 16\%$ (RCC, $n=2$) of $[^{18}\text{F}]\text{6-1}$ (Entry 2). Product was obtained radiochemically pure by radioHPLC, and identity was confirmed by overlay of a chromatogram of an authentic reference.

Addition of 1.5 equivalents of NBS to these conditions readily gave $37 \pm 5\%$ (RCC, $n=2$) of $[^{18}\text{F}]\text{6-2}$ and use of PhIF_2 (0.8 equivalents) as the carrier with $\text{Sn}(\text{OTf})_2$ (8 mol%) in place of $\text{BF}_3\cdot\text{OEt}_2$ gave $39 \pm 0\%$ (RCC, $n=2$) of the difluorinated product, 4-(perfluoroethyl)-1,1'-biphenyl ($[^{18}\text{F}]\text{6-3}$) (Entries 3 and 4). Notably in the latter two reactions, the products were not obtained radiochemically pure, with the radioTLC having to be corrected for radiochemical purity ($\text{RCP} = 70 \pm 8\%$ ($n=2$) and $77 \pm 4\%$ ($n=2$) for $[^{18}\text{F}]\text{6-2}$ and $[^{18}\text{F}]\text{6-3}$, respectively). The majority ($> 95\%$) of the remaining $[^{18}\text{F}]$ fluoride incorporation was identified to be in the form of $[^{18}\text{F}]\text{6-1}$ in both cases.



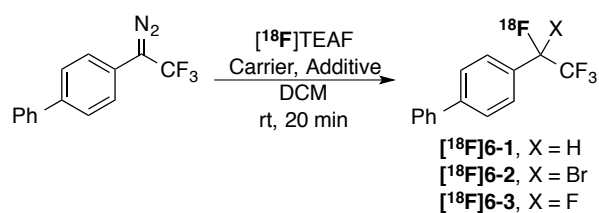
Entry	Carrier	Additive	RCC (%)			n
			[^{18}F]6-1	[^{18}F]6-2	[^{18}F]6-3	
1	HF·pyridine ^a (1.0 eq.)	-	0			2
2	HF·pyridine (1.0 eq.)	-	71 ± 16			2
3	HF·pyridine (1.0 eq.)	 (1.5 eq.)	15 ± 3	37 ± 5		2
4	PhIF ₂ (0.8 eq.)	Sn(OTf) ₂ (8 mol%)	12 ± 3		39 ± 0	2

a) HF·pyridine prepared in glass.

Table 6.3: Carrier-added radiofluorination with [^{18}F]KF/K_{2.2.2}.

Whilst these results are c.a. procedures, this is the first report of [^{18}F]labelling of CF₃CF₂- with nucleophilic [^{18}F]fluoride, as well as the first reports of [^{18}F]labelled ArCHF CF₃ and ArCFBrCF₃.

The effect of [^{18}F]TEAF as the [^{18}F]fluoride source, rather than [^{18}F]KF/K_{2.2.2} was subsequently examined as the use of tetraalkylammonium cations as the counter-ion to the fluoride can lead to greater solubility in organic solvents and, therefore, the possibility of greater incorporation.³³¹ Initially, similar reactivity was found on examination of the monofluorination, with RCC = 64 ± 2% (n=4) [^{18}F]6-1 obtained (Table 6.4, Entry 1). The bromofluorination performed better with [^{18}F]TEAF, giving 47 ± 4% [^{18}F]6-2 (RCC, n=4) (Entry 3). Interestingly, MeCN has a detrimental effect on both of these reactions when it is not removed after being used to dispense the activity, reducing RCC to 39 ± 15% (n=2) and 28 ± 3% (n=2) respectively (Entries 2 and 4).



Entry	Carrier	Additive	RCC (%)			n
			$[\text{F}]6\text{-1}$	$[\text{F}]6\text{-2}$	$[\text{F}]6\text{-3}$	
1	HF·pyridine (1.0 eq.)	-	64 ± 2			4
2 ^a	HF·pyridine (1.0 eq.)	-	39 ± 15			2
3	HF·pyridine (1.0 eq.)	 (1.5 eq.)	12 ± 2	47 ± 4		4
4 ^a	HF·pyridine (1.0 eq.)	 (1.5 eq.)	3 ± 1	28 ± 3		2
5	PhIF ₂ (0.8 eq.)	Sn(OTf) ₂ (8 mol%)	3 ± 1		0 ± 0	2
6	PhIF ₂ ^b (0.8 eq.)	Sn(OTf) ₂ (8 mol%)	7 ± 1		16 ± 3	4
7 ^a	PhIF ₂ ^b (0.8 eq.)	Sn(OTf) ₂ (8 mol%)	1 ± 1		1 ± 1	2

a) MeCN not removed after $[\text{F}]$ TEAF dispensing; b) New PhIF₂ used.

Table 6.4: Carrier-added radiofluorination with $[\text{F}]$ TEAF.

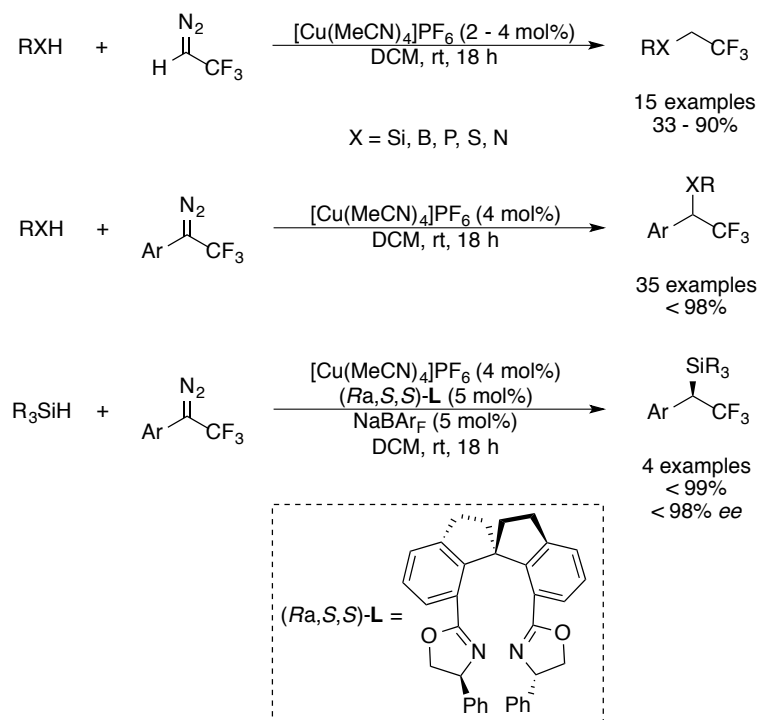
For the difluorination, the use of $[\text{F}]$ TEAF was detrimental to the yield. The greatest RCC found was $16 \pm 3\%$ (n=4) $[\text{F}]6\text{-3}$, with $7 \pm 1\%$ of $[\text{F}]6\text{-1}$ (Entry 6). Neglecting the removal of MeCN resulted in a drop in yield to $1 \pm 1\%$ (RCC, n=2) (Entry 7). During the course of this investigation, it was found that the PhIF₂ used needs to be freshly bought or prepared, with old samples giving no difluorinated and $3 \pm 1\%$ (RCC, n=2) of $[\text{F}]6\text{-1}$ (Entry 5). It is believed that this is likely due to the hygroscopic nature³³² of (difluoroiodo)arenes abstracting water which is poorly tolerated by diazo reactions.

The use of [^{18}F]TEAF over [^{18}F]KF/ $\text{K}_{2.2.2}$ did not significantly change the radiochemical purity of the products, as identified by radioHPLC, and used to correct the radioTLC to acquire the RCC. RCPs obtained were found as $98 \pm 2\%$ ($n=4$), $81 \pm 3\%$ ($n=4$) and $61 \pm 9\%$ ($n=4$) for [^{18}F]6-1, [^{18}F]6-2 and [^{18}F]6-3 respectively. For the latter two products, the majority of the remaining [^{18}F]fluoride incorporation was in the form of the [^{18}F]6-1.

6.4. Summary

This project has taken hydro-, bromo- and difluorination reactions, developed by Emer and Twilton, and adapted the reactions for radiofluorination of 1-(diaz-2,2,2-trifluoroethyl)arenes. Despite only succeeding under a c.a. approach, this project has resulted in the implementation of a diversity oriented strategy resulting in formal [^{18}F]HF, [^{18}F]FBr and [^{18}F]F₂ α,α -substitution from two [^{18}F]fluoride sources, [^{18}F]KF/ $\text{K}_{2.2.2}$ and [^{18}F]TEAF. Whilst the use of carriers in this reaction may limit its application for the study of sensitive tracers, this is the first report of [^{18}F]labelled CF₃CF₂- with nucleophilic [^{18}F]fluoride, as well as the first reports of [^{18}F]labelled ArCHF₂CF₃ and ArCF₂CF₃.

The use of 1-(diaz-2,2,2-trifluoroethyl) arenes as building blocks remains of interest to the Gouverneur group, with a recent report from Hyde *et al.*, detailing their use, along with 2,2,2-trifluoro-1-diazoethane in copper-catalysed X-H insertion reactions (X = B, N, Si, P, S) (Scheme 6.15).³³³ Use of a chiral ligand enabled the formation of enantioenriched product for the B-H and Si-H insertion reactions.



Scheme 6.15: Copper-catalysed X-H insertion³³³

Thesis Summary

This thesis describes the development of novel methodologies for ^{18}F -radiolabelling, carried out at the Siemens Organic Molecular Imaging Laboratory, University of Oxford, and the PET Core facility, Massachusetts General Hospital.

Chapter 1 discussed the current state of art for ^{18}F -radiolabelling and production of ^{18}F -radiolabelling reagents, as well as the limitations and critical factors inherent to radiochemistry.

The use of hypervalent iodine reagents to mediate oxidative ^{18}F -radiofluorination of *N*-arylsulfonamides was developed in Chapter 2, following an umpolung strategy developed in the Gouverneur group.⁸³ Initial reaction development under [^{19}F]fluoride conditions revealed that the tosyl protecting group was optimal, with a good substrate scope tolerated. Conversion to [^{18}F]fluoride only gave low conversion under n.c.a. conditions, however when HF·pyridine was used as a carrier, $\text{RCC} = 52 \pm 6\%$ ($n=4$) could be achieved on an unsubstituted model substrate.

Application of automated technology is an important aspect of transferring advancements in ^{18}F -radiochemistry research into clinical environments for use in PET imaging. Chapter 3 disclosed the successful application of a NanoTek® microfluidic system to the radiofluorination of spirocyclic iodonium ylides. For electron neutral and deficient substrates, the use of microfluidics lead to significantly improved incorporation when compared to the manual precedent,⁷² though for electron rich substrates the RCCs were reduced. Furthermore, this methodology could be fully automated, as shown for 4-[^{18}F]fluorobenzyl azide ($\text{RCY} = 24 \pm 0\%$ ($n=3$)), and used for the ^{18}F -radiolabelling of [^{18}F]FPEB, a highly sought radiopharmaceutical, in $\text{RCC} = 68 \pm 5\%$ ($n=2$), an improvement on the literature precedent.²³⁸

The transfer of reactions run under research conditions to production of radiopharmaceuticals also suffers from an increase in eluting base in the reaction, which can be detrimental to the overall efficiency. This was the case for the copper-mediated radiofluorination of pinacolyl arylboronates, developed by Tredwell, Preshlock and Taylor in the Gouverneur group.⁵³ Chapter 4 discussed two new strategies for resolving this issue; by reduction of the base used and its elimination entirely by use of Cu(OTf)₂py₄ to elute the [¹⁸F]fluoride. By use of the reduced base elution, two sets of complimentary conditions were found for electron rich and electron deficient substrates, which were taken forward to produce eight important radiotracers, with RCYs similar or better than the literature precedent in each case.

Radiofluorination of aliphatic motifs that bear more than one fluorine has severe limitations, despite being an area of importance in drug development, an area covered by Chapters 5 and 6. In Chapter 5, initial investigations toward decarboxyfluorination with electrophilic fluorine sources was limited by substrate synthesis difficulties, though the first example of a double *geminal* decarboxyfluorination was established, a concept that would be amenable to [¹⁸F]Selectfluor bis(triflate), generating ¹⁸F-radiolabelled aliphatic *geminal* difluorinated moieties. Nucleophilic strategies toward halogen exchange were originally hindered by poor choice of substrates, though application to α,α-fluorobromoesters to give the corresponding α,α-[¹⁸F]difluoroesters or carboxylic acids, with *in situ* ester hydrolysis, was highly successful. Attempts to induce proto- or fluorodecarboxyfluorination of these substrates, to give the corresponding ¹⁸F-radiolabelled ArOCF₃ or ArOCF₂H, proved futile, however, these motifs were successfully labelled by silver triflate mediated halogen exchange, along with ArSCF₃, ArCF₃ and ArCF₂H.

The use of single precursors to access several ^{18}F -radiolabelled motifs is desirable for drug development to assess the effect of incrementally varying fluorine content for pharmaceuticals. An adaption of hydro-, bromo- and difluorination of a common 1-(diazot-2,2,2-trifluoroethyl)arene, developed in the Gouverneur group by Emer and Twilton is presented in Chapter 6. In this manner, formal ^{18}F]HF, ^{18}F]FBr and ^{18}F]F₂ α,α -substitution from two ^{18}F]fluoride sources, ^{18}F]KF/K_{2.2.2} and ^{18}F]TEAF, was established under carrier added conditions. This is the first report of ^{18}F]ArCHFCF₃ and ^{18}F]ArCF₂CF₃, as well as the first nucleophilic route to ^{18}F]labelled -CF₂CF₃.

Results from this thesis have been published in the following peer-reviewed articles:

Chapter 2 - F. Buckingham, S. Calderwood, B. Checa, T. Keller, M. Tredwell, T. Collier, I. Newington, R. Bhalla, M. Glaser and V. Gouverneur, *Journal of Fluorine Chemistry*, 2015, **180**, 33-39.

Chapter 3 - S. Calderwood, T. Collier, V. Gouverneur, S. Liang and N. Vasdev, *Journal of Fluorine Chemistry*, 2015, **178**, 249-253.

Chapter 4 - S. Preshlock, S. Calderwood, S. Verhoog, M. Tredwell, M. Huiban, A. Hienzsch, S. Gruber, T. C. Wilson, N. J. Taylor, T. Cailly, M. Schedler, T. L. Collier, J. Passchier, R. Smits, J. Mollitor, A. Hoepping, M. Mueller, C. Genicot, J. Mercier, V. Gouverneur, *Chemical Communications*, 2016, **52**, 8361-8364.

Chapter 5 - S. Verhoog, L. Pfeifer, T. Khotavivattana, S. Calderwood, T. Collier, K. Wheelhouse, M. Tredwell and V. Gouverneur, *Synlett*, 2016, **27**, 25-28. T. Khotavivattana, S. Verhoog, M. Tredwell, L. Pfeifer, S. Calderwood, K. Wheelhouse, T. Collier and V. Gouverneur, *Angewandte Chemie-International Edition*, 2015, **54**, 9991-9995.

Chapter 6 - E. Emer, J. Twilton, M. Tredwell, S. Calderwood, T. Collier, B. Liegault, M. Taillefer and V. Gouverneur, *Organic Letters*, 2014, **16**, 6004-6007.

EXPERIMENTAL AND REFERENCES

7. Experimental

7.1. General Information

Commercial reagents and solvents were purchased from Acros Organics, Alfa Aesar, Apollo Scientific, Fisher Scientific, Fluorochem or Sigma-Aldrich and, unless otherwise stated, used as received. When anhydrous solvents were required they were purified by expression through an activated alumina column built according to the procedures described by Pangborn and Grubbs.³³⁴

All reactions were performed in oven-dried apparatus with magnetic stirring under an inert atmosphere of argon or nitrogen unless otherwise indicated. All solvents were dried on a column of alumina prior to use. Thin layer chromatography (TLC) was performed using Merck aluminium-foil baked plates precoated with Kieselgel 60 F₂₄₅. The products were visualized using UV fluorescence (254 nm) and/or potassium permanganate stain. Flash column chromatography was performed over Merck silica gel C60 (40-60 mm) using eluent systems as described for each experiment.

¹H, ¹³C and ¹⁹F NMR spectra were recorded on Bruker DPX200, DPX250 or AVIII400 and AVII500 spectrometers. ¹H NMR and ¹³C NMR spectra are reported as chemical shifts (δ) in parts per million (ppm) relative to the solvent peak using the Bruker internal referencing procedure (edlock). ¹⁹F NMR spectra are referenced relative to CFCl₃ in CDCl₃. Coupling constants (*J*) are reported in units of Hertz (Hz) to the nearest 0.1 Hz. Multiplicities are reported as observed in the spectra with the following abbreviations are used to describe multiplets: s (singlet), d (doublet), t (triplet), q (quartet), sext (sextet), sept (septet), m (multiplet) and br. s (broad singlet). Low Resolution Mass Spectra (LRMS, *m/z*) were recorded on a Waters LCT Premier spectrometer using positive (ESI⁺) or negative (ESI⁻) electrospray ionization. High

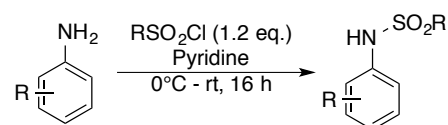
resolution mass spectra (HRMS, m/z) were recorded on a Bruker MicroTOF spectrometer using positive (ESI⁺) or negative electrospray ionization (ESI⁻) or on a Micromass GCT spectrometer using field ionisation (FI⁺) or chemical ionization (CI⁺). Infrared (IR) spectra were recorded as neat compound or in a solution using a Bruker Tensor 27 FT-IR spectrometer. Absorptions are reported in wavenumbers (cm⁻¹). Melting points (MP) of solids were measured using a Leica Griffin III apparatus and are uncorrected.

The following characterisation data are provided for each novel compound: ¹H NMR spectra, ¹³C NMR spectra, IR spectra and HRMS. ¹⁹F NMR spectra are also provided for those compounds containing ¹⁹F nuclei. MP are provided for solids. The following characterisation data are provided for known compounds: ¹H NMR spectra and ¹³C NMR spectra. ¹⁹F NMR spectra are provided for those compounds containing ¹⁹F nuclei. This data is consistent with the cited literature values. All compounds used for which a preparative procedure does not appear were commercially available or synthesised by persons named in this thesis. IUPAC names were obtained using the ACD I-Lab 2.0 service.

7.2. Oxidative Fluorination and Radiofluorination of *N*-Protected Anilines

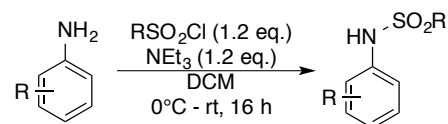
7.2.1. General Procedures

General Procedure 2A (GP2A):



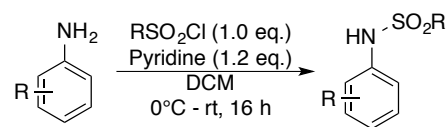
To a solution of aniline (1.0 eq.) in pyridine (0.6 M) at 0°C was added the sulfonyl chloride (1.2 eq.). The reaction was warmed to room temperature and stirred for 16 hours before concentration *in vacuo*. The residue was dissolved in EtOAc and washed with HCl (1 M, aq.), NaOH (1 M, aq.) and brine. The organic phase was dried over MgSO₄ and the solvent removed *in vacuo*. Purification was performed by flash column chromatography.

General Procedure 2B (GP2B):



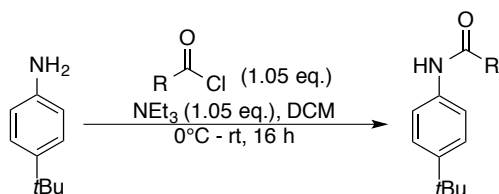
To a solution of aniline (1.0 eq.) and triethylamine (1.2 eq.) in DCM (0.2 M) at 0°C, was added the sulfonyl chloride (1.2 eq.). The reaction was warmed to room temperature and stirred for 16 hours before quenching with water and stirred for a further 30 minutes. The reaction was then extracted into DCM, the organic phase was washed with HCl (1 M, aq.), NaHCO₃ (sat., aq.) and brine, dried over MgSO₄ and the solvent removed *in vacuo*. Purification was performed by flash column chromatography.

General Procedure 2C (GP2C):



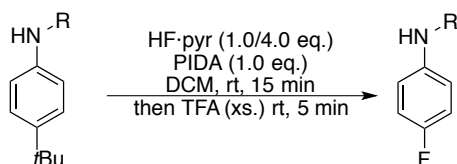
To a solution of aniline (1.0 eq.) and pyridine (1.2 eq.) in DCM (0.2 M) at 0°C, was added the sulfonyl chloride (1.0 eq.). The reaction was warmed to room temperature and stirred for 16 hours before quenching with water and stirred for a further 30 minutes. The reaction was then extracted into DCM and the organic phase was washed with HCl (1 M, aq.), NaHCO₃ (sat., aq.) and brine, dried over MgSO₄ and the solvent removed *in vacuo*. Purification was performed by flash column chromatography.

General Procedure 2D (GP2D):



To a solution of 4-*tert*-butylaniline (1.0 eq.) and triethylamine (1.05 eq.) in DCM (0.5 M) at 0°C, was added the acyl chloride (1.05 eq.) dropwise. The reaction was warmed to room temperature and stirred for 16 hours, then quenched with water and extracted into DCM. The organic phase was washed with HCl (1 M, aq.), NaHCO₃ (sat., aq.) and brine, dried over MgSO₄ and the solvent removed *in vacuo*. The crude residue was purified by flash column chromatography or washing with hexane.

General Procedure 2E (GP2E):



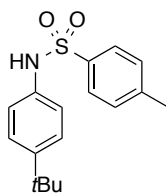
To a solution of *N*-arylsulfonamide (1.0 eq.) in DCM (0.5 M) in a Falcon tube was added HF·pyridine (70 %) (1.0/4.0 eq.) followed by PIDA (1.0 eq.). The reaction was stirred at room temperature for 15 minutes before the addition of TFA (1.0 mL). After stirring for a further 5 minutes the reaction was quenched with NaHCO₃ (sat., aq.) and extracted into DCM. The combined organic phases were washed with brine, dried over MgSO₄ and the solvent removed *in vacuo*.

To obtain ¹⁹F NMR yields, the reaction was performed on a 0.50 mmol scale. The crude residue was fully dissolved in CDCl₃ before the addition of 1-fluoro-3-nitrobenzene (53 μL, 0.50 mmol, 1.0 eq.) as an internal standard. An aliquot of the resulting solution was taken for NMR analysis.

Reactions for isolated yields were typically carried out on a 1.0 mmol scale. Purification was performed by flash column chromatography, under specified conditions.

7.2.2. Substrates - Protecting Group Scope

N-(4-(*tert*-Butyl)phenyl)-4-methylbenzenesulfonamide (2-1aa)

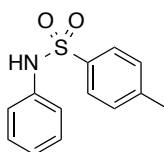


Prepared according to **GP2A** from 4-(*tert*-butyl)aniline (800 μL, 5.00 mmol, 1.0 eq.) and *p*-toluenesulfonyl chloride (1.14 g, 6.00 mmol, 1.2 eq.). Purification by flash column chromatography (Petroleum Ether 30-40/EtOAc 9:1 - 0:1) afforded the title compound as a white solid (1.41 g, 4.64 mmol, 93%).

^1H NMR (400 MHz, CDCl_3): δ = 7.67 (d, J = 8.1 Hz, 2H), 7.28-7.21 (m, 4H), 6.99 (d, J = 8.6 Hz, 2H), 6.67 (br. s, 1 H), 2.39 (s, 3H), 1.27 (s, 9H); ^{13}C NMR (101 MHz, CDCl_3): δ = 148.5, 143.7, 136.4, 133.7, 129.6, 127.3, 126.2, 121.6, 34.4, 31.3, 21.6.

Data consistent with literature values.³³⁵

***N*-Phenyl-4-methylbenzenesulfonamide (2-2aa)**

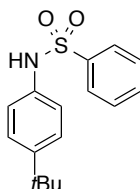


Prepared according to **GP2A** from aniline (1.00 mL, 11.0 mmol, 1.0 eq.) and *p*-toluenesulfonyl chloride (2.52 g, 13.2 mmol, 1.2 eq.). Purification by flash column chromatography (Petroleum Ether 30-40/EtOAc 9:1 - 4:1) afforded the title compound as a white solid (1.90 g, 7.67 mmol, 70%).

^1H NMR (400 MHz, CDCl_3): δ = 7.67 (d, J = 8.3 Hz, 2H), 7.27-7.21 (m, 4H), 7.12 (dt, J = 7.5 Hz, J = 1.4 Hz, 1H), 7.10-7.05 (m, 2H), 6.80 (br. s, 1H), 2.38 (s, 3H); ^{13}C NMR (101 MHz, CDCl_3): δ = 143.9, 136.5, 136.0, 129.7, 129.4, 127.3, 125.4, 121.6, 21.6.

Data consistent with literature values.³³⁶

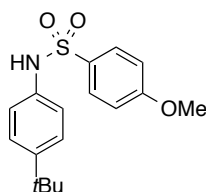
***N*-(4-(*tert*-Butyl)phenyl)benzenesulfonamide (2-1ba)**



Prepared according to **GP2A** from 4-(*tert*-butyl)aniline (1.00 mL, 6.28 mmol, 1.0 eq.) and benzenesulfonyl chloride (962 μL , 7.54 mmol, 1.2 eq.). Purification by flash column chromatography ($\text{CHCl}_3/\text{MeOH}$ 1:0 - 9:1) afforded the title compound as a white solid (1.59 g, 5.48 mmol, 87% yield).

¹H NMR (400 MHz, CDCl₃): δ = 7.80 (d, *J* = 7.3 Hz, 2H), 7.55 (m, 1H), 7.49-7.40 (m, 2H), 7.25 (d, *J* = 8.8 Hz, 2H), 6.99 (d, *J* = 8.6 Hz, 2H), 6.76 (br. s, 1H), 1.26 (s, 9H); ¹³C NMR (101 MHz, CDCl₃): δ = 148.7, 139.3, 133.5, 132.9, 129.0, 127.2, 126.2, 121.8, 34.4, 31.3; HRMS (ESI⁺, *m/z*): [C₁₆H₁₉NNaO₂]⁺ (M+Na)⁺ calc. 312.1029, found 312.1034; IR (ν, cm⁻¹): 3204, 1513, 1363, 1157; MP: 154-155°C.

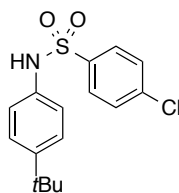
***N*-(4-(*tert*-Butyl)phenyl)-4-methoxybenzenesulfonamide (2-1ca)**



Prepared according to **GP2B** from 4-(*tert*-butyl)aniline (1.00 mL, 6.28 mmol, 1.0 eq.) and *p*-methoxybenzenesulfonyl chloride (1.56 g, 7.54 mmol, 1.2 eq.). Purification by flash column chromatography (Petroleum Ether 30-40/EtOAc 4:1 - 0:1) afforded the title compound as a white solid (2.01 g, 6.21 mmol, 99%).

¹H NMR (400 MHz, DMSO-*d*₆): δ = 10.06 (br. s, 1H), 7.69 (d, *J* = 8.8 Hz, 2H), 7.22 (d, *J* = 8.6 Hz, 2H), 7.04 (d, *J* = 8.8 Hz, 2H), 6.99 (d, *J* = 8.6 Hz, 2H), 1.17 (s, 9H), 3.77 (s, 3H); ¹³C NMR (101 MHz, DMSO-*d*₆): δ = 163.2, 147.0, 136.0, 132.3, 129.7, 126.7, 120.5, 115.2, 56.4, 34.8, 31.9; HRMS (ESI⁺, *m/z*): [C₁₇H₂₁NNaO₃S]⁺ (M+Na)⁺ calc. 342.1134, found 342.1123; IR (ν, cm⁻¹): 3235, 1445, 1326, 1181; MP: 163-164°C.

***N*-(4-(*tert*-Butyl)phenyl)-4-chlorobenzenesulfonamide (2-1da)**

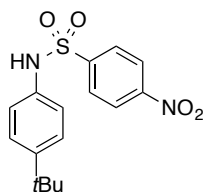


Prepared according to **GP2B** from 4-(*tert*-butyl)aniline (1.00 mL, 6.28 mmol, 1.0 eq.) and *p*-chlorobenzenesulfonyl chloride (1.59 g, 7.54 mmol, 1.2 eq.). Purification by flash

column chromatography (CHCl₃/MeOH 1:0 - 9:1) afforded the title compound as a white solid (1.25 g, 3.86 mmol, 61%).

¹H NMR (400 MHz, DMSO-d₆): δ = 10.27 (br. s, 1H), 7.75 (d, *J* = 8.6 Hz, 2H), 7.63 (d, *J* = 8.6 Hz, 2H), 7.25 (d, *J* = 8.6 Hz, 2H), 6.99 (d, *J* = 8.8 Hz, 2H), 1.19 (s, 9H); ¹³C NMR (101 MHz, DMSO-d₆): δ = 147.6, 139.5, 138.5, 135.5, 130.3, 129.4, 126.8, 121.1, 34.9, 31.9; HRMS (ESI⁺, *m/z*): [C₁₆H₁₈ClNNaO₂S]⁺ (M+Na)⁺ calc. 346.0639, found 346.0628; IR (ν, cm⁻¹): 3218, 1477, 1328, 1180, 757; MP: 182-183°C.

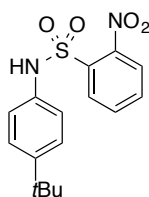
***N*-(4-(*tert*-Butyl)phenyl)-4-nitrobenzenesulfonamide (2-1ea)**



Prepared according to GP2A from 4-(*tert*-butyl)aniline (1.00 mL, 6.28 mmol, 1.0 eq.) and *p*-nitrobenzenesulfonyl chloride (1.67 g, 7.54 mmol, 1.2 eq.). Purification by flash column chromatography (CHCl₃) afforded the title compound as a yellow solid (1.79 g, 5.36 mmol, 85%).

¹H NMR (400 MHz, CDCl₃): δ = 8.29 (d, *J* = 8.8 Hz, 2H), 7.95 (d, *J* = 8.8 Hz, 2H), 7.29 (d, *J* = 8.6 Hz, 2H), 7.01 (d, *J* = 8.6 Hz, 2H), 6.91 (s, 1H), 1.27 (s, 9H); ¹³C NMR (101 MHz, CDCl₃): δ = 150.2, 149.7, 144.8, 132.4, 128.5, 126.5, 124.2, 122.4, 34.5, 31.2; HRMS (ESI⁺, *m/z*): [C₁₆H₁₈N₂NaO₄S]⁺ (M+Na)⁺ calc. 357.0879, found 357.0874; IR (ν, cm⁻¹): 3248, 1530, 1466, 1349, 1308, 1166; MP: 143-144°C.

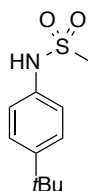
***N*-(4-(*tert*-Butyl)phenyl)-2-nitrobenzenesulfonamide (2-1fa)**



Prepared according to **GP2B** from 4-(*tert*-butyl)aniline (749 μ L, 4.70 mmol, 1.0 eq.) and *o*-nitrobenzenesulfonyl chloride (1.25 g, 5.64 mmol, 1.2 eq.) Purification by flash column chromatography (Petroleum Ether 30-40/EtOAc 17:3 - 4:1) afforded the title compound as a pale yellow solid (1.22 g, 3.65 mmol, 78%).

^1H NMR (400 MHz, CDCl_3): 7.86 (m, 2H), 7.70 (td, $J = 7.8$ Hz, $J = 1.3$ Hz, 1H), 7.59 (td, $J = 7.6$ Hz, $J = 1.0$ Hz, 1H), 7.28 (d, $J = 8.9$ Hz, 2H), 7.19 (br. s, 1H), 7.11 (d, $J = 8.5$ Hz, 2H), 1.27 (s, 9H); ^{13}C NMR (101 MHz, CDCl_3): $\delta = 149.7, 148.2, 133.8, 132.6, 132.5, 132.4, 131.8, 126.3, 125.2, 123.0, 34.4, 31.2$; HRMS (ESI $^+$, m/z): $[\text{C}_{16}\text{H}_{18}\text{N}_2\text{NaO}_4\text{S}]^+$ (M+Na) $^+$ calc. 357.0879, found 357.0872; IR (ν , cm^{-1}): 3290, 1537, 1458, 1343, 1307, 1164; MP: 146-148°C.

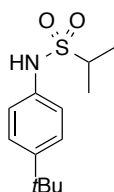
N-(4-(*tert*-Butyl)phenyl)methanesulfonamide (**2-1ga**)



Prepared according to **GP2B** from 4-(*tert*-butyl)aniline (800 μ L, 5.00 mmol, 1.0 eq.) and methanesulfonyl chloride (464 μ L, 6.00 mmol, 1.2 eq.). Purification by flash column chromatography (Petroleum Ether 30-40/EtOAc 4:1) afforded the title compound as a white solid (1.04 g, 4.58 mmol, 92%).

^1H NMR (400 MHz, CDCl_3): $\delta = 7.38$ (dt, $J = 8.8$ Hz, $J = 2.7$ Hz, 2H), 7.17 (dt, $J = 8.8$ Hz, $J = 2.7$ Hz, 2H), 6.60 (br. s, 1H), 3.02 (s, 3H), 1.33 (s, 9H); ^{13}C NMR (101 MHz, CDCl_3): $\delta = 148.8, 133.8, 126.6, 121.1, 39.2, 34.4, 31.3$; HRMS (ESI $^+$, m/z): $[\text{C}_{11}\text{H}_{17}\text{NNaO}_2\text{S}]^+$ (M+Na) $^+$ calc. 250.0872, found 250.0867; IR (ν , cm^{-1}): 3258, 1465, 1323, 1147; MP: 80-81°C.

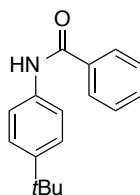
***N*-(4-(*tert*-Butyl)phenyl)propane-2-sulfonamide (2-1ha)**



Prepared according to **GP2C** from 4-*tert*-butylaniline (0.49 mL, 2.50 mmol, 1.0 eq.) and 2-propanesulfonyl chloride (0.31 mL, 2.75 mmol, 1.1 eq.). Purification by flash column chromatography (Hexane/EtOAc 4:1) afforded the title compound as a yellow solid (594 mg, 2.33 mmol, 92%).

¹H NMR (400 MHz, CDCl₃): δ = 7.34 (d, *J* = 8.6 Hz, 2H), 7.18 (d, *J* = 8.6 Hz, 2H), 6.73 (br. s, 1H), 3.30 (sept., *J* = 6.8 Hz, 1H), 1.41 (d, *J* = 6.8 Hz, 6H), 1.31 (s, 9H); ¹³C NMR (101 MHz, CDCl₃): δ = 148.2, 134.5, 126.6, 120.7, 52.3, 34.6, 31.5, 16.7; HRMS (ESI⁺, *m/z*): [C₁₃H₂₁NNaO₂S]⁺ (*M*+Na)⁺ calc. 278.1185, found 278.1196; IR (ν, cm⁻¹): 3257, 1514, 1327, 1170; MP: 74-76°C.

***N*-(4-(*tert*-Butyl)phenyl)benzamide (2-1ia)**

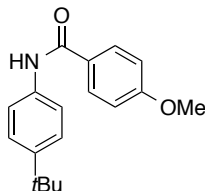


Prepared according to **GP2D** from 4-*tert*-butylaniline (800 μL, 5.00 mmol, 1.0 eq.) and benzoyl chloride (610 μL, 5.25 mmol, 1.05 eq.). Purified by washing with hexane to afford the title compound as a white solid (1.12 g, 4.42 mmol, 88%).

¹H NMR (400 MHz, CDCl₃): 7.90-7.85 (m, 2H), 7.81 (br. s, 1H), 7.60-7.53 (m, 3H), 7.49 (tt, *J* = 6.8 Hz, *J* = 1.5 Hz, 2H), 7.40 (d, *J* = 8.8 Hz, 2H), 1.34 (s, 9H); ¹³C NMR (101 MHz, CDCl₃): δ = 165.7, 147.6, 135.3, 135.1, 131.8, 128.8, 127.0, 126.0, 120.0, 34.5, 31.4.

Data consistent with literature values.³³⁷

***N*-(4-(*tert*-Butyl)phenyl)-4-methoxybenzamide (2-1ja)**

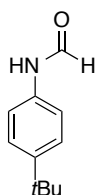


Prepared according to **GP2D** from 4-*tert*-butylaniline (800 μ L, 5.00 mmol, 1.0 eq.) and 4-methoxybenzoyl chloride (711 μ L, 5.25 mmol, 1.05 eq.). Purified by flash column chromatography (Petroleum Ether 30-40/EtOAc 4:1 - 0:1) to afford the title compound as a white solid (1.34 g, 4.73 mmol, 95%).

¹H NMR (400 MHz, CDCl₃): δ = 7.84 (d, J = 9.0 Hz, 2H), 7.76 (br. s, 1H), 7.56 (d, J = 8.6 Hz, 2H), 7.39 (d, J = 8.8 Hz, 2H), 6.97 (d, J = 9.0 Hz, 2H), 3.88 (s, 3H), 1.44-1.28 (m, 9H); ¹³C NMR (101 MHz, CDCl₃): δ = 165.1, 162.4, 147.3, 135.4, 128.8, 127.3, 125.9, 119.9, 113.9, 55.4, 34.4, 31.4.

Data consistent with literature values.³³⁷

***N*-(4-(*tert*-Butyl)phenyl)formamide (2-1ka)**



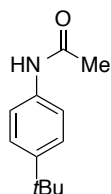
A flask containing 4-*tert*-butylaniline (1.00 mL, 6.28 mmol, 1.0 eq.) in ethyl formate (5 mL) was fitted with a reflux condenser and heated to 70°C for 16 hours before concentration under reduced pressure. Purification by flash column chromatography (Petroleum Ether 30-40/EtOAc 19:1 - 3:1) afforded the title compound as a pale yellow solid (974 mg, 5.50 mmol, 88%). Formed as a mixture of rotamers (1:1).

Trans isomer: ^1H NMR (400 MHz, CDCl_3): δ = 8.66 (d, J = 11.6 Hz, 1H), 8.04 (br. d, J = 9.6 Hz, 1H), 7.51-7.43 (m, 2H), 7.43-7.35 (m, 2H), 1.32 (s, 9H); ^{13}C NMR (101 MHz, CDCl_3): δ = 162.8, 148.5, 134.1, 126.6, 118.8, 34.4, 31.3.

Cis isomer: ^1H NMR (400 MHz, CDCl_3): δ = 8.36 (d, J = 1.7 Hz, 1H), 7.39-7.33 (m, 3H), 7.08-6.99 (m, 2H), 1.31 (s, 9H); ^{13}C NMR (101 MHz, CDCl_3): δ = 159.1, 147.8, 134.3, 125.9, 119.9, 34.4, 31.3.

Data consistent with literature values.³³⁸

N-(4-(*tert*-Butyl)phenyl)acetamide (2-11a)

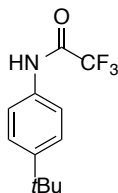


To a solution of 4-*tert*-butylaniline (1.60 mL, 10.0 mmol, 1.0 eq.) in DCM (20 mL) at 0°C, was added acetic anhydride (1.20 mL, 11.1 mmol, 1.1 eq.) dropwise. The reaction was stirred for 30 minutes at 0°C before concentration under reduced pressure. The crude residue was washed with hexane and filtered to afford the title compound as a white solid (1.70 g, 8.86 mmol, 89%).

^1H NMR (400 MHz, CDCl_3): δ = 7.48-7.40 (m, 2H), 7.40-7.32 (m, 2H), 7.23 (br. s, 1H), 2.19 (s, 3H), 1.33 (s, 9H); ^{13}C NMR (101 MHz, CDCl_3): δ = 168.2, 147.4, 135.2, 125.8, 119.8, 34.4, 31.4, 24.6.

Data consistent with literature values.³³⁷

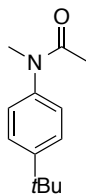
***N*-(4-(*tert*-Butyl)phenyl)-2,2,2-trifluoroacetamide (2-1ma)**



To a solution of 4-*tert*-butylaniline (3.00 g, 20.0 mmol, 1.0 eq.) and pyridine (3.20 mL, 40.0 mmol, 2.0 eq.) in DCM (50 mL) at 0°C was added trifluoroacetic anhydride (2.80 mL, 20 mmol, 1.0 eq.). The reaction was stirred for 3 hours at 0°C, then quenched with NaHCO₃ (sat., aq.) and extracted into DCM. The organic phase was dried over MgSO₄ and the solvent removed *in vacuo*. Purification by flash column chromatography (Petroleum Ether 30-40/EtOAc 4:1) afforded the title compound a pale yellow solid (4.36 g, 17.8 mmol, 89%).

¹H NMR (400 MHz, CDCl₃): δ = 7.91 (br. s, 1H), 7.50 (d, *J* = 9.2 Hz, 2H), 7.41 (d, *J* = 9.2 Hz, 2H), 1.33 (s, 9H); ¹³C NMR (101 MHz, CDCl₃): δ = 149.6 (q, *J* = 37.9 Hz), 132.4, 126.2, 120.3, 114.4 (q, *J* = 288.7 Hz), 34.6, 31.3; ¹⁹F NMR (377 MHz, CDCl₃) δ = -75.7; HRMS (ESI⁺, *m/z*): [C₁₂H₁₄F₃NNaO]⁺ (*M*+Na)⁺ calc. 268.0920, found 268.0921; IR (ν, cm⁻¹): 3300, 1705, 1518, 1161; MP: 49-50°C.

***N*-(4-(*tert*-Butyl)phenyl)-*N*-methylacetamide (2-1na)**

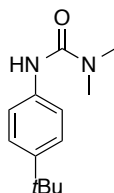


To a solution of *N*-(4-(*tert*-butyl)phenyl)acetamide (1.00 g, 5.23 mmol, 1.0 eq.) in THF (25 mL), was added methyl iodide (358 μL, 5.75 mmol, 1.1 eq.) and sodium hydride (60% in mineral oil) (314 mg, 7.85 mmol, 1.5 eq.). After stirring at room temperature for 14 hours, the reaction was poured onto water and extracted into DCM. The organic phase was

dried over MgSO_4 and the solvent removed *in vacuo*. Purification by flash column chromatography (Petroleum Ether 30-40/EtOAc 4:1) afforded the title compound as a white solid (725 mg, 3.53 mmol, 71%).

^1H NMR (400 MHz, CDCl_3): δ = 7.42 (d, J = 8.6 Hz, 2H), 7.10 (d, J = 8.3 Hz, 2H), 3.25 (s, 3H), 1.88 (s, 3H), 1.34 (s, 9H); ^{13}C NMR (101 MHz, CDCl_3): δ = 170.8, 150.7, 141.9, 126.5, 126.5, 37.1, 34.6, 31.3, 22.4; HRMS (ESI^+ , m/z): $[\text{C}_{13}\text{H}_{19}\text{NNaO}]^+$ ($M+\text{Na}$) $^+$ calc. 228.1359, found 228.1365; IR (ν , cm^{-1}): 1663, 1511; MP: 55-57°C.

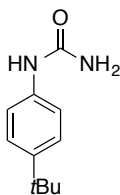
3-(4-(*tert*-Butyl)phenyl)-1,1-dimethylurea (2-10a)



Prepared according to modified literature procedure.³³⁹ To a solution of dimethylamine hydrochloride (294 mg, 3.00 mmol, 1.0 eq.) in DCM (15 mL) at 0°C was added triethylamine (495 μL , 3.60 mmol, 1.2 eq.). After stirring for 10 minutes, 4-*tert*-butylphenyl isocyanate (530 μL , 3.00 mmol, 1.0 eq.) was added before the reaction was warmed to room temperature and stirred for 16 hours. The solution was washed with HCl (2 M, aq.) and extracted into DCM. The organic phase was dried over Na_2SO_4 and the solvent removed *in vacuo* to afford the title compound directly as a white solid (657 mg, 2.98 mmol, 99%).

^1H NMR (400 MHz, CDCl_3): δ = 7.30 (d, J = 8.8 Hz, 2H), 7.22 (d, J = 8.8 Hz, 2H), 7.04 (br. s, 1H), 2.88 (s, 6H), 1.28 (s, 9H); ^{13}C NMR (101 MHz, CDCl_3): δ = 156.3, 145.3, 136.8, 125.2, 120.2, 36.2, 34.0, 31.3; HRMS (ESI^+ , m/z): $[\text{C}_{13}\text{H}_{20}\text{N}_2\text{NaO}]^+$ ($M+\text{Na}$) $^+$ calc. 243.1468, found: 243.1474; IR (ν , cm^{-1}): 3306, 1685, 1538; MP: 98-99°C.

1-(4-(*tert*-Butyl)phenyl)urea (2-1pa)



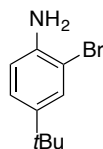
To 4-*tert*-butylaniline (895 mg, 6.00 mmol, 1.0 eq.) in HCl (2 M. aq.) (3 mL) at 0°C was added potassium cyanate (585 mg, 7.20 mmol, 1.2 eq.) portionwise over 30 minutes. The reaction was stirred for 4 hours at room temperature and then left to stand, without stirring, at 0°C for 1 hour. The resultant precipitate was removed by filtration, washed with ice-cold water and dried under vacuum. Purification by flash column chromatography (Hexane/EtOAc 1:1 - 0:1) afforded the title compound as a white solid (554 mg, 2.88 mmol, 48%).

¹H NMR (400 MHz, CDCl₃): δ = 7.23 (d, *J* = 8.6 Hz, 2H), 7.13 (d, *J* = 8.6 Hz, 3H), 4.93 (br. s, 2H), 1.21 (s, 9H); ¹³C NMR (101 MHz, CDCl₃): δ = 157.4, 147.5, 135.6, 126.2, 121.7, 34.4, 31.4.

Data consistent with literature values.³⁴⁰

7.2.3. Substrates - *N*-Aryl Scope

2-Bromo-4-(*tert*-butyl)aniline (2-3)



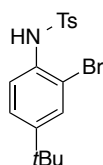
Prepared according to a literature procedure.³⁴¹ To a solution of 4-(*tert*-butyl)aniline (5.50 mL, 34.5 mmol, 1.0 eq.) in chloroform (200 mL) at 0°C was added *N*-bromosuccinimide (6.76 g, 37.9 mmol, 1.1 eq.). The reaction was warmed to room temperature and stirred for 5 hours, then washed with water and extracted into chloroform. The organic phase was dried over Na₂SO₄ and the solvent removed *in*

vacuo. Purification by flash column chromatography (Hexane) afforded the title compound as a brown oil (5.35 g, 23.5 mmol, 68%).

¹H NMR (400 MHz, CDCl₃): δ = 7.45 (d, *J* = 1.7 Hz, 1H), 7.16 (dd, *J* = 8.3 Hz, *J* = 2.2 Hz, 1H), 6.47 (d, *J* = 8.3 Hz, 1H), 3.95 (br. s, 2H), 1.30 (s, 9H); ¹³C NMR (101 MHz, CDCl₃): δ = 141.4, 142.7, 129.2, 125.3, 115.5, 109.2, 33.9, 31.3.

Data consistent with literature values.³⁴²

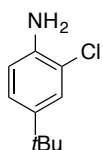
***N*-(2-Bromo-4-*tert*-butylphenyl)-4-methylbenzenesulfonamide (2-1ab)**



Prepared according to GP2C from 2-bromo-4-(*tert*-butyl)aniline (2-3) (684 mg, 3.00 mmol, 1.0 eq.) and *p*-toluenesulfonyl chloride (572 mg, 3.00 mmol, 1.0 eq.). Purification by flash column chromatography (Petroleum Ether 30-40/EtOAc 9:1) afforded the title compound as a white solid (945 mg, 2.47 mmol, 82%).

¹H NMR (400 MHz, CDCl₃): δ = 7.66 (d, *J* = 8.3 Hz, 2H), 7.56 (d, *J* = 8.6 Hz, 1H), 7.40 (d, *J* = 2.2 Hz, 1H), 7.28 (dd, *J* = 8.6 Hz, *J* = 2.2 Hz, 1H), 7.23 (d, *J* = 8.3 Hz, 2H), 6.87 (br. s, 1H), 2.39 (s, 3H), 1.26 (s, 9H); ¹³C NMR (101 MHz, CDCl₃): δ = 149.9, 144.0, 136.2, 132.1, 129.6, 129.4, 127.3, 125.7, 122.3, 115.6, 34.5, 31.1, 21.6; HRMS (ESI⁺, *m/z*): [C₁₇H₂₀BrNNaO₂S]⁺ (M+Na)⁺ calc. 404.0290, found 404.0282; IR (ν, cm⁻¹): 3268, 1499, 1336, 1164, 611; MP: 92-93°C.

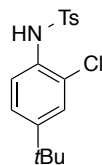
4-(*tert*-Butyl)-2-chloroaniline (2-4)



To a solution of 4-(*tert*-butyl)aniline (5.00 ml, 31.4 mmol, 1.0 eq.) in chloroform (200 mL) at 0°C was added *N*-chlorosuccinimide (4.61 g, 34.5 mmol, 1.1 eq.). The reaction was warmed to room temperature and stirred for 5 hours, then washed with water and extracted into chloroform. The organic phase was dried over MgSO₄ and the solvent removed *in vacuo*. Purification by flash column chromatography (Petroleum Ether 30-40/EtOAc 9:1) afforded the title compound as a brown oil (1.43 g, 9.82 mmol, 31%).

¹H NMR (400 MHz, CDCl₃): δ = 7.17 (d, *J* = 2.2 Hz, 1 H), 7.01 (dd, *J* = 8.3 Hz, *J* = 2.2 Hz, 1H), 6.63 (d, *J* = 8.3 Hz, 1H), 3.83 (br. s, 2H), 1.19 (s, 9H); ¹³C NMR (101 MHz, CDCl₃): δ = 142.5, 140.3, 126.3, 124.7, 119.1, 115.7, 34.1, 31.4; HRMS (ESI⁺, *m/z*): [C₁₀H₁₅ClN]⁺ (M+H)⁺ calc. 184.0888, found 184.0883; IR (ν, cm⁻¹): 3384, 1622, 1508, 1273, 725.

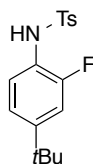
***N*-(4-(*tert*-Butyl)-2-chlorophenyl)-4-methylbenzenesulfonamide (2-1ac)**



Prepared according to GP2C from 4-(*tert*-butyl)-2-chloroaniline (2-4) (735 mg, 4.00 mmol, 1.0 eq.) and *p*-toluenesulfonyl chloride (763 mg, 4.00 mmol, 1.0 eq.). Purification by flash column chromatography (Hexane/EtOAc 9:1) afforded the title compound as a purple solid (879 mg, 2.60 mmol, 65%).

¹H NMR (400 MHz, CDCl₃): δ = 7.66 (d, *J* = 8.3 Hz, 2H), 7.55 (d, *J* = 9.3 Hz, 1H), 7.26-7.21 (m, 4H), 6.90 (br. s, 1H), 2.39 (s, 3H), 1.26 (s, 9H); ¹³C NMR (101 MHz, CDCl₃): δ = 149.7, 144.2, 136.4, 130.9, 129.8, 127.4, 126.5, 125.1, 125.0, 122.3, 34.7, 31.3, 21.8; HRMS (ESI⁺, *m/z*): [C₁₇H₂₀ClNNaO₂S]⁺ (M+Na)⁺ calc. 360.0795, found 360.0786; IR (ν, cm⁻¹): 3266, 1493, 1337, 1163, 664; MP: 105-106°C

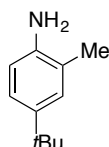
***N*-(4-(*tert*-Butyl)-2-fluorophenyl)-4-methylbenzenesulfonamide (2-1ad)**



To a solution of *N*-(4-(*tert*-butyl)phenyl)-4-methylbenzenesulfonamide (**2-1aa**) (1.21 g, 4.00 mmol, 1.0 eq.) in acetonitrile (40 mL) was added Selectfluor (1.42 g, 4.00 mmol, 1.0 eq.). The reaction was heated to reflux for 16 hours, then cooled to room temperature and concentrated *in vacuo*. The crude residue was dissolved in DCM and washed with water, NaHCO₃ (sat., aq.) and brine. The organic phase was dried over NaSO₄ and the solvent removed *in vacuo*. Purification by flash column chromatography (Hexane/EtOAc 9:1) afforded the title compound as a red solid (887 mg, 2.76 mmol, 69%).

¹H NMR (400 MHz, CDCl₃): δ = 7.67 (d, *J* = 8.3 Hz, 2H), 7.47 (t, *J* = 8.6 Hz, 1H), 7.23 (d, *J* = 7.8 Hz, 2H), 7.10 (dd, *J* = 8.4 Hz, *J* = 1.6 Hz, 1H), 6.97 (dd, *J* = 12.5 Hz, *J* = 2.0 Hz, 1H), 6.71 (br. s, 1H), 2.39 (s, 3H), 1.25 (s, 9H); ¹³C NMR (101 MHz, CDCl₃): δ = 155.1 (d, *J* = 243.2 Hz), 150.6 (d, *J* = 5.6 Hz), 144.2, 136.3, 129.8, 127.4, 123.3, 121.8, 121.7 (d, *J* = 3.2 Hz), 112.7 (d, *J* = 19.9 Hz), 34.7, 31.3, 21.7; ¹⁹F NMR (377 MHz, CDCl₃): δ = -129.6; HRMS (ESI⁺, *m/z*): [C₁₇H₂₀FNNaO₂S]⁺ (M+Na)⁺ calc. 344.1091, found 344.1091; IR (ν, cm⁻¹): 3258, 1506, 1338, 1166, 1092; MP: 114-115°C.

4-(*tert*-Butyl)-2-methylaniline (2-5)



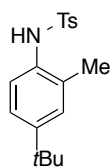
Prepared according to a modified literature procedure.³⁴³ To a solution of **2-3** (1.00g, 4.38 mmol, 1.0 eq.) in DMF (10 mL) was added potassium carbonate (1.81 g, 13.1 mmol,

3.0 eq.), tetrakis(triphenylphosphine)palladium(0) (508 mg, 0.44 mmol, 0.1 eq.) and trimethylboroxine (612 μ L, 4.38 mmol, 1.0 eq.). The reaction was heated to 115°C for 20 hours before being cooled to room temperature and filtered through Celite® (Et₂O). The organic phase was washed several times with brine, dried over MgSO₄ and the solvent removed *in vacuo*. Purification by flash column chromatography (Petroleum Ether 30-40/EtOAc 9:1) afforded the title compound as a bright pink oil (249 mg, 1.52 mmol, 35%).

¹H NMR (400 MHz, CDCl₃): δ = 7.14-7.07 (m, 2H), 6.66 (d, *J* = 8.1 Hz, 1H), 3.52 (br. s, 2H), 2.21 (s, 3H), 1.31 (s, 9H); ¹³C NMR (101 MHz, CDCl₃): δ = 142.1, 141.5, 127.4, 123.7, 122.0, 114.8, 33.9, 31.6, 17.7.

Data consistent with literature values.³⁴⁴

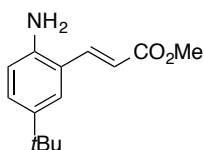
N-(4-(*tert*-Butyl)-2-methylphenyl)-4-methylbenzenesulfonamide (2-1ae)



Prepared according to GP2C from 4-(*tert*-butyl)-2-methylaniline (2-5) (230 mg, 1.41 mmol, 1.0 eq.) and *p*-toluenesulfonyl chloride (269 mg, 1.41 mmol, 1.0 eq.). Purification by flash column chromatography (Petroleum Ether 30-40/EtOAc 9:1 - 4:1) afforded the title compound as a pink solid (418 mg, 1.32 mmol, 93%).

¹H NMR (400 MHz, CDCl₃): δ = 7.63 (d, *J* = 8.2 Hz, 2H), 7.24 (d, *J* = 8.2 Hz, 2H), 7.19-7.07 (m, 3H), 6.19 (br. s, 1H), 2.41 (s, 3H), 2.02 (s, 3H), 1.27 (s, 9H); ¹³C NMR (101 MHz, CDCl₃): δ = 149.4, 143.6, 137.1, 137.0, 131.1, 129.6, 127.7, 127.2, 124.3, 123.9, 34.3, 31.3, 21.5, 17.9; HRMS (ESI⁺, *m/z*): [C₁₈H₂₃NNaO₂S]⁺ (M+Na)⁺ calc. 340.1342, found 340.1352; IR (ν , cm⁻¹): 3274, 1506, 1363, 1161; MP: 132-133°C.

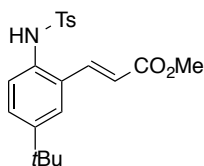
(E)-Methyl 3-(2-amino-5-(*tert*-butyl)phenyl)acrylate (2-6)



Prepared according to a modified literature procedure.³⁴⁵ To a solution of 2-bromo-4-(*tert*-butyl)aniline (**2-3**) (684 mg, 3.00 mmol, 1.0 eq.) in acetonitrile (6 mL) at room temperature, was added methyl acrylate (675 μ L, 7.50 mmol, 2.5 eq.), palladium acetate (135 mg, 0.6 mmol, 20 mol%), tri-*o*-tolyl phosphine (640 mg, 2.10 mmol, 0.7 eq.) and triethylamine (1.67 mL, 12.0 mmol, 4.0 eq.). The reaction was heated to reflux for 9 hours, cooled to room temperature and concentrated *in vacuo*. The crude residue was dissolved in EtOAc, washed with water and the aqueous phase extracted with EtOAc. The combined organic phases were dried over MgSO₄ and the solvent removed under reduced pressure. Purification by flash column chromatography (Petroleum Ether 30-40/EtOAc 9:1 - 4:1) afforded the title compound as a yellow solid (531 mg, 2.28 mmol, 76%).

¹H NMR (400 MHz, CDCl₃): δ = 7.86 (d, J = 15.8 Hz, 1H), 7.39 (d, J = 2.3 Hz, 1H), 7.24 (dd, J = 8.4 Hz, J = 2.3 Hz, 1H), 6.68 (d, J = 8.4 Hz, 1H), 6.38 (d, J = 15.8 Hz, 1H), 3.88 (br. s, 2H), 3.82 (s, 3H), 1.29 (s, 9H); ¹³C NMR (101 MHz, CDCl₃): δ = 167.8, 143.2, 141.8, 141.0, 128.8, 124.6, 119.4, 117.3, 116.8, 51.7, 34.0, 31.4; HRMS (ESI⁺, m/z): [C₁₄H₁₉NNaO₂]⁺ (M+Na)⁺ calc. 256.1308, found 256.1302; IR (ν , cm⁻¹): 3371, 3243, 1699, 1618, 1460; MP: 77-78°C.

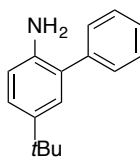
(E)-Methyl 3-(5-(*tert*-butyl)-2-(4-methylphenylsulfonamido)phenyl)acrylate (2-1af)



Prepared according to **GP2C** from (*E*)-methyl 3-(2-amino-5-(*tert*-butyl)phenyl)acrylate (**2-6**) (512 mg, 2.19 mmol, 1.0 eq.) and *p*-toluenesulfonyl chloride (418 mg, 2.19 mmol, 1.0 eq.). Purification by flash column chromatography (Petroleum Ether 30-40/EtOAc 4:1) afforded the title compound as a yellow solid (513 mg, 1.32 mmol, 60%).

¹H NMR (400 MHz, CDCl₃): δ = 7.59 (d, *J* = 8.3 Hz, 2H), 7.53 (d, *J* = 15.8 Hz, 1H), 7.46 (d, *J* = 2.2 Hz, 1H), 7.38 (dd, *J* = 8.6 Hz, *J* = 2.2 Hz, 1H), 7.27 (d, *J* = 8.6 Hz, 1H), 7.22 (d, *J* = 8.3 Hz, 2H), 6.52 (br. s, 1H), 6.18 (d, *J* = 15.8 Hz, 1H), 3.80 (s, 3H), 2.39 (s, 3H), 1.30 (s, 9H); ¹³C NMR (101 MHz, CDCl₃): δ = 166.7, 150.5, 144.0, 139.5, 136.1, 131.9, 130.0, 129.7, 128.4, 127.3, 127.1, 123.9, 120.0, 51.8, 34.7, 31.2, 21.5; HRMS (ESI⁺, *m/z*): [C₂₁H₂₅NNaO₄S]⁺ (M+Na)⁺ calc. 410.1397, found 410.1381; IR (ν, cm⁻¹): 3244, 1698, 1634, 1494, 1324; MP: 118-119°C.

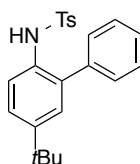
5-*tert*-Butylbiphenyl-2-amine (**2-7**)



According to a modified literature procedure.³⁴⁶ To phenyl boronic acid (731 mg, 6.00 mmol, 1.5 eq.), potassium carbonate (2.20 g, 16.0 mmol, 4.0 eq.) and tetrakis(triphenylphosphine)palladium(0) (461 mg, 0.40 mmol, 10 mol%) in toluene (30 mL) was added water (6 mL) and ethanol (10 mL), followed by 2-bromo-4-(*tert*-butyl)aniline (**2-3**) (912 mg, 4.00 mmol, 1.0 eq.). The reaction was heated to 100°C for 16 hours before cooling to room temperature, quenching with ammonium chloride and extracting into DCM. The organics were washed with water and NaHCO₃ (sat., aq.), then dried over MgSO₄ before removal of solvent *in vacuo*. Purification by flash column chromatography (CHCl₃/MeOH 99:1) afforded the title compound as a white solid (588 mg, 2.61 mmol, 65%).

¹H NMR (400 MHz, CDCl₃): δ = 7.52-7.43 (m, 4 H), 7.39-7.34 (m, 1H), 7.22 (dd, *J* = 8.3 Hz, *J* = 2.2 Hz, 1H), 7.17 (d, *J* = 2.2 Hz, 1H), 6.76 (d, *J* = 8.3 Hz, 1H), 3.66 (br. s, 2H), 1.32 (s, 9H); ¹³C NMR (101 MHz, CDCl₃): δ = 141.7, 140.8, 140.8, 140.0, 129.2, 128.8, 127.4, 127.1, 125.4, 115.6, 34.0, 31.6; HRMS (ESI⁺, *m/z*): [C₁₆H₂₀N]⁺ (*M*+H)⁺ calc. 226.1590, found 226.1588; IR (ν, cm⁻¹): 3451, 3370, 1463; MP: 68-69°C.

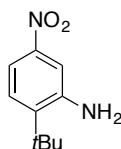
***N*-(5-(*tert*-Butyl)-[1,1'-biphenyl]-2-yl)-4-methylbenzenesulfonamide (2-1a)**



Prepared according to a modified GP2C from 5-*tert*-butylbiphenyl-2-amine (2-7) (550 mg, 2.00 mmol, 1.0 eq.) and *p*-toluenesulfonyl chloride (381 mg, 2.00 mmol, 1.0 eq.). After stirring for 24 hours, starting material was still visible by TLC and so DMAP (5 mol%) was added and the reaction was stirred for a further 24 hours. Purification by flash column chromatography (Petroleum ether 30-40/EtOAc 19:1 - 3:2) afforded the title compound as a white solid (755 mg, 1.99 mmol, 99%).

¹H NMR (400 MHz, CDCl₃): δ = 7.60 (d, *J* = 8.6 Hz, 1H), 7.49 (d, *J* = 8.3 Hz, 2H), 7.38-7.33 (m, 4H), 7.20 (d, *J* = 8.3 Hz, 2H), 7.11 (d, *J* = 2.4 Hz, 1H), 6.91-6.87 (m, 2H), 6.51 (br. s, 1H), 2.42 (s, 3H), 1.30 (s, 9H); ¹³C NMR (101 MHz, CDCl₃): δ = 147.9, 143.7, 137.9, 136.5, 134.2, 133.6, 131.0, 129.6, 129.0, 129.0, 127.9, 127.2, 125.7, 121.2, 34.4, 31.3, 21.6; HRMS (ESI⁺, *m/z*): [C₂₃H₂₅NNaO₂S]⁺ (*M*+Na)⁺ calc. 402.1498, found 402.1486; IR (ν, cm⁻¹): 3341, 1488, 1337, 1166; MP: 103-104°C.

2-(*tert*-Butyl)-5-nitroaniline (2-8)

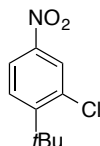


Prepared according to a modified literature procedure.³⁴⁷ To a solution of 2-*tert*-butylaniline (2.00 mL, 12.8 mmol, 1.0 eq.) in conc. sulfuric acid (6.5 mL) at 0°C was added nitric acid (846 µL, 19.2 mmol, 1.5 eq.) dropwise, whilst ensuring that the reaction temperature remained below 5°C. The reaction was stirred for a further 30 minutes at room temperature before being poured onto ice water, neutralised with NaOH (10 M, aq.) and the resultant precipitate removed by filtration. Purification by flash column chromatography (Petroleum Ether 30-40/EtOAc 9:1 - 4:1) afforded the title compound as a yellow solid (1.98 g, 10.2 mmol, 80%).

¹H NMR (400 MHz, CDCl₃): δ = 7.54 (dd, *J* = 8.7, 2.3 Hz, 1H), 7.47 (d, *J* = 2.4 Hz, 1H), 7.35 (d, *J* = 8.8 Hz, 1H), 4.17 (br. s, 2H), 1.45 (s, 9H); ¹³C NMR (101 MHz, CDCl₃): δ = 147.0, 145.5, 140.5, 127.4, 113.1, 111.4, 34.8, 29.2.

Data consistent with literature values.³⁴⁸

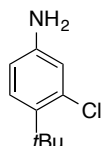
1-(*tert*-Butyl)-2-chloro-4-nitrobenzene (2-9)



Prepared according to a modified literature procedure.³⁴⁹ To a solution of 2-(*tert*-butyl)-5-nitroaniline (2-8) (194 mg, 1.00 mmol, 1.0 eq.) in acetonitrile (5 mL) was added *p*-toluenesulfonic acid (228 mg 1.20 mmol, 1.0 eq.), *tert*-butyl nitrite (238 µL, 2.00 mmol, 2.0 eq.), benzyltriethyl ammonium chloride (456 mg, 2.00 mmol, 2.0 eq.) and copper(I) chloride (2 mg, 0.01 mmol, 1 mol%). The reaction was heated to 60°C for 1 hour and cooled to room temperature before concentration under reduced pressure. Purification of the crude residue by flash column chromatography (Petroleum Ether 30-40/EtOAc 19:1 - 9:1) afforded the title compound as a yellow solid (134 mg, 0.63 mmol, 64%).

¹H NMR (400 MHz, CDCl₃): δ = 8.19 (d, *J* = 2.5 Hz, 1H), 8.02 (dd, *J* = 8.9 Hz, *J* = 2.5 Hz, 1H), 7.61 (d, *J* = 8.9 Hz, 1H), 1.43 (s, 9H); ¹³C NMR (101 MHz, CDCl₃): δ = 154.1, 146.3, 134.6, 128.5, 126.8, 121.5, 36.8, 29.2; HRMS (EI⁺, *m/z*): [C₁₀H₁₂NO₂Cl]⁺ (M)⁺ calc. 195.1, found 195.2; IR (ν, cm⁻¹): 1524, 1467, 1343; MP: 66-67 °C.

4-(*tert*-Butyl)-3-chloroaniline (2-10)

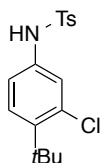


To 1-(*tert*-butyl)-2-chloro-4-nitrobenzene (2-9) (560 mg, 2.62 mmol, 1.0 eq.) and tin (872 mg, 7.54 mmol, 2.8 eq.) in water (8 mL) was added conc. HCl (3 mL). The reaction was heated to reflux for 3 hours and cooled to room temperature before neutralisation with NaOH (10 M, aq.). The resultant precipitate was removed by filtration and washed with cold water. The solid was then dissolved in EtOAc and filtered before the organic phase was washed with brine, dried over MgSO₄ and the solvent removed under reduced pressure. Purification by flash column chromatography (Petroleum Ether 30-40/EtOAc 9:1) afforded the title compound as a colourless oil (117 mg, 0.64 mmol, 24%).

¹H NMR (400 MHz, CDCl₃): δ = 7.19 (d, *J* = 8.6 Hz, 1H), 6.73 (d, *J* = 2.7 Hz, 1H), 6.53 (dd, *J* = 8.6 Hz, *J* = 2.7 Hz, 1H), 3.65 (br. s, 2H), 1.44 (s, 9H); ¹³C NMR (101 MHz, CDCl₃): δ = 144.9, 136.5, 134.1, 128.3, 118.4, 113.4, 35.3, 30.0.

Data consistent with literature values.³⁵⁰

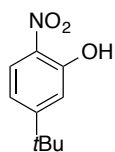
N-(4-(*tert*-Butyl)-3-chlorophenyl)-4-methylbenzenesulfonamide (2-1ah)



Prepared according to GP2C from 4-(*tert*-butyl)-3-chloroaniline (**2-10**) (114 mg, 0.62 mmol, 1.0 eq.) and *p*-toluenesulfonyl chloride (118 mg, 0.62 mmol, 1.0 eq.). Purification by flash column chromatography (Petroleum Ether 30-40/EtOAc 7:3) afforded the title compound as a white solid (183 mg, 0.54 mmol, 87%).

¹H NMR (400 MHz, CDCl₃): δ = 7.72 (d, *J* = 8.3 Hz, 2H), 7.27 (d, *J* = 8.3 Hz, 2H), 7.29-7.24 (m, 1H), 7.08 (d, *J* = 2.4 Hz, 1H), 7.00 (br. s, 1H), 6.94 (dd, *J* = 8.7 Hz, *J* = 2.6 Hz, 1H), 2.40 (s, 3H), 1.41 (s, 9H); ¹³C NMR (101 MHz, CDCl₃): δ = 144.1, 143.3, 136.1, 135.2, 134.1, 129.8, 128.4, 127.3, 124.0, 118.9, 35.7, 29.5, 21.6; HRMS (ESI⁺, *m/z*): [C₁₇H₂₀ClNNaO₂S]⁺ (M+Na)⁺ calc. 360.0795, found 360.0788; IR (ν, cm⁻¹): 3254, 1490, 1321, 1158; MP: 136-138°C.

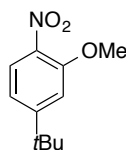
5-(*tert*-Butyl)-2-nitrophenol (**2-11**)



To 2-*tert*-butylphenol (3.00 g, 20.0 mmol, 1.0 eq.) in glacial acetic acid (5 mL) at 0°C was added nitric acid (1.07 mL, 24.0 mmol, 1.2 eq.) in glacial acetic acid (5 mL). The reaction was stirred at 0°C for 15 minutes and then for a further hour at room temperature. The reaction was then poured onto ice water and extracted into Et₂O. The combined organic phases were washed with brine, dried over MgSO₄ and the solvent removed *in vacuo*. Purification by flash column chromatography (Petroleum Ether 30-40/EtOAc 9:1) afforded the title compound as a yellow oil (964 mg, 4.94 mmol, 25%).

¹H NMR (400 MHz, CDCl₃): δ = 10.63 (s, 1H), 8.03 (d, *J* = 9.0 Hz, 1H), 7.14 (d, *J* = 2.2 Hz, 1H), 7.02 (dd, *J* = 9.0 Hz, *J* = 2.2 Hz, 1H), 1.33 (s, 9H); ¹³C NMR (101 MHz, CDCl₃): δ = 162.7, 155.0, 128.1, 124.7, 118.2, 116.4, 35.6, 30.7; HRMS (FI⁺, *m/z*): [C₁₀H₁₃NO₂]⁺ (M)⁺ calc. 195.0895, found 195.0893; IR (ν, cm⁻¹): 1621, 1529, 1322, 1227.

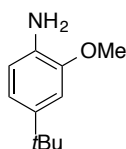
4-(*tert*-Butyl)-2-methoxy-1-nitrobenzene (**2-12**)



A slurry of 5-(*tert*-butyl)-2-nitrophenol (**2-11**) (900 mg, 4.61 mmol, 1.0 eq.) and potassium carbonate (796 mg, 5.76 mmol, 1.25 eq.) in DMF (25 mL) was stirred for 15 minutes before the addition of iodomethane (301 μ L, 4.84 mmol, 1.05 eq.). The reaction was stirred for a further 14 hours then quenched with water and extracted in EtOAc. The combined organic phases were washed with brine, dried over MgSO_4 and the solvent removed *in vacuo* to afford the title compound directly as a brown solid (919 mg, 4.39 mmol, 95%).

^1H NMR (400 MHz, CDCl_3): δ = 7.84 (d, J = 8.5 Hz, 1H), 7.07 (d, J = 1.8 Hz, 1H), 7.05 (dd, J = 8.5 Hz, J = 1.8 Hz, 1 H), 3.98 (s, 3H), 1.35 (s, 9H); ^{13}C NMR (101 MHz, CDCl_3): δ = 159.0, 153.0, 137.2, 125.7, 117.6, 110.6, 56.4, 35.6, 31.0; HRMS (ESI^+ , m/z): $[\text{C}_{11}\text{H}_{15}\text{NNaO}_3]^+$ ($\text{M}+\text{Na}$) $^+$ calc. 232.0944, found 232.0943; IR (ν , cm^{-1}): 1603, 1518, 1363, 1242, 1026; MP: 41-42°C.

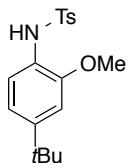
4-(*tert*-Butyl)-2-methoxyaniline (**2-13**)



To a solution of 4-(*tert*-butyl)-2-methoxy-1-nitrobenzene (**2-12**) (850 mg, 4.06 mmol, 1.0 eq.) in MeOH (25 mL) was added palladium on carbon (10 wt. % loading) (100 mg, 0.1 mmol, 2 mol%). The reaction was stirred under an atmosphere of hydrogen for 16 hours before filtration through a pad of Celite[®] (MeOH). The solvent was removed *in vacuo* to afford the title compound directly as a dark purple solid (444 mg, 2.47 mmol, 61%).

¹H NMR (400 MHz, CDCl₃): δ = 6.86 (d, *J* = 2.0 Hz, 1H), 6.83 (dd, *J* = 8.1 Hz, *J* = 2.0 Hz, 1H), 6.68 (d, *J* = 8.1 Hz, 1H), 3.88 (s, 3H), 3.70 (br. s, 2H), 1.31 (s, 9H); ¹³C NMR (101 MHz, CDCl₃): δ = 147.0, 141.9, 133.6, 117.6, 114.7, 108.2, 55.5, 34.3, 31.6; HRMS (ESI⁺, *m/z*): [C₁₁H₁₈NO]⁺ (M+H)⁺ calc. 180.1383, found 180.1375; IR (ν, cm⁻¹): 3430, 3342, 1519, 1218, 1028; MP: 40-41°C.

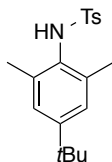
***N*-(4-(*tert*-Butyl)-2-methoxyphenyl)-4-methylbenzenesulfonamide (2-1ai)**



Prepared according to GP2C from 4-(*tert*-butyl)-2-methoxyaniline (2-13) (430 mg, 2.40 mmol, 1.0 eq.) and *p*-toluenesulfonyl chloride (458 mg, 2.40 mmol, 1.0 eq.). Purification by flash column chromatography (Hexane/EtOAc 4:1) afforded the title compound as a light brown solid (738 mg, 2.21 mmol, 92%).

¹H NMR (400 MHz, CDCl₃): δ = 7.66 (d, *J* = 8.3, 2H), 7.40 (d, *J* = 8.4 Hz, 1H), 7.20 (d, *J* = 8.3 Hz, 2H), 6.91 (dd, *J* = 8.3, *J* = 2.0 Hz, 2H), 6.75 (d, *J* = 2.0 Hz, 1H), 3.65 (s, 3H), 2.37 (s, 3H), 1.27 (s, 9H); ¹³C NMR (101 MHz, CDCl₃): δ = 149.3, 148.9, 143.6, 136.8, 129.5, 127.4, 123.6, 120.7, 118.0, 108.1, 55.7, 34.9, 31.5, 21.7; HRMS (ESI⁺, *m/z*): [C₁₈H₂₄NO₃S]⁺ (M+Na)⁺ calc. 334.1471, found 334.1461; IR (ν, cm⁻¹): 3266, 1517, 1339, 1163, 1130; MP: 94-95°C.

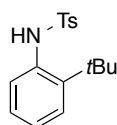
***N*-(4-(*tert*-Butyl)-2,6-dimethylphenyl)-4-methylbenzenesulfonamide (2-1aj)**



Prepared according to GP2C from 4-(*tert*-butyl)-2,6-dimethylaniline (710 mg, 4.00 mmol, 1.0 eq.) and *p*-toluenesulfonyl chloride (763 mg, 4.00 mmol, 1.0 eq.). Purification by flash column chromatography (Petroleum Ether 30-40/EtOAc 9:1 - 3:2) afforded the title compound as a white solid (1.25 g, 3.76 mmol, 94%).

¹H NMR (400 MHz, CDCl₃): δ = 7.63 (d, *J* = 8.3 Hz, 2H), 7.26 (m, *J* = 8.3 Hz, 2H), 7.02 (s, 2H), 5.83 (br. s, 1H), 2.44 (s, 3H), 2.04 (s, 6H), 1.28 (s, 9H); ¹³C NMR (101 MHz, CDCl₃): δ = 150.7, 143.5, 138.1, 137.1, 129.6, 130.0, 127.2, 125.8, 34.3, 31.3, 21.6, 19.0; HRMS (ESI⁺, *m/z*): [C₁₉H₂₅NNaO₂S]⁺ (*M*+Na)⁺ calc. 354.1498, found 354.1488; IR (ν, cm⁻¹): 3259, 1484, 1327, 1158; MP: 123-124°C.

***N*-(2-(*tert*-Butyl)phenyl)-4-methylbenzenesulfonamide (2-2ak)**

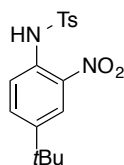


Prepared according to **GP2C** from 2-*tert*-butylaniline (1.00 mL, 7.00 mmol, 1.0 eq.) and *p*-toluenesulfonyl chloride (1.33 g, 7.00 mmol, 1.0 eq.). Purification by flash column chromatography (Petroleum Ether 30-40/EtOAc 4:1) afforded the title compound as a white solid (2.11 g, 6.95 mmol, 99%).

¹H NMR (400 MHz, CDCl₃): δ = 7.76 (d, *J* = 8.6 Hz, 2H), 7.45 (dd, *J* = 7.8 Hz, *J* = 1.5 Hz, 1H), 7.34 (dd, *J* = 7.8 Hz, *J* = 1.7 Hz, 1H), 7.27 (d, *J* = 8.1 Hz, 2H), 7.15 (td, *J* = 7.6 Hz, *J* = 1.6 Hz, 1H), 7.08 (td, *J* = 7.7 Hz, *J* = 1.6 Hz, 1H), 6.73 (s, 1H), 2.41 (s, 3H), 1.36 (s, 9H); ¹³C NMR (101 MHz, CDCl₃): δ = 143.8, 140.2, 137.1, 135.0, 129.5, 127.3, 127.0, 126.9, 125.1, 122.4, 34.2, 30.9, 21.5.

Data consistent with literature values.³⁵¹

***N*-(4-(*tert*-butyl)-2-nitrophenyl)-4-methylbenzenesulfonamide (2-1al)**

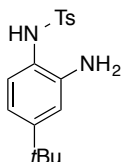


Prepared according to **GP2A** from 4-(*tert*-butyl)-2-nitroaniline (1.00 g, 5.14 mmol, 1.0 eq.) and *p*-toluenesulfonyl chloride (1.18 g, 6.17 mmol, 1.2 eq.). Purification by flash column

chromatography (Petroleum Ether 30-40/EtOAc 19:1 - 9:1) afforded the title compound as a yellow solid (1.30 g, 3.73 mmol, 73%).

^1H NMR (400 MHz, CDCl_3): δ = 9.74 (s, 1H), 8.08 (d, J = 2.2 Hz, 1H), 7.75 (d, J = 8.8 Hz, 1H), 7.74 (d, J = 8.2 Hz, 2H), 7.61 (dd, J = 8.8 Hz, J = 2.2 Hz, 1H), 7.27 (d, J = 8.2 Hz, 2H), 2.40 (s, 3H), 1.30 (s, 9H); ^{13}C NMR (101 MHz, CDCl_3): δ = 147.6, 144.7, 136.9, 136.0, 133.4, 131.4, 130.0, 127.3, 122.6, 120.9, 34.6, 30.9, 21.6; HRMS (ESI^+ , m/z): $[\text{C}_{17}\text{H}_{20}\text{N}_2\text{NaOS}]^+$ ($\text{M}+\text{Na}$) $^+$ calc. 371.1036, found 371.1036; IR (ν , cm^{-1}): 3294, 1530, 1464, 1347, 1278, 1159; MP: 88-90°C.

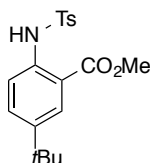
***N*-(2-Amino-4-(*tert*-butyl)phenyl)-4-methylbenzenesulfonamide (2-1am)**



To a solution of **2-1al** (1.25 g, 3.59 mmol, 1.0 eq.) in EtOH (25 mL) was added palladium on carbon (10 wt. % loading) (383 mg, 0.36 mmol, 10 mol%). The reaction was stirred under a balloon of hydrogen for 2 hours before filtration through a pad of Celite (EtOH). The solvent was removed under reduced pressure to afford the title compound directly as a pink solid (706 mg, 2.21 mmol, 62%).

^1H NMR (400 MHz, CDCl_3): δ = 7.66 (d, J = 8.2 Hz, 2H), 7.27 (d, J = 8.2 Hz, 2H), 6.77 (d, J = 2.2 Hz, 1H), 6.56 (dd, J = 8.3 Hz, J = 2.2 Hz, 1H), 6.40 (d, J = 8.3 Hz, 1H), 6.05 (br. s., 1H), 3.28 (br. s, 2H), 2.44 (s, 3H), 1.24 (s, 9H); ^{13}C NMR (101 MHz, CDCl_3): δ = 152.5, 143.9, 143.8, 136.3, 129.6, 128.2, 127.6, 118.5, 116.1, 114.4, 34.5, 31.2, 21.6; HRMS (ESI^+ , m/z): $[\text{C}_{17}\text{H}_{22}\text{N}_2\text{NaO}_2\text{S}]^+$ ($\text{M}+\text{Na}$) $^+$ calc. 341.1294, found 341.1294; IR (ν , cm^{-1}): 3385, 3257, 1509, 1320, 1159; MP: 160-161°C.

Methyl 5-(*tert*-butyl)-2-(4-methylphenylsulfonamido)benzoate (2-1an)

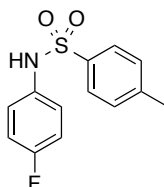


Prepared according to **GP2A** from methyl 2-amino-5-*tert*-butyl benzoate ester (544 mg, 2.60 mmol, 1.0 eq.) and *p*-toluenesulfonyl chloride (595 mg, 3.12 mmol, 1.2 eq.), with the reaction time reduced to 2 hours. Purification by flash column chromatography (Hexane/DCM 9:1 - 0:1) afforded the title compound as a yellow solid (585 mg, 1.61 mmol, 62%).

¹H NMR (400 MHz, CDCl₃): δ = 10.52 (br. s, 1H), 7.91 (d, *J* = 2.2 Hz, 1H), 7.74 (d, *J* = 8.3 Hz, 2H), 7.59 (d, *J* = 8.8 Hz, 1H), 7.48 (dd, *J* = 8.6 Hz, *J* = 2.2 Hz, 1H), 7.22 (d, *J* = 8.3 Hz, 2H), 3.88 (s, 3H), 2.37 (s, 3H), 1.27 (s, 9H); ¹³C NMR (101 MHz, CDCl₃): δ = 168.4, 145.7, 143.7, 137.9, 136.7, 131.8, 129.6, 127.5, 127.2, 118.8, 115.4, 52.3, 34.2, 31.1, 21.5; HRMS (ESI⁺, *m/z*): [C₁₉H₂₃NNaO₄S]⁺ (M+Na)⁺ calc. 384.1240, found 384.1234; IR (ν, cm⁻¹): 2960, 1686, 1249, 1167; MP: 110-113°C.

7.2.4. Fluorinated Products

N-(4-Fluorophenyl)-4-methylbenzenesulfonamide (2-14aa)



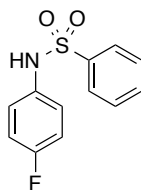
Prepared according to **GP2E** from *N*-(4-(*tert*-butyl)phenyl)-4-methylbenzenesulfonamide (2-1aa) (303 mg, 1.00 mmol, 1.0 eq.) and HF·pyridine (70%) (26 μL, 1.00 mmol, 1.0 eq.). Purification by flash column chromatography (Petroleum

Ether 30-40/EtOAc 9:1 - 4:1) afforded the title compound as a yellow solid (162 mg, 0.61 mmol, 61%).

^1H NMR (400 MHz, CDCl_3): δ = 7.68 (d, J = 8.1 Hz, 2H), 7.64 (br. s, 1H, NH), 7.21 (d, J = 8.1 Hz, 2H), 7.13-7.05 (m, 2H), 6.90 (t, J = 6.9 Hz, 2H), 2.36 (s, 3H); ^{13}C NMR (101 MHz, CDCl_3): δ = 160.5 (d, J = 244.5 Hz), 144.1, 135.5, 132.5 (d, J = 3.2 Hz), 129.7, 127.3, 124.3 (d, J = 8.0 Hz), 116.0 (d, J = 22.4 Hz), 21.5; ^{19}F NMR (377 MHz, CDCl_3) δ = -116.6.

Data consistent with literature values.³⁵²

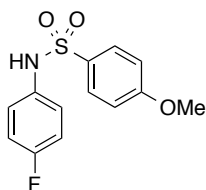
N-(4-Fluorophenyl)benzenesulfonamide (**2-14ba**)



Prepared according to GP2E from *N*-(4-(*tert*-butyl)phenyl)benzenesulfonamide (**2-1ba**) (289 mg, 1.00 mmol, 1.0 eq.) and HF·pyridine (70%) (26 μL , 1.00 mmol, 1.0 eq.). Purification by flash column chromatography (Petroleum Ether 30-40/EtOAc 9:1) afforded the title compound as a white solid (151 mg, 0.60 mmol, 60%).

^1H NMR (400 MHz, CDCl_3): δ = 7.79-7.75 (m, 2H), 7.60-7.52 (m, 1H), 7.51-7.40 (m, 2H), 7.19 (br. s, 1H), 7.11-7.03 (m, 2H), 6.99-6.87 (m, 2H); ^{13}C NMR (101 MHz, CDCl_3): δ = 160.7 (d, J = 246.4 Hz), 138.6, 133.2, 132.1 (d, J = 3.2 Hz), 129.1, 127.3, 124.7 (d, J = 9.5 Hz), 116.1 (d, J = 22.3 Hz); ^{19}F NMR (471 MHz, CDCl_3) δ = -116.1; HRMS (ESI^+ , m/z): $[\text{C}_{12}\text{H}_{10}\text{FNNaO}_2\text{S}]^+$ ($\text{M}+\text{Na}$) $^+$ calc. 274.0308, found 274.0302; IR (ν , cm^{-1}): 3259, 1507, 1328, 1157, 1091; MP: 106-108°C.

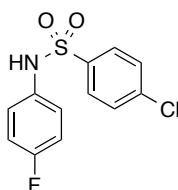
N-(4-Fluorophenyl)-4-methoxybenzenesulfonamide (2-14ca)



Prepared according to **GP2E** from *N*-(4-(*tert*-butyl)phenyl)-4-methoxybenzenesulfonamide (**2-1ca**) (319 mg, 1.00 mmol, 1.0 eq.) and HF·pyridine (70%) (26 μ L, 1.00 mmol, 1.0 eq.). Purification by flash column chromatography (Petroleum Ether 30-40/EtOAc 17:3 - 7:3) afforded the title compound as a white solid (176 mg, 0.59 mmol, 59%).

^1H NMR (400 MHz, CDCl_3): δ = 7.66 (d, J = 8.8 Hz, 1H), 7.06-7.01 (m, 2H), 6.97-6.92 (m, 2H), 6.90 (d, J = 8.8 Hz, 2H), 6.58 (br. s, 1H), 3.84 (s, 3H); ^{13}C NMR (101 MHz, CDCl_3): δ = 158.8, 156.2 (d, J = 244.5 Hz), 128.1 (d, J = 3.2 Hz), 125.7, 125.1, 120.1 (d, J = 9.6 Hz), 111.7 (d, J = 24.0 Hz), 109.9, 51.2; ^{19}F NMR (471 MHz, CDCl_3) δ = -116.4; HRMS (ESI^+ , m/z): $[\text{C}_{13}\text{H}_{12}\text{FNNaO}_3\text{S}]^+ (\text{M}+\text{Na})^+$ calc. 304.0414, found 304.0403; IR (ν , cm^{-1}): 3246, 1449, 1333, 1149, 1090; MP: 72-74°C.

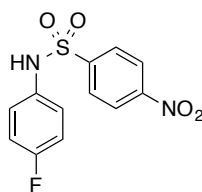
4-Chloro-*N*-(4-fluorophenyl)benzenesulfonamide (2-14da)



Prepared according to **GP2E** from *N*-(4-(*tert*-butyl)phenyl)-4-chlorobenzenesulfonamide (**2-1da**) (323 mg, 1.00 mmol, 1.0 eq.) and HF·pyridine (70%) (26 μ L, 1.00 mmol, 1.0 eq.). Purification by flash column chromatography (Petroleum Ether 30-40/EtOAc 9:1 - 7:3) afforded the title compound as an off-white solid (166 mg, 0.58 mmol, 58%).

¹H NMR (400 MHz, DMSO-d₆): δ = 10.32 (br. s, 1H), 7.74-7.67 (m, 2H), 7.66-7.61 (m, 2H), 7.15-7.04 (m, 4H); ¹³C NMR (126 MHz, DMSO-d₆): δ = 159.3 (d, *J* = 242.2 Hz), 138.0, 137.8, 133.5 (d, *J* = 2.9 Hz), 129.4, 128.6, 123.2 (d, *J* = 8.6 Hz), 116.0 (d, *J* = 21.9 Hz); ¹⁹F NMR (471 MHz, DMSO-d₆) δ = -115.5; HRMS (ESI⁺, *m/z*): [C₁₂H₉ClFNNaO₂S]⁺ (*M*+Na)⁺ calc. 307.9199, found 307.9906; IR (ν, cm⁻¹): 3261, 1507, 1332, 1163, 1094, 755; MP: 106-108°C.

***N*-(4-Fluorophenyl)-4-nitrobenzenesulfonamide (2-14ea)**

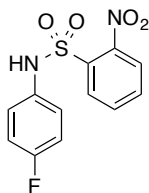


Prepared according to GP2E from *N*-(4-(*tert*-butyl)phenyl)-4-nitrobenzenesulfonamide (2-1ea) (334 mg, 1.00 mmol, 1.0 eq.) and HF·pyridine (70%) (104 μL, 4.00 mmol, 1.0 eq.). Purification by flash column chromatography (Petroleum Ether 30-40/EtOAc 17:3 - 7:3) afforded the title compound as a yellow solid (193 mg, 0.65 mmol, 65%).

¹H NMR (400 MHz, DMSO-d₆): δ = 10.56 (br. s, 1H), 8.36 (d, *J* = 8.8 Hz, 2H) 7.94 (d, *J* = 8.8 Hz, 2H), 7.10 (d, *J* = 1.3 Hz, 2H), 7.09 (br. s, 2H); ¹³C NMR (101 MHz, DMSO-d₆): δ = 160.4 (d, *J* = 241.3 Hz), 150.7, 145.4, 133.9, 129.2, 125.5, 124.5 (d, *J* = 8.0 Hz), 117.0 (d, *J* = 22.4 Hz); ¹⁹F NMR (471 MHz, CDCl₃) δ = -114.2.

Data consistent with literature values.³⁵³

***N*-(4-Fluorophenyl)-2-nitrobenzenesulfonamide (2-14fa)**

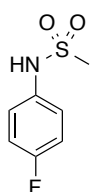


Prepared according to **GP2E** from *N*-(4-(*tert*-butyl)phenyl)-2-nitrobenzenesulfonamide (**2-1fa**) (334 mg, 1.00 mmol, 1.0 eq.) and HF·pyridine (70%) (104 μ L, 4.00 mmol, 1.0 eq.). Purification by flash column chromatography (Petroleum Ether 30-40/EtOAc 17:3 - 7:3) afforded the title compound as a yellow solid (118 mg, 0.40 mmol, 40%).

^1H NMR (400 MHz, CDCl_3): δ = 7.87 (dd, J = 8.0 Hz, J = 1.1 Hz, 1H), 7.77 (dd, J = 7.8 Hz, J = 1.5 Hz, 1H), 7.72 (td, J = 7.8 Hz, J = 1.4 Hz, 1H), 7.60 (dd, J = 7.8 Hz, J = 1.3 Hz, 1H), 7.26 (s, 1H), 7.17 (dd, J = 8.8 Hz, J = 4.8 Hz, 2H), 6.92-7.01 (m, 2H); ^{13}C NMR (101 MHz, CDCl_3): δ = 161.3 (d, J = 247.7 Hz), 148.2, 134.1, 132.7, 131.9, 131.8, 131.3 (d, J = 3.2 Hz), 126.0 (d, J = 9.6 Hz), 125.3, 116.3 (d, J = 22.4 Hz); ^{19}F NMR (471 MHz, CDCl_3): δ = -114.3.

Data consistent with literature values.³⁵⁴

***N*-(4-Fluorophenyl)methanesulfonamide (2-14ga)**

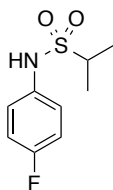


Prepared according to **GP2E** from *N*-(4-(*tert*-butyl)phenyl)methanesulfonamide (**2-1ga**) (227 mg, 1.00 mmol, 1.0 eq.) and HF·pyridine (70%) (26 μ L, 1.00 mmol, 1.0 eq.). Purification by flash column chromatography (Petroleum Ether 30-40/EtOAc 4:1) afforded the title compound as an off-white solid (102 mg, 0.54 mmol, 54%).

^1H NMR (400 MHz, CDCl_3): δ = 7.21-7.15 (m, 2H), 7.03-6.95 (m, 2H), 6.90 (br. s, 1H), 2.92 (s, 3H); ^{13}C NMR (101 MHz, CDCl_3): δ = 160.7 (d, J = 244.8 Hz), 132.5 (d, J = 3.2 Hz), 123.9 (d, J = 7.9 Hz), 116.5 (d, J = 23.8 Hz), 39.1; ^{19}F NMR (377 MHz, CDCl_3) δ = -116.2.

Data consistent with literature values.³⁵⁵

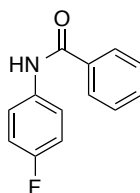
***N*-(4-Fluorophenyl)propane-2-sulfonamide (2-14ha)**



Prepared according to GP2E from *N*-(4-(*tert*-butyl)phenyl)propane-2-sulfonamide (2-14a) (255 mg, 1.00 mmol, 1.0 eq.) and HF·pyridine (70%) (104 μ L, 4.00 mmol, 4.0 eq.). Purification by flash column chromatography (Petroleum Ether 30-40/EtOAc 17:3) afforded the title compound as a pale orange solid (125 mg, 0.57 mmol, 57%).

^1H NMR (400 MHz, CDCl_3): δ = 7.27-7.21 (m, 2H), 7.08-7.00 (m, 2H), 6.60 (br. s, 1H), 3.27 (sept., J = 6.9 Hz, 1H), 1.40 (d, J = 6.8 Hz, 6H); ^{13}C NMR (101 MHz, CDCl_3): δ = 160.3 (d, J = 244.8 Hz), 132.8 (d, J = 3.2 Hz), 123.1 (d, J = 9.5 Hz), 116.4 (d, J = 22.3 Hz), 52.5, 16.5; ^{19}F NMR (377 MHz, CDCl_3) δ = -117.1; HRMS (ESI^+ , m/z): $[\text{C}_9\text{H}_{12}\text{FNNaO}_2\text{S}]^+$ ($M+\text{Na}$) $^+$ calc. 240.0465, found 240.0474; IR (ν , cm^{-1}): 3257, 1506, 1322, 1140, 1099; MP: 74-76°C.

***N*-(4-Fluorophenyl)benzamide (2-14ia)**



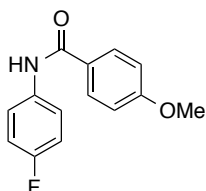
Prepared according to GP2E from *N*-(4-(*tert*-butyl)phenyl)benzamide (2-11a) (253 mg, 1.00 mmol, 1.0 eq.) and HF·pyridine (70%) (104 μ L, 4.00 mmol, 4.0 eq.). Purification by flash column chromatography (Petroleum Ether 30-40/EtOAc 19:1 - 9:1) afforded the title compound as a white solid (148 mg, 0.69 mmol, 69%).

^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ = 10.32 (br. s, 1H), 7.99-7.93 (m, 2H), 7.84-7.76 (m, 2H), 7.65-7.58 (m, 1H), 7.58-7.51 (m, 2H), 7.26-7.16 (m, 2H); ^{13}C NMR (101 MHz, $\text{DMSO}-d_6$): δ =

165.9, 158.8 (d, $J = 240.0$ Hz), 136.0, 135.3, 132.1, 115.7 (d, $J = 22.3$ Hz), 128.9, 128.1, 122.6 (d, $J = 7.9$ Hz); ^{19}F NMR (377 MHz, DMSO- d_6) $\delta = -118.9$.

Data consistent with literature values.³⁵⁶

***N*-(4-Fluorophenyl)-4-methoxybenzamide (2-14ja)**

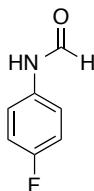


Prepared according to GP2E, from *N*-(4-(*tert*-butyl)phenyl)-4-methoxybenzamide (2-1ja) (283 mg, 1.00 mmol, 1.0 eq.) and HF·pyridine (70%) (104 μL , 4.00 mmol, 4.0 eq.). Purification by flash column chromatography (Petroleum Ether 30-40/EtOAc 4:1 - 3:2) afforded the title compound as a white solid (104 mg, 0.42 mmol, 42%).

^1H NMR (400 MHz, DMSO- d_6): $\delta = 10.16$ (s, 1H), 7.96 (d, $J = 9.0$ Hz, 2H), 7.82-7.76 (m, 2H), 7.19 (t, $J = 8.8$ Hz, 2H), 7.07 (d, $J = 8.8$ Hz, 2H), 3.85 (s, 3H); ^{13}C NMR (101 MHz, DMSO- d_6): $\delta = 165.3$, 162.4, 158.6 (d, $J = 240.0$ Hz), 136.2 (d, $J = 3.2$ Hz), 130.0, 127.3, 122.6 (d, $J = 7.9$ Hz), 115.6 (d, $J = 22.3$ Hz), 114.1, 55.9; ^{19}F NMR (377 MHz, DMSO- d_6) $\delta = -119.3$.

Data consistent with literature values.³⁵⁶

***N*-(4-Fluorophenyl)formamide (2-14ka)**



Prepared according to GP2E, from *N*-(4-(*tert*-butyl)phenyl)formamide (2-1ka) (177 mg, 1.00 mmol, 1.0 eq.) and HF·pyridine (70%) (104 μL , 4.00 mmol, 4.0 eq.), with reaction time increased to 30 minutes. Purification by flash column chromatography

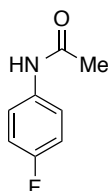
(Petroleum Ether 30-40/EtOAc 9:1) afforded the title compound as a white solid (38 mg, 0.27 mmol, 27%). Formed as a mixture of rotamers (1:1).

Trans isomer: ^1H NMR (400 MHz, DMSO- d_6): δ = 10.13 (d, J = 11.0 Hz, 1H), 8.68 (d, J = 11.0 Hz, 1H), 7.24-7.11 (m, 4H); ^{13}C NMR (101 MHz, DMSO- d_6): δ = 163.6, 159.0 (d, J = 239.7 Hz), 135.6 (d, J = 3.2 Hz), 120.4 (d, J = 8.0 Hz), 116.9 (d, J = 22.4 Hz); ^{19}F NMR (377 MHz, DMSO- d_6) δ = -119.7.

Cis isomer: ^1H NMR (400 MHz, DMSO- d_6): δ = 10.23 (br. s, 1H), 8.25 (d, J = 2.0 Hz, 1H), 7.63-7.57 (m, 2H), 7.24-7.11 (m, 2H); ^{13}C NMR (101 MHz, DMSO- d_6): δ = 160.4, 159.0 (d, J = 239.7 Hz), 135.5 (d, J = 3.2 Hz), 121.8 (d, J = 8.0 Hz), 116.3 (d, J = 22.4 Hz); ^{19}F NMR (377 MHz, DMSO- d_6) δ = -118.8.

Data consistent with literature values.³⁵⁷

N-(4-(Fluoro)phenyl)acetamide (2-14la)

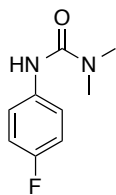


Prepared according to GP2E, from *N*-(4-(*tert*-butyl)phenyl)acetamide (2-11a) (191 mg, 1.00 mmol, 1.0 eq.) and HF·pyridine (70%) (104 μL , 4.00 mmol, 4.0 eq.). Purification by flash column chromatography (Petroleum Ether 30-40/EtOAc 7:3 - 3:2) afforded the title compound as a white solid (81 mg, 0.53 mmol, 53%).

^1H NMR (400 MHz, DMSO- d_6): δ = 10.00 (br. s, 1H), 7.63-7.55 (m, 2H), 7.17-7.08 (m, 2H), 2.03 (s, 3H); ^{13}C NMR (101 MHz, DMSO- d_6): δ = 168.6, 158.3 (d, J = 235.2 Hz), 136.2, 121.1 (d, J = 7.9 Hz), 115.7 (d, J = 22.3 Hz), 24.3; ^{19}F NMR (377 MHz, DMSO- d_6) δ = -119.8.

Data consistent with literature values.³⁵⁸

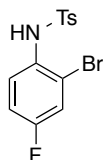
3-(4-Fluorophenyl)-1,1-dimethylurea (2-140a)



Prepared according to **GP2E**, from 3-(4-(*tert*-butyl)phenyl)-1,1-dimethylurea (**2-10a**) (205 mg, 1.00 mmol, 1.0 eq.) and HF·pyridine (70%) (104 μ L, 4.00 mmol, 4.0 eq.). Purification by flash column chromatography (Hexane/EtOAc 3:1) afforded the title compound as a white solid (93 mg, 0.51 mmol, 51%).

^1H NMR (400 MHz, CDCl_3): δ = 7.34-7.28 (m, 2H), 6.99-6.92 (m, 2H), 6.40 (br. s, 1H), 3.00 (s, 6H); ^{13}C NMR (101 MHz, CDCl_3): δ = 160.0 (d, J = 241.6 Hz), 156.0, 135.3 (d, J = 2.4 Hz), 122.1 (d, J = 8.0 Hz), 115.5 (d, J = 22.3 Hz), 36.6; ^{19}F NMR (377 MHz, CDCl_3): δ = -120.4; HRMS (ESI $^+$, m/z): $[\text{C}_9\text{H}_{11}\text{FN}_2\text{NaO}]^+$ ($\text{M}+\text{Na}$) $^+$ calc. 205.0748, found 205.0748; IR (ν , cm^{-1}): 3293, 1641, 1511, 1098; MP: 117-118°C.

N-(2-Bromo-4-fluorophenyl)-4-methylbenzenesulfonamide (2-14ab)

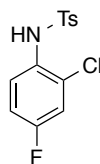


Prepared according to **GP2E** from *N*-(2-bromo-4-*tert*-butylphenyl)-4-methylbenzenesulfonamide (**2-1ab**) (382 mg, 1.00 mmol, 1.0 eq.) and HF·pyridine (70%) (104 μ L, 4.00 mmol, 4.0 eq.). Purification by flash column chromatography (Petroleum Ether 30-40/EtOAc 19:1 - 9:1) afforded the title compound as a pale orange solid (179 mg, 0.52 mmol, 52%).

^1H NMR (400 MHz, CDCl_3): δ = 7.68 (dd, J = 9.0 Hz, J = 5.4 Hz, 1H), 7.60 (d, J = 8.3 Hz, 2H), 7.22 (d, J = 8.3 Hz, 2H), 7.16 (dd, J = 7.7 Hz, J = 2.8 Hz, 1H), 7.03 (ddd, J = 8.9 Hz, J = 7.9 Hz, J

= 2.9 Hz, 1H), 6.80 (br. s, 1H), 2.39 (s, 3H); ^{13}C NMR (101 MHz, CDCl_3): δ = 160.0 (d, J = 249.5 Hz), 144.5, 135.8, 131.3 (d, J = 3.2 Hz), 129.9, 127.5, 125.2 (d, J = 8.7 Hz), 119.8 (d, J = 25.4 Hz), 117.1 (d, J = 9.5 Hz), 115.9 (d, J = 22.3 Hz), 21.8; ^{19}F NMR (377 MHz, CDCl_3) δ = -114.2; HRMS (ESI $^+$, m/z): $[\text{C}_{13}\text{H}_{11}^{79}\text{BrFNNaO}_2\text{S}]^+$ ($M+\text{Na}$) $^+$ calc. 365.9570, found 365.9570; IR (ν , cm^{-1}): 3260, 1486, 1334, 1161, 1090; MP: 92-93°C.

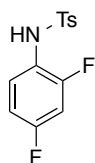
***N*-(2-Chloro-4-fluorophenyl)-4-methylbenzenesulfonamide (2-14ac)**



Prepared according to GP2E from *N*-(2-chloro-4-*tert*-butylphenyl)-4-methylbenzenesulfonamide (2-1ac) (338 mg, 1.00 mmol, 1.0 eq.) and HF·pyridine (70%) (104 μL , 4.00 mmol, 4.0 eq.). Purification by flash column chromatography (Hexane/EtOAc 9:1 - 4:1) afforded the title compound as a pale orange solid (162 mg, 0.54 mmol, 54%).

^1H NMR (400 MHz, CDCl_3): δ = 7.66 (dd, J = 9.1 Hz, J = 5.4 Hz, 1H), 7.61 (d, J = 8.4 Hz, 2H), 7.14 (d, J = 8.0 Hz, 2H), 7.22 (d, J = 8.1 Hz, 1H), 7.02-6.95 (m, 1H), 6.89 (br. s, 1H), 2.38 (s, 3H); ^{13}C NMR (101 MHz, CDCl_3): δ = 159.7 (d, J = 249.5 Hz), 144.5, 135.8, 129.9 (d, J = 3.2 Hz), 129.7, 127.4, 127.0 (d, J = 10.3 Hz), 125.2 (d, J = 8.7 Hz), 116.7 (d, J = 26.2 Hz), 115.2 (d, J = 22.3 Hz), 21.7; ^{19}F NMR (377 MHz, CDCl_3): δ = -114.2; HRMS (ESI $^+$, m/z): $[\text{C}_{13}\text{H}_{11}\text{ClFNNaO}_2\text{S}]^+$ ($M+\text{Na}$) $^+$ calc. 322.0075, found 322.0075; IR (ν , cm^{-1}): 3250, 1490, 1339, 1165, 1091, 729; MP: 102-103°C.

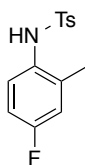
***N*-(2,4-Difluorophenyl)-4-methylbenzenesulfonamide (2-14ad)**



Prepared according to GP2E from *N*-(2-fluoro-4-*tert*-butylphenyl)-4-methylbenzenesulfonamide (**2-1ad**) (193 mg, 0.60 mmol, 1.0 eq.) and HF·pyridine (70%) (62 μ L, 2.40 mmol, 4.0 eq.). Purification by flash column chromatography (Hexane/EtOAc 9:1) afforded the title compound as an orange solid (77 mg, 0.27 mmol, 45%).

^1H NMR (400 MHz, CDCl_3): δ = 7.63 (d, J = 8.3 Hz, 2H), 7.56 (td, J = 9.0 Hz, J = 5.8 Hz, 1H), 7.23 (d, J = 8.1 Hz, 2H), 6.88-6.81 (m, 2H), 6.71 (ddd, J = 10.2 Hz, J = 8.3 Hz, J = 2.8 Hz, 1H), 2.39 (s, 3H); ^{13}C NMR (101 MHz, CDCl_3): δ = 160.2 (dd, J = 248.8 Hz, J = 11.1 Hz), 155.0 (dd, J = 248.8 Hz, J = 11.9 Hz), 144.4, 135.8, 129.9, 127.3, 126.1 (dd, J = 9.5 Hz, J = 1.6 Hz), 120.8 (dd, J = 12.7 Hz, J = 4.0 Hz), 111.9 (dd, J = 22.3 Hz, J = 4.8 Hz), 104.2 (dd, J = 27.0 Hz, J = 23.8 Hz), 21.7; ^{19}F NMR (377 MHz, CDCl_3): δ = -123.4 (d, J = 5.7 Hz, 1F), -112.0 (d, J = 5.7 Hz, 1F); HRMS (ESI⁺, m/z): $[\text{C}_{13}\text{H}_{11}\text{F}_2\text{NNaO}_2\text{S}]^+$ ($M+\text{Na}$)⁺ calc. 306.0371, found 306.0368; IR (ν , cm^{-1}): 3250, 1506, 1335, 1160, 1092; MP: 102-103°C.

N-(4-Fluoro-2-methylphenyl)-4-methylbenzenesulfonamide (**2-14ae**)

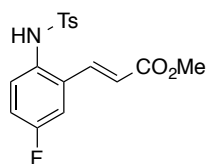


Prepared according to GP2E from *N*-(2-bromo-4-*tert*-butylphenyl)-4-methylbenzenesulfonamide (**2-1ae**) (190 mg, 0.60 mmol, 1.0 eq.) and HF·pyridine (70%) (62 μ L, 2.40 mmol, 4.0 eq.). Purification by flash column chromatography (Petroleum Ether 30-40/EtOAc 17:3) afforded the title compound as a pink solid (100 mg, 0.36 mmol, 60%).

^1H NMR (400 MHz, CDCl_3): δ = 7.60 (d, J = 8.2 Hz, 2H), 7.24 (d, J = 8.2 Hz, 2H), 7.18-7.23 (m, 1H), 6.85-6.82 (m, 1H), 6.81 (d, J = 8.8 Hz, 1H), 6.65 (br. s, 1H), 2.41 (s, 3H), 1.99 (s, 3H); ^{13}C NMR (101 MHz, CDCl_3): δ = 161.0 (d, J = 246.4 Hz), 143.9, 136.5, 135.6 (d, J = 7.9 Hz), 130.2 (d,

$J = 3.2$ Hz), 129.7, 127.7 (d, $J = 9.5$ Hz), 127.2, 117.3 (d, $J = 22.3$ Hz), 113.5 (d, $J = 22.3$ Hz), 21.6, 17.8; ^{19}F NMR (377 MHz, CDCl_3) $\delta = -115.5$; HRMS (ESI^+ , m/z): $[\text{C}_{14}\text{H}_{14}\text{FNNaO}_2\text{S}]^+$ ($\text{M}+\text{Na}$) $^+$ calc. 302.0621, found 302.0620; IR (ν , cm^{-1}): 3270, 1497, 1329, 1161, 1092; MP: 95–96°C.

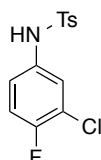
(E)-Methyl 3-(5-fluoro-2-(4-methylphenylsulfonamido)phenyl)acrylate (2-14af)



Prepared according to GP2E from methyl 5-(*tert*-butyl)-2-(4-methylphenylsulfonamido)benzoate (**2-1af**) (170 mg, 0.44 mmol, 1.0 eq.) and $\text{HF}\cdot\text{pyridine}$ (70%) (46 μL , 1.76 mmol, 4.0 eq.). Purification by flash column chromatography (Petroleum Ether 30-40/EtOAc 17:3) afforded the title compound as a white solid (80 mg, 0.23 mmol, 52%).

^1H NMR (400 MHz, CDCl_3): $\delta = 7.53$ (d, $J = 8.2$ Hz, 2H), 7.55–7.48 (m, 1H), 7.36 (dd, $J = 9.0$ Hz, $J = 5.1$ Hz, 1H), 7.20 (d, $J = 8.2$ Hz, 2H), 7.15 (dd, $J = 9.0$ Hz, $J = 2.9$ Hz, 1H), 7.04–7.10 (m, 1H), 7.03 (br. s, 1H), 6.08 (d, $J = 15.9$ Hz, 1H), 3.79 (s, 3H), 2.37 (s, 3H); ^{13}C NMR (101 MHz, CDCl_3): $\delta = 166.6$, 161.5 (d, $J = 246.4$ Hz), 144.2, 138.3, 135.5, 133.4 (d, $J = 7.9$ Hz), 130.7 (d, $J = 9.5$ Hz), 130.6 (d, $J = 3.2$ Hz), 129.7, 127.4, 121.1, 117.9 (d, $J = 22.3$ Hz), 113.3 (d, $J = 23.8$ Hz), 52.0, 21.5; ^{19}F NMR (377 MHz, CDCl_3): $\delta = -113.1$; HRMS (ESI^+ , m/z): $[\text{C}_{17}\text{H}_{16}\text{FNNaO}_4\text{S}]^+$ ($\text{M}+\text{Na}$) $^+$ calc. 372.0676, found 372.0663; IR (ν , cm^{-1}): 3244, 1700, 1632, 1490, 1328, 1161, 1092; MP: 152–155°C.

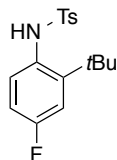
N-(3-Chloro-4-fluorophenyl)-4-methylbenzenesulfonamide (2-1ah)



Prepared according to **GP2E** from *N*-(4-(*tert*-butyl)-3-chlorophenyl)-4-methylbenzenesulfonamide (**2-1ah**) (169 mg, 0.50 mmol, 1.0 eq.) and HF·pyridine (70%) (52 μ L, 2.00 mmol, 4.0 eq.). Purification by flash column chromatography (Hexane/EtOAc 9:1 - 4:1) afforded the title compound as an off white solid (91 mg, 0.30 mmol, 61%).

^1H NMR (400 MHz, CDCl_3): δ = 7.67 (d, J = 8.3 Hz, 2H), 7.27 (d, J = 8.1 Hz, 2H), 7.19 (dd, J = 6.3 Hz, J = 2.5 Hz, 1H), 7.15 (br. s, 1H), 7.03-6.94 (m, 2H), 2.41 (s, 3H); ^{13}C NMR (101 MHz, CDCl_3): δ = 156.0 (d, J = 247.8 Hz), 144.4, 135.4, 133.1 (d, J = 3.4 Hz), 129.2, 127.3, 124.3, 121.9 (d, J = 7.2 Hz), 121.6 (d, 19.1 Hz), 117.0 (d, J = 22.3 Hz), 21.6; ^{19}F NMR (377 MHz, CDCl_3): δ = -118.9; HRMS (ESI $^+$, m/z): $[\text{C}_{13}\text{H}_{11}\text{ClFNNaO}_2\text{S}]^+$ ($\text{M}+\text{Na}$) $^+$ calc. 322.0075, found 322.0075; IR (ν , cm^{-1}): 3251, 1499, 1326, 1161, 1091, 669; MP: 110-112°C.

***N*-(2-(*tert*-Butyl)-4-fluorophenyl)-4-methylbenzenesulfonamide (2-14ak)**

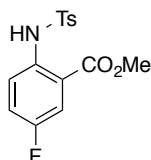


Prepared according to **GP2E** from *N*-(2-(*tert*-butyl)phenyl)-4-methylbenzenesulfonamide (**2-2ak**) (303 mg, 1.00 mmol, 1.0 eq.) and HF·pyridine (70%) (104 μ L, 4.00 mmol, 4.0 eq.). Purification by flash column chromatography (Hexane/EtOAc 9:1) afforded the title compound as a purple solid (125 mg, 0.39 mmol, 39%).

^1H NMR (400 MHz, CDCl_3): δ = 7.68 (d, J = 8.3 Hz, 2H), 7.26-7.22 (m, 3H), 7.01 (dd, J = 11.5 Hz, J = 2.9 Hz, 1H), 6.77 (ddd, J = 8.8 Hz, J = 7.1 Hz, J = 2.9 Hz, 1H), 6.54 (br. s, 1H), 2.38 (s, 3H), 1.28 (s, 9H); ^{13}C NMR (101 MHz, CDCl_3): δ = 160.5 (d, J = 244.0 Hz), 145.2 (d, J = 7.2 Hz), 144.1, 137.4, 130.9 (d, J = 2.4 Hz), 129.8, 127.5, 126.0 (d, J = 8.7 Hz), 114.6 (d, J = 23.8 Hz), 113.4 (d, J = 22.3 Hz), 34.9, 30.9, 21.7; ^{19}F NMR (377 MHz, CDCl_3): δ = -115.7; HRMS (ESI $^+$, m/z):

$[\text{C}_{17}\text{H}_{20}\text{FNNaO}_2\text{S}]^+ (\text{M}+\text{Na})^+$ calc. 344.1091, found 344.1086; IR (ν , cm^{-1}): 3281, 1481, 1326, 1186, 1093; MP: 82-84°C.

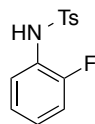
Methyl 5-fluoro-2-(4-methylphenylsulfonamido)benzoate (2-14an)



Prepared according to **GP2E** from methyl 5-(*tert*-butyl)-2-(4-methylphenylsulfonamido)benzoate (**2-1an**) (285 mg, 0.78 mmol, 1.0 eq.) and HF·pyridine (70%) (81 μL , 3.12 mmol, 4.0 eq.). Purification by flash column chromatography (Hexane/EtOAc 9:1 - 4:1) afforded the title compound as a white solid (52 mg, 0.16 mmol, 21%).

^1H NMR (400 MHz, CDCl_3): δ = 10.28 (br. s, 1H), 7.72 (dd, J = 9.2 Hz, J = 4.8 Hz, 1H), 7.68 (d, J = 8.3 Hz, 2H), 7.58 (dd, J = 9.0 Hz, J = 3.2 Hz, 1H), 7.22 (d, J = 8.1 Hz, 2H), 7.22-7.16 (m, 1H), 3.87 (s, 3H), 2.37 (s, 3H); ^{13}C NMR (101 MHz, CDCl_3): δ = 167.2 (d, J = 3.2 Hz), 158.0 (d, J = 246.4 Hz), 144.0, 136.6 (d, J = 3.2 Hz), 136.1, 129.6, 127.3, 121.9 (d, J = 4.8 Hz), 121.7 (d, J = 22.3 Hz), 117.7 (d, J = 6.4 Hz), 117.2 (d, J = 25.4 Hz), 52.7, 21.5; ^{19}F NMR (377 MHz, CDCl_3): δ = -118.3; HRMS (ESI $^+$, m/z): $[\text{C}_{15}\text{H}_{14}\text{FNNaO}_4\text{S}]^+ (\text{M}+\text{Na})^+$ calc. 346.0520, found 346.0513; IR (ν , cm^{-1}): 3184, 1691, 1494, 1342, 1229, 1162, 1121, 1090; MP: 65-67°C.

***N*-(2-Fluorophenyl)-4-methylbenzenesulfonamide (2-17)**



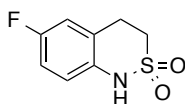
Prepared according to **GP2C** from 2-fluoroaniline (556 mg, 5.00 mmol, 1.0 eq.) and *p*-toluenesulfonyl chloride (1143.9 mg, 6.0 mmol, 1.2 eq.) (763 mg, 4.00 mmol, 1.0 eq.).

Purification by flash column chromatography (Hexane/EtOAc 9:1) afforded the title compound as a white solid (1.11 g, 4.20 mmol, 84%).

^1H NMR (400 MHz, CDCl_3): δ = 7.59 (d, J = 8.31 Hz, 2H) 7.51 (td, J = 7.64 Hz, J = 2.32 Hz, 1H) 7.14 (d, J = 8.07 Hz, 2H) 7.04-6.94 (m, 2H) 6.91-6.84 (m, 1H) 6.72 (br. s, 1 H) 2.30 (s, 3 H); ^{13}C NMR (101 MHz, CDCl_3): δ = 153.9 (d, J = 244.8 Hz), 144.2, 135.9, 129.7, 127.2, 126.1 (d, J = 8.0 Hz), 124.8 (d, J = 4.0 Hz), 123.3, 115.4 (d, J = 19.1 Hz), 21.6; ^{19}F NMR (377 MHz, CDCl_3): δ = -129.7.

Data consistent with literature values.³⁵⁹

6-Fluoro-3,4-dihydro-1*H*-2,1-benzothiazine 2,2-dioxide (2-18)



Prepared according to GP2E from 6-*tert*-butyl-3,4-dihydro-1*H*-2,1-benzothiazine 2,2-dioxide (220 mg, 0.92 mmol, 1.0 eq.) and HF·pyridine (70%) (96 μL , 3.68 mmol, 4.0 eq.). Purification by flash column chromatography (DCM/MeOH 9:1) afforded the title compound as a off-white solid (97 mg, 0.48 mmol, 52%).

^1H NMR (400 MHz, MeOD): δ = 6.94 (dd, J = 8.8 Hz, J = 3.0 Hz, 1H), 6.88 (dd, J = 8.0 Hz, J = 3.0 Hz, 1H), 6.74 (dd, J = 8.8 Hz, J = 5.0 Hz, 1H), 3.37 (t, J = 7.0 Hz, 2H), 3.23 (t, J = 7.0 Hz, 2H); ^{13}C NMR (101 MHz, MeOD): δ = 160.0 (d, J = 240.8 Hz), 135.6 (d, J = 2.4 Hz), 124.7 (d, J = 7.2 Hz), 121.4 (d, J = 7.9 Hz), 116.7 (d, J = 23.1 Hz), 115.5 (d, J = 23.1 Hz), 45.9, 29.3; ^{19}F NMR (471 MHz, MeOD): δ = -122.8; HRMS (ESI $^+$, m/z): $[\text{C}_8\text{H}_7\text{FNO}_2\text{S}]^+$ (M-H) $^+$ calc. 201.0187, found 200.0184; IR (ν , cm^{-1}): 3185, 1324, 1155; MP: 135-137°C.

7.2.5. Radiochemistry

7.2.5.1. General Information

[¹⁸F]Fluoride Preparation

[¹⁸F]Fluoride was produced by Erigal Ltd (Keele, UK) via the ¹⁸O(p,n)¹⁸F reaction and delivered as [¹⁸F]fluoride in [¹⁸O]water. Radiosynthesis and azeotropic drying was performed on a NanoTek® automated microfluidic device (Advion). [¹⁸F]Fluoride was separated from ¹⁸O-enriched-water using anion exchange cartridges (Chromafix, Macherey-Nagel, Düren, Germany) and subsequently released with 600 µL of a solution of NEt₄HCO₃ (7 mg) in MeCN/H₂O (4:1) (1 mL) into CEI. The solution was dried with five cycles of azeotropic drying with acetonitrile (300 µL) and redissolved in anhydrous DCM (1 mL) to form a stock solution of [¹⁸F]TEAF.

Radiofluorination Procedure

[¹⁸F]TEAF (15 - 30 MBq) was dispensed from the stock solution into a v-vial containing a stirrer bar and *N*-(4-(*tert*-butyl)phenyl)-4-methylbenzenesulfonamide (**2-1aa**) (12 mg, 40 µmol, 1.0 eq.). PIDA (13 mg, 40 µmol, 1.0 eq.) in DCM (150 µL) was added, followed by HF·pyridine (70%) (1 µL, 40 µmol, 1.0 eq.) in DCM (50 µL). The reaction mixture was stirred for 15 minutes before TFA (22 µL) was added and stirred for a further 10 minutes prior to radioHPLC and radioTLC analysis.

Alternatively, TFA (12 µL, 160 µmol, 4.0 eq.) was used in the place of HF·pyridine.

Analysis

For all reactions, an aliquot was removed for analysis by radioTLC and radioHPLC.

RadioTLC was carried out on Merck Kiesegel 60 F254 plates in EtOAc/Hexane (1:1) and analysed using a plastic scintillator/PMT detector.

HPLC analysis was performed using a Dionex Ultimate 3000 dual channel HPLC system with a shared autosampler, parallel UV-detectors and LabLogic NaI/PMT-radiodetectors with Flowram analogue output. A representative radioHPLC trace of the crude reaction mixture, with UV trace (254 nm) of authentic reference material overlaid, is shown below.

HPLC Gradient Settings: Water/MeCN, 1 mL/min, Waters Nova-Pak C18 Column, 4 μ m, 3.9 x 150 mm:

0 – 1 min (5 % MeCN) isocratic

1 – 10 min (5 % MeCN to 95 % MeCN) linear increase

10 – 14 min (95 % MeCN) isocratic

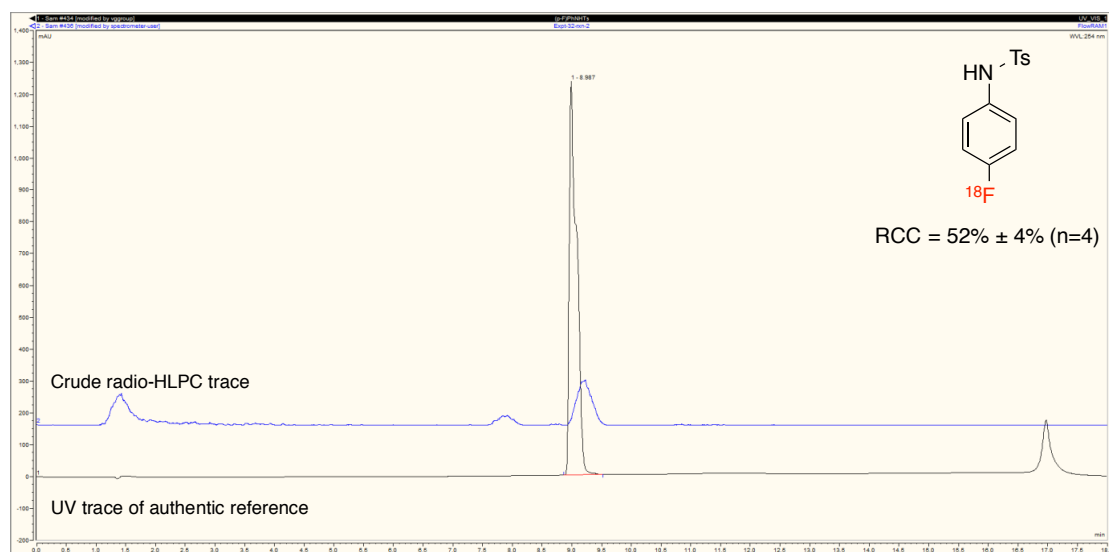
14 – 15 min (95 % MeCN to 5 % MeCN) linear decrease

15 – 17 min (5 % MeCN) isocratic.

Reported radiochemical conversions are decay corrected and calculated by radioTLC taking into account the radiochemical purity as determined by radioHPLC.

7.2.5.2. HPLC Characterisation

N-(4-[¹⁸F]Fluorophenyl)-4-methylbenzenesulfonamide ([¹⁸F]2-14aa)



7.3. Continuous-Flow Microfluidic Radiofluorination of Spirocyclic

Iodonium Ylides

This project was carried out in the radiochemistry labs situated in the PET Core of Massachusetts General Hospital, Boston, Massachusetts, USA. It was carried out in collaboration with the Vasdev group (Division of Nuclear Medicine and Molecular Imaging, Massachusetts General Hospital; Department of Radiology, Harvard Medical School).

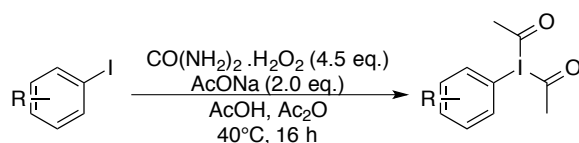
All commercial reagents were purchased from Sigma-Aldrich, Alfa Aesar, Fisher Scientific, Acros, Strem Chemicals, Oakwood Chemical, or Matrix Scientific and, unless otherwise stated, used as received. All solvents were of reagent or anhydrous grade quality and purchased from Sigma-Aldrich, Alfa Aesar, or Fisher Scientific. All deuterated solvents were purchased from Cambridge Isotopes.

Flash column chromatography was performed using a Biotage Isolera One system and preloaded Biotage Zip or refillable Snap silica gel columns. Silica gel for flash chromatography was high purity grade 40 – 63 μm pore size and purchased from Sigma-Aldrich. Yields refer to purified and spectroscopically pure compounds.

^1H , ^{13}C , and ^{19}F NMR spectra were recorded on a Bruker 300 MHz spectrometer.

7.3.1. General Procedures

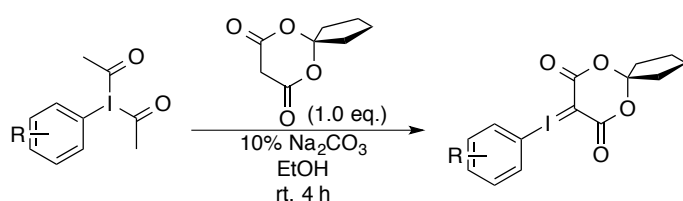
General Procedure 3A (GP3A):⁷²



To a solution of glacial acetic acid (1.8 mL) and acetic anhydride (0.7 mL) was added urea – hydrogen peroxide adduct (1.06 g, 11.25 mmol, 4.5 eq.) followed by aryl iodide

(2.50 mmol, 1.0 eq.). The mixture was then cooled to 0°C before sodium acetate (410 mg, 5.00 mmol, 2.0 eq.) was added slowly. The reaction was heated to 40°C for 16 hours, then cooled to room temperature and diluted with water (10 mL), before being extracted with DCM (3 x 10 mL). Combined organic extracts were dried over MgSO₄ and the solvent was removed *in vacuo*. The residue was washed with Et₂O and filtered to give the desired product.

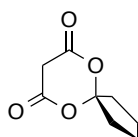
General Procedure 3B (GP3B):⁷²



A solution of 6,10-dioxaspiro[4.5]decane-7,9-dione (**3-1**) (43 mg, 0.25 mmol, 1.0 eq.) in 10% Na₂CO₃ (0.75 mL) was made up, to which was added ethanol (1 mL) and the diacetoxyiodoarene (0.25 mmol, 1.0 eq.) immediately after. The reaction was left to stir at room temperature for 4 hours or until TLC analysis showed the reaction complete. Water (8 mL) was used to dilute the mixture, and this was then extracted with DCM (3 x 10 mL). Combined organics were dried over Na₂SO₄, filtered and concentrated *in vacuo*. Residue was resolubilised in EtOAc and hexanes were added to precipitate out the product, which was collected by filtration.

7.3.2. Substrates

6,10-Dioxaspiro[4.5]decane-7,9-dione (**3-1**)

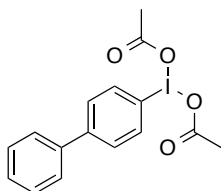


A mixture of malonic acid (5.00 g, 48.0 mmol, 1.0 eq.) in acetic anhydride (4.8 mL) and conc. H₂SO₄ (24 µL) was heated to 60°C for 15 minutes then allowed to cool to room temperature. Cyclopentanone (4.25 mL, 48.0 mmol, 1.0 eq.) was added over 45 minutes before the reaction was left to stir at room temperature for 6 hours. Volatiles were removed *in vacuo* and the residue was resolubilised in Et₂O and consequently washed three times with water. Organic layer was dried over MgSO₄, filtered and solvent was removed *in vacuo*. Crude product was recrystallized from Et₂O/Hexanes with cooling to -25°C to give a white solid (2.37 g, 13.9 mmol, 29%).

¹H NMR (300 MHz, CDCl₃): δ = 3.61 (s, 2H), 2.18 (t, *J* = 7.5 Hz, 4H), 1.92-1.86 (m, 4H); ¹³C NMR (75 MHz, CDCl₃): δ = 163.6, 115.6, 38.7, 37.7, 23.5.

Data consistent with literature values.⁷²

4-(Diacetoxyiodo)-1,1'-biphenyl (3-2a)

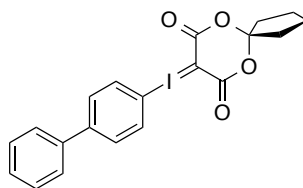


4-Iodobiphenyl (700 mg, 2.50 mmol) was used under GP3A to give a white solid (405 mg, 1.02 mmol, 41%).

¹H NMR (300 MHz, CDCl₃): δ = 8.15 (d, *J* = 8.6 Hz, 2H), 7.68 (d, *J* = 8.6 Hz, 2H), 7.60-7.55 (m, 2H), 7.52-7.38 (m, 3H), 2.03 (s, 6H); ¹³C NMR (75 MHz, CDCl₃): δ = 176.6, 145.1, 139.3, 135.6, 129.8, 129.2, 128.7, 127.5, 120.2, 20.6.

Data consistent with literature values.³⁶⁰

6,10-Dioxaspiro[4.5]decane-7,9-dion-[1,1'-biphenyl-4-iodonium] ylide (3-3a)

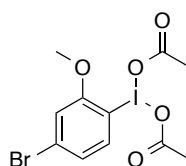


4-(Diacetoxyiodo)-1,1'-biphenyl (**3-2a**) (100 mg, 0.25 mmol) was used under **GP3B** to give a white solid (72.4 mg, 0.16 mmol, 65%).

¹H NMR (300 MHz, CDCl₃): δ = 7.93 (d, *J* = 8.0 Hz, 2H), 7.59 (d, *J* = 8.0 Hz, 2H), 7.56-7.40 (m, 5H), 2.20-2.12 (m, 4H), 1.83-1.76 (m, 4H); ¹³C NMR (75 MHz, CDCl₃): δ = 164.5, 145.7, 138.8, 134.1, 130.7, 129.3, 128.9, 127.4, 114.3, 112.3, 57.2, 37.5, 23.5.

Data consistent with literature values.⁷²

4-Bromo-1-(diacetoxyiodo)-2-methoxybenzene (3-2b)

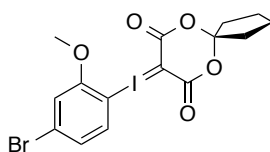


5-Bromo-2-iodoanisole (782 mg, 2.50 mmol) was used under **GP3A** to give a white solid (894 mg, 2.07 mmol, 83%).

¹H NMR (300 MHz, CDCl₃): δ = 7.99 (d, *J* = 8.4 Hz, 1H), 7.27 (d, *J* = 2.0 Hz, 1H), 7.18 (dd, *J* = 8.4, *J* = 2.0 Hz, 1H), 3.99 (s, 3H), 1.96 (s, 6H); ¹³C NMR (75 MHz, CDCl₃): δ = 176.9, 157.1, 138.7, 129.0, 126.1, 115.9, 112.2, 57.4, 20.5.

Data consistent with literature values.³⁶¹

6,10-Dioxaspiro[4.5]decane-7,9-dion-[4-bromo-2-methoxybenzene-1-iodonium] ylide (3-3b)

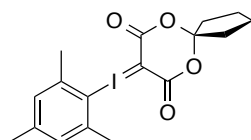


4-Bromo-1-(diacetoxyiodo)-2-methoxybenzene (**3-2b**) (108 mg, 0.25 mmol) was used under **GP3B** to give a white solid (90 mg, 0.19 mmol, 75%).

^1H NMR (300 MHz, CDCl_3): δ = 7.23-7.21 (m, 2H), 7.12 (d, J = 1.7 Hz, 1H), 3.99 (s, 3H), 2.27-2.20 (m, 4H), 1.87-1.81 (m, 4H); ^{13}C NMR (75 MHz, CDCl_3): δ = 164.5, 155.8, 130.1, 127.6, 127.1, 116.2, 114.5, 100.2, 57.5, 48.9, 37.6, 23.6.

Data consistent with literature values.⁷²

6,10-Dioxaspiro[4.5]decane-7,9-dion-[1,3,5-trimethylbenzene-2-iodonium] ylide (3-3c)

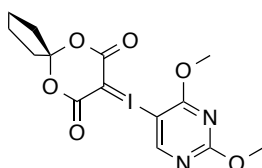


4-(Diacetoxyiodo)-1,3,5-trimethylbenzene (91 mg, 0.25 mmol) was used under **GP3B** to give a white solid (85 mg, 0.20 mmol, 82%).

^1H NMR (300 MHz, CDCl_3): δ = 7.02 (s, 2H), 2.77 (s, 6H), 2.33 (s, 3H), 2.11-2.03 (m, 4H), 1.78-1.72 (m, 4H); ^{13}C NMR (75 MHz, CDCl_3): δ = 164.1, 143.7, 142.8, 130.0, 120.7, 113.9, 56.2, 37.4, 27.4, 23.5, 21.1.

Data consistent with literature values.⁷²

6,10-Dioxaspiro[4.5]decane-7,9-dione-[2,4-dimethoxypyrimidine-5-iodonium] ylide (3-3d)

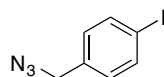


To a solution of 5-iodo-2,4-dimethoxypyrimidine (200 mg, 0.75 mmol, 1.0 eq.) in chloroform (0.75 mL), trifluoroacetic acid (2.3 mL) was added, followed by oxone (360 mg, 1.20 mmol, 1.6 eq.), which was then allowed to stir at room temperature for 2 hours or until complete by TLC. Volatiles were removed *in vacuo* and the residue was suspended in EtOH (2 mL). 6,10-Dioxaspiro[4.5]decane-7,9-dione (128 mg, 0.75 mmol, 1.0 eq.) was added followed quickly by 10% (w/v) Na₂CO₃ (1.5 mL). The pH of the solution was tested and addition of 10% (w/v) Na₂CO₃ was continued until pH ≤ 10. Reaction was allowed to stir for 4 hours, until complete by TLC, before being diluted with water (5 mL) and extracted with chloroform (3 x 5 mL). Combined organics were washed with water (5 mL), brine (5 mL), dried over MgSO₄, filtered and solvents removed *in vacuo*. Product was purified by recrystallization from EtOAc/Hexanes (rt to -25°C) to yield a white solid (52 mg, 0.12 mmol, 16%)

¹H NMR (300 MHz, CDCl₃): δ = 8.56 (s, 1H), 4.13 (s, 3H), 4.05 (s, 3H), 2.21-2.13 (m, 4H), 1.85-1.78 (m, 4H); ¹³C NMR (75 MHz, CDCl₃): δ = 167.3, 167.1, 164.4, 162.9, 114.5, 87.4, 56.3, 56.1, 53.7, 37.5, 23.5.

Data consistent with literature values.⁷²

4-Iodobenzyl azide (3-4)



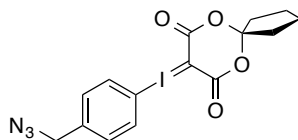
Sodium azide (585 mg, 9.00 mmol, 3.0 eq.) was added to a solution of 4-iodobenzyl bromide (891 mg, 3.00 mmol, 1.0 eq.) in DMF (5 mL) at room temperature. Reaction was allowed to stir for 3 hours before being quenched with water (10 mL) and extracted with DCM (3 x 10 mL). Combined organics were washed with water (3 x 20 mL), dried over MgSO₄ and concentrated to an oil. Product was purified by flash column chromatography (Hexane/EtOAc 9:1 - 0:1) to yield a white solid (389 mg, 1.50 mmol, 50%).

¹H NMR (300 MHz, CDCl₃): δ = 7.72 (d, *J* = 8.3 Hz, 2H), 7.07 (d, *J* = 8.3 Hz, 2H), 4.30 (s, 2H);

¹³C NMR (75 MHz, CDCl₃): δ = 138.1, 135.2, 130.2, 94.2, 54.3.

Data consistent with literature values.⁷²

6,10-Dioxaspiro[4.5]decane-7,9-dione-[1-(azidomethyl)benzene-4-iodonium] ylide (3e)

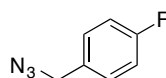


m-Chloroperoxybenzoic acid (77%) (200 mg, 0.90 mmol, 1.29 eq.) was added to 4-iodobenzyl azide (181 mg, 0.70 mmol, 1.0 eq.) in chloroform (8 mL) and reaction was allowed to stir at room temperature until complete by TLC (2 hours). A solution of 6,10-dioxaspiro[4.5]decane-7,9-dione (170 mg, 1.00 mmol, 1.43 eq.) in 10% (w/v) Na₂CO₃ (2 mL) was then added and reaction allowed to stir for further 4 hours or until complete by TLC. Reaction was diluted with water (10 mL) and extracted with chloroform (3 x 10 mL). Combined organics were washed with brine (10 mL), dried over MgSO₄ and solvent removed *in vacuo*. Product was purified by flash column chromatography (Hexane/EtOAc 9:1 - 0:1) to yield an off-white solid (218 mg, 0.51 mmol, 73%).

¹H NMR (300 MHz, CDCl₃): δ = 7.88 (d, *J* = 8.5 Hz, 2H), 7.37 (d, *J* = 8.5 Hz, 2H), 4.43 (s, 2H), 2.18-2.10 (m, 4H), 1.82-1.75 (m, 4H); ¹³C NMR (75 MHz, CDCl₃): δ = 164.5, 140.5, 133.9, 131.3, 114.4, 113.3, 57.1, 53.8, 37.5, 23.5.

Data consistent with literature values.⁷²

4-Fluorobenzyl azide (3-5e)



Sodium azide (195 mg, 3.00 mmol, 3.0 eq.) was added to a solution of 4-fluorobenzyl bromide (0.12 mL, 1.00 mmol, 1.0 eq.) in DMF (1.5 mL) at room temperature. Reaction was allowed to stir for 3 hours before being quenched with water (3 mL) and extracted with DCM (3 x 3 mL). Combined organics were washed with water (3 x 6 mL), dried over MgSO₄ and concentrated to an oil. Product was purified by flash column chromatography (Hexanes/EtOAc 9:1 - 1:0) to yield a volatile colourless oil (48 mg, 0.32 mmol, 32%).

¹H NMR (300 MHz, CDCl₃): δ = 7.33-7.26 (m, 2H), 7.08 (t, *J* = 8.5 Hz, 2H), 4.32 (s, 2H); ¹³C NMR (75 MHz, CDCl₃): δ = 162.8 (d, *J* = 247.0 Hz), 131.3 (d, *J* = 2.8 Hz), 130.2 (d, *J* = 8.3 Hz), 115.9 (d, *J* = 21.7 Hz), 54.2; ¹⁹F NMR (282 MHz, CDCl₃): δ = -109.6 - -109.7 (m, 1F).

Data consistent with literature values.²⁴⁵

7.3.3. Radiochemistry

7.3.3.1. General Information

[¹⁸F]Fluoride Production

[¹⁸F]Fluoride was produced from the irradiation of ¹⁸O-enriched water, via the ¹⁸O(p,n)¹⁸F reaction using a GE PETtrace 16.5 MeV cyclotron. Nitrogen gas pressure was used to deliver this [¹⁸F]fluoride to a lead shielded hot cell in ¹⁸O-enriched water, from which a fraction (4.0 – 8.0 mCi/148 – 296 MBq) was taken forward be azeotropically dried on a NanoTek® (Advion) automated microfluidic device before use in the radiofluorination.

General Procedure for Optimisation reactions

[¹⁸F]Fluoride was separated from ¹⁸O-enriched-water using anion exchange cartridges (MP1, ORTG, Tennessee, USA or Chromafix, Macherey-Nagel, Düren, Germany) and subsequently released with 450 µL of a solution of Et₄NHCO₃ (14mg) in 0.6 – 2.0 mL MeCN/H₂O (1:1) into CEI. The solution was dried with three cycles of azeotropic drying with acetonitrile (100 µL) and resolvated in the desired solvent (500 µL). Five cycles of mixing were performed by Pump 3 (P₃) in the drying vial to maximise efficiency of resolution before the [¹⁸F]fluoride was loaded onto the P₃ storage loop. A solution of the precursor (2 – 8 mg) in anhydrous solvent (500 µL) was loaded onto the Pump 1 (P₁) storage loop. For each reaction, carried out in Discovery mode in the NanoTek® software, a volume of each solution (15 µL) was introduced concurrently at a set total flow rate (20 – 120 µL/min) into reactor 1 (4 – 8 m, 32 – 64 µL) which had been heated the appropriate temperature (100 – 220°C). The reaction was flushed from the reactor using the same solvent as the reaction was carried out it, and collected to be analysed by radioTLC and radioHPLC.

Anion exchange cartridges were recycled using potassium carbonate (0.04 M, 1 mL) followed by washing with water (4 mL), with no noticeable reduction in trapping efficiency over the course of this project.

Procedure for Isolation of 4-[¹⁸F]Fluorobenzyl azide ([¹⁸F]3-5e)

This entire procedure was carried out under automated macros (available in Section 7.3.3.3.). Prior to delivery of [¹⁸F]fluoride, the C18 Sep-Pak was activated using acetonitrile (3 mL) and water (10 mL). Concentrator 2 (CE2) was loaded with MeCN/0.1M NH₄·HCO₂ (60:40) (2 mL) and H₂O (8 mL) in preparation of delivery from the reactor. [¹⁸F]Fluoride was prepared with the same procedure as for the optimization reactions and was then loaded onto the P3 loop. The precursor was loaded onto P1 concurrently. 500 µL was dispensed at a rate of 30 µL/min (total rate of 60 µL/min) simultaneously from each loop into the reactor, heated to 210°C and the reaction bolus was collected in CE2. The contents of CE2 were mixed with a flow of nitrogen gas before being pushed across a Sep-Pak C18 Plus cartridge. The cartridge was washed with H₂O (3mL) before the product was eluted with EtOH (2 mL), which was collected to be analysed by radioTLC and radioHPLC.

Analysis of Radiofluorination reactions

Radioactivity was quantified using a Capintec Radioisotope Calibrator (CRC-712M) ion chamber.

RadioTLC was carried out on Merck Kiesegel 60 F254 plates in EtOAc and analysed using a Bioscan AR-2000 radioTLC imaging scanner and WinScan software.

Radiochemical identity and purity were determined by radioHPLC. A Phenomenex Luna C18, 250 x 4.6 mm, 5 µm HPLC column was used with a Waters 1515 Isocratic HPLC Pump equipped with a Waters 2487 Dual λ Absorbance Detector, a Bioscan

Flow-Count equipped with a NaI crystal, and Breeze software. Product identity was confirmed by co-injection of a reference sample or comparison to a reference sample run under identical conditions.

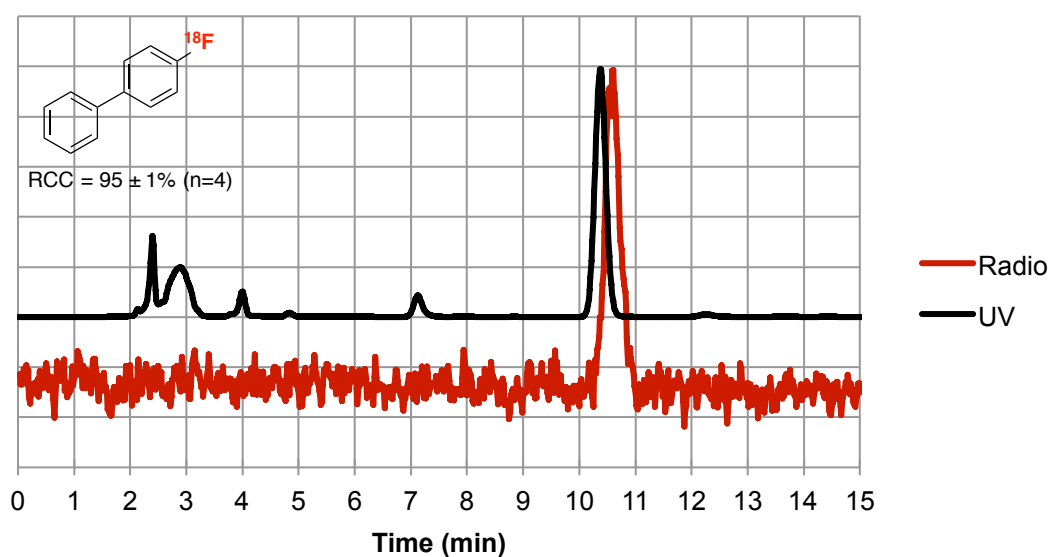
Reported radiochemical conversions are decay corrected and calculated by radioTLC taking into account the radiochemical purity as determined by radioHPLC.

Reported radiochemical yields are non-decay corrected and calculated by collected activity over starting activity prior to azeotropic drying.

7.3.3.2. HPLC Characterisation

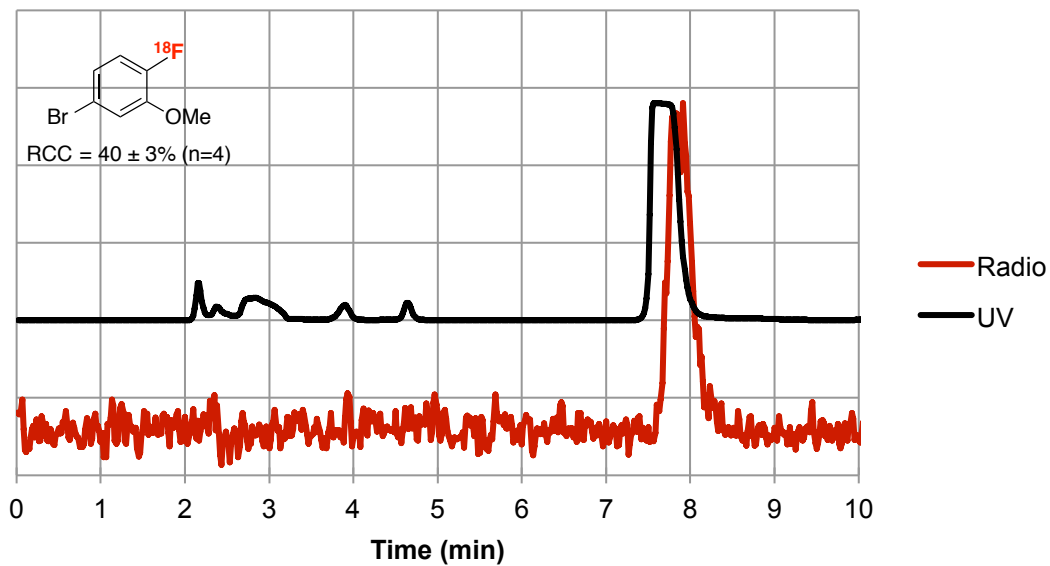
4-[¹⁸F]Fluorobiphenyl ([¹⁸F]3-5a)

Co-injection, 70% MeCN: 30% 0.1 M NH₄·HCO₂, 1 mL/min.



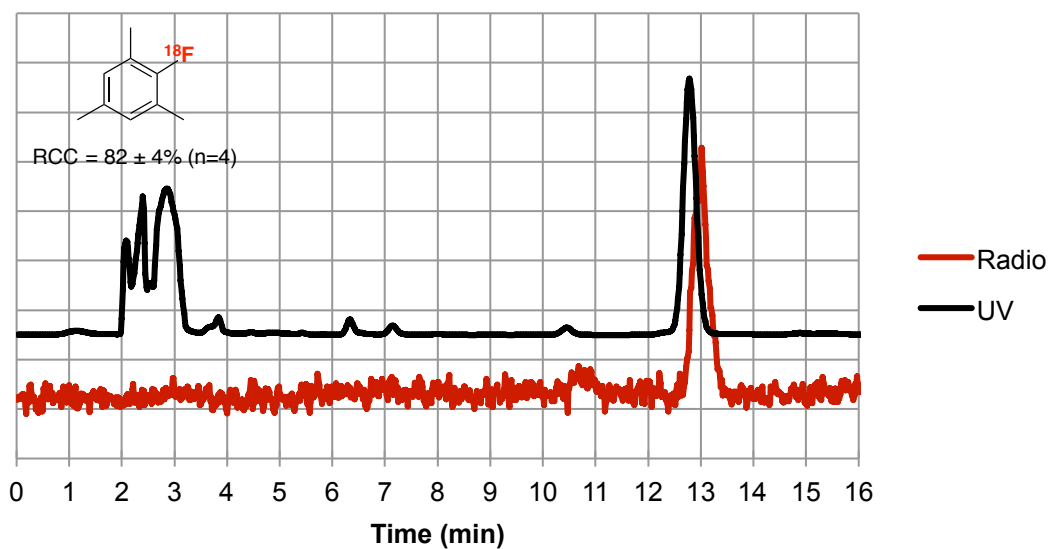
4-Bromo-1-[¹⁸F]fluoro-2-methoxybenzene ([¹⁸F]3-5b)

Co-injection, 70% MeCN: 30% 0.1 M NH₄·HCO₂, 1 mL/min



2-[¹⁸F]Fluoro-1,3,5-trimethylbenzene ([¹⁸F]3-5c)

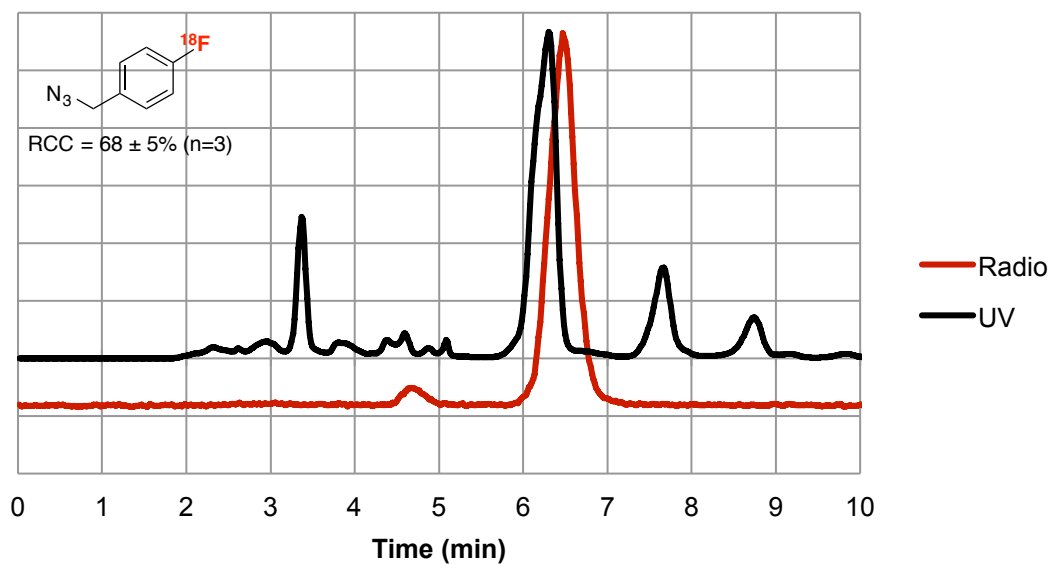
Co-injection, 60% MeCN: 40% 0.1 M NH₄·HCO₂, 1 mL/min



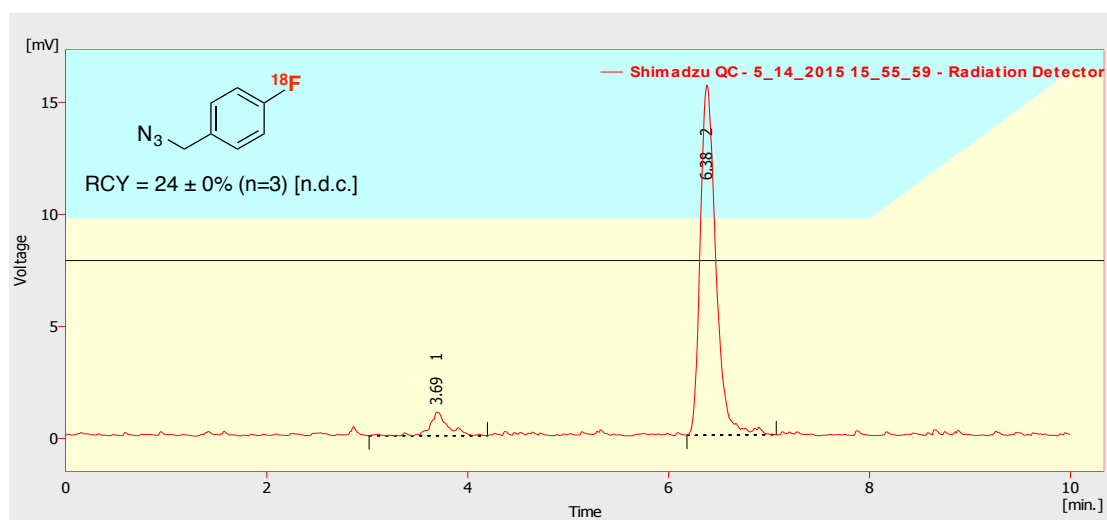
4- ^{18}F Fluorobenzyl azide (^{18}F 3-5e)

Co-injection, 70% MeCN: 30% 0.1 M $\text{NH}_4\cdot\text{HCO}_2$, 1 mL/min

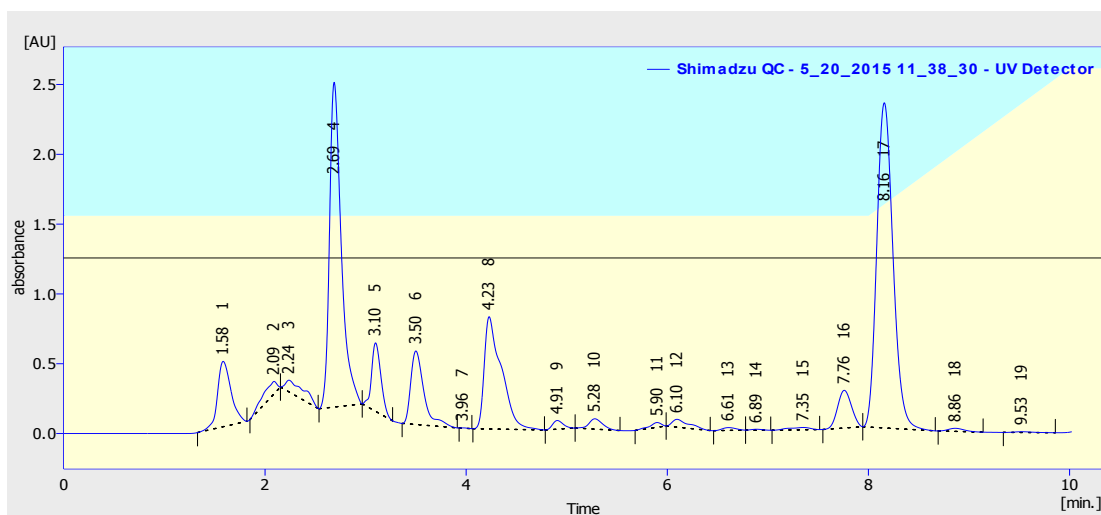
Optimisation



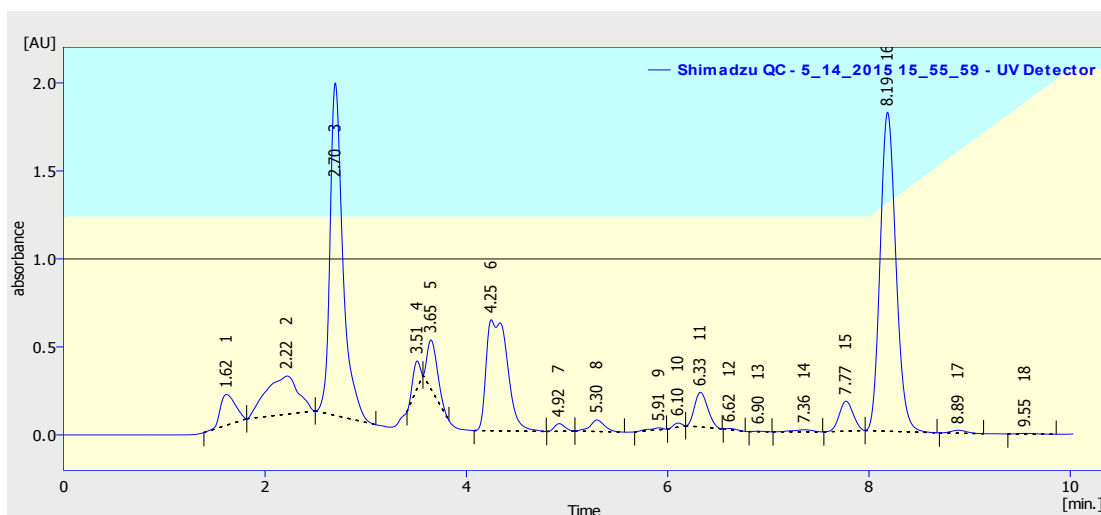
Isolation



RadioHPLC trace



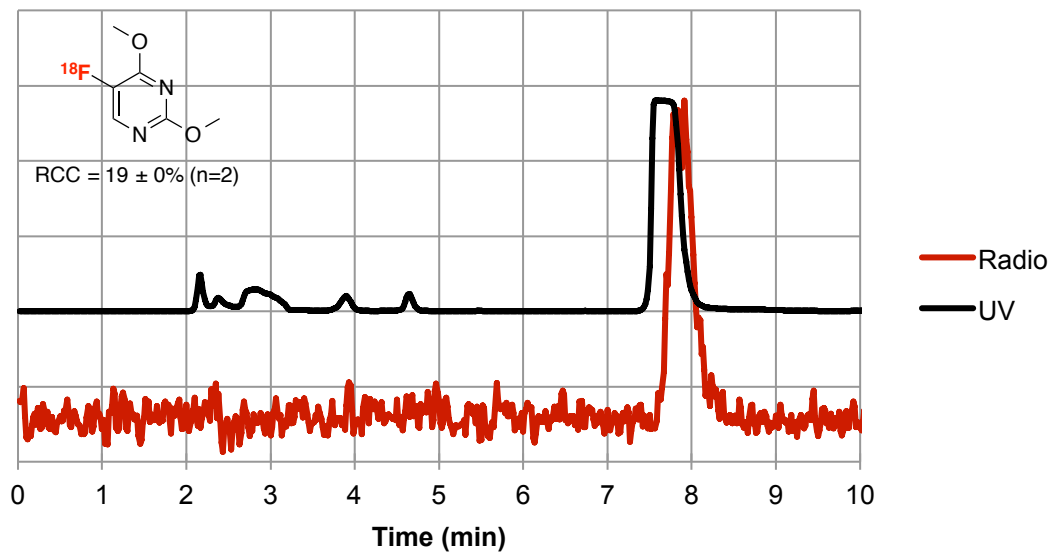
Unspiked UV trace



Co-injection UV trace

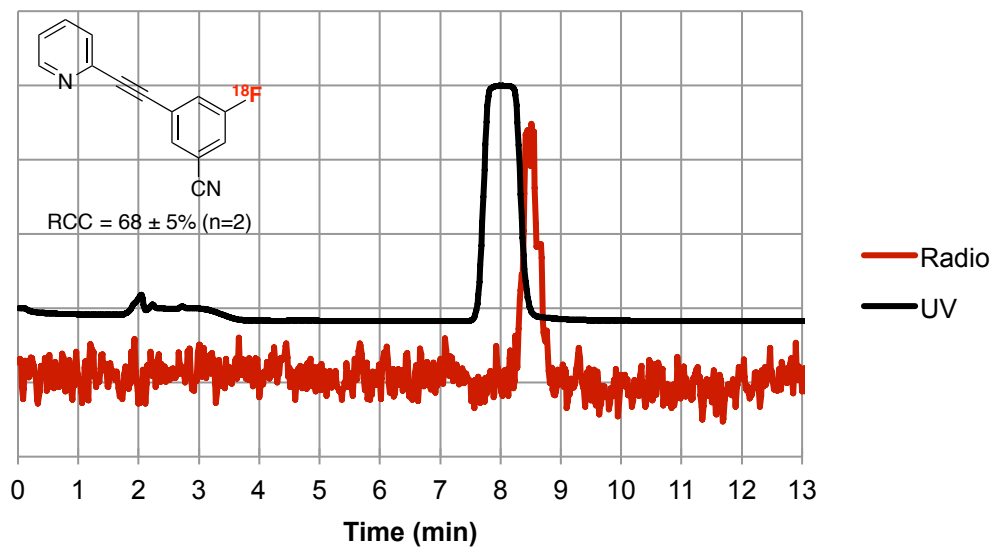
5-¹⁸F]Fluoro-2,4-dimethoxypyrimidine

Reference spectra, 70% MeCN: 30% 0.1 M NH₄·HCO₂, 1 mL/min



3-¹⁸F]Fluoro-5-[(pyridin-3-yl)ethynyl]benzonitrile (¹⁸F]FPEB) (¹⁸F]3-5f)

Co-injection, 60% MeCN: 40% 0.1 M NH₄·HCO₂, 1 mL/min



7.3.3.3. NanoTek® Automation Macros

Preparation of C18 Sep-Pak

0	/2u3R	Make sure we are on Water
10	/604V3200AoR	Make sure syringe is empty
10	/2u1R	Make sure we are on SPE waste
15000	/6g03V3200A1200005V1600AoG3g01V3200A1200005V1600AoG10R	Clean SPE with 3 ml of Acetonitrile and 10 ml of water
170000	/602V3200A1200004V800D12000g02V3200A1200006V800D12000G201V3200A1200004V800D12000g01V3200A1200006V800D12000G8R	Addition of 2mL Quench and 8mL Water to vial

Fluoride Drying routine

0	/2u2R	Make sure we are on Acetonitrile
100	/501V3200AoR	Empty Syringe
100	L3702000095005A_____L36 02000300004E_____	
2000	Wait	Fluoride Drying, A: Target Water, B: Kryptofix, C: Acetonitrile, D: Waste, E: Fluoride Trap, F: Bottom Vessel. ^T^T Make sure 1/32" lines area at Bottom of Vessel, ^T Make sure Acetonitrile is Full and Waste is Empty
1000	L3702000095005A_____L36 02000300004E_____	CE: Set Heater to 95oC
1000	L37020001100059_____L360 2000300004E_____	Set CE heater to 110oC
60000	Wait	Press OK when Fluoride is delivered and You are Ready to Start
10000	/5g01V3200A12000M200005V1200AoM500G5g03V3200A6000M100001AoM500A800005V1200AoM500G1g06V6400A12000M100004AoG7R	CE: Load Target Water
180000	/7U2M5000U1M5000u2R	G: Turn on Nitrogen
100	AO-2 2.5	User 2 AO 2.5 VDC
10000	/502V3200A180004V3200AoR	Prime K222 Line
20000	/502V2000A7200M3000g05V400D1350M15000G402V2000AoR	CE: Add 450 uL K222/K2CO3
120000	/503V2000A2000M200005V75D60006V75D120002V2000AoR	CE: Add MeCN
15000	/308V3200A4800M100006V300D2400M50001V2000AoM50002R	P3: Add MeCN
210000	/503V2000A2000M200005V75D60006V75D120002V2000AoR	CE: Add MeCN
15000	/308V3200A4800M100006V300D2400M50001V2000AoM50002R	P3: Add MeCN
120000	/503V2000A2000M200005V75D60006V75D120002V2000AoR	CE: Add MeCN
15000	/308V3200A4800M100006V300D2400M50001V2000AoM50002R	P3: Add MeCN

120000	/503V2000A2000M200005V75D60006V75D120002V2000AoR	CE: Add MeCN
15000	/308V3200A4800M100006V300D2400M50001V2000AoM50002R	P3: Add MeCN
120000	/505V4000A1200006V800AoR	Remove solvent from Lines E and F
180000	L37020000260054—————L36 02000300004E—————	set temp to 26C
2000	/7u3R	Switch Vessel to Atmosphere
5000	/7u1R	Turn Off Gas
1000	AO-2 o.o	Turn Gas off at MFC
2000	L37020000260054—————L36 02000300004E—————	CE: Set Heater to 260C

Reformulate in Alternate Solvent

0	/301V4800A006V3200P480001V3200AoR	Empty Syringe to waste
20000	/2U2R	Select Alternate Solvent for P3
5000	/308V3200A4800001V3200A008V3200A2400006V360D23500R	Clean Syringe with Alternate solvent and use the alternate for all Discovery Operations, dissolve in 450 ul
120000	/3MoR	Fluoride now in Alternate Solvent and system ready to use alternate solvent

Mix Fluoride through P3

0	/3g04V800P1920004V3200D19200G508V32000P307206V320D3072R	Mix solvent in Fluoride vial 5 times
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Preheat Reactor 1 to 150C

0	L3202000150004D—————	Set Reactor 1 to 150C
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Load Loops P1 and P3 and fill to Reactor

0	/706R	Make sure we are on Waste line from Distribution Hub
10	/2U2R	Make sure we are on DMSO
10	L33020001800051—————	Pre-heat Reactor 2 to 180C
100	L3202000180004D—————	Pre-heat Reactor 1 to 180C
1000	/101V6400A008V6400A4800001V6400AoR	Empty Pump 1 and Flush Syringe with Acetonitrile to Waste

1000	/301V3200A008V3200A4800001V3200AoR	Empty P3 Syringe and clean with Acetonitrile
50000	/106V96P373401V1600AoR	Fill Reagent line with Precursor and empty syringe to waste
100	/306V72A508801V3200AoR	Fill Reagent line with Fluoride and empty syringe to waste
95000	/104V640P42624R	Fill Precursor Loop with Precursor in one minute
1000	/304V160A21168R	Fill Fluoride Loop with Fluoride
145000	/101V3200A008V6400A4800005V80D292808V6400A48000R	Empty P1 Syringe and fill with Acetonitrile push to reactor and refill syringe
100	/301V3200A008V3200A4800005gv700DiM10G91208V3200A48000R	Empty P3 Syringe and fill with Acetonitrile push to reactor and refill syringe

Perform Incorporation Reaction

0	/706R	Set Distribution hub to waste
100	L32020002100050—————	Set Reactor 1 to 210
30000	/105ggv700DiM6G24000G2R	Push out 500 ul at 30 ul/min
1000	/305gv700DiM27G24000R	Push out 500 ul at 30 ul/min
50000	/702R	Switch to Concentrator 2

Set Reactor back to RT

0	L3202000026004F—————	Set reactors back to RT
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SPE Purification

0	/7U1M5000U2M5000u1R	Depressurize N2 line
1000	AO-2 0.2	Set Gas flow low
15000	/2u1R	Make sure we are on SPE waste and allow solution to mix
10	/604V3200AoR	Make sure syringe is empty
10	L39020000250055—————L38020003000050—————	Set Concentrator to RT
10	/7u2R	Turn off Concentrator 2 gas off
15000	/6g06V3200A1200005V1600AoG15g01V3200A1200006V3200AoG3g06V3200A1200005V1600AoG5R	Push all of vial solution across SPE rinse vial with 3 ml of water then push across SPE
300000	/2U3R	Switching to Ethanol
100	/601V3200A1200004V3200A001V3200A12000R	Clean syringe with ethanol and fill syringe with ethanol
20000	/2U1R	Switch to SPE product line
10	/605V800A003V3200A1200005V800A006V3200A1200005V3200A1200005V800AoR	Flush SPE and rinse with a second aliquot of ethanol fill with air and flush out SPE and lines
60000	/2u1R	Switch SPE back to waste

Concentrator I Clean

0	/1u2R	Make sure O-18 recovery line is closed
1000	Wait	Remove reaction vessel, place cap in container to collect waste and place lines for fluoride and Kryptofix in waste containers. Remove fluoride trap and replace with length of tubing. Make sure Acetonitrile bottle is full. Press OK when Ready to start
2000	/503V3200A12000M100001A003A12000M100001A003A12000M100002A003A12000M100002A0R	Clean A&B
50000	/503A12000M100004A003A12000M100004A003A12000M100006A003A12000M100006A0R	Clean D&F
50000	/503A12000M100005A003A12000M100005A003A12000M100005A0R	Clean E
50000	Wait	Clean outside of lines with solvent or Alcohol wipe
1000	Wait	Remove target line from waste container
1000	/501V3200A1200004V3200A001V3200A1200002V3200A001V3200A1200005V3200A001V3200A1200006V3200A001V3200A1200007V3200A001V3200A1200008V3200A001V3200A1200009V3200A001V3200A1200010V3200A001V3200A1200011V3200A001V3200A1200012V3200A001V3200A1200013V3200A001V3200A1200014V3200A001V3200A1200015V3200A001V3200A1200016V3200A001V3200A1200017V3200A001V3200A1200018V3200A001V3200A1200019V3200A001V3200A1200020V3200A001V3200A1200021V3200A001V3200A1200022V3200A001V3200A1200023V3200A001V3200A1200024V3200A001V3200A1200025V3200A001V3200A1200026V3200A001V3200A1200027V3200A001V3200A1200028V3200A001V3200A1200029V3200A001V3200A1200030V3200A001V3200A1200031V3200A001V3200A1200032V3200A001V3200A1200033V3200A001V3200A1200034V3200A001V3200A1200035V3200A001V3200A1200036V3200A001V3200A1200037V3200A001V3200A1200038V3200A001V3200A1200039V3200A001V3200A1200040V3200A001V3200A1200041V3200A001V3200A1200042V3200A001V3200A1200043V3200A001V3200A1200044V3200A001V3200A1200045V3200A001V3200A1200046V3200A001V3200A1200047V3200A001V3200A1200048V3200A001V3200A1200049V3200A001V3200A1200050V3200A001V3200A1200051V3200A001V3200A1200052V3200A001V3200A1200053V3200A001V3200A1200054V3200A001V3200A1200055V3200A001V3200A1200056V3200A001V3200A1200057V3200A001V3200A1200058V3200A001V3200A1200059V3200A001V3200A1200060V3200A001V3200A1200061V3200A001V3200A1200062V3200A001V3200A1200063V3200A001V3200A1200064V3200A001V3200A1200065V3200A001V3200A1200066V3200A001V3200A1200067V3200A001V3200A1200068V3200A001V3200A1200069V3200A001V3200A1200070V3200A001V3200A1200071V3200A001V3200A1200072V3200A001V3200A1200073V3200A001V3200A1200074V3200A001V3200A1200075V3200A001V3200A1200076V3200A001V3200A1200077V3200A001V3200A1200078V3200A001V3200A1200079V3200A001V3200A1200080V3200A001V3200A1200081V3200A001V3200A1200082V3200A001V3200A1200083V3200A001V3200A1200084V3200A001V3200A1200085V3200A001V3200A1200086V3200A001V3200A1200087V3200A001V3200A1200088V3200A001V3200A1200089V3200A001V3200A1200090V3200A001V3200A1200091V3200A001V3200A1200092V3200A001V3200A1200093V3200A001V3200A1200094V3200A001V3200A1200095V3200A001V3200A1200096V3200A001V3200A1200097V3200A001V3200A1200098V3200A001V3200A1200099V3200A001V3200A1200100V3200A001V3200A1200101V3200A001V3200A1200102V3200A001V3200A1200103V3200A001V3200A1200104V3200A001V3200A1200105V3200A001V3200A1200106V3200A001V3200A1200107V3200A001V3200A1200108V3200A001V3200A1200109V3200A001V3200A1200110V3200A001V3200A1200111V3200A001V3200A1200112V3200A001V3200A1200113V3200A001V3200A1200114V3200A001V3200A1200115V3200A001V3200A1200116V3200A001V3200A1200117V3200A001V3200A1200118V3200A001V3200A1200119V3200A001V3200A1200120V3200A001V3200A1200121V3200A001V3200A1200122V3200A001V3200A1200123V3200A001V3200A1200124V3200A001V3200A1200125V3200A001V3200A1200126V3200A001V3200A1200127V3200A001V3200A1200128V3200A001V3200A1200129V3200A001V3200A1200130V3200A001V3200A1200131V3200A001V3200A1200132V3200A001V3200A1200133V3200A001V3200A1200134V3200A001V3200A1200135V3200A001V3200A1200136V3200A001V3200A1200137V3200A001V3200A1200138V3200A001V3200A1200139V3200A001V3200A1200140V3200A001V3200A1200141V3200A001V3200A1200142V3200A001V3200A1200143V3200A001V3200A1200144V3200A001V3200A1200145V3200A001V3200A1200146V3200A001V3200A1200147V3200A001V3200A1200148V3200A001V3200A1200149V3200A001V3200A1200150V3200A001V3200A1200151V3200A001V3200A1200152V3200A001V3200A1200153V3200A001V3200A1200154V3200A001V3200A1200155V3200A001V3200A1200156V3200A001V3200A1200157V3200A001V3200A1200158V3200A001V3200A1200159V3200A001V3200A1200160V3200A001V3200A1200161V3200A001V3200A1200162V3200A001V3200A1200163V3200A001V3200A1200164V3200A001V3200A1200165V3200A001V3200A1200166V3200A001V3200A1200167V3200A001V3200A1200168V3200A001V3200A1200169V3200A001V3200A1200170V3200A001V3200A1200171V3200A001V3200A1200172V3200A001V3200A1200173V3200A001V3200A1200174V3200A001V3200A1200175V3200A001V3200A1200176V3200A001V3200A1200177V3200A001V3200A1200178V3200A001V3200A1200179V3200A001V3200A1200180V3200A001V3200A1200181V3200A001V3200A1200182V3200A001V3200A1200183V3200A001V3200A1200184V3200A001V3200A1200185V3200A001V3200A1200186V3200A001V3200A1200187V3200A001V3200A1200188V3200A001V3200A1200189V3200A001V3200A1200190V3200A001V3200A1200191V3200A001V3200A1200192V3200A001V3200A1200193V3200A001V3200A1200194V3200A001V3200A1200195V3200A001V3200A1200196V3200A001V3200A1200197V3200A001V3200A1200198V3200A001V3200A1200199V3200A001V3200A1200200V3200A001V3200A1200201V3200A001V3200A1200202V3200A001V3200A1200203V3200A001V3200A1200204V3200A001V3200A1200205V3200A001V3200A1200206V3200A001V3200A1200207V3200A001V3200A1200208V3200A001V3200A1200209V3200A001V3200A1200210V3200A001V3200A1200211V3200A001V3200A1200212V3200A001V3200A1200213V3200A001V3200A1200214V3200A001V3200A1200215V3200A001V3200A1200216V3200A001V3200A1200217V3200A001V3200A1200218V3200A001V3200A1200219V3200A001V3200A1200220V3200A001V3200A1200221V3200A001V3200A1200222V3200A001V3200A1200223V3200A001V3200A1200224V3200A001V3200A1200225V3200A001V3200A1200226V3200A001V3200A1200227V3200A001V3200A1200228V3200A001V3200A1200229V3200A001V3200A1200230V3200A001V3200A1200231V3200A001V3200A1200232V3200A001V3200A1200233V3200A001V3200A1200234V3200A001V3200A1200235V3200A001V3200A1200236V3200A001V3200A1200237V3200A001V3200A1200238V3200A001V3200A1200239V3200A001V3200A1200240V3200A001V3200A1200241V3200A001V3200A1200242V3200A001V3200A1200243V3200A001V3200A1200244V3200A001V3200A1200245V3200A001V3200A1200246V3200A001V3200A1200247V3200A001V3200A1200248V3200A001V3200A1200249V3200A001V3200A1200250V3200A001V3200A1200251V3200A001V3200A1200252V3200A001V3200A1200253V3200A001V3200A1200254V3200A001V3200A1200255V3200A001V3200A1200256V3200A001V3200A1200257V3200A001V3200A1200258V3200A001V3200A1200259V3200A001V3200A1200260V3200A001V3200A1200261V3200A001V3200A1200262V3200A001V3200A1200263V3200A001V3200A1200264V3200A001V3200A1200265V3200A001V3200A1200266V3200A001V3200A1200267V3200A001V3200A1200268V3200A001V3200A1200269V3200A001V3200A1200270V3200A001V3200A1200271V3200A001V3200A1200272V3200A001V3200A1200273V3200A001V3200A1200274V3200A001V3200A1200275V3200A001V3200A1200276V3200A001V3200A1200277V3200A001V3200A1200278V3200A001V3200A1200279V3200A001V3200A1200280V3200A001V3200A1200281V3200A001V3200A1200282V3200A001V3200A1200283V3200A001V3200A1200284V3200A001V3200A1200285V3200A001V3200A1200286V3200A001V3200A1200287V3200A001V3200A1200288V3200A001V3200A1200289V3200A001V3200A1200290V3200A001V3200A1200291V3200A001V3200A1200292V3200A001V3200A1200293V3200A001V3200A1200294V3200A001V3200A1200295V3200A001V3200A1200296V3200A001V3200A1200297V3200A001V3200A1200298V3200A001V3200A1200299V3200A001V3200A1200300V3200A001V3200A1200301V3200A001V3200A1200302V3200A001V3200A1200303V3200A001V3200A1200304V3200A001V3200A1200305V3200A001V3200A1200306V3200A001V3200A1200307V3200A001V3200A1200308V3200A001V3200A1200309V3200A001V3200A1200310V3200A001V3200A1200311V3200A001V3200A1200312V3200A001V3200A1200313V3200A001V3200A1200314V3200A001V3200A1200315V3200A001V3200A1200316V3200A001V3200A1200317V3200A001V3200A1200318V3200A001V3200A1200319V3200A001V3200A1200320V3200A001V3200A1200321V3200A001V3200A1200322V3200A001V3200A1200323V3200A001V3200A1200324V3200A001V3200A1200325V3200A001V3200A1200326V3200A001V3200A1200327V3200A001V3200A1200328V3200A001V3200A1200329V3200A001V3200A1200330V3200A001V3200A1200331V3200A001V3200A1200332V3200A001V3200A1200333V3200A001V3200A1200334V3200A001V3200A1200335V3200A001V3200A1200336V3200A001V3200A1200337V3200A001V3200A1200338V3200A001V3200A1200339V3200A001V3200A1200340V3200A001V3200A1200341V3200A001V3200A1200342V3200A001V3200A1200343V3200A001V3200A1200344V3200A001V3200A1200345V3200A001V3200A1200346V3200A001V3200A1200347V3200A001V3200A1200348V3200A001V3200A1200349V3200A001V3200A1200350V3200A001V3200A1200351V3200A001V3200A1200352V3200A001V3200A1200353V3200A001V3200A1200354V3200A001V3200A1200355V3200A001V3200A1200356V3200A001V3200A1200357V3200A001V3200A1200358V3200A001V3200A1200359V3200A001V3200A1200360V3200A001V3200A1200361V3200A001V3200A1200362V3200A001V3200A1200363V3200A001V3200A1200364V3200A001V3200A1200365V3200A001V3200A1200366V3200A001V3200A1200367V3200A001V3200A1200368V3200A001V3200A1200369V3200A001V3200A1200370V3200A001V3200A1200371V3200A001V3200A1200372V3200A001V3200A1200373V3200A001V3200A1200374V3200A001V3200A1200375V3200A001V3200A1200376V3200A001V3200A1200377V3200A001V3200A1200378V3200A001V3200A1200379V3200A001V3200A1200380V3200A001V3200A1200381V3200A001V3200A1200382V3200A001V3200A1200383V3200A001V3200A1200384V3200A001V3200A1200385V3200A001V3200A1200386V3200A001V3200A1200387V3200A001V3200A1200388V3200A001V3200A1200389V3200A001V3200A1200390V3200A001V3200A1200391V3200A001V3200A1200392V3200A001V3200A1200393V3200A001V3200A1200394V3200A001V3200A1200395V3200A001V3200A1200396V3200A001V3200A1200397V3200A001V3200A1200398V3200A001V3200A1200399V3200A001V3200A1200400V3200A001V3200A1200401V3200A001V3200A1200402V3200A001V3200A1200403V3200A001V3200A1200404V3200A001V3200A1200405V3200A001V3200A1200406V3200A001V3200A1200407V3200A001V3200A1200408V3200A001V3200A1200409V3200A001V3200A1200410V3200A001V3200A1200411V3200A001V3200A1200412V3200A001V3200A1200413V3200A001V3200A1200414V3200A001V3200A1200415V3200A001V3200A1200416V3200A001V3200A1200417V3200A001V3200A1200418V3200A001V3200A1200419V3200A001V3200A1200420V3200A001V3200A1200421V3200A001V3200A1200422V3200A001V3200A1200423V3200A001V3200A1200424V3200A001V3200A1200425V3200A001V3200A1200426V3200A001V3200A1200427V3200A001V3200A1200428V3200A001V3200A1200429V3200A001V3200A1200430V3200A001V3200A1200431V3200A001V3200A1200432V3200A001V3200A1200433V3200A001V3200A1200434V3200A001V3200A1200435V3200A001V3200A1200436V3200A001V3200A1200437V3200A001V3200A1200438V3200A001V3200A1200439V3200A001V3200A1200440V3200A001V3200A1200441V3200A001V3200A1200442V3200A001V3200A1200443V3200A001V3200A1200444V3200A001V3200A1200445V3200A001V3200A1200446V3200A001V3200A1200447V3200A001V3200A1200448V3200A001V3200A1200449V3200A001V3200A1200450V3200A001V3200A1200451V3200A001V3200A1200452V3200A001V3200A1200453V3200A001V3200A1200454V3200A001V3200A1200455V3200A001V3200A1200456V3200A001V3200A1200457V3200A001V3200A1200458V3200A001V3200A1200459V3200A001V3200A1200460V3200A001V3200A1200461V3200A001V3200A1200462V3200A001V3200A1200463V3200A001V3200A1200464V3200A001V3200A1200465V3200A001V3200A1200466V3200A001V3200A1200467V3200A001V3200A1200468V3200A001V3200A1200469V3200A001V3200A1200470V3200A001V3200A1200471V3200A001V3200A1200472V3200A001V3200A1200473V3200A001V3200A1200474V3200A001V3200A1200475V3200A001V3200A1200476V3200A001V3200A1200477V3200A001V3200A1200478V3200A001V3200A1200479V3200A001V3200A1200480V3200A001V3200A1200481V3200A001V3200A1200482V3200A001V3200A1200483V3200A001V3200A1200484V3200A001V3200A1200485V3200A001V3200A1200486V3200A001V3200A1200487V3200A001V3200A1200488V3200A001V3200A1200489V3200A001V3200A1200490V3200A001V3200A1200491V3200A001V3200A1200492V3200A001V3200A1200493V3200A001V3200A1200494V3200A001V3200A1200495V3200A001V3200A1200496V3200A001V3200A1200497V3200A001V3200A1200498V3200A001V3200A1200499V3200A001V3200A1200500V3200A001V3200A1200501V3200A001V3200A1200502V3200A001V3200A1200503V3200A001V3200A1200504V3200A001V3200A1200505V3200A001V3200A1200506V3200A001V3200A1200507V3200A001V3200A1200508V3200A001V3200A1200509V3200A001V3200A1200510V3200A001V3200A1200511V3200A001V3200A1200512V3200A001V3200A1200513V3200A001V3200A1200514V3200A001V3200A1200515V3200A001V3200A1200516V3200A001V3200A1200517V3200A001V3200A1200518V3200A001V3200A1200519V3200A001V3200A1200520V3200A001V3200A1200521V3200A001V3200A1200522V3200A001V3200A1200523V3200A001V3200A1200524V3200A001V3200A1200525V3200A001V3200A1200526V3200A001V3200A1200527V3200A001V3200A1200528V3200A001V3200A1200529V3200A001V3200A1200530V3200A001V3200A1200531V3200A001V3200A1200532V3200A001V3200A1200533V3200A001V3200A1200534V3200A001V3200A1200535V3200A001V3200A1200536V3200A001V3200A1200537V3200A001V3200A1200538V3200A001V3200A1200539V3200A001V3200A1200540V3200A001V3200A1200541V3200A001V3200A1200542V3200A001V3200A1200543V3200A001V3200A12	

Concentrator 2 Clean and SPE Clean

0	Wait	Remove SPE from Valve, make sure water vial is full and waste is empty, Acetonitrile should be full
10	/604V3200AoR	empty syringe
100	/2u3R	Make sure we are on water
15000	/6g03V3200A1200004V3200AoG3g01V3200A1200004V3200AoG3R	Clean syringe with Acetonitrile and water
60000	/6g03V3200A1200002V3200AoG3g01V3200A1200002V3200AoG3R	Clean Base line with Acetonitrile and water
60000	/6g03V3200A1200006V3200AoG3g01V3200A1200006V3200AoG3R	Clean vessel line with Acetonitrile and water
60000	/6g03V3200A1200005V3200AoG3g01V3200A1200005V3200AoG6R	Clean SPE line with Acetonitrile and water
090000	/2U1R	Switch SPE to product line
100	/6g03V3200A1200005V3200AoG3g01V3200A1200005V3200AoG6R	Clean SPE Product line with Acetonitrile and water
90000	Wait	Remove cap from vial, so port F can supply air
100	/6g06V3200A1200005V3200AoG3g06V3200A1200005V3200AoG3R	
60000	/2u1R	Switch back to waste line on SPE

Master Clean

0	/2u2R	Set Solvent selection for P3 to ACN Vial
0	/60iV3200AoR	Con. 2 Move
1000	/50iV3200AoR	Con.1 Move
1000	/30iV3200AoR	P3 Move
1000	/20iV6400AoR	P2 Move
1000	/10iV6400AoR	P1 Move
1000	L39020000250055_____L38 020003000050_____	Set all temps to 25C
1000	L37020000250053_____L36 02000300004E_____	Set all temps to 25C
1000	L33020001000049_____	Set Reactor 2 to 100C
1000	L32020001000048_____	Set Reactor 1 to 100C
1000	L35020000250051_____	Set all temps to 25C
1000	L34020000250050_____	Set all temps to 25C
9000	Wait	Make sure Acetonitrile Bottle is full and Waste container is Empty. Make sure Outlet of Reactor is in a collection vessel. Press OK when Ready
1000	/10iV3200A008A48000M100001A008A48000M100004V1 600A008V3200A48000M100003V400AoR	Zero 1 Fill
5000	/20iV3200A008A48000M100001A008A48000M100004V 1600A008V3200A48000M100003V400AoR	Zero 2 Fill
0	/706R	Hub to Waste (F)
5000	/30iV3200A008A48000M100001A008A48000M100004V 1600A008V3200A4800003V120A2400002gv700D1M48G 480002V60AoR	Zero 3 Fill and System Sweep
260000	/102V61PoR	Change to a plugged port
2000	/202V61PoR	Change to a plugged port
670000	L3202000025004E_____	Set to 25C again
100	L3302000025004F_____	Set to 25C again

7.4. Copper-Mediated [^{18}F]Labelling of Radiopharmaceuticals

Precursor synthesis was carried out by members of the Gouverneur group: Dr S. Preshlock ([^{18}F]Flumazenil), Dr S. Gruber ([^{18}F]FMTEB, [^{18}F]FPEB), Dr T. Cailly ([^{18}F]MFBG, [^{18}F]FDA), T. Wilson ([^{18}F]MFBG, [^{18}F]FMT, [^{18}F]FDA) and N. Taylor ([^{18}F]DAA1106, [^{18}F]FDOPA).

7.4.1. Radiochemistry

7.4.1.1. General Information

[^{18}F]Fluoride Preparation

[^{18}F]Fluoride was produced by Alliance Medical (UK) via the $^{18}\text{O}(\text{p},\text{n})^{18}\text{F}$ reaction and delivered as [^{18}F]fluoride in ^{18}O -enriched-water. Radiosynthesis and azeotropic drying was performed on a NanoTek microfluidic device (Advion). Anion exchange cartridges used were either a 'Waters' (Waters Sep-Pak Accell Plus QMA Carbonate Plus Light Cartridge (46 mg) (Part #186004540 from Waters)) or 'Chromafix' (Chromafix PS- HCO_3 , ^{18}F separation cartridge (45 mg) (Product No. 731876 from ABX)).

General procedure under 'Research Mode'

Radiosynthesis and azeotropic drying was performed on a NanoTek[®] microfluidic device (Advion). [^{18}F]Fluoride (3.0 - 4.0 GBq) was separated from ^{18}O -enriched-water using a Chromafix cartridge and subsequently released with 900 μL (in 6 x 150 μL portions) of a solution of $\text{K}_{2.2.2}/\text{K}_2\text{CO}_3$ (Kryptofix 222 (15 mg) and K_2CO_3 (3 mg) in 1 mL of MeCN/ H_2O , 4:1) into a 5 mL v-vial containing a magnetic stir bar in CEI. The solution was dried with five cycles of azeotropic drying with MeCN (200 μL) under a flow of N_2 at 105°C. The dried [^{18}F]KF/ $\text{K}_{2.2.2}$ residue was redissolved in anhydrous MeCN (500 - 1000 μL). Small aliquots of this solution of [^{18}F]KF/ $\text{K}_{2.2.2}$ in MeCN (20 - 30 MBq, 10 - 40

μL) are dispensed into a v-vial containing $\text{Cu}(\text{OTf})_2(\text{py})_4$, aryl pinacol boronate, any further spiking additives and a magnetic stirrer bar. Air was flushed through the reaction vial using a syringe and then DMF (300 μL) was added via syringe. The sealed vial was heated at 110°C for 20 minutes. The reaction was quenched by addition of water (200 μL).

General procedure for elution experiments

An aliquot of aqueous [^{18}F]fluoride (20 - 40 MBq) was dispensed via CE1 in to a v-vial in CE2 and diluted with water up to 800 μL . This solution was taken up in P3 and loaded onto a QMA cartridge and washed with MeCN (500 μL), after which the activity trapped was measured. The eluent ($\text{K}_2\text{CO}_3/\text{K}_{2.2.2}$ or Cu(II) complex) was pushed across the cartridge, followed by 1.5 mL air. The cartridge was rinsed with a further 1 mL of solvent and 1.5 mL air and the activity remaining on the cartridge and the activity eluted was measured. Elution efficiency was calculated by percentage of activity eluted over sum of activity eluted and QMA post-elution.

Analysis

For all reactions, an aliquot was removed for analysis by radioTLC and radioHPLC.

RadioTLC was carried out on Merck Kiesegel 60 F254 plates in EtOAc/Hexane (1:1) and analysed using a plastic scintillator/PMT detector.

HPLC analysis was performed using a Dionex Ultimate 3000 dual channel HPLC system with a shared autosampler, parallel UV-detectors and LabLogic NaI/PMT-radiodetectors with Flowram analogue output.

HPLC Gradient Settings: Water/MeCN, 1 mL/min, Waters Nova-Pak C18 Column, 4 μm , 3.9 x 150 mm:

0 – 1 min (5 % MeCN) isocratic

1 – 10 min (5 % MeCN to 95 % MeCN) linear increase

10 – 14 min (95 % MeCN) isocratic

14 – 15 min (95 % MeCN to 5 % MeCN) linear decrease

15 – 17 min (5 % MeCN) isocratic.

Reported radiochemical conversions are decay corrected and calculated by radioTLC taking into account the radiochemical purity as determined by radioHPLC.

7.4.1.2. Isolation Procedures

General Procedure for Azeotropic Drying

[¹⁸F]Fluoride (3.0 - 10.0 GBq) was separated from ¹⁸O-enriched-water using the appropriate anion exchange cartridge (Table 7.1) and subsequently released with 900 µL (in 6 x 150 µL portions) of a solution of K_{2.2.2}/K₂C₂O₄/K₂CO₃ (kryptofix 222 (6.3 mg), K₂C₂O₄ (1 mg) and K₂CO₃ (0.1 mg) in 1 mL of MeCN/H₂O, 4:1) into a 5 mL V-vial containing a magnetic stir bar in the concentrator. The solution was dried with five cycles of azeotropic drying with MeCN (5 x 200 µL) under a flow of N₂ at 105 °C.

Entry	Radiotracer		QMA Cartridge	QMA Counter-ion
1	[¹⁸ F]Flumazenil	[¹⁸ F]4-2	Chromafix	Oxalate
2	[¹⁸ F]FMTEB	[¹⁸ F]4-3	Chromafix	Oxalate
3	[¹⁸ F]FPEB	[¹⁸ F]4-4	Chromafix or Waters	Oxalate
4	[¹⁸ F]DAA1106	[¹⁸ F]4-5	Waters	Carbonate
5	[¹⁸ F]MFBG	[¹⁸ F]4-6	Waters	Carbonate
6	[¹⁸ F]FDOPA	[¹⁸ F]4-7	Waters	Carbonate
7	[¹⁸ F]FMT	[¹⁸ F]4-8	Waters	Carbonate
8	[¹⁸ F]FDA	[¹⁸ F]4-9	Waters	Carbonate

Table 7.1: Anion exchange cartridges used in azeotropic drying for isolation reactions

General Procedure for Pre-conditioning with Oxalate Counter-ions

A Waters or a Chromafix cartridge was washed with 3 mL of K₂C₂O₄ (10 mg/mL, aq.) solution followed by 5 mL H₂O at a flow rate of 3 mL/min.

Analysis

Following reaction and deprotection steps, isolation was achieved by semi-prep HPLC and product identity was confirmed by analytical HPLC, as detailed in each procedure.

Reported radiochemical yields are non-decay corrected and calculated by collected activity over starting activity prior to azeotropic drying.

Procedure for [¹⁸F]Flumazenil ([¹⁸F]4-2)

The 5 mL vial containing the dried [¹⁸F]KF/K_{2.2.2} complex was purged with 30 mL of air using a syringe and then a solution of arylboronate precursor (12 mg, 0.03 mmol) and Cu(OTf)₂(py)₄ (27 mg, 0.04 mmol) in anhydrous DMA (400 µL) was added. The mixture was heated at 120 °C for 20 min in a sealed vial with stirring, after which, the reaction mixture was diluted with 1 mL of 15% MeCN/ 85% 25 mM NH₄·HCO₂ (aq.) and loaded directly onto a 2 mL HPLC loop and injected on a semi-prep HPLC column (Synergi

4 μ m Hydro-RP 250 x 10mm) and eluted with 25% MeCN/ 75% 25 mM NH₄·HCO₂ (isocratic 4 mL/min) monitoring with UV (254 nm) and radioactive traces.

Product identity and SA of [¹⁸F]4-2 in collected fraction was assessed using an analytical Synergi 4 μ m Hydro-RP 80A, 150 x 4.6 mm with 25% MeCN/ 75% 25 mM NH₄·HCO₂ (aq.) (isocratic 1 mL/min) monitoring with UV (254 nm) and radioactive traces.

Procedure for [¹⁸F]flumazenil ([¹⁸F]4-2) using Cu(OTf)₂py₄ elution

[¹⁸F]Fluoride (4.0 GBq) was separated from ¹⁸O-enriched-water using a Chromafix cartridge and subsequently released with by 900 μ L (in 6 x 150 μ L portions) of a solution of 27 mg Cu(OTf)₂py₄ in 1 mL of MeCN/H₂O (1:1) into a 5 mL v-vial containing a magnetic stir bar in the concentrator. The solution was dried with six cycles of azeotropic drying with MeCN (6 x 500 μ L) under a flow of N₂ at 120°C. To the dried [¹⁸F]KF/K_{2.2.2} complex was added a solution of arylboronate precursor (12 mg, 0.03 mmol) in anhydrous DMF/pyridine (9:1, 400 μ L) after which 30 mL of air was flushed through the vial using a syringe. The mixture was heated at 120°C for 20 min in a sealed vial with stirring, after which, the reaction mixture was diluted with 1 mL of 15% MeCN/ 85% 25 mM NH₄·HCO₂ (aq.) and loaded directly onto a 2 mL HPLC loop and injected on a semi-prep HPLC column (Synergi 4 μ m Hydro-RP 250x10mm) and eluted with 25% MeCN/ 75% 25 mM NH₄·HCO₂ (aq.) (isocratic 4 mL/min) monitoring with UV (254 nm) and radioactive traces.

Product identity and SA of [¹⁸F]4-2 in collected fraction was assessed using an analytical Synergi 4 μ m Hydro-RP 80A, 150 x 4.6 mm with 25% MeCN/ 75% 25 mM NH₄·HCO₂ (aq.) (isocratic 1 mL/min) monitoring with UV (254 nm) and radioactive traces.

Procedure for [^{18}F]FMTEB ([^{18}F]4-3)

The 5 mL vial containing the dried [^{18}F]KF/ $\text{K}_{2.2.2}$ complex was purged with 30 mL of air using a syringe and then a solution of arylboronate precursor (10.5 mg, 0.03 mmol) and $\text{Cu}(\text{OTf})_2(\text{py})_4$ (27 mg, 0.04 mmol) in anhydrous DMA (400 μL) was added. The mixture was heated at 120 $^{\circ}\text{C}$ for 20 min in a sealed vial with stirring, after which, the reaction mixture was diluted with 1 mL of 40% MeCN/ 60% 25 mM $\text{NH}_4\cdot\text{HCO}_2$ (aq.) and loaded directly onto a 2 mL HPLC loop and injected on a semi-prep HPLC column (Synergi 4 μm Hydro-RP 250 x 10mm) and eluted with 50% MeCN/ 50% 25 mM $\text{NH}_4\cdot\text{HCO}_2$ (isocratic 4 mL/min) monitoring with UV (254 nm) and radioactive traces.

Product identity and SA of [^{18}F]4-3 in collected fraction was assessed using an analytical Synergi 4 μm Hydro-RP 80A, 150 x 4.6 mm with 50% MeCN/ 50% 25 mM $\text{NH}_4\cdot\text{HCO}_2$ (aq.) (isocratic 1 mL/min) monitoring with UV (254 nm) and radioactive traces.

Procedure for [^{18}F]FPEB ([^{18}F]4-4)

The 5 mL vial containing the dried [^{18}F]KF/ $\text{K}_{2.2.2}$ complex was purged with 30 mL of air using a syringe and then a solution of arylboronate precursor (10 mg, 0.03 mmol) and $\text{Cu}(\text{OTf})_2(\text{py})_4$ (27 mg, 0.04 mmol) in anhydrous DMA (400 μL) was added. The mixture was heated at 120 $^{\circ}\text{C}$ for 20 min in a sealed vial with stirring, after which, the reaction mixture was diluted with 1 mL of 40% MeCN/ 60% 25 mM $\text{NH}_4\cdot\text{HCO}_2$ (aq.) and loaded directly onto a 2 mL HPLC loop and injected on a semi-prep HPLC column (Synergi 4 μm Hydro-RP 250 x 10mm) and eluted with 50% MeCN/ 50% 25 mM $\text{NH}_4\cdot\text{HCO}_2$ (aq.) (isocratic 4 mL/min) monitoring with UV (254 nm) and radioactive traces.

Product identity and SA of [^{18}F]4-4 in collected fraction was assessed using an analytical Synergi 4 μm Hydro-RP 80A, 150 x 4.6 mm with 40% MeCN/ 60% H_2O (isocratic 1 mL/min) monitoring with UV (254 nm) and radioactive traces.

Procedure for [^{18}F]DAA1106 ([^{18}F]4-5)

The 5 mL vial containing the dried [^{18}F]KF/ $\text{K}_{2.2.2}$ complex was purged with 30 mL of air using a syringe and then a solution of arylboronate precursor (10 mg, 0.02 mmol) and $\text{Cu}(\text{OTf})_2(\text{py})_4$ (14 mg, 0.02 mmol) in anhydrous DMA (400 μL) was added. The mixture was heated at 120°C for 20 min in a sealed vial with stirring, after which, the reaction mixture was diluted with 1 mL of 40% MeCN/ 60% 25 mM $\text{NH}_4\cdot\text{HCO}_2$ (aq.) and loaded directly onto a 2 mL HPLC loop and injected on a semi-prep HPLC column (Synergi 4 μm Hydro-RP 250x10mm) and eluted with 60% MeCN/ 40% 25 mM $\text{NH}_4\cdot\text{HCO}_2$ (aq.) (isocratic 4 mL/min) monitoring with UV (254 nm) and radioactive traces.

Product identity and SA of [^{18}F]4-5 in collected fraction was assessed using an analytical Synergi 4 μm Hydro-RP 80A, 150 x 4.6 mm with 60% MeCN/ 35% H_2O (isocratic 1 mL/min) monitoring with UV (254 nm) and radioactive traces.

Procedure for [^{18}F]MFBG ([^{18}F]4-6)

The 5 mL vial containing the dried [^{18}F]KF/ $\text{K}_{2.2.2}$ complex was purged with 30 mL of air using a syringe and then a solution of arylboronate precursor (13 mg, 0.02 mmol) and $\text{Cu}(\text{OTf})_2(\text{py})_4$ (14 mg, 0.02 mmol) in anhydrous DMA (400 μL) was added. The mixture was heated at 120°C for 20 min in a sealed vial with stirring. HI (57%, aq.) (300 μL) was added via syringe and the reaction was stirred at 120°C for 10 min. The reaction mixture was then allowed to cool to room temperature and partially neutralized with NaOH (6.75 M, aq.) (300 μL) and further diluted with 25 mM $\text{NH}_4\cdot\text{HCO}_2$ (aq.) (800 μL) and filtered before loading onto a 2 mL HPLC loop and injected on a semi-prep HPLC

column (Synergi 4 μ m Hydro-RP 250 x 10mm) and eluted with 10% MeCN/ 90% 25 mM NH_4HCO_2 (aq.) (isocratic 4 mL/min) monitoring with UV (254 nm) and radioactive traces. (Note: Precipitate formed after HI deprotection and led to poor transfer efficiency and loss of activity deposited on the syringe filter prior to loading HPLC.)

Product identity and SA of [^{18}F]4-6 in collected fraction was assessed using an analytical Synergi 4 μ m Hydro-RP 80A, 150 x 4.6 mm with 10% MeCN/ 90% 25 mM NH_4HCO_2 (aq.) (isocratic 1 mL/min) monitoring with UV (254 nm) and radioactive traces.

Procedure for [^{18}F]FDOPA ([^{18}F]4-7)

The 5 mL vial containing the dried [^{18}F]KF/ $\text{K}_{2.2.2}$ complex was purged with 30 mL of air using a syringe and then a solution of arylboronate precursor (11 mg, 0.02 mmol) and $\text{Cu}(\text{OTf})_2(\text{py})_4$ (14 mg, 0.02 mmol) in anhydrous DMA (400 μ L) was added. The mixture was heated at 120°C for 20 min in a sealed vial with stirring. The reaction mixture was then diluted into 8 mL of H_2O and loaded onto a Sep-Pak® Plus C18 cartridge and washed with two 1 mL portions of H_2O . 1 mL of air was then flushed through the cartridge and the product was eluted back into the reaction vial using two 1 mL washes of acetone and then flushing the cartridge with 1 mL air. The acetone was evaporated under a flow of N_2 while heated to 120°C. The dry residue was then redissolved in HI (57%, aq.) (400 μ L) and the reaction was stirred at 150°C for 10 min. The reaction mixture was then allowed to cool to room temperature and partially neutralized with NaOH (6.75 M, aq.) (400 μ L) and further diluted with 25 mM NH_4HCO_2 (aq.) solution containing 0.2 mg/mL of ascorbic acid (1000 μ L) and loaded directly onto a 2 mL HPLC loop and injected on a semi-prep HPLC column (Synergi 4 μ m Hydro-RP 250 x 10mm) and eluted with a 50 mM AcOH / 2.5 mM NaOAc buffer containing 0.1 mg/mL ascorbic acid (isocratic 4 mL/min) monitoring with UV (254 nm) and radioactive traces.

Product identity and SA of [^{18}F]4-7 in collected fraction was assessed using an analytical Synergi 4 μm Hydro-RP 80A, 150 x 4.6 mm with 50 mM AcOH/ 2.5 mM NaOAc buffer containing 0.1 mg/mL ascorbic acid (isocratic 1 mL/min) monitoring with UV (280 nm) and radioactive traces.

Procedure for [^{18}F]FMT ([^{18}F]4-8)

The 5 mL vial containing the dried [^{18}F]KF/ $\text{K}_{2.2.2}$ complex was purged with 30 mL of air using a syringe and then a solution of arylboronate precursor (11 mg, 0.02 mmol) and $\text{Cu}(\text{OTf})_2(\text{py})_4$ (14 mg, 0.02 mmol) in anhydrous DMF (400 μL) was added. The mixture was heated at 120°C for 20 min in a sealed vial with stirring. The reaction mixture was then diluted into 8 mL of H_2O and loaded onto a Sep-Pak® Plus C18 cartridge and washed with two 1 mL portions of H_2O . 1 mL of air was then flushed through the cartridge and the product was eluted back into the reaction vial using two 1 mL washes of acetone and then flushing the cartridge with 1 mL air. The acetone was evaporated under a flow of N_2 while heated to 120°C. The dry residue was then redissolved in HI (57%, aq.) (400 μL) and the reaction was stirred at 150°C for 10 min. The reaction mixture was then allowed to cool to room temperature and partially neutralized with NaOH (6.75 M, aq.) (400 μL) and further diluted with 50 mM AcOH/ 2.5 mM NaOAc buffer containing 0.1 mg/mL ascorbic acid (1000 μL) and loaded directly onto a 2 mL HPLC loop and injected on a semi-prep HPLC column (Synergi 4 μm Hydro-RP 250 x 10mm) and eluted with a 50 mM AcOH/ 2.5 mM NaOAc buffer containing 0.1 mg/mL ascorbic acid (isocratic 4 mL/min) monitoring with UV (254 nm) and radioactive traces.

Product identity and SA of [^{18}F]4-8 in collected fraction was assessed using an analytical Synergi 4 μm Hydro-RP 80A, 150 x 4.6 mm with 50 mM AcOH/ 2.5 mM NaOAc buffer containing 0.1 mg/mL ascorbic acid (isocratic 1 mL/min) monitoring with UV (280 nm) and radioactive traces. The enantiomeric purity of [^{18}F]4-8 was

determined on a separate analytical method. HPLC analysis was performed on Daicel crownpak cr(+) (HClO_4 0.01M, isocratic 0.8 mL/min), UV was monitored at 280 nm and radioactive traces.

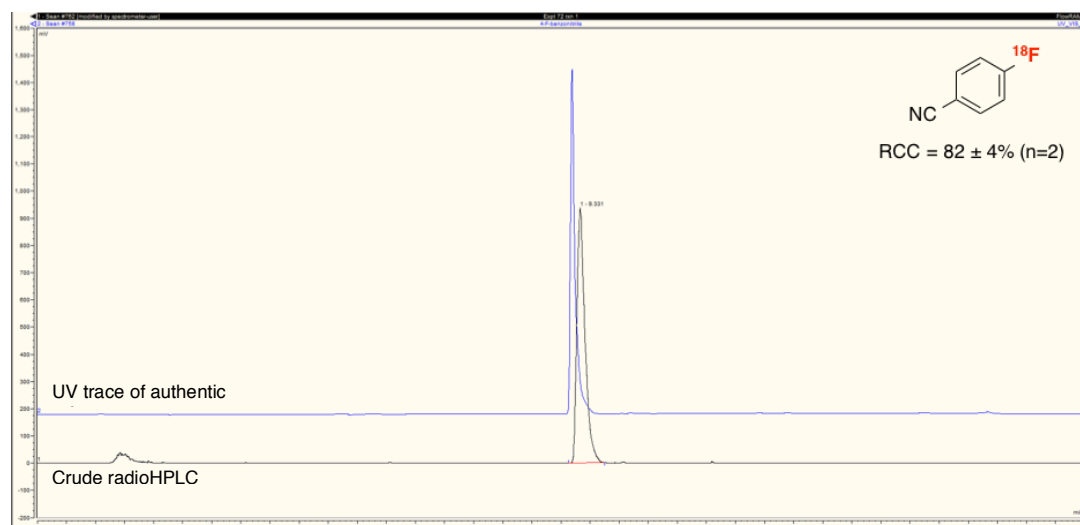
Procedure for [^{18}F]FDA ([^{18}F]4-9)

The 5 mL vial containing the dried [^{18}F]KF/ $\text{K}_{2.2.2}$ complex was purged with 30 mL of air using a syringe and then a solution of arylboronate precursor (10.1 mg, 0.02 mmol) and $\text{Cu}(\text{OTf})_2(\text{py})_4$ (14 mg, 0.02 mmol) in anhydrous DMA (400 μL) was added. The mixture was heated at 120°C for 20 min in a sealed vial with stirring. The reaction mixture was then diluted into 8 mL of H_2O and loaded onto a Sep-Pak® Plus C18 cartridge and washed with two 1 mL portions of H_2O . 1 mL of air was then flushed through the cartridge and the product was eluted back into the reaction vial using two 1 mL washes of acetone and then flushing the cartridge with 1 mL air. The acetone was evaporated under a flow of N_2 while heated to 120°C. The dry residue was then redissolved in HI (57%, aq.) (400 μL) and the reaction was stirred at 130°C for 10 min. The reaction mixture was then allowed to cool to room temperature and partially neutralized with NaOH (6.75 M, aq.) (400 μL) and further diluted with 50 mM AcOH/ 2.5 mM NaOAc buffer containing 0.1 mg/mL ascorbic acid (1000 μL) and loaded directly onto a 2 mL HPLC loop and injected on a semi-prep HPLC column (Synergi 4 μm Hydro-RP 250 x 10mm) and eluted with a 50 mM AcOH/ 2.5 mM NaOAc buffer containing 0.1 mg/mL ascorbic acid (isocratic 4 mL/min) monitoring with UV (254 nm) and radioactive traces.

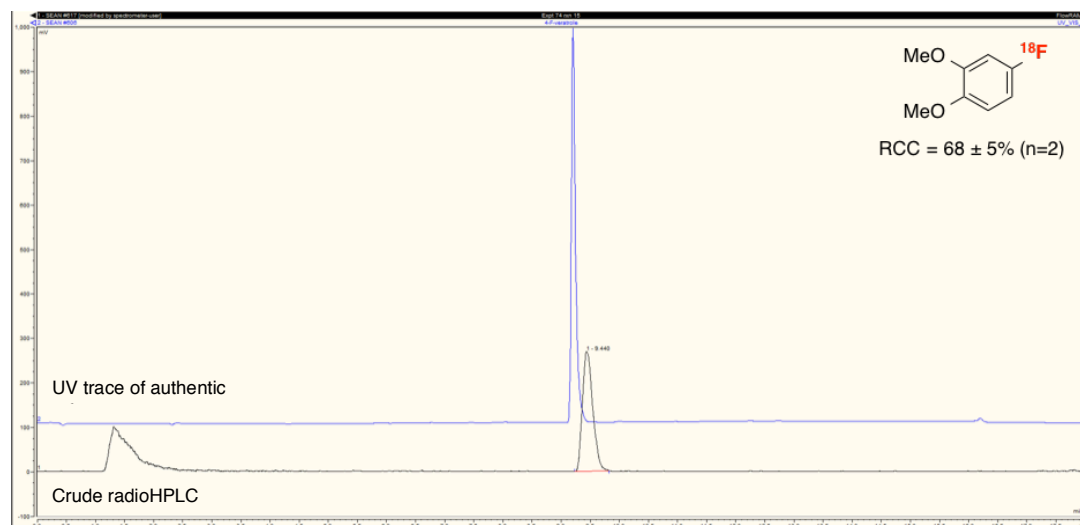
Product identity and SA of [^{18}F]4-9 in collected fraction was assessed using an analytical Synergi 4 μm Hydro-RP 80A, 150 x 4.6 mm with 50 mM AcOH/ 2.5 mM NaOAc buffer containing 0.1 mg/mL ascorbic acid (isocratic 1 mL/min) monitoring with UV (280 nm) and radioactive traces.

7.4.1.3. HPLC Characterisation

4-[¹⁸F]Fluorobenzonitrile ([¹⁸F]4-1a)

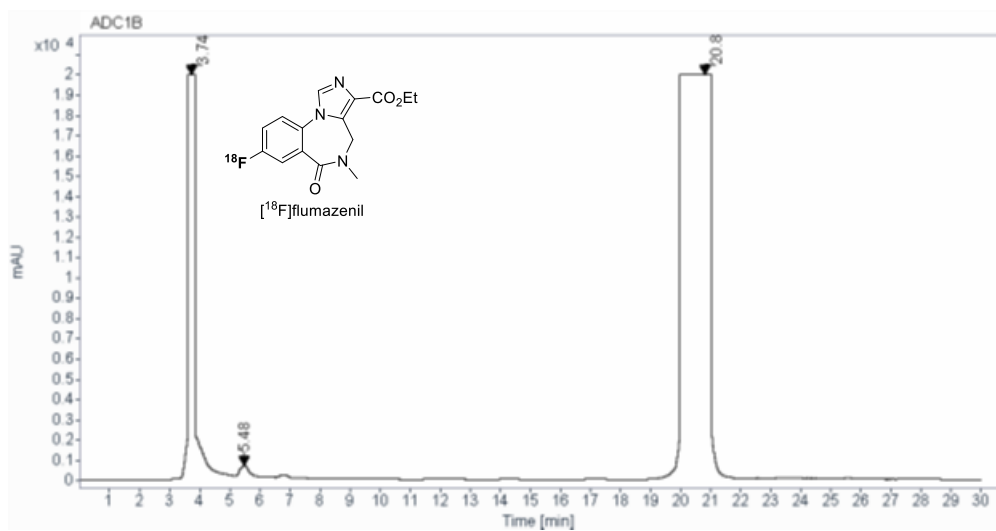


4-[¹⁸F]Fluoro-1,2-dimethoxybenzene ([¹⁸F]4-1b)

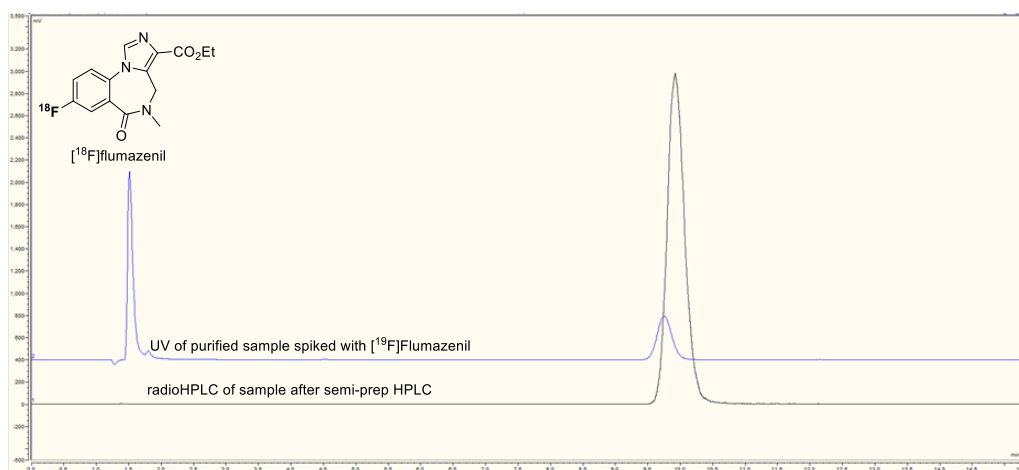


$[^{18}\text{F}]$ Flumazenil ($[^{18}\text{F}]$ 4-2)

RadioHPLC trace of semi-prep HPLC

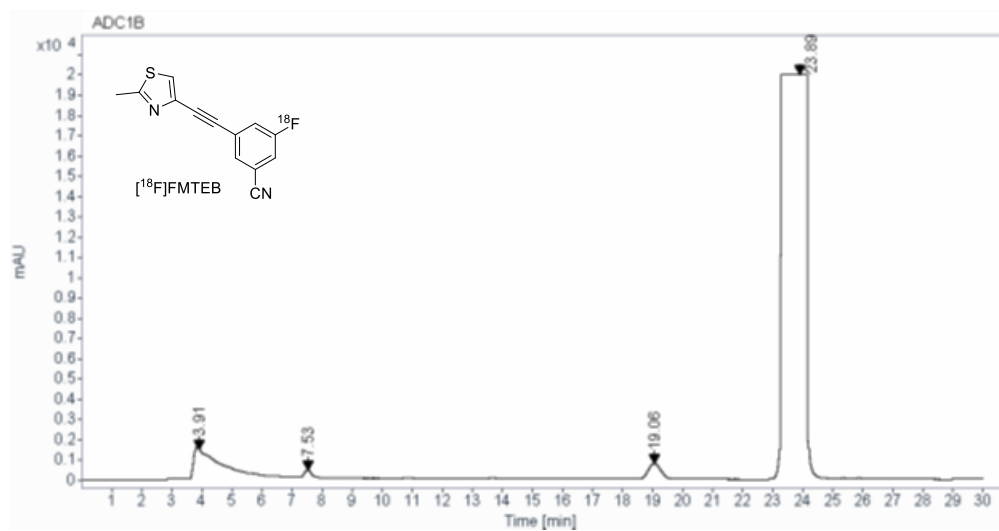


RadioHPLC trace of analytical HPLC with spiked reference UV spectra overlaid

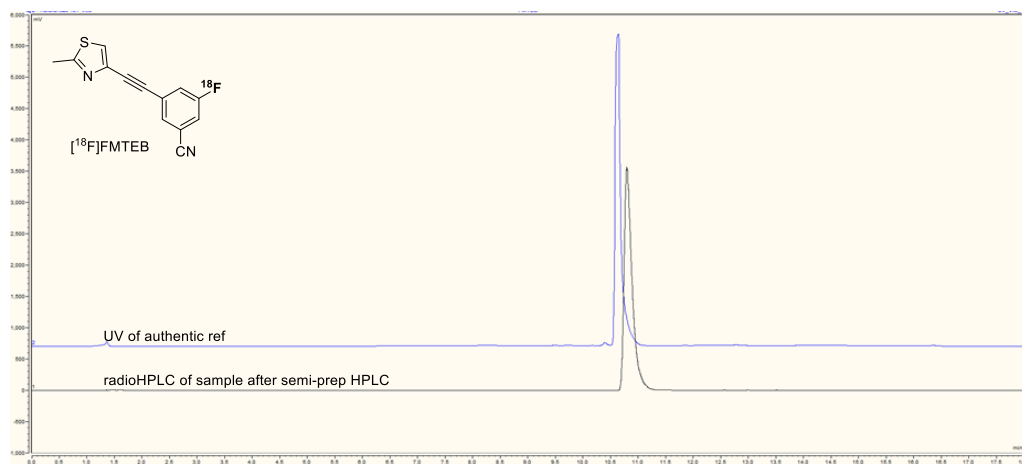


$[^{18}\text{F}]$ FMTEB ($[^{18}\text{F}]$ 4-3)

RadioHPLC trace of semi-prep HPLC

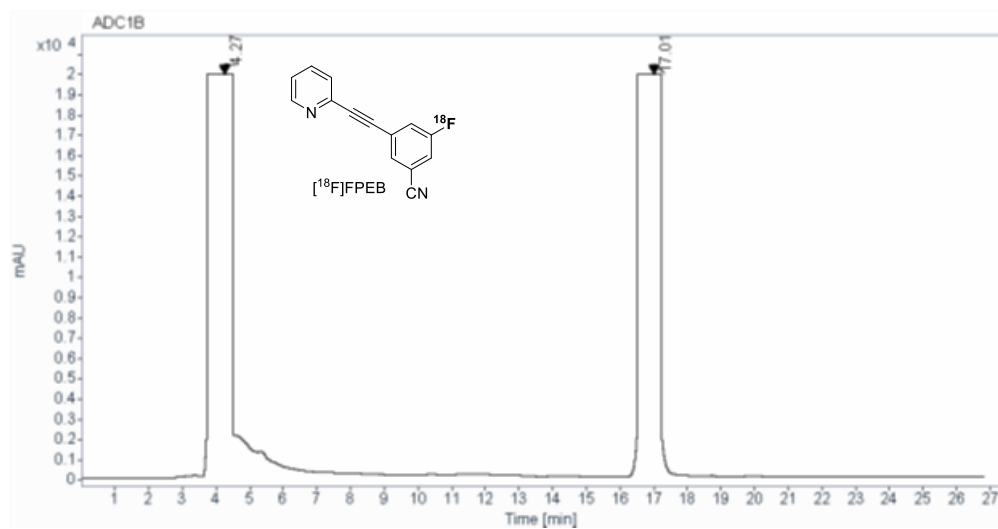


RadioHPLC trace of analytical HPLC with authentic reference UV spectra overlaid

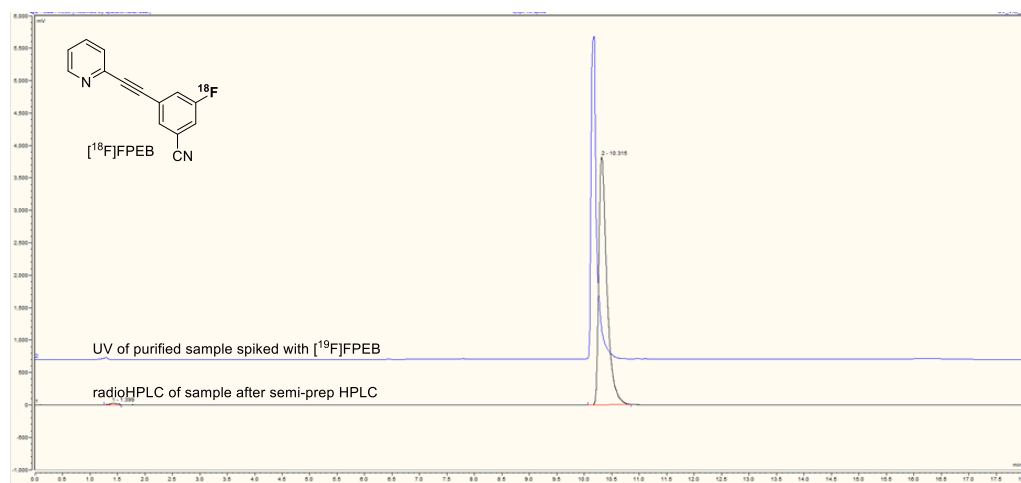


$[^{18}\text{F}]\text{FPEB}$ ($[^{18}\text{F}]\text{4-4}$)

RadioHPLC trace of semi-prep HPLC

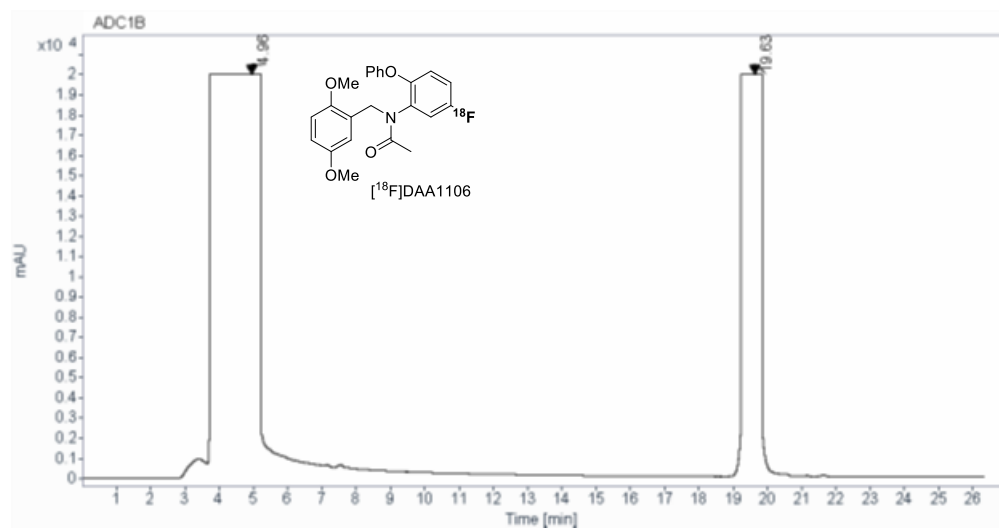


RadioHPLC trace of analytical HPLC with spiked reference UV spectra overlaid

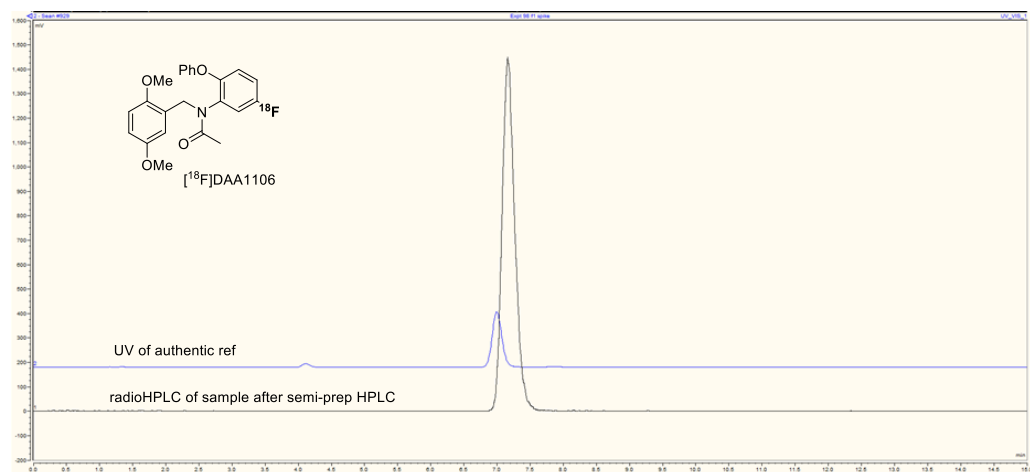


[¹⁸F]DAA1106 ([¹⁸F]4-5)

RadioHPLC trace of semi-prep HPLC

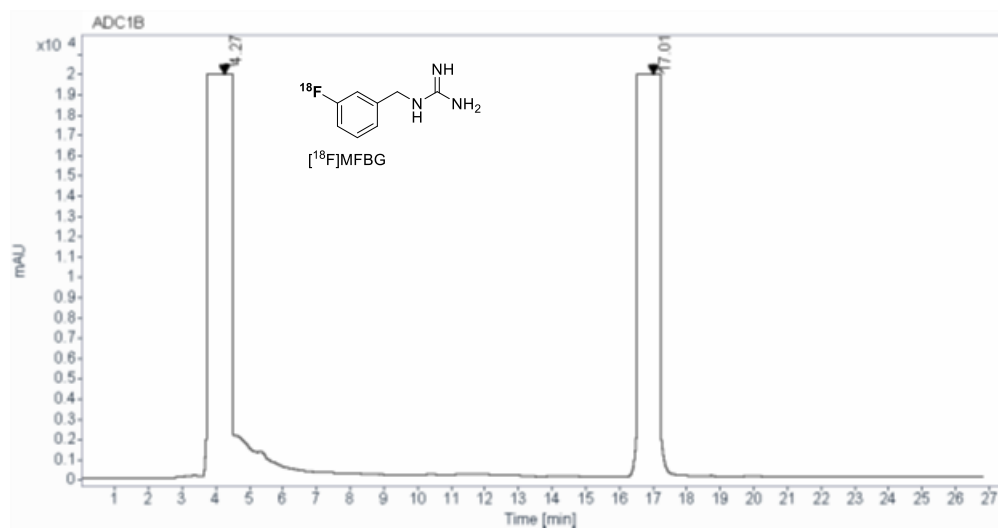


RadioHPLC trace of analytical HPLC with authentic reference UV spectra overlaid

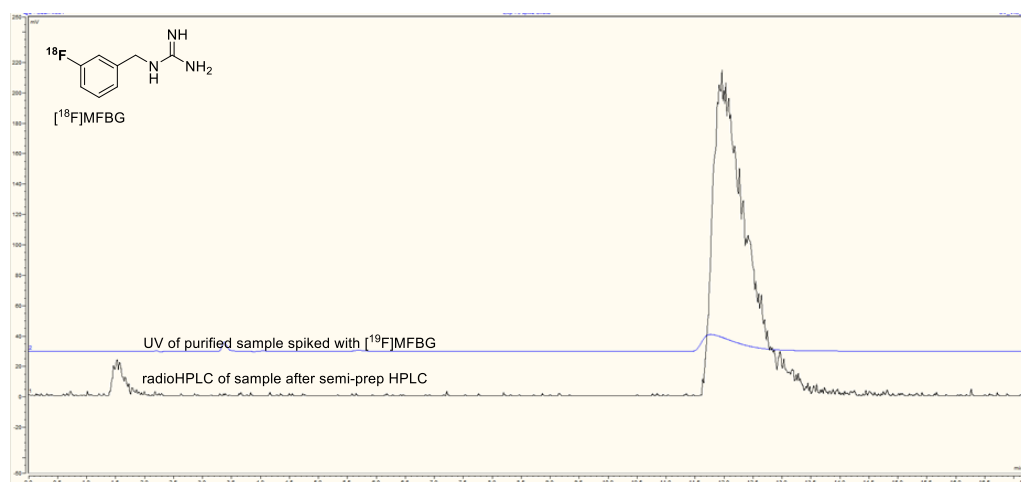


$[^{18}\text{F}]$ MFBG ($[^{18}\text{F}]$ 4-6)

RadioHPLC trace of semi-prep HPLC

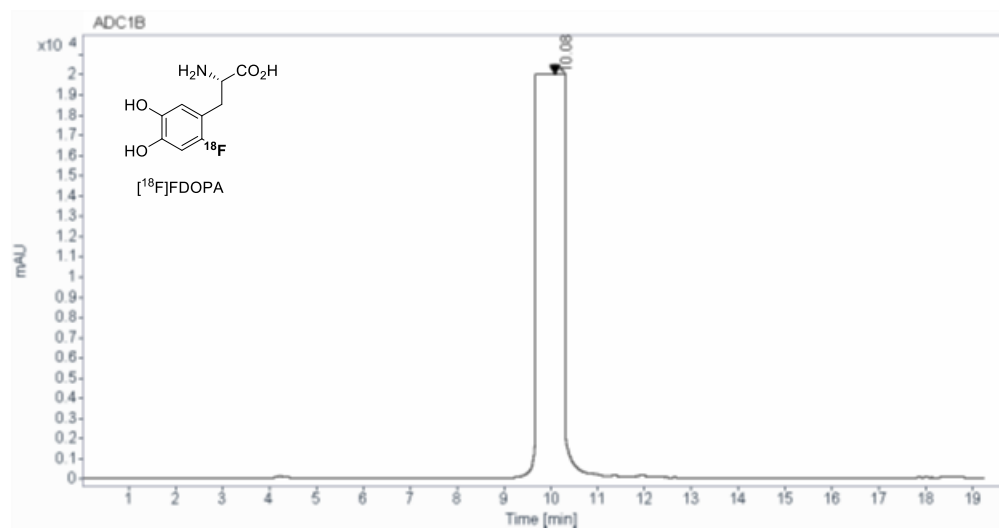


RadioHPLC trace of analytical HPLC with spiked reference UV spectra overlaid

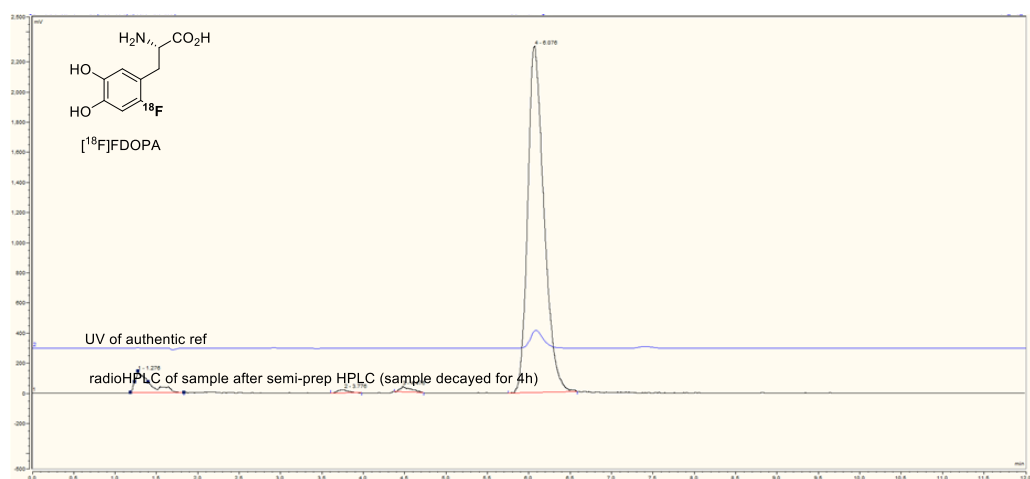


$[^{18}\text{F}]\text{FDOPA}$ ($[^{18}\text{F}]\text{4-7}$)

RadioHPLC trace of semi-prep HPLC

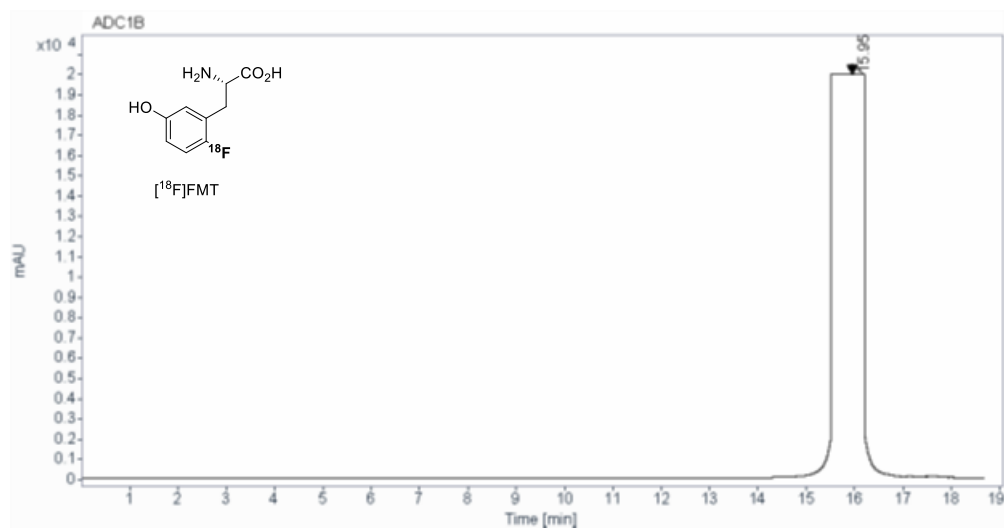


RadioHPLC trace of analytical HPLC with authentic reference UV spectra overlaid

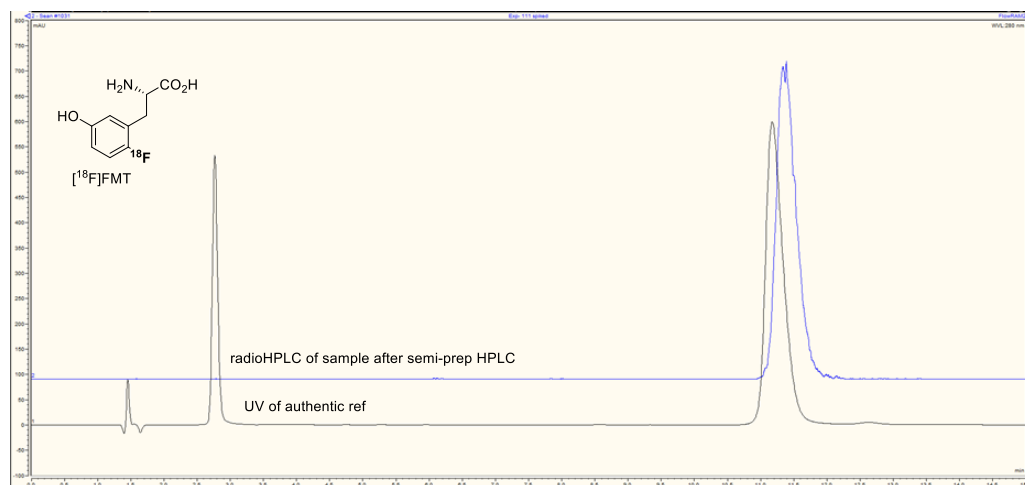


$[^{18}\text{F}]$ FMT ($[^{18}\text{F}]$ 4-8)

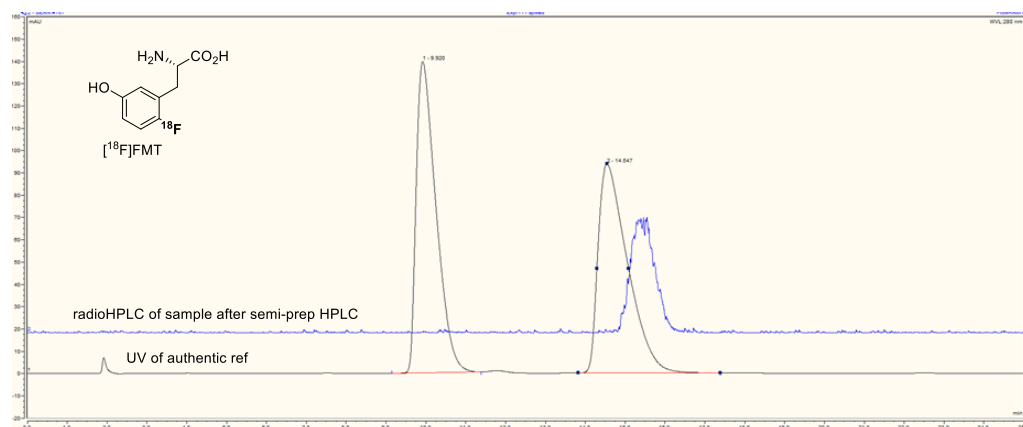
RadioHPLC trace of semi-prep HPLC



RadioHPLC trace of analytical HPLC with authentic reference UV spectra overlaid

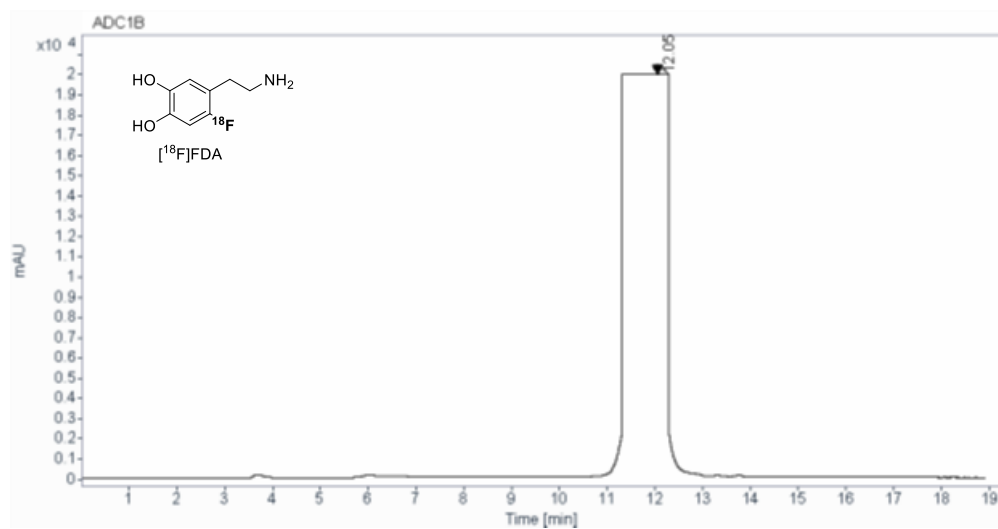


The enantiomeric purity was assessed by injecting the radiotracer alone. Identity of the radiolabelled product was confirmed by comparison with a racemic sample of inlabelled FMT.

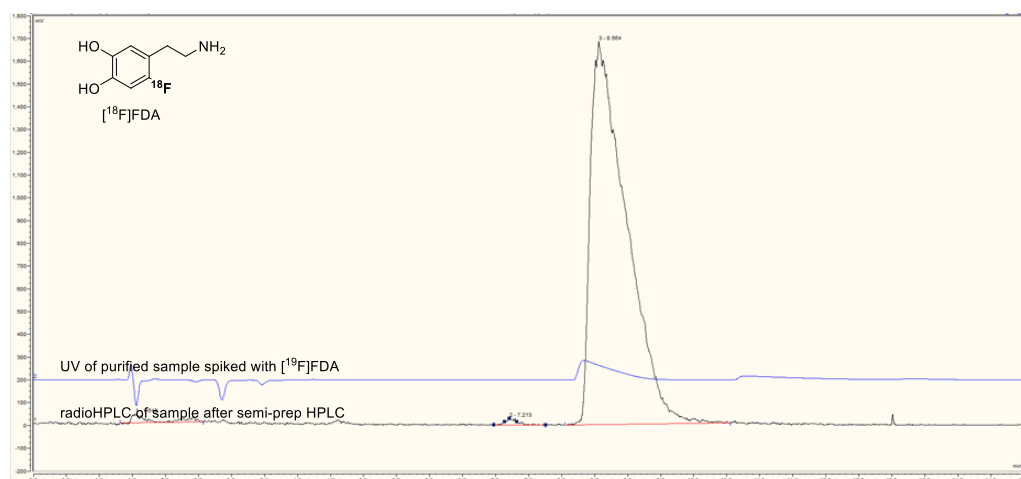


$[^{18}\text{F}]\text{FDA}$ ($[^{18}\text{F}]\text{4-9}$)

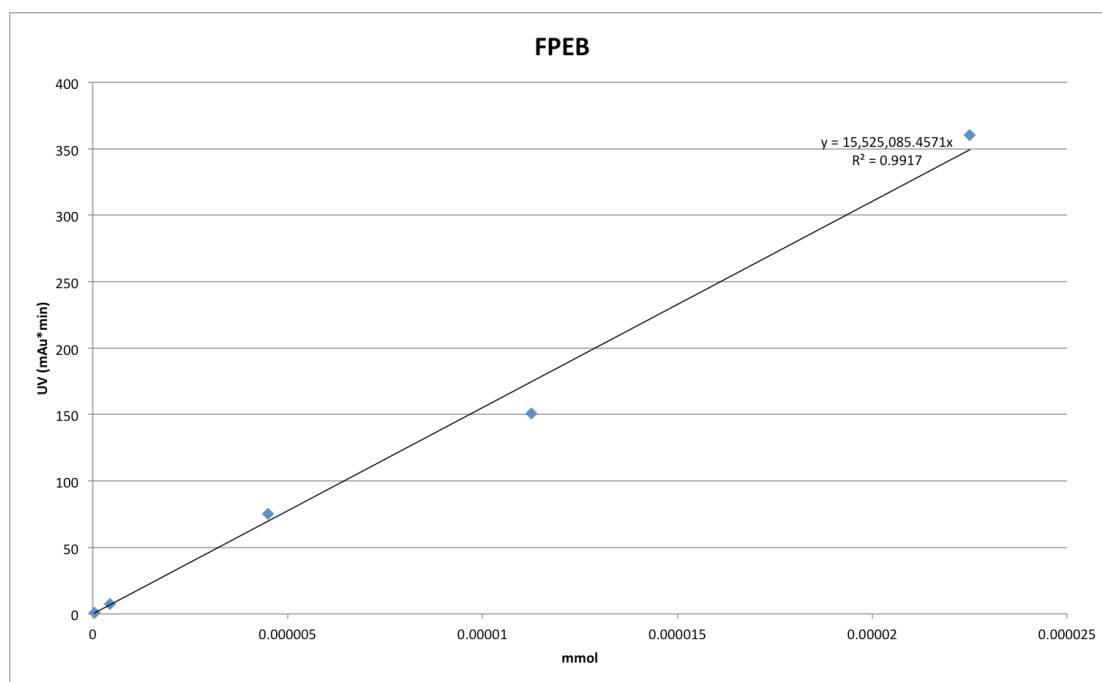
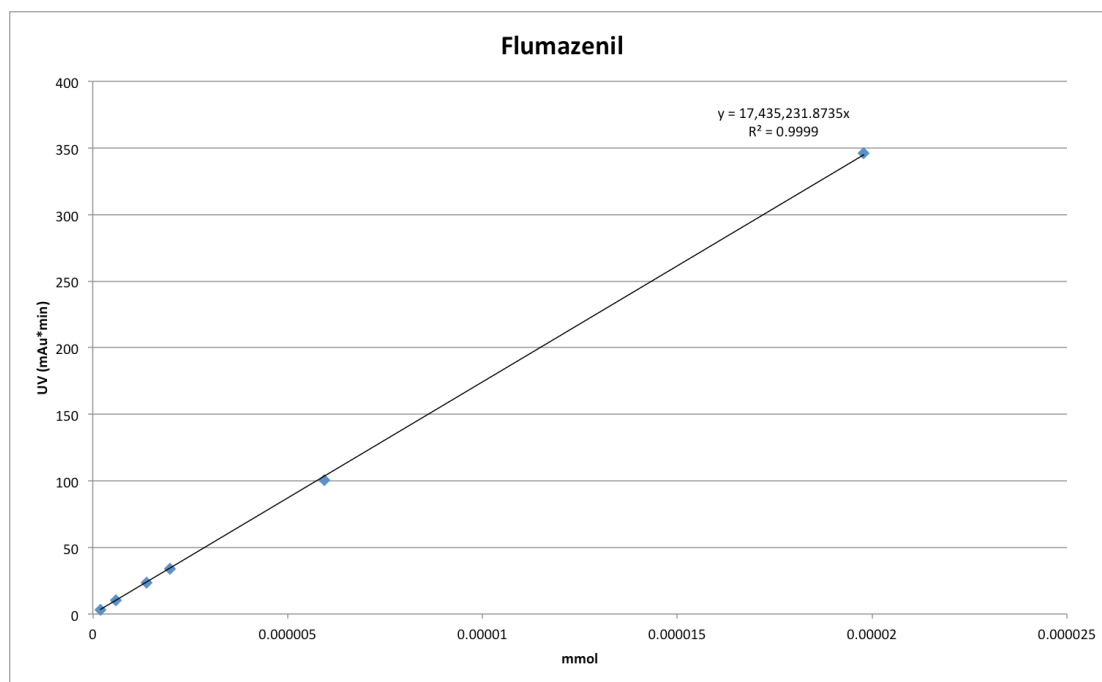
RadioHPLC trace of semi-prep HPLC



RadioHPLC trace of analytical HPLC with spiked reference UV spectra overlaid



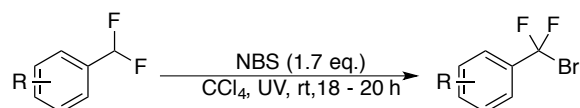
7.4.1.4. Specific Activity Calibration Curves



7.5. Radiofluorination of *Geminal* Difluorinated Motifs

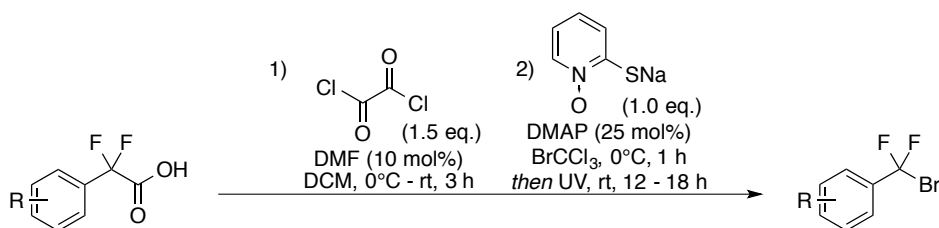
7.5.1. General Procedures

General Procedure 5A (GP5A):



Degassed carbon tetrachloride (3 mL) was added to a two-necked round bottomed flask fitted with an air condenser, containing the appropriate difluoromethyl arene (1.0 mmol, 1.0 eq.) and *N*-bromosuccinimide (303 mg, 1.7 mmol, 1.7 eq.) under an argon atmosphere. Reaction was subjected to UV light irradiation (300 W) for 18 – 20 hours before being diluted with DCM (5 mL), washed with Na₂S₂O₃ (sat., aq.) (10 mL), water (10 mL), dried over MgSO₄ and filtered. Crude product was loaded onto Celite and purified by flash column chromatography.

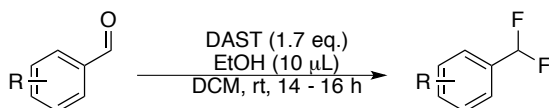
General Procedure 5B (GP5B):



To a solution of appropriate 2,2-difluoro-2-arylacetic acid (1.0 mmol, 1.0 eq.) at 0°C in DCM (2 mL) was added DMF (8 µL, 0.1 mmol, 0.1 eq.) and oxalyl chloride (129 µL, 1.5 mmol, 1.5 eq.). Reaction was allowed to warm to room temperature and stir for a further 3 hours before being concentrated *in vacuo*. Degassed bromotrichloromethane (3 mL) was used to transfer the crude 2,2-difluoro-2-arylacetyl chloride into a round-bottom flask containing DMAP (31 mg, 0.25 mmol, 0.25 eq.) and 2-mercaptopyridine *N*-oxide sodium salt (149 mg, 1.0 mmol, 1.0 eq.) under an argon atmosphere at 0°C

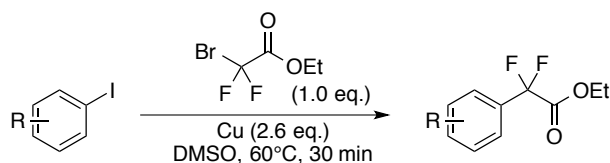
excluded from light. Reaction was stirred for 1 hour before being left for a further 12 – 18 hours under UV light irradiation at room temperature. Reaction was then concentrated *in vacuo* and purified by flash column chromatography.

General Procedure 5C (GP5C):



Diethylaminosulfur trifluoride (DAST) (1.12 mL, 8.5 mmol, 1.7 eq.), followed by a single drop of ethanol, was added to a stirred solution of appropriate aryl aldehyde (5.0 mmol, 1.0 eq.) in DCM (5 mL) at room temperature. The reaction was left to stir overnight, before being cooled to 0°C and quenched with excess NaHCO₃ (sat. aq.). Phases were separated, and the aqueous layer was further extracted with DCM (2 x 10 mL). Combined organics were washed with brine, dried over MgSO₄, filtered and solvents removed *in vacuo*. Crude products were purified by flash column chromatography.

General Procedure 5D (GP5D):

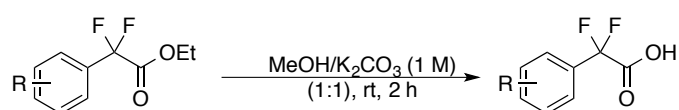


Copper powder (1.65g, 26.0 mmol) was stirred in HCl (1 M, aq.) (10 mL) for 10 minutes at room temperature before liquid was decanted off. This process was repeated with water (10 mL), methanol (10 mL) and finally acetone (10 mL) before the copper powder was dried under vacuum for 15 minutes.

Activated copper powder (1.65 g, 26.0 mmol, 2.6 eq.) was suspended in DMSO (26 mL) under a N₂ atmosphere, before the appropriate aryl iodide (10.0 mmol, 1.0 eq.) and ethyl bromodifluoroacetate (1.28 mL, 10.0 mmol, 1.0 eq.) were added. This suspension

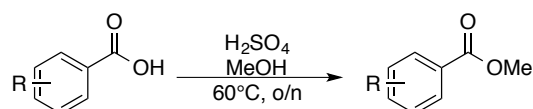
was heated to 60°C for 14 – 18 hours, after which the reaction was poured into a mixture of NH₄Cl (sat., aq.) (50 mL) and ice and then filtered through Celite. The aqueous phase was extracted with Et₂O (3 x 50 mL) and the combined organic layers were washed with NH₄Cl (sat., aq.) (2 x 50 mL), brine (2 x 50 mL), dried over MgSO₄, filtered and solvents removed *in vacuo*. Crude product was purified by flash column chromatography.

General Procedure 5E (GP5E):



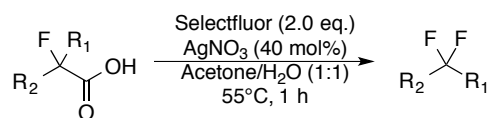
Appropriate ethyl 2,2-difluoro-2-aryl acetate (3.0 mmol), was dissolved in a mixture of methanol (9 mL) and K₂CO₃ (1 M, aq.) (9 mL) and left to stir for 2 hours at room temperature. The reaction was then acidified with HCl (6 M, aq.) (to pH 1) and the aqueous phase was extracted with EtOAc (3 x 10 mL), washed with brine (10 mL), dried over Na₂SO₄, filtered and solvents removed *in vacuo*. Products were purified by washing with petroleum ether 30-40.

General Procedure 5F (GP5F):



Sulfuric acid (6 mL) was added cautiously to the appropriate benzoic acid (11.0 mmol), dissolved in methanol (60 mL), under a N₂ atmosphere. Reaction was heated to 60°C overnight before being cooled to room temperature and diluted with Et₂O (60 mL) and washed with water (2 x 60 mL). Organic layer was further washed with NaHCO₃ (sat., aq.) (60 mL) and brine (60 mL), dried over MgSO₄, filtered and solvents removed *in vacuo*. Further purification was not necessary unless otherwise specified.

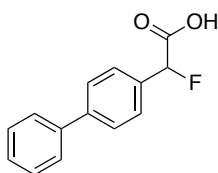
General Procedure 5G (GP5G):



Carboxylic acid (0.20 mmol, 1.0 eq.), Selectfluor (142 mg, 0.40 mmol, 2.0 eq.) and silver nitrate (14 mg, 0.08 mmol, 40 mol%) were added to a Schlenk tube equipped with a magnetic stirrer bar. The Schlenk tube was sealed with a rubber septum and was purged under vacuum and filled with nitrogen. Water (2 mL) and acetone (2 mL) were added and the reaction was placed in an oil bath at 55°C and stirred for 1 hour. Reaction was diluted with water (5 mL) before being extracted with DCM (3 × 5 mL), dried over MgSO₄ and concentrated *in vacuo*. Crude product was either purified by flash column chromatography using indicated solvent systems, or ¹⁹F NMR yields were determined against an internal standard of 1-fluoro-3-nitrobenzene (0.20 mmol, 21 μL, 1.0 eq.) which was added to the reaction after workup.

7.5.2. Substrates

Biphenyl-4-yl(fluoro)acetic acid (5-1)



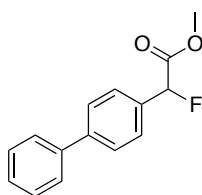
Lithium bis(trimethylsilyl)amide (1 M in THF) (22.0 mL, 22.0 mmol, 2.2 eq.) was slowly added to a solution of 4-biphenylacetic acid (2.12 g, 10.0 mmol, 1.0 eq.) and tert-butyldimethylsilyl chloride (3.47 g, 23.0 mmol, 2.3 eq.) in THF (20 mL) at 0°C. The reaction was allowed to warm to room temperature and stir overnight, before being concentrated *in vacuo* and redissolved in hexane (50 mL). The solids were filtered off, washed with hexane (50 mL) and the filtrate was concentrated *in vacuo*. The residual oil

was redissolved in MeCN (60 mL) before Selectfluor (4.60 g, 13.0 mmol, 1.3 eq.) was added as one portion. The reaction was allowed to stir for 15 minutes, then poured into HCl (1 M, aq.) (100 mL) in a separating funnel and extracted with Et₂O (2 x 100 mL). Combined organic layers were extracted with NaOH (1 M, aq.) (2 x 60 mL) and the combined basic phase was washed with Et₂O (50 mL). Organic extracts were discarded and the basic phase was acidified with HCl (6 M, aq.) to pH < 2. Et₂O (2 x 100 mL) was used to extract the acidic phase and combined organic layers were dried over MgSO₄ and the solvent was removed *in vacuo* to yield a pale yellow solid (2.21 g, 9.61 mmol, 96%).

¹H NMR (400 MHz, CDCl₃): δ = 13.57 (br. s., 1H), 7.75 (d, *J* = 7.8 Hz, 2H), 7.69 (d, *J* = 7.3 Hz, 2H), 7.55 (d, *J* = 7.3 Hz, 2H), 7.49 (t, *J* = 7.6 Hz, 2H), 7.40 (t, *J* = 7.3 Hz, 1H), 6.06 (d, *J* = 47.4 Hz, 1H); ¹³C NMR (101 MHz, CDCl₃): δ = 170.2 (d, *J* = 27.0 Hz), 141.7 (d, *J* = 2.4 Hz), 139.9, 134.6 (d, *J* = 19.9 Hz), 129.5, 128.3, 128.0, 127.5, 127.3, 88.9 (d, *J* = 181.2 Hz); ¹⁹F NMR (377 MHz, CDCl₃): δ = -175.7 (d, *J* = 46.9 Hz).

Data consistent with the literature values.¹¹³

Methyl biphenyl-4-yl(fluoro)acetate (5-2)

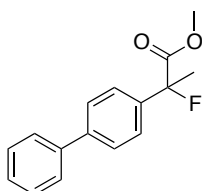


Biphenyl-4-yl(fluoro)acetic acid (670 mg, 2.91 mmol, 1.0 eq.) and *p*-toluenesulfonic acid (50 mg, 0.29 mmol, 0.1 eq.) were dissolved in MeOH (10 mL), which was then refluxed for 1 hour, before being allowed to cool to room temperature. Reaction was concentrated under reduced pressure and the residue was partitioned between water (30 mL) and Et₂O (30 mL). The aqueous layer was washed with Et₂O (30 mL) and

combined organics were washed with brine, dried over MgSO_4 and the solvent removed in vacuo to yield a pale yellow oil (531 mg, 2.18 mmol, 87%).

^1H NMR (400 MHz, CDCl_3): δ = 7.54 - 7.69 (m, 6H), 7.48 (t, J = 7.3 Hz, 2H), 7.40 (t, J = 7.3 Hz, 1H), 5.87 (d, J = 47.7 Hz, 1H), 3.83 (s, 3 H); ^{13}C NMR (101 MHz, CDCl_3): δ = 168.9 (d, J = 27.8 Hz), 142.6, 140.2, 132.9 (d, J = 20.7 Hz), 128.8, 127.7, 127.5, 127.1, 127.1, 89.1 (d, J = 185.2 Hz), 52.6; ^{19}F NMR (377 MHz, CDCl_3): δ = -179.4 (d, J = 46.9 Hz); HRMS (ESI^+ , m/z): $[\text{C}_{15}\text{H}_{13}\text{FNaO}_2]^+$ ($\text{M}+\text{Na}$) $^+$ calc. 267.0729, found 267.0787; IR (ν , cm^{-1}): 2955, 1762, 1220, 1057, 1009, 840, 760.

Methyl 2-(biphenyl-4-yl)-2-fluoropropanoate (5-3)

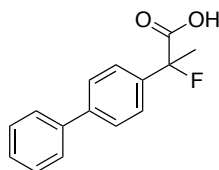


Diisopropylamine (0.43 mL, 3.05 mmol, 1.4 eq.) in THF (20 mL) was cooled to -78°C before *n*-butyllithium (2.5 M in hexane) (1.05 mL, 2.62 mmol, 1.2 eq.) was added slowly. The reaction was stirred for 10 minutes, then methyl biphenyl-4-yl(fluoro)acetate (531 mg, 2.18 mmol, 1.0 eq.) was added dropwise, before being allowed to stir for a further 1 hour. Methyl iodide (0.41 mL, 6.54 mmol, 3.0 eq.) was added, the reaction was allowed to slowly warm to room temperature and stirred overnight. The reaction was quenched with NH_4Cl (sat., aq.), and extracted with Et_2O (3 x 20 mL). The combined organic layers were washed with NaHCO_3 (sat., aq.), water and brine before being dried over Na_2SO_4 . The solvents were removed *in vacuo*, to yield a pale yellow oil (385 mg, 1.49 mmol, 49%).

^1H NMR (400 MHz, CDCl_3): δ = 7.67-7.60 (m, 6H), 7.50-7.45 (m, 2H), 7.42-7.37 (m, 1H), 3.82 (s, 3H), 2.02 (d, J = 22.5 Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3): δ = 171.4 (d, J = 26.7 Hz), 141.6,

140.3, 138.0 (d, $J = 22.9$ Hz) 128.8, 127.6, 127.2, 127.1, 125.0 (d, $J = 76.0$ Hz), 94.7 (d, $J = 186.0$ Hz), 53.0, 24.8 (d, $J = 23.8$ Hz); ^{19}F NMR (377 MHz, CDCl_3): $\delta = -151.2$ (q, $J = 21.8$ Hz); HRMS (ESI $^+$, m/z): $[\text{C}_{16}\text{H}_{15}\text{FNaO}_2]^+$ ($M+\text{Na}$) $^+$ calc. 281.0948, found 281.0941; IR (ν , cm^{-1}): 2956, 1743, 1262, 1126, 1008, 762.

2-(4-Biphenyl)-2-fluoropropanoic acid (5-4)

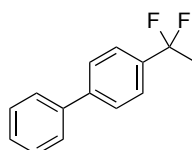


Methyl 2-(biphenyl-4-yl)-2-fluoropropanoate (385 mg, 1.49 mmol) was dissolved in MeOH (6 mL) and to this was added K_2CO_3 (2 M, aq.) (6 mL). The reaction was allowed to stir at room temperature for 2 hours before it was acidified with HCl (2 M, aq.) and extracted with Et_2O (2 x 10 mL). The combined organic extracts were dried over Na_2SO_4 and the solvent removed *in vacuo*, to yield a pale yellow solid (346 mg, 1.42 mmol, 95%).

^1H NMR (400 MHz, CDCl_3): $\delta = 11.53$ (br. s, 1H), 7.61-7.49 (m, 6H), 7.34 (t, $J = 7.1$ Hz, 2H), 7.24 (tt, $J = 7.3$ Hz, $J = 1.2$ Hz, 1H), 1.83 (d, $J = 22.3$ Hz, 3H); ^{13}C NMR (101 MHz, CDCl_3): $\delta = 171.2$ (d, $J = 27.0$ Hz), 141.3 (d, $J = 1.6$ Hz), 140.2, 138.8 (d, $J = 23.1$ Hz), 128.9, 127.6, 127.0, 126.9, 125.3 (d, $J = 8.0$ Hz), 94.2 (d, $J = 184.4$ Hz), 24.0 (d, $J = 23.8$ Hz); ^{19}F NMR (377 MHz, CDCl_3): $\delta = -144.4$ (q, $J = 21.8$ Hz).

Data consistent with the literature values.³⁶²

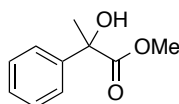
4-(1,1-Difluoroethyl)biphenyl (5-5)



Prepared according to GP5G using 2-(4-biphenyl)-2-fluoropropanoic acid (49 mg, 0.20 mmol). Purified by flash column chromatography (Hexane) to yield a white solid (40 mg, 0.18 mmol, 92%).

^1H NMR (400 MHz, CDCl_3): δ = 7.68-7.59 (m, 6H), 7.51-7.46 (m, 2H), 7.43-7.38 (m, 1H), 1.99 (t, J = 18.1 Hz, 3H); ^{13}C NMR (101 MHz, CDCl_3): δ = 142.6, 140.3, 137.0 (t, J = 27.0 Hz), 128.9, 127.7, 127.2, 127.2, 125.1 (t, J = 6.0 Hz), 121.8 (t, J = 238.4 Hz), 25.9 (t, J = 30.2 Hz); ^{19}F NMR (377 MHz, CDCl_3): δ = -87.2 (q, J = 18.3 Hz); HRMS (FI^+ , m/z): $[\text{C}_{14}\text{H}_{12}\text{F}_2] (\text{M})^+$ calc. 218.0907, found 218.0911; IR (ν , cm^{-1}): 1305, 1112, 839, 766; MP: 49-51°C.

Methyl 2-hydroxy-2-phenylpropanoate (5-6)

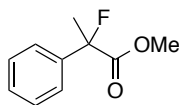


Methyl pyruvate (0.20 mL, 2.20 mmol, 1.1 eq.) in THF (4 mL) was added slowly to phenylmagnesium bromide (1 M in THF) (2.00 mL, 2.00 mmol, 1.0 eq.) at -78°C, before the reaction was allowed to warm to room temperature and quenched with NH_4Cl (sat., aq.) (6 mL). Aqueous layer was extracted with Et_2O (3 x 5 mL) and combined organic layers were dried over Na_2SO_4 before solvent was removed *in vacuo*. Crude product was purified by flash column chromatography (Petroleum Ether 40-60/ Et_2O 19:1) to yield a colourless oil (180 mg, 1.00 mmol, 50%).

^1H NMR (400 MHz, CDCl_3): δ = 7.47-7.44 (m, 2H), 7.28-7.23 (m, 2H), 7.22-7.18 (m, 1H), 3.66 (s, 3H), 1.69 (s, 3H); ^{13}C NMR (101 MHz, CDCl_3): δ = 176.1, 142.8, 128.4, 127.9, 125.2, 75.8, 53.2, 26.7.

Data consistent with the literature values.³⁶³

Methyl 2-fluoro-2-phenylpropanoate (5-7)

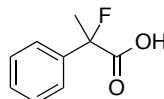


Methyl 2-hydroxy-2-phenylpropanoate (180 mg, 1.00 mmol, 1.0 eq.) in DCM (1 mL) was added dropwise to a stirred solution of diethylaminosulfur trifluoride (DAST) (0.26 mL, 2.00 mmol, 2.0 eq.) in DCM (1.5 mL) which had been cooled to -78°C in a Falcon tube. Reaction was allowed to warm to room temperature and stirred for a further 2 hours, before being quenched with NaHCO_3 (sat., aq.) and extracted with DCM (2 x 5 mL). Combined organic layers were washed with brine (10 mL), dried over Mg_2SO_4 before the solvent was removed *in vacuo* to yield a colourless oil (172 mg, 0.94 mmol, 94%).

^1H NMR (400 MHz, CDCl_3): δ = 7.44-7.39 (m, 2H), 7.32-7.23 (m, 3H), 3.66 (s, 3H), 1.85 (d, J = 22.0 Hz, 3H); ^{13}C NMR (101 MHz, CDCl_3): δ = 171.3 (d, J = 27.0 Hz), 139.2 (d, J = 23.0 Hz), 128.6, 128.4, 124.4 (d, J = 8.7 Hz), 94.6 (d, J = 186.8 Hz), 52.8, 24.7 (d, J = 23.8 Hz); ^{19}F NMR (377 MHz, CDCl_3): δ = -151.6 (q, J = 22.9 Hz).

Data consistent with the literature values.³⁶⁴

2-Fluoro-2-phenylpropanoic acid (5-8)

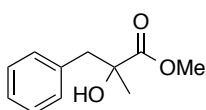


Methyl 2-fluoro-2-phenylpropanoate (172 mg, 0.94 mmol) was stirred overnight in K_2CO_3 (1 M, aq.) (3 mL) and MeOH (2 mL). Reaction was acidified to pH < 2 with HCl (2 M, aq.), before being extracted with Et_2O (2 x 10 mL). Combined organic layers were dried over Mg_2SO_4 , and solvent removed *in vacuo* to yield a pale yellow solid (123 mg, 0.73 mmol, 78%).

¹H NMR (400 MHz, CDCl₃): δ = 10.70 (br. s, 1H), 7.44 (dd, *J* = 7.9 Hz, *J* = 1.6 Hz, 2 H), 7.34-7.25 (m, 3H), 1.87 (d, *J* = 22.5 Hz, 3H); ¹³C NMR (101 MHz, CDCl₃): δ = 176.9 (d, *J* = 30.2 Hz), 138.3 (d, *J* = 22.3 Hz), 129.0, 128.6, 124.8 (d, *J* = 7.9 Hz), 94.1 (d, *J* = 186.8 Hz), 24.4 (d, *J* = 24.6 Hz); ¹⁹F NMR (377 MHz, CDCl₃): δ = -151.8 (q, *J* = 22.9 Hz).

Data consistent with the literature values.³⁶⁴

Methyl 2-hydroxy-2-methyl-3-phenylpropanoate (5-11)

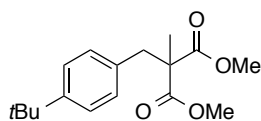


To a stirred solution of magnesium chips (243 mg, 10.0 mmol, 2.0 eq.) in THF (20 mL) was added an iodine bead, followed by benzyl bromide (0.50 mL, 5.00 mmol, 1.0 eq.). Reaction was heated to reflux for 1 hour before being cooled to room temperature and transferred by cannula to a round-bottomed flask equipped with a stirrer bar. Solution was cooled to -78°C before methyl pyruvate (0.50 mL, 1.10 mmol, 1.1 eq.) in THF (5 mL) was added dropwise, after which the reaction was allowed to warm to room temperature and stirred for a further 1 hour. Reaction was quenched with NH₄Cl (sat., aq.), extracted with Et₂O (3 x 20 mL) and combined organic layers were dried over Na₂SO₄ before the solvent was removed *in vacuo*. Purified by flash column chromatography (Hexane/EtOAc 19:1) to yield a colourless oil (332 mg, 1.69 mmol, 34%).

¹H NMR (400 MHz, CDCl₃): δ = 7.23-7.12 (m, 3H), 7.11- 7.06 (m, 2H), 3.64 (s, 3H), 2.92 (dd, *J* = 68.0 Hz, *J* = 12.7 Hz, 2H), 1.42 (s, 3H); ¹³C NMR (101 MHz, CDCl₃): δ = 176.5, 135.8, 129.9, 128.2, 126.9, 75.2, 52.5, 46.4, 25.7.

Data consistent with the literature values.³⁶⁵

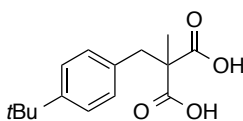
Dimethyl (4-*tert*-butylbenzyl)(methyl)propanedioate (5-13)



Sodium hydride (60% in mineral oil) (368 mg, 9.20 mmol, 1.3 eq.) was suspended in dry THF (20 mL) and cooled to 0°C, before dimethyl methyl malonate (0.94 mL, 7.06 mmol, 1.0 eq.) in THF (10 mL) was added slowly, followed by 4-*tert*-butylbenzyl bromide (1.30 mL, 7.06 mmol, 1.0 eq.). The reaction was left to stir for 1 hour, then quenched with NH₄Cl (sat., aq.) and diluted with EtOAc. The organic layer was washed with water and brine, dried over Na₂SO₄ and solvent removed *in vacuo* to yield a colourless oil (2.04 g, 6.97 mmol, 99%).

¹H NMR (400 MHz, CDCl₃): δ = 7.20 (d, *J* = 8.3 Hz, 2H), 6.95 (d, *J* = 8.3 Hz, 2H), 3.67 (s, 6H), 3.13 (s, 2H), 1.28 (s, 3H), 1.22 (s, 9H); ¹³C NMR (101 MHz, CDCl₃): δ = 172.5, 149.7, 132.9, 129.8, 125.2, 54.9, 52.5, 40.7, 34.4, 31.4, 19.8; HRMS (ESI⁺, *m/z*): [C₁₇H₂₄NaO₄]⁺ (*M*+Na)⁺ calc. 315.1567, found 315.1572; IR (ν, cm⁻¹): 2955, 1734, 1241, 1108, 839.

(4-*tert*-Butylbenzyl)(methyl)propanedioic acid (5-14)

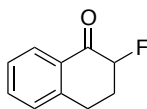


Lithium hydroxide monohydrate (285 mg, 6.80 mmol, 3.4 eq.) in water (2.5 mL) was added to dimethyl (4-*tert*-butylbenzyl)(methyl)propanedioate (585 mg, 2.00 mmol, 1.0 eq.) in THF (4 mL) and the reaction was stirred overnight at room temperature. After being diluted with water (7.5 mL) and acidified to pH < 2 with HCl (2 M, aq.), the aqueous layer was extracted with Et₂O (3 x 10 mL). Combined organics were washed with brine, dried over Na₂SO₄, filtered and the solvent removed *in vacuo*. The crude product was ground up in Petroleum Ether 30-40 (4 mL), filtered and washed with

more Petroleum Ether 30-40 (6 mL) before being dried under high-vac to yield a white solid (383 mg, 1.45 mmol, 73%).

¹H NMR (400 MHz, DMSO-d₆): δ = 7.29 (d, *J* = 8.3 Hz, 2H), 7.09 (d, *J* = 8.3 Hz, 2H), 3.03 (s, 2H), 1.26 (s, 9H), 1.15 (s, 3H); ¹³C NMR (101 MHz, CDCl₃): δ = 177.7, 154.4, 138.9, 135.2, 130.1, 59.2, 45.6, 39.2, 36.0, 24.4; HRMS (ESI⁺, *m/z*): [C₁₅H₂₀NaO₄]⁺ (*M*+Na)⁺ calc. 287.1254, found 287.1244; IR (ν, cm⁻¹): 2964, 1702, 1289, 838; MP: 165°C (decomposition).

2-Fluoro-3,4-dihydronaphthalen-1(2H)-one (5-17)

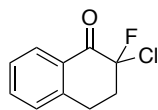


To a stirred solution of 1-tetralone (1.33 mL, 10.0 mmol, 1.0 eq.) and Selectfluor (4.25 g, 12.0 mmol, 1.2 eq.) in methanol (10 mL) was added sulfuric acid (0.05 mL, 1.0 mmol, 0.1 eq.). The reaction was heated to 50°C for 16 hours, before being filtered and the solvent removed under vacuum. Et₂O (50 mL) was added and organics were washed with water (50 mL) and brine (50 mL), dried over Na₂SO₄ and solvent removed *in vacuo*. Purified by flash column chromatography (Hexane/EtOAc 9:1) to yield a white solid (1.56 g, 9.50 mmol, 95%).

¹H NMR (400 MHz, CDCl₃): δ = 8.08 (d, *J* = 8.1 Hz, 1H), 7.55 (td, *J* = 7.5 Hz, *J* = 1.3 Hz, 1H), 7.38 (t, *J* = 7.6 Hz, 1H), 7.29 (d, *J* = 7.6 Hz, 1H), 5.17 (ddd, *J* = 47.9 Hz, *J* = 12.7 Hz, *J* = 5.1 Hz, 1H), 3.16 (dd, *J* = 9.3 Hz, *J* = 3.9 Hz, 2H), 2.66-2.54 (m, 1H), 2.45-2.31 (m, 1H); ¹³C NMR (101 MHz, CDCl₃): δ = 193.4 (d, *J* = 15.1 Hz), 143.0, 134.2, 131.2, 128.7, 127.8 (d, *J* = 2.4 Hz), 127.2, 91.2 (d, *J* = 187.6 Hz), 30.1 (d, *J* = 19.1 Hz), 27.1 (d, *J* = 11.1 Hz); ¹⁹F NMR (377 MHz, CDCl₃): δ = -190.3 (dt, *J* = 48.1 Hz, *J* = 6.9 Hz).

Data consistent with the literature values.³⁶⁶

2-Chloro-2-fluoro-3,4-dihydronaphthalen-1(2H)-one (5-18)

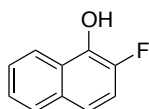


To a stirred solution of 2-fluoro-3,4-dihydronaphthalen-1(2H)-one (1.56 g, 9.50 mmol, 1.0 eq.) in DCM (20 mL) at 0°C, triethylamine (1.46 mL, 10.45 mmol, 1.1 eq.) and trimethylsilyl trifluoromethylsulfonate (1.72 mL, 9.50 mmol 1.0 eq.) were added. The solution was allowed to warm to room temperature and stir for 45 minutes. It was again cooled to 0°C before *N*-chlorosuccinimide (1.40 g, 10.45 mmol, 1.1 eq.) was added, and the reaction was allowed to warm to room temperature and stir for 2.5 hours. The reaction was quenched with water (50 mL) and extracted with Et₂O (2 x 25 mL). The organic layer was dried over Na₂SO₄ and concentrated *in vacuo*. Purified by flash column chromatography (Hexane/EtOAc 9:1) to yield a white solid (1.66 g, 8.37 mmol, 88%).

¹H NMR (400 MHz, CDCl₃): δ = 8.07 (dd, *J* = 8.0, 1.1 Hz, 1H), 7.51 (td, *J* = 7.5 Hz, *J* = 1.3 Hz, 1H), 7.34 (t, *J* = 7.6 Hz, 1H), 7.23 (d, *J* = 7.8 Hz, 1H), 3.35-3.23 (m, 1H), 3.04 (ddt, *J* = 17.4 Hz, *J* = 5.0 Hz, *J* = 2.5 Hz, *J* = 2.5 Hz, 1H), 2.79-2.70 (m, 1H), 2.70-2.59 (m, 1H); ¹³C NMR (101 MHz, CDCl₃): δ = 185.3, 142.0, 134.8, 129.2, 129.0, 128.8, 127.6, 105.2 (d, *J* = 256.7 Hz), 37.3 (d, *J* = 20.7 Hz), 27.0 (d, *J* = 8.0 Hz); ¹⁹F NMR (377 MHz, CDCl₃): δ = -116.3 (t, *J* = 5.72 Hz).

Data consistent with the literature values.²⁹⁵

2-Fluoronaphthalen-1-ol (5-20)



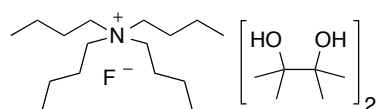
2-Chloro-2-fluoro-3,4-dihydronaphthalen-1(2H)-one (40 mg, 0.20 mmol, 1.0 eq.) and potassium fluoride (12 mg, 0.20 mmol, 1.0 eq.) were heated to 150°C for 4 hours in DMF

(0.5 mL). After cooling to room temperature, CDCl_3 (0.5 mL) was added along with trifluorotoluene (25 μL , 0.20 mmol, 1.0 eq.). [^{19}F NMR - 99%]. Solvents were consequently removed *in vacuo*, and the residue was dissolved in Et_2O (5 mL) and water (5 mL). Aqueous layer was extracted with Et_2O (5 mL) and combined organics were washed with brine, dried over Na_2SO_5 and solvent was removed *in vacuo*. Purified by flash column chromatography (Hexane/ EtOAc 9:1) to yield a white solid (30 mg, 0.19 mmol, 93%).

^1H NMR (400 MHz, CDCl_3): δ = 8.12 (d, J = 8.6 Hz, 1H), 7.71 (d, J = 8.1 Hz, 1H), 7.44 (t, J = 7.1 Hz, 1H), 7.38 (t, J = 7.1 Hz, 1H), 7.30 (dd, J = 8.8 Hz, J = 5.4 Hz, 1H), 7.20 (t, J = 10.0 Hz, 1H), 5.5 (d, J = 4.4 Hz, 1H); ^{13}C NMR (101 MHz, CDCl_3): δ = 145.5 (d, J = 232.9 Hz), 136.3 (d, J = 14.3 Hz), 130.0, 126.6, 124.8, 124.5, 124.5, 120.5 (d, J = 7.2 Hz), 119.4 (d, J = 7.2 Hz), 114.4 (d, J = 22.3 Hz); ^{19}F NMR (377 MHz, CDCl_3): δ = -145.4 (m).

Data consistent with the literature values.³⁶⁷

Tetrabutylammonium fluoride bis(pinacol) (5-21)

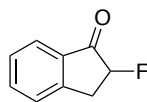


A stirred solution of tetrabutylammonium fluoride trihydrate (947 mg, 3.00 mmol, 1.0 eq.) and pinacol (709 mg, 6.00 mmol, 2.0 eq.) were refluxed in hexane for 2 hours before being allowed to cool to room temperature without stirring. The solid was filtered, washed with hexane (90 mL) and dried under high-vac., to yield a white crystalline solid (1.30 g, 2.61 mmol, 87%).

^1H NMR (400 MHz, CDCl_3): δ = 3.353.26 (m, 8H), 1.70-1.58 (m, 8H), 1.44 (sxt, J = 7.0 Hz, 8H), 1.19 (s, 24H), 1.01 (td, J = 7.3 Hz, J = 1.5 Hz, 12H); ^{13}C NMR (101 MHz, CDCl_3): δ = 74.6, 58.6, 25.2, 24.1, 19.7, 13.7; ^{19}F NMR (377 MHz, CDCl_3): δ = -114.3.

Data consistent with the literature values.²⁹⁸

2-Fluoro-2,3-dihydro-1H-inden-1-one (5-22)

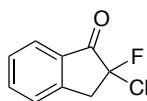


Sulfuric acid (0.05 mL, 1.0 mmol, 0.1 eq.) was added to a stirred solution of 1-indanone (1.20 mL, 10.0 mmol, 1.0 eq.) and Selectfluor (4.25 g, 12.0 mmol, 1.2 eq.) in MeOH (10 mL) under nitrogen and the reaction was heated to 50°C overnight. Reaction was then cooled to room temperature, solids filtered off, and concentrated under reduced pressure. Residue was redissolved in Et₂O (20 mL) and washed with water (20 mL) and brine (20 mL), dried over MgSO₄ and solvents removed in vacuo. Purified by flash column chromatography (Hexane/EtOAc 9:1) to yield a white solid (1.22 g, 8.13 mmol, 81%).

¹H NMR (400 MHz, CDCl₃): δ = 7.59 (d, *J* = 7.6 Hz, 1H), 7.53 (td, *J* = 7.5 Hz, *J* = 1.2 Hz, 1H), 7.33 (d, *J* = 7.8 Hz, 1H), 7.28 (t, *J* = 7.8 Hz, 1H), 5.12 (ddd, *J* = 50.9 Hz, *J* = 7.8 Hz, *J* = 4.2 Hz, 1H), 3.49 (dt, *J* = 17.0 Hz, *J* = 7.6 Hz, 1H), 3.12-2.95 (m, 1H); ¹³C NMR (101 MHz, CDCl₃): δ = 200.0 (d, *J* = 14.3 Hz), 149.8 (d, *J* = 5.6 Hz), 136.4, 128.4, 126.9 (d, *J* = 1.6 Hz), 124.5, 90.5 (d, *J* = 190.7 Hz), 33.3 (d, *J* = 21.5 Hz); ¹⁹F NMR (377 MHz, CDCl₃): δ = -193.9 (ddd, *J* = 51.5 Hz, *J* = 24.0 Hz, *J* = 6.9 Hz).

Data consistent with the literature values.³⁶⁸

2-Chloro-2-fluoro-2,3-dihydro-1H-inden-1-one (5-23a)

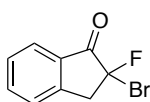


To a stirred solution of 2-fluoro-2,3-dihydro-1H-inden-1-one (601 mg, 4.00 mmol, 1.0 eq.) in DCM (10 mL) at 0°C, triethylamine (0.61 mL, 4.40 mmol, 1.1 eq.) and trimethylsilyl

trifluoromethylsulfonate (0.72 mL, 4.00 mmol 1.0 eq.) were added. The solution was allowed to warm to room temperature and stirred for 1 hour. It was again cooled to 0°C before *N*-chlorosuccinimide (588 mg, 4.40 mmol, 1.1 eq.) was added, and the reaction was allowed to warm to room temperature and stirred for 3 hours. The reaction was quenched with water (30 mL) and extracted with Et₂O (30 mL). The organic layer was washed with NaHCO₃ (sat., aq.), (30 mL), dried over Na₂SO₄ and concentrated *in vacuo*. Purified by flash column chromatography (Hexane/EtOAc 9:1) to yield a pale yellow solid (585 mg, 3.17 mmol, 79%).

¹H NMR (400 MHz, CDCl₃): δ = 7.88 (d, *J* = 7.6 Hz, 1H), 7.75 (td, *J* = 7.5 Hz, *J* = 1.0 Hz, 1H), 7.49 (q, *J* = 7.6 Hz, 2H), 3.90-3.80 (m, 2H); ¹³C NMR (101 MHz, CDCl₃): δ = 191.5 (d, *J* = 22.3 Hz), 147.0 (d, *J* = 5.6 Hz), 137.3, 131.0 (d, *J* = 1.6 Hz), 129.0, 126.5 (d, *J* = 1.6 Hz), 126.1, 105.9 (d, *J* = 262.3 Hz), 43.8 (d, *J* = 23.8 Hz); ¹⁹F NMR (377 MHz, CDCl₃): δ = -120.4 (dd, *J* = 13.7 Hz, *J* = 9.2 Hz); HRMS (ESI⁺, *m/z*): [C₉H₆ClFNaO]⁺ (M+Na)⁺ calc. 206.9983, found 206.9990; MP: 36-37°C.

2-Bromo-2-fluoro-2,3-dihydro-1H-inden-1-one (5-23b)



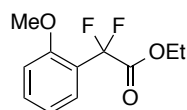
To a stirred solution of 2-fluoro-2,3-dihydro-1H-inden-1-one (601 mg, 4.00 mmol, 1.0 eq.) in DCM (10 mL) at 0°C, triethylamine (0.61 mL, 4.40 mmol, 1.1 eq.) and trimethylsilyl trifluoromethylsulfonate (0.72 mL, 4.00 mmol 1.0 eq.) were added. The solution was allowed to warm to room temperature and stirred for 1 hour. It was again cooled to 0°C before *N*-bromosuccinimide (783 mg, 4.40 mmol, 1.1 eq.) was added, and the reaction was allowed to warm to room temperature and stirred for 3 hours. The reaction was quenched with water (30 mL) and extracted with Et₂O (30 mL). The organic layer was washed with NaHCO₃ (sat., aq.), (30 mL), dried over Na₂SO₄ and concentrated *in vacuo*.

Purified by flash column chromatography (Hexane/ EtOAc 9:1) to yield a pale yellow solid (782 mg, 3.42 mmol, 85%).

^1H NMR (400 MHz, CDCl_3): δ = 7.87 (dd, J = 7.6 Hz, J = 0.5 Hz, 1H), 7.74 (td, J = 7.5 Hz, J = 1.1 Hz, 1H), 7.52-7.43 (m, 2H), 4.01 (dd, J = 18.1 Hz, J = 3.9 Hz, 1H), 3.89 (d, J = 17.4 Hz, 1H); ^{13}C NMR (101 MHz, CDCl_3): δ = 191.9 (d, J = 19.9 Hz), 146.0 (d, J = 5.6 Hz), 137.2, 130.1, 129.0, 126.5 (d, J = 1.6 Hz), 126.1, 99.9 (d, J = 275.8 Hz), 44.9 (d, J = 21.5 Hz); ^{19}F NMR (377 MHz, CDCl_3): δ = -122.3 (dd, J = 17.2 Hz, J = 3.4 Hz).

Data consistent with the literature values.³⁶⁹

Ethyl difluoro(2-methoxyphenyl)acetate (5-31)

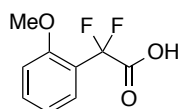


Synthesised from 2-iodoanisole (1.30 mL, 10.0 mmol) following GP5D. Purified by flash column chromatography (Pentane/ Et_2O 1:0 - 9:1) to yield a colourless oil (2.22 g, 9.63 mmol, 96%).

^1H NMR (400 MHz, CDCl_3): δ = 7.64 (d, J = 7.7 Hz, 1H), 7.46 (t, J = 7.9 Hz, 1H), 7.05 (t, J = 7.6 Hz, 1H), 6.94 (d, J = 8.3 Hz, 1H), 4.32 (q, J = 7.1 Hz, 2H), 3.80 (s, 3H), 1.29 (t, J = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, CDCl_3): δ = 164.2 (t, J = 33.8 Hz), 156.8 (t, J = 5.1 Hz), 132.5, 126.4 (t, J = 7.5 Hz), 122.1 (t, J = 24.2 Hz), 120.7, 112.4 (t, J = 247.9 Hz), 111.4, 62.7, 55.8, 14.0; ^{19}F NMR (377 MHz, CDCl_3): δ = -102.7.

Data consistent with literature values.¹¹³

Difluoro(2-methoxyphenyl)acetic acid (5-32)

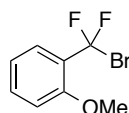


Synthesised from ethyl difluoro(2-methoxyphenyl)acetate (691 mg, 3.0 mmol) following GP5E to yield a white solid (403 mg, 1.99 mmol, 66%).

^1H NMR (400 MHz, CDCl_3): δ = 10.52 (br. s, 1H), 7.66 (dd, J = 7.7 Hz, J = 1.7 Hz, 1H), 7.51-7.47 (m, 1H), 7.08 (t, J = 7.6 Hz, 1H), 6.97 (dd, J = 8.4 Hz, J = 0.8 Hz, 1H), 3.84 (s, 3H); ^{13}C NMR (101 MHz, CDCl_3): δ = 168.9 (t, J = 34.7 Hz), 156.8 (t, J = 5.4 Hz), 132.9, 126.6 (t, J = 7.3 Hz), 121.2 (t, J = 21.3 Hz), 121.0, 112.2 (t, J = 248.7 Hz), 111.7, 56.0; ^{19}F NMR (377 MHz, CDCl_3): δ = -103.5.

Data consistent with literature values.¹¹³

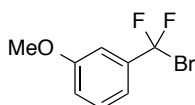
1-[Bromo(difluoro)methyl]-2-methoxybenzene (5-33)



Synthesised from difluoro(2-methoxyphenyl)acetic acid (303 mg, 1.5 mmol) following GP5B. Purified by flash column chromatography (Pentane) to yield a colourless oil (contains <9% inseparable impurity by ^{19}F NMR) (215 mg, 0.90 mmol, 60%, >91% purity).

^1H NMR (400 MHz, CDCl_3): δ = 7.54-7.48 (m, 2H), 7.02 (t, J = 8.0 Hz, 2H), 3.98 (s, 3H); ^{13}C NMR (101 MHz, CDCl_3): δ = 156.5 (t, J = 3.1 Hz), 132.9, 125.8 (t, J = 21.6 Hz), 125.0 (t, J = 7.2 Hz), 119.9, 115.9 (t, J = 303.6 Hz), 112.3, 55.9; ^{19}F NMR (377 MHz, CDCl_3): δ = -43.9 (d, J = 21.0 Hz); HRMS (EI, m/z): $[\text{C}_8\text{H}_7^{79}\text{BrF}_2\text{O}]$ (M)⁺ calc. 235.9648 found 235.9656; IR (ν , cm^{-1}): 1604, 1494, 1467, 1438, 1295, 1260, 1248, 1096, 1054, 1035, 875, 847.

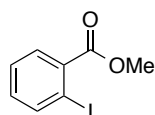
1-[Bromo(difluoro)methyl]-3-methoxybenzene (5-34)



Synthesised from difluoro(3-methoxyphenyl)acetic acid (202 mg, 1.0 mmol) following **GP5B**. Purified by flash column chromatography (Pentane) to yield a colourless oil (131 mg, 0.55 mmol, 55%).

^1H NMR (400 MHz, CDCl_3): δ = 7.37 (td, J = 8.0 Hz, J = 0.4 Hz, 1H), 7.22-7.19 (m, 1H), 7.12-7.11 (m, 1H), 7.02 (ddt, J = 8.3 Hz, J = 2.6 Hz, J = 0.4 Hz, 1H), 3.85 (s, 3H); ^{13}C NMR (101 MHz, CDCl_3): δ = 159.7, 139.5 (t, J = 23.7 Hz), 129.9, 118.3 (t, J = 304.5 Hz), 117.2, 116.6 (t, J = 4.8 Hz), 109.9 (t, J = 5.4 Hz) 55.6; ^{19}F NMR (377 MHz, CDCl_3): δ = -43.6 (s, 2F); HRMS (EI, m/z): $[\text{C}_8\text{H}_7^{79}\text{BrF}_2]^+$ (M) $^+$ calc. 235.9648, found 235.9655; IR (ν , cm^{-1}): 1605, 1493, 1455, 1434, 1319, 1290, 1221, 1124, 1087, 1038, 917, 807, 771.

Methyl 2-iodobenzoate (5-35)

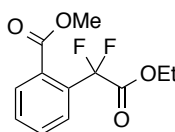


Synthesised from 2-iodobenzoic acid (4.46 g, 18.0 mmol) following **GP5F** to yield a pale yellow oil (3.32 g, 12.67 mmol, 70%).

^1H NMR (400 MHz, CDCl_3): δ = 7.95 (ddd, J = 7.9 Hz, J = 1.2 Hz, J = 0.3 Hz, 1H), 7.76 (ddd, J = 7.8 Hz, J = 1.7 Hz, J = 0.4 Hz, 1H), 7.36 (ddd, J = 7.8 Hz, J = 7.4 Hz, J = 1.2 Hz, 1H), 7.11 (ddd, J = 7.9 Hz, J = 7.4 Hz, J = 1.7 Hz, 1H), 3.89 (s, 3H); ^{13}C NMR (101 MHz, CDCl_3): δ = 166.9, 141.3, 135.0, 132.6, 130.9, 127.9, 94.1, 52.5.

Data consistent with literature values.³⁷⁰

Methyl 2-(2-ethoxy-1,1-difluoro-2-oxoethyl)benzoate (5-36)

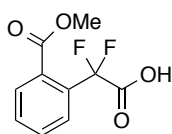


Synthesised from methyl 2-iodobenzoate (2.62 g, 10.0 mmol) following **GP5D**. Purified by flash column chromatography (Pentane/Et₂O 1:0 - 17:3) to yield a colourless oil (1.05 g, 4.05 mmol, 41%).

¹H NMR (400 MHz, CDCl₃): δ = 8.00 (d, *J* = 7.7 Hz, 1H), 7.85 (d, *J* = 7.8 Hz, 1H), 7.65 (t, *J* = 7.6 Hz, 1H), 7.57 (t, *J* = 7.6 Hz, 1H), 4.33 (q, *J* = 7.1 Hz, 2H), 3.87 (s, 3H), 1.31 (t, *J* = 7.1 Hz, 3H); ¹³C NMR (101 MHz, CDCl₃): δ = 166.5, 163.3 (t, *J* = 33.5 Hz), 133.6 (t, *J* = 23.8 Hz), 132.3, 130.9, 130.6, 128.8 (t, *J* = 3.7 Hz), 126.8 (t, *J* = 10.2 Hz), 113.1 (t, *J* = 250.1 Hz), 62.7, 52.4, 13.9; ¹⁹F NMR (377 MHz, CDCl₃): δ = -99.2.

Data consistent with literature values.³⁷¹

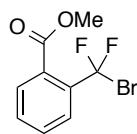
Difluoro[2-(methoxycarbonyl)phenyl]acetic acid (5-37)



Synthesised from methyl 2-(2-ethoxy-1,1-difluoro-2-oxoethyl)benzoate (775 mg, 3.0 mmol) following **GP5E** to yield a white solid (567 mg, 2.46 mmol, 82%).

¹H NMR (400 MHz, DMSO-d₆): δ = 7.95 (dd, *J* = 7.6 Hz, *J* = 0.9 Hz, 1H), 7.84 (ddd, *J* = 7.9 Hz, *J* = 1.5 Hz, *J* = 0.4 Hz, 1H), 7.78 (td, *J* = 7.6 Hz, *J* = 1.5 Hz, 1H), 7.71 (td, *J* = 7.5 Hz, *J* = 1.5 Hz, 1H), 3.81 (s, 3H). ¹³C NMR (101 MHz, DMSO-d₆): δ = 166.7, 164.3 (t, *J* = 32.6 Hz), 133.3 (t, *J* = 24.0 Hz), 133.0, 131.5, 130.9, 129.2 (t, *J* = 2.7 Hz), 127.0 (t, *J* = 9.7 Hz), 113.9 (t, *J* = 249.4 Hz), 52.8; ¹⁹F NMR (377 MHz, DMSO-d₆): δ = -97.8; HRMS (ESI⁻, *m/z*): [C₁₀H₇O₄F₂]⁻ (M-H)⁻ calc. 229.0318, found 229.0319; IR (ν, cm⁻¹): 1739, 1717, 1436, 1283, 1246, 1130, 1037, 994, 908, 766, 743, 709; MP: 92-93°C.

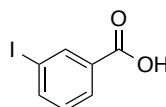
Methyl 2-[bromo(difluoro)methyl]benzoate (5-38)



Synthesised from difluoro[2-(methoxycarbonyl)phenyl]acetic acid (460 mg, 2.0 mmol) following **GP5B**. Purified by flash column chromatography (Pentane) to yield a colourless oil (294 mg, 1.11 mmol, 56%).

^1H NMR (400 MHz, CDCl_3): δ = 7.69-7.64 (m, 2H), 7.60-7.52 (m, 2H), 3.94 (s, 3H); ^{13}C NMR (101 MHz, CDCl_3): δ = 167.9, 135.9 (t, J = 23.9 Hz), 131.3, 131.1, 129.8, 125.6 (t, J = 7.1 Hz), 116.3 (t, J = 303.6 Hz), 100.1, 52.9; ^{19}F NMR (377 MHz, CDCl_3): δ = -42.5; HRMS (ESI $^+$, m/z): $[\text{C}_9\text{H}_7\text{O}_2^{79}\text{BrF}_2\text{Na}]^+$ (M+Na) $^+$ calc. 286.9490, found 286.9490; IR (ν , cm^{-1}): 1733, 1434, 1299, 1273, 1247, 1145, 1096, 1034, 957, 892, 867, 827, 759.

3-Iodobenzoic acid (5-39)

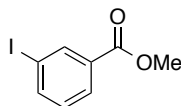


Ethyl 3-iodobenzoate (3.31 g, 12.0 mmol, 1.0 eq.) was dissolved in methanol (4 mL) at 35°C before solid potassium hydroxide (1.35 g, 24.0 mmol, 2.0 eq.) was added. Reaction was left to stir for 1 hour, then diluted with water (15 mL). Aqueous layer was extracted with Et_2O (2 x 10 mL), then acidified with HCl (6 M, aq.) and extracted with Et_2O (3 x 10 mL). Combined organics were dried over MgSO_4 and solvents removed *in vacuo* to yield a white solid (2.84 g, 11.45 mmol, 95%).

^1H NMR (400 MHz, DMSO-d_6): δ = 13.27 (br. s, 1H), 8.24-8.24 (m, 1H), 8.00 (ddd, J = 7.8 Hz, J = 1.8 Hz, J = 1.1 Hz, 1H), 7.95 (ddd, J = 7.8 Hz, J = 1.6 Hz, J = 1.1 Hz, 1H), 7.33 (td, J = 7.8 Hz, J = 0.4 Hz, 1H); ^{13}C NMR (101 MHz, DMSO-d_6): δ = 165.9, 141.3, 137.6, 132.8, 130.8, 128.6, 94.7.

Data consistent with literature values.³⁷²

Methyl 3-iodobenzoate (5-40)

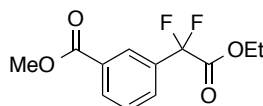


Synthesised from 3-iodobenzoic acid (2.73 g, 11.0 mmol) following **GP5F** to yield a pale orange solid (2.59 g, 9.88 mmol, 90%).

¹H NMR (400 MHz, CDCl₃): δ = 8.37-8.36 (m, 1H), 7.99 (ddd, *J* = 7.8 Hz, *J* = 1.6 Hz, *J* = 1.1 Hz, 1H), 7.87 (ddd, *J* = 7.9 Hz, *J* = 1.8 Hz, *J* = 1.1 Hz, 1H), 7.17 (td, *J* = 7.8 Hz, *J* = 0.4 Hz, 1H), 3.91 (s, 3H); ¹³C NMR (101 MHz, CDCl₃): δ = 165.6, 141.7, 138.5, 132.0, 130.0, 128.7, 93.8, 52.4.

Data consistent with literature values.³⁷⁰

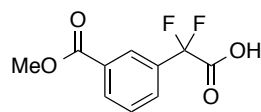
Methyl 3-(2-ethoxy-1,1-difluoro-2-oxoethyl)benzoate (5-41)



Synthesised from methyl 3-iodobenzoate (2.36 g, 9.0 mmol) following **GP5D**. Purified by flash column chromatography (Pentane/Et₂O 1:0 - 19:1) to yield a colourless oil (1.06 g, 4.10 mmol, 46%).

¹H NMR (400 MHz, CDCl₃): δ = 8.29 (d, *J* = 0.5 Hz, 1H), 8.18 (d, *J* = 7.8 Hz, 1H), 7.81 (dt, *J* = 7.8 Hz, *J* = 0.6 Hz, 1H), 7.56 (t, *J* = 7.8 Hz, 1H), 4.32 (qd, *J* = 7.2 Hz, *J* = 1.1 Hz, 2H), 3.95 (d, *J* = 1.6 Hz, 3H), 1.31 (td, *J* = 7.1 Hz, *J* = 1.5 Hz, 3H); ¹³C NMR (101 MHz, CDCl₃): δ = 166.0, 163.7 (t, *J* = 35.2 Hz), 133.3 (t, *J* = 26.3 Hz), 132.1, 130.8, 129.8 (t, *J* = 5.9 Hz), 128.9, 126.7 (t, *J* = 6.3 Hz), 112.9 (t, *J* = 252.7 Hz), 63.3, 52.4, 13.8; ¹⁹F NMR (377 MHz, CDCl₃): δ = -103.95; HRMS (ESI⁺, *m/z*): [C₁₂H₁₂O₄F₂Na]⁺ (*M*+Na)⁺ calc. 281.0607, found 281.0596; IR (ν, cm⁻¹): 1765, 1727, 1434, 1303, 1232, 1099, 1028, 967, 855, 822, 718.

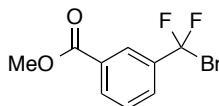
Difluoro[3-(methoxycarbonyl)phenyl]acetic acid (5-42)



Synthesised from methyl 3-(2-ethoxy-1,1-difluoro-2-oxoethyl)benzoate (775 mg, 3.0 mmol) following GP5E to yield a white solid (487 mg, 2.12 mmol, 71%).

¹H NMR (400 MHz, CDCl₃): δ = 9.66 (br. s, 1H), 8.33-8.32 (m, 1H), 8.21 (ddd, *J* = 7.8 Hz, *J* = 1.7 Hz, *J* = 1.1 Hz, 1H), 7.86 (dtd, *J* = 7.8 Hz, *J* = 1.2 Hz, *J* = 0.6 Hz, 1H), 7.59 (td, *J* = 7.8 Hz, *J* = 0.6 Hz, 1H), 3.98 (s, 3H); ¹³C NMR (101 MHz, CDCl₃): δ = 167.4 (t, *J* = 35.8 Hz), 166.4, 132.7 (t, *J* = 21.8 Hz), 132.4, 130.8, 130.0 (t, *J* = 6.1 Hz), 129.1, 126.9 (t, *J* = 6.2 Hz), 112.6 (t, *J* = 253.3 Hz), 52.7; ¹⁹F NMR (377 MHz, CDCl₃): δ = -105.0; HRMS (ESI⁺, *m/z*): [C₁₀H₇O₄F₂]⁺ (M-H)⁺ calc. 229.0318, found 229.0324; IR (ν, cm⁻¹): 1756, 1725, 1431, 1287, 1234, 1120, 1077, 1024, 961, 914, 786, 742; MP: 68-69°C.

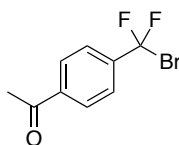
Methyl 3-[bromo(difluoro)methyl]benzoate (5-43)



Synthesised from difluoro[3-(methoxycarbonyl)phenyl]acetic acid (345 mg, 1.5 mmol) following GP5B. Purified by flash column chromatography (Pentane) to yield a pale yellow oil (174 mg, 0.66 mmol, 44%).

¹H NMR (400 MHz, CDCl₃): δ = 8.30 (s, 1H), 8.18 (d, *J* = 7.8 Hz, 1H), 7.81 (dd, *J* = 7.8 Hz, *J* = 0.4 Hz, 1H), 7.57 (t, *J* = 7.5 Hz, 1H), 3.98 (dd, *J* = 1.9 Hz, *J* = 0.8 Hz, 3H); ¹³C NMR (101 MHz, CDCl₃): δ = 165.72, 138.55 (t, *J* = 24.3 Hz), 132.23, 130.87, 128.96, 128.52 (t, *J* = 4.8 Hz), 125.50 (t, *J* = 5.2 Hz), 117.56 (t, *J* = 303.6 Hz), 52.50; ¹⁹F NMR (377 MHz, CDCl₃): δ = -44.3; HRMS (EI, *m/z*): [C₉H₇O₂⁷⁹BrF₂]⁺ (M)⁺ calc. 263.9597, found 263.9604; IR (ν, cm⁻¹): 1727, 1434, 1307, 1237, 1133, 1082, 1061, 980, 894, 814, 757, 720.

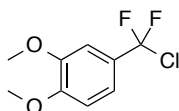
1-[4-[Bromo(difluoro)methyl]phenyl]ethanone (5-44)



Synthesised from (4-acetylphenyl)(difluoro)acetic acid (428 mg, 2.0 mmol) following GP5B. Purified by flash column chromatography (Pentane/Et₂O 19:1 - 9:1) to yield a colourless oil (contains <3% inseparable impurity by ¹⁹F NMR) (162 mg, 0.65 mmol, 43%, >97% purity).

¹H NMR (400 MHz, CDCl₃): δ = 8.06 (d, *J* = 8.4 Hz, 2H), 7.73 (d, *J* = 8.4 Hz, 2H), 2.66 (s, 3H); ¹³C NMR (101 MHz, CDCl₃): δ = 196.8, 141.8 (t, *J* = 23.9 Hz), 139.1, 128.6, 124.7, 117.5 (t, *J* = 304.1 Hz), 26.8; ¹⁹F NMR (377 MHz, CDCl₃): δ = -45.3; HRMS (EI, *m/z*): [C₉H₇⁷⁹BrF₂O]⁺ (*M*)⁺ calc. 247.9648 found 247.9645; IR (ν, cm⁻¹): 1690, 1407, 1360, 1262, 1137, 1100, 1077, 1051, 1015, 959, 886, 823, 754, 718.

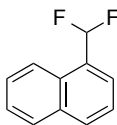
4-[Chloro(difluoro)methyl]-1,2-dimethoxybenzene (5-45)



Synthesised from (3,4-dimethoxyphenyl)(difluoro)acetic acid (464 mg, 2.0 mmol) following GP5B. Purified by flash column chromatography (Pentane/CHCl₃ 4:1) to yield a colourless oil (60 mg, 0.22 mmol, 11%).

¹H NMR (400 MHz, CDCl₃): δ = 7.24 (dd, *J* = 8.5 Hz, *J* = 1.6 Hz, 1H), 7.11 (d, *J* = 1.9 Hz, 1H), 6.91 (d, *J* = 8.5 Hz, 1H), 3.94 (s, 3H), 3.93 (s, 3H); ¹³C NMR (101 MHz, CDCl₃): δ = 151.3 (t, *J* = 1.2 Hz), 148.9, 128.8 (t, *J* = 26.7 Hz), 126.6 (t, *J* = 289.5 Hz), 117.6 (t, *J* = 5.4 Hz), 110.5, 107.8 (t, *J* = 4.5 Hz), 56.0, 56.0; ¹⁹F NMR (377 MHz, CDCl₃): δ = -46.7; HRMS (EI, *m/z*): [C₉H₉³⁵ClF₂O₂]⁺ (*M*)⁺ calc. 222.0259 found 222.0217; IR (ν, cm⁻¹): 1606, 1519, 1465, 1417, 1345, 1300, 1270, 1219, 1175, 1148, 1109, 1066, 1025, 945, 861, 831, 804, 766;

1-(Difluoromethyl)naphthalene (5-46)

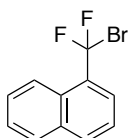


Synthesised from 1-naphthaldehyde (1.56 g, 10.0 mmol) following **GP5C**. Purified by flash column chromatography (Pentane) to yield a colourless crystalline solid (1.05 g, 5.90 mmol, 59%).

^1H NMR (400 MHz, CDCl_3): δ = 8.22 (d, J = 8.2 Hz, 1H), 7.98 (d, J = 8.3 Hz, 1H), 7.94 (d, J = 8.0 Hz, 1H), 7.72 (d, J = 7.0 Hz, 1H), 7.65-7.57 (m, 2H), 7.52 (t, J = 7.7 Hz, 1H), 7.16 (t, J = 55.2 Hz, 1H); ^{13}C NMR (101 MHz, CDCl_3): δ = 133.9, 131.6, 129.8, 129.6 (t, J = 21.0 Hz), 128.9, 127.3, 126.5, 124.9 (t, J = 8.7 Hz), 124.8, 123.7, 115.6 (t, J = 238.3 Hz); ^{19}F NMR (377 MHz, CDCl_3): δ = -110.8 (d, J = 55.2 Hz).

Data consistent with literature values.³⁷³

1-[Bromo(difluoro)methyl]naphthalene (5-47)

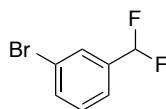


Synthesised from 1-(difluoromethyl)naphthalene (535 mg, 3.0 mmol) following **GP5A** (run for 72 h). Purified by flash column chromatography (Hexane) to yield a colourless oil (122 mg, 0.47 mmol, 16%).

^1H NMR (400 MHz, CDCl_3): δ = 8.46 (d, J = 8.7 Hz, 1H), 8.03 (d, J = 8.3 Hz, 1H), 7.97 (d, J = 8.1 Hz, 1H), 7.85 (d, J = 7.4 Hz, 1H), 7.74-7.69 (m, 1H), 7.62 (t, J = 7.5 Hz, 1H), 7.52 (t, J = 7.8 Hz, 1H); ^{13}C NMR (101 MHz, CDCl_3): δ = 134.2, 132.9 (t, J = 21.5 Hz), 132.6, 128.9, 128.1, 127.3, 126.6, 124.8 (t, J = 2.9 Hz), 124.2, 122.6 (t, J = 8.7 Hz), 117.8 (t, J = 304.7 Hz); ^{19}F NMR (377 MHz,

CDCl_3): $\delta = -41.6$; HRMS (FI, m/z): $[\text{C}_{11}\text{H}_7^{79}\text{BrF}_2]^+ (\text{M})^+$ calc. 255.9699, found 255.9698; IR (ν , cm^{-1}): 1514, 1351, 1286, 1250, 1189, 1111, 1064, 1027, 983, 897, 858, 785.

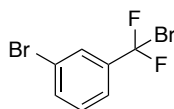
1-Bromo-3-(difluoromethyl)benzene (5-48)



Synthesised from 3-bromobenzaldehyde (0.58 mL, 5.0 mmol) following GP5C. Purified by flash column chromatography (Pentane) to yield a colourless oil (600 mg, 2.90 mmol, 58%).

^1H NMR (400 MHz, CDCl_3): $\delta = 7.67$ (s, 1H), 7.61 (ddd, $J = 8.0$ Hz, $J = 1.9$ Hz, $J = 0.9$ Hz, 1H), 7.44 (dt, $J = 7.7$ Hz, $J = 1.0$ Hz, 1H), 7.33 (t, $J = 7.8$ Hz, 1H), 6.61 (t, $J = 56.2$ Hz, 1H); ^{13}C NMR (101 MHz, CDCl_3): $\delta = 136.4$ (t, $J = 23.0$ Hz), 134.0, 130.5, 128.9 (t, $J = 6.3$ Hz), 124.3 (t, $J = 6.2$ Hz), 122.8, 113.8 (t, $J = 240.0$ Hz); ^{19}F NMR (377 MHz, CDCl_3): $\delta = -111.4$ (d, $J = 56.4$ Hz); HRMS (FI, m/z): $[\text{C}_7\text{H}_5^{79}\text{BrF}_2]^+ (\text{M})^+$ calc. 205.9543, found 205.9539; IR (ν , cm^{-1}): 1578, 1480, 1434, 1367, 1281, 1211, 1108, 1030, 889, 861, 786.

1-Bromo-3-[bromo(difluoro)methyl]benzene (5-49)

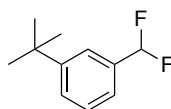


Synthesised from 1-bromo-3-(difluoromethyl)benzene (207 mg, 1.0 mmol) following GP5A. Purified by flash column chromatography (Pentane) to yield a colourless oil (110 mg, 0.39 mmol, 39%).

^1H NMR (400 MHz, CDCl_3): $\delta = 7.76$ (t, $J = 1.8$ Hz, 1H), 7.63-7.61 (m, 1H), 7.55 (ddd, $J = 7.4$ Hz, $J = 1.1$ Hz, $J = 0.6$ Hz, 1H), 7.34 (t, $J = 8.0$ Hz, 1H); ^{13}C NMR (101 MHz, CDCl_3): $\delta = 140.0$ (t, $J = 24.5$ Hz), 134.5, 130.4, 127.7 (t, $J = 4.8$ Hz), 123.2 (t, $J = 5.6$ Hz), 122.7, 117.1 (t, $J = 304.4$ Hz);

^{19}F NMR (377 MHz, CDCl_3): $\delta = -44.5$; HRMS (EI, m/z): $[\text{C}_{10}\text{H}_{11}\text{OF}_3]^+$ (M) $^+$ calc. 283.8642, found 283.8630; IR (ν , cm^{-1}): 2360, 1423, 1254, 1133, 1055, 871, 787, 727.

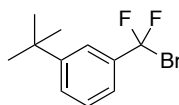
1-*tert*-Butyl-3-(difluoromethyl)benzene (5-50)



Synthesised from 3-*tert*-butylbenzaldehyde (811 mg, 5.0 mmol) following GP5C. Purified by flash column chromatography (Pentane) to yield a colourless oil (498 mg, 2.70 mmol, 54%).

^1H NMR (400 MHz, CDCl_3): $\delta = 7.59$ -7.56 (m, 2H), 7.45 (td, $J = 7.5$ Hz, $J = 0.6$ Hz, 1H), 7.39 (dd, $J = 7.6$ Hz, $J = 0.8$ Hz, 1H), 6.70 (t, $J = 56.6$ Hz, 1H), 1.41 (t, $J = 1.5$ Hz, 9H); ^{13}C NMR (101 MHz, CDCl_3): $\delta = 151.9$, 134.1 (t, $J = 22.0$ Hz), 128.5, 127.8, 122.7 (t, $J = 6.3$ Hz), 122.4 (t, $J = 5.9$ Hz), 115.2 (t, $J = 238.4$ Hz), 34.8, 31.3; ^{19}F NMR (377 MHz, CDCl_3): $\delta = -109.9$ (d, $J = 56.5$ Hz); HRMS (FI, m/z): $[\text{C}_{11}\text{H}_{14}\text{F}_2]^+$ (M) $^+$ calc. 184.1064, found 184.1065; IR (ν , cm^{-1}): 2965, 1372, 1212, 1063, 1024, 893, 828, 797, 733, 701.

1-[Bromo(difluoro)methyl]-3-*tert*-butylbenzene (5-51)

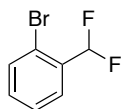


Synthesised from 1-*tert*-butyl-3-(difluoromethyl)benzene (368 mg, 2.0 mmol) following GP5A. Purified by flash column chromatography (Pentane) to yield a colourless oil (237 mg, 0.90 mmol, 45%).

^1H NMR (400 MHz, CDCl_3): $\delta = 7.65$ (s, 1H), 7.55 (d, $J = 7.6$ Hz, 1H), 7.46 (d, $J = 7.8$ Hz, 1H), 7.41 (t, $J = 7.7$ Hz, 1H), 1.39 (s, 9H); ^{13}C NMR (101 MHz, CDCl_3): $\delta = 151.9$, 137.9 (t, $J = 23.0$ Hz), 128.4, 128.3, 121.6 (t, $J = 5.2$ Hz), 121.1 (t, $J = 5.3$ Hz), 118.8 (t, $J = 303.9$ Hz), 34.9, 31.2; ^{19}F NMR (377 MHz, CDCl_3): $\delta = -42.8$; HRMS (FI, m/z): $[\text{C}_{11}\text{H}_{13}^{79}\text{BrF}_2]^+$ (M) $^+$ calc. 262.0169,

found 262.0158; IR (ν , cm^{-1}): 2966, 1429, 1367, 1294, 1242, 1136, 1110, 1092, 1062, 924, 889, 836, 796, 743.

1-Bromo-2-(difluoromethyl)benzene (5-52)

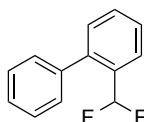


Synthesised from 2-bromobenzaldehyde (0.58 mL, 5.0 mmol) following GP5C. Purified by flash column chromatography (Pentane) to yield a colourless oil (543 mg, 2.62 mmol, 52%).

^1H NMR (400 MHz, CDCl_3): δ = 7.68-7.66 (m, 1H), 7.61 (dq, J = 8.0 Hz, J = 1.2 Hz, 1H), 7.45-7.40 (m, 1H), 7.36-7.32 (m, 1H), 6.92 (t, J = 54.9 Hz, 1H); ^{13}C NMR (101 MHz, CDCl_3): δ = 133.5 (t, J = 23.7 Hz), 133.3, 132.3, 127.9, 127.3 (t, J = 5.5 Hz), 121.7 (t, J = 6.5 Hz) 113.9 (t, J = 238.4 Hz); ^{19}F NMR (377 MHz, CDCl_3): δ = -114.6 (d, J = 54.9 Hz).

Data consistent with literature values.³⁷⁴

2-(Difluoromethyl)biphenyl (5-54)

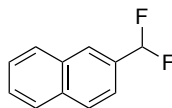


Synthesised from 2-biphenylcarbaldehyde (1.82 g, 10.0 mmol) following GP5C. Purified by flash column chromatography (Pentane) to yield a colourless oil (1.38 g, 6.74 mmol, 67%).

^1H NMR (400 MHz, CDCl_3): δ = 7.87-7.85 (m, 1H), 7.58-7.47 (m, 5H), 7.44-7.40 (m, 3H), 6.61 (t, J = 54.9 Hz, 1H); ^{13}C NMR (101 MHz, CDCl_3): δ = 141.42 (t, J = 7.2 Hz), 138.7, 131.8 (t, J = 22.1 Hz), 130.5, 130.2, 129.5, 128.4, 127.9, 127.9, 125.6 (t, J = 4.7 Hz), 113.2 (t, J = 235.5 Hz); ^{19}F NMR (377 MHz, CDCl_3): δ = -107.3 (d, J = 54.9 Hz).

Data consistent with literature values.³⁷⁴

2-(Difluoromethyl)naphthalene (5-56)

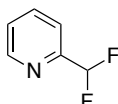


Synthesised from 2-naphthaldehyde (781 mg, 5.0 mmol) following GP5C. Purified by flash column chromatography (Pentane) to yield a white solid (688 mg, 3.86 mmol, 77%). Stored in freezer in Falcon tube.

¹H NMR (400 MHz, CDCl₃): δ = 7.99 (t, *J* = 0.6 Hz, 1H), 7.94 (d, *J* = 8.5 Hz, 1H), 7.92-7.89 (m, 2H), 7.62 (dd, *J* = 8.8 Hz, *J* = 1.7 Hz, 1H), 7.59-7.54 (m, 2H), 6.82 (t, *J* = 56.4 Hz, 1H); ¹³C NMR (101 MHz, CDCl₃): δ = 134.5, 132.7, 131.8 (t, *J* = 22.3 Hz), 129.0, 128.7, 128.0, 127.5, 126.9, 126.0 (t, *J* = 7.4 Hz), 122.1 (t, *J* = 4.7 Hz) 115.2 (t, *J* = 238.5 Hz); ¹⁹F NMR (377 MHz, CDCl₃): δ = -109.8 (d, *J* = 56.4 Hz).

Data consistent with literature values.³⁷³

2-(Difluoromethyl)pyridine (5-58a)



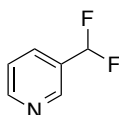
Synthesised from pyridine-2-carbaldehyde (1.07 g, 10.0 mmol) following GP5C. Purified by flash column chromatography (Pentane/Et₂O 3:2 - 1:1) to yield a colourless oil (283 mg, 2.19 mmol, 22%). Stored in freezer in Falcon tube.

¹H NMR (400 MHz, CDCl₃): δ = 8.65 (br. s, 1H), 7.83 (tdd, *J* = 7.7 Hz, *J* = 3.8 Hz, *J* = 1.7 Hz, 1H), 7.63 (dd, *J* = 7.8 Hz, *J* = 1.8 Hz, 1H), 7.40 (ddtd, *J* = 8.4 Hz, *J* = 4.0 Hz, *J* = 2.1 Hz, *J* = 1.0 Hz, 1H), 6.64 (td, *J* = 55.5 Hz, *J* = 2.2 Hz, 1H); ¹³C NMR (101 MHz, CDCl₃): δ = 152.8 (t, *J* = 25.7

Hz), 149.5, 137.3, 125.4, 120.1 (t, $J = 2.5$ Hz), 113.9 (t, $J = 240.0$ Hz); ^{19}F NMR (377 MHz, CDCl_3): $\delta = -115.85$ (d, $J = 55.5$ Hz).

Data consistent with literature values.³⁷⁵

3-(Difluoromethyl)pyridine (5-58b)

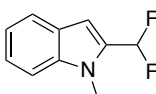


Synthesised from pyridine-2-carbaldehyde (1.07 g, 10.0 mmol) following GP5C. Purified by flash column chromatography (Pentane/ Et_2O 7:3 - 4:6) to yield a colourless oil (676 mg, 5.24 mmol, 52%). Stored in freezer in Falcon tube.

^1H NMR (400 MHz, CDCl_3): $\delta = 8.77$ -8.74 (m, 2H), 7.85 (d, $J = 7.9$ Hz, 1H), 7.41 (t, $J = 6.4$ Hz, 1H), 6.73 (t, $J = 55.8$ Hz, 1H); ^{13}C NMR (101 MHz, CDCl_3): $\delta = 152.0$, 147.3 (t, $J = 7.1$ Hz), 133.2 (t, $J = 5.5$ Hz), 130.1, 123.5, 113.4 (t, $J = 239.2$ Hz, 1C); ^{19}F NMR (377 MHz, CDCl_3): $\delta = -112.4$ (d, $J = 55.8$ Hz).

Data consistent with literature values.³⁷⁵

2-(Difluoromethyl)-1-methyl-1H-indole (5-61)



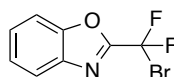
Synthesised from 1-methyl-1H-indole-2-carbaldehyde (760 mg, 5.0 mmol) following GP5C. Purified by flash column chromatography (Pentane/ Et_2O 1:0 - 19:1) to yield a white solid (339 mg, 1.87 mmol, 37%). Stored in freezer in Falcon tube.

^1H NMR (400 MHz, CDCl_3): $\delta = 7.72$ (d, $J = 8.0$ Hz, 1H), 7.43 (d, $J = 8.2$ Hz, 1H), 7.39 (t, $J = 7.5$ Hz, 1H), 7.25-7.21 (m, 1H), 6.87 (t, $J = 53.7$ Hz, 1H), 6.80 (t, $J = 2.5$ Hz, 1H), 3.92 (s, 3H); ^{13}C NMR (101 MHz, CDCl_3): $\delta = 138.7$, 131.0 (t, $J = 23.1$ Hz), 126.3, 123.8, 121.9, 120.2, 111.4 (t, $J =$

234.6 Hz), 109.6, 104.5 (t, $J = 7.5$ Hz) 30.8 (d, $J = 2.7$ Hz); ^{19}F NMR (377 MHz, CDCl_3): $\delta = -109.4$ (d, $J = 53.7$ Hz).

Data consistent with literature values.³⁷⁶

2-[Bromo(difluoro)methyl]-1,3-benzoxazole (5-63)



2-Aminophenol (153 mg, 1.4 mmol, 1.4 eq.) was added to trimethylsilyl polyphosphate (PPSE, 3 mL) in a flame dried round bottomed flask equipped with a stirrer bar. Bromodifluoroacetic acid (191 mg, 1.0 mmol, 1.0 eq.) was then added and the reaction was heated to 140°C for 3 hours before being allowed to cool to room temperature. The reaction was taken up in DCM (6 mL) and then neutralised with NaOH (1 M, aq.). Layers were separated and the aqueous layer was further extracted with DCM (3 x 6 mL). Combined organics were dried over MgSO_4 , concentrated *in vacuo*. Purified by flash column chromatography (Pentane) to yield a colourless oil (166 mg, 0.67 mmol, 67%).

^1H NMR (400 MHz, CDCl_3): $\delta = 7.89$ (ddd, $J = 7.9$ Hz, $J = 1.4$ Hz, $J = 0.7$ Hz, 1H), 7.68 (ddd, $J = 8.2$ Hz, $J = 1.2$ Hz, $J = 0.7$ Hz, 1H), 7.55 (td, $J = 7.8$ Hz, $J = 1.4$ Hz, 1H), 7.49 (td, $J = 7.6$ Hz, $J = 1.2$ Hz, 1H); ^{13}C NMR (101 MHz, CDCl_3): $\delta = 155.7$ (t, $J = 32.7$ Hz), 150.6, 139.6, 127.7, 125.9, 121.9, 111.6, 108.8 (t, $J = 301.9$ Hz); ^{19}F NMR (377 MHz, CDCl_3): $\delta = -51.4$.

Data consistent with literature values.³⁷⁷

7.5.3. Radiochemistry

7.5.3.1. General Information

[¹⁸F]Fluoride Preparation

[¹⁸F]Fluoride was produced by Erigal (Keele, UK) via the ¹⁸O(p,n)¹⁸F reaction and delivered as [¹⁸F]fluoride in [¹⁸O]water. Radiosynthesis and azeotropic drying was performed on a NanoTek® automated microfluidic device (Advion). [¹⁸F]Fluoride was separated from ¹⁸O-enriched-water using anion exchange cartridges (MPI, ORTG, Tennessee, USA) and subsequently released with 550 µL of a solution of K_{2.2.2}/K₂CO₃ (kryptofix 2.2.2 (15 mg) and K₂CO₃ (3 mg) in 1 mL of MeCN/H₂O, 4:1) into the concentrator to form [¹⁸F]KF/K_{2.2.2}. The solution was dried with five cycles of azeotropic drying with acetonitrile (300 µL) and redissolved in anhydrous acetonitrile (1000 µL). [¹⁸F]KF/K_{2.2.2} (ca. 30 MBq) was dispensed as aliquots of this stock solution into a v-vial containing the necessary reagents and a magnetic stirrer.

Procedure for 'Research Mode' [¹⁸F]fluorination

To a v-vial containing K₂CO₃ (2 mg, 0.014 mmol), K_{2.2.2} (9 mg, 0.024 mmol) and a magnetic stirrer bar was added [¹⁸F]KF/K_{2.2.2} in MeCN. A solution of appropriate starting material (0.01 mmol) in acetone (200 µL) was added via syringe. The sealed vial was heated at 50°C for 20 minutes, before being quenched with water (200 µL). An aliquot was removed for analysis by radioTLC and radioHPLC for radiochemical yield and product identification.

Procedure for Large Scale [¹⁸F]fluorination

[¹⁸F]Fluoride was dried following the same azeotropic procedure as previously described, however it was not resolubilised in acetonitrile. A solution of ethyl bromo(4-

tert-butylphenoxy)fluoroacetate in acetone (250 μ L) was added directly into the concentrator vial, which was then heated to 50°C for 20 min. An aliquot was taken for analysis by radioTLC and radioHPLC and the remaining solution was diluted with acetone (250 - 500 μ L) to give a stock solution of [18 F]5-27a for post-fluorination studies.

Analysis

For all reactions, an aliquot was removed for analysis by radioTLC and radioHPLC.

RadioTLC was carried out on Merck Kiesegel 60 F254 plates in EtOAc/Hexane (1:1) or Methanol and analysed using a plastic scintillator/PMT detector.

HPLC analysis was performed using a Dionex Ultimate 3000 dual channel HPLC system with a shared autosampler, parallel UV-detectors and LabLogic NaI/PMT-radiodetectors with Flowram analogue output. A representative radioHPLC trace of the crude reaction mixture, with UV trace (254 nm) of authentic reference material overlaid, is shown below.

HPLC Gradient Settings: Water + 0.1% TFA/ MeCN + 0.1% TFA, 1 mL/min, Waters Nova-Pak C18 Column, 4 μ m, 3.9 x 150 mm:

0 – 1 min (5 % MeCN + 0.1% TFA) isocratic

1 – 11 min (5 % to 95 % MeCN + 0.1% TFA) linear increase

11 – 15 min (95 % MeCN + 0.1% TFA) isocratic

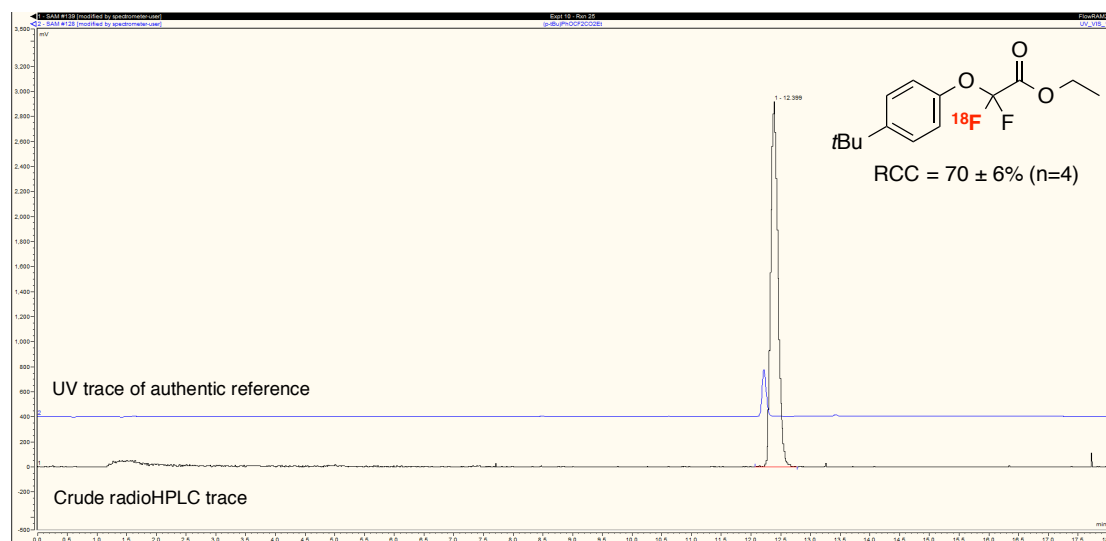
15 – 17 min (95 % to 5 % MeCN + 0.1% TFA) linear decrease

17 – 18 min (5 % MeCN + 0.1% TFA) isocratic.

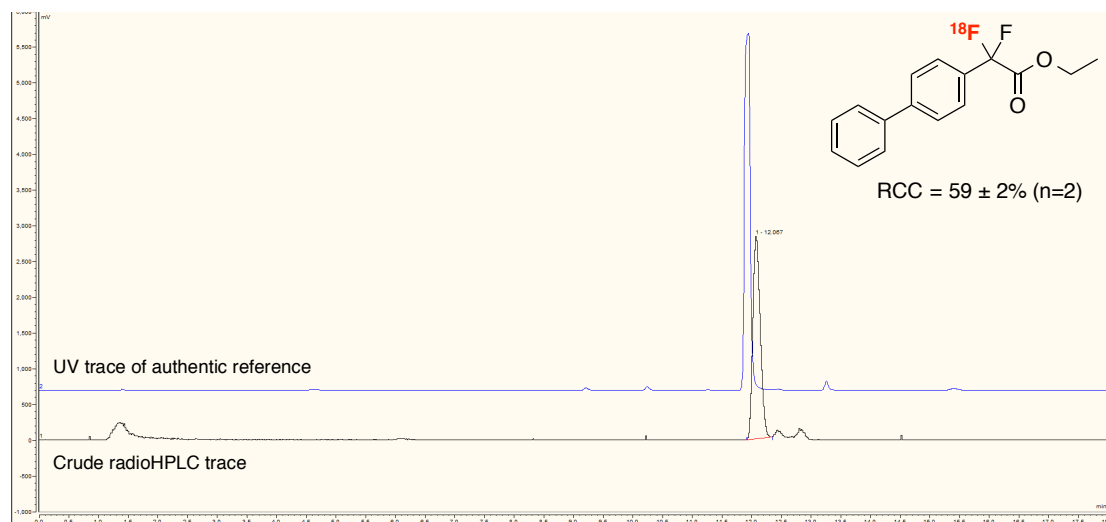
Reported radiochemical conversions are decay corrected and calculated by radioTLC taking into account the radiochemical purity as determined by radioHPLC.

7.5.3.2. HPLC Characterisation

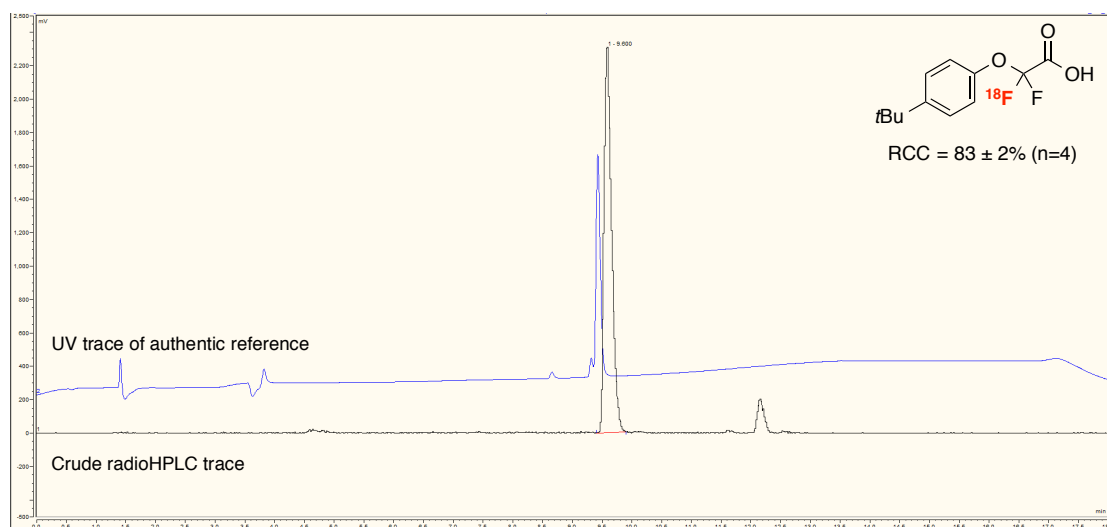
Ethyl (4-*tert*-butylphenoxy)([¹⁸F]difluoro)acetate ([¹⁸F]5-26a)



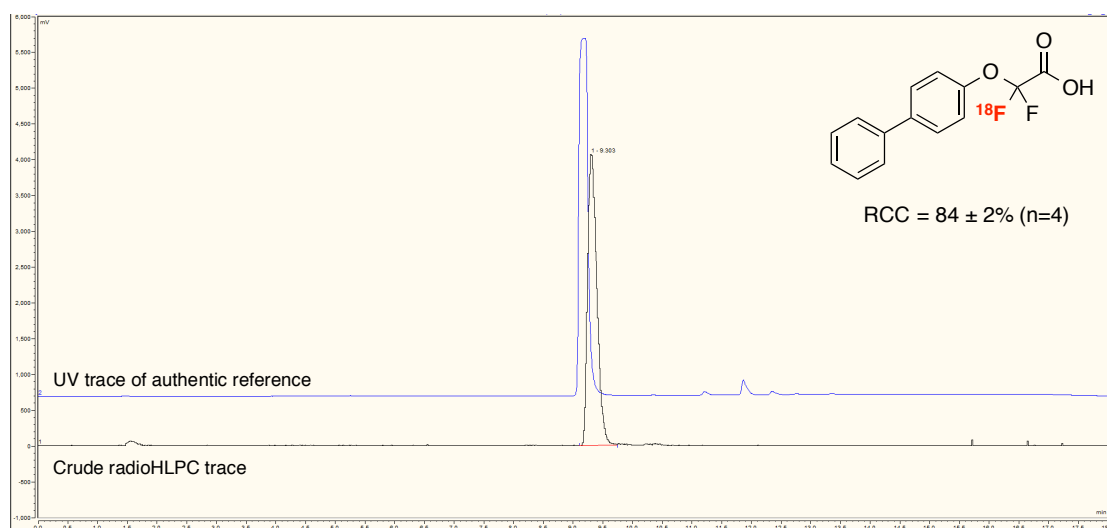
Ethyl [(1,1'-biphenyl)-4-yl]oxy([¹⁸F]difluoro)acetate ([¹⁸F]5-26b)



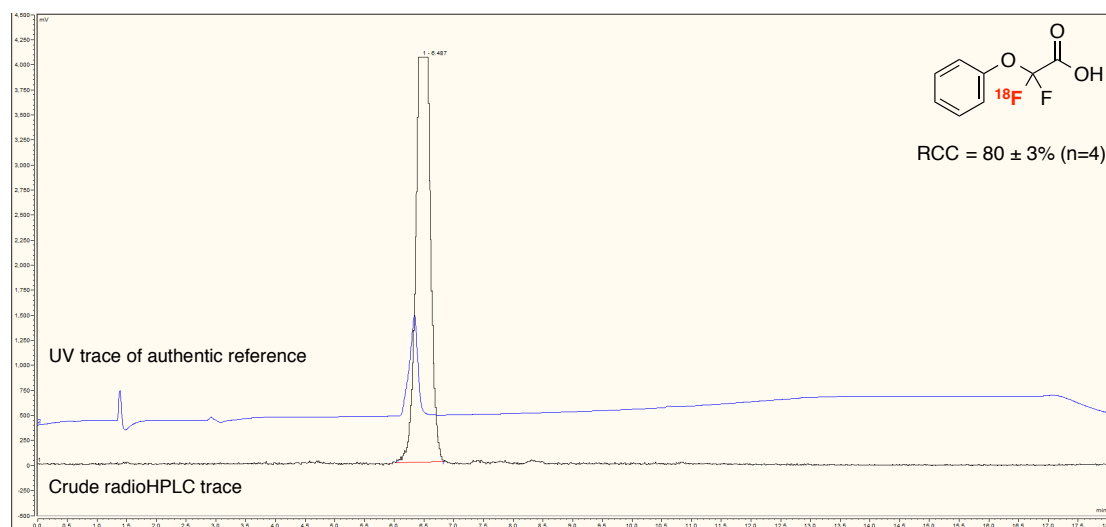
(4-*tert*-Butylphenoxy)([¹⁸F]difluoro)acetic acid ([¹⁸F]5-27a)



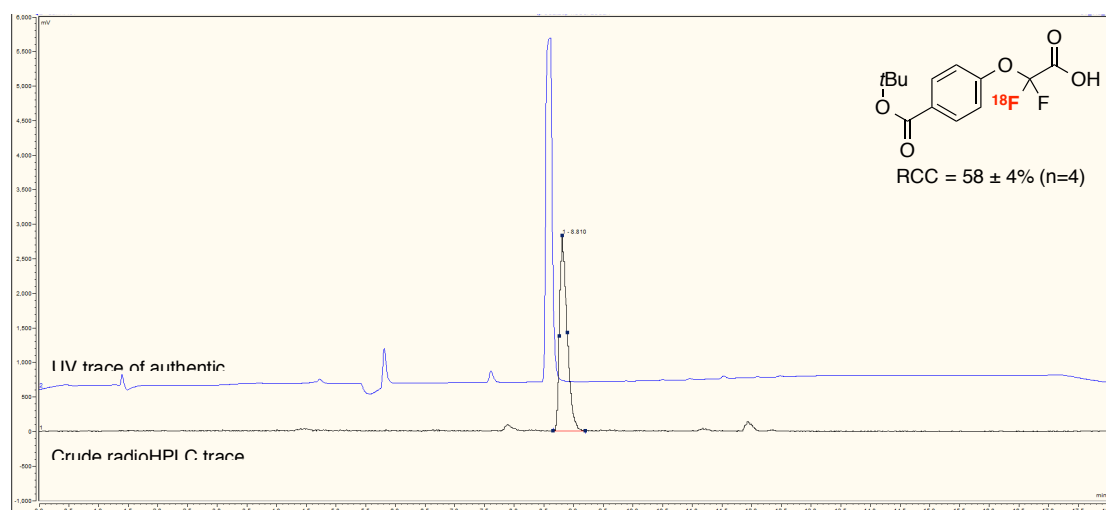
[[1,1'-Biphenyl]-4-yl]oxy)([¹⁸F]difluoro)acetic acid ([¹⁸F]5-27b)



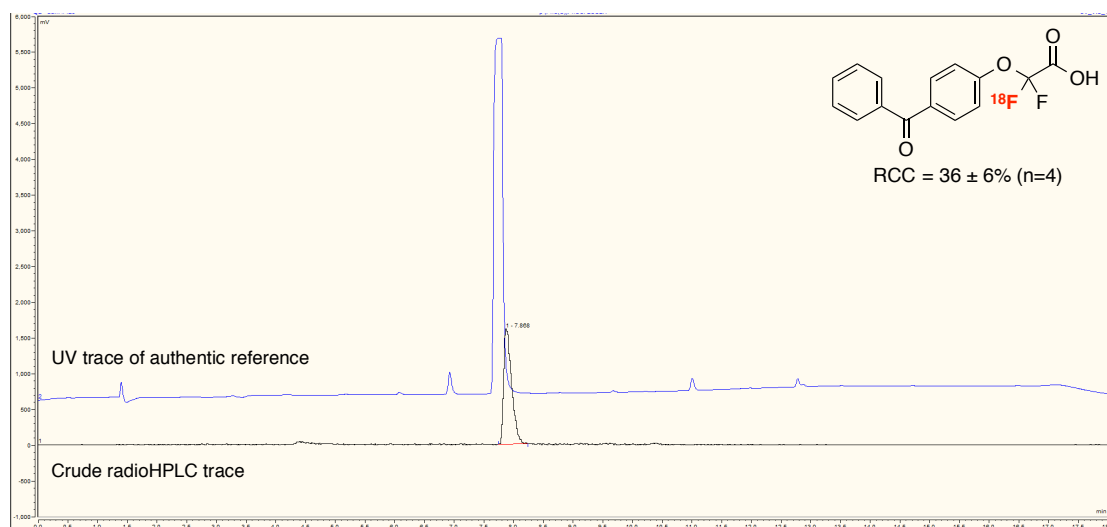
[¹⁸F]Difluoro(phenoxy)acetic acid ([¹⁸F]5-27c)



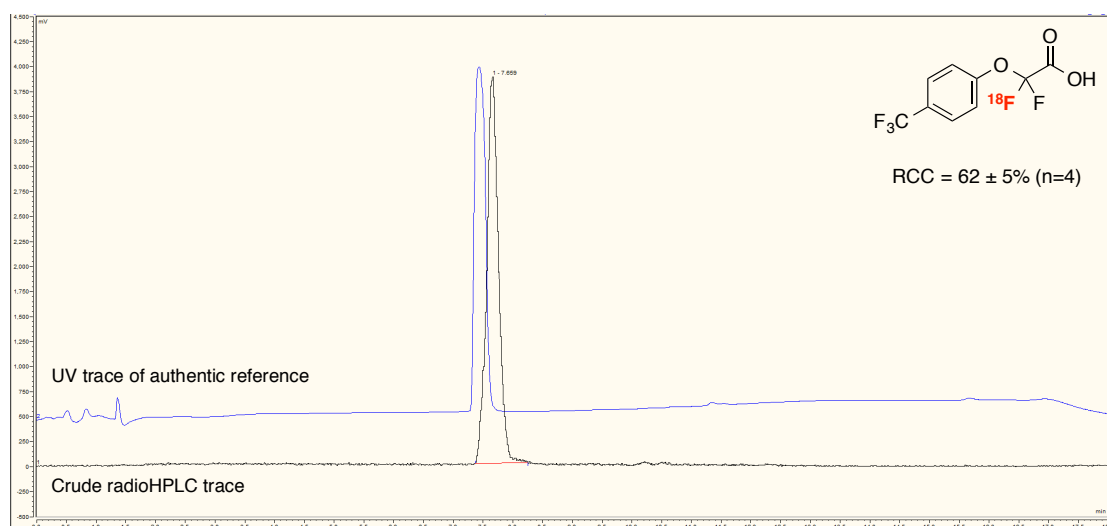
[4-(*tert*-Butoxycarbonyl)phenoxy]([¹⁸F]difluoro)acetic acid ([¹⁸F]5-27d)



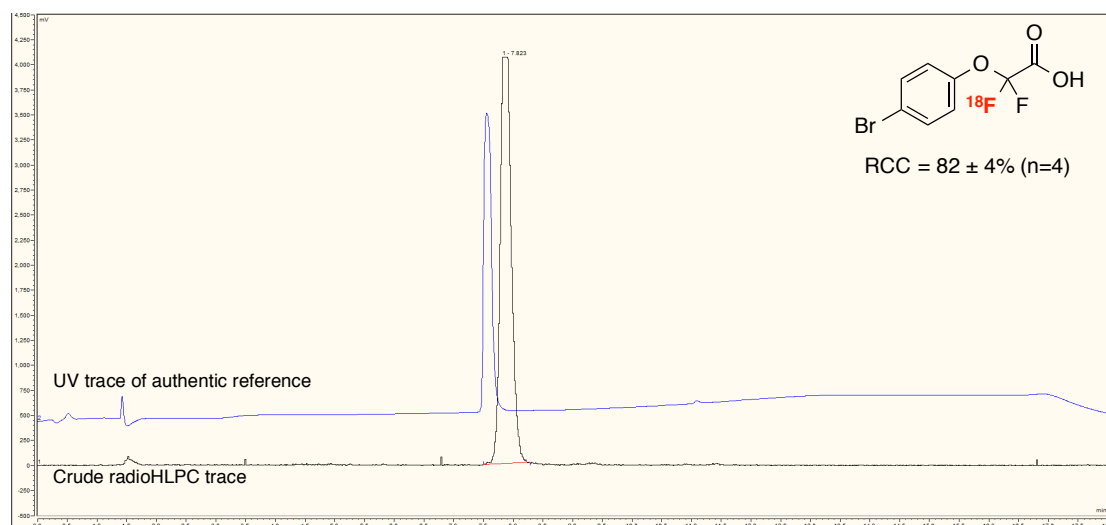
(4-Benzoylphenoxy)([¹⁸F]difluoro)acetic acid ([¹⁸F]5-27e)



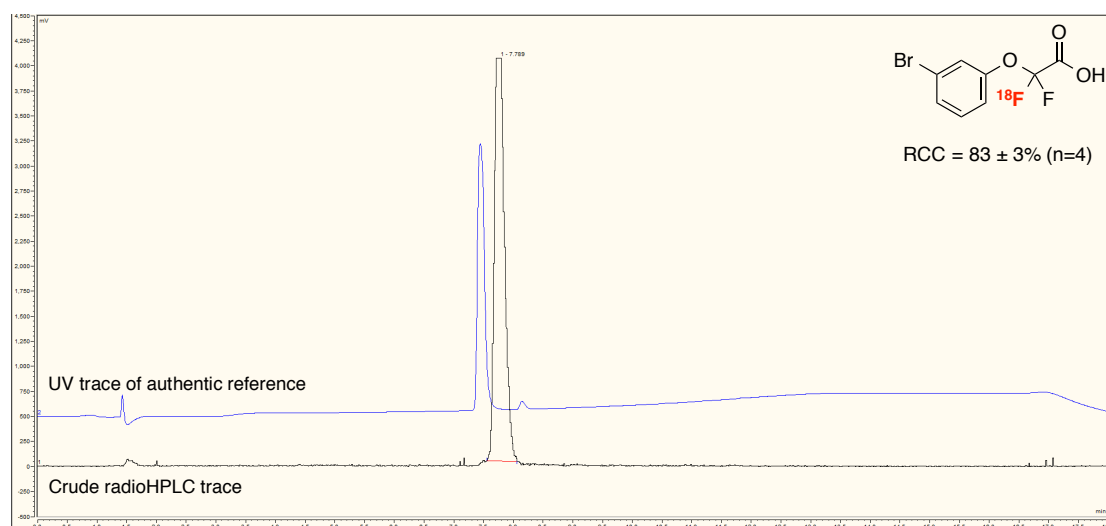
[¹⁸F]Difluoro[4-(trifluoromethyl)phenoxy]acetic acid ([¹⁸F]5-27f)



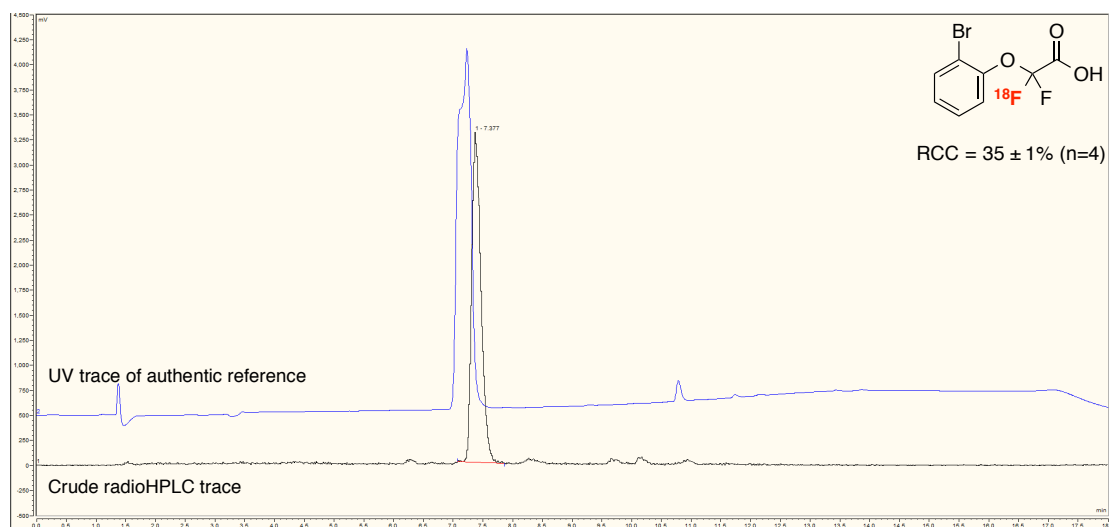
(4-Bromophenoxy)([¹⁸F]difluoro)acetic acid ([¹⁸F]5-27g)



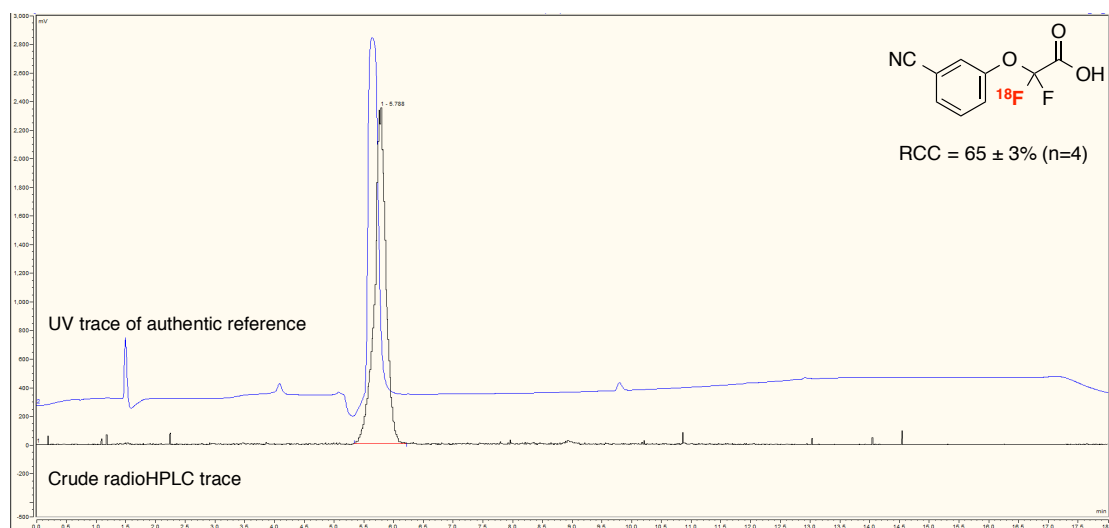
(3-Bromophenoxy)([¹⁸F]difluoro)acetic acid ([¹⁸F]5-27h)



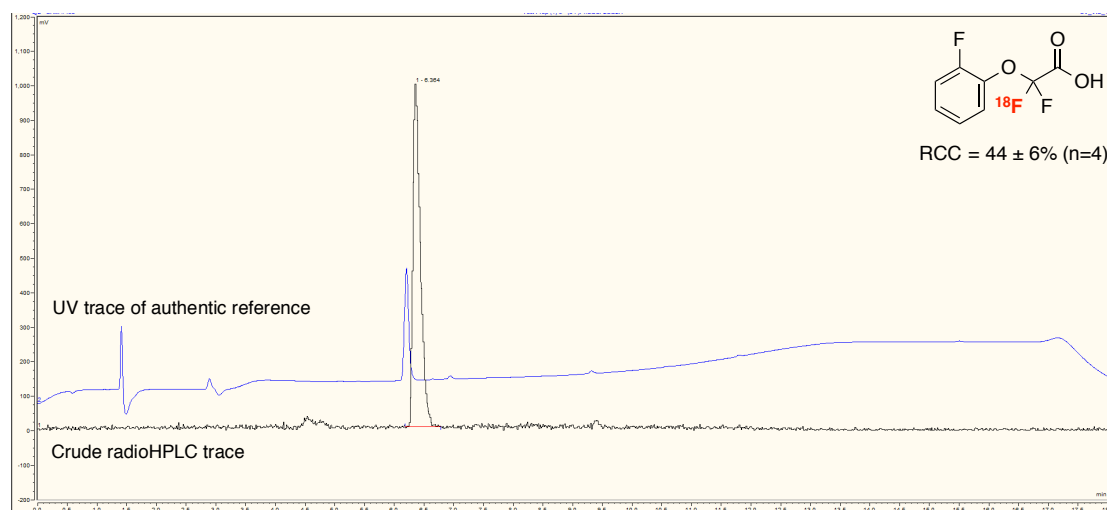
(2-Bromophenoxy)([¹⁸F]difluoro)acetic acid ([¹⁸F]5-27i)



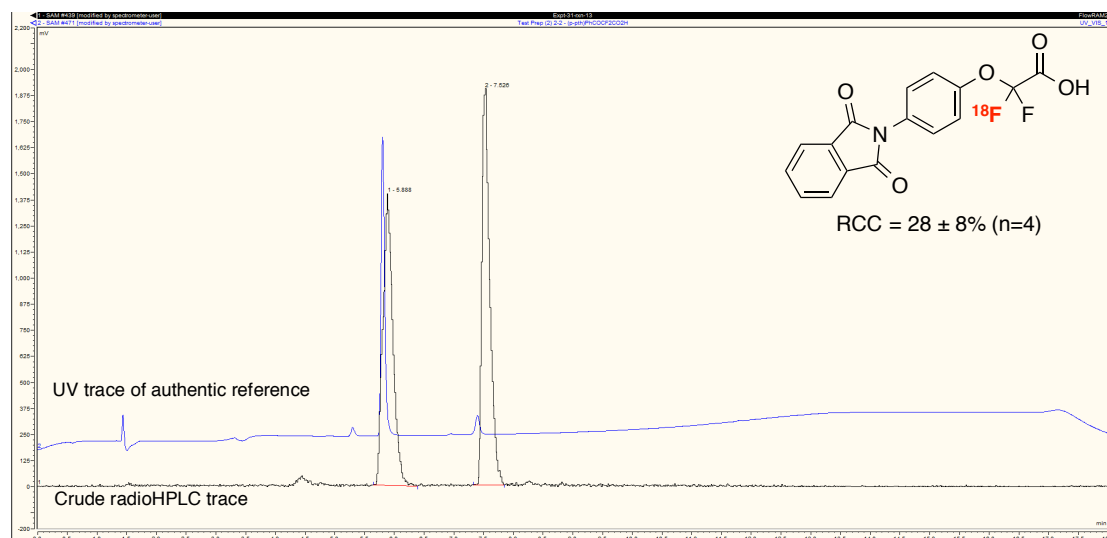
(3-Cyanophenoxy)([¹⁸F]difluoro)acetic acid ([¹⁸F]5-27j)



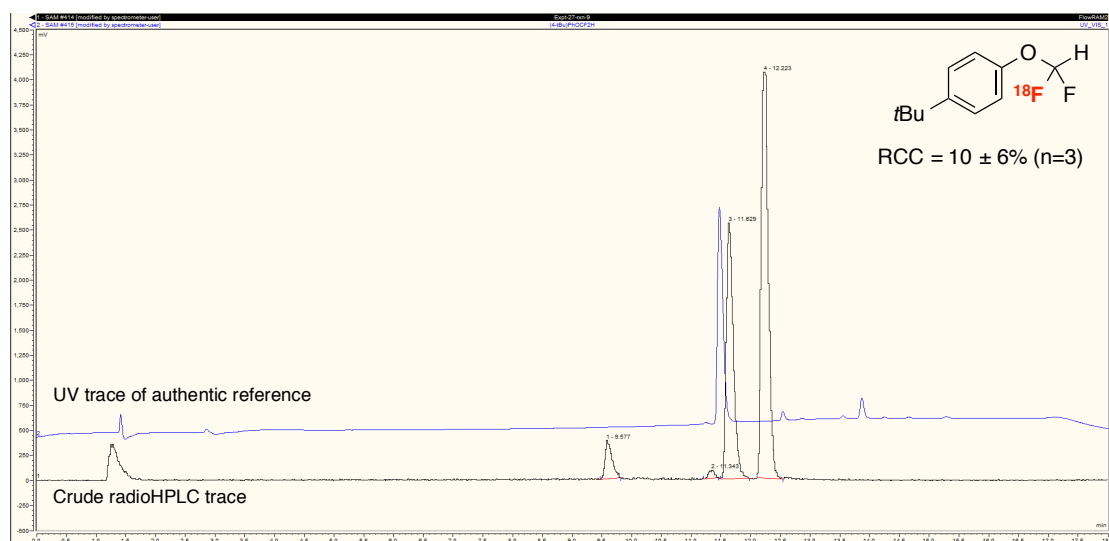
[¹⁸F]Difluoro(2-fluorophenoxy)acetic acid ([¹⁸F]5-27k)



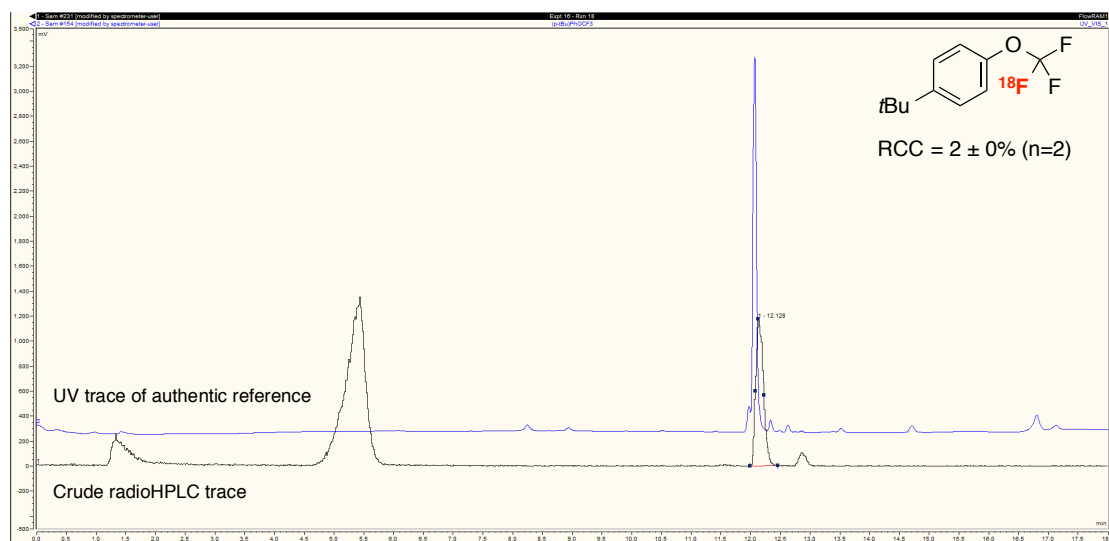
[4-(1,3-Dioxo-1,3,3a,7a-tetrahydro-2H-isoindol-2-yl)phenoxy][¹⁸F]difluoro)acetic acid ([¹⁸F]5-27l)



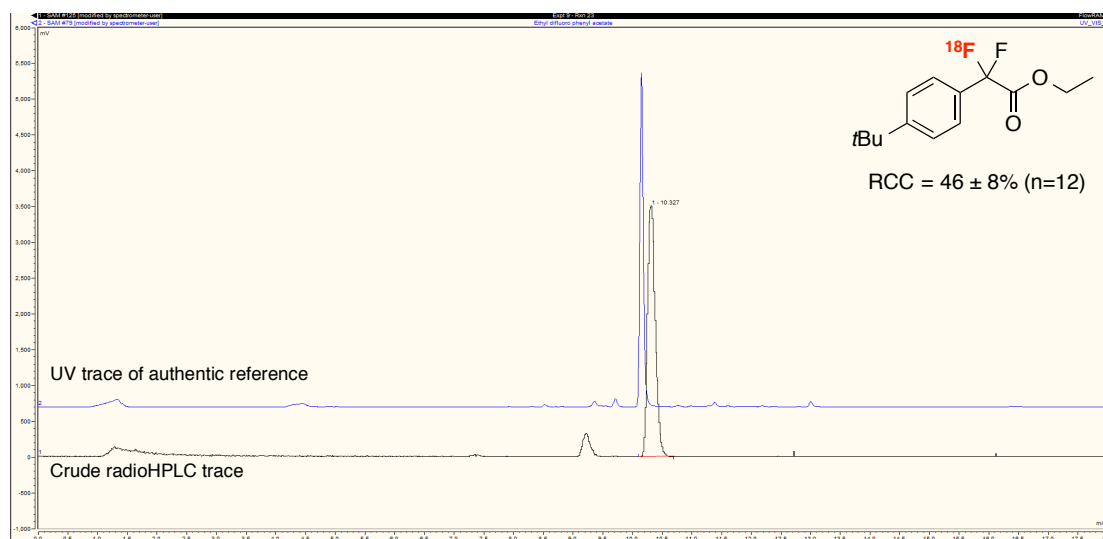
1-*tert*-Butyl-4-([¹⁸F]difluoromethoxy)benzene ([¹⁸F]5-28)



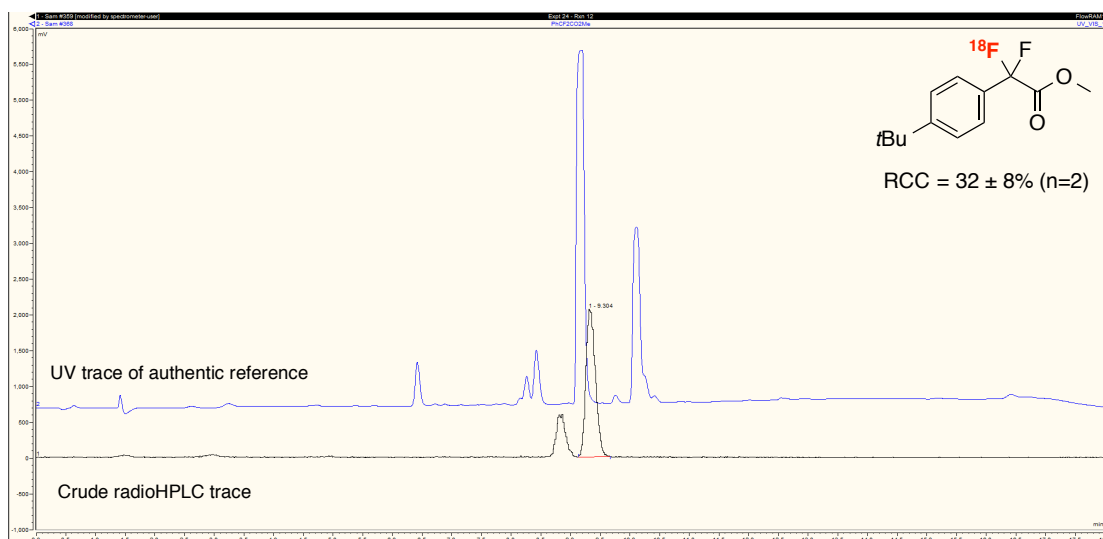
1-*tert*-Butyl-4-([¹⁸F]trifluoromethoxy)benzene ([¹⁸F]5-29)



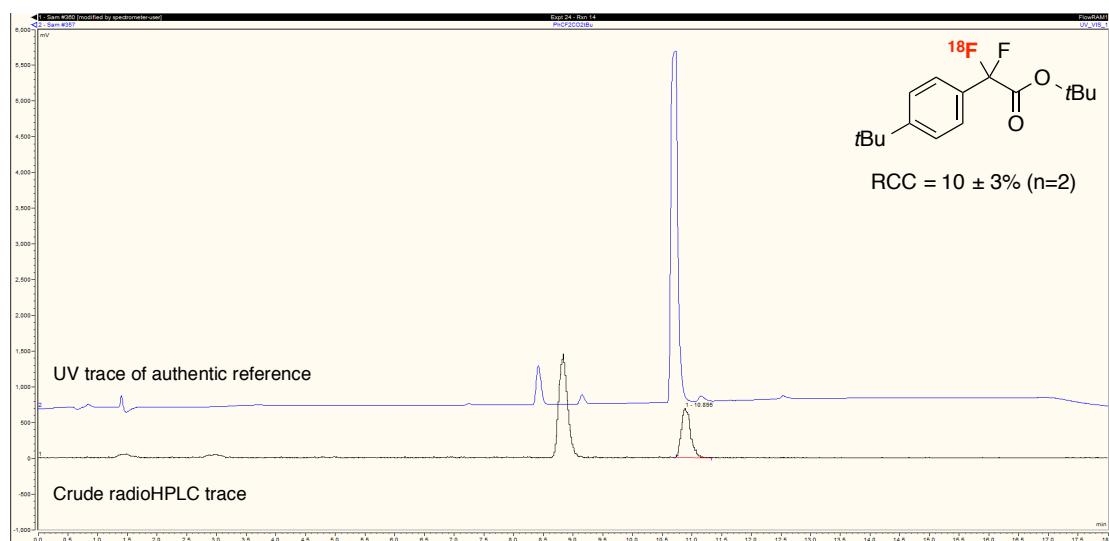
Ethyl [¹⁸F]difluoro(phenyl)acetate ([¹⁸F]5-30a)



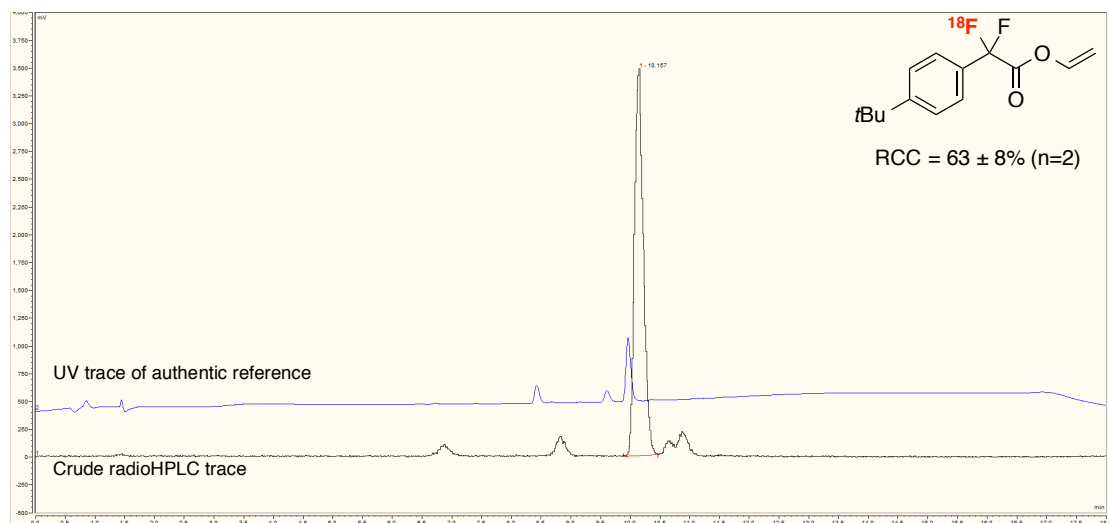
Methyl [¹⁸F]difluoro(phenyl)acetate ([¹⁸F]5-30b)



***tert*-Butyl [¹⁸F]difluoro(phenyl)acetate ([¹⁸F]5-30c)**



Ethenyl [¹⁸F]difluoro(phenyl)acetate ([¹⁸F]5-30d)



7.6. [^{18}F]Fluorination of 1-(Diazo-2,2,2-trifluoroethyl)arenes

Synthesis of 4-(1-diazo-2,2,2-trifluoroethyl)-1,1'-biphenyl and HPLC reference compounds was carried out by J. Twilton.³²⁴

7.6.1. Radiochemistry

7.6.1.1. General Information

[^{18}F]Fluoride Preparation

[^{18}F]Fluoride was produced by Erigal Ltd (Keele, UK) via the $^{18}\text{O}(\text{p},\text{n})^{18}\text{F}$ reaction and delivered as [^{18}F]fluoride in [^{18}O]water. Radiosynthesis and azeotropic drying was performed on a NanoTek® automated microfluidic device (Advion). [^{18}F]Fluoride was separated from ^{18}O -enriched-water using anion exchange cartridges (MPI, ORTG, Tennessee, USA) and subsequently released with 550 μL of a solution of K_2CO_3 (3 mg) and $\text{K}_{2.2.2}$ (15 mg) in $\text{MeCN}/\text{H}_2\text{O}$ (4:1) (1 mL) into CEI for [^{18}F]KF/ $\text{K}_{2.2.2}$. Alternatively, [^{18}F]TEAF was prepared by releasing the [^{18}F]fluoride with 550 μL of a solution of NEt_4HCO_3 (8 mg) in $\text{MeCN}/\text{H}_2\text{O}$ (4:1) (1 mL). The solution was dried with five cycles of azeotropic drying with acetonitrile (300 μL) and redissolved in anhydrous acetonitrile (1 mL). For each reaction [^{18}F]KF/ $\text{K}_{2.2.2}$ or [^{18}F]TEAF (15 - 30 MBq) was dispensed in as aliquots of this stock solution into a V-vial containing a magnetic stirrer and the MeCN was removed from the vial by heating to 100°C under a stream of N_2 .

Analysis

For all reactions, an aliquot was removed for analysis by radioTLC and radioHPLC.

RadioTLC was carried out on Merck Kiesegel 60 F254 plates in $\text{EtOAc}:\text{Hexane}$ (1:1) and analysed using a plastic scintillator/PMT detector.

HPLC analysis was performed using a Dionex Ultimate 3000 dual channel HPLC system with a shared autosampler, parallel UV-detectors and LabLogic NaI/PMT-radiodetectors with Flowram analogue output. A representative radioHPLC trace of the crude reaction mixture, with UV trace (254 nm) of authentic reference material overlaid, is shown below.

HPLC Gradient Settings: Water/MeCN, 1 mL/min, Waters Nova-Pak C18 Column, 4 μ m, 3.9 x 150 mm:

0 – 1 min (5 % MeCN) isocratic

1 – 10 min (5 % MeCN to 95 % MeCN) linear increase

10 – 14 min (95 % MeCN) isocratic

14 – 15 min (95 % MeCN to 5 % MeCN) linear decrease

15 – 17 min (5 % MeCN) isocratic.

Reported radiochemical conversions are decay corrected and calculated by radioTLC taking into account the radiochemical purity as determined by radioHPLC.

7.6.1.2. Procedures

4-(1,2,2,2-Tetrafluoroethyl)-1,1'-biphenyl ($[^{18}\text{F}]6-1$)

To the V-vial containing $[^{18}\text{F}]$ TEAF, 4-(1-diazo-2,2,2-trifluoroethyl)-1,1'-biphenyl (8 mg, 0.03 mmol) in DCM (150 μ L) and HF-pyridine (1 μ L) in DCM (150 μ L) were added. Reaction was stirred at room temperature for 20 minutes, before being quenched with H_2O (200 μ L).

4-(1-Bromo-1,2,2,2-tetrafluoroethyl)-1,1'-biphenyl ($[^{18}\text{F}]6-2$)

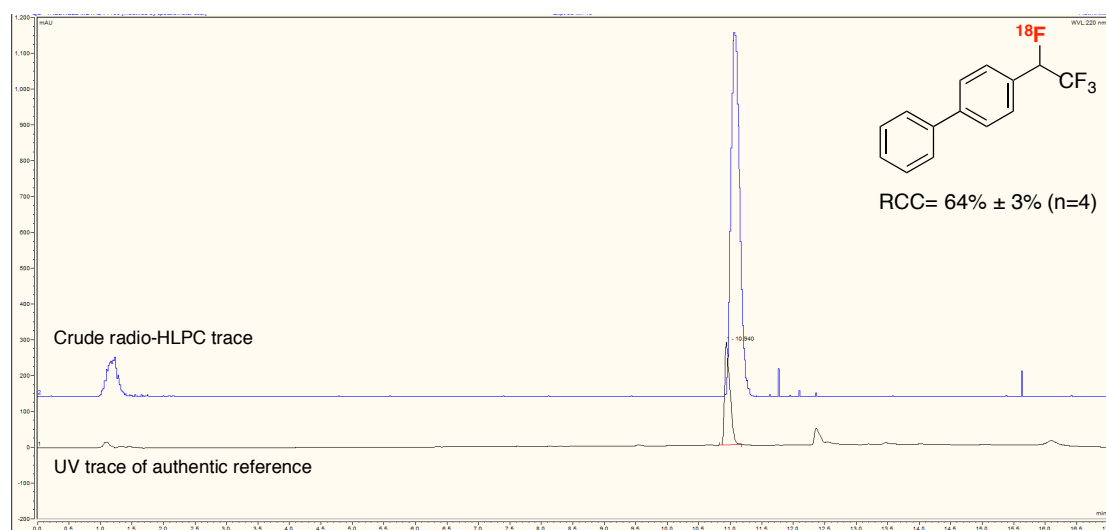
To the V-vial containing $[^{18}\text{F}]\text{TEAF}$, N-bromosuccinimide (12 mg, 0.07 mmol) was added before 4-(1-diazo-2,2,2-trifluoroethyl)-1,1'-biphenyl (8 mg, 0.03 mmol) in DCM (150 μL) and HF·pyridine (1 μL) in DCM (150 μL) were added consecutively. Reaction was stirred at room temperature for 20 minutes, before being quenched with H_2O (200 μL).

4-(Perfluoroethyl)-1,1'-biphenyl ($[^{18}\text{F}]6-3$)

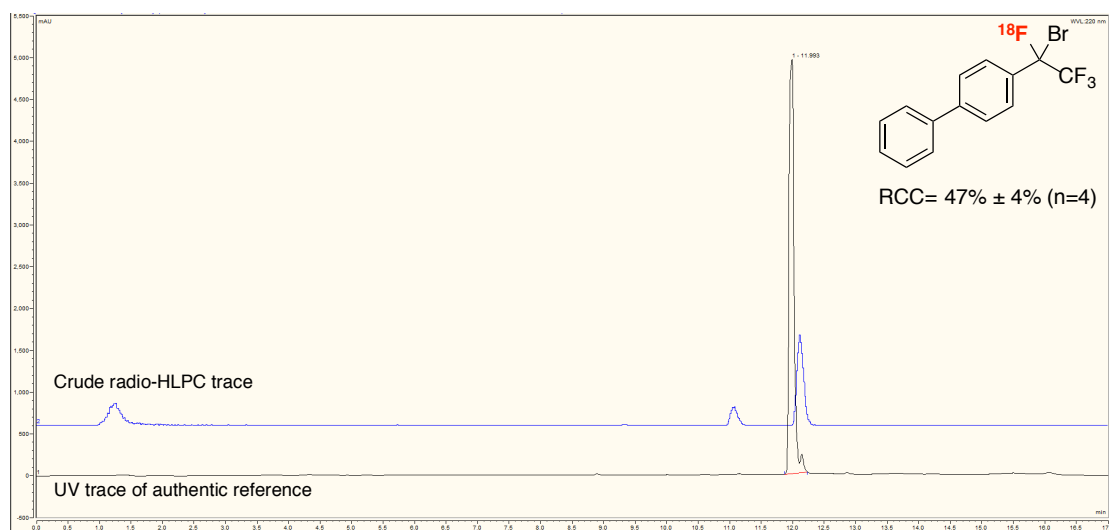
Before the addition of $[^{18}\text{F}]\text{KF}/\text{K}_{2.2.2}$, tin(II) trifluoromethanesulfonate (1 mg, 0.002 mmol) was added to the V-vial. Following dispensation of $[^{18}\text{F}]\text{KF}/\text{K}_{2.2.2}$, 4-(1-diazo-2,2,2-trifluoroethyl)-1,1'-biphenyl (8 mg, 0.03 mmol) in DCM (150 μL) and difluoro(4-methylphenyl)- I^3 -iodane (6 mg, 0.02 mmol) in DCM (150 μL) were added. Reaction was stirred at 40°C for 20 minutes, before being quenched with H_2O (200 μL).

7.6.1.3. HPLC Characterisation

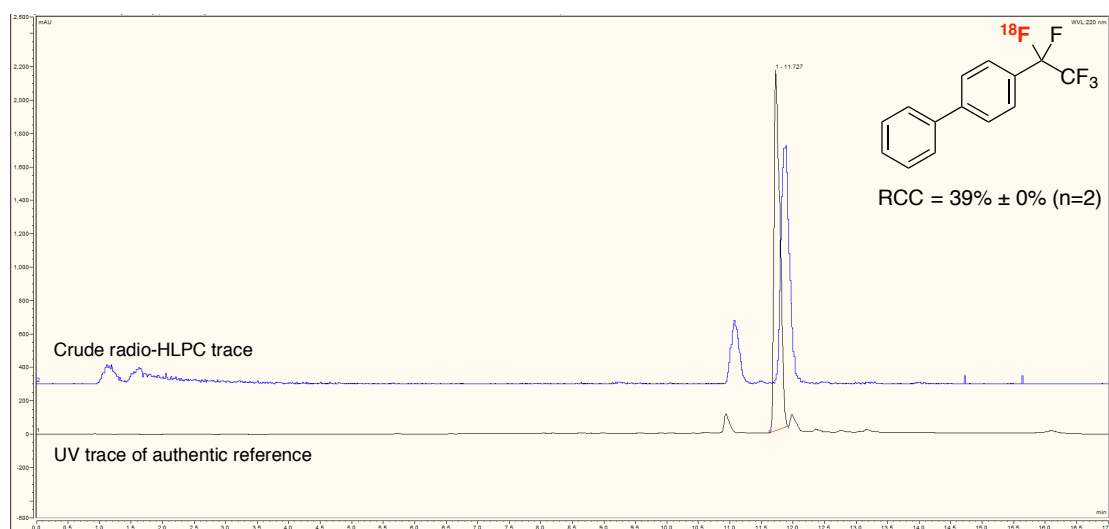
4-(1,2,2,2- $[^{18}\text{F}]$ Tetrafluoroethyl)-1,1'-biphenyl ($[^{18}\text{F}]6-1$)



4-(1-Bromo-1,2,2,2-[¹⁸F]tetrafluoroethyl)-1,1'-biphenyl ([¹⁸F]6-2)



4-[¹⁸F](Perfluoroethyl)-1,1'-biphenyl ([¹⁸F]6-3)



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