Synthesis of [^{18}F]F-DOPA Using Hypervalent Iodine Compounds

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Richard Edwards

Dedicated to Mum, Dad, Katherine and John

List of Abbreviations

°C	Degree Celsius
µmol	Micromol
AAAD	Aromatic L-amino acid decarboxylase
Ar	Aryl
Boc	*tert*-Butyloxycarbonyl
CT	Computed Tomography
[^{15}O]DG	6-[^{15}O]-2-Deoxy-D-glucose
DMAP	4-Dimethylaminopyridine
DMDO	Dimethyldioxirane
DMF	*N,N*-Dimethylformamide
DMSO	Dimethylsulfoxide
DVB	Divinylbenzene
e.e.	Enantiomeric excess
EOB	End of bombardment
[^{18}F]F-DOPA	[^{18}F]6-fluoro-3,4-dihydroxy- L -phenylalanine
[^{18}F]FBA	[^{18}F]Fluorobenzaldehyde
[^{18}F]FDA	[^{18}F]Fluorodopamine
[^{18}F]FDG	[^{18}F]Fluorodeoxyglucose
[^{18}F]FMISO	[^{18}F]Fluoromisonidazole
GBq	Gigabequerel
GC	Gas chromatography
h	Hour/hours

|	
HI	Hydrogen iodide
HPLC	High pressure liquid chromatography
HRMS	High resolution mass spectrometry
Hz	Hertz
K_{222}	Kryptofix®
L-DOPA	L-3,4-dihydroxyphenylalanine
M	Molarity (mol/l)
m-CPBA	3-Chloroperoxybenzoic acid
MeCN	Acetonitrile
MHz	Megahertz
min	Minute
mL	Millilitre
mmol	Millimol
m.p.	Melting point
MRI	Magnetic resonance imaging
n.c.a.	No carrier added
NADPH	Nicotinamide adenine dinucleotide phosphate
NMR	Nuclear magnetic resonance
PEG	Polyethylene glycol
PET	Positron emission tomography
Phth	Phthalimide protection
ppm	Parts per million
PTC	Phase transfer catalyst

QC	Quality Control
QMA	Quaternary methyl ammonium
r.t.	Room temperature
RCC	Radiochemical conversion
RCR	Radiochemical recovery
RCY	Radiochemical yield
R_f	Retention factor
SA	Specific activity
SET	Single electron transfer
T_3P	Propylphosphonic anhydride
THF	Tetrahydrofuran
TFA	Trifluoroacetic acid
TMAF	Tetramethylamoniumfluoride
TsOH	*p*-Toluenesulfonic acid
TfOH	Trifluoromethanesulfonic acid
TLC	Thin layer chromatography
TFE	2,2,2-Trifluoroethanol
TfOH	Triflic acid
TEMPO	(2,2,6,6-Tetramethylpiperidin-1-yl)oxy
UHP	Urea hydrogen peroxide

Abstract

Synthesis and Fluorination of Iodonium Salt Precursors for the Formation of [18F]F-DOPA (CH2)

[^{18}F]F-DOPA is a widely used radiotracer most commonly employed in the diagnosis of Parkinson's disease[1] and neuroendocrine tumours (NETs).[2]

In this thesis, the syntheses of suitable diaryliodonium salt precursors for [^{18}F]F-DOPA production via fluorination with nucleophilic, no carrier added (n.c.a.) [^{18}F]fluoride are described. The complex iodonium salt precursors are prepared by a simple and robust procedure in good yields and are bench stable compounds. Incorporation of both 'cold' [^{19}F]fluoride and 'hot' [^{18}F]fluoride using the prepared precursors has been investigated.[3]
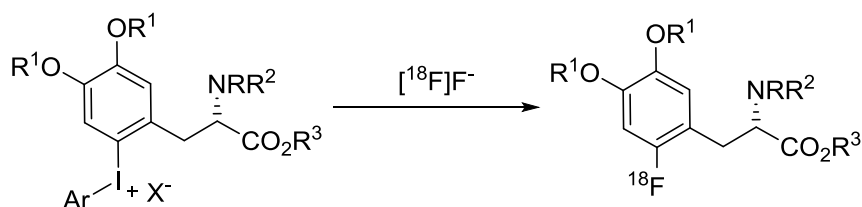
Fluorinations occur with complete regioselectivity for fluorination at the DOPA moiety when using a range of precursors with varying protecting group strategies. Optimisation of the radiofluorination and subsequent isolation method allowed for isolation of a protected [^{18}F]F-DOPA species in 2% radiochemical yield (RCY).

Solid-Supported Iodonium Salts for Fluorinations (CH3)

Secondly, solid-supported iodonium salt precursors have been prepared and used for the production of fluoroarenes. The importance of the resin functionality for the attachment of the iodonium salt moieties has been demonstrated. Use of a tris(aminoethyl) funtionalised resin rather than aminomethyl resin as starting material gives improved reproducibility and yields for precursor formation.

The successful radiofluorination of a simple solid-supported precursor with no carrier added (n.c.a) [^{18}F]fluoride is also reported, producing [^{18}F]fluorobenzene with 3% radiochemical conversion (RCC).[4]
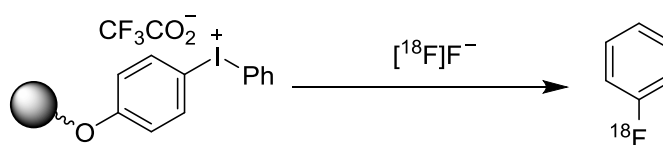
Extension of the solid-supported methodology to the production of synthetically useful fluoroarenes was investigated. Preparation of benzyl protected 4-fluorophenol was accomplished using this strategy. Optimisation of the fluorination conditions gave 24% yield of the aryl fluoride from the resin bound iodonium salt precursor.

References

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1

Introduction

1.1   Positron Emission Tomography (PET)

1.1.1   Overview

Positron emission tomography (PET) is a highly sensitive and versatile molecular imaging technique that can be used to non-invasively study the pharmacokinetics and biodistribution of positron emitting radiotracers *in vivo*. It has become crucial for the diagnosis and evaluation of diseases, including cancers[1–3] and neurodegenerative diseases such as Parkinson's disease.[4,5]

Molecular imaging may be defined as 'the visualisation of *in vivo* biological processes at the molecular level using specific imaging probes', covering methods such as magnetic resonance imaging (MRI), radiotracer imaging, optical imaging and ultrasound.[5] The basic requirements for PET tracers include those necessitated by any of the 'imaging probes' alluded to above. These comprise of the following:[6]

1. Be useable in concentrations small enough to not alter the system under investigation
2. Interact with the system in a predictable, informative and reproducible manner
3. The concentration should be measurable quantitatively

The use of such positron emitting radiotracers relies on the incorporation of positron emitting nuclides into molecules of biological interest. This is what enables the 'molecular visualisation'. However, it is not the emitted positron that is detected:

PET relies on the three dimensional detection of gamma rays arising from the annihilation of a positron emitted from the radionuclide. The gamma rays are emitted in almost exactly opposite directions allowing for the origin of annihilation to be calculated upon detection of the gamma rays. The positron travels a short distance before decelerating enough to interact with an electron (approx. 2 mm in water for ^{18}F)[7] which means that high resolution images of the tracers' distribution can be constructed subsequent to computational analysis (Figure 1).

PET is often used in conjunction with X-ray computed tomography (CT) to form a superimposed image incorporating both the anatomical information provided by CT and the functional data for tracer distribution provided by the PET image.[8]
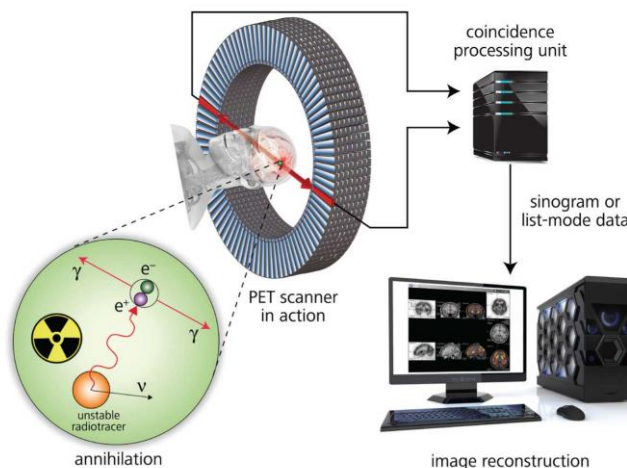
Figure 1 – Imaging with PET. Image courtesy of Metrohm AG, taken with permission from Separation Science [http://www.sepscience.com/Sectors/Pharma/Articles/429-/Radio-IC-for-Quality-Control-in-PET-Diagnostic].[9]

1.1.2   Production of radiotracers for PET

A number of radionuclides are available to be inserted or added to the compound of interest. The most commonly used of these are ^{18}F, ^{11}C, ^{13}N and ^{15}O. These isotopes can be substituted into a biomolecule without significantly altering its behaviour, allowing *in vivo* application.[10] In fact the use of carbon, nitrogen and oxygen isotopes allows for the direct replacement of the stable isotope with the radionuclide, producing a tracer without any alteration to its biological activity.[11]

The use of more unusual radiolabels such as ^{123}I and ^{125}I, has also been evaluated.[12,13] Furthermore, the coordination chemistry of radionuclides such as ^{64}Cu and ^{89}Zr has led to their application with a number of chelator systems for PET imaging and targeted radiotherapy of cancer.[14,15] Properties of some more commonly used radionuclides can be seen in Table 1.

Table 1 – Common radioisotopes and their properties.[5,6]

Isotope	β^+ decay (%)	Half-life (min)	Decay Product
^{18}F	97	110	^{18}O
^{11}C	100	20.4	^{11}B
^{13}N	100	9.96	^{13}C
^{15}O	100	2.03	^{15}N
^{76}Br	57	966	^{76}Se
^{124}I	23	6048	^{124}Te
^{68}Ga	89	68.1	^{68}Zn
^{64}Cu	18	762	^{64}Ni

The use of radiotracers for PET imaging requires the formation and purification of the labelled compounds. This challenge necessitates the employment of multiple disciplines and can be broken down into 3 major steps: Production of the radioisotope, incorporation of the radioisotope and isolation of the radiotracer. The details of these steps are outlined below.

Step 1: Production of the radioisotope

Emission of a positron from proton rich radioisotopes is the key to detecting the radiolabelled tracer of interest. The production of such proton rich isotopes therefore provides an important start to the production of any PET tracer and is achieved by bombardment of a 'target' with a proton source at high velocity.

The proton source is most commonly a proton or deuteron and is accelerated to high velocities using a particle accelerator called a cyclotron (Figure 2).
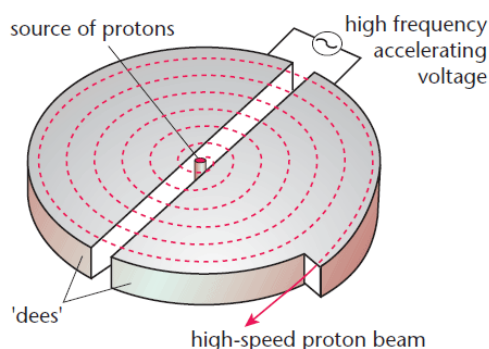
Figure 2 – Principals of a cyclotron. Image courtesy of Metrohm AG, taken with permission from 'Radio IC for Quality Control in PET Diagnostics', Separation Science, 4(2), 2012. [16]

The cyclotron achieves acceleration by utilising a combination of magnetic and electric fields. The two dees (Figure 2) are separated by an electric field, which accelerates the proton (or deuteron) into one of the dees as it enters the gap between them. A magnetic field perpendicular to the dee then influences the positively charged particle causing it to move in a semi-circle, and back towards the gap. Reversal of the electric field then accelerates the particle across the gap into the other dee, where it follows a slightly wider semi-circle back to the gap. The electric field is switched to accelerate the particle back to the original dee, and the process is repeated, accelerating the particle with every transition through the accelerating electric field. Eventually the particle exits the cyclotron at high velocity for bombardment of the target.[6]

A number of different targets are used for the production of desired radionuclides. These transformations involve a nuclear reaction in which the charged particle accelerated by the cyclotron hits the target isotope, prompting the emission of another particle from the nucleus and producing the radioisotope product.

As a quick manner of communicating the details of the nuclear reaction, a short hand has been developed (Figure 3). Target isotope (A), particle bombarding the target (b), particle emitted by the target isotope (c) and the produced radioisotope (D) are all shown.

$$^{z}A(b,c)^{z}D$$

Target Isotope

Bombarding Particle

Emitted Particle

Isotope Produced

(Z = atomic mass)
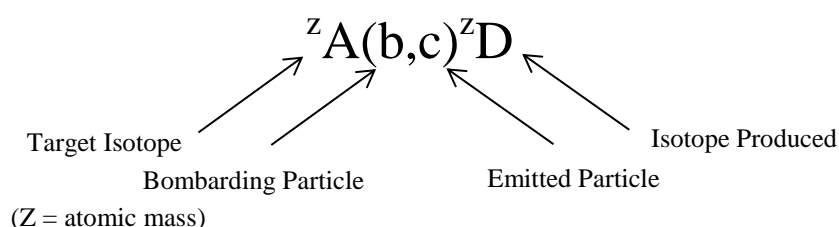
Figure 3 – Nuclear reaction short hand

Some common targets and their corresponding nuclear reactions are shown in Table 2.

Table 2 – Targets for production of radioisotopes.[6,17]

Target	Nuclear Reaction	Product
N_2+0.1% O_2	$^{14}N(p,\alpha)^{11}C$	$[^{11}C]CO_2$
N_2+5% H_2	$^{14}N(p,\alpha)^{11}C$	$[^{11}C]CH_4$
N_2+0.2% O_2	$^{14}N(d,n)^{15}O$	$[^{15}O]O_2$
$H_2^{18}O$	$^{18}O(p,n)^{18}F$	$[^{18}F]F^-(H_2O)_n$
$^{18}O_2$ + 0.6% F_2	$^{18}O(p,n)^{18}F$	$[^{18}F]F_2$
H_2O/ethanol	$^{16}O(p,\alpha)^{13}N$	$[^{13}N]NH_3$
CO_2 (trace N_2)	$^{12}C(d,n)^{13}N$	$[^{13}N]N_2$

In some instances the product of the nuclear reaction is the sought after labelled molecule. An example is $[^{15}O]O_2$ which is produced by the $^{14}N(d,n)^{15}O$ reaction and subsequently used for the study of oxygen utilisation. In the majority of cases, once the desired radioisotope has been produced, its delivery to a destination for manipulation and chemical transformation is required. This is generally a suitably equipped, heavily shielded compartment known as a 'hot cell'.

Step 2: Incorporation of the radioisotope

The short half-lives of the most commonly used radioisotopes (^{11}C, ^{18}F, ^{13}N and ^{15}O) present radiochemists with a significant challenge for the synthesis and purification of the radiotracer before unacceptable loss of activity (typically < 2 half-lives). Such a problem must be addressed by a combination of rapid, selective reactions and a quick purification. Reactivity of the radioactive moiety, reaction stoichiometry and precursor design are key factors in achieving this.

Reactivity of the Radioactive Moiety

This necessitates the use of the radioisotope in a 'reactive form'. Some radioisotopes are produced as reactive species directly from the bombardment of the appropriate target. For example the production of $[^{18}F]F_2$ gas. This allows for direct reaction with an appropriate substrate after delivery to the hot cell.[18]

In target formation of the radioisotope as a moiety with desirable reactivity isn't always possible. However, a chemical transformation after delivery can be performed in order

to attain the radioisotope in a more reactive or suitable reagent. A common example is the formation of [^{11}C]MeI from [^{11}C]CO$_2$ or [^{11}C]CH$_4$.[19–21]

In other cases it is necessary to adjust the environment of the radioactive species in order to improve reactivity, for example in the azeotropic drying of [^{18}F]fluoride to improve its nucleophilicity. This is required for the majority of reactions it is used for.[22]

Reaction Stoichiometry

The super-stoichiometric amounts of precursor used relative to the radioisotope can also help to speed up the reaction by giving pseudo first order kinetics.[5]

Precursor Design

To further reduce the time from estimated time of bombardment (EOB) to obtaining a product suitable for application, it is desirable to introduce the isotope at as late a stage as possible. This often requires highly functionalised 'activated' precursors which typically undergo a labelling step followed by a deprotection. It should be mentioned, however, that the use of quite lengthy multistep syntheses, subsequent to labelling, have proved successful for certain isotopes by optimisation of the subsequent transformations.[23]

A quick reaction for the incorporation of the short-lived radioisotope is a very important consideration when designing the synthesis of a tracer. However, there are many other factors that are required for an ideal radiochemical synthesis. A list of essential requirements and further desirable properties is given below.

Essential

1. *The reaction must cope with the unusual stoichiometry of these reactions:* Large differences in the concentration of non-radioactive (or 'cold') precursor and radioactive (or 'hot') radionuclide can make translation from 'cold' to 'hot' chemistry challenging.[7]

2. *Short reaction and purification time (< 2 half-lives):* Subsequent to purification and isolation of the tracer (in a form suitable to administer to the patient - commonly as an isotonic and sterile solution), the tracer must undergo rigorous

quality control (QC).[24] Short reaction and purification times are crucial if the tracer is to be available for patient administration with suitable radioactivity.

3. *High enantiomeric excess (> 98% ee):* When applicable, enantiomerically pure tracers should be produced, as different enantiomers can exhibit very different biological behaviour. Chiral integrity is tested using the appropriate QC procedures (HPLC on chiral stationary phases).

4. *Operationally simple procedure suitable for automation:* The nature of the tracers and their positron emitting nuclides necessitate manipulation within heavily shielded compartments called 'hot cells'. In order to perform chemistry within the hot cell, an automated system must be programmed to perform the necessary manipulation of reagents. If a tracer synthesis is to be successful, an automated synthesis is compulsory. As improvements in such automated systems evolve, the term 'operationally simple' covers an ever growing number of operations, allowing success for previously daunting multistep syntheses.[23]

5. *Reproducible:* Due to the time restrictions involved in tracer production, tracers are often produced in close vicinity to the patient and just minutes before administration. Tracer synthesis failure severely inconveniences patients, and reliability is of upmost importance.

Desirable

1. *Starting from a bench stable and accessible precursor:* For a tracer synthesis to be implicated it is necessary for the precursor synthesis to be viable financially (both in terms of the expense of the reagents and the time needed to synthesise it). Furthermore, bench stable/ storable compounds greatly improve convenience for PET centres.

2. *High radiochemical yield (RCY):* High radiochemical yield is clearly desirable. While not essential, a high radiochemical yield has important implications, including the number of patients that can be scanned with the isolated tracer. Additionally, transportation of the radiotracer is possible for certain radioisotopes if the RCY is suitably high.

3. *Ambient conditions:* Ambient conditions are desirable for simplification of procedure. This allows facile reproducibility of the synthesis in PET centres that may not have specialist radiochemists.

4. *High specific activity (SA):* Specific activity is a measure of the radioactivity per unit mass of tracer. A tracer with a greater SA will be administered with a lower concentration of 'cold' compound. This means a lower dose of potentially harmful compound for the patient. High SA is essential in some cases where dilution with the unlabelled analogue must be low to achieve acceptable resolution.[22]

The methods available for the incorporation of different desirable radioisotopes are vast and a number of labelled reagents are available depending on the chemistry required. A brief description into some of the more important techniques and strategies used for radioisotope introduction is given bellow.

Carbon – 11

The most common method used to produce the ^{11}C isotope is the $^{14}N(p,\alpha)^{11}C$ reaction.[11] As shown in Table 2, when performed in the presence of oxygen the product is $[^{11}C]CO_2$, whilst in the presence of hydrogen $[^{11}C]CH_4$ is obtained. From these two labelled compounds a variety of reagents can be produced for further chemical reactions. Those regularly used are shown in Scheme 1.[5]
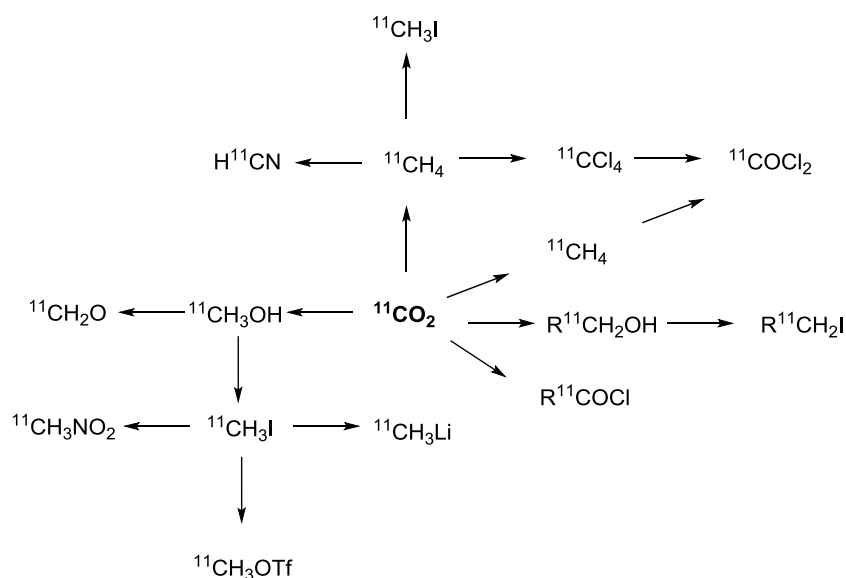
Scheme 1 – [^{11}C]Reagents produced from [^{11}C]CO$_2$.[5]

The most important reagent for ^{11}C labelling is $[^{11}C]CH_3I$. Its successful utility for the $[^{11}C]$methylation of a number of heteroatoms (generally S, O and N methylation) has produced a large number of $[^{11}C]$tracers.[11] Its production traditionally follows what is

called the 'wet' method: Reduction of [^{11}C]CO$_2$ with LiAlH$_4$, followed by iodination with HI yields the [^{11}C]CH$_3$I.[19] A second method for the generation of [^{11}C]CH$_3$I, termed the 'dry' or 'gas-phase' method, employs high temperatures for the iodination of [^{11}C]CH$_4$ with I$_2$ (Scheme 2).[20,21] The 'dry' method has become the method of choice due to improved specific activity (SA) of the produced reagent.[5]

^{14}N(p,α)^{11}C ^{14}N(p,α)^{11}C

$\downarrow$ H$_2$ $\downarrow$ O$_2$

^{11}CH$_3$I $\xleftarrow{\text{I}_2,\ 720\ °C}$ ^{11}CH$_4$ $\xleftarrow[\text{Ni, 410 °C}]{\text{H}_2}$ ^{11}CO$_2$ $\xrightarrow{\text{LiAlH}_4}$ ^{11}CH$_3$OLi $\xrightarrow{\text{HI}}$ ^{11}CH$_3$I

$\longleftarrow$ The 'dry' or 'solid-phase' method   The 'wet' method $\longrightarrow$
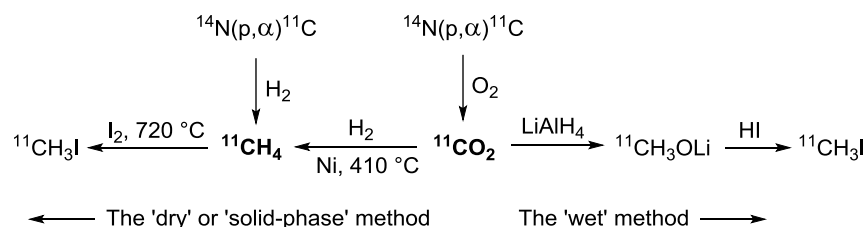
Scheme 2 – 'Wet' and 'Dry' methods for the production of [^{11}C]CH$_3$I
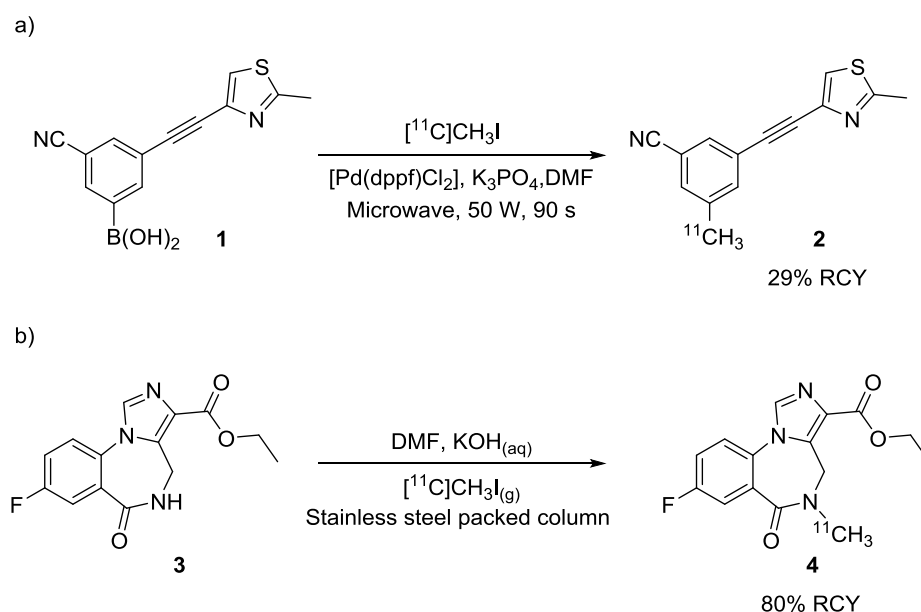
Whilst most commonly used for heteroatom [^{11}C]methylation, other strategies for incorporation such as C-^{11}C bond formation via Stille- and Suzuki-couplings, have also been reported.[25,26] Some reported syntheses of [^{11}C]tracers are shown in Scheme 3.

Scheme 3 – Application of [^{11}C]CH$_3$I for the production of [^{11}C]radiotracers. a) Suzuki coupling for the formation of M-MTEB 2 reported by Burns *et al.*[26] b) [^{11}C]methylation reaction for the formation of [^{11}C]flumazenil 4 using a 'microreactor' column reported by Aigbirhio *et al.*[27]

The use of [^{11}C]CH$_3$OTf provides a more reactive alternative to [^{11}C]CH$_3$I.[28] Other incorporation strategies include the use of carbonyl chemistry with [^{11}C]phosgene and introduction of [^{11}C]CN and [^{11}C]CO functionality with various cyanation and carbonylation reactions.[11]

Nitrogen – 13

The short half-life of ^{13}N (9.96 min), along with the lower resolution of [^{13}N]tracers, has limited the isotopes widespread application in tracer synthesis. However, the presence of nitrogen in a large number of biologically interesting compounds offers an incentive to overcome these short falls and a number of attractive applications have been reported. The process most commonly used for the formation of ^{13}N is the ^{16}O(p,α)^{13}N reaction. When performed with water as the target a mixture of [^{13}N]NO$_3^-$, [^{13}N]NO$_2^-$ and [^{13}N]NH$_3$ is produced. Subsequent treatment of the mixture with DeVarda's alloy reduces the nitrate and nitrite products to the [^{13}N]ammonia product. Conveniently, when performed with the addition of ethanol or acetic acid to water target (5 mM), a higher percentage of initially produced [^{13}N]NH$_3$ is obtained (95%).[17]

The [^{13}N]NH$_3$ produced by these reactions is the most common reagent used for incorporation of the ^{13}N isotope. Along with its uses as a nucleophile (for example in the attack of acyl chloride derivatives)[29] another useful reaction is its employment in enzymatic [^{13}N]amino acid synthesis.[30–32] Also notable is the use of [^{13}N]NH$_3$ for the synthesis of [^{13}N]*cis*-platin using a solid phase methodology.[33] Examples of radiochemistry performed with [^{13}N]NH$_3$ are shown in Scheme 4.
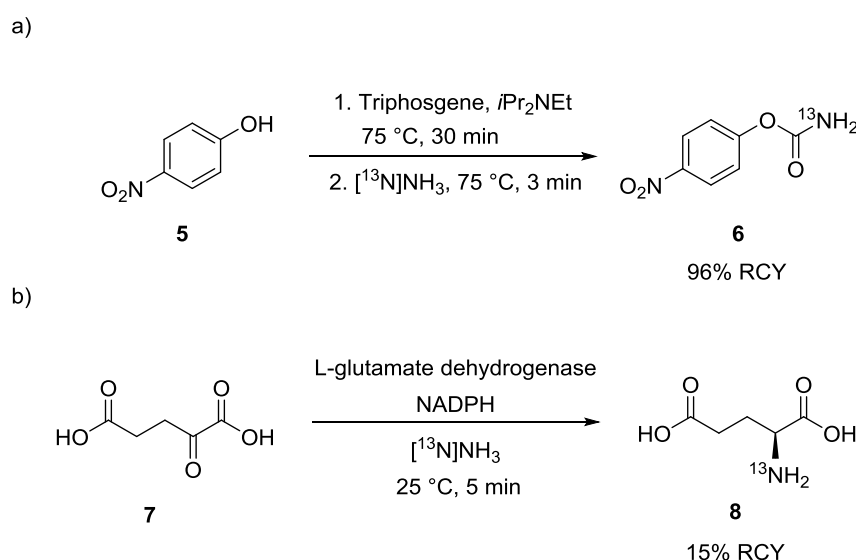
Scheme 4 - Application of [^{13}N]NH$_3$ for the production of [^{13}N]radiotracers. a) A one-pot synthesis of the tracer [^{13}N]NCP 6 reported by Zhang *et al*.[34] b) Enzymatic incorporation of ^{13}N for the production of L-[^{13}N]glutamate 8 reported by Lathrop *et al*.[32]

Additionally, in target incorporation is possible for more simple tracers. [^{13}N]N$_2$ is produced by the ^{12}C(d,n)^{13}N nuclear reaction and has found utility in nitrogen fixation

and ventilation studies,[35] while [13N]NH$_3$ has been applied to study blood flow and perfusion in the brain and myocardium.[36–38]

Oxygen – 15

The time constraints present for manipulation of the 15O isotope are severe due to its 2 minute half-life. Tracers with 15O incorporation are generally simple, for example [15O]H$_2$O and [15O]O$_2$ for the study of blood flow and oxygen utilisation respectively.[39] Nonetheless, very rapid synthesis of a labelled glucose analogue [15O]ODG has been made possible by the use of a mild, radical reaction not requiring the use of protecting groups.[40] Scheme 5 shows conditions for the production of some simple [15O]tracers from [15O]O$_2$.[11]

$$^{11}N(d,n)^{15}O$$

[15O]CO$_2$ $\xleftarrow{\text{C, 400 °C}}$ **[15O]O$_2$** $\xrightarrow{\text{H}_2/\text{Pt or H}_2/\text{Pd}}$ [15O]H$_2$O

C, 1025 °C

B(*n*-butyl)$_3$
THF

[15O]CO   [15O]*n*-butanol
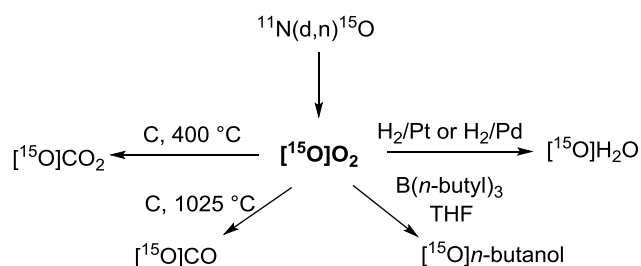
Scheme 5 – Incorporation of 15O into simple tracer molecules.[11]

Positron emitting metals

Some positron emitting metals such as 89Zr, 68Ga and 64Cu, have shown utility for PET imaging as well.[14,15,41] Rather than being incorporated directly into the molecule of interest, coordination chemistry is used to tag the positron emitting isotope to the molecule of interest. The coordinating ligand is coupled to the biomolecule of interest by various linkage strategies. Substitution reactions with reactive amines and thiols found on the biomolecule are a common approach.[15] Click chemistry has also been implemented successfully.[15]

Fluorine – 18

Incorporation of the 18F isotope is not ubiquitous for the majority of tracers and yet it has become the radioisotope of choice for production of a huge variety of PET tracers. This is due to a number of desirable properties. As late stage introduction of 18F is a focus of this thesis, a discussion on these 'desirable properties' and the methods used for the isotopes incorporation will be presented in the following pages ('PET and Radiochemistry with the 18F Isotope', Pg. 14).

Step 3: Isolation of the radiotracer

Finally, suitable purification and quality control needs to be conducted before the tracer can be used for imaging.

Purification

Successful purification is crucial after synthesis of the tracer has been completed. Likewise to the synthesis of the tracer, fast procedures suitable for automation are required of the purification process. HPLC is commonly used for more complex purifications; however, if possible the use of cartridges is preferable as these provide a simplified and faster purification. Once the tracer has been isolated in a form suitable for injection (generally as an isotonic solution), it is finally passed through a sterile filter. A portion is dispensed for performing quality control.

Quality Control (QC)

Quality control (QC) is required to make sure the standard of the tracer meets the established criteria before its use in the clinic. Some typical QC procedures include:[24]

- Visual Inspection.
- Analytical HPLC – determining radiochemical purity and identity.
- Radio TLC – determining radiochemical purity and identity.
- Radioisotope dose calibrator – validating the half-life.
- GC – determining the quantity of any residual solvent in the sample.
- pH reading.
- Residual Kryptofix analysis by a spot test is required if the reagent has been used.
- Testing the integrity of the sterile filter used for purification.
- Endotoxin analysis using an appropriate testing system.

1.1.3   Conclusion

Obtaining a radiotracer for PET is far from trivial, but can be achieved using multiple disciplines and innovative techniques to perform rapid transformations. A list of some PET tracers that have been produced using such methodologies is shown in Table 3.

Table 3 - Common PET Tracers[42]

Tracer	Use/ Biological Target
Carbon 11	
[^{11}C]methionine	Amino-acid transport
[^{11}C]leucine	Protein synthesis
[^{11}C]methyl-spiperone	Dopamine and serotonin receptors
[^{11}C]PK-11195	Peripheral benzodiazepine receptors
[^{11}C]diprenorphine	Nonselective opiate receptors
[^{11}C]carfentanil	μ-Opioid receptor
[^{11}C]flumazenil (FMZ)	Central benzodiazepine receptors
[^{11}C]raclopride	Dopamine type 2 (D2) receptor
[^{11}C]Schering-23390	Dopamine type 1 (D1) receptor
[^{11}C]nomifensine	Dopamine transporter (DAT)
[^{11}C]deprenyl	Monoamine oxidase type-B (MAO-B)
[^{11}C]McNiel 5652	Serotonin transporter (SERT/5-HTT)
[^{11}C]WAY 100635	Serotonin 5-HT1A receptor
[^{11}C]FBL 457	Dopamine (D2/3) receptors
L-1-[^{11}C]tyrosine	Brain tumor protein synthesis
[^{11}C]MDL 100907	Serotonin 5-HT2A receptor
[^{11}C]b-CIT-FE	Dopamine transporter (DAT)
[^{11}C]PMP	Acetylcholinesterase (ACE)
[^{11}C]verapamil	P-glycoprotein (P-gp) substrate
[^{11}C]MP4A	Acetylcholinesterase (ACE)
[^{11}C]NNC112	Dopamine (D1) receptor
[^{11}C]a-methyl-l-tryptophan	Tryptophan activity
[^{11}C]DASB	Serotonin transporter (SERT/5-HTT)
[^{11}C]Rol5-4513	GABA-benzodiazepine receptors
[^{11}C]temozolomide	Temozolomide pharmacokinetics
[^{11}C]PIB	β-Amyloid
[^{11}C]harmine	Monoamine oxidase type-A (MAO-A)
[^{11}C]methylreboxetine (MRB)	Norepinephrine transporter (NET)
[^{11}C]ABP688	Glutamate receptor 5 (mGluR5)
Fluorine 18	
[^{18}F]FDG	Glucose utilisation
[^{18}F]F-DOPA	Dopamine synthesis
[^{18}F]A-85380	Nicotine acetylcholine receptors
[^{18}F]fallypride	Dopamine (D2) receptor
[^{18}F]SPA-RQ	Neurokinin-1 receptor
[^{18}F]fluoroethyl-L-tyrosine	Brain tumor protein synthesis
[^{18}F]fluorothymidine	Brain tumor proliferation

[18F]MK-9470	Cannabinoid receptor type 1 (CBR-1)
[18F]fluoromisonidazole	Brain tumor hypoxia
Oxygen 15	
[15O]oxygen	Oxygen utilisation
[15O]water	Blood flow

1.2   PET and Radiochemistry with the ^{18}F Isotope

As mentioned earlier, the ^{18}F isotope has become the radioisotope of choice for the production of a huge variety of PET tracers despite not being ubiquitous for incorporation into the majority of tracers. This is due to a number of desirable characteristics the radioisotope possesses. Primarily, a half-life of 110 min provides considerably more time for target synthesis and purification than ^{11}C, ^{13}N and ^{15}O, and can even allow for transportation of tracers. This longer half-life is also an important consideration for investigation of systems with slower biological kinetics.[22] Some properties of the ^{18}F isotope are shown in Table 4.

Table 4 – Properties of the ^{18}F nuclide[22]

Property	Value
half-life	110 min
maximum energy of e^+	0.64 MeV
mode of decay	β^+(97%)
decay product	^{18}O

PET imaging with [18F]tracers also provide high resolution images with respect to positron emitters such as ^{13}N and ^{11}C.[11] This is due to the emission of lower energy positrons (maximal 0.64 MeV).[22] Once emitted, the positron only travels a short distance ($\approx$ 2 mm) before annihilation with an electron producing the detectable 511 KeV gamma rays.[7,11] Furthermore, its production via the ^{18}O(p,n)^{18}F nuclear reaction is high yielding with low energy protons (< 16 MeV), producing enough activity for multiple patient doses on the scale of several curies.[22] This reaction also produces ^{18}F with high specific activity in the absence of 'cold' [19F]F_2 (used for the production of [18F]F_2). Radiochemistry using [18F]fluoride produces high specific activity tracers suitable for imaging with very low concentrations of the tracer.

There are of course possible drawbacks of using [18]F. Due to its high electronegativity, incorporation of fluorine into a molecule can alter its biological behaviour. In the cases where radiolabelling with the ^{18}F isotope changes the structure of the molecule of interest (i.e. when it is not directly replacing ^{19}F), investigation into the effects of this structural modification are required. If incorporation of ^{18}F is in a position that will affect the distribution or metabolism of the compound then the tracer will generally not serve its purpose. Another consideration is the *in vivo* stability of the C-F bond. Whilst C-F bonds are generally stable under *in vivo* conditions, some aliphatic C-F bonds undergo enzymatic cleavage. Aromatic C-F bonds show greater stability.[22]

Fluorine commonly replaces hydrogen or hydroxyl functionalities. It is isoelectronic to a hydroxyl substituent and possesses similar steric bulk to an oxygen atom.[22] This allows for its widespread use for labelling a number of compounds without adverse effects regarding influence on the system under investigation. The subject of this thesis, [^{18}F]F-DOPA **9**, for example has the hydrogen atom in the 6 position of L-DOPA replaced by the ^{18}F nuclide. Despite the alteration to the compound, the labelled DOPA tracer is biologically equivalent to its parent compound and therefore can be used to monitor L-DOPA metabolism and more importantly the distribution of L-DOPAs metabolite dopamine.

There are examples where modification of the tracers' metabolism can be beneficial. One such example is that of the most successful PET tracer to date – [^{18}F]fluorodeoxyglucose ([^{18}F]FDG) **10**.
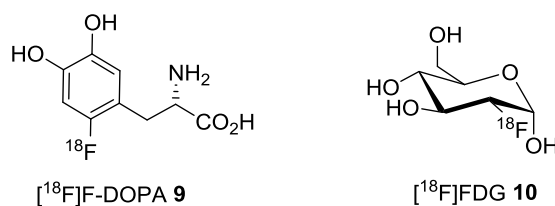

Figure 4 – Structures of tracers [^{18}F]F-DOPA 9 and [^{18}F]FDG 10.

[^{18}F]FDG **10** is used to show the biodistribution of glucose and therefore can show high uptake in tumours where sugar metabolism is accelerated.[2] The mechanism for the uptake into the cell is uninhibited by the replacement of the hydroxyl group for the [^{18}F]fluorine. Once in the cell phosphorylation occurs preventing the [^{18}F]FDG **10** from being released. However, further metabolism (glycolysis) is no longer possible due to the lack of the OH functionality in the 2 position. This process is known as metabolic

trapping and means that the [^{18}F]FDG **10** does not exit the cell but accumulates to provide high uptake images for cells with accelerated sugar metabolism (see Figure 5). Upon decay of the ^{18}F to ^{18}O, normal metabolism of the product ensues.
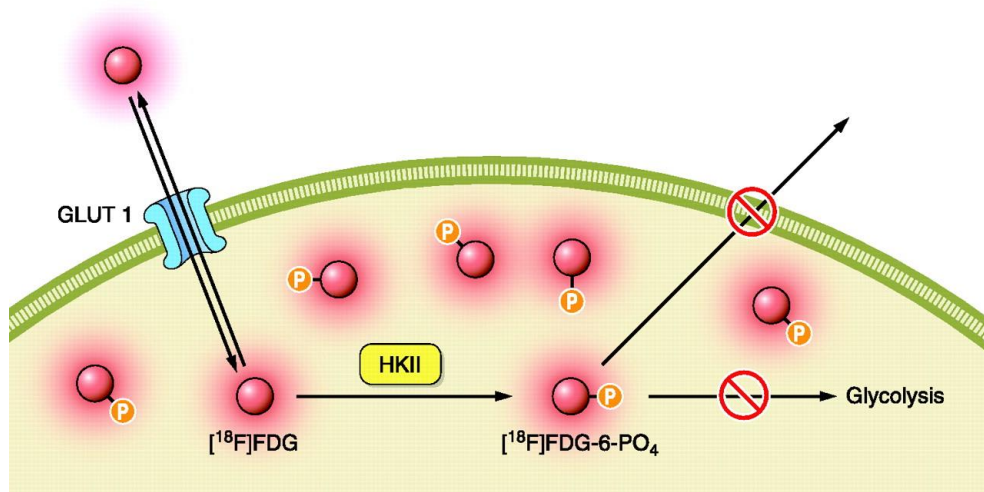

Figure 5 – Mechanism for [^{18}F]FDG accumulation in cells with high glucose metabolism. Image obtained from reference 43 (no permission required).[43]

1.3   Fluorination chemistry for radiotracer synthesis

Incorporation of [^{18}F]fluorine into a molecule for radiotracer production generally involves the formation of a C-F bond. Despite the considerable amount of work done in this field, such transformations are far from trivial and general reaction conditions for the formation of C-F bonds have yet to be realised. This is predominantly due to the nature of the element itself. It is often mentioned that fluorine is available in only an extremely reactive or almost inert state. This refers to the very low reactivity of the fluoride anion, which is generally highly solvated in solution, and the severe reactivity of F$_2$ gas, which can rarely be tamed for a selective fluorination. The challenge for radiochemists is increased due to difficulties in translating such methods using the ^{19}F isotope to reactions using ^{18}F.[44] These difficulties have been attributed largely to the huge differences in reagent concentration and stoichiometry.[7] However, a number of advances in fluorination chemistry are providing a platform for advances in radiofluorination chemistry. A summary of important aromatic fluorination methods precedes a review on radiofluorination chemistry as the field is of great importance within the subject of this thesis.

Aromatic Fluorinations

The formation of aromatic C-F bonds is key for the production of ^{18}F labelled radiotracers. Indeed, the subject of this thesis, [^{18}F]F-DOPA, is labelled via aromatic fluorination. A summary of important fluorination methods for aryl fluoride formation is given below to show the 'tool box' currently available. Conversion of some of the presented methods to radiochemistry has already been accomplished (Late Stage Incorporation of the ^{18}F Nuclide, Pg. 20), while other methods offer avenues of investigation to provide new radiofluorination approaches. Reactions for aryl fluoride formation are shown in Scheme 6 (General aromatic fluorinations) and Scheme 7 (Metal catalysed and mediated fluorinations).

General aromatic fluorinations
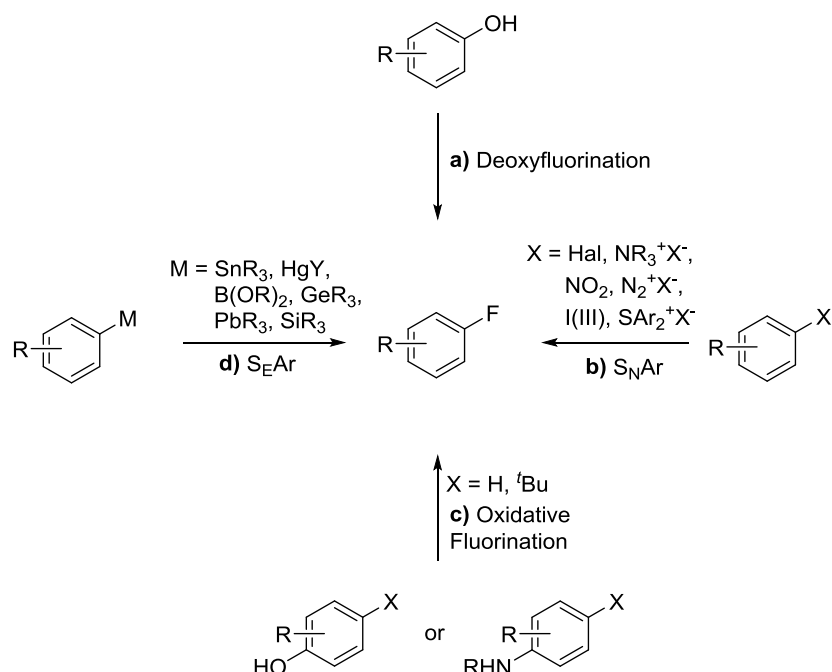
Scheme 6 – Summary of fluorination methods for the production of arylfluorides. a) Deoxyfluorination of phenols: Using deoxyfluorination reagents such as PhenoFluor$^{®[45–47]}$ **or an oxidation-fluorination-reduction protocol**[48]**. b) Nucleophilic aromatic substitution: Substrates include aryl chlorides, aryl bromides, aryl quaternary ammonium salts, nitro arenes and aryl diazonium salts. Furthermore hypervalent iodine species (iodonium ylides**[49]**, iodyl species**[50]** and iodonium salts**[51–54]**) and sulfonium salts**[55,56]** are utilised for aromatics bearing more complex functionality. c) Oxidative fluorination: Phenols**[57,58]** and monoprotected aniline derivatives**[58,59]** are fluorinated in the presence of a hypervalent iodine oxidant. d) Electrophilic aromatic substitution: Electrophilic sources of fluorine are incorporated by reaction with aryl metal compounds to give improved selectivity and scope over reactions using Ar-H. Aryl metal species for fluorination include aryl-tin**[60–62]**, -mercury**[60,61,63]**, -boron**[64,65]**, -germanium**[61,62]**, -lead**[61]**, and -silicon**[62,66]**.

a) The use of deoxyfluorination reagents for the conversion of phenoxy substrates to arylfluorides has been accomplished using both deoxyfluorinating reagents[44–47] and

oxidation-fluorination-reduction reactions.[48] The current reagent of choice for this reaction is Phenofluor® due to its impressive substrate scope and the operational simplicity of the reaction, as reported by Ritter *et al.*[45–47] **b)** Nucleophilic aromatic substitution reactions with appropriate leaving groups is a common method for the introduction of fluorine into electron deficient aromatic moieties. While generally substrate scope is limited, complex aryl fluoride formation has been achieved by appropriate precursor design and judicious choice of leaving group.[23] Furthermore, the use of super effective leaving groups such as iodonium salts allows access to electron rich aryl fluorides (Hypervalent Iodine for late stage fluoriantions, Pg. 30).[67] **c)** Oxidative fluorination of phenols and protected aniline derivitives has been reported.[58,59] Gouverneur *et al.* demonstrated the use of this methodology for radiofluorination.[57] The reactions use hypervalent iodine species as the oxidant. The fluorine atom replaces a proton or tBu group in the para position of the phenol or anilide. **d)** Electrophilic aromatic substitution provides a traditional method to access electron rich arylfluorides not suitable for nucleophilic methods. Many aryl metal species have been employed as substrates to improve the regioselectivity of such reactions with respect to the corresponding C-H precursor. Aryl-tin[60–62], -mercury[60,61,63], -boron[64,65], -germanium[61,62], -lead[61], and -silicon[62,66] have been used with varying degrees of success. One method of particular note is the fluorodestannylation, which is used for the production of [^{18}F]F-DOPA ([^{18}F]F-DOPA, Pg. 37, Scheme 24).[7]

Metal-catalysed and metal-mediated fluorinations

The use of metals for to mediation and catalyse fluorination reactions is an area of great interest and a large number of reactions have been reported in recent years. A brief overview of aromatic fluorination reactions using metals is given below.
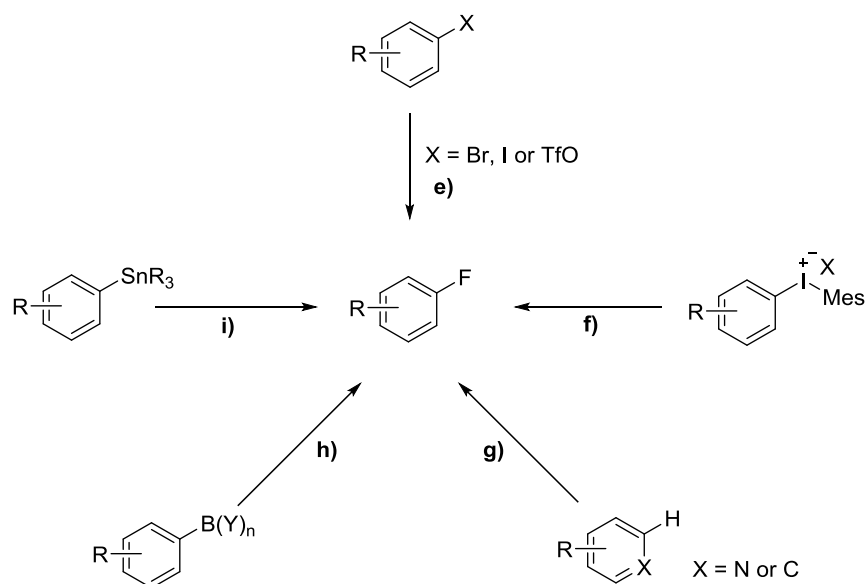
Scheme 7 - Summary of metal catalysed fluorination methods for the production of arylfluorides. a) **Metal catalysed fluorination of halides and triflates: Pd catalysed[68–72] or Cu catalysed.[73] b) Metal catalysed fluorination of mesityl iodonium salt: Using Cu catalyst.[74,75] c) Metal catalysed and mediated fluorination of aryl C-H bonds. Production of 2-fluoropyridines using AgF$_2$ in process analogous to the Chichibabin reaction.[76] Aromatic fluorination via C-H activation using Pd catalysts[77–79] or Cu catalyst[80]. d) Metal catalysed fluorination of boronic acid derivatives: Pd catalysed[81], Ag mediated[82] and Cu mediated[83,84]. e) Metal catalysed fluorination of stannanes: Ag catalysed[85] and Cu mediated[86].**

e) Buchwald has pioneered work on aryl fluoride formation via palladium catalysed nucleophilic fluorination. Substrates include aryl bromide, iodides and triflates.[68–72] The difficulties associated with the reductive elimination step to form the aryl fluoride were overcome by use of the bulky monodentate *t*-BuBrettPhos ligand. The use of a copper catalyst for nucleophilic fluorination has been reported by Hartwig *et al.* using aryl iodide substrates.[73] **f)** The use of mesityl iodonium salts for fluorination in the presence of a copper catalyst has been reported by Sandford *et al.* with excellent selectivity and substrates scope.[75] This work was adapted for radiofluorination with [^{18}F]fluoride (Pg. 24 Scheme 21).[74] **g)** C-H fluorination has been accomplished by the use of activating groups, as was first reported by Sandford *et al.*[77] Work using this methodology has been accomplished using both palladium[77–79] and copper[80] catalysts. Hartwig also published an important paper on the fluorination of pyridines using silver(II) fluoride in a reaction analogous to the Chichibabin reaction.[76] **h)** The use of aryl boronic acid derivatives for metal catalysed and mediated reactions has been accomplished using palladium catalysis[81], copper mediation[83,84,86] and silver mediation.[82] The radiofluorination of boronic esters in the presence of copper(II) triflate was reported by Gouverneur *et al.* (Pg. 27, Scheme 17).[87] **i)** Aryl stannanes

have also been used as substrates for metal catalysed and mediated fluorinations. The use of copper to mediate the fluorination of aryl stannanes was described by Sanford *et al.* [86] Late stage fluorination of aryl stannanes using a silver catalyst was published by Ritter *et al.*[85] Fluorination of a range of small complex molecules was accomplished using this method.

The number of methods available for the production of aryl fluorides has expanded rapidly over the past decade. While substrate scope and applicability to ^{18}F reactions may hinder the use of some protocols for radiotracer production, this ever expanding tool box for aryl C-F bond formation provides a platform for radiochemistry to build on.

1.4   Late Stage Incorporation of the [18]F Nuclide

Incorporation of the ^{18}F nuclide can proceed by either electrophilic or nucleophilic fluorination. The most common and preferred synthetic route is with nucleophilic fluoride. This is because of the higher specific activity (higher radioactivity per unit mass) of the reagent and its availability to a wider number of PET centres. However, synthesis is highly dependent on the target compound and both strategies must be considered important tools to allow for the formation of a wide variety of different labelled compounds.

1.4.1   Electrophilic Synthesis

The disadvantages found when using electrophilic sources of fluorine stem from the fact that most reagents are derived from carrier added [^{18}F]fluorine gas.[5,10,11] This compound is dangerous and difficult to handle, leading to its unavailability at many PET centres. Also, due to its carrier added nature, it is only available with poor specific activity (approx. 1 GBq μmol^{-1}).[7] The contamination of the ^{18}F nuclide with its 'cold' [19]F isotope means that the reagent and any subsequent radiochemistry performed with it will have lower radioactivity per mol. The result is a greater mass of 'cold' compound being administered to the patient. This can give lower resolution images and is especially problematic for compounds that do not benefit from accumulative uptake or 'metabolic trapping' as seen by that of [^{18}F]FDG. It should be mentioned that improved specific activity can be attained with the "Solin method" which uses a smaller quantity of carrier [^{19}F]F$_2$ gas (55 GBq μmol^{-1}).[88,89]

1.4.1.1   Reagents

Scheme 8 shows some electrophilic reagents which can be derived from [^{18}F]F$_2$ gas.[5]

$^{18}O(p,n)^{18}F$
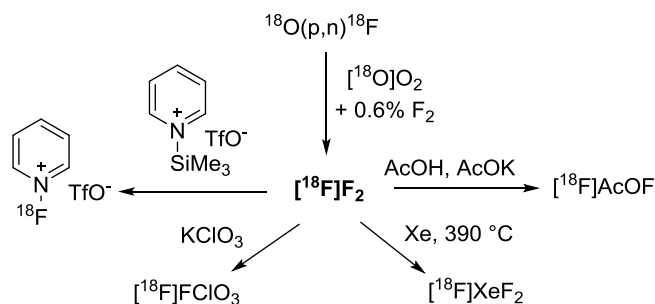
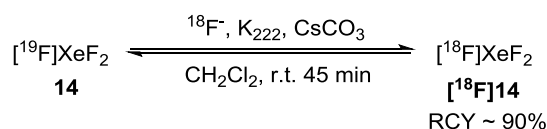**Scheme 8 – Electrophilic reagents derived from [^{18}F]F$_2$ for the incorporation of ^{18}F.**

There are a number of electrophilic fluorination reagents available for the introduction of ^{18}F. The most commonly used is [^{18}F]F$_2$ gas which advantageously can be delivered directly from the cyclotron. Reagents for electrophilic incorporation include O-F reagents such as [^{18}F]perchloryl fluoride ([^{18}F]FClO$_3$) and [^{18}F]acetyl hypofluorite ([^{18}F]AcOF).[90–92] The high reactivity of [^{18}F]F$_2$ gas and these O-F reagents derived from it creates problems with selectivity for more complex precursors. This provided a strong incentive to produce milder more selective electrophilic ^{18}F sources and the production of a number of N-F reagents accomplished this. Such reagents include [^{18}F]-*N*-fluoropyridinium salts and [^{18}F]-*N*-fluorosulfonimides.[93,94] One N-F reagent of particular note is [^{18}F]Selectfluor bis(triflate) **12** which was developed and used by Gouverneur *et al.*[88] The reagent has also been used for the production of [^{18}F]F-DOPA **9** from various precursors including the appropriate stannane and a novel boronic ester precursor **13** (Scheme 9).
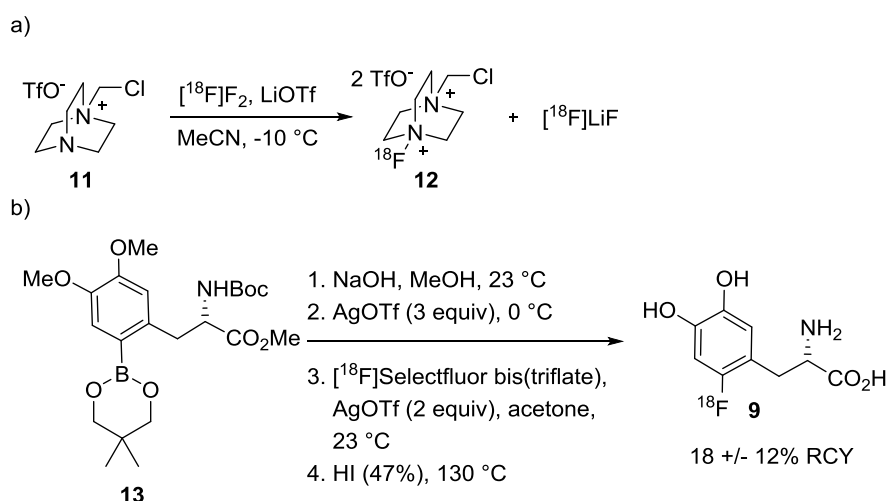
Scheme 9 – Gouverneur's synthesis of [^{18}F]selectfluor bis(triflate) and its utility in the production of [^{18}F]F-DOPA[88,95]

Another notable electrophilic reagent is xenon difluoride [^{18}F]XeF$_2$ **[^{18}F]14**, due to its possible production from nucleophilic fluoride.[96,97] This route means it should be an accessible reagent at any PET facility able to produce [^{18}F]fluoride. However, due to its production from [^{19}F]XeF$_2$ **14**, the [^{18}F]XeF$_2$ **[^{18}F]14** reagent is still of lower specific activity and its widespread utility in radiotracer synthesis has yet to be realised. Scheme 10 shows the production of [^{18}F]XeF$_2$ **[^{18}F]14** from nucleophilic [^{18}F]fluoride.

$$[^{19}F]XeF_2 \quad \underset{CH_2Cl_2,\ r.t.\ 45\ min}{\overset{^{18}F^-,\ K_{222},\ CsCO_3}{\rightleftharpoons}} \quad [^{18}F]XeF_2$$

$$\mathbf{14} \qquad\qquad\qquad\qquad\qquad \mathbf{[^{18}F]14}$$
$$RCY \sim 90\%$$

Scheme 10 – Formation of [^{18}F]XeF$_2$ by exchange with [^{18}F]fluoride

1.4.2   Nucleophilic Synthesis

The use of nucleophilic [^{18}F]fluoride as the source of the radioisotope is preferred due to its high specific activity and wide availability. However, as alluded to in '*Reactivity of the Radioactive Moiety*' (Pg. 5), [^{18}F]fluoride is delivered in an aqueous medium in which the [^{18}F]fluoride anion is unreactive (in most cases) due to its high energy of solvation. To improve its reactivity the water must be removed by azeotropic distillation to give the more reactive 'naked fluoride'. Figure 6 shows the general process used to provide the anion in its 'naked' form. It should be mentioned that full dehydration of the anion does not occur.[22]
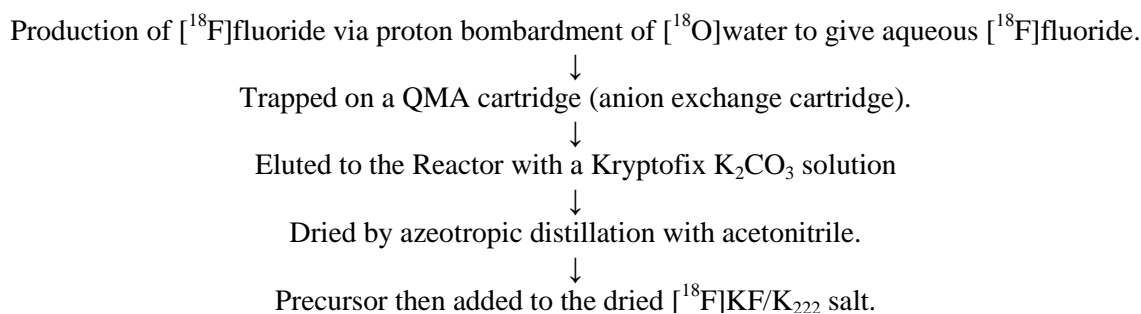
Production of [^{18}F]fluoride via proton bombardment of [^{18}O]water to give aqueous [^{18}F]fluoride.

↓

Trapped on a QMA cartridge (anion exchange cartridge).

↓

Eluted to the Reactor with a Kryptofix K$_2$CO$_3$ solution

↓

Dried by azeotropic distillation with acetonitrile.

↓

Precursor then added to the dried [^{18}F]KF/K$_{222}$ salt.

Figure 6 - General procedure for the drying of [^{18}F]fluoride

Once isolated in its 'reactive form', the [^{18}F]fluoride can be used in a wide range of reactions. Historically, aliphatic incorporation has had greater success for the production of radiotracers. [^{18}F]FDG **10** for example is produced via an S$_N$2 reaction of the mannose triflate precursor **15** with the nucleophilic [^{18}F]fluoride (Scheme 11).[24]

68% RCY
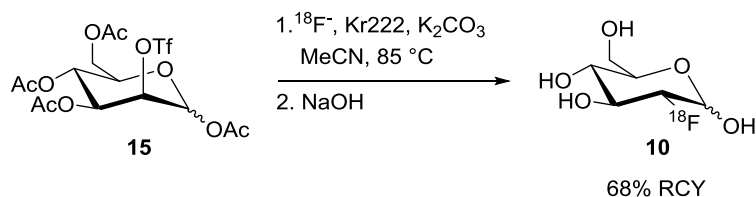
Scheme 11 – Synthesis of [^{18}F]FDG from mannose triflate

1.4.2.1   Aliphatic Incorporation of [^{18}F]Fluoride

Substitution reactions for the incorporation of ^{18}F into aliphatic moieties are common and a number of leaving groups have been employed along with the triflate leaving group shown above. Commonly used as leaving groups are halides (Cl, Br or I) and other sulfonates such as mesylates, tosylates and nosylates.[22]

Metal-Mediated Incorporation

The metal-mediated incorporation of ^{18}F into aliphatic compounds has seen a number of recent advances. For example, multiple procedures have been developed for allylic fluorination with nucleophilic fluoride using various metal catalysts.[98–100] Iridium complexes have proved to be very successful in this area.

The chiral introduction of [^{18}F]fluoride has also been reported. Doyle *et al*. were able to access [^{18}F]fluorohydrins **18** using a cobalt salen ligand complex **16OTs(a)** and epoxide precursors **17** (Scheme 12a).[101] The chiral ring opening of the epoxide proceeded with good stereocontrol and showed its utility in the production of [^{18}F]FMISO.

Further developments include a late stage benzylic fluorination reported by Groves *et al.* (Scheme 12b).[102] Here a Mn(salen) complex **16OTs(b)** was used for the introduction of [^{18}F]fluoride, providing the labelled targets **20** without the need for 'pre-activated' precursors. Both Doyle and Groves' work advantageously avoid the need for azeotropic drying of the [^{18}F]fluoride by direct elution of the [^{18}F]fluoride from the QMA with the respective Mt(salen)OTs complexes.
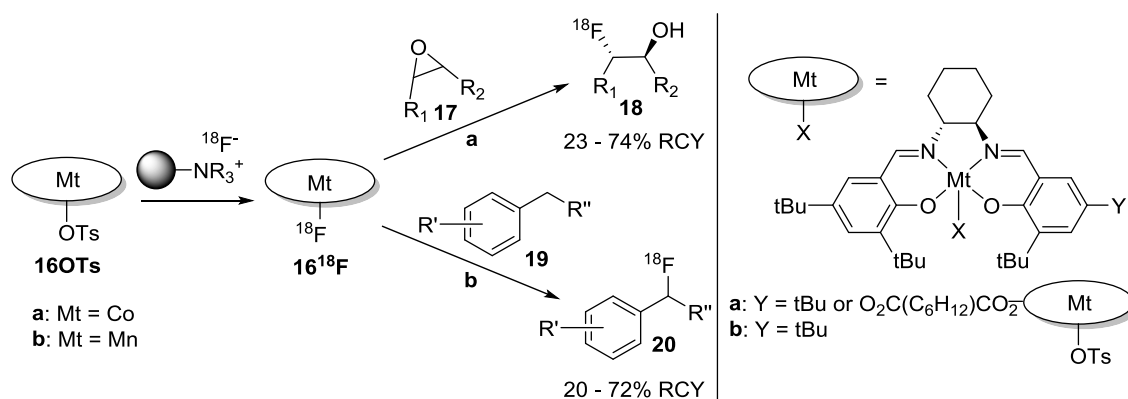
Scheme 12 – Mt(salen) based fluorinations. a) Stereoselective formation of [¹⁸F]fluorohydrins utilising a monomeric or dimeric Co(salen)OTs reported by Doyle et al.[101] b) Late stage benzylic [¹⁸F]fluorinations with a Mn(salen)OTs complex reported by Groves et al.[102]

Another area of fruitful developments has been the synthesis of [^{18}F]CF$_3$ functionalities. As trifluoromethyl groups are prevalent in a number of pharmaceuticals, such reactions can be valuable tools for any required ^{18}F incorporation. Methods for the generation of high specific activity [^{18}F]CF$_3$ functionality have been reported for both alkyl and aryl functionalization.

A promising strategy for aliphatic targets is the [^{18}F]fluorination of *gem*-difluoro vinyl precursors by nucleophilic addition of [^{18}F]HF.[103] A common strategy for aromatic substrates is to perform a cross-coupling reaction with [^{18}F]CuCF$_3$ which can be produced *in situ*.[104–107] The strategy was first reported by Gouverneur *et al.* who showed *in situ* produced [^{18}F]CuCF$_3$ could be coupled to a wide range of both aryl and heteroaryl iodides **21** (Scheme 13).[104] Boronic acids have also been used for this type of cross-coupling reaction.[105,107]
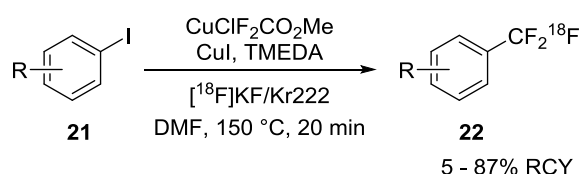

Scheme 13 – *In situ* generation and cross-coupling of [¹⁸F]CuCF₃ with aryl and heteroaryl iodides 21 reported by Gouverneur et al.[104]

Enzymatic Fluorination

Radiochemists have also exploited nature's solution to forming carbon fluorine bonds. The fluorinase enzyme is used to catalyse the formation of 5'-fluoro-5'-deoxyadenosine from *S*-adenosyl-L-methionine.[108] Mild radiofluorination conditions have been developed using the fluorinase enzyme for the labelling of peptides and other

biomolecules.[109–111] Advantageously such reactions are carried out under aqueous conditions. Disadvantages include the high substrate specificity of the enzyme, which limits the scope of such reactions. However improved understanding of these reactions has led to an enhanced scope of peptide substrates.[109]
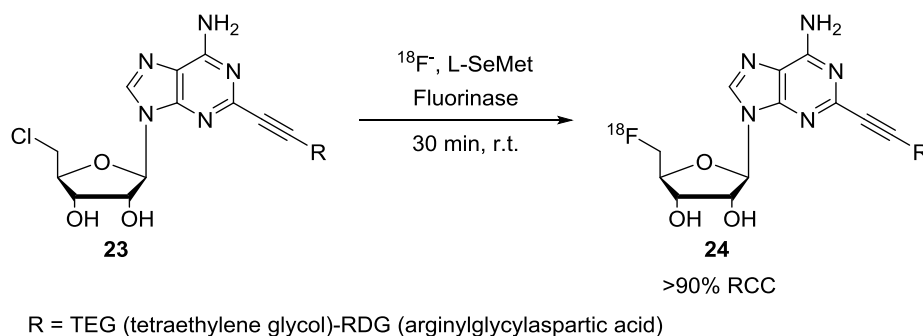
Scheme 14 – Enzymatic [^{18}F]fluorination of a peptide 23 with fluorinase. O'Hagan *et al.* utilised an acetylene functionality to exploit an "Achillies heel" in the enzyme substrate specificity.[109]

1.4.2.2 Aromatic Incorporation of [^{18}F]Fluoride

The synthesis of [^{18}F]fluoroarene tracers with [^{18}F]fluoride is very desirable due to the reasons already discussed ('PET and Radiochemistry with the [18]F Isotope', Pg. 14). However, the wide spread utility of such reactions for tracer synthesis has been hampered by the lack of a reliable, robust methodology for [^{18}F]fluoride incorporation. This is especially true for the synthesis of electron rich [^{18}F]fluoroarenes.

Traditional nucleophilic routes for labelling aromatic compounds include aromatic substitution of halides and other leaving groups such as nitro groups and ammonium salts. Unfortunately, these reactions are generally limited to aromatic compounds bearing electron-withdrawing groups and regioselectivity remains an issue. Introduction of [^{18}F]fluoride using Balz-Schiemann and Wallach reactions is also possible but these methods generally suffer from poor radiochemical yields (RCYs) and the harsh conditions used limit the substrate scope of such transformations.[112,113] Extending these traditional methodologies to complex systems can be difficult and often requires multistep synthesis.

A number of recent developments in late stage fluorination are combating these problems. Among these progressions are new reagents and novel 'activating' functionalization of precursors.

Metal Mediated Aromatic [^{18}F]Fluorination

One strategy that has generated a lot of interest is the use of transition metal catalysts/ precursors for fluorination with [^{18}F]fluoride.

Ritter and co-workers showed that palladium complexes could be used to generate electrophilic ^{18}F from nucleophilic [^{18}F]fluoride.[114] These palladium complexes **26** could be used for the introduction of the ^{18}F isotope into a range of pre-functionalised targets **27** (Scheme 15).
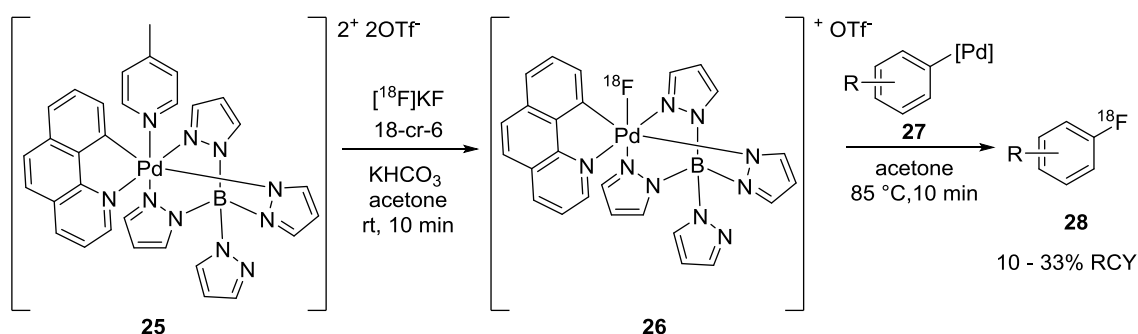
Scheme 15 – Palladium-catalysed fluorination of aromatics.

Mechanistic investigation suggests a single electron transfer (SET) mechanism for the oxidative transfer of the [^{18}F]fluoride from **26** to **27**. Subsequent reductive elimination affords the [^{18}F]aryl fluoride products.[115]

Another metal mediated [^{18}F]fluorination of aryl moieties reported by Ritter *et al.* uses nickel complex precursors in the presence of an oxidant **30**.[116] The reaction proceeds using aqueous, no carrier added (n.c.a) [^{18}F]fluoride to give the [^{18}F]labelled product in under one minute with high specific activity (SA). The use of aqueous fluoride for the reaction negates the need for time-consuming azeotropic drying steps, creating an extremely rapid procedure from end of bombardment (EOB). Disadvantages include a complex precursor synthesis and the instability of the oxidant. Scheme 16 shows the methods utility for the production of protected [^{18}F]F-DOPA **31**.
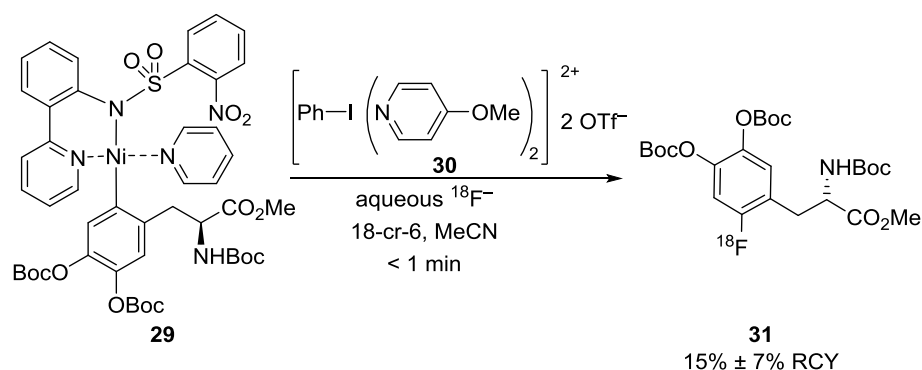
Scheme 16 – Oxidative fluorination of Nickel precursors in the presence of an oxidant with aqueous fluoride reported by Ritter et al.[116]

Gouverneur *et al.* have recently reported the reaction of pinacol-derived boronic esters with [18F]KF/K$_{222}$ in the presence of a copper catalyst.[87] The optimised protocol proved to be a robust methodology for the synthesis of a diverse range of 18F labelled compounds. The suitability of the method for production of known tracers was proved by the synthesis of [18F]F-DOPA **9**. Reaction of the protected DOPA boronic ester **32** gave the 18F labelled compound **33** in good yields (Scheme 17). Deprotection with HI and HPLC purification provided the isolated [18F]F-DOPA **9** with an impressive decay corrected RCY of 12%. All PET centres with the capacity to produce 2-[18F]fluoro-L-deoxyglucose **10** should be able to use this very promising method.
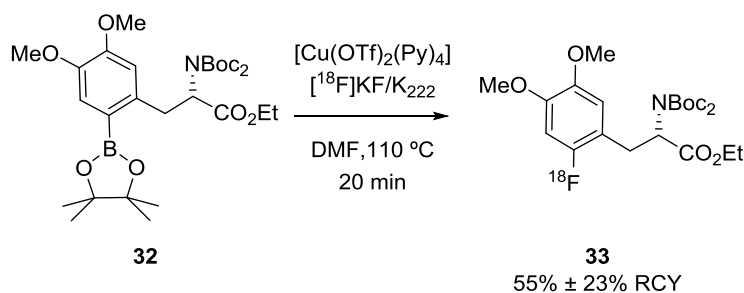
Scheme 17 – Copper mediated [18F]fluorination of arylboronic esters reported by Gouverneur *et al.*[87]

The recent advance in radiochemistry, especially with regard to late-stage aromatic fluorinations, has been considerable. A recent review by Scott *et al.* entitled '*Late-stage [18F]fluorination: New solutions to old problems*', highlights a variety of significant achievements in the area that have overcome shortfalls in the previously quite limited methodology.[117] The use of hypervalent iodine for late stage incorporation of [18F]fluorine is a very active field and is responsible for a number of important advances. As the subject of this thesis, a more thorough overview of hypervalent iodine

compounds and their use in late stage fluorination reactions is presented below (Hypervalent iodine for late stage fluorinations, Pg. 30).

Radiochemistry has a rapidly expanding toolbox with many new reagents and methods becoming available for the incorporation of isotopes. Just as with every area of chemistry, it is also benefiting from new technologies and methodologies. Flow chemistry using microreactors for ^{18}F incorporation is a substantial field.[118–120] In fact recently the first human use of a tracer made using microfluidic radiofluorination was published by Liang *et al.*[121] The use of microwaves has also found utility in the field of late stage ^{18}F fluorinations.[122] It is unsurprising that these technologies, recognised to accelerate many reactions, have gained considerable attention in a field where short reaction times are of upmost importance. Electrochemistry is also an area receiving attention for its application in ^{18}F incorporation.[123–125]

Another methodology of interest is solid-supported synthesis of labelled compounds.[126] Such reactions can provide the advantage of a simplified purification in which the labelled compound can be washed directly from the resin, with other side products (generally a leaving group) left bound to the resin. Both electrophilic and nucleophilic methods for ^{18}F incorporation using resin bound precursors have been explored (Scheme 18).[127,128] Despite the potential advantages of this methodology, its mainstream application for the production of tracers or prosthetic groups (Prosthetic Groups, Pg. 29) has not yet been seen.
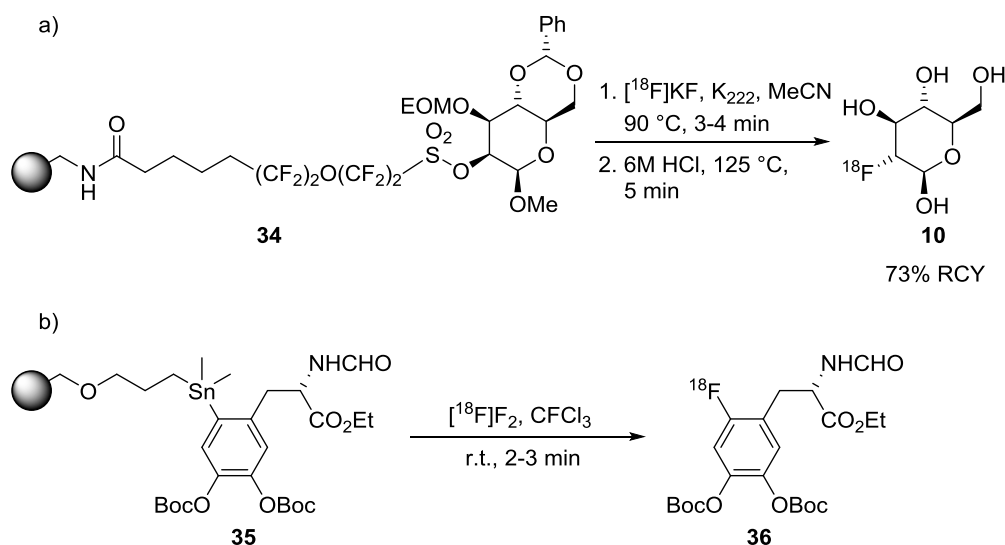
Scheme 18 – Solid supported synthesis of ^{18}F labelled tracers. a) Solid-supported synthesis of [^{18}F]FDG 10 reported by Brown et al.[127] **b) Solid-supported synthesis of a protected [^{18}F]F-DOPA moiety 36 reported in a patent published by Wadsworth et al.**[128]

1.4.3 Prosthetic Groups

Direct incorporation of ^{18}F into the compound of interest is not always necessary and sometimes it is desirable to label the biological moiety by linkage to an already labelled compound. These compounds are known as prosthetic groups and are generally used to label larger molecules such as peptides and antibodies where direct labelling is not feasible.[5,11,22] Some examples of prosthetic groups are shown below (Scheme 19).
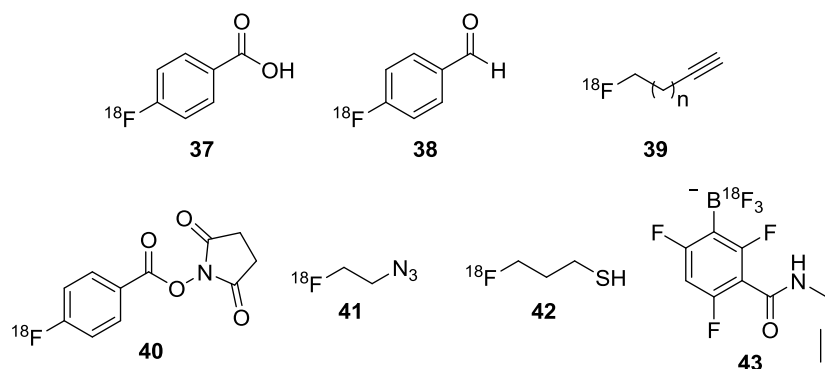
Scheme 19 - Examples of prosthetic goups. 4-[^{18}F]fluorobenzoic acid ([^{18}F]FBzA) 37.[129] **4-[^{18}F]fluorobenzaldehyde ([^{18}F]FBA) 38.**[130] **^{18}F labelled alkyne for 'click' conjugation 39.**[131] ***N*-succinimidyl-4-[^{18}F]fluorobenzoate ([^{18}F]SFB) 40.**[132] **^{18}F labelled azide for 'click' conjugation 41.**[133] **^{18}F labelled thiol 42.**[134] **High specific activity [^{18}F]aryltrifluoroborate for 'click' conjugation 43.**[135]

A number of linker strategies are available to attach the prosthetic group to the bioactive molecule of interest. Traditionally alkylation, acylation and amidation reactions have been used. Modern methodologies include the use of click chemistry with copper

catalysed cycloaddition.[131,133,135] Linkage of a particularly high specific activity prosthetic group; [18F]aryltrifluoroborate **43**, utilised such 'click' chemistry (Scheme 19). Prosthetic groups with [18F]fluoride bound to elements such as boron, aluminium and silicon have become an important labelling strategy.[136]

It is noteworthy that indirect incorporation of 18F by functionalization with cross coupling reactions has also proved desirable for some applications.[137–139] Such incorporation is generally used for the construction of smaller labelled compounds.

1.5   Hypervalent Iodine for late stage fluorinations

1.5.1   Hypervalent Iodine

The first organic hypervalent iodine compound was discovered in 1886 by Willgerodt who synthesised $PhICl_2$.[140] Many years since this discovery, hypervalent iodine compounds have found themselves in routine use in organic laboratories, most commonly as mild oxidants.[140,141] The attractive nickel fluorination reported by Ritter *et al.* used a hypervalent iodine compound **30** as an oxidant for the incorporation.[116] More directly impacting the field of radio fluorinations however, are hypervalent iodine precursors; the most widely used and investigated of which are diaryliodonium salts.[67]

1.5.2   Iodonium Salts

Iodonium salts have generated a lot of interest as precursors for the nucleophilic incorporation of [18F]fluoride into electron rich target molecules. This is because their properties make them ideal precursors for aromatic radiotracer synthesis using nucleophilic [18F]fluorination. A quick, selective reaction is crucial for short reaction and purification times to increase RCY. This is achieved by the salts high reactivity, attributed to the 'hyperleaving group ability' of the PhI group, which is approximately 10^6 times greater than that of a triflate.[142]

The use of diaryliodonium salts for the formation of 18F labelled aromatic compounds was first reported by Pike *et al.* using both symmetrical and unsymmetrical diaryliodonium precursors.[51] These compounds have a characteristic T-shaped geometry, which means that if the iodonium salt is unsymmetrical then two interconverting isomers exist (Figure 7).[143] The aromatic substituent at which the fluorination takes place is dependent on both the electronic and steric properties of the two attached aryl moieties. This allows precursors to be designed for selective

fluorination at the desired aromatic ring by employing a small, electron rich aryl group (commonly 2-thienyl and 4-methoxyphenyl) as the 'non-participating' aryl ring. One directing group of particular superiority is the [2,2]paracyclophane moiety. Dimagno *et al.* showed the group to be capable of directing fluorination to even 2-thienyl and 4-methoxyphenyl aromatics.[144]

1.5.2.1   Mechanism and Selectivity

The mechanism of fluorination at the I(III) centre has been investigated computationally by Togni *et al.* and shows why such directing groups can achieve regioselective fluorination, for the production of the ^{18}F labelled target molecule.[143]
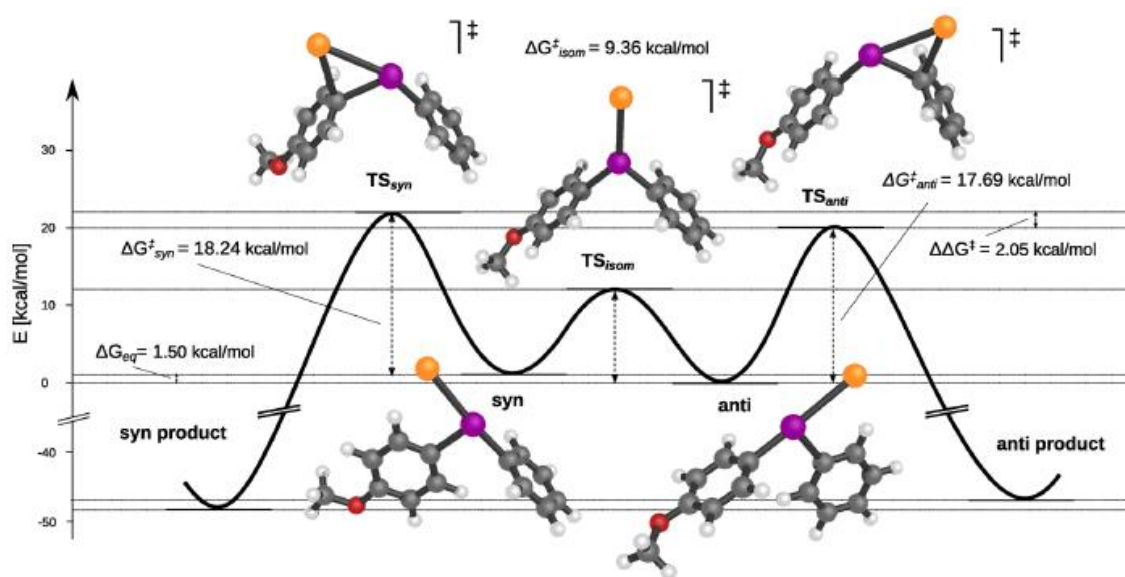
Figure 7 – Reaction profile for the reductive elimination of an unsymmetrical iodonium bromide.[143]

Nucleophilic attack at the I(III) centre proceeds via ligand exchange to form the T-shaped nucleophile salt. Two T-shaped iodane isomers exist and can interconvert via a Y-shaped transition state. Ipso-attack of the nucleophile leads to functionalisation of the aromatic. The Gibbs free energy of each transition state is dependent on both the electronic and steric properties of the aromatics present. An electron rich arene will have a higher energy transition state and therefore directs functionalisation to the more electron poor aromatic. Selectivity complies with the Curtin-Hammett principle.[143]

As alluded to above, the electronics of the aromatic are not the only factor influencing the regioselectivity of the fluorination. A steric consequence known as the '*ortho* effect' can have a major influence on this selectivity. This effect occurs due to differences in

the steric interactions between the two isomers of an unsymmetrical diaryliodonium salt. In Figure 8 it is shown that the more sterically bulky / *ortho* substituted aromatic can either be found in the axial or equatorial position. The more compact axial produces a greater steric interaction than the roomier equatorial position. This increases the energy of the axial isomer (and its transition state) and hence, the isomer in which the sterically bulky / *ortho* substituted aromatic is equatorial is predominant. From the transition state it can be seen that this leaves the bulky aromatic substituent available for fluorination. Aside from this argument, the selectivity has also been partly attributed to the lipophilicity of the substituent. Hydrophobic groups create a 'lipophilic microenvironment' which improves the nucleophilicity of the $[^{18}F]$fluoride nucleophile.[119]
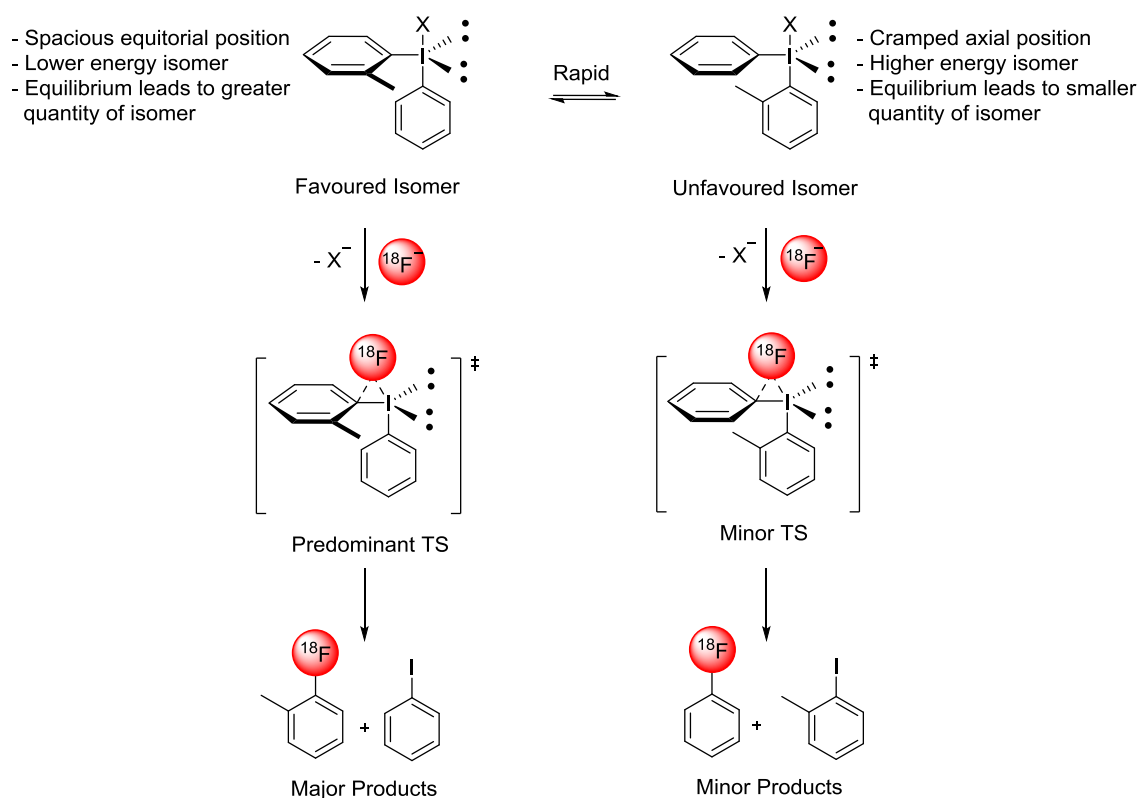
Figure 8 – Regioselectivity induced by the "*ortho* effect".

1.5.2.2   Utility

The utility of diaryliodonium salts in radiotracer formation offers a selective and widely applicable methodology for the introduction of $[^{18}F]$fluoride into a large number of functionalised arenes. Nevertheless, the use of iodonium salts for the introduction of fluoride cannot be described as general, with a large range of fluorination conditions reported for a range of substrates. The radical scavenger TEMPO has been shown in

some cases to increase the reproducibility and RCY of reactions,[145,52,146] whilst in other cases TEMPO offers no improvement.[119] Of even greater curiosity is the addition of water to these reactions which is avoided in many cases and can be critical to the success of the reaction in others.[52,54,147] It has been speculated that beneficial addition of water could be attributed to the catalysed formation of an intimate ion-molecule pair produced under such conditions.[54] Another factor alluded to is the improved solubility of the [18F]fluoride salts.[52]

The production and fluorination of more complicated, biomedically relevant iodonium precursors has until recently also experienced difficulties. However, as the understanding and experience in this methodology has grown, the use of iodonium salts as precursors to form more complex, electron-rich radiotracers has seen much recent success.[52,146,54] Scheme 20 shows some [18F]tracers synthesised using diaryliodonium salt precursors.
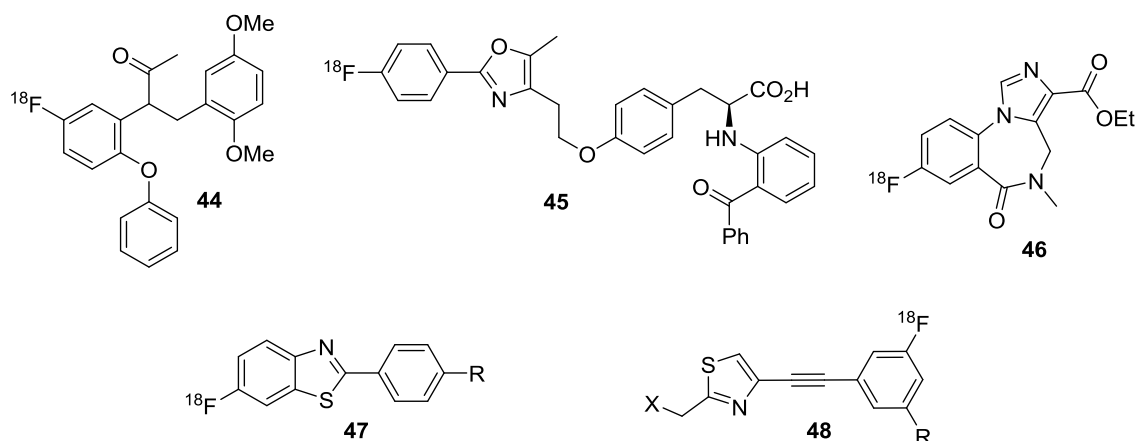
Scheme 20 - [18F]tracers synthesised using diaryliodonium salt precursors. [18F]DAA1106 44 synthesised by Zhang *et al.*[148] PPARγ ligand 45 synthesised by Katzenellenbogen *et al.*[149] [18F]flumazenil 46 synthesised by Kim *et al.*[150] 2-aryl-6-[18F] fluorobenzothiazoles 47 synthesised by Kim *et al.*[151] 18F labelled mGluR5 radioligands 48 synthesised by Pike *et al.*[152]

The use of iodonium salts in the presence of a transition metal catalyst can also be fruitful for the introduction of fluorine. Scott *et al.* used mesityl-substituted iodonium salts for late stage [18F]fluorination in the presence of a copper catalyst.[74] The selectivity for the radiofluorination is governed by sterics, with fluorination occurring at the smaller aryl group irrespective of its electronic properties. The methods utility for the production of a protected [18F]F-DOPA moiety **50** was successful, with a radiochemical conversion (RCC) of ~31% (Scheme 21). However, the isolated RCY of **50** was 1% (non-decay corrected).
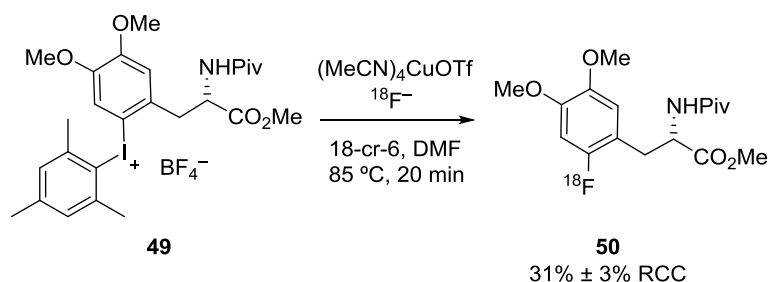
Scheme 21 - Copper catalysed fluorination of a mesityl diaryliodonium precursor.

1.5.3 Other hypervalent precursors.

Also of interest for ^{18}F incorporation are iodonium ylides. Liang *et al*. recently published a procedure for the regiospecific fluorination of iodonium ylides.[153] This attractive methodology was adapted from previous work and has also been reported by Barrio *et al*. for the synthesis of [18F]F-DOPA **9** via the appropriately functionalised precursor **51** (Scheme 22a).[50] The advances reported by Liang and co-workers include the use of a spirocyclic iodonium ylide which provides a precursor more stable to I(III) decomposition and disproportionation.

This class of hypervalent iodine compound lends itself well to the synthesis of electron rich aryl radiotracers: While the fluorination is proposed to occur through a similar intermediate to that of a diaryliodonium salt precursor,[153] it is claimed to occur with complete regiospecificity.[50] This is due to the presence of a carbon with carbanionic character producing a charge distribution which severely disfavours nucleophilic attack at the ylide auxiliary. The methodology has proven to be a reliable and suitable method for radiotracer production by its recent utility in the production of [18F]FPEB **54** validated for human use (Scheme 22b).[154]

a)

b)

20% RCY
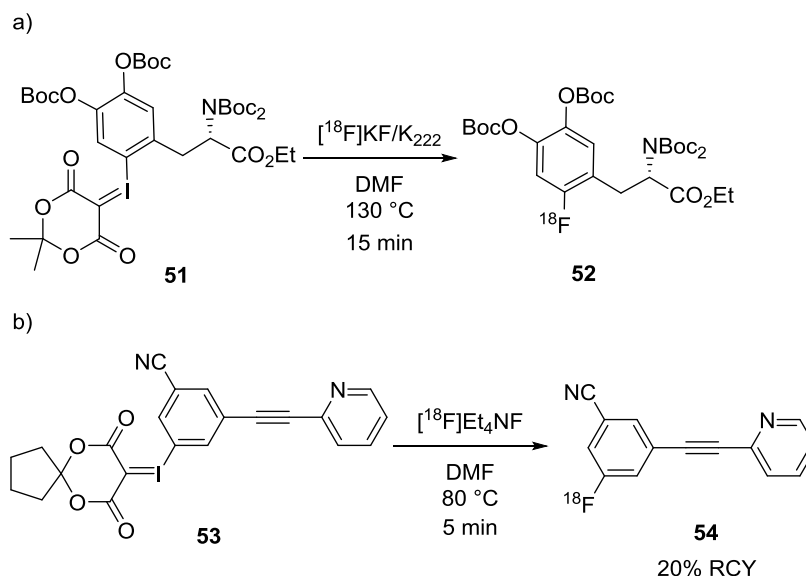
Scheme 22 – Iodonium ylides precursors for the production of ^{18}F labelled tracers. a) Synthesis of a protected [^{18}F]F-DOPA 52 compound from a meldrums acid derived iodonium ylide reported by Barrio *et al.*[50] b) Production of [^{18}F]FPEB 54 using Liang's modified spirocyclic iodonium ylide methodology reported by Vasdev *et al.*[154]

The use of iodyl compounds as precursors for the synthesis of ^{18}F labelled compounds isn't common. However Barrio *et al.* have shown these hypervalent iodine species to be suitable precursors for fluorination with [^{18}F]fluoride.[155] Precursors are produced by oxidation of the iodine(I) compound with dimethyl dioxirane. The iodyl precursor can then undergo fluorination to yield the corresponding [^{18}F]labelled product. Scheme 23 shows the successful fluorination of the corresponding protected [^{18}F]F-DOPA precursor **55**. The explosive nature of the precursors may hinder the widespread utility of such compounds.

R = H or Boc   5-10% RCY
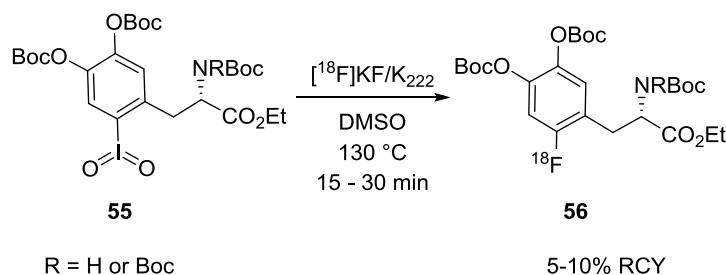
Scheme 23 - Iodyl precursor 55 undergoes radiofluorination to yield the protected [^{18}F]F-DOPA species 56.[155]

1.6   [^{18}F]F-DOPA

1.6.1   Introduction

[^{18}F]6-Fluoro-3,4-dihydroxy-L-phenylalanine ([^{18}F]F-DOPA) **9** is a radiotracer of considerable interest due to its employment in the diagnosis and evaluation of diseases, including cancers[1] and neurodegenerative disorders such as Parkinson's disease.[4] The radiolabelled L-DOPA behaves with similar kinetics and equivalent biochemical behaviour to its unlabelled analogue.[156] After injection, [^{18}F]F-DOPA **9** is subjected to the metabolism of L-DOPA and is therefore transported into presynaptic neurons where aromatic L-amino-acid decarboxylase (AAAD) converts the tracer into [^{18}F]fluorodopamine ([^{18}F]FDA) which is retained in catecholamine storage.[157] Importantly, unlike [^{18}F]FDA, [^{18}F]F-DOPA **9** can cross the blood-brain barrier.[156] This allows for uptake of the tracer in the dopaminergic cells in the brain where conversion to [^{18}F]FDA is again facilitated by AAAD.[156] Hence, the production and metabolism of dopamine can be monitored. This allows for diagnosis and investigation of diseases in which [^{18}F]FDA production and metabolism is lacking or abnormal. Such conditions include Parkinson's disease and schizophrenia.[4,158,159] Increased uptake into the brain can be accomplished by administering carbidopa to the patient prior to injection. This inhibits initial decarboxylation of [^{18}F]F-DOPA **9** to [^{18}F]FDA after injection, increasing the availability of [^{18}F]F-DOPA **9** for transportation and accumulation in the brain.[160]

Furthermore, [^{18}F]F-DOPA **9** shows accumulation in cells with an increased amino acid uptake. This includes brain tumours and neuroendocrine tumours (NETs).[1] Increased amino acid transport and AADC activity in neuroendocrine tumours are responsible for the greater accumulation of the tracer and its metabolites. Cerebral gliomas show an increased uptake of [^{18}F]F-DOPA **9** due to over expression of the LAT1 transporter protein, giving the positive PET image.[1]

It should be mentioned that the injected [^{18}F]F-DOPA **9** undergoes a number of transformations during its metabolism (following that of L-DOPA's) and much of the activity injected will not be accumulated in the area under scrutiny.[161]

While [^{18}F]F-DOPA **9** has been known to be a useful radiotracer for over 30 years,[162] its widespread clinical use has been hampered by the lack of a robust, high yielding process for incorporation of the ^{18}F nuclide ($t_{1/2} = 110$ min).

1.6.2   Synthesis

Recent Developments

Currently [^{18}F]F-DOPA **9** is produced by electrophilic destannylation of **57** with [^{18}F]fluorine gas (Scheme 24).[7] This reaction suffers from several disadvantages including poor radiochemical yield (RCY) and low specific activity (SA) due to the use of carrier added [^{18}F]F$_2$ gas. Furthermore, the procedure is unavailable to PET centres not equipped with [^{18}F]F$_2$ gas production facilities.
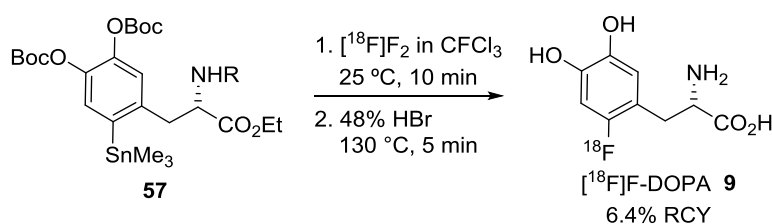
Scheme 24 - Current electrophilic synthesis of [^{18}F]F-DOPA 9

Much research into [^{18}F]F-DOPA **9** synthesis has been conducted in order to overcome these limitations, with a large focus on nucleophilic incorporation of no carrier added (n.c.a.) [^{18}F]fluoride, due to the benefits already mentioned (Nucleophilic Synthesis, Pg. 22). [^{18}F]F-DOPA **9** with a high specific activity has become more sought after due to the tracers increasing importance in peripheral oncologic diagnosis. Employing [^{18}F]F-DOPA **9** with low specific activity requires an increased dose which can have severe adverse effects on the patient such as carcinoid crisis.[163]

The advances in the nucleophilic incorporation of [^{18}F]fluoride outlined above (Aromatic Incorporation of [^{18}F]Fluoride, Pg. 25) have contributed significantly to providing alternative nucleophilic routes to this important tracer. Methods that have already been presented for their useful employment in [^{18}F]F-DOPA **9** synthesis are outlined in Table 5 (Pg. 40). Some further advances in the synthesis of [^{18}F]F-DOPA **9** are described below.

1.6.2.1   *Synthesis with Diaryliodonium Salt Precursors.*

The synthesis of [^{18}F]F-DOPA **9** using diaryliodonium salts is a recent development. Unfortunately, the reported synthesis and application are only covered by scant patent literature. The reported information is outlined below along with some further information provided by the website 'http://www.gfpharma.com/'.[164,165]

DiMagno *et al.* investigated the synthesis of the diaryliodonium triflate **58(TfO)a**,[166] which forms the [18F]iodonium fluoride in dry acetonitrile by anion exchange. Subsequent to a filtration to remove any insoluble salts, successful fluorination via breakdown of the iodonium fluoride **58(18F)a** in a non-polar solvent yields the protected [18F]F-DOPA **59a**. Deprotection with HBr produces [18F]F-DOPA **9** (Scheme 25). Such 'salt-free' conditions can improve fluorinations using diaryliodonium salts.[167]

Details of the reaction success are not disclosed in the patent. However, using an analogous precursor; ALPDOPA[TM] **58(TfO)b**, Ground Fluor Pharmaceuticals Inc. claim >30-40% RCY, >4000 Ci/mmol SA and >98% ee when using diglyme as the breakdown solvent.[164]
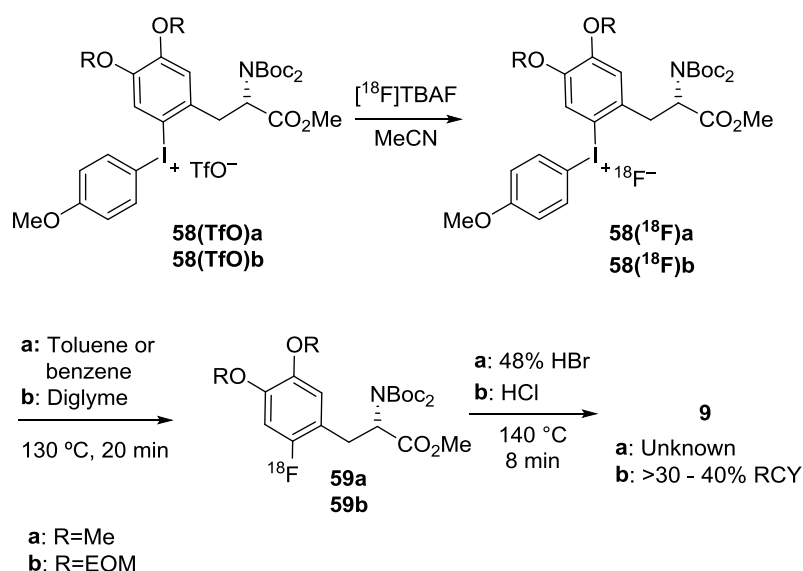
Scheme 25 - Diaryliodonium triflate precursor 58 undergoes anion exchange followed by thermal decomposition to yield [18F]F-DOPA 9 after a subsequent deprotection step.[164,166]

High specific activity [18F]F-DOPA **9** (synthesised using the ALPDOPA[TM] iodonium salt precurosor) has been used in a study to compare with [18F]F-DOPA **9** prepared by the traditional electrophilic method. It was found that imaging qualities in mice were identical. Using the high specific activity [18F]F-DOPA **9** was advantageous due to its facil production procedure and the lower administered mass of [19F]F-DOPA **9**.[168]

1.6.2.2   *Multistep Syntheses*

Multistep synthesis provides a challenge for the production of 18F labelled compounds due to problems with complex automation. However, developments in this area are now providing methods for reliable nucleophilic [18F]F-DOPA **9** production.

Trasis have developed a reliable nucleophilic method by optimising and automating chemistry reported by Lemaire *et al.*[169–171] The multistep synthesis involves nucleophilic aromatic substitution of an electron poor nitrobenzaldehyde **60** with [18F]fluoride. The activating aldehyde functionality is then converted to the iodide to give [18F]fluorobenzyl iodide **63**. Enantioselective carbon-carbon bond formation with Schiff's base **64** in the presence of a chiral phase-transfer catalyst is a key step and optimisation showed compounds **66** and **67** to be of equal efficacy for this transformation. The protected DOPA moiety **65** is produced with ≥97% *ee* and high specific activity (35000 Ci/mmol).[165,169] Subsequent deprotection with HI yields [18F]F-DOPA **9** (Scheme 26).
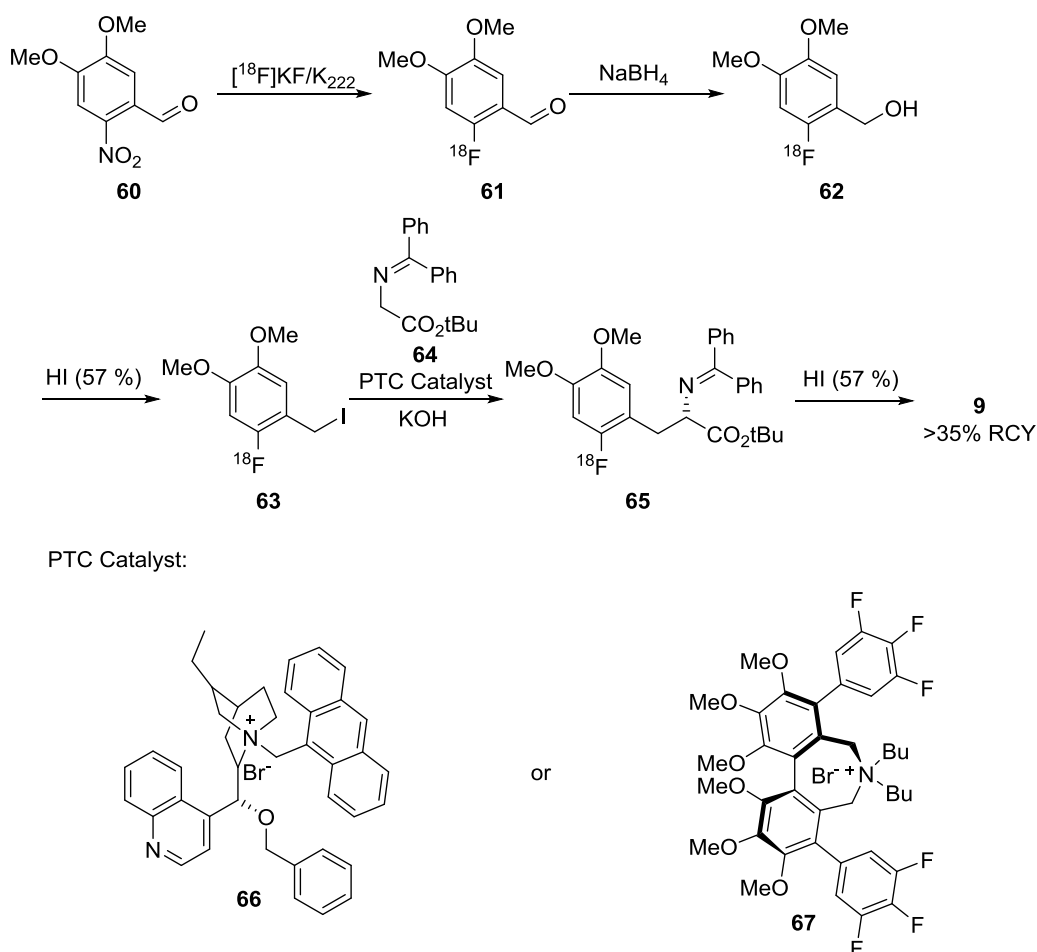
Scheme 26 - Multistep synthesis to [18F]F-DOPA using chiral phase-transfer catalysts.[165]

In addition, ABX now provide a nitro precursor **68** for nucleophilic [18F]F-DOPA **9** formation.[23] The strategy makes use of previously developed carbonyl activating chemistry for the S_NAr reaction with [18F]fluoride.[172] After radio-fluorination is

achieved, the activating aldehyde group can be removed by a sequence of Baeyer-Villiger oxidation and hydrolysis to give the desired hydroxyl functionality (Scheme 27).
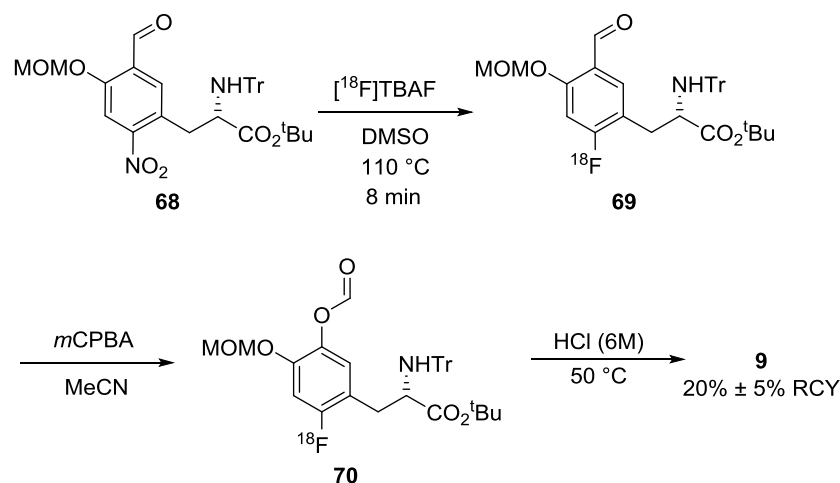
Scheme 27 - Aldehyde activated [^{18}F]fluorination of ABX's nitro precursor 68 with [^{18}F]fluoride.[23]

A summary of the most promising syntheses for [^{18}F]F-DOPA is shown in Table 5.

Table 5 - Summary of the most promising syntheses for [^{18}F]F-DOPA 9

Precursor	Method	RCY (%)	SA (Ci/ mmol)	ee
29	Nickel	15 ± 7 [p]	-	-
60	PTC Nitro (Trasis)	>35 [uc]	35000	>97
68	Nitro (ABX)	20 ± 7	-	>99
58b	IS	>30 – 40	4000	>98
49	IS + Cu	>1 [p uc]	290	-
51	Ylide	-	-	-
55	Iodyl	5 – 10 [p]	-	-
32	BPin	12	-	>99

[uc] Uncorrected RCY. [p] Protected [^{18}F]F-DOPA moiety. IS = Iodonium Salt. PTC = Phase-transfer Catalyst

1.7   Conclusion

[^{18}F]F-DOPA **9** is a radiotracer of high interest for diagnosis and evaluation in oncology and central nervous system disorders. Its use has been impeded by the lack of a reliable automated, nucleophilic synthesis, but recent developments are now enabling access to this elusive tracer incorporating more of the requirements outlined for an "ideal synthesis". Improvements in automation of multistep synthesis are providing robust, nucleophilic routes. Furthermore, developments in hypervalent iodine chemistry and

transition metal-mediated fluorinations are allowing fast nucleophilic reactions using bench stable and easily accessible precursors, providing excellent alternatives to the traditional electrophilic route.

1.8   References

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Synthesis of Iodonium Salt Precursors for the Formation of [^{18}F]F-DOPA

1.1 Introduction

The synthesis and utility of iodonium salts for the synthesis of [^{18}F]F-DOPA **9** is an area of substantial interest but has not experienced extensive investigation. Before commencing this research no academic publications were available, whilst scant patent literature was lacking in detail.[1] Therefore, it seemed promising to investigate this avenue for a new precursor and synthesis strategy towards [^{18}F]F-DOPA **9**. Investigation into whether this approach would be suitable for conversion to a solid supported methodology is reported in chapter 3.

1.2 Iodonium salt precursor synthesis

Aims and Objectives

- Produce and test simple iodonium salts for the formation of [^{19}F]fluorobenzene **77** and [^{18}F]fluorobenzene **[^{18}F]77**
- Translate these reactions to the synthesis and testing of iodonium salt precursors for [^{18}F]F-DOPA **9** production
- Assess the possibility for adoption to a solid supported procedure

1.2.1 Synthesis of simple iodonium salts for fluorination

To probe the chemistry for iodonium salt synthesis and fluorination, a number of simple diaryliodonium salt precursors were targeted. This would allow for an understanding of the chemistry to be established before moving on to more elaborate syntheses for the production and testing of [^{18}F]F-DOPA **9** precursors.

Design of iodonium salt precursor:

As mentioned in the introduction (Chapter 1, Pg. 31-22), the regioselectivity of the fluorination reaction is dictated by the electronic and steric properties of the two aryl substituents. With this in mind, the following precursor design was established (Figure

1). The two directing aromatics proposed were chosen for their highly electron rich nature. The high electron density should direct fluorination regioselectively to the other aryl moiety (Pg. 31).
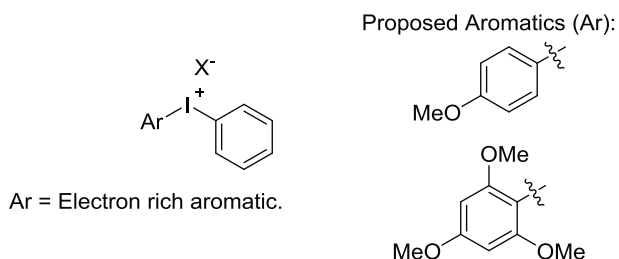
Figure 1 - Design of iodonium salt precursor

Directing aromatic: 4-iodoanisole
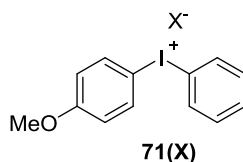
Figure 2 – Target precursor for [^{18}F]fluorobenzene production: 4-methoxyphenyl(phenyl)iodonium salt 71(X).

Two synthetic routes to the salt were investigated. Firstly, similar conditions were used to those reported by Carroll *et al.* for a solid supported synthesis (Chapter 3 Pg. 131). A second route proceeded *via* the anisole derived Koser compound **73** to give the iodonium tosylate (Scheme 1b). Reaction of the Koser reagent **73** with the stannane proceeded quantitatively when performed with a mixture of dichloromethane and 2,2,2-trifluoroethanol. The use of fluorinated solvents to enhance reaction success when using hypervalent iodine species is well reported. It is suggested to occur due to stabilisation of charged intermediates by the polar solvent.[2]

a)

b)
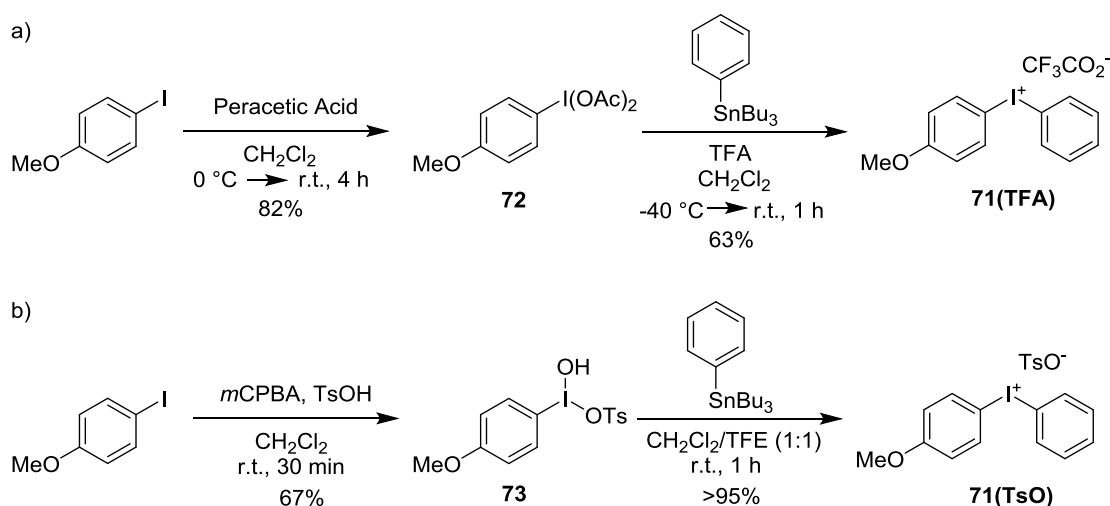
Scheme 1 – Formation of simple diaryliodonium salts 71(TFA) and 71(TsO). a) Synthesis of diaryliodonium trifluoro acetate 71(TFA) via diacetate 72. b) Synthesis of diaryliodonium tosylate 71(TsO) via Koser type reagent 73.

Directing aromatic: 1,3,5-trimethoxy-4-iodobenzene

74(X)
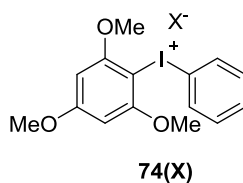
Figure 3 - Target precursor for [^{18}F]fluorobenzene production: 2,4,6-trimethoxyphenyl(phenyl)iodonium salt 74(X).

To probe the directing effect of the electron rich ring, a salt containing a 1,3,5-trimethoxybenzene moiety was also synthesised (Scheme 2).
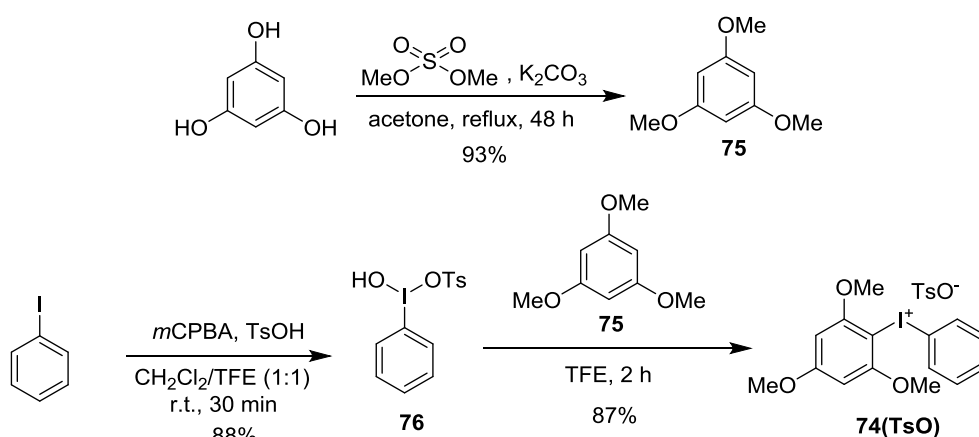
Scheme 2 – Formation of iodonium tosylate 74(TsO) via reaction of Koser 76 with electron rich aromatic 75.

Both Koser reagent formation and reaction with electron rich aromatic 1,3,5-trimethoxybenzene **75** to form iodonium tosylate **74(TsO)** proceeded with good yields.

1.2.1.1 *'Hot' Fluorinations using Automated Modules*

Testing of the simple iodonium salt precursors for the incorporation of [^{18}F]fluoride was now looked into. As mentioned in the introduction, such reactions are carried out using automated systems contained in heavily shielded compartments called 'hot cells'. The figure below shows the modules used for the automated reactions conducted.
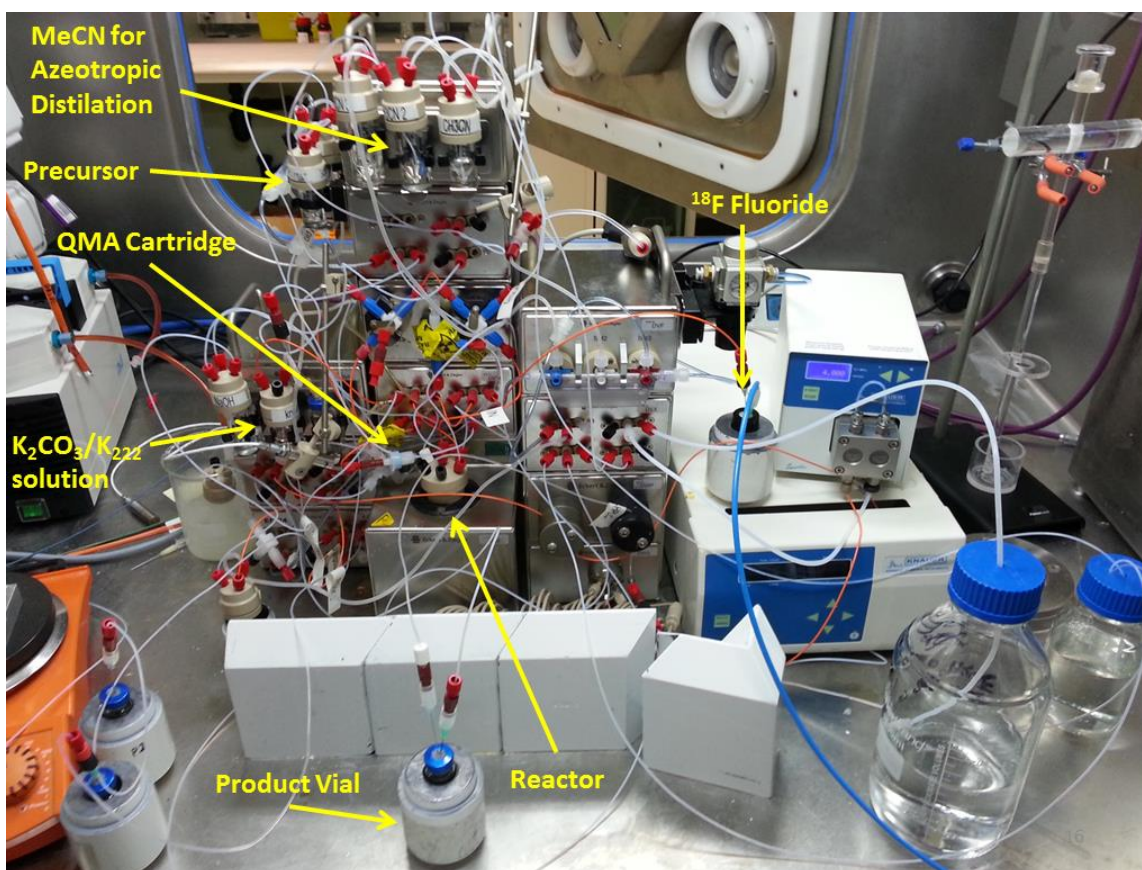
Figure 4 – Eckert and Ziegler modules used for radiofluorination reactions

Manipulation of the different reaction components is achieved using a combination of valves and nitrogen pressure. Figure 5 shows a schematic of the module set up, as seen on the computer controlling the modular apparatus.
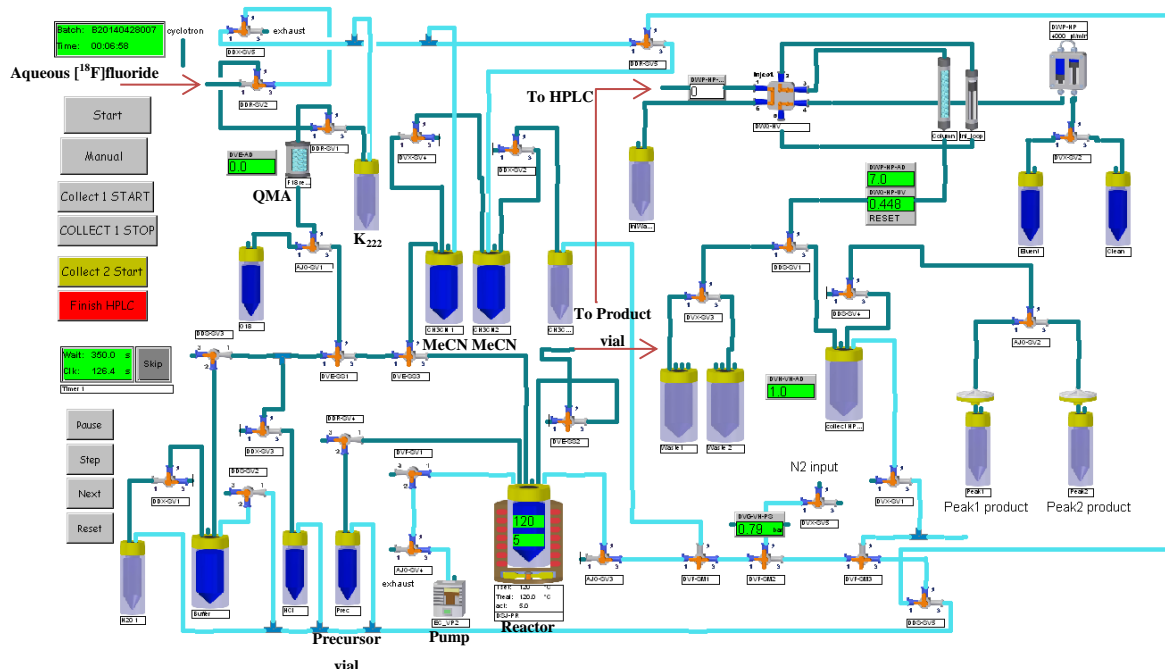
Figure 5 – Schematic of automated apparatus used for radiofluorination reactions

During a standard reaction the following manipulations are carried out:

1. Transfer of aqueous [^{18}F]fluoride (delivered from the cyclotron) to the QMA (anion exchange resin) cartridge where [^{18}F]fluoride is trapped and [^{18}O]water is carried through to a waste vial.

2. A solution of Kryptofix® (K$_{222}$) K$_2$CO$_3$ is passed from its storage vial to the reaction vial via the QMA cartridge. The trapped [^{18}F]fluoride is carried to the reaction vial during this process as a [^{18}F]KF/K$_{222}$ complex in aqueous acetonitrile solution.

3. Azeotropic drying of the [^{18}F]KF/K$_{222}$ is now conducted. This is achieved by heating the reaction and subjecting the contents to vacuum followed by nitrogen flow multiple times. Acetonitrile (1 mL) is then transferred to the reaction vial before the drying process is again commenced. The azeotropic drying is carried out twice (2×1 mL acetonitrile).

4. The precursor and reagents are transferred to the dried [^{18}F]KF/K$_{222}$ complex in the reaction medium and the reaction conducted in a sealed vessel.

5. After completion of the reaction the entire mixture is ejected and analysis conducted to obtain radiochemical recovery (RCR), radiochemical conversion (RCC) and radiochemical yield (RCY). From the product vial, the crude reaction mixture can be transferred to the HPLC injection loop for preparative

purification. Transfer to the injection loop is also possible directly from the reaction vial.

1.2.1.2   Testing of [^{18}F]fluorobenzene precursors

'Hot' fluorination of the two [^{18}F]fluorobenzene **[^{18}F]77** precursors occurred successfully with both electron rich aryl moieties providing excellent directing properties for the fluorination (Table 1). Both directing groups showed complete selectivity for the formation of [^{18}F]fluorobenzene **[^{18}F]77** with no formation of [^{18}F]4-fluoroanisole or [^{18}F]1,3,5-trimethoxy-4-fluorobenzene. In the case of precursor **74(TsO)** it shows that the highly electron rich nature of the aromatic has overcome any directing influence of an '*ortho*-effect' which would direct fluorination for the formation of [^{18}F]1,3,5-trimethoxy-4-fluorobenzene.

Table 1 - 'Hot' fluorination of simple precursors 71(TFA) and 74(TsO) for the formation of [^{18}F]fluorobenzene
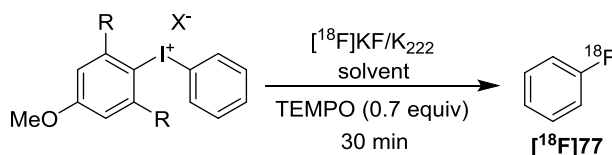
Precursor Scale (mmol)	R	X	Solvent	Conversion (%)*	Recovery (%)	RCY (%)
0.12	H	CF$_3$CO$_2$	MeCN	90	30	27
0.12	H	CF$_3$CO$_2$	toluene/MeCN (2/1)	91	25	23
0.0047(2mg)	H	CF$_3$CO$_2$	MeCN/DMSO (6/1)	0	-	0
0.029(10mg)	H	CF$_3$CO$_2$	MeCN/DMSO (6/1)	20	74	15
0.12	OMe	TsO	MeCN/DMSO (6/1)	91	48	44
0.06	OMe	TsO	MeCN/DMSO (6/1)	93	51	47

*Conversion calculated from HPLC analysis

It is apparent from the results that both precursors provide excellent radiochemical conversion (RCC) of [^{18}F]fluoride to the desired [^{18}F]fluorobenzene product **[^{18}F]77**, without any significant advantage observed for using either precursor. Solvent conditions used thus far do not appear to have an effect on the RCC but certainly can be used to improve the RCY by improving the recovery of activity from the apparatus to the product vial. The use of acetonitrile/DMSO (6:1) as the reaction solvent significantly improved the recovery of activity contributing to the improved RCYs.

The effect of scale is also evident in Table 1. Despite the overwhelming excess of precursor compared to the [^{18}F]fluoride ($\approx 10^8$ equivalents) the reaction does not take place on a 4.7 µmol mmol scale (2 mg) and affords poor conversion on a 29 µmol scale (10 mg). It is only once the precursor is present on 60 µmol scale that the reaction occurs satisfactorily.

Radiochemical conversions were calculated using radio HPLC. When analysis was conducted with radio TLC, radiochemical conversion was diminished. The volatility of the product was assumed to be responsible. This has previously been observed.[3]

1.2.1.3   Oxidation of 1,3,5-trimethoxy-4-iodobenzene

Despite providing a useful comparison to the anisole derived salts **71(TFA)** and **71(TsO)**, the synthetic route used to produce the 1,3,5-trimethoxybenzene derived salt **74(TsO)** is not applicable for the production of the [^{18}F]F-DOPA precursor using the commercially available methyl N-*t*-butoxycarbonyl-3,4-di(*t*-butoxycarbonyloxy)-6-trimethylstannylphenylalanine **82**. Therefore a synthetic strategy for the production of a 1,3,5-trimethoxy-4-iodobenzene Koser reagent **79** was looked into (Table 2).
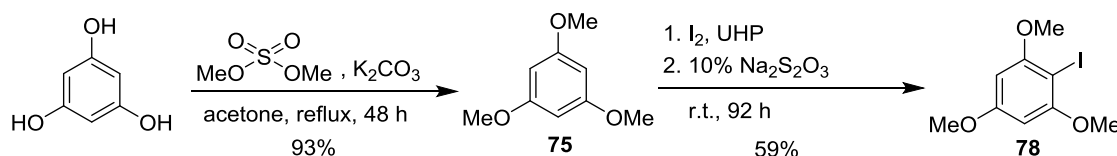
Scheme 3 - Formation of 1,3,5-trimethoxy-4-iodobenzene 78

Table 2 - Conditions for the attempted production of Koser reagent 79
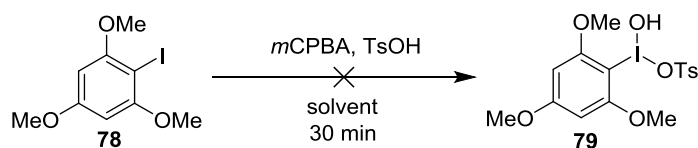
Entry	Temp (°C)	Solvent
1	25	TFE/CH$_2$Cl$_2$ (1:1)
2	25	CH$_2$Cl$_2$
3	0	CH$_2$Cl$_2$

After failure to produce the Koser type compound **79**, attempts to synthesise the corresponding diacetate **80** were conducted. These compounds can show a greater stability to their Koser counterparts.[4][5]

Table 3 - Conditions for the attempted production of 80.
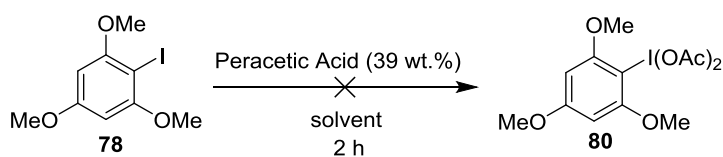
Entry	Temp (°C)	Solvent
1	0	CH$_2$Cl$_2$
2	0 -> 25	CH$_2$Cl$_2$
3	0 -> 25	TFE/CH$_2$Cl$_2$ (1:1)

Diacetate **80** production also proved unsuccessful. Both oxidation to the Koser reagent **79** and diacetate **80** gave complete degradation of starting material and showed no sign of product formation. It is proposed that this is due to the highly electron rich nature of the arene. This would cause the oxidised product to be very unstable. Such problems with electron rich substrates have been reported previously.[4]

1.2.2   Production of [^{18}F]F-DOPA precursor iodonium salts

Synthesis of a precursor derived from the trimethoxybenzene moiety therefore, looked unfeasible. However, the synthesis route using 4-iodoanisole looked appropriate to adapt to the production of a protected DOPA functionalised anisyl iodonium salt **81(X)**. Therefore the following precursor was targeted (Figure 6).
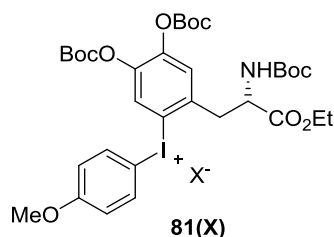
Figure 6 – Target precursor for the production of [^{18}F]F-DOPA 9.

Translation of the methods used for simple iodonium salt synthesis to produce an unsupported [^{18}F]F-DOPA precursor was troublesome. Initial conditions using the diacetate **72** for reaction with stannane **82** in the presence of trifluoroacetic acid were unsuccessful (Scheme 4).

59
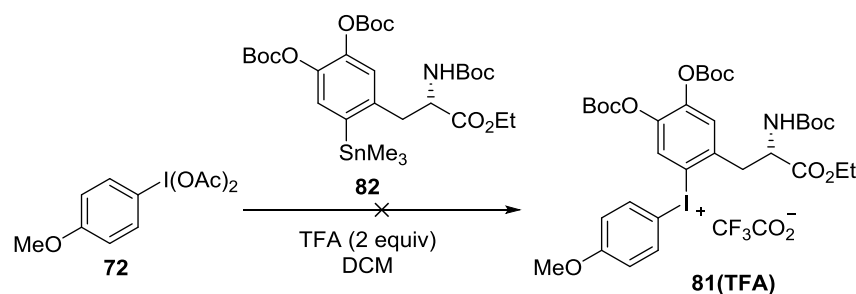
Scheme 4 – Attempts to produce iodonium salt 81(TFA) employing conditions used to produce iodonium salt 71(TFA).

However, analysis of the partially purified (precipitated) product from the reaction of Koser reagent **73** with stannane **82** in dichloromethane (Table 4, entry 1) suggested some iodonium salt formation (Figure 7).
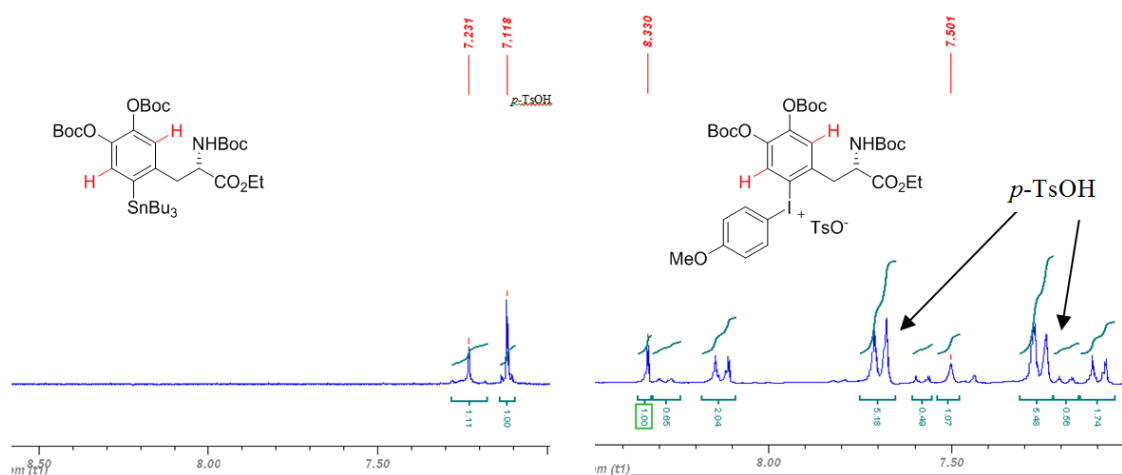
Figure 7 – ^{1}H NMR analysis of the iodonium salt 83(TsO)

Shifts of the aromatic protons on the DOPA aromatic moiety from 7.23 and 7.12 to 8.33 and 7.50 ppm, respectively, suggested the formation of an iodonium salt. However, the isolation of the product was not possible, making characterisation difficult. A number of impurities were still present after precipitation of the salt, the most prominent of which was *p*-toluenesulfonic acid. Different conditions were investigated to see if the reaction would proceed more cleanly (Table 4).

Table 4 – Initial reaction conditions for the production of iodonium salt 81(TsO)
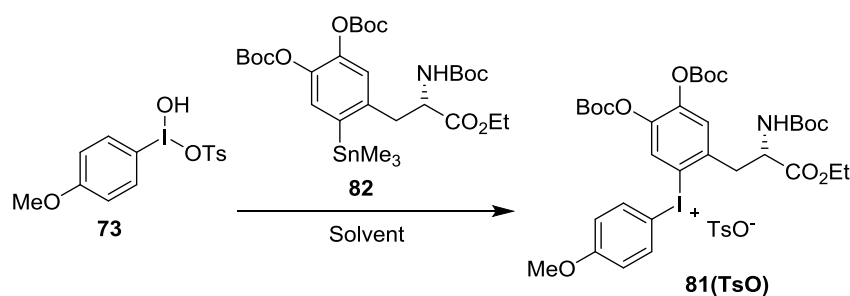
Entry	Reaction Time (h)	Temp (°C)	Solvent	Koser Equiv	TsOH:Salt(81)*
1	12	R.T	CH$_2$Cl$_2$	1.2	4.5:1
2	23	R.T	CH$_2$Cl$_2$	1.5	4:1
3	60	R.T	TFE/CH$_2$Cl$_2$ (1:1)	1.2	14:1
4	7	R.T	TFE/CH$_2$Cl$_2$ (1:1)	1.2	2.5:1
5	5	40	TFE/CH$_2$Cl$_2$ (1:1)	1.2	No Product
6	10	0	TFE/CH$_2$Cl$_2$ (1:1)	1.2	3:1
7	10	0	Toluene/TFE (3:1)	1.2	3:1

*Determined by integration of the crude precipitate ^{1}H NMR

The significant *p*-toluenesulfonic acid impurity could be reduced by lowering the reaction time and temperature but was still a major component of the precipitate. Higher temperatures (Table 4, Entry 5) are detrimental to the reaction. Washing the precipitated crude product with water did not remove any of the *p*-TsOH impurities.

Entries 3 to 7 in Table 4 utilise a fluorinated solvent. This is due to a number of publications that have reported such solvents to be beneficial in reactions involving hypervalent iodine species.[2] Whilst observed for the synthesis of simple iodonium salt **71(TsO)** (Scheme 1), such benefits were not seen for the production of **81(TsO)**.

Attempted Purification by Recrystallization

A wide range of recrystallization conditions were attempted without success, including one method outlined below (Scheme 5). The procedure had been used successfully for the purification of other iodonium salts bearing complex functionality.[6]

a)

b)
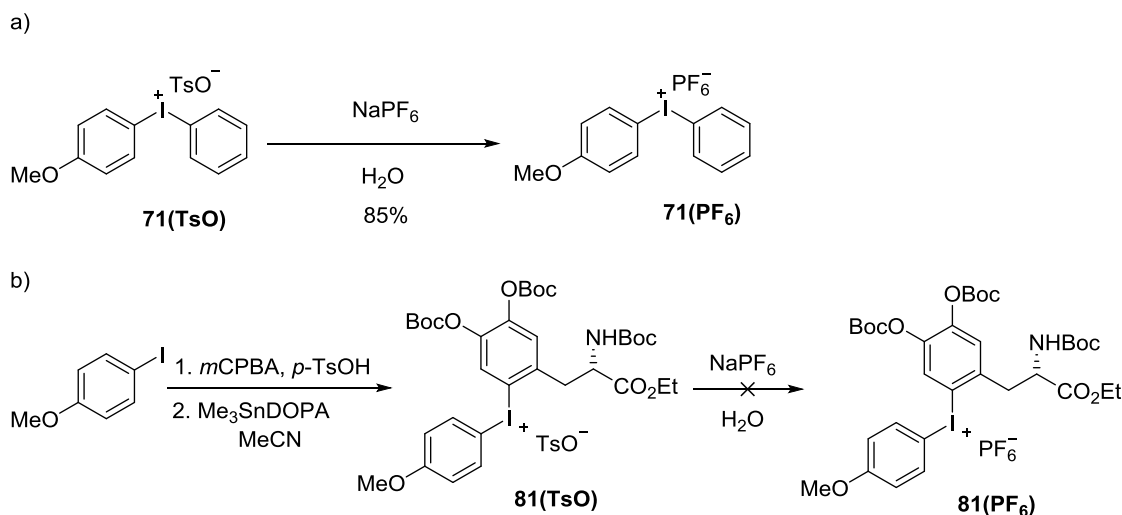
Scheme 5 – Counter ion exchange and recrystallization of iodonium salts from aqueous solutions of NaPF$_6$ (0.3 M).

Recrystallization by counter ion exchange in water is an attractive purification strategy and worked well for the simple salt **71(TsO)** (Scheme 5a). However, application for the work up of the functionalised salt **81(TsO)** was unsuccessful, presumably due to the more lipophilic nature of the protecting groups (Scheme 5b).

1.2.3 Alternative Syntheses for Precursor Formation

Due to problems isolating the current precursor, other options for precursor formation were considered. Two different approaches were investigated.

The first route was to alter the reactants and oxidise the iodoDOPA compound **83** for reaction with an electron rich aromatic compound (Scheme 6). The second strategy was to alter the target molecule slightly in the hope that an alternative precursor would be more easily isolated. An obvious choice for alteration was the 'non-participating' aryl ring as this would be easily implemented from similar starting materials (Scheme 7). The 2-iodo thienyl directing group was chosen due to its common utility in the synthesis of other iodonium salt precursors used in [^{18}F]fluorination reactions.[7,8]

1. The formation of a hypervalent protected iodoDOPA reagent for the reaction with an electron rich arylstannane.
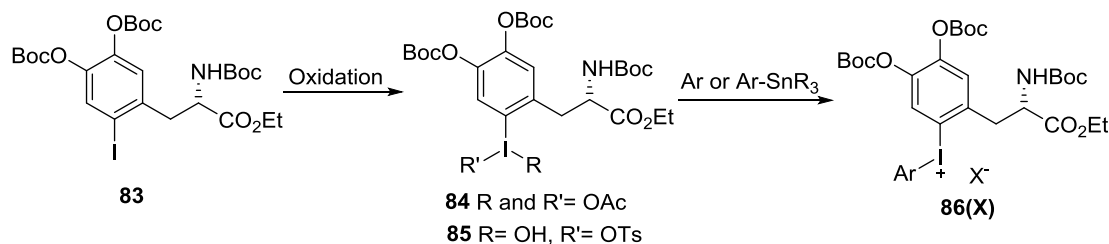
Scheme 6 – Proposed synthesis of the iodonium salt precursor 86(X) via oxidation of an iodoDOPA moiety 83.

2. The use of an alternative electron rich directing group   .
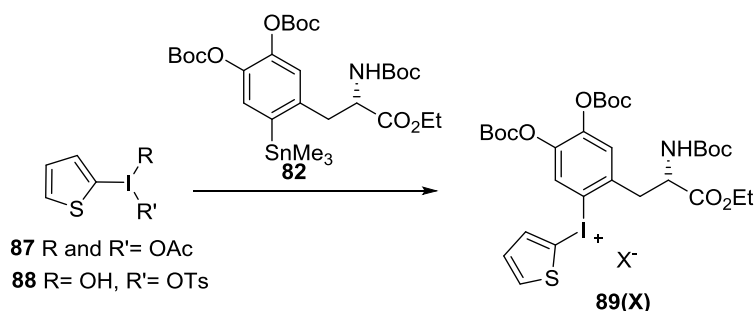
Scheme 7 – Proposed synthesis for an iodonium salt precursor bearing a 2-thienyl directing group 89(X)

1.2.3.1 *Formation of a hypervalent protected iodoDOPA reagent*

Formation of the iodonium salt precursor via oxidation of the iodoDOPA moiety would provide a more advantageous synthesis route. The main advantage would be the avoidance of the undesirable stannylation step used in the synthesis of stannane **82**. It would also allow for salt formation with electron rich aromatics not available for synthesis via the DOPA stannane **82**, i.e. with 1,3,5-trimethoxybenzene. The strategy attempted is shown in Scheme 9. Formation of the protected iodoDOPA compound **83** was achieved using a synthetic route reported by Dolle *et al.*[9]
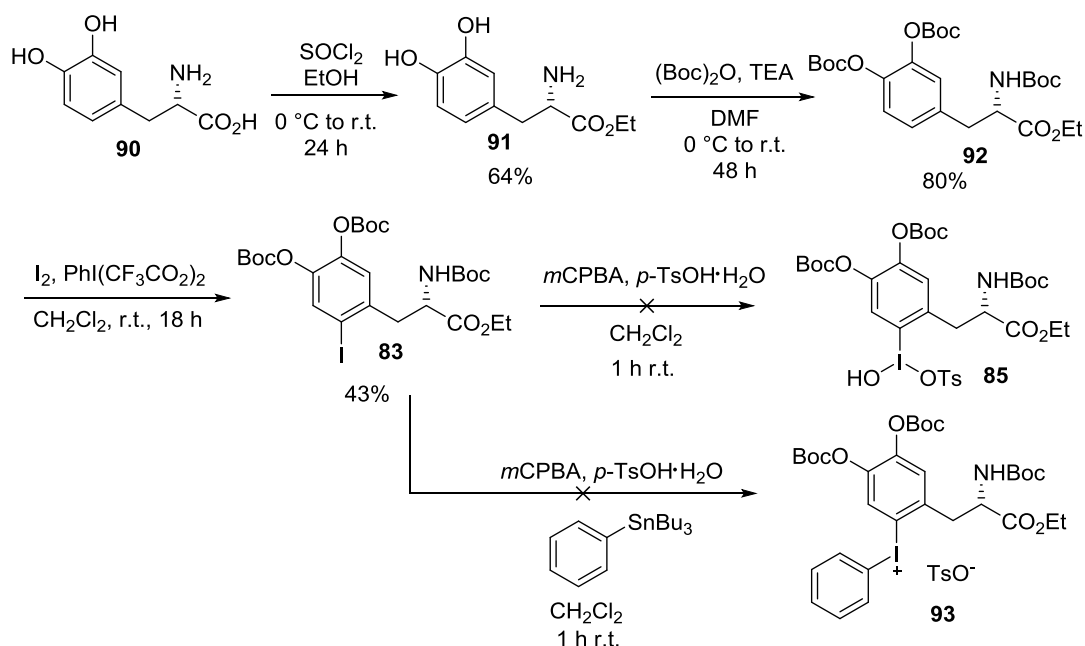
Scheme 8 – Synthesis and attepted oxidation of protected iodoDOPA moiety 83

After formation of the protected iodoDOPA moiety **83**, the compound was subjected to oxidative conditions with the aim to produce a hypervalent species, i.e. the Koser reagent **85**, diacetate **84** or iodonium salt **93**.

These preliminary investigations proceeded unprofitably. Therefore, further investigation was at this point abandoned, as the second strategy under investigation (changing the electron rich aryl group) was providing more promising results (see below). Further investigation into the methodology hypothesised was looked into later and is discussed in section 1.3.15 (Oxidation of IodoDOPA, Pg. 90).

1.2.3.2   *Use of an alternative electron rich directing group*

The use of a thiophene directing group was chosen due to its electron rich nature and previous utility in successful iodonium salt precursors for ^{18}F labelling.[14, 21]

The reaction of the stannane **82** with 2- (diacetoxyiodo)thiophene showed improvements with the reaction showing fewer impurities in the crude ^{1}H NMR. However, the *p*-TsOH impurity was still present. Investigation into whether the impurity would remain after exchange of the counter ion was conducted. Thankfully the counter ion exchange (conducted by washing a dichloromethane solution of the crude salt with a saturated aqueous solution of KOTf) resulted in isolation of the pure iodonium triflate precursor **89(TfO)**.

A protocol was devised for the purification and isolation of the iodonium salts. The iodonium salt was first triturated before the precipitated crude was dissolved in dichloromethane. The solution was then washed with aqueous KX (to introduce the counter ion X) or water (to obtain the iodonium tosylate). A second trituration then provided the pure iodonium salt **89(X)**.
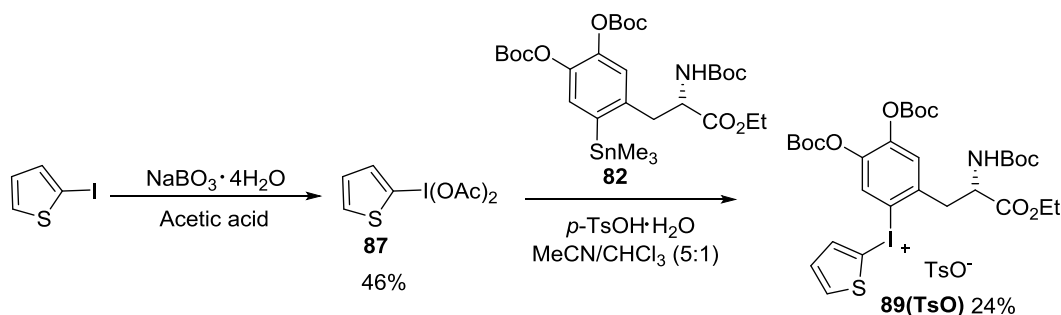
Scheme 9 – Synthesis of 2-thienyliodonium tosylate 89(TsO) via diacetoxyiodothiophene 87.

Further optimisation of salt formation is shown in Table 5 and leads to an acceptable yield of 44%.

Table 5 – Optimisation for the synthesis of 89(TsO)
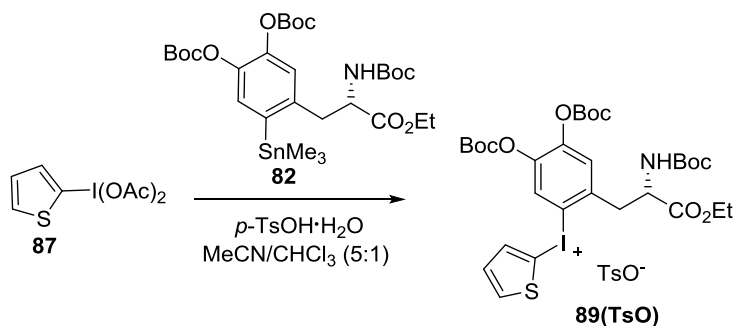
Entry	RT (h)	Temp °C	Diacetate / p-TsOH Equiv	Yield (%)
1	18	reflux	1.02	24
2	24	50	1.02	25
3	18	reflux	1.2	37
4	18	reflux	1.5	44
5ª	18	reflux	1.5	24

ª Reaction of isolated Koser rather than *in situ* produced Koser reagent.

When using 1.02 equivalents of both, the diacetate and *p*-TsOH, some stannane **82** remained unreacted. By increasing the equivalents of the Koser derivative (1.2 and 1.5 equivalents), a higher conversion of stannane to the diaryliodonium salt was observed (Table 5, entries 3 and 4). The addition of 1.5 equivalents **72** was found to be the

optimum as the addition of larger amounts resulted in purification difficulties. The reaction with *in situ* produced Koser reagent **73** proceeded much better than when using the isolated Koser compound **73**.

<u>Attempt to produce iodonium triflate precursor **89(TfO)** directly</u>

As isolation of the pure iodonium triflate **89(TfO)** was possible after counter ion exchange, it was briefly investigated if salt formation from *in situ* produced 2-(bistriflateiodo)thiophene was possible. Unfortunately, this highly reactive species did not undergo successful reaction with arylstannane **82** (Scheme 10).
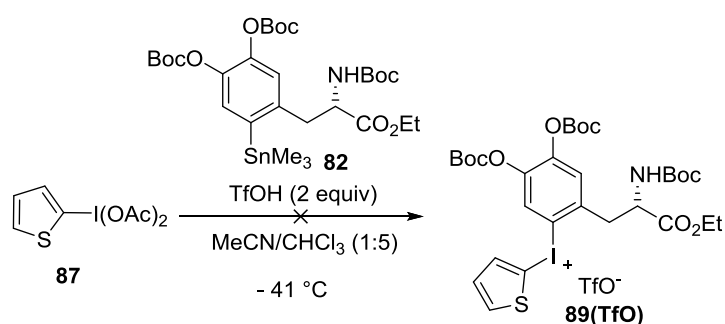
Scheme 10 – Attempted salt 89(TfO) formation from *in situ* produced 2-iodo(bistriflate)thiophene

1.2.3.3   *Precursor Stability Testing*

It was decided that the precursor's stability should be tested in a number of common solvents to prevent future use of unsuitable solvents for the fluorination reaction and other manipulations (Scheme 11).

Solvent = MeOH, Et$_2$O, MeCN, DMSO, CHCl$_3$, Benzene or DMF
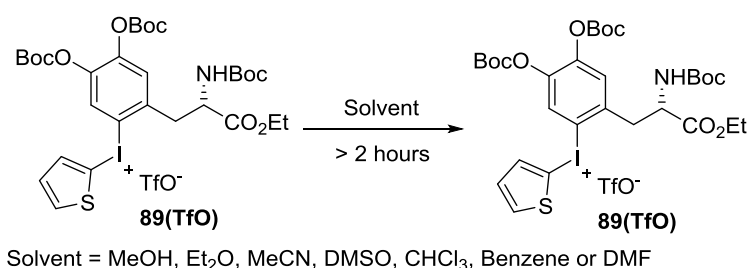
Scheme 11 – Precursor 89(TfO) stability in various solvents

Iodonium triflate **89(TfO)** proved to be stable in all solvents tested, showing convenient properties for its potential utility as a tracer precursor.

1.2.4   Preliminary Testing of the Precursor

Testing the precursor's suitability for fluorination was subsequently conducted. Firstly, 'cold' fluorination was looked into using ^{19}F NMR analysis to provide information about the regioselectivity of the fluorination.

1.2.5   'Cold' Fluorination of Iodonium Precursors

Preliminary testing of the precursor for the formation of protected [^{19}F]F-DOPA **95** was successful with ^{19}F NMR experiments showing full selectivity for fluorination at the DOPA functionalised aromatic.

A range of solvents were tested to discover if the regioselectively of the fluorination would be affected. This was carried out for both the simple and functionalised iodonium salts (Table 6). The use of the radical scavenger TEMPO is due to reports of improved yields and reproducibility when the fluorination is conducted with this additive.[10] It is proposed that the radical scavenger helps to prevent the breakdown of the iodonium salt via radical pathways.

Table 6 – 'Cold' fluorination selectivities for F-DOPA precursor 89(TfO) and fluorobenzene precursor 96(TfO) in different solvents

89(TfO) R=Protected DOPA moiety
96(TfO) R=H

94

95 R=Protected DOPA moiety
77 R=H
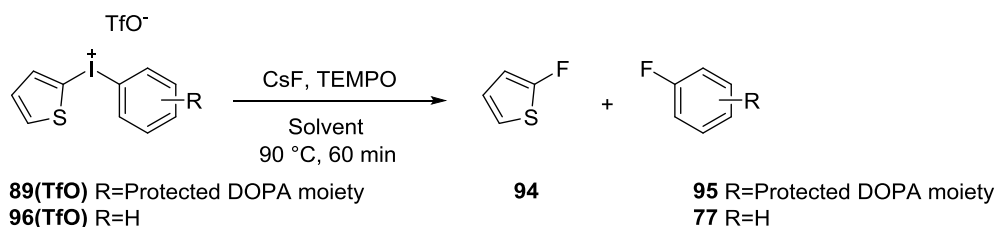
Solvent	Product Ratio for 89(TfO) (94:95)[a]	Product Ratio for 96(TfO) (94:77)[a]
Acetonitrile	0:100	0:100
DMSO	Neither product observed	0:100
DMF	0:100	0:100
Benzene	0:100	0:100
PEG[b]	Neither product observed	Neither product observed

[a] Compounds detected by ^{19}F NMR. [b] PEG = Polyethylene glycol (M$_n$ 380-420)

Fluorination of the simple iodonium triflate **96(TfO)** with caesium fluoride in the presence of TEMPO proceeded with full selectivity for fluorobenzene production in all solvents except for polyethylene glycol (PEG) in which neither product was observed. Fluorination of the functionalised iodonium triflate **89(TfO)** also proceeded with excellent selectivity in the majority of solvents. Reactions in acetonitrile, DMF and

benzene all proceeded with complete selectivity for selective fluorination at the DOPA functionalised aromatic. In contrast to the simple iodonium salt reactions, neither product was observed when the reaction was performed in DMSO with the functionalised precursor. PEG again proved to be an unsuitable solvent for the fluorination.

Confirmation of the iodonium triflates' suitability as a precursor for the production of protected F-DOPA species **95** in the 'cold' fluorination experiments provided a proof of concept for production of [^{18}F]DOPA using the synthesised precursor. It was now important to test the precursor's suitability for fluorination of the DOPA aromatic under 'hot' fluorination conditions.

1.2.6   'Hot' Fluorination of Iodonium Precursors

Fluorination with [^{18}F]fluoride proved unsuccessful (Table 7). These reactions were monitored by radio TLC and showed no conversion of [^{18}F]fluoride to any non-polar ^{18}F labelled product.

Table 7 - Unsuccessful [^{18}F]fluorination of isolated precursors 89(Br) and 89(TfO)
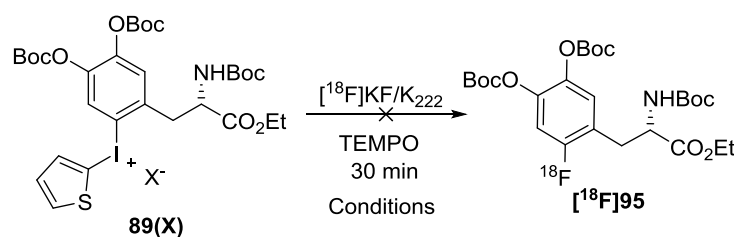
Counter Ion (X$^-$)	Temperature (°C)	Solvent
TfO$^-$	90	MeCN/DMSO (6:1)
TfO$^-$	90	MeCN/DMSO (3:1)
Br$^-$	90	MeCN
TfO$^-$	130	Toluene

1.2.7   Potential Alterations for New Precursor Design

With a number of conditions proving unfruitful, a careful analysis of the precursor was conducted and a number of changes looked plausible to test (Figure 8).
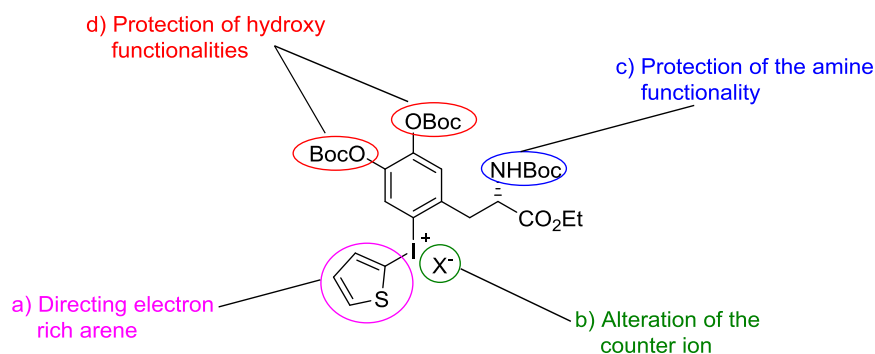
Figure 8 – Possible changes to the iodonium salt precursor

Alterations to be considered for precursor design:

a) Investigation into the effect of the 'non-participating' arene substituent on the fluorination reaction could also be conducted. The ideal directing group is not always predictable: Despite anisyl and thienyl groups commonly being used to direct nucleophilic fluorination, it has been shown that electron density of the directing group is not always proportional to the success of the fluorination reaction.[11]

Tolyl and mesityl precursors **97(X)** and **98(X)** were targeted as new potential precursors along with the original anisyl directing group precursor **81(X)** (Figure 10).
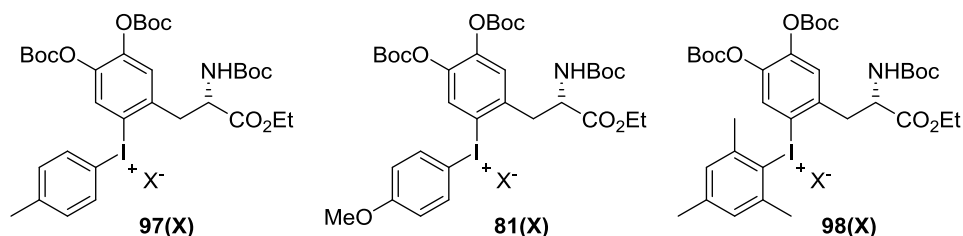
Figure 9 - Possible targets to probe the directing group effect on the precursors efficacy

The tolyl directing group was considered a suitable avenue of investigation due to its successful use in the synthesis of [^{18}F]Flumazenil **46** (Scheme 13).[11] Here, it outperforms anisyl, thienyl and other directing aromatics to produce the highest radiochemical yield.
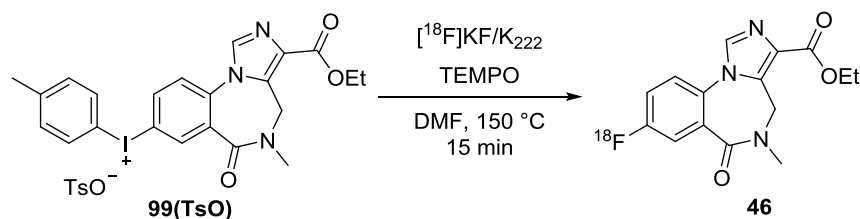
Scheme 13 – Formation of [^{18}F]Flumazenil 46 via fluorination of iodonium salt 99(TsO) in DMF.[11]

The mesityl aromatic exhibits a considerable *ortho* effect and hence would not generally be considered suitable for use as a 'non-participating' directing group. However, Sanford *et al.* showed that the mesityl group can be used to direct fluorination to less bulky aromatics in the precence of a copper catalyst.[12] Hence, the mesityl substituted precursor was also targeted. It is noteworthy that subsequent to these investigations, the methodology was adapted for the radiofluorination of a number of aromatic moieties by Sanford and Scott.[13]

The anisyl functionalised salt **81(X)** was targeted for those reasons already mentioned, namely due to its high electron density and utility in many other iodonium salt precursors.

b) The ability to change the counter ion of the iodonium salt during the work up allows for facile preparation of precursors with a variety of anions. Investigation into the effect of the counter ion would be important, although this can be considered more of a 'fine tuning' alteration. Optimisation of other factors such as reaction conditions were a priority.

c) It was considered that the full protection of the amine group might prove more suitable, as the presence of the N-H proton may have been interfering with the fluorination. Two simple strategies were available. DiBoc protection of the amine could be accomplished, or if a more robust protecting group was desired; phthalamide protection could be used (Figure 10).
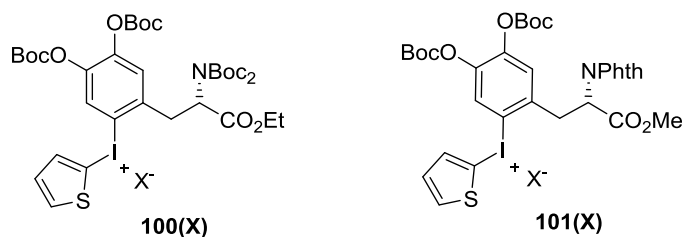
Figure 10 - Possible targets to test the influence of the amine protection strategy

d) The *O*-Boc protection of the hydroxyl functionalities provides an accessible and commercial stannane for the precursor synthesis. However, it was envisaged that changing the protection to a substituent that would further decrease the electron density at the aromatic would be beneficial. TFA protection was considered as a candidate for this protection.

It was also considered that *O*-Me protection may deliver a more robust protection strategy for the precursor. This adaption would obviously come with the disadvantage of increased electron density at the aromatic desired for fluorination; hence, the regioselectivity of the fluorination would need to be investigated for such a precursor.

1.2.8   Alternative 'Non-Participating' Arene Precursors (a)
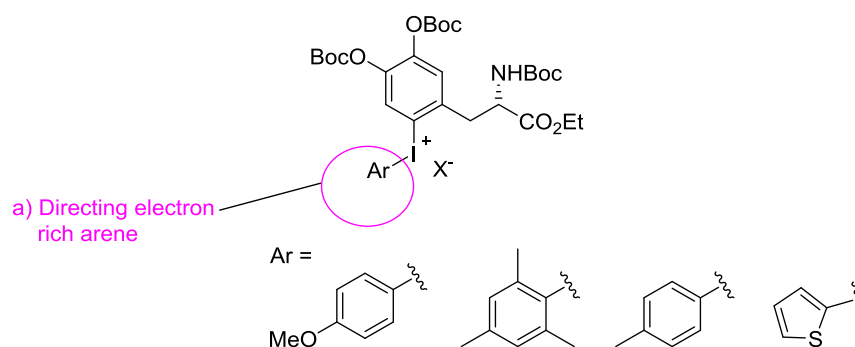
Figure 11 – **Target precursors to probe the effect of the 'non-participating' arene functionality.**

1.2.9   Formation of salts with alternative directing groups

The first alteration looked into was the synthesis of iodonium salt precursors with alternative directing aromatics.

The first step was formation of the appropriate diacetate compounds and successful production of both hypervalent iodine compounds **102** and **103** was achieved using conditions adapted from the literature.[14]

102 R = H: 68 %
103 R = Me: 69 %
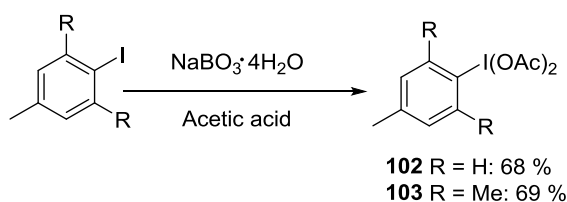
Scheme 14 – Diacetate formation of 102 and 103

102 R = H
103 R = Me

97(TsO) R = H
98(TsO) R = Me

97(TfO) R = H: 59%
98(TfO) R = Me: 0%
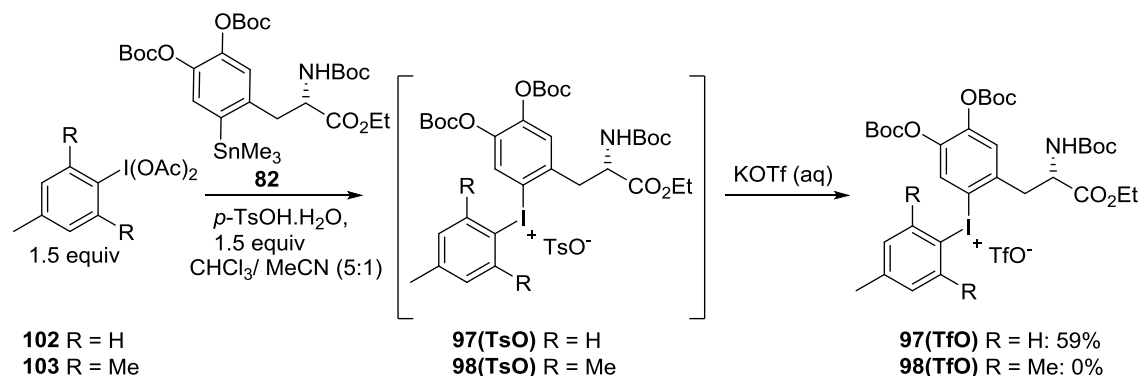
Scheme 15 – Production of salts with alternative 'directing' arenes.

Using the optimised conditions production of precursors with a tolyl and mesityl directing group were investigated. This was successful for the tolyl salt **97(TfO)** but the pure mesityl salt **98(TfO)** could not be isolated (Scheme 16).

Using the optimised conditions, the anisyl salt could also be produced and isolated from both the Koser **73** and diacetate **72** starting materials in 37% and 30% yield, respectively (Scheme 16).

a)

72

1. *p*-TsOH·H$_2$O

2. SnMe$_3$DOPA **82**

3. KX (aq)

81(X)

37%

b)

73

1. SnMe$_3$DOPA **82**

2. KX (aq)

81(X)

30%
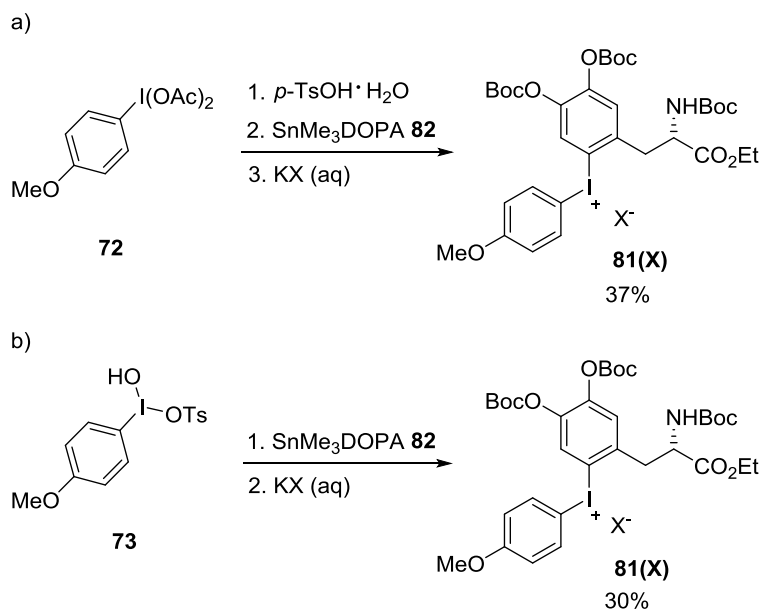
Scheme 16 – Formation of anisyl salt 81(X). a) Reaction of *in situ* produced Koser reagent 73 with arylstannane 84. b) Reaction of preformed Koser reagent 73 with arylstannane 82.

Interestingly, the reaction proceeded with higher yields when the stannane was reacted with the *in situ* produced Koser reagent (compound **72** and *p*-toluenesulfonic acid) rather than preformed Koser reagent. This was also found to be the case for the thiophene derived salts (Table 5). It should be mentioned that diacetate **72** was now produced under improved conditions reported by Kraszkiewicz *et al.*[15] (Chapter 4, Pg. 164).

1.2.10 Alteration of the counter ion (b)

b) Alteration of the counter ion
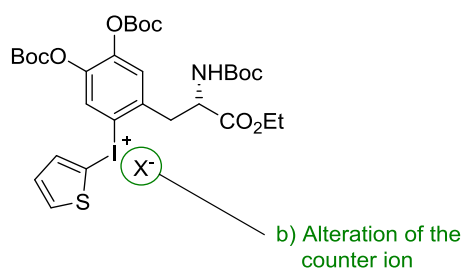
A number of counter ion exchanges had already been carried out previously and could be extended to those shown below (Scheme 17). It should be mentioned that exchange to the perchlorate anion did not proceed using the conditions below, but could be achieved using an exchange method developed by Dinkelborg *et al.*[8] Here a reverse phase cartridge is used to trap the salt **89(TsO)** and to perform the exchange. The ligand

exchange is characterised by the disappearance of the tosylate signals in the ^{1}H and ^{13}C NMR.
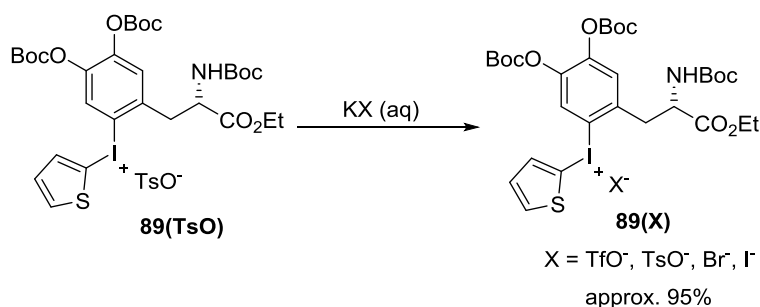
Scheme 17 - Anion Exchange

1.2.11 Suitability of Precursors Bearing Alternative Directing Arenes.

Testing the suitability of the newly designed and produced iodonium salt precursors with altered directing arenes was conducted using the 'cold' fluorination conditions. Precursors with different counter ions were also tested. Results are shown in Table 8.

Table 8 – 'Cold' fluorination of iodonium precursors bearing different directing arenes

89(X) a : Ar = 2-thienyl
81(X) b : Ar = 4-anisyl
98(X) c : Ar = mesityl
97(X) d : Ar = 4-tolyl
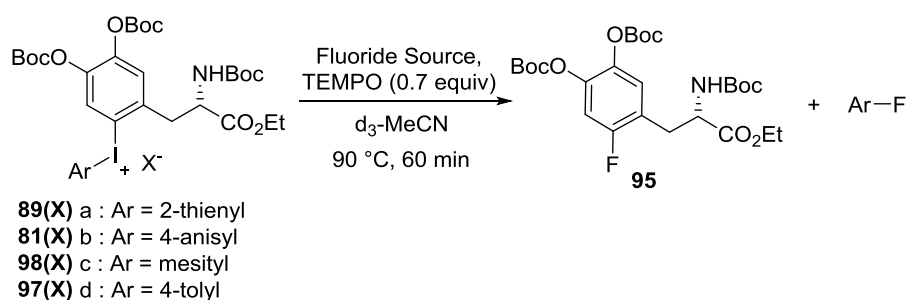
Entry	Ar	X	F⁻ Source	Product Ratio (95:Ar-F)[a]
1	d	TfO	CsF	100:0
2	c[b]	TfO	CsF	Neither product observed
3	b	TfO	CsF	100:0
4	a	TfO	KF/K$_{222}$	100:0
5	a	Br	CsF	100:0

[a] Compounds detected by ^{19}F NMR. [b] Impure product used due to isolation difficulties.

Use of the impure mesityl salt **98(TfO)** did not provide fluorination products for fluorination at either the DOPA or the mesityl moiety. However, the use of the other purified precursors was successful. All directing aryl groups produced the fluorinated DOPA compound **95** with full regioselectivity, as determined by ^{19}F NMR.

For the tolyl functionalised salt the ^{19}F chemical shift of both possible fluorinated products (**95** and 4-fluorotoluene) were very similar (literature value for protected F-DOPA **95** = −117.6 ppm in CDCl$_3$,[16] literature value for 4-fluorotoluene = −118.1 ppm in CDCl$_3$[17]). Therefore a reference sample of 4-fluorotoluene was added to the NMR reaction mixture. This confirmed that 4-fluorotoluene was not produced in the reaction (chemical shift for added 4-fluorotoluene = −120.5 ppm).

Changing the fluoride source to KF/K$_{222}$ for the fluorination of iodonium salt **89(TfO)** did not change the reaction outcome. Fluorination of the thiophene iodonium triflate precursor **89(TfO)** with CsF has been described previously (Table 6). Alteration of the counter ion to the corresponding bromide **89(Br)** also did not affect the reaction.

Mechanistic Investigations Using Thienyl Salt **89(X)**

As such fluorination reactions are proposed to proceed via formation of an iodonium fluoride intermediate, it was investigated into whether such an intermediate **89(F)** could be detected. The reaction reagents were combined and warmed beneath the decomposition temperature of the salt (Scheme 18).
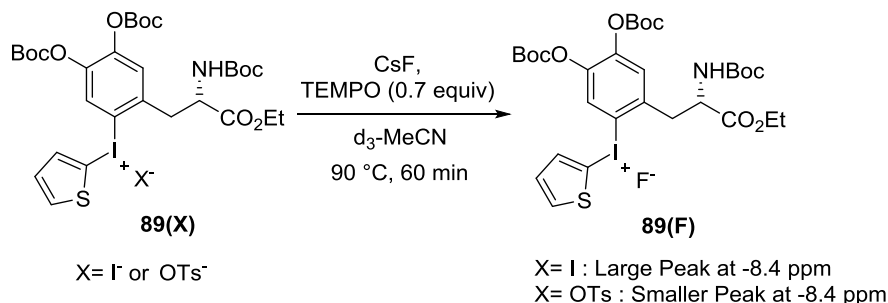
Scheme 18 – Ligand exchange to iodonium fluoride 89(F) from its corresponding iodide and tosylate salts

Iodonium tosylate **89(TsO)** and iodonium iodide **89(I)** were tested. Both precursors showed evidence for ligand exchange to the iodonium fluoride giving characteristic peaks in the ^{19}F NMR at −8.4 ppm.[6] Ligand exchange appeared to proceed more effectively with iodonium iodide **89(I)**. This stands in agreement with the literature, as the tosylate anion is reported to be a poor counter ion for fluorination reactions.[8,18]

These results inspired variable temperature ^{19}F NMR investigations to elucidate the temperatures required for intermediate and product formation.

1.2.11.1 Variable temperature investigations

To gain a better insight into how the fluorination was proceeding, variable temperature ^{19}F NMR was conducted. It was envisaged that the formation of intermediates could be visualised and a better understanding of the temperature dependence of the reaction could be attained (Table 9).

Table 9 - Variable temperature NMR analysis of the fluorination reaction with CsF
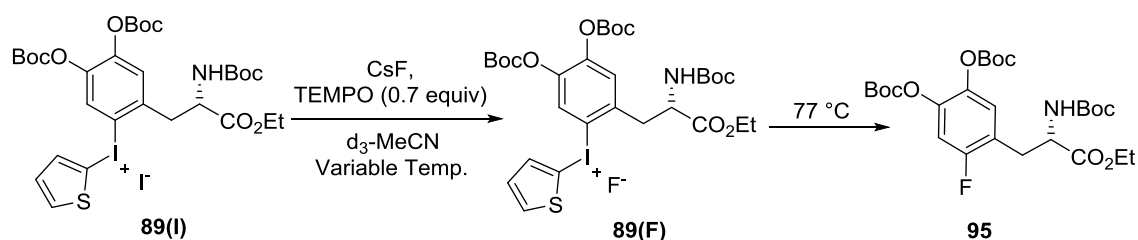
Time (min)	Temp (°C)	Analysis*
0-30	50	-8.4 ppm (iodonium fluoride **89(F)**)
30-45	55	-8.4 ppm (iodonium fluoride **89(F)**)
45-60	55	-8.4 ppm (iodonium fluoride **89(F)**)
60-75	60	-8.4 ppm (iodonium fluoride **89(F)**)
75-90	65	-8.4 ppm (iodonium fluoride **89(F)**)
90-105	70	-8.4 ppm (iodonium fluoride **89(F)**)
105-150	77	-8.4 ppm (iodonium fluoride **89(F)**) and -119 ppm (**95**)

*Recorded after time interval at temperature displayed

The results gave strong evidence for the formation of iodonium fluoride **89(F)** before thermal decomposition of the salt to yield fluorinated product **95** begins at 77 °C.

Figure 12 shows the ^{19}F NMR obtained at 60 °C, 70 °C and 77 °C.
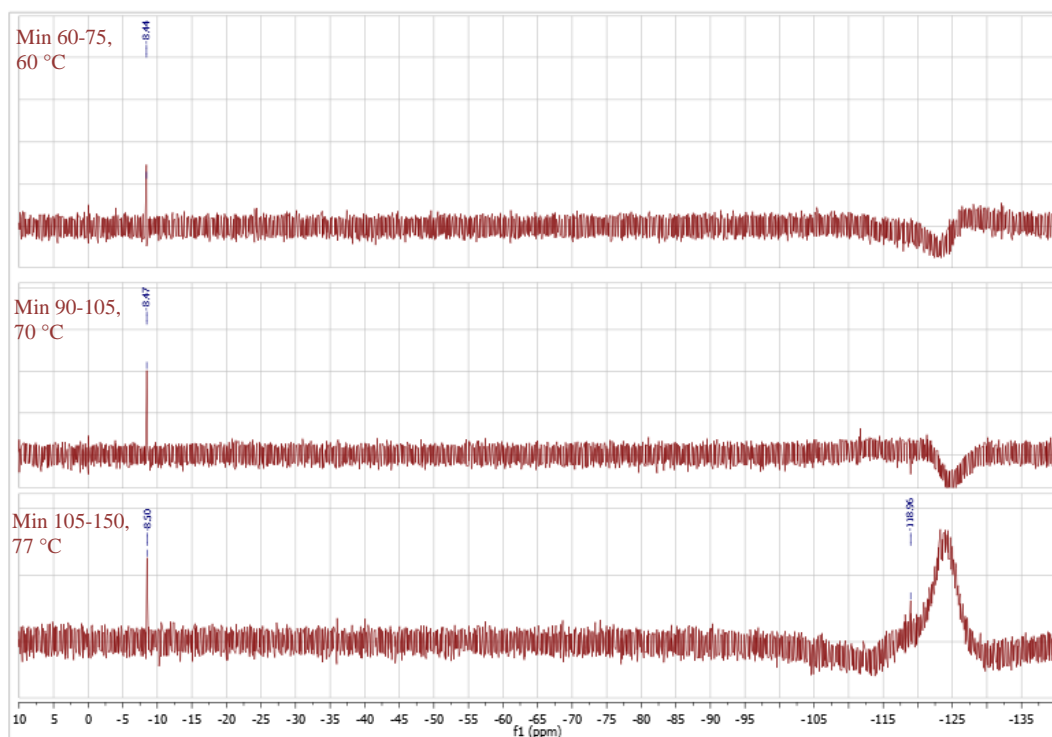
Figure 12 – Variable temperature analysis for the fluorination of 89(I) with CsF

1.2.12 Alternative protection of the amine (c)
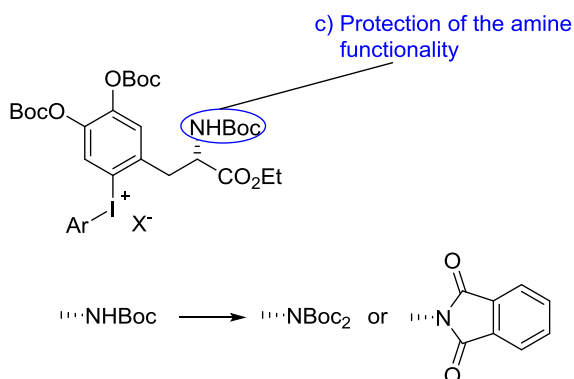
Figure 13 – Possible alterations to the amine protection strategy of the precursor

It was considered that the N-H proton on the monoprotected amine may be interfering with the radiofluorination. Therefore, it was decided that iodonium salt precursors with alternative full protections would be synthesised in order to test this hypothesis. Most easily adapted to the current synthesis was the production of a di-Boc protected amine. Another alternative protection was the phthalimide protection.

1.2.12.1 Di-Boc Protected Amine
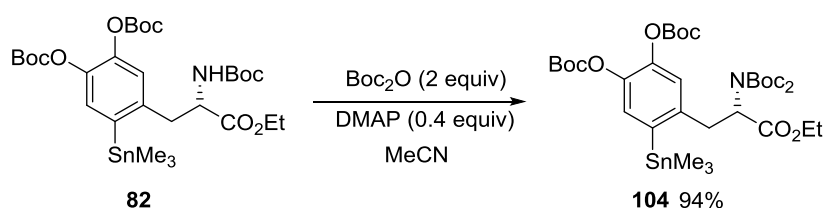
Scheme 19 – Synthesis of stannane 104 for the formation of a precursor with a fully protected amine

Synthesis of the tetraBoc stannane **104** was achieved by further protection of the already available triBoc stannane **82**. The reaction proceeded in high yield in the presence of catalytic 4-(dimethylamino)pyridine (DMAP). TetraBoc aryl stannane **104** was then used for the formation of tetraBoc protected salts.

1.2.12.2 Formation of TetraBoc Protected Iodonium Salt Precursors

Firstly reaction with 4-iodo(diacetate)toluene **102** was investigated for the formation of tolyl functionalised precursor **105(TfO)**.
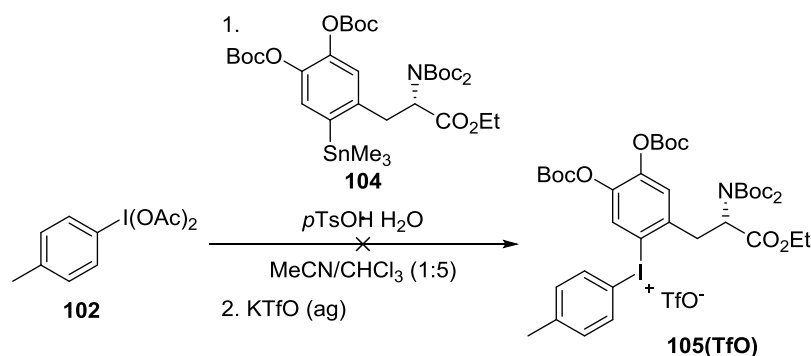
Scheme 20 - Attempts to synthesise tolyliodonium salt 105(TfO) with a fully protected amine

Unfortunately, despite the impure product being observed in the crude, compound **105(TfO)** could not be isolated. Furthermore, decomposition of the product occurred after approximately 30 minutes in solution. This significant change in stability for the tetraBoc salt is surprising.

Reaction of tetraBoc aryl stannane **104** with 2-iodo(diacetate)thiophene **87** however was more successful. Optimisation of the reaction is shown in Table 10. The pure thienyl salt **100(TsO)** could be obtained in reasonable yield using 1.5 equivalence of *in situ* produced Koser reagent. Increasing the equivalence resulted in deprotection of one of the *N*-Boc groups (Table 10, Entry 5). Again the presence of TFE was detrimental to the reaction (Table 10, Entry 3). Iodonium bromide **100(Br)** could also be obtained directly by washing with KBr rather than KI (Table 10, Entry 6).

Table 10 – Optimisation for the formation of Tetraboc protected iodonium salt precursors
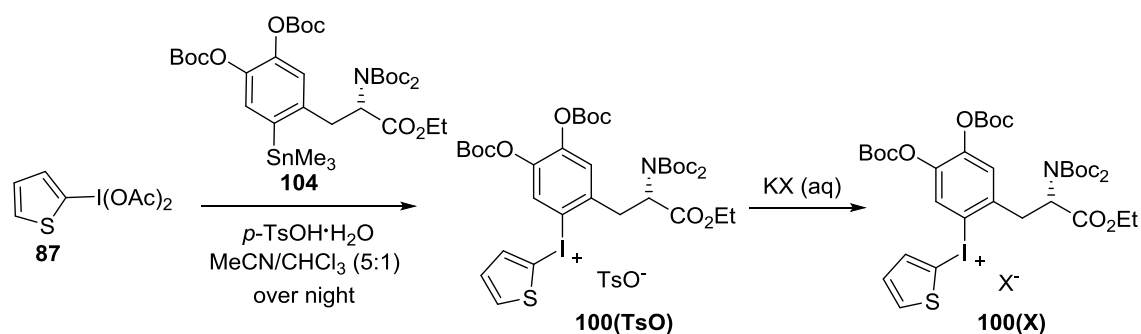
Entry	X=	Temp (°C)	Solvent	Diacetate Equiv	Yield (%)
1	I	reflux	MeCN/CHCl$_3$ (1:5)	1.02	8
2	I	reflux	MeCN/CHCl$_3$ (1:5)	1.2	14
3	I	reflux	MeCN/DCM/TFE (1:2.5:2.5)	1.2	-
4	I	reflux	MeCN/CHCl$_3$ (1:5)	1.5	29
5	I	reflux	MeCN/CHCl$_3$ (1:5)	2.0	-
6	Br	reflux	MeCN/CHCl$_3$ (1:5)	1.5	20

The use of the optimised conditions with 4-(diacetoxyiodo)anisole **72** as the starting material also produced the anisyl tetraboc salt **106(X)** in acceptable yields (Scheme 21).
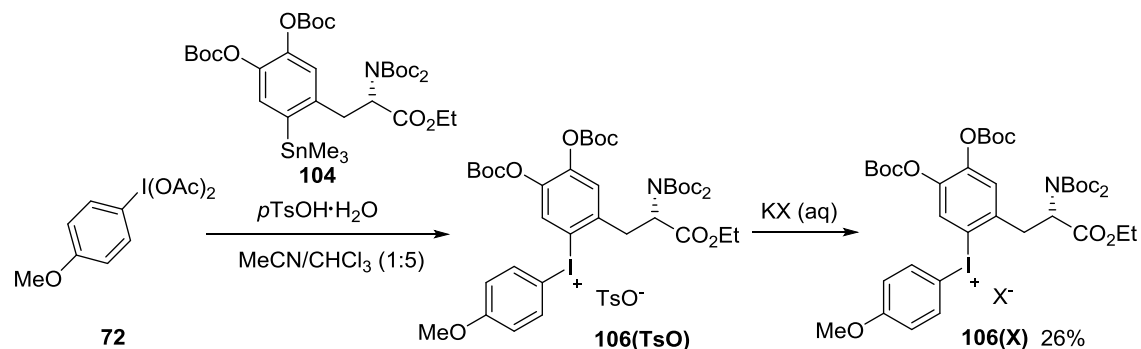
Scheme 21 - Synthesis of an anisyl iodonium salt 106(X) with a fully protected amine

1.2.12.3 Phthalimide Protected Amine

After successful production of tetraBoc protected precursors **100(X)** and **106(X)**, a strategy for the formation of a phthalimide protected precursor was looked into. Initially, the appropriate aryl stannane **111** was synthesised (Scheme 22).
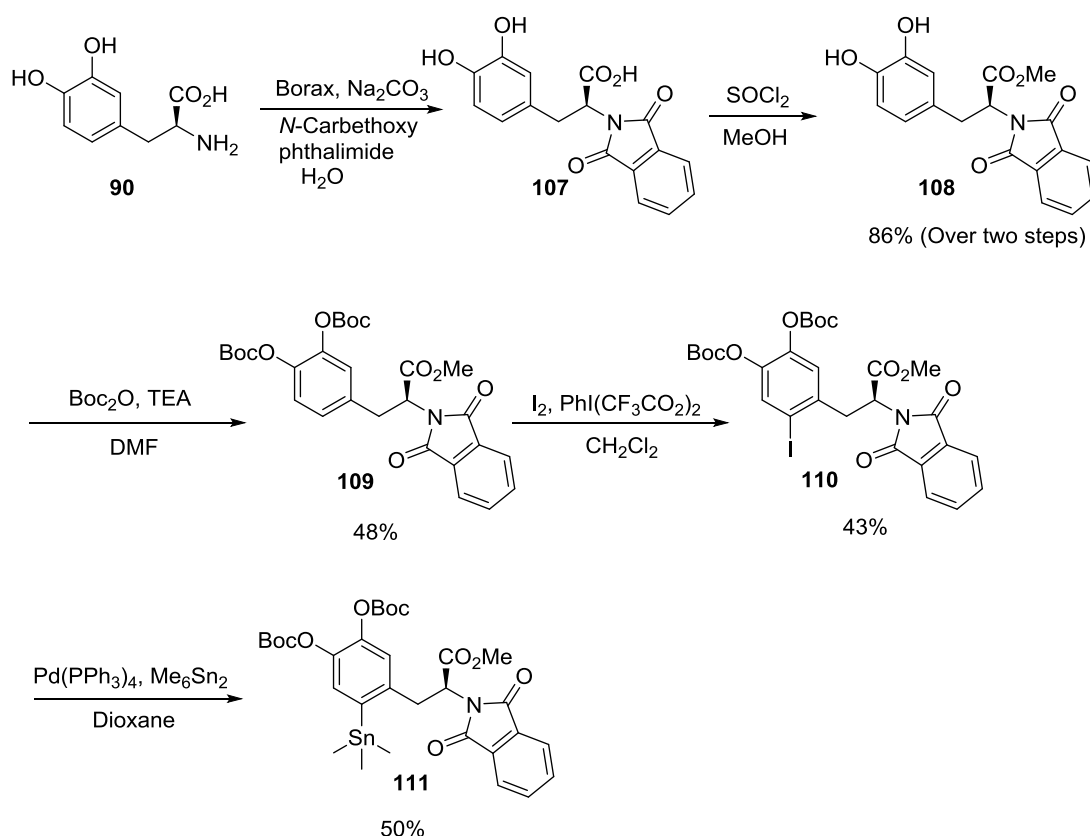
Scheme 22 – Synthesis of stannane 111

The synthesis of stannane **111** adapting reported methods proceeded well.[19,20] Further reaction of the stannane for the synthesis of iodonium salts gave mixed success. Unexpectedly, the reaction with 2-(diacetoxyiodo)thiophenene **87** did not proceed well under the optimum conditions. Again, the problem was isolating the pure hypervalent compound. Changing the work up of the reaction to chromatography purification also failed to isolate the pure iodonium salt (Scheme 23a).

Reaction with 4-(diacetoxyiodo)anisole **72** under the optimised conditions however, proceeded satisfactorily and the product could be isolated by either precipitation or column chromatography (isopropanol and dichloromethane gradient) in 29% yield (Scheme 23b).
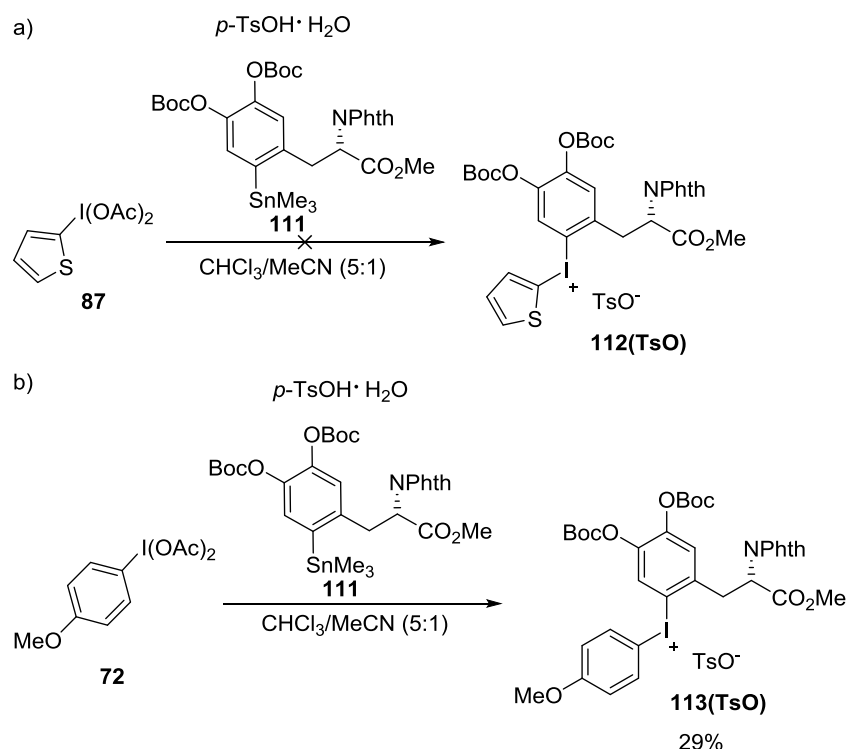
Scheme 23 – Salt formation with stannane 111. a) Unsuccessful reaction with 2-(diacetoxyiodo)thiophene **87. b)** Successful formation of the anisyl precursor **113(TsO).**

Attempted Production of Phthalimide Protected Iodonium Salt 113 via Oxidation of iodoDOPA moiety 110.

Attempts were made to directly oxidise the iodoDOPA compound **111** in order to attain the thienyl iodonium salt **113(X)** through this route. The slight alteration in protection of the iodoDOPA moiety did not alter this reaction and as with previous attempts (Scheme 9), the reaction was unsuccessful (Scheme 24).
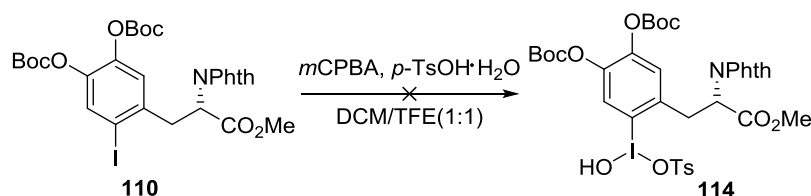
Scheme 24 – Direct oxidation of Phth protected iodoDOPA 110

1.2.13 Alteration of hydroxyl protecting groups (d)
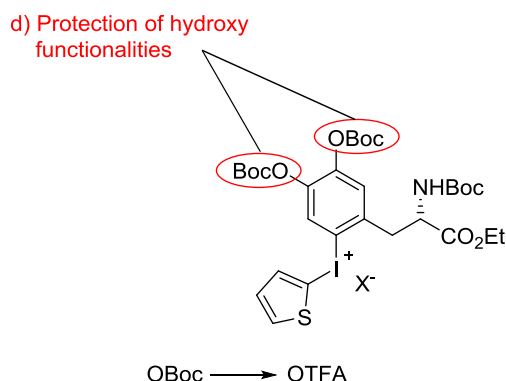
Figure 14 – Possible alteration to the hydroxyl protecting strategy of the precursor

The final precursor alteration strategy outlined in Figure 8 was to change the hydroxyl protecting groups. We envisaged that TFA protection would decrease the electron density of the DOPA moiety, therefore possibly improving the compounds utility in the fluorination reaction.

The synthesis of a TFA protected compound **115** was not trivial. When conditions were eventually established for the TFA protection (Table 11), it was found that the iodination of the TFA protected product **115** did not proceed as desired (Scheme 25).

Table 11 – TFA protection of DOPA moiety 115
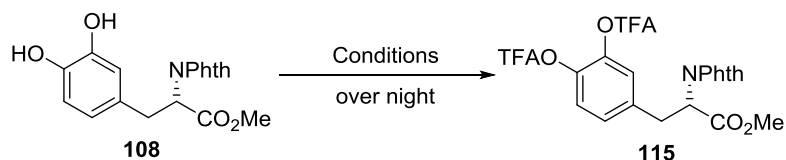
Conditions	Yield (%)
TFAA, TEA, DMF	0
TFAA, CH$_2$Cl$_2$	0
TFAA, DMAP (0.4 equiv), MeCN	46
TFAA, reflux	88
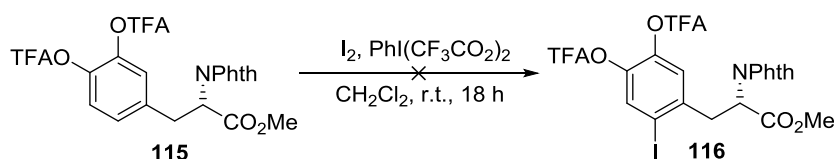
Scheme 25 – Attempted iodination of 115

Due to these complications it was decided the strategy could be tested on some simplified precursors before lengthier synthesis was conducted to obtain the iodoDOPA target **116**. Hence, the iodonium salts below **117** and **118** were targeted (Figure 15). It was hoped that the two precursors would reveal any advantages or disadvantages of the two differing protection strategies.
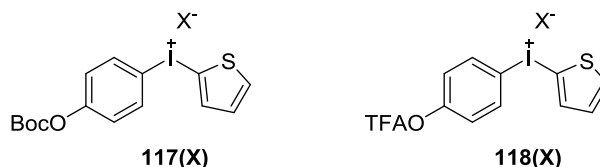
Figure 15 - Two iodonium salts targeted to probe the effect of the hydroxyl protection.

1.2.14   Protected Phenol salts

O-Boc 4-iodophenol salts
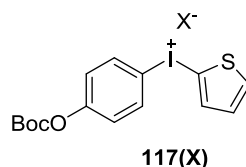
Figure 16 – Targeted OBoc protected iodonium salt precursor 117(X).

Oxidation of O-Boc 4-iodophenol **119** with peracetic acid produced the corresponding diacetate **120** and was optimised to achieve a 59 % yield (Table 12).

Table 12 – Optimisation for the formation of diacetate 120
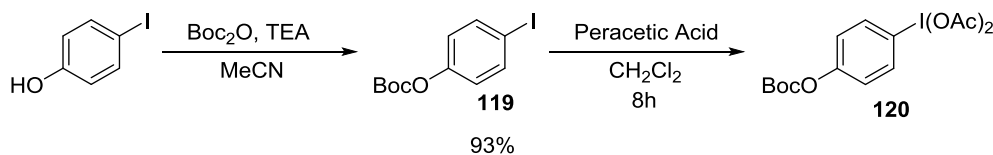
Entry	Peracetic Acid Conc. (Wt. %)	Temperature (°C)	Yield (%)
1	13	r.t.	31
2	19.5	r.t.	27
3	9.75	r.t.	40
4	**9.75**	**0**	**59**

Subsequent reaction of the diacetate **120** with the 2-(tributylstannyl)thiophene under the previously optimised conditions produced the salt **117(X)** in good yield. Counter ion exchange could also be achieved using the appropriate work up (Scheme 26).
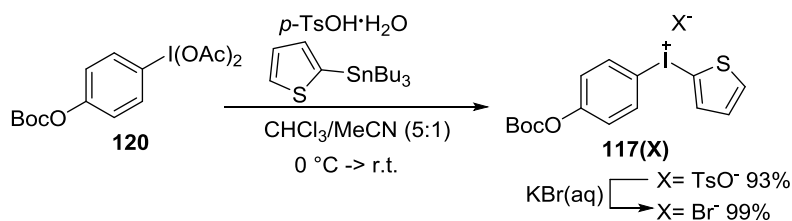
Scheme 26 – Production of thiophene derived salts 117(TsO) and 117(Br)

1.2.14.1 Fluorination of O-Boc 4-iodophenol salts

'Cold' fluorinations:

Iodonium salt **117** was fluorinated with tetramethylammonium fluoride (TMAF) using conditions reported by DiMagno et al.[6] Initial treatment with TMAF in acetonitrile affords the corresponding iodonium fluoride **117(F)**. Subsequent thermal breakdown was tested in both acetonitrile and toluene. The thermal breakdown in toluene is conducted after a filtration step: Initially, acetonitrile is removed by evaporation before solvation of the iodonium fluoride **117(F)** in dry toluene. Filtration during transfer into a new vessel is conducted in order to remove any insoluble salts before the breakdown is performed.
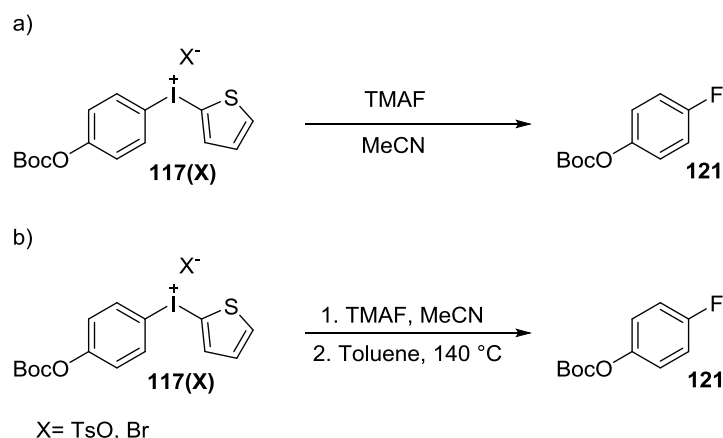
Scheme 27 – Cold fluorination of iodonium salts 117(Br) and 117(TsO). a) Fluorination in acetonitrile. b) Iodonium fluoride 117(F) formation in acetonitrile before thermal decomposition in toluene.

Both conditions lead to the desired fluorinated product **121** as detected by ¹⁹F NMR. Iodonium bromides and tosylates were tolerated for this reaction. Unfortunately,

isolation of **121** was not possible using column chromatography due to the presence of impurities with the same R_f value.

'Hot' Fluorinations:

Table 13 – 'Hot' fluorination of iodonium salts 118 for the production of [^{18}F]121
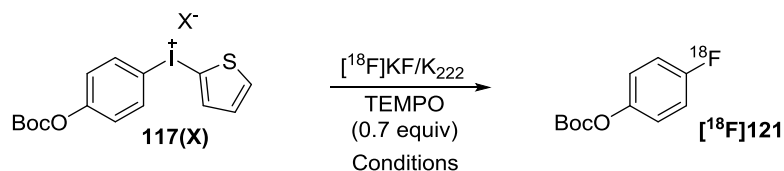
Entry	Reacton Time (min)	Temp (°C)	X	Solvent	Conversion (%)(HPLC)	Recovery (%)	RCY (%)
1[a]	30	90	TsO	MeCN/DMSO (5/1)	75	91	68
2[a]	30	90	Br	MeCN/DMSO (2/1)	64	70	45
3[a]	30	90	TsO	MeCN/DMSO (2/1)	47	60	28
4[b]	30	90	TsO	MeCN/DMSO (5/1)	90	35	32
5[b]	20	65(10min), 110(10min)	TsO	MeCN/DMSO (5/1)	95	63	60
6[bc]	5	100	TsO	DMSO (2% H$_2$O)	no product	n/a	n/a
7[b]	20	130	TsO	DMF	46	47	22

[a] 0.1mmol precursor used. [b] 0.05mmol precursor used. [c] No TEMPO used for this reaction

The *O*-Boc protected iodonium salt precursors **117** performed well for the synthesis of [^{18}F]*O*-Boc 4-fluorophenol **[^{18}F]121**. HPLC analysis by co-elution with the produced ^{19}F reference compound **121** was successful and showed good RCC to the product for the majority of conditions.

It can be seen that the bromide counter ion slightly outperforms the tosylate (entry 2 vs entry 3). The ratio of acetonitrile to DMSO was also an important factor with a 5:1 ratio providing improved RCC (entry 1 vs entry 3). It should be mentioned that the iodonium bromide **117(Br)** could not be tested under these conditions due to solubility issues.

It was then tested if the amount of precursor **117** could be reduced. It was found that halving the quantity of the precursor to 0.05 mmol had no detrimental effect on the RCC (entry 1 vs entry 4). The lower radiochemical yield observed in entry 4 is due to

an unusually low recovery from the reaction vial. This was caused by a failure of the equipment. Loss of a portion of the reaction mixture occurred during transfer to the product vial due to a leak.

Conditions to try and encourage the formation of the iodonium fluoride **117(^{18}F)** intermediate were also investigated (Entry 5). It was hypothesised that ligand exchange could be accelerated by heating the reaction mixture at temperatures below that for thermal breakdown of the iodonium fluoride **117(^{18}F)**. Therefore, the reaction was heated at 65 °C before the thermal breakdown was induced at 110 °C. This gave an excellent RCC of 95%.

Despite being encouraged by the excellent radiochemical conversions, radio TLC analysis did not agree with the radio HPLC analysis and suggested very poor conversions to the ^{18}F labelled product **[^{18}F]121**. This was unexpected and could not be attributed to the volatility of the product, as was assumed with [^{18}F]fluorobenzene **[^{18}F]77** (Pg. 58). The cause for these analytical problems was eventually ascertained and is reported later in this chapter (Pg. 115). The figures below show the contradictory chromatograms obtained.
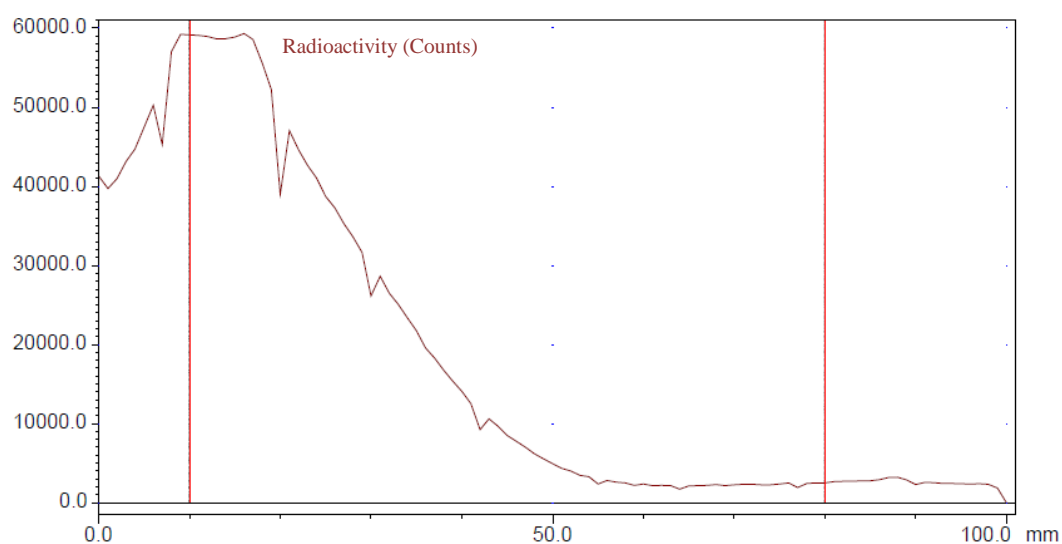
Figure 17 – Radio TLC of reaction mixture containing [^{18}F]O-Boc 4-fluorophenol [^{18}F]121
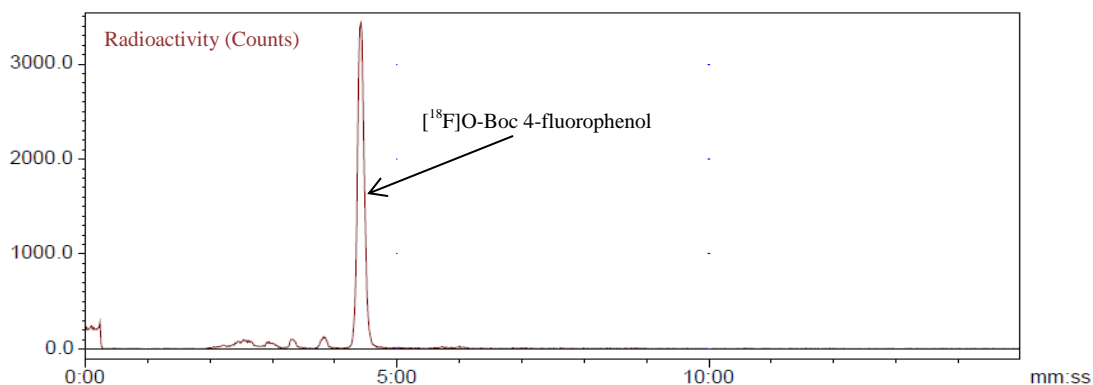
Figure 18 – Radio HPLC of reaction mixture containing [^{18}F]O-Boc 4-fluorophenol [^{18}F]121

At this point other literature methods were tested to see if an improved TLC chromatogram would be obtained for these reported conditions. Entry 6 used reaction conditions adapted from those reported by Dinkelborg *et al.* for the formation of an ^{18}F labelled gelatinase inhibitor.[8] However, performing the reaction in DMSO with addition of water (2 vol%) gave no conversion of [^{18}F]fluoride to product **[^{18}F]121**.

Entry 7 used conditions adapted from those reported by Coenen *et al.* for the formation of 4-[^{18}F]fluorophenol.[21] It was considered that higher temperature breakdown may produce an improved yield for the fluorination. The conversion analysed by radio HPLC was low while the radio TLC showed no change in result.

TFA protected 4-iodophenol salt

Oxidation of the TFA protected moiety proved more difficult than with the OBoc protected salt. No product could be isolated after treatment of **122** with peracetic acid (Scheme 28a). However, production of an iodonium salt was achieved via *in situ* formation of the Koser reagent **124** and reaction with the 2-(tributylstannyl)thiophene (Scheme 28b). Upon addition of methanol to the reaction there was a change of colour and the isolated salt was confirmed to be the unprotected 4-hydroxy substituted iodonium salt **125**. While there is no strong evidence for the proposed intermediates, this observation suggested that the TFA protection became very labile once the iodonium salt **118(TsO)** had been produced. This is possibly due to the electron withdrawing nature of the hypervalent iodine. It was thus decided that the TFA protection was unsuitable and plans to synthesise TFA protected iodonium salt were abandoned.
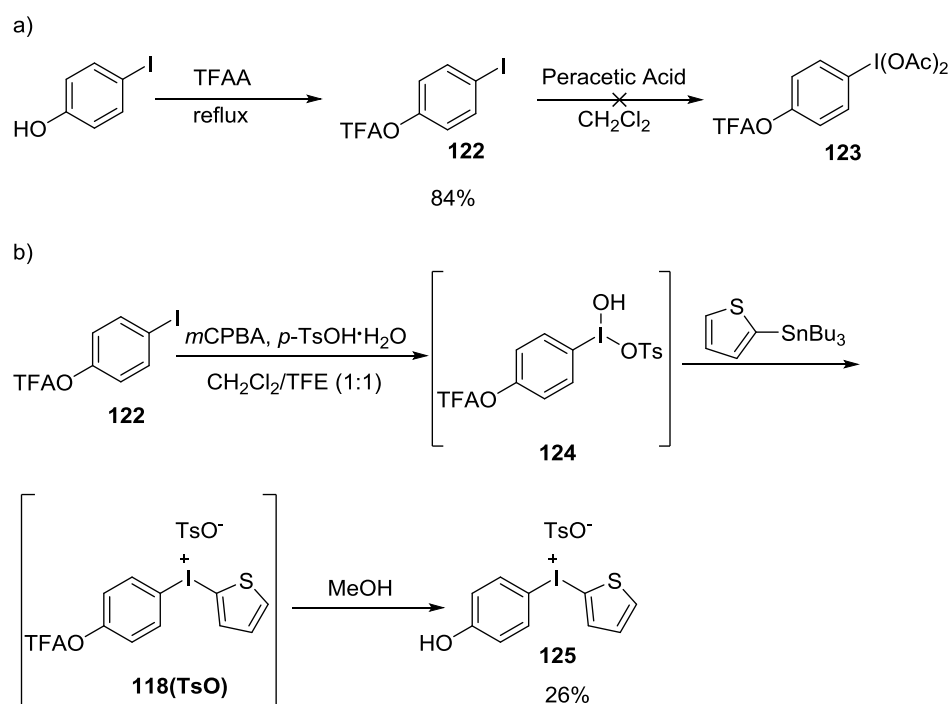
Scheme 28 – Attempts to produce an *O*-TFA protected hypervalent iodoarene 118(TsO).

1.2.15 Oxidation of iodoDOPA

Attempts to design a precursor synthesis via the oxidation of an iodoDOPA moiety had been briefly looked into at different stages in the investigation for different protecting group strategies (Scheme 29). For details of these reactions see Scheme 8 and 24.
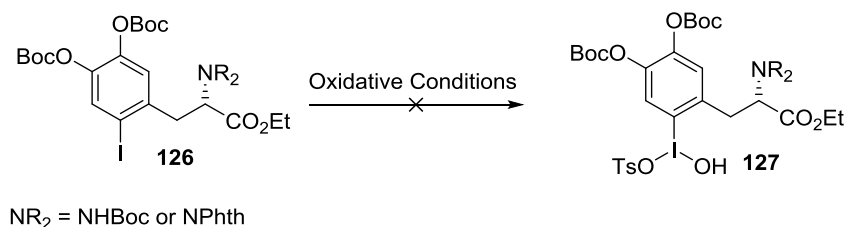
Scheme 29 – Failed attempts to oxidise iodoDOPA moieties previously seen in Schemes 8 and 24

Whilst not looked into thoroughly at the time, further work was now conducted in this area due to the possible advantages of this synthesis route. These advantages included the removal of an undesirable stannylation reaction and difficult purification step. It was also considered that any residual tin not completely removed in the purification of the precursor may interfere with the fluorination reaction. The alternative synthesis would allow the synthesis of a precursor not exposed to potentially interfering tin reagents.

Subjecting the protected iodoDOPA moiety **83** to the standard oxidative conditions for Koser reagent formation had proved unsuccessful. Both isolation of the desired Koser type compound and *in situ* reaction with an aryl stannane for the formation of a diaryliodonium tosylate **93** were unfruitful (Scheme 8).

The formation of the corresponding iodoDOPA diacetate was then investigated. Due to the more robust nature of the phthalimide protection, compound **110** was chosen for diacetate **128** production using peracetic acid.
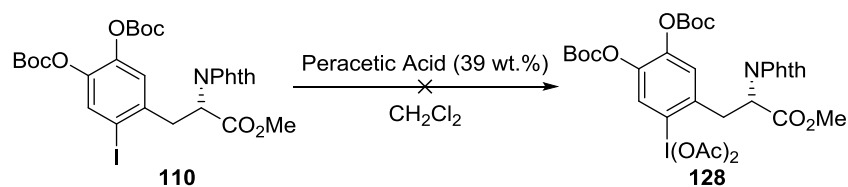
Scheme 30 – Attempted oxidation of 110 to the corresponding diacetate 128.

Oxidation to the diacetate **128** was not possible under the attempted conditions and only starting material with small amounts of undesirable products remained.

However, looking through some patent literature showed conditions for the very transformation needed: Work by Barrio *et al.* uses dimethyldioxirane (DMDO) as a clean oxidant for the formation of the diacetoxy and iodyl compounds **129** and **130**, respectively (Figure 19). [22,23]
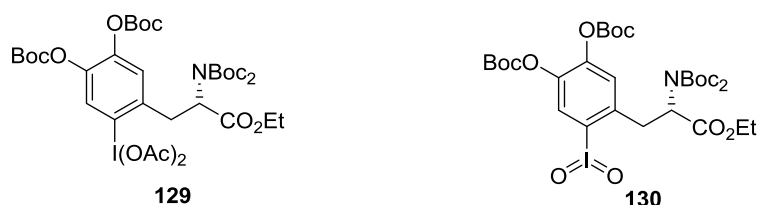
Figure 19 – Iodyl compound 130 and Diacetate 129 produced by oxidation using DMDO

Due to the very clean nature of the reaction it was assumed that this would be worthwhile investigating for the synthesis of the diaryliodonium salt precursors.

Formation and analysis of the dimethyldioxirane (DMDO) solution used:
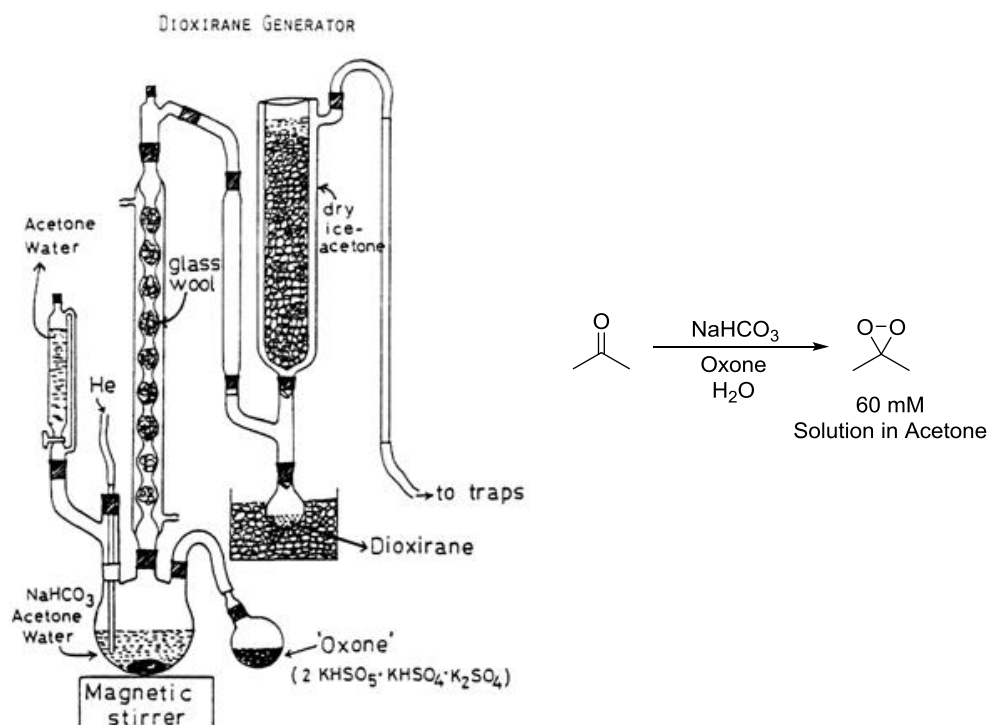
Figure 20 – Setup for DMDO production as described by Singh *et al.*[24]

A solution of DMDO in acetone was produced by distillation using the above apparatus as previously reported.[24] The DMDO solution obtained was stored in the freezer over Na$_2$SO$_4$. Under these storage conditions, the concentration of DMDO was not diminished after 2 weeks storage as was described by Fröhlich *et al.*[25] Its concentration was assessed by oxidation of thioanisole to the corresponding sulfoxide and determined

by ^{1}H NMR integration of the different phenyl protons according to the literature (Chapter 4; Pg. 198).[26]

Oxidation to the iodyl compound **131** from iodoDOPA **110** proceeded very well (Scheme 31a), but unfortunately the diacetate **132** formation experienced problems with reproducibility (Scheme 31b).
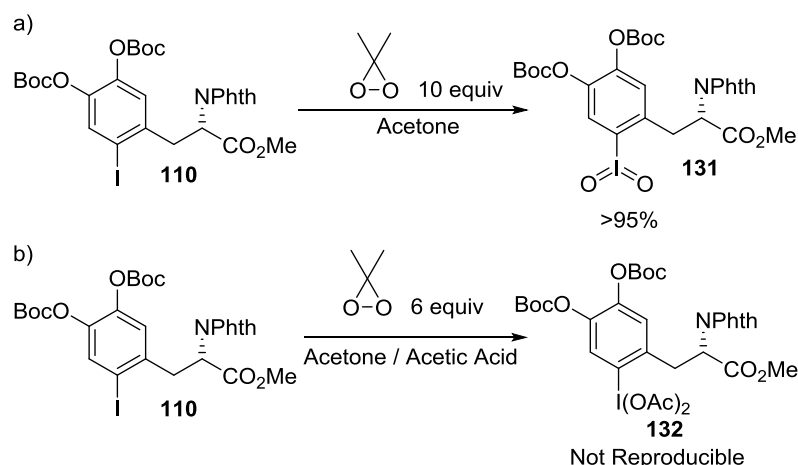
Scheme 31 – Oxidation reactions using DMDO. a) Oxidation of 110 to its corresponding iodoyl compound 131. b) Oxidation of 110 to its corresponding diacetate 132.

It was hypothesised that under milder conditions using fewer equivalents of DMDO, oxidation to the iodosyl compound **133** would proceed more reliably. Subsequent reaction with acetic acid would in theory yield the desired diacetoxy iodoDOPA compound **132**. Unfortunately, the preliminary conditions looked into generally proceeded with over-oxidation. Even using just one equivalent of oxidant at low temperatures produced a mixture of inseparable oxidised compounds **131** and **133** along with starting material (Scheme 32).

a)

b)
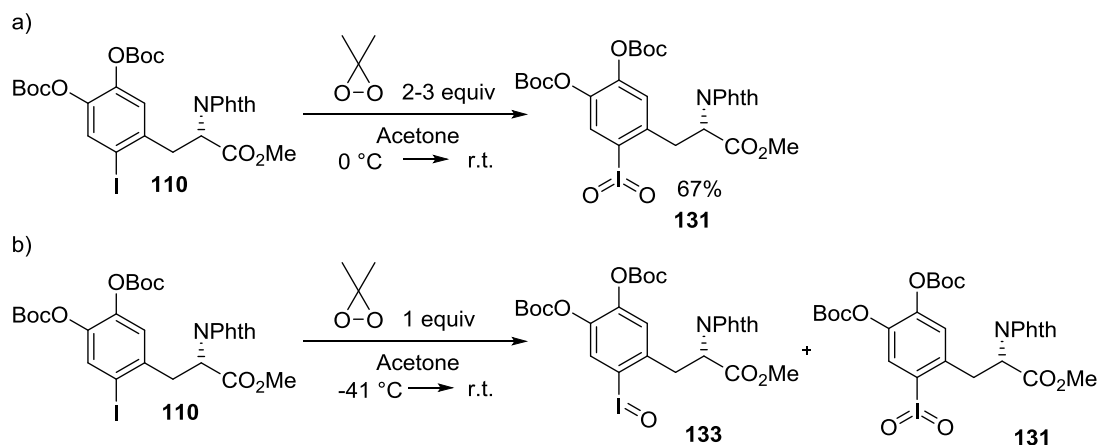
Scheme 32 – DMDO oxidations at lower temperature. a) Oxidation at low temperature with fewer equivalents of DMDO still yields the iodyl species 131. b) 1 equivalent of DMDO added at -40 °C yields a mixture of oxidised products 133 and 131.

It was also looked into whether *in situ* produced DMDO could produce the diacetate **132**. This would also be much more convenient as it negates the need for a complex distillation set up. This unfortunately was unsuccessful (Scheme 33).
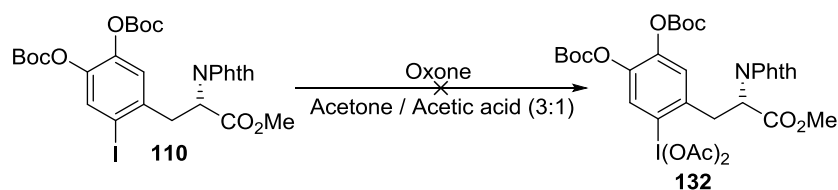
Scheme 33 – Attempted diacetate formation using *in situ* produced DMDO as an oxidant.

1.3   Mid Chapter Summary

A number of simple iodonium salt precursors have been synthesised and tested for their suitability for incorporation of ^{18}F and ^{19}F fluoride. Production and fluorination of simple diaryliodonium salt precursors proceeded well suggesting the methodology was worth investigating for [^{18}F]F-DOPA **9** synthesis.
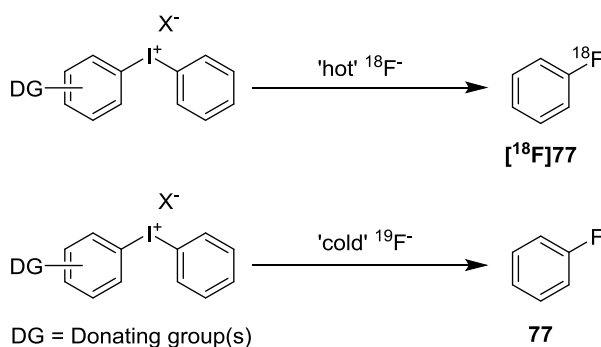
Scheme 34 – 'Hot' and 'cold' fluorinations were tested for a variety of precursors.

A procedure for the synthesis of protected DOPA functionalised iodonium salts was also established and optimised. Initial 'cold' fluorinations showed formation of the desired fluorinated product **95**. However, 'hot' radio fluorination reaction conditions did not provide any labelled compound **[^{18}F]95** as determined by radio TLC. Therefore, using the optimised conditions, certain alterations to the iodonium salt precursor were investigated (Figure 21).

Altering the precursor
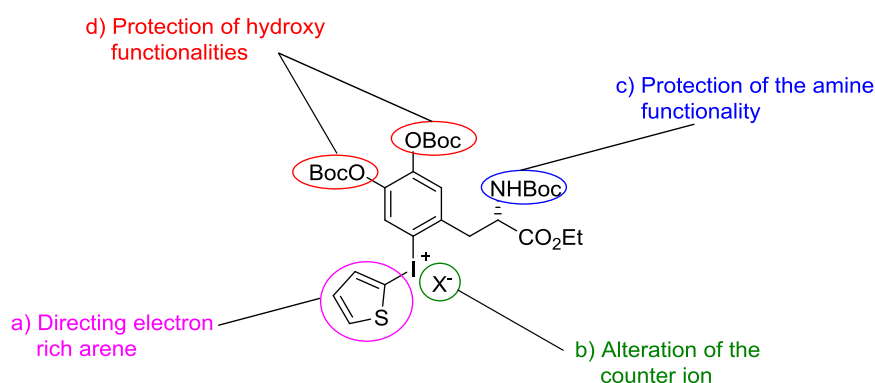
Figure 21 – Iodonium salt precursor design and possible areas for alteration.

a) Altering the directing arene
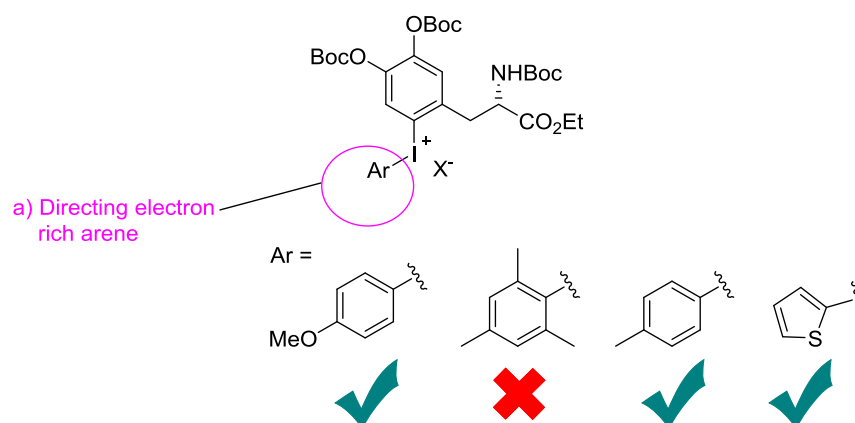
Figure 22 – Alteration of the directing electron rich arene

Altering the directing arene functionality was possible for anisyl and toly aromatics. Furthermore, 'cold' fluorination conditions showed that both precursors were suitable for directing fluorination to the DOPA aromatic. Isolation of the pure mesityl salt was unfortunately not possible.

b) Changing the counter ion
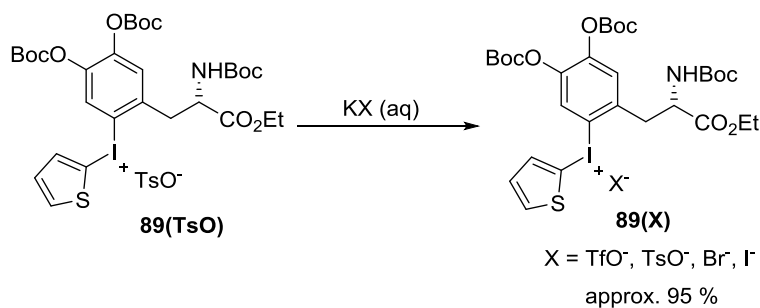
Scheme 35 – Anion exchange by simple work up alteration

Counter ion exchange to a variety of anions was possible using a simple work up alteration.

c) Altering the amine protection
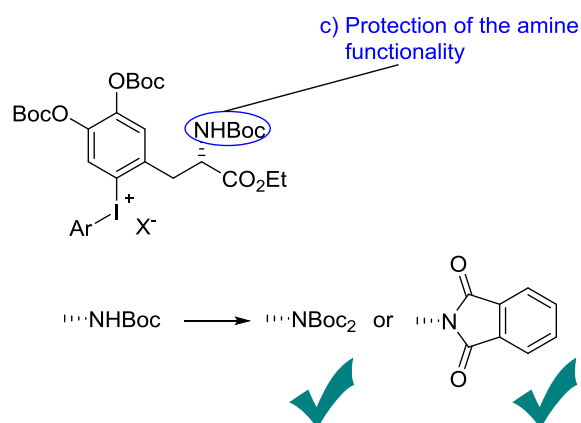
Figure 23 – Alterations to the protecting strategy of the amine

Both tetraBoc and phthalimide protected precursors could be produced. However, not all directing arene substituents could be tolerated. The tolyl iodonium salt proved unstable when the diBoc protected amine was present. Also the thienyl iodonium salt was not isolatable when functionalised with the phthalimide protected amine.

d) Alteration of the hydroxyl protecting strategy
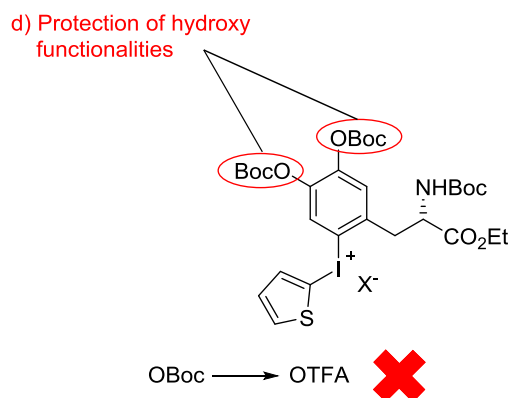
Figure 24 – Alteration of hydroxyl protecting strategy to TFA protection is unsuitable

Changing the OBoc protection to a TFA protection was problematic and testing of the strategy on simplified precursors suggested a high liability of the protecting group. The change in protection was therefore considered unsuitable for an alternative iodonium salt precursor. Production of a methoxy substituted precursor remains an option to be explored.

During the 'hot' fluorination testing of simple OBoc protected precursor **117** for the production of OBoc 4-[¹⁸F]fluorophenol **[¹⁸F]121** (Scheme 36), a discrepancy between the TLC analysis and HPLC analysis was highlighted.
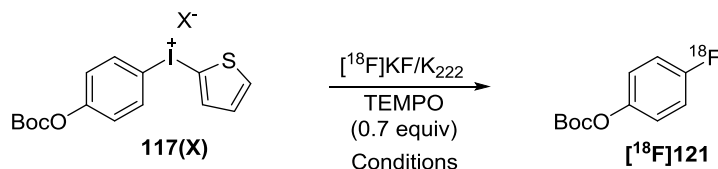
Scheme 36 – Radiofluorination of 117(X) for the production of OBoc 4-[¹⁸F]fluorophenol [¹⁸F]121

Alternative synthesis

Synthesis of a suitable precursor via oxidation of iodoDOPA compounds **126** was unsuccessfully investigated (Scheme 37). Diacetate **132** formation was possible using DMDO as an oxidant in the presence of acetic acid. However, poor reproducibility hinders the use of this protocol for precursor synthesis.

NR$_2$ = NHBoc or NPhth
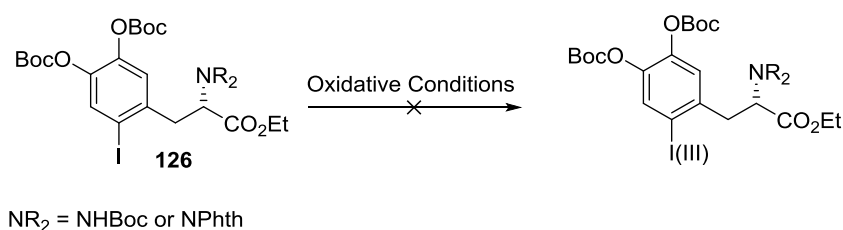
Scheme 37 – Oxidation of iodoDOPA moieties was unsuccessfull

1.4   Outlook

'Cold' Fluorination Reactions

A number of precursors have shown their suitability for the fluorination of the protected DOPA aromatic. Quantitative analysis of these fluorination reactions however has not yet been conducted. Isolation of the fluorinated compound proved difficult, therefore preventing isolated yields being obtained. However, analysis using HPLC could provide a good platform to obtain accurate yields without isolation of the compound.

'Hot' Fluorination Reactions

Radiofluorination of the [¹⁸F]F-DOPA precursors has been unsuccessful as monitored by TLC. Further, investigation into the lack of conversion needs to be conducted. Furthermore, HPLC analysis using the appropriate ¹⁹F standards may provide a more sensitive technique for the detection of any product produced. A range of altered

precursors have been produced which are now available to test in the radiofluorination reaction. These results may reveal some of the problems responsible for the poor conversion.

<u>Discrepancies in Analysis of 'Hot' Fluorination Reactions</u>

The contradictory analysis of TLC and HPLC results was a strong concern. Original conflicting analysis of [^{18}F]fluorobenzene **[^{18}F]77** was proposed to be due to the volatility of the product. However, analysis of the non-volatile compound OBoc 4-[^{18}F]fluorophenol **[^{18}F]121** also gave contradictory analysis. Investigation into the cause of these discrepancies is highly important in order to establish which analysis is correct and if the current conversions calculated by HPLC analysis are accurate.

1.5 Further investigation into the suitability of functionalised diaryl iodonium salts for the synthesis of [^{18}F]F-DOPA

The optimisation of precursor synthesis reported above allowed for the synthesis of a number of iodonium salts for [^{18}F]F-DOPA **9** production with varying protecting strategies (Table 14).

Table 1 – Yields for the synthesis of iodonium salts with varying protection groups
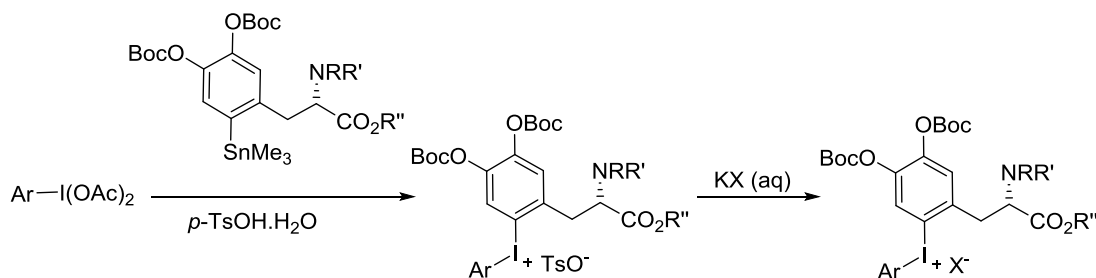
a: Ar = 2-thienyl
b: Ar = 4-methoxyphenyl

Entry	Ar	NRR'	R''	Yield (%)
1	a	NHBoc	Et	44
2	a	NBoc$_2$	Et	28
3	a	NPhth	Me	0
4	b	NHBoc	Et	60
5	b	NBoc$_2$	Et	26
6	b	NPhth	Me	29

After devising this suitable protocol for precursor production, further investigation into the fluorination of these compounds was needed.

Additionally, discrepancies in the analysis of the radiofluorination reaction were discovered. Radio HPLC and radio TLC gave contradictory results. Investigation into this problem was imperative if accurate conclusions were to be made.

1.6   Testing of precursors

1.6.1   'Cold' Fluorination

Firstly, 'cold' fluorination of the tetraboc protected precursor **100(I)** was conducted in order to check if the additional protection of the amine had any effect on the fluorination.
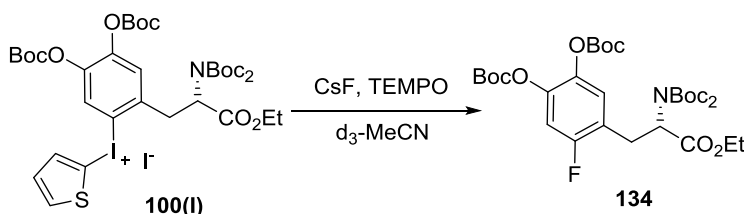
Scheme 38 – Cold fluorination of precursor 100(I)

The tetraboc protected precursor **100(I)** was subjected to 'cold' fluorination conditions using cesium fluoride as the source of fluoride. Full selectivity for fluorination at the DOPA moiety was observed with just one signal detected by ^{19}F NMR, corresponding to the fluorinated product **134**. No isolated product could be obtained using chromatographic purification due to the presence of impurities with the same R$_f$ value.

1.6.2   'Hot' Fluorination

Investigations into the radiofluorination of precursor **100(I)** were then conducted (Table 15).

Table 15 – Radiofluorination of tetraboc iodonium salt 100(I)
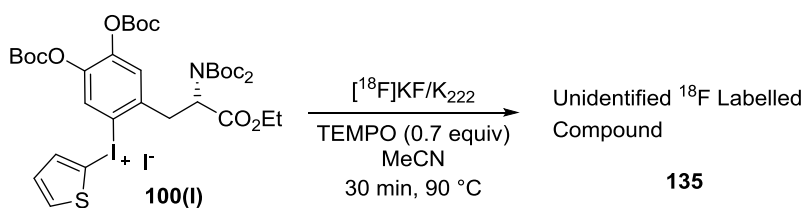
Entry	Scale (mmol)	TLC Conversion (%)[a]
1	0.084	5
2	0.06	2.5

[a]Unidentified [^{18}F]fluorinated compound

Reaction of the iodonium salt **100(I)** with [^{18}F]KF/K$_{222}$ showed low radio TLC conversion to a fluorinated product **135**. Conversion varied between 2.5% and 5%

depending on the quantity of precursor used. A greater quantity of precursor increased the radio TLC conversion.

Attempted deprotections to yield [^{18}F]F-DOPA **9** were unsuccessful with HPLC analysis showing no peak corresponding to [^{18}F]F-DOPA **9** subsequent to the deprotection conditions (Scheme 39).
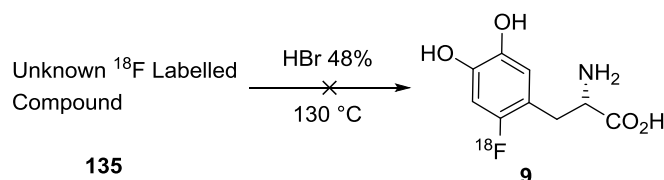
Scheme 39 – Unpurified labelled compound 135 subjected to deprotection conditions

It was unclear whether the radiofluorination or the deprotection had failed. Confirmation as to whether the unknown ^{18}F labelled compound was the protected [^{18}F]F-DOPA species **[^{18}F]134** was needed to address these uncertainties. This required the use of tetraboc [^{19}F]fluoroDOPA **134** as a standard for HPLC analysis.

As mentioned, attempts to isolate the [^{19}F]fluorinated product from the 'cold' fluorination reaction of the iodonium salts were unsuccessful. Therefore an alternative protocol was required.

A publication by Ritter *et al.* describes a suitable procedure for the formation of a protected [^{19}F]F-DOPA compound **134** from the corresponding aryl stannane **104**.[16] Stannane **104** was available due to its application for the synthesis of the iodonium salt precursors **100** and **106**. It therefore looked like an ideal route to the required [^{19}F]standards **95**, **134** and **136**.

The reaction proceeded well enough to obtain standards for all of the different protected salts. Interestingly, despite providing a clean ^{1}H NMR spectrum, the triboc protected [^{19}F]fluoroDOPA **95** was found to be impure by analytical HPLC using reverse phase conditions. Therefore the compound was further purified using a C-18 cartridge (Biotage® KP-C18-HS 12g SNAP cartridge). This gave the product **95** with significantly enhanced purity (checked using HPLC), suitable to be used as a reference for the analysis of the 'hot' fluorinations.

82: NRR'= NHBoc , R"= Et
104: NRR'= NBoc$_2$, R"= Et
111: NRR'= NPhth , R"= Me

95: NRR'= NHBoc , R"= Et, 22%
134: NRR'= NBoc$_2$, R"= Et, 60%
136: NRR'= NPhth , R"= Me, 34%
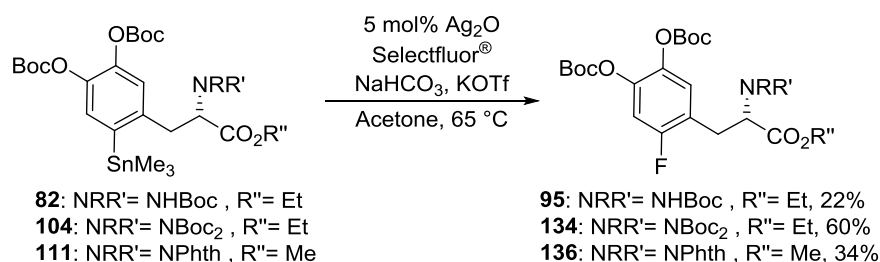
Scheme 40 – Silver mediated electrophilic fluorination of stannanes 82, 104 and 111 for the production of [^{19}F]standards 95, 134 and 136.

The produced standards could now be used to aid the analysis of both the 'hot' and 'cold' fluorination reactions. Firstly, addition of the standards to the 'cold' fluorination reaction mixtures confirmed the identity of the fluorinated product as the protected [^{19}F]F–DOPA compound by ^{19}F NMR. Furthermore, quantitative analysis could be conducted using HPLC.

'Cold' fluorinations of DOPA precursors with quantitative analysis

A paper published by DiMagno *et al.* describes the use of tetramethylammonium fluoride (TMAF) for the fluorination reaction of iodonium salts.[6] This publication describes the production of fluoroarenes in good yields. Therefore, the use of this fluoride source looked very promising. The reagent was tested for the fluorination reactions of the iodonium bromide precursors produced (Table 16).

Table 16 – 'Cold' fluorination of triboc protected iodonium salts with TMAF.

a: 89(Br)
b: 81(Br)

a: 89(F)
b: 81(F)

a: Ar = 2-thienyl
b: Ar = 4-MeOC$_6$H$_4$
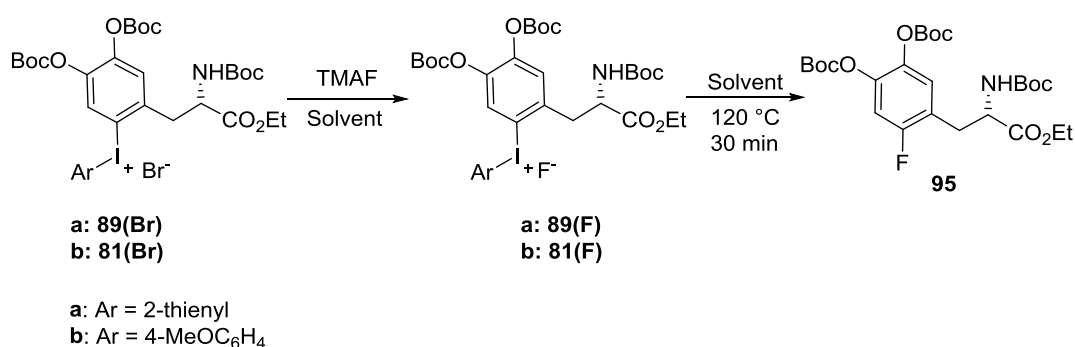
Entry	Ar	Solvent	Yield (%)^a
1	**b**	DMSO	0
2	**b**	DMF	2
3	**b**	Acetonitrile	5

4[b]	**b**	Toluene	2
5	**a**	Acetonitrile	3
6[b]	**a**	Toluene	5

[a] Yields were calculated using HPLC analysis. [b] Iodonium fluoride **89(F)** or **81(F)** was produced in acetonitrile before removal of the solvent. Compound **89(F)** or **81(F)** was then re-dissolved in toluene and passed through a filter into a clean vessel for the thermal decomposition to **95**.

Aside from the reaction performed in DMSO, formation of the fluorinated product **95** was observed in all reactions by ^{19}F NMR. This was again confirmed by addition of the already isolated cold standard to the reaction mixture. Furthermore, the formation of **95** was confirmed by HPLC. The formation of the iodonium fluoride intermediates **91(F)** and **81(F)** was also observed by ^{19}F NMR in all cases (Table 17).

Table 17 – Iodonium fluoride ^{19}F NMR peak observed for iodonium salts 89(F) and 81(F) in the different reaction solvents

a: 89(F)   **a**: Ar = 2-thienyl
b: 81(F)   **b**: Ar = 4-MeOC$_6$H$_4$
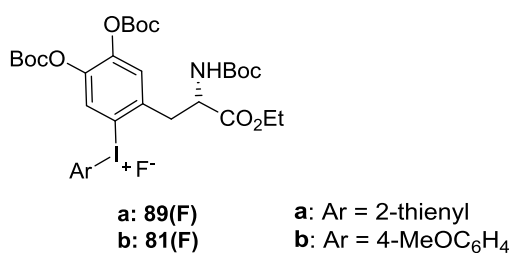
Entry	Ar	Solvent	δ (ppm)
1	**b**	DMSO	-6.18
2	**b**	DMF	-8.16
3	**b**	Acetonitrile	-8.46
4	**b**	Toluene	-8.30
5	**a**	Acetonitrile	-8.45
6	**a**	Toluene	-7.47

It is unclear why thermal decomposition of the iodonium fluoride **81(F)** in DMSO did not proceed to give the fluorinated product.

It was promising that no production of 4-fluoroanisole or 2-fluorothiophene was observed in any of the reactions showing that both directing groups tested gave the desired regioselectivity. The reaction proceeded with both the thiophene and the anisole derived iodonium salts. Neither 'non-participating' arene showed a clear advantage over the other. All yields, determined by HPLC, varied between 2% and 5%. The use of toluene as a break down solvent did not benefit the reaction as described by DiMagno *et al.*[6]

Due to the low yields and the moisture sensitive nature of the reaction it was investigated whether more stringent drying of the reagents would benefit the reaction. In this study solutions of the iodonium salts **81(F)** and **89(F)** were dried over molecular sieves for 24 h before addition to the NMR tube containing TMAF under nitrogen atmosphere. These extra measures did not benefit or change the results of the reaction in any way.

1.6.3   Radiofluorinations evaluated with HPLC analysis

Despite the low yields of the 'cold' reaction, further investigation into the 'hot' reaction was now conducted. Firstly, radiofluorination of tetraboc precursor **100(I)** was conducted to discover whether the identity of the ^{18}F labelled compound was the tetraboc protected [^{18}F]F-DOPA compound **[^{18}F]134**.
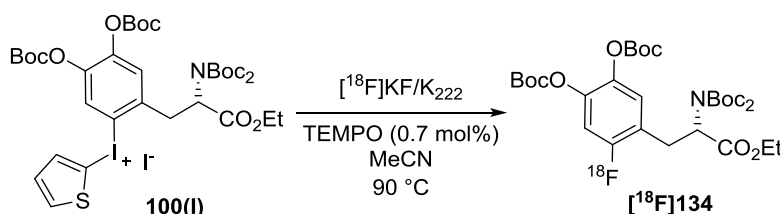
Scheme 41 – Radiofluorination of precursor 100(I)

The production of tetraboc [^{18}F]F-DOPA **[^{18}F]134** was confirmed by HPLC analysis of the reaction mixture. This was conducted with and without the addition of the cold standard to the sample. However, the tetraboc [^{18}F]F-DOPA **[^{18}F]134** was a minor product among many other side products showing the reaction had not proceeded cleanly and that the RCY was significantly lower than that calculated from radio TLC conversion.

Radiofluorination of the triboc precursors **81** and **89** was also re-evaluated to check if a small amount of product was detectable using the radio HPLC analysis (Table 18).

Table 18 – Radiofluorination of triboc protected iodonium salts 89 and 81

a: 89(X)
b: 81(X)

a: Ar = 2-thienyl
b: Ar = 4-MeOC$_6$H$_4$
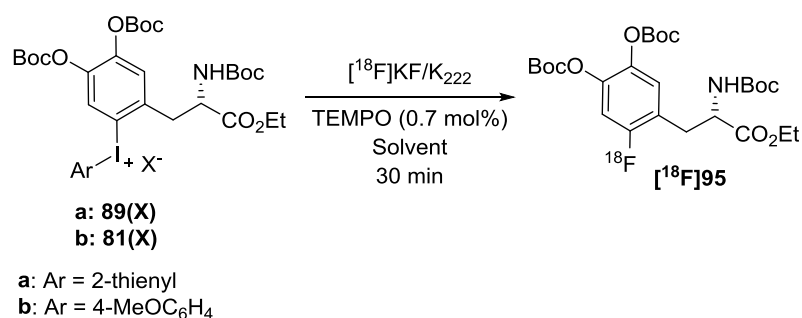
Entry[a]	Temp (°C)	X⁻	Ar	Solvent	Conversion (%)(HPLC)	Recovery (%)	RCY (%)
1	90	Br⁻	b	MeCN/DMSO (5/1)	25	77	19
2	90	Br⁻	a	MeCN/DMSO (2/1)	19	68	13
3	130	Br⁻	b	DMF	8	42	3
4	90	Br⁻	b	MeCN	5	65	3
5	130	Br⁻	b	DMSO	0	-	-
6	130	Br⁻	b	DMSO (2 % H$_2$O)	0	-	-
7[b]	130	Br⁻	b	DMF	0	-	-

[a]Reactions were carried out using 0.04-0.06 mmol precursor, [b]Reaction carried out with 0.02 mmol precursor in accordance to literature.[8,27]

Interestingly, the HPLC analysis showed that radiofluorination of triboc precursors proceeded much more efficiently than with tetraboc protected precursor **100(I)**. Further optimisation of the reaction showed that addition of DMSO to the reaction improved the conversion from 5% to 25%. Additionally, these conditions obtained high radiochemical recovery (RCR) from the reaction vessel. Reactions in DMSO alone, like those performed with [^{19}F]fluoride, did not proceed with or without the addition of a small quantity of water. The addition of water to DMSO has been crucial for the success of other fluorinations using iodonium salts.[8]

DMF was tolerated as a reaction solvent but reactions did not proceed as well as in a mixture of DMSO and acetonitrile. Both radiochemical conversion and radiochemical recovery were diminished (entry 3). The use of DMF with lower precursor quantity

produced no desired product (entry 7). Scale seems to play a significant role in the reaction as seen with the basic precursors (Table 19).

It had been observed previously that the quantity of precursor had an influence on the success of the radiofluorination of the iodonium salts (Table 1). Further investigation into the effect of the quantity of precursor used on the reaction was therefore conducted. Such optimisation was important with regards to avoiding the waste of valuable precursor used in future investigations.

Table 19 – Effect of precursor quantity on reaction success.
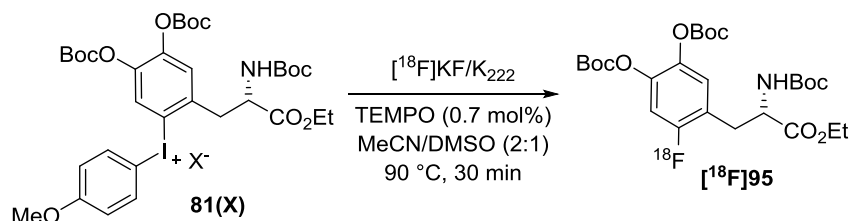
Entry	Scale (mmol)	X$^-$	Solvent Volume (ml)	Salt Conc (mmoldm^{-3})	Conversion (%)(HPLC)	Recovery (%)	RCY (%)
1	0.03	Br$^-$	1.5	20	52	79	41
2	0.015	Br$^-$	0.75	20	0	76	0
3	0.015	Br$^-$	1.5	10	75	66	50
4[a]	0.015	Br$^-$	1.5	10	0	na	0
5	0.015	Br$^-$	1.5	10	0	na	0
6	0.015	TfO$^-$	1.5	10	0	na	0

[a] Reaction carried out in MeCN/DMSO (3:1)

The results obtained were unusual. Entry 3 shows a very good conversion and radiochemical yield while entry 2 with the same quantity of precursor but a lower volume was completely unsuccessful. Entry 3 shows what appeared to be the optimal conditions but further reactions using this quantity of precursor showed problems with

reproducibility (entries 4 to 6). This helped to explain the unusual results when using a lower quantity of precursor (0.015 mmol).

The negative result obtained for entry 2 indicates that the quantity of precursor is of importance rather than its concentration (entry 1 vs entry 2). While this is not true for entry 3, the result can be discounted due to the reactions irreproducibility.

Table 20 – Addressing the reproducibility of the radiofluorination reaction

Entry	Scale (mmol)	X$^-$	Solvent	Conversion (%) (HPLC)	RCY (%)
1	0.015	Br$^-$	MeCN/DMSO (2:1)	75	50[ab]
2	0.030	OTf$^-$	MeCN/DMSO (2:1)	76	47[b]
3	0.030	OTf$^-$	MeCN/DMSO (2:1)	81	<5
4	0.030	Br$^-$	MeCN/DMSO (2:1)	50	<5

[a] Irreproducible result obtained (See Table 19), [b]Erroneous results obtained due to errors in HPLC analysis (See following Section)

The issue of reproducibility could be solved by increasing the quantity of precursor used. 0.03 mmol produces the fluorinated product **[^{18}F]95** successfully using a mixture of acetonitrile and DMSO (2:1) (Table 20, entry 2).

RCC (calculated from radio HPLC analysis) varied from 50% to 81%. Changing the counter ion of the precursor had little effect on the reaction, the triflate counter ion provided slightly improved results.

1.7   Establishing reasons for discrepancies in analysis

After finding a reproducible method for the production of protected [^{18}F]F-DOPA **[^{18}F]95** it was essential to establish the reason for inconsistency between the radio TLC

and radio HPLC. It was decided that the ambiguity would be solved if the ^{18}F labelled product could be isolated using semi-preparative HPLC. Once isolated, the yield could be obtained by measurement in a well counter before radio TLC and HPLC analysis were conducted. This would give an indisputable yield whilst also revealing which analytical technique was giving an incorrect result. Therefore, the semi preparative version of the analytical reverse phase column was obtained (Chapter 4, Pg. 182).

Isolation of the product was successful using conditions optimised on the analytical set up. The obtained product was measured in a well counter revealing a very low decay corrected radiochemical yield of 0.15%. Further analysis showed that the TLC condition used gave the expected chromatogram; with the protected [^{18}F]F-DOPA **[^{18}F]95** product moving with the solvent front (Figure 25).
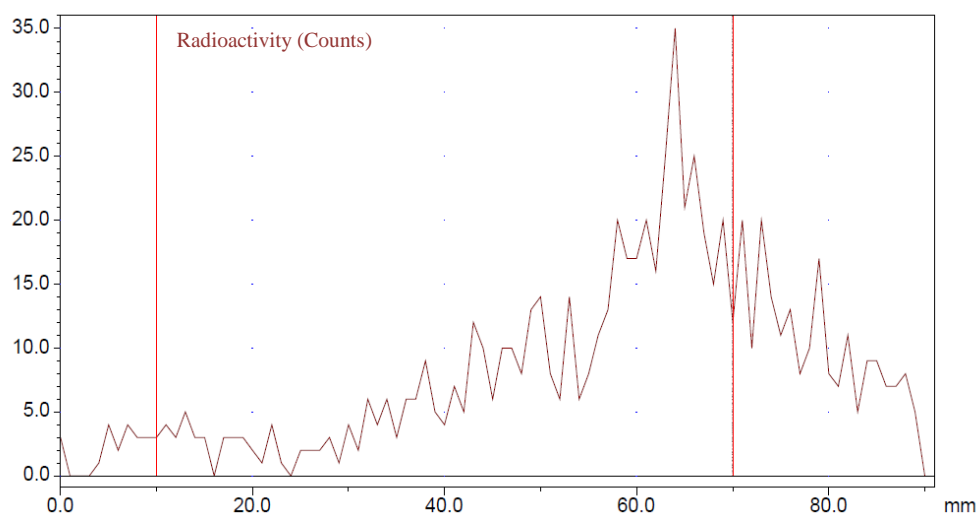
Figure 25 – Radio TLC of HPLC purified [^{18}F]95

The HPLC revealed just one peak giving a radiochemical purity of > 95% (Figure 26).
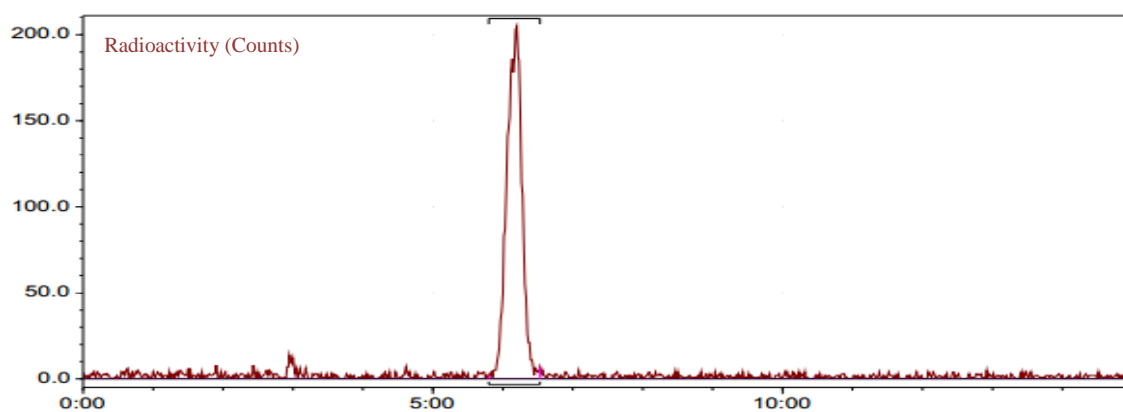
Figure 26 – Radio HPLC chromatogram for isolated [^{18}F]95

Measuring the activity of the semi preparative column after the purification in a well counter revealed that the vast majority of the radioactivity remained on the column. This suggested that the majority of the activity was not passing through the column for detection by the radio detector, thus giving erroneous analysis of the reaction mixture. The trapping / removal of the starting [^{18}F]fluoride or another highly polar analogue looked probable due to the abundance of polar radioactivity observed when analysis was conducted on the crude reaction mixture using the radio TLC.

This was surprising as the analytical HPLC of the [^{18}F]KF/K$_{222}$ had previously been run (Figure 27). This was firstly to determine the retention time of the fluoride and secondly to check if the starting fluoride was passing through the column. The 'trapping' of the [^{18}F]fluoride on the column had already been considered as a reason for the analytical problems. It transpires that while a small quantity passes through the column giving the obtained chromatogram, the vast majority does not pass through the column for analysis. This was further confirmed by injection of azeotropically dried [^{18}F]KF/K$_{222}$ in acetonitrile on to the semi preparative column resulting in the same observation, with very little elution of any radioactive component.
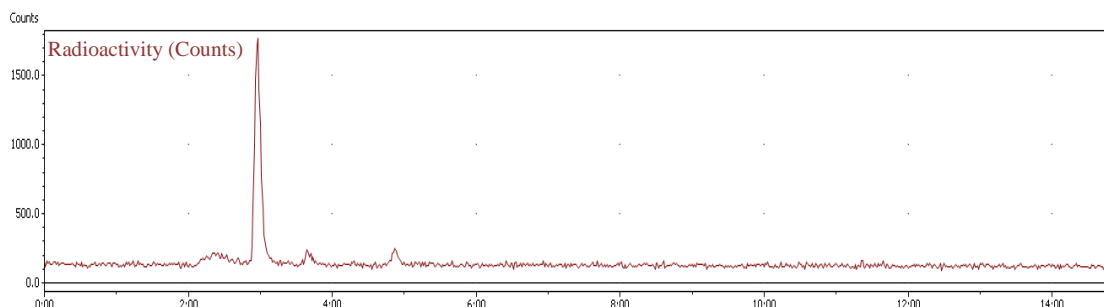
Figure 27 - HPLC chromatogram of [^{18}F]KF/K$_{222}$ in acetonitrile

As a consequence, the HPLC shows analysis of the non-polar radioactive components produced from the [^{18}F]fluoride. Rather than revealing the conversion of [^{18}F]fluoride to the product, it indicates the purity/ ratio of the labelled organic components that have been produced.

This discovery had significant implications to the research so far conducted. Thus, radiochemical conversions (RCCs) calculated from HPLC analysis are erroneous and can only indicate the ratio of labelled components. Radiochemical yields (RCYs) calculated from the analysis must also be disregarded.

The investigation had, however, established two important points: Firstly, the reaction was proceeding with very low conversion of [^{18}F]fluoride to product. Secondly, HPLC analysis was an unreliable tool in this case for monitoring the success of the reaction. Hence, two areas needed to be looked into:

1. What adjustments could be made to improve the conversion of [^{18}F]fluoride?
2. Why was the HPLC system giving incorrect results and how could this be resolved?

1.8   Modifications to improve the conversion of [^{18}F]fluoride to product

Protecting groups of precursor: The majority of the optimisation had been conducted with the triboc protected precursors **89** and **81**. This left the tetraboc and phthalimide protected precursors to be tested under the optimum conditions (Table 20, entries 2-4). Furthermore, the synthesis and testing of a precursor bearing methoxy protection rather than *O*-Boc for the hydroxyl groups remained of interest.

Precursor purity: Changing the work-up process to isolate the iodonium salt precursors with a greater purity. Recrystallization methods had proved unsuccessful but conditions published by Scott *et al.* for the chromatographic purification of iodonium salts looked like a promising alternative.[13] It should be mentioned that NMR analysis of the precipitated precursor showed that it is of a high purity already.

Reaction Conditions: The fact that the conversion of [^{18}F]fluoride to product was very low suggested a possible problem with the initial ligand exchange to form the iodonium fluoride intermediate. Investigation into conditions to encourage this anion exchange was a priority.

1.8.1   Investigation into the fluorination of precursors with alternative protections

Investigations into the effect of different protecting strategies on the radiofluorination reaction were conducted. Two areas were focused on:

Alternative amine protection: The precursors synthesised with alternative amine protection needed to be subjected to the optimised conditions (Table 20, entries 2-4).

Synthesis and testing of methoxy-protected precursors: A route needed to be established for the production of methoxy-protected precursors **137(X)**. Investigations

into the potential advantages and problems of this more robust protecting strategy could then be conducted.

The precursors to be tested are shown in Figure 28.
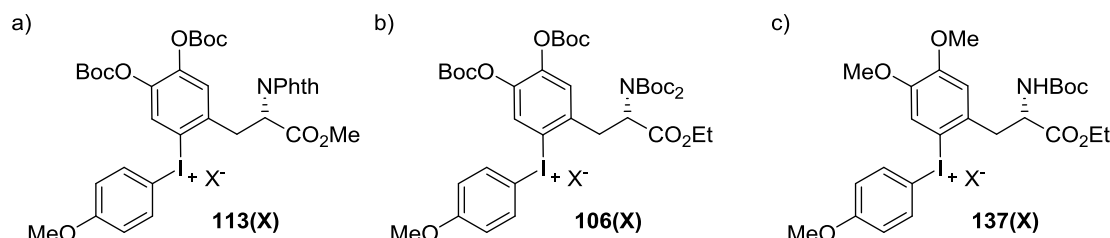
Figure 28 – Precursors with alternative protections to test under optimised radiofluorination conditions. a) N-Phthalimide protected Precursor 113(X). b) N-DiBoc protected Precursor 106(X). c) O-Me protected Precursor 137(X).

1.8.1.1   *Alternative amine protections*

Precursors **113(Br)** and **106(Br)** were submitted to the optimised reaction conditions to check for their efficacy in the fluorination reaction (Scheme 42).
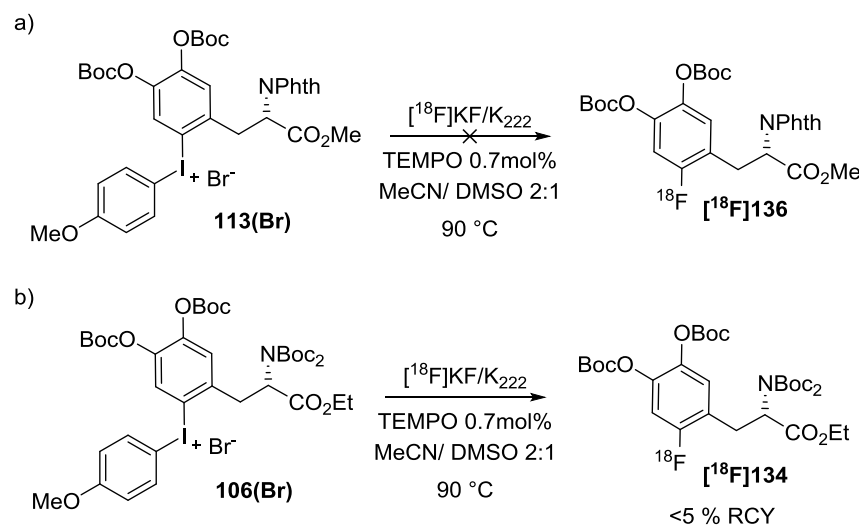
Scheme 42 – Radiofluorination of precursors with alternative protections. a) Fluorination of phthalimide protected precursor 113(Br). b) Fluorination of NBoc$_2$ protected precursor 106(Br).

No product was detected for the fluorination reaction of phthalimide protected precursor **113(Br)** under the optimised conditions. This was determined using analytical HPLC with a coeluted standard. The reaction of the tetraboc protected precursor **106(Br)** was successful. However, the reaction proceeded less cleanly than with the triboc protected precursor and isolation of the product using semi preparative HPLC was not possible. Conversion was too small to be detected by radio TLC.

1.8.1.2 *Methoxy protected iodonium precursor*

With the alternative amine protection strategies proving detrimental to the reaction, an alternative hydroxyl protection was considered. As mentioned earlier (Pg. 71), the use of a methoxy protection for the hydroxyl groups would offer a robust alternative to the *O*-Boc protection.

The use of methoxy protection is not ideal for the electronics of the DOPA aromatic ring as the increased electron density may alter the selectivity of the fluorination. Furthermore, conditions for MeO deprotection are harsher than those needed for OBoc deprotection. However, such protection strategies have been used commonly for previously reported [^{18}F]F-DOPA precursors by Gouverneur, Scott and DiMagno.[13,28,29] Consequently, deprotection strategies are well established and furthermore the protection is compatible under a range of fluorination conditions. Investigation to probe whether the more robust nature of the MeO protection may benefit the iodonium salt precursor was therefore conducted.

Synthesis of the appropriate stannane **141** was accomplished using conditions published by Gouverneur for the synthesis of iodoDOPA moiety **140**[30] followed by stannylation using the previously employed conditions[20] (Scheme 43).
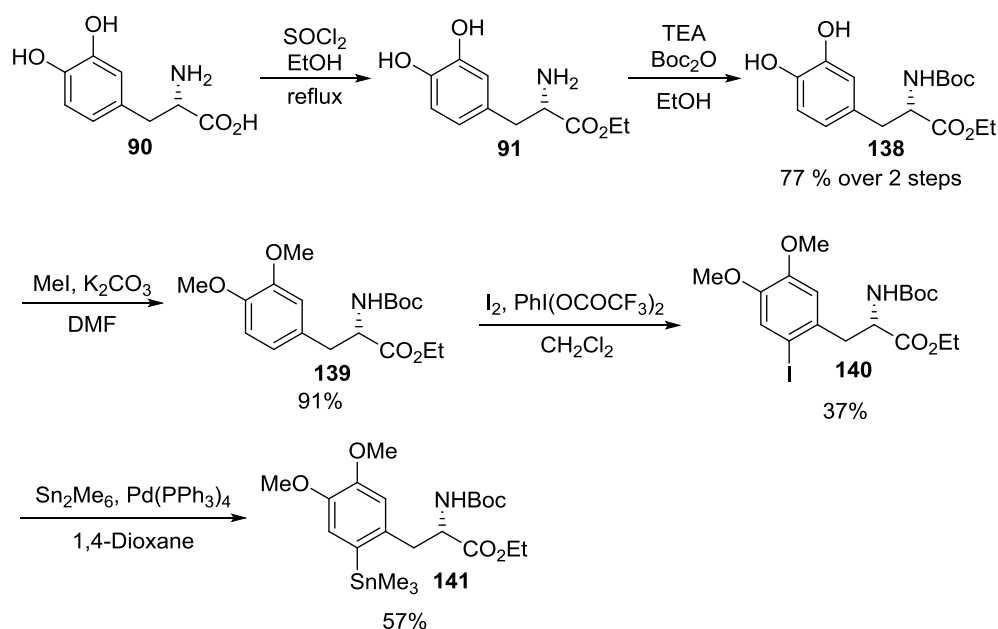
Scheme 43 – Synthesis of stannane 141

Reaction of the stannane with diacetate **72** under the previously optimised conditions proceeded with good yield. In fact no heating was necessary as the reaction showed

significant depletion of the *in situ* produced Koser-type compound **73** immediately after addition of the stannane. This was evaluated by observing the depletion of the characteristic yellow colour of the Koser to a colourless solution. The reaction was left overnight as TLC revealed a small quantity of stannane remained unreacted. Anion exchange to the corresponding iodonium bromide **137(Br)** occurred quantitatively by washing with aqueous saturated KBr (Scheme 44).
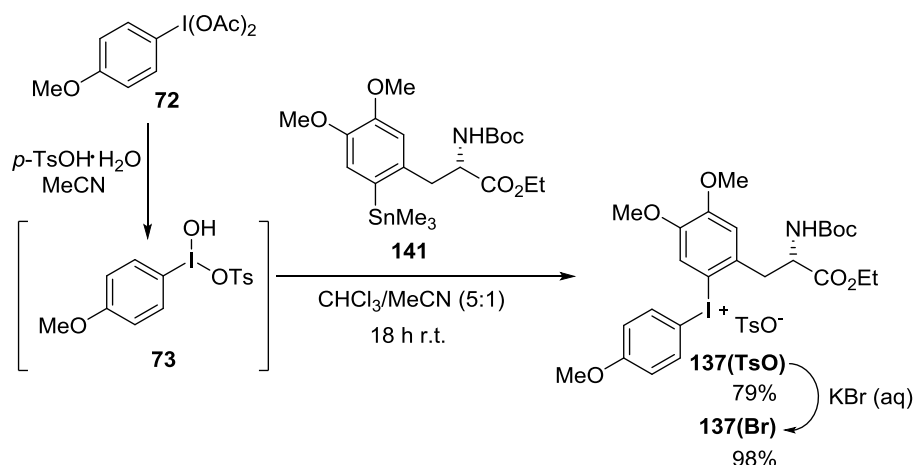
Scheme 44 – Formation of MeO protected iodonium precursor 137TsO and 137Br.

The faster transformation and higher yields observed in this case are likely due to the aryl stannanes increased electron density (due to the methoxy substituents) and therefore greater reactivity.

1.8.1.3   Attempts to improve the synthesis of MeO protected precursor 137

Direct salt formation with 'unactivated' DOPA moiety **139**

After the success of the previous reaction, it was speculated that the 'unactivated' protected DOPA aromatic **139** may be electron rich enough for direct reaction with *in situ* produced Koser **73**. This would attractively remove two steps (including a very unappealing stannylation) along with two difficult chromatographic purifications. Unfortunately, the preliminary experiment was unsuccessful.
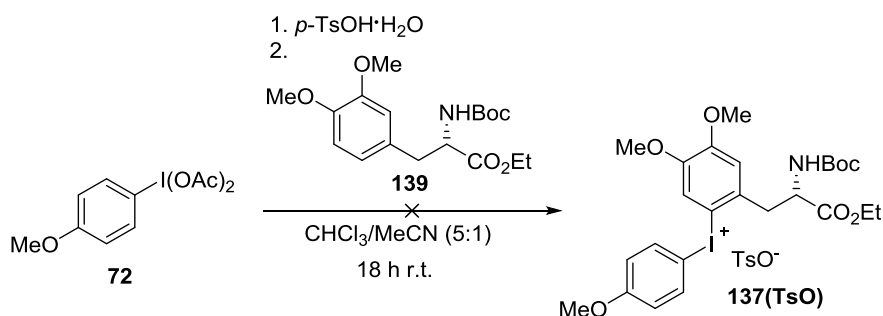
Scheme 45 – Attempted synthesis of precursor 137(TsO) via DOPA moiety 139.

Oxidation of iodoDOPA

Oxidation of the iodoDOPA moiety **140** was also explored. The diacetate product **142** offers a possible route to the iodonium salt precursor which avoids the unattractive stannylation step. As with the previous attempts to oxidise protected iodoDOPA compounds (Pg. 90), this transformation was unsuccessful (Scheme 46).
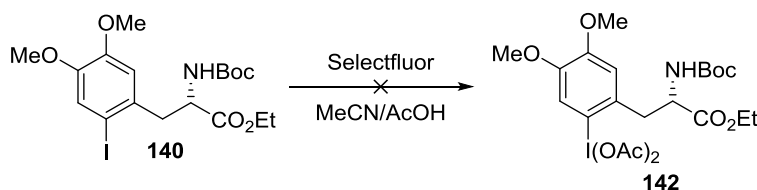
Scheme 46 – Attempted oxidation of iodoDOPA moiety 140 using conditions reported by Ishihara *et al.*[31]

1.8.1.4   *Testing of MeO Protected Precursor 137*

After the successful production of methoxy protected iodonium salt **137**, its utility as a precursor for radio fluorination of the DOPA aromatic was tested. First, the appropriate standard **143** was synthesised for radio HPLC analysis (Scheme 47).
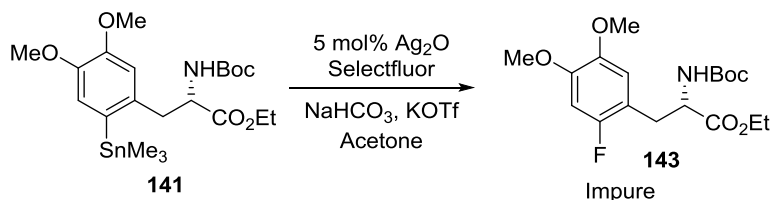
Scheme 47 – Synthesis of MeO protected [¹⁹F]F-DOPA standard 143.

Synthesis of the protected [¹⁹F]F-DOPA compound **143** was conducted in the usual manner. Unfortunately, the purification of the standard proved very difficult. Reverse phase HPLC analysis did not provide full separation under the usual conditions used (Figure 29) therefore eliminating the possibility of purification using a C-18 cartridge.
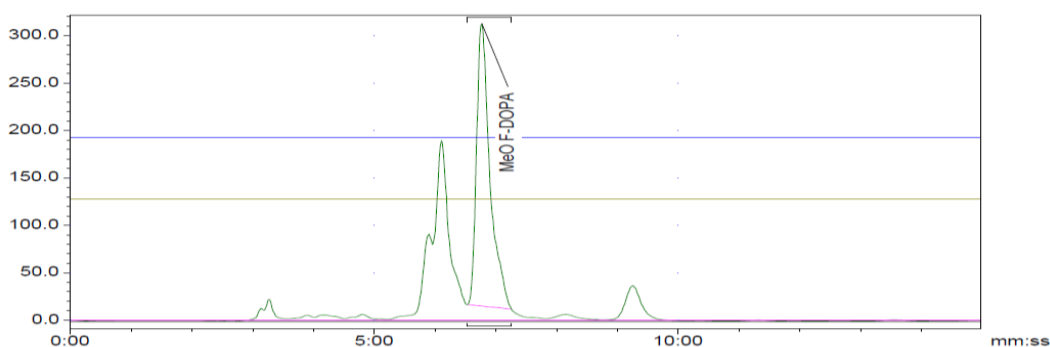
Figure 29 – C-18 HPLC analysis of impure standard 143

However, the impure standard was used to analyse the success of the reaction. Scheme 48 shows the radiofluorination of precursor **137(Br)** under the optimised conditions.
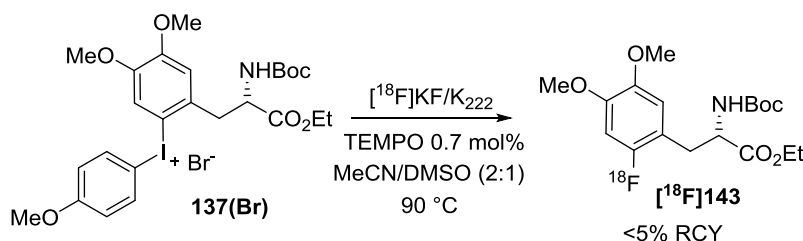
Scheme 48 – Radiofluorination of iodonium salt 137(Br) using the optimised conditions

HPLC revealed the production of the ^{18}F labelled protected DOPA moiety **[^{18}F]143** with a purity of 90% but again TLC conversion was too small to be calculated. Thus, while the new precursor **137(Br)** was as effective as triboc precursor **81(Br)**, no significant improvement resulted from the change in protecting strategy.

1.9   Probing the problems behind the HPLC analysis

After finding what was causing the erroneous HPLC analysis, it was looked into whether any such problems had been observed by others in the field. The use of HPLC for determining the success of radiofluorination reactions is common.[18,32] Communication with several radiochemists in industry revealed that our situation was unusual. Recommendations to further dilute the sample with water did not produce any difference to the chromatogram. Analysis of the reaction sample after removal of the guard column was conducted in order to check if contaminants on this part of the column were trapping the [^{18}F]fluoride, but this was not the case.

Eventually changing the solvent system provided us with a chromatogram that signalled the presence of a significant amount of another radioactive species. Chromatograms obtained using the original solvent system (acetonitrile and water) and the new solvent

system (acetonitrile and aqueous ammonium formate solution 50 mM) are shown in Figure 30 - 32.
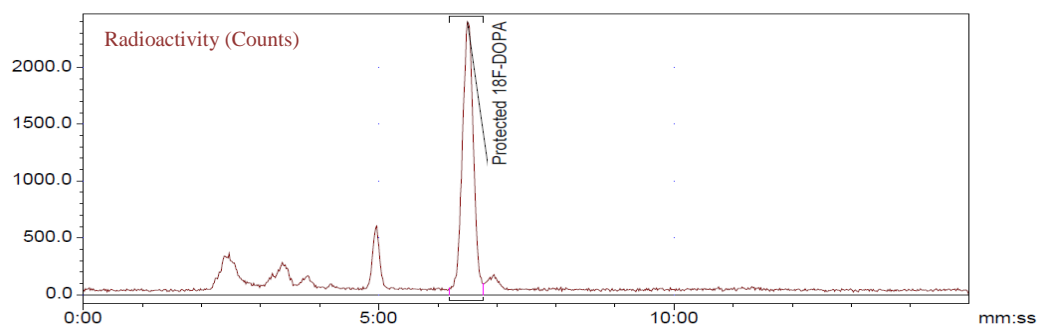
Figure 30 - [^{18}F]Triboc F- DOPA [^{18}F]95 analysis: Gradient: 80% MeCN in H$_2$O (0.01% formic acid) (Isocratic)
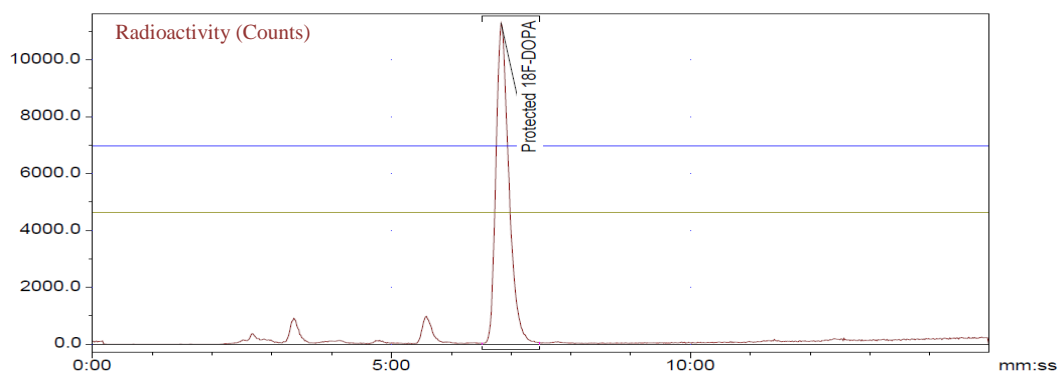
Figure 31 - [^{18}F]MeO Protected F-DOPA [^{18}F]143 analysis: Gradient: 60% MeCN in H$_2$O (0.01% formic acid) (Isocratic)
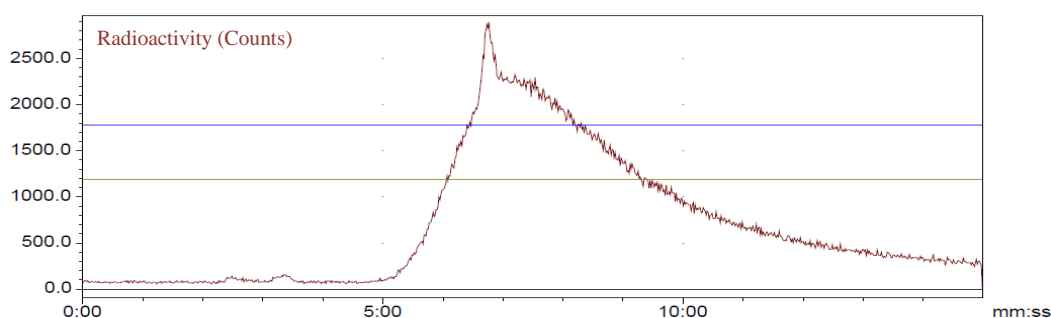
Figure 32 - [^{18}F]MeO Protected F-DOPA [^{18}F]143 analysis: Gradient: 60% MeCN: 40% Aqueous Ammonium Formate (50mM) (Isocratic)

The unreacted [^{18}F]fluoride passes through the column, but not as a peak that can be analysed with any specificity. However, this analysis at least gives an indication of the true state of the reaction mixture.

Further discussion with radiochemists from Imanova revealed that very low isolated radiochemical yields despite promising radiochemical conversion (RCC) had been an

issue for them and others in the field.[33] Examples in the literature include the work by Scott *et al*. in which only 1% non-decay corrected product was isolated from a conversion of 31%.[13] A more suitable method for analysis clearly needs to be established for such reactions.

Subsequent to our investigations, a paper on the retention of [^{18}F]fluoride on reverse phase HPLC columns was published by Bormans *et al*.[34] The paper describes a number of factors that can influence the retention of [^{18}F]fluoride. A brief overview of the papers findings is given below, along with the original conditions used for our analytical system for comparison.

Factors affecting [^{18}F]fluoride retention when using reverse phase HPLC:

1. The pH of the eluent
2. The type of column
3. Composition of the buffer
4. Concentration of the organic component
5. Nature of organic component

The pH has a significant effect on the retention of [^{18}F]fluoride with low pH giving the highest retention. For the tested column (XBridge C18), with an eluent pH of 2, the recovered radioactivity was 42.4±11.6% whilst pH 4 - 9 gave recoveries above 90%.

The type of column also had a strong influence on the retention of [^{18}F]fluoride. Columns were tested at pH 3 and 5. The highest retention of fluoride was found when using the Phenomenex C18 column (radioactivity recovered: pH 3 = 16.6±17.3%, pH 5 = 90.7±3.5%), whilst Hamilton PRP-1 column showed the lowest retention (radioactivity recovered: pH 3 = 95.3±1.2%, pH 5 = 97.4±1.6%).

The type of buffer had only a limited influence on the retention of [^{18}F]fluoride. A slightly higher recovery of radioactivity was found when using sodium phosphate buffer compared to sodium acetate buffer: Sodium phosphate buffer (pH 5, 12.5 mM)/MeCN (95/5), recovery = 93.4±1.8%. Sodium acetate buffer (pH 5, 12.5 mM)/MeCN (95/5), recovery = 87.2±2.3%.

However, when using 0.1% TFA H$_2$O/ 0.1% TFA MeCN (95/5) (pH 1.7) as the eluent the radioactivity recovered was severely diminished (recovery = 34.5±9.9%). This is in agreement with observations regarding the pH (see above).

[^{18}F]fluoride retention on the column was found to slightly increase with higher *concentrations of the eluents' organic component*. The conditions tested were; sodium phosphate buffer (pH 3, 12.5 mM)/MeCN (95/5) and sodium phosphate buffer (pH 3, 12.5 mM)/MeCN (50/50). When the mobile phase contained acetonitrile at 50%, the recovered radioactivity from the column diminished to 62.0±8.1% from 72.2±8.0% at 5% acetonitrile.

The tested *organic components* were ethanol and acetonitrile. Recovery of radioactivity was tested at both pH 3 and 5. Ethanol showed a greater recovery of [^{18}F]fluoride from the column than acetonitrile using 95/5 aqueous/organic conditions: H$_2$O/EtOH (95.5) radioactivity recovered: pH 3 = 81.2±5.1%, pH 5 = 100.0±3.8%). H$_2$O/MeCN (95.5) radioactivity recovered: pH 3 = 72.2±6.0%, pH 5 = 93.4±1.8%).

Table 21 - Summary and Comparison

Literature conditions producing an increased retention of [^{18}F]fluoride	Our initial conditions used for radio HPLC analysis
Low pH	pH 1.7
The Phenomenex C18 column shows a significantly higher retention of [^{18}F]fluoride than the others tested	Column used: Phenomenex C18 column
Addition of 0.1 % TFA to mobile phase	Addition of 0.1 % TFA to mobile phase
High organic component in mobile phase	0.1% TFA H$_2$O/ 0.1% TFA MeCN - between (10/90) and (30/70) depending on the compound.
Using acetonitrile for the organic component gives a higher retention of [^{18}F]fluoride than ethanol	Acetonitrile used as organic component of mobile phase

Looking at the summary above, it is evident why the original radio HPLC conditions used gave analytical problems and provided erroneous results.

Bormans *et al.* suggest that the retention is produced by a low binding affinity to silica based columns and showed that retention could be alleviated by saturation with [^{19}F]fluoride.

The authors also highlight a number of papers in which radio HPLC analysis with a low pH mobile phase has been used to determine the radiochemical purity of a radiotracer, potentially giving misleading results.

1.10 Alternative work-up to improve precursor purity

With the alternative protection strategies not providing a solution to the poor RCYs, investigations into alternative work-ups that might provide a purer and therefore more suitable precursor were conducted. After failing to recrystallize the iodonium salts, chromatographic purification was investigated. Firstly, column chromatography using a gradient of acetone and hexane reported by DiMagno *et al.* was looked into, but gave unsatisfactory results with significant quantities of the compound being retained on the column. A solvent system of isopropanol and dichloromethane reported by Scott *et al.*, however, gave excellent results.[13] Separation of a very small amount of impurity from the precipitated product (approx. 2% impurity) was achieved using this method. The chromatogram for the purification run on an automated Biotage® system is shown in Figure 9. The impurity could not be identified due to the small quantities available for analysis.
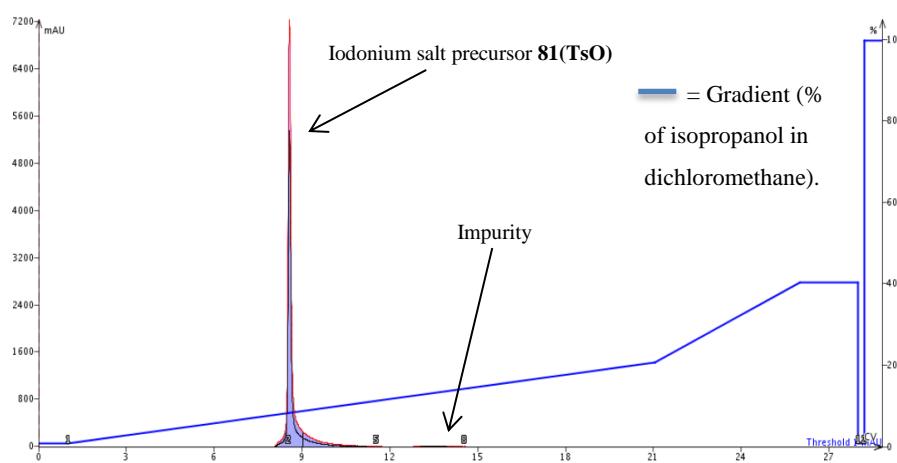
Figure 33 – Chromatogram for purification of precursor 81(TsO)

After isolation of the iodonium salt **81(TsO)** from the pure fractions as a gum, the salt was re-precipitated and dried ready for testing under radiofluorination conditions.

1.10.1 Testing of column purified iodonium salt 81(TsO)

The purified iodonium salt gave no improvement to the reaction, which again proceeded with low radiochemical yields (Table 22). The reaction was also performed without the radical scavenger TEMPO. No difference in the reaction was observed under these conditions (Table 22, entry 2).

Table 22 – Fluorination results for iodonium salt 81(TsO) with and without TEMPO
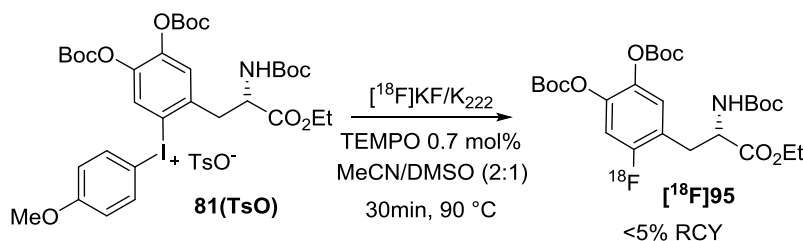
Entry	TEMPO (equiv)	RCY (%)
1	0.7	<5
2	0	<5

1.10.2 Attempts to encourage iodonium fluoride formation

Due to the low conversion of [^{18}F]fluoride to labelled product it was hypothesised that low conversion to the iodonium fluoride intermediate could be responsible. To try and encourage ligand exchange to the iodonium fluoride the reactants were first warmed to a temperature at which breakdown of the iodonium salt would not occur but may encourage the ligand exchange. Breakdown of the salt was then achieved by subsequent heating to 90 °C (Scheme 49).
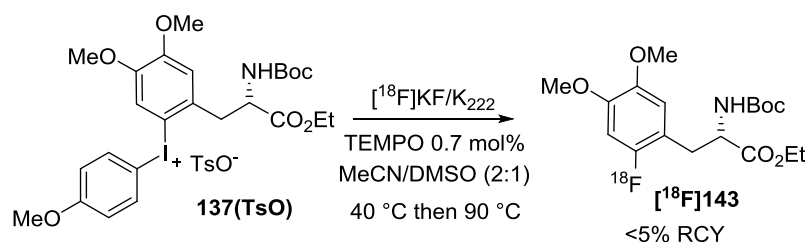
Scheme 49 – Fluorination of iodonium tosylate 137(TsO) under conditions to encourage ligand exchange

Unfortunately, these preliminary investigations showed no improvement in radiochemical yield (RCY).

1.11 Conducting literature radiofluorination procedures using the Eckert and Ziegler equipment

The lack of success in optimisation of the radiofluorination reaction prompted a look into the success of other reactions employing the Eckert and Ziegler equipment used for the fluorination.

1.11.1 Minimalist radiofluorination of iodonium salts

One recent publication looked of interest due to its simplicity of procedure and methodology. The use of iodonium salts without any additives provides a simple and minimalist approach to fluorination. Firstly, the [^{18}F]fluoride is eluted from the QMA cartridge by a solution of the iodonium salt in methanol. Evaporation of the methanol is then conducted before resolvation of the iodonium salt and [^{18}F]fluoride in the solvent of choice. The reaction is then heated to induce breakdown of the salt, generating the fluorinated product(s). Precursor **146** was chosen as the substrate for this reaction. Scheme 50 shows the synthesis of the precursor **146** and subsequent radiofluorination reaction.
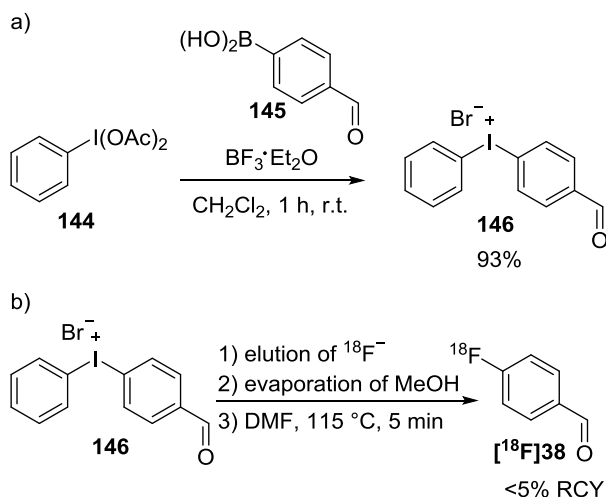
Scheme 50 – Synthesis and radiofluorination of iodonium salt 146 for [^{18}F]4-fluorobenzaldehyde production under minimalistic conditions

The reaction was successful (showing product formation in the HPLC analysis) but again proceeded with poor radiochemical conversion (measured by radio TLC).

Investigation into the analytical procedures used in the publication shows that yields were determined using radio HPLC. In light of the work published by Bormans *et al.*[34] further investigation by the publishers may be needed to ascertain whether these results are accurate.

1.11.2 Copper catalysed fluorination of a boronic ester precursor 32

Another investigation considered worthwhile was the production of protected [^{18}F]F-DOPA **143** using the method reported by Gouverneur *et al.* (Scheme 51b). The synthesis of the precursor was adapted slightly to the following route as protected iodoDOPA compound **140** was already available to us from the synthesis of iodonium salt **137** (Scheme 51a).

a)

b)
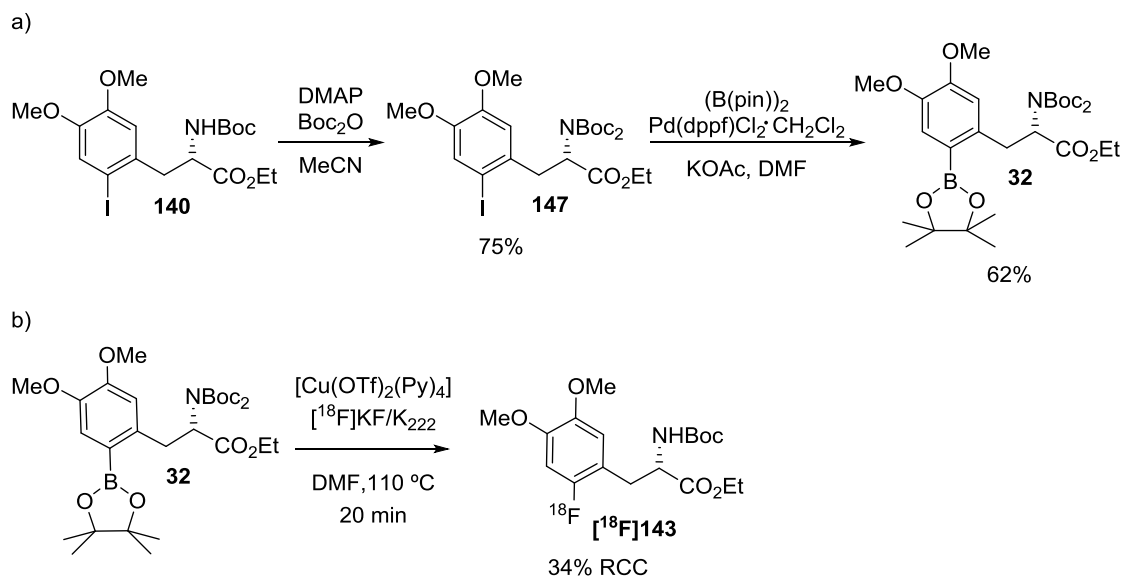
Scheme 51 – a) Synthesis and b) Radiofluorination of boronic ester 32 using conditions reported by Gouverneur *et al.*[28]

Repeating the literature procedure was successful with the reaction proceeding with a RCC of 34% as measured by radio TLC. It should be noted that confirmation of the products' identity by coelution with a cold standard **143** was not performed as this compound was not available at the time of the experiment.

The results suggest that while the Eckert and Ziegler set up is appropriate for certain radiofluorination methods, the use of iodonium salts with the current set up certainly needs further optimisation. This irreproducibility is a concern especially for such conditions described in Scheme 50b where minimalistic conditions should greatly simplify reproduction of the reported reaction.

1.12 Isolation of the protected DOPA moiety

The use of semi preparative HPLC for the purification and isolation of **[^{18}F]95** was successful. However, it is also long winded and loss of some product during transfer to the injection loop was unavoidable using the Eckert and Ziegler set up (Figure 34). This encouraged investigation into a cartridge purification.
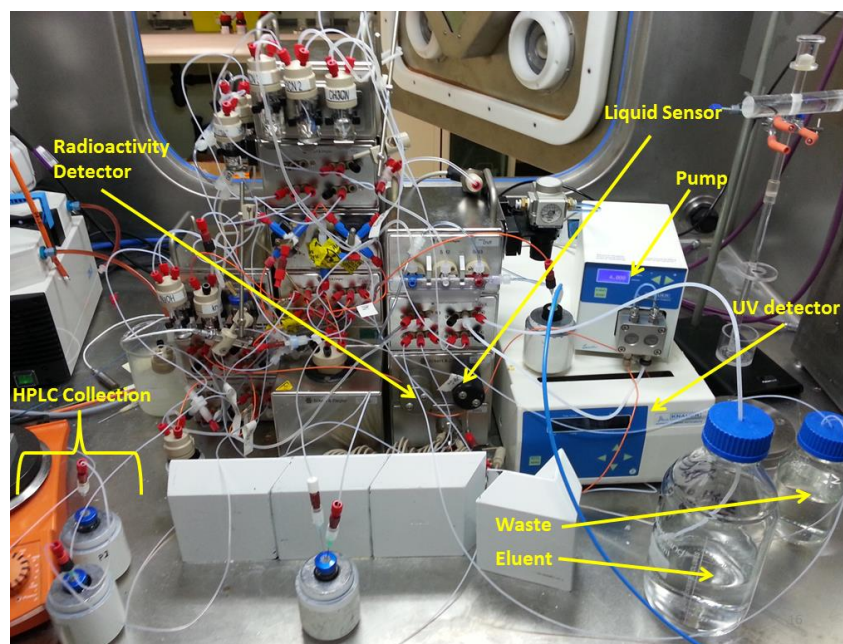
Figure 34 – HPLC purification system for isolation of ^{18}F labelled compounds

Using a Waters^{TM} alumina cartridge to remove the remaining fluoride was successful providing the product with a radio TLC purity of 80% (20% [^{18}F]fluoride) and radio HPLC purity of 82%. RCR was 3%, providing a decay corrected RCY of 2% (based on a purity of 64%). This is a much improved RCY compared to that obtained using HPLC purification (0.15%). The product **[^{18}F]95** could also be trapped on a C-18 cartridge before elution with ethanol to provide the product with an improved purity of 94%. This seems a more suitable purification strategy before conducting the required deprotection as valuable time is saved, therefore improving the non-decay corrected yields.

1.13 Conclusion

A number of iodonium salt precursors for [^{18}F]F-DOPA synthesis have been synthesised and tested under radiofluorination conditions. The reaction proceeds to produce the desired radiolabelled products **[^{18}F]95**, **[^{18}F]134** and **[^{18}F]143**, but unfortunately RCYs are low.

Attempts to improve radiochemical yields by altering the precursor and aspects of the reaction conditions were all unsuccessful, although an improved isolated yield could be obtained using cartridge based purification. This came at the cost of lower radiochemical and chemical purity.

Significant problems with analysis of the radiofluorination reactions were discovered and addressed. This highlights an important issue for analysis of radiofluorination

reactions. Furthermore, it emphasises the value of isolated radiochemical yields for confirmation of calculated yields from radio HPLC and TLC. Indeed, a quick look through the literature on radiofluorination of iodonium salts showed publications that reported yields based only on HPLC analysis.[18,32] More robust analysis for radiofluorination reactions needs to be implemented across the field.

1.14 Outlook

For the current method to be of use as a synthesis route to [^{18}F]F-DOPA **9**, considerable optimisation needs to be conducted to improve RCYs. If improvements to the radiochemical yield can be made, the simplicity of precursor production and the stability of the iodonium salt compounds would make this a very attractive route for nucleophilic synthesis of this radiotracer.

1.15 References

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Solid Supported Iodonium Salts for Fluorinations

1.1 Introduction

Solid-phase organic synthesis may be defined as 'synthesis in which the starting material and synthetic intermediates are linked to an insoluble support'.[1] The use of a solid support for synthesis was first reported by Merrifield in 1963.[2] Merrifield utilised chloromethyl functionalised resin for the production of peptides. It was shown that solid supported synthesis could provide a simple and quick methodology for synthesising such molecules.

Since this pioneering work, the use of polymer bound precursors and reagents have become widespread in organic synthesis.[3–6] The general advantage provided by the methodology is the ability to mechanically separate intermediates from reagents and solvents.[1] This relies on using a polymer support with the correct properties with regards to insolubility, robustness and swelling behaviour. Most commonly used are polystyrene supports. These resins are cross-linked with divinylbenzene (DVB) to varying degrees depending on the properties desired. 1-2% cross-linking with DVB is typical as this provides a desirable balance between high insolubility and robustness (increasing with DVB cross-linking) and good swelling behaviour (decreasing with DVB cross-linking).[5] Other resins used for solid phase synthesis include TentaGel and ArgoGel resins. These resins are co polymers of weakly cross-linked polystyrene/DVB and linear poly(ethylene glycol).[7]

Functionalization of the solid support varies with its demands. Commonly used starting functionalities include the use of polymer bound alkyl halides or alcohols for ether linkage to the resin. Alkyl amino functionality is also popular for linker attachment using the more robust amide bond formation. This is a frequent strategy for synthesis requiring resilience to strongly acidic conditions. Some commercially available, functionalised polystyrene supports are shown in Figure 1.
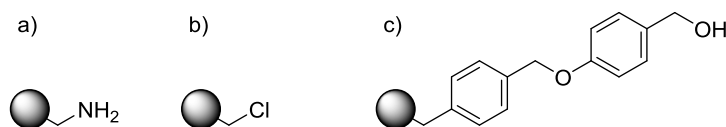
Figure 1 – Commercially available resins. a) Amino methyl resin. b) Merrifield resin c) Wang resin

The cleavage of the polymer-bound molecule is a key step in solid-supported organic synthesis and can be used to introduce functionality into the molecule being cleaved. This includes the introduction of halogens such as fluorine.[4] The use of solid-supported precursors for the introduction of the ^{18}F isotope during this cleavage step has already been described in Chapter 1 (Pg. 29). Both introduction by electrophilic and nucleophilic methods found utility.

More appropriate to this work is the use of solid-supported iodonium salts for the introduction of fluorine. Work in this area includes radiofluorination of solid supported iodonium salt precursors for the production of [^{18}F]fluorobenzene and [^{18}F]fluorouracil reported by Brady *et al.*[8] Scheme 1 shows the radiofluorination of solid-supported [^{18}F]fluorouracil precursor **148(TfO)**.
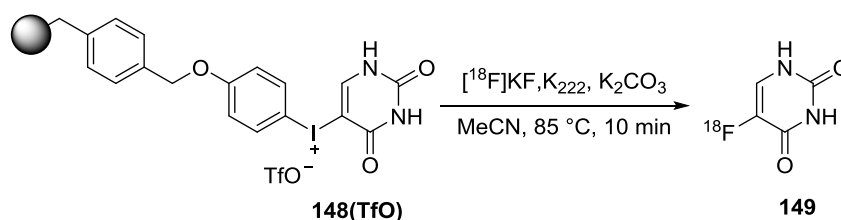
Scheme 1 - Radiofluorination of solid supported [^{18}F]fluorouracil precursor 148[8]

Furthermore, a patent published by Carroll *et al.* shows the synthesis of diaryliodonium salt precursors for radiofluorination linked to an amino resin via amide linkage.[9] Here, a solid supported precursor for the production of [^{18}F]F-DOPA **9** is described. The patent therefore provided a solid platform to expand on and is the basis for the earlier work in this chapter.

1.2   Results and Discussion

1.2.1   Initial Investigations into a solid Supported Precursor for [^{18}F]F-DOPA Synthesis

The investigations started with precursor synthesis, with an initial focus on a precursor for the production of [^{18}F]fluorobenzene **[^{18}F]77**.

Resin Functionalisation

As alluded to above, a synthesis route for the production of solid supported diaryliodonium salts was reported by Carroll *et al.*[9] providing a suitable starting point. The strategy uses amide bond formation as the key step, linking the precursor to the resin. Amino methyl functionalised polystyrene resin is used for coupling to the following carboxylic acids **150** and **151(TFA)**.
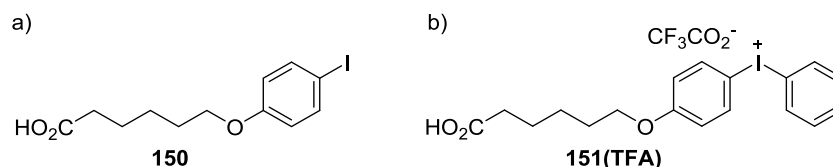
Figure 2 – Two carboxylic acids for the formation of a solid supported iodonium salt precursor. a) Iodoaryl linker 150 for amide coupling followed by oxidation to the iodonium salt. b) Iodonium salt functionalised linker 151(TFA) ready for amide coupling to the amine resin.

The two carboxylic acids **150** and **151(TFA)** provide two possible routes to the same resin bound precursor. Linker **150** takes part in subsequent transformations to produce the polymer supported iodonium salt while amide linkage of **151(TFA)** to the amino methyl resin affords the resin bound precursor directly. The two routes are shown in Scheme 2 and Scheme 3.

Route A using linker **150**
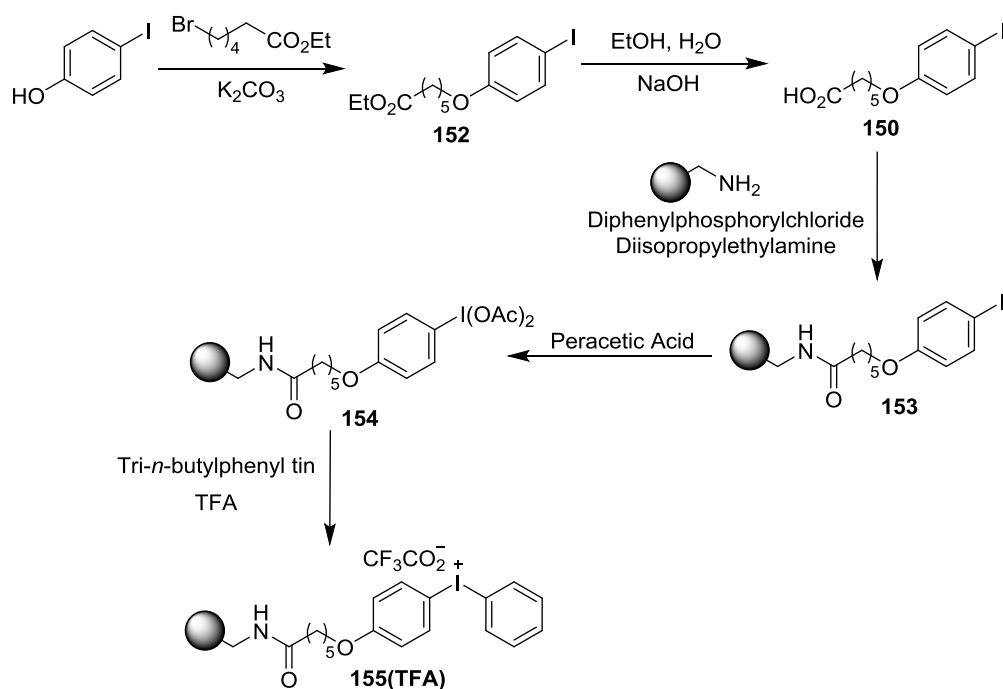
Scheme 2 – Synthesis of resin bound iodonium salt 155(TFA) via linker 150

Route B using linker **151(TFA)**
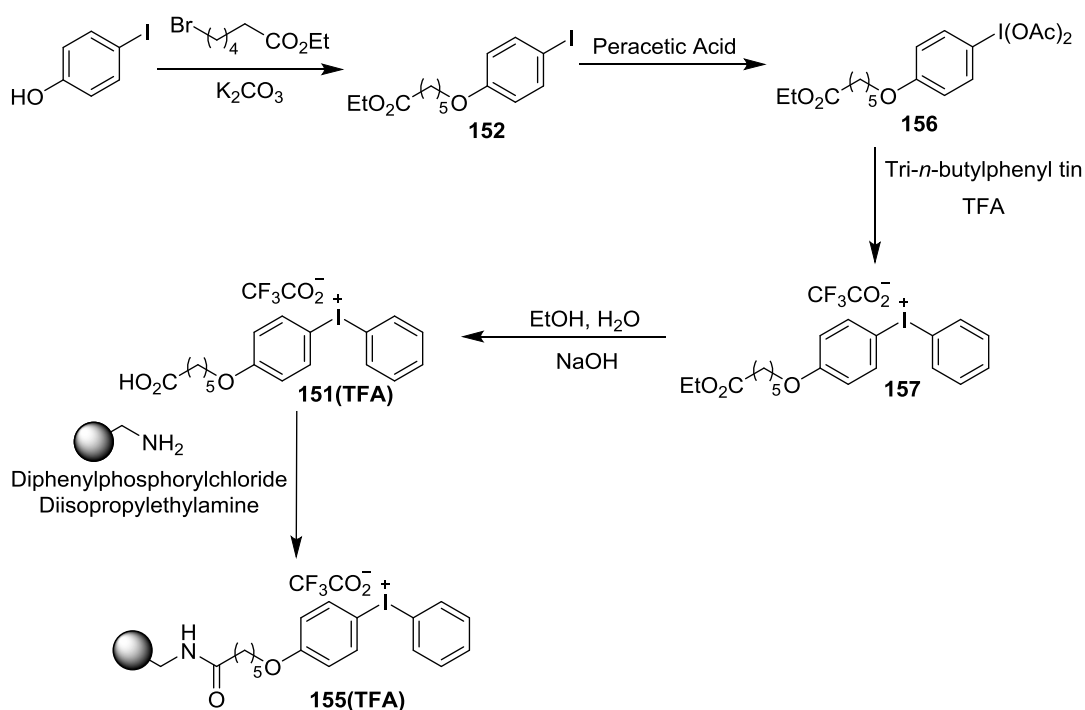
Scheme 3 - Synthesis of resin bound iodonium salt 155(TFA) via linker 151(TFA)

Route A was chosen for the investigation as the patent revealed a higher loading with regards to iodine for this method (11.59% I for route A vs 7.49% I for route B using elemental analysis).

Synthesis of carboxylic acid linker 150

Formation of the iodoaryl-linker **150** was very successful with both the formation and hydrolysis of ethyl 6-(4-iodophenoxy) hexanoate **152** proceeding with excellent yields (Scheme 4).
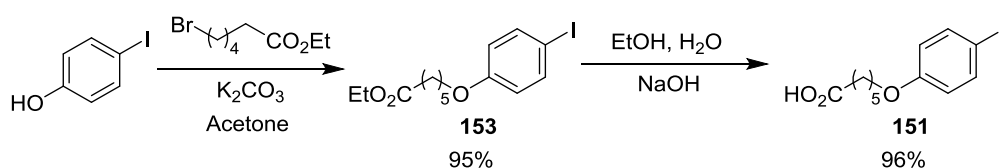
Scheme 4 – Formation of iodoaryl linker 150

However, functionalisation of the amino methyl resin with the aforementioned linker **150** proved to be troublesome and only a low functionality could be attained (Table 1, entries 1-3). A number of different conditions were used to try and obtain a more adequate loading (Amide coupling of linker to the resin as shown in Table 1).

Amide coupling of linker to resin

Table 1 – Optimisation for amide coupling of linker 150 to aminomethyl resin
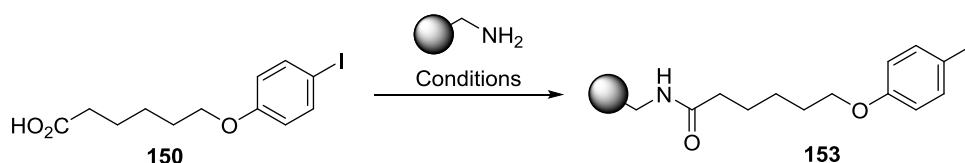
Entry	Resin	Coupling Agent	Time (h)	DIPEA Equiv	Solvent	mmolg^{-1}	Yield (%)[a,]	E/A (% I)
1	aminomethyl	DPPC	18	2.25	CH_2Cl_2	0.36	37	3.5
2	aminomethyl	DPPC	18	2.25	CH_2Cl_2	0.27	18	-
3	aminomethyl	DPPC	18	2.25	CH_2Cl_2	0.17	12	-
4	aminomethyl	DPPC	18	2.25	CH_2Cl_2	0.66	44	-
5	aminomethyl	DPPC	25	3	CH_2Cl_2	0.49	33	-
6	aminomethyl	DPPC	25	3	DMF	0.07	4	-
7	aminomethyl	T$_3$P	48	2	EtOAc	0.33	37	-
8	aminomethyl	T$_3$P	25	2	DMF	0.19	13	-
9	aminomethyl	T$_3$P	25	2	CH_2Cl_2	0.29	19	-
10	tris (aminoethyl)	T$_3$P	65	2	EtOAc	1.73	69	12.32
11	tris (aminoethyl)	DPPC	43	2.25	CH_2Cl_2	2.11	85	13.6

[a] Yields based on gain in mass of resin or by elemental analysis when available (See supplementary information for details).

DIPA = Diisopropylethylamine, DPPC = Diphenylphosphoryl Chloride, T$_3$P = Propylphosphonic anhydride

After analysis of entries 1-3 showed inconsistent and poor yields the procedure was carried out under inert conditions to afford an increase in the loading (entry 4). All future experiments were carried out under inert conditions (entries 5-11). Despite the improvement, yields were still poor and repeats of the experiment gave inconsistencies in the loading.

Increasing in the equivalents of diisopropylethylamine was unsuccessful in increasing the loading (entry 5). The use of anhydrous DMF as solvent was also tested as such polar aprotic solvents can give beneficial 'swelling' of the support. However, this was detrimental to the reaction (entries 6 and 8). The use of T$_3$P (propylphosphonic anhydride) as a coupling agent also failed to improve functionalisation of the support in a number of solvents (entries 7-9).

The poor results prompted a test reaction in which the amide linkage was performed between the 6-(4-iodophenoxy)hexanoic acid **150** and aniline to give **158** in excellent yield (Scheme 5).
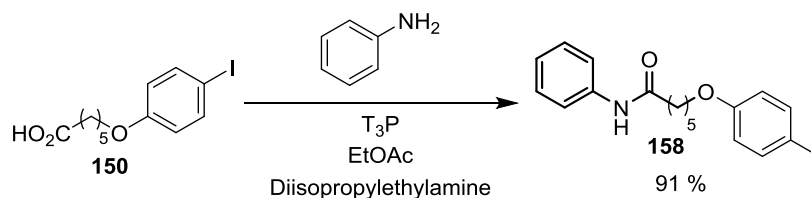
Scheme 5 – Amide coupling of linker 150 to aniline

These results implied complications had originated from the solid supported amine and a solution was realised by the use of an alternatively functionalised resin. Coupling reactions with tris (aminoethyl) resin gave substantially improved loading with both coupling agents (Table 1, entries 10 and 11). This suggested that a steric effect from the resin may have inhibited penetration of the reagents to the supports functionalised sites. The optimized conditions for iodoaryl functionalisation of the resin are shown below (Scheme 6).
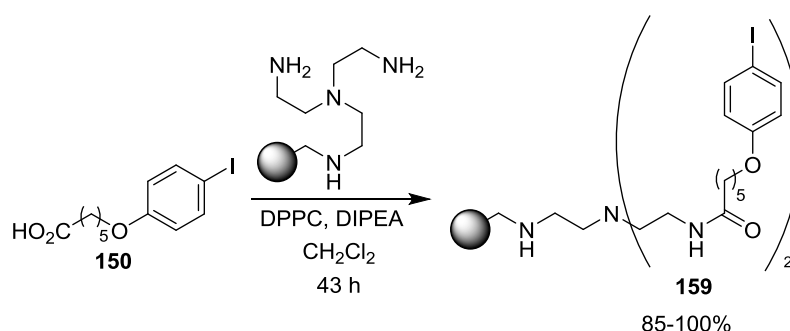
Scheme 6 – Amide coupling of linker 150 to tris (2-aminoethyl)amine resin

Oxidation and iodonium salt formation

Oxidation of the supported iodoaryl moiety with peracetic acid proceeded to give diacetate **160** in ≈97% yield before addition of tri-*n*-butylphenyltin and TFA afforded the solid supported diaryliodonium salt **161(TFA)** in ≈58% yield. The entire precursor synthesis is shown in Scheme 7.
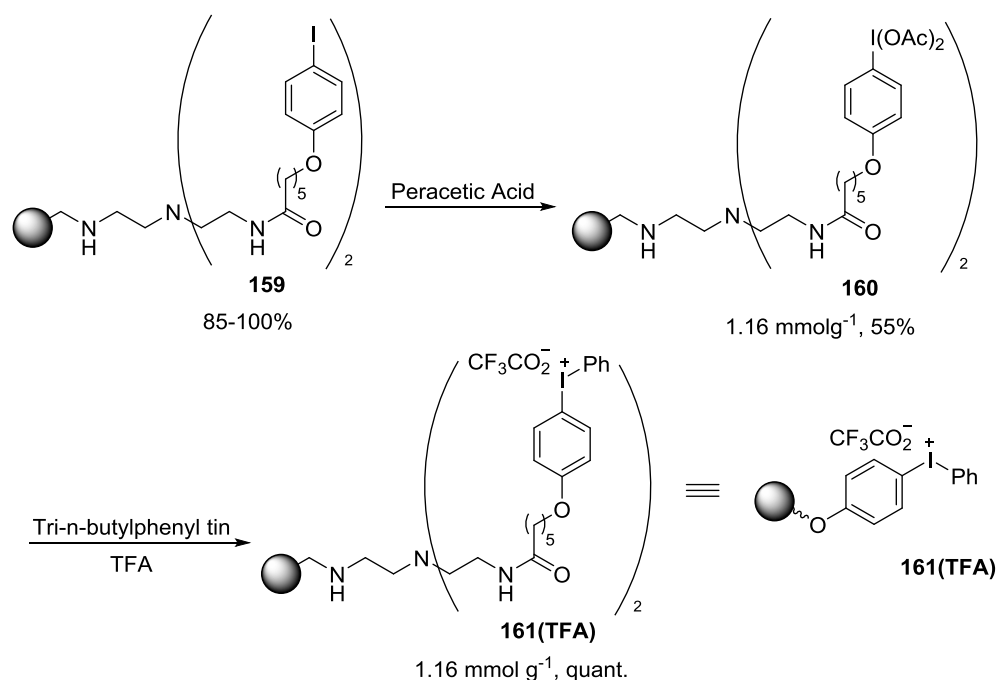
Scheme 7 – Production of solid supported iodonium salt precursor 161(TFA).

Radiofluorination of Solid Supported Resin

Fluorination of the solid supported salt produced [^{18}F]fluorobenzene **[18F]77**. The product was characterised by HPLC (Figure 3) showing a 74% conversion and 12% RCY (Scheme 8). TLC showed a radiochemical conversion of 3% and can be considered the true result of the reaction due to the problems discovered with the HPLC analysis (Chapter 2, Pg. 115).
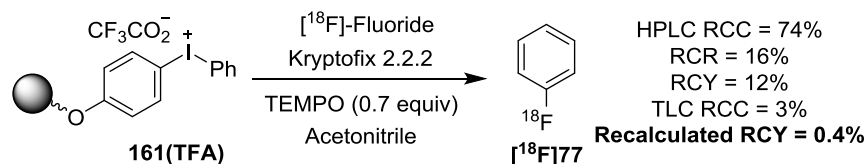
Scheme 8 – 'Hot' fluorination of polymer supported iodonium salt precursor 161(TFA)

Identity of the radiolabelled compound was confirmed by co-elution with a 'cold' standard **77**.
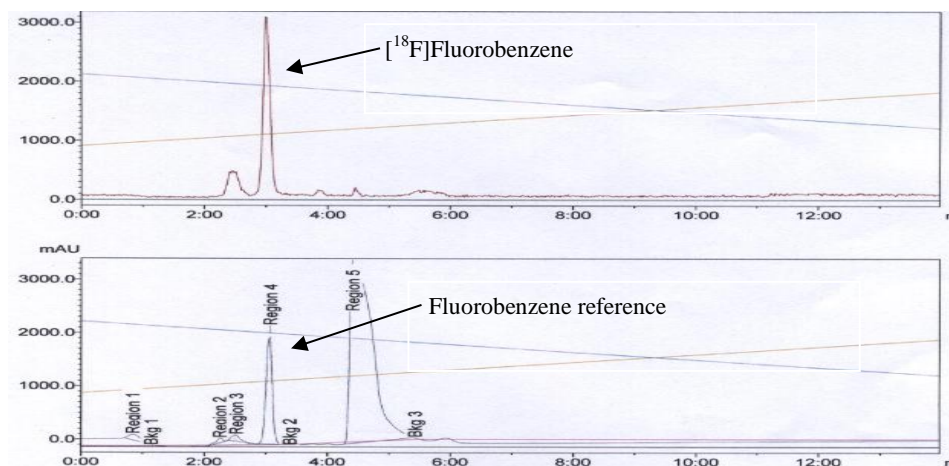
Figure 3 - Product sample spiked with fluorobenzene reference

In order to achieve the maximum potential of the solid-supported methodology, it was proposed that solid-supported TEMPO could be used in conjunction with the solid-supported precursor **161(TFA)**. This meant that in the event of a clean and selective reaction it should be possible to isolate pure product with simple cartridge purification. The reaction with solid-supported TEMPO (2.0 mmol g^{-1}), however, was not as successful as that reported for the unsupported TEMPO. Not only did the extra resin in the reaction mixture cause an increase in the amount of activity retained by the resin (12% unsupported TEMPO, 19 % supported TEMPO) but the radio HPLC analysis showed a significant increase in impurities (Figure 4).
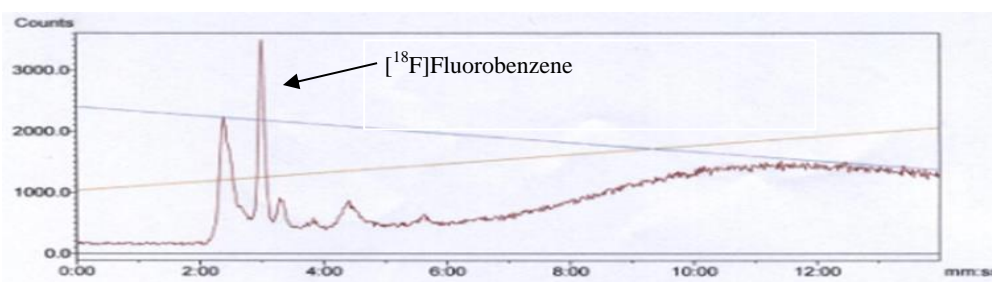
Figure 4 – Solid-supported TEMPO reaction

Production of solid supported [^{18}F]F-DOPA precursor

Formation of a solid supported [^{18}F]F-DOPA precursor **162** was unsuccessful. The same conditions used for the formation of the fluorobenzene precursor were employed aside from the addition of methyl *N-t*-butoxycarbonyl-3,4-di(*t*-butoxycarbonyloxy)-6-trimethylstannylphenylalanine **82** instead of the tri-*n*-butylphenyltin (Scheme 9).
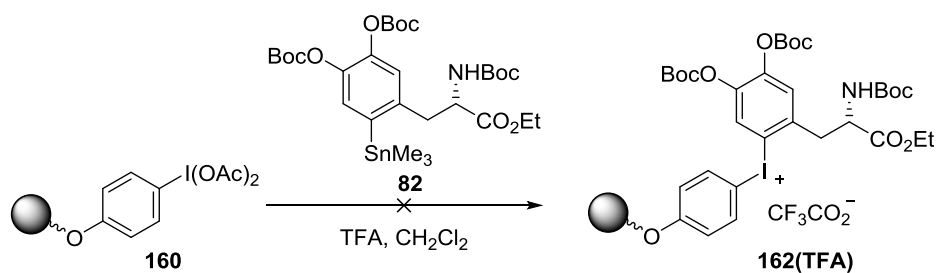
Scheme 9 – Attempted synthesis of polymer supported [^{18}F]F-DOPA precursor 162(TFA)

The change in mass of the resin suggested a loading of 1.26 mmol g^{-1} (88%). However, elemental analysis was inconsistent with this and suggested that impurities remained on the resin. Attempts to produce protected [^{18}F]F-DOPA **9** were unsuccessful using the supported precursor providing further evidence for the previous reactions failure.

Using a Solid Support for the Production of ^{18}F Labelled Prosthetic Groups

I am very grateful to Wilke de Vries (Erasmus student) for his hard work on this project.

The ^{18}F labelling of other simple molecules using solid supported precursors appeared an attractive avenue of investigation. Two compounds considered for their valuable application were [^{18}F]4-fluorobenzaldehyde **[^{18}F]38** and [^{18}F]4-fluorophenol.

[^{18}F]4-fluorobenzaldehyde ([^{18}F]FBA) **[^{18}F]38** is a prosthetic group used for the ^{18}F labelling of peptides. Conjugation to unprotected peptides can be achieved under mild conditions via oxime formation with aminooxy-functionalised peptides.[10]

The second target, [^{18}F]4-fluorophenol, is an important ^{18}F labelled synthon for the production of labelled molecules bearing [^{18}F]4-fluorophenoxy functionality. The labelled species is employed in the synthesis of a number of valuable tracers of biological interest.[11,12]

With these targets in mind, the following solid supported precursors were proposed (Figure 5).
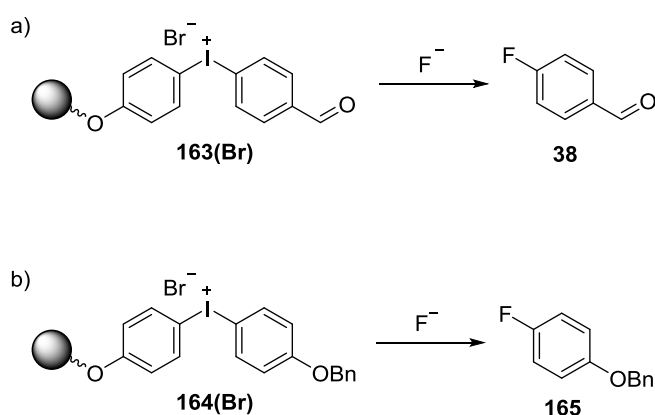
Figure 5 – Proposed solid supported precursors. a) Precursor for [^{18}F]FBA production. b) Precursor for [^{18}F]4-fluorophenol production.

Synthesis of the corresponding unsupported analogues would also provide important information for comparison.

Precursors for [¹⁸F]FBA production

Investigations begun with attempts to synthesise the precursors for [¹⁸F]FBA production; iodonium salts **163(Br)** and **166(Br)** (Figure 6).
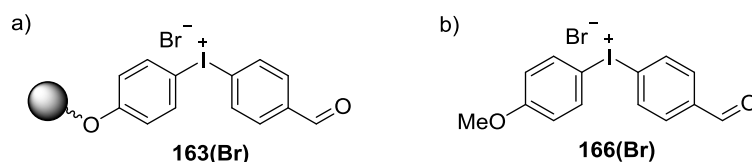
Figure 6 – Target precursors for [¹⁸F]FBA production. a) Solid supported precursor. b) Solution phase precursor
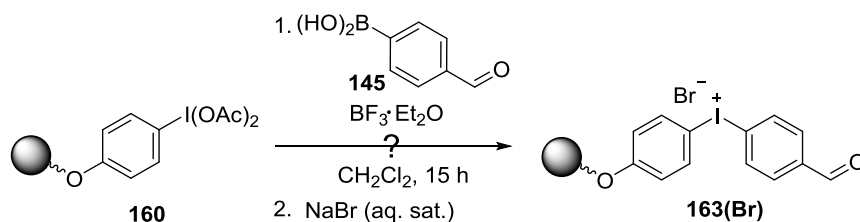
Scheme 10 – Attempted synthesis of solid supported [¹⁸F]FBA precursor 163(Br)

Solid supported diacetate compound **160** was produced using the methods previously reported (Pg. 135). Reaction of the diacetate with the boronic acid **145** was, however, problematic. A very low increase in the mass of the resin suggested a low conversion of the diacetate to the diaryliodonium salt **163(Br)**. Attempted fluorination of the supported precursor did not produce the desired fluorinated product **38**, providing further evidence for the lack of success in the previous step (Scheme 11).
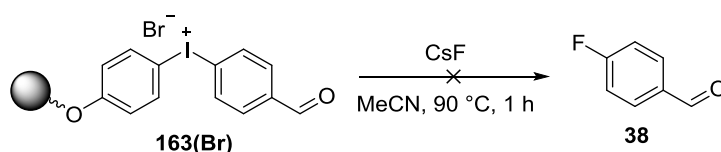
Scheme 11 – Attempted fluorination of solid supported precursor 163(Br)

To probe the iodonium salt forming reaction further, the corresponding solution phase reaction was carried out (Table 2, Entry 1). This confirmed that the reaction was not proceeding satisfactorily. This is presumably due to the electron rich nature of the hypervalent iodine compound as reaction with (diacetoxyiodo)benzene proceeds well as described in the previous chapter (Chapter 2, Pg. 122, Scheme 50).

Table 2 – Conditions attempted for the production of iodonium salt 166 from boronic acid 145
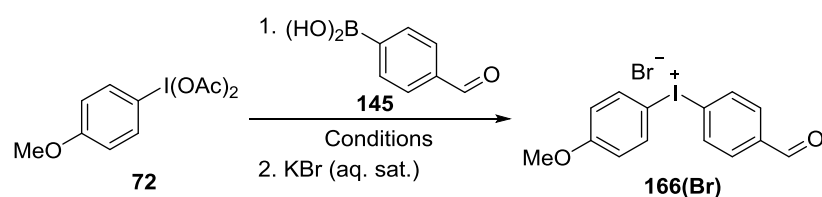
Entry	Reagents (order of addition)	Time	Solvent	Temperature	Yield (%)
1	Boronic Acid **145**		CH_2Cl_2		18
	1. $BF_3 \cdot Et_2O$	10 min		0 °C	
	2. Diacetate **72**	1 h[a]		0 °C → rt	
2	Boronic Acid **145**		CH_2Cl_2		-
	1. Diacetate **72**	10 min		-41 °C	
	2. $BF_3 \cdot Et_2O$	40 + 120 min[b]		-41 °C → rt	
3	Boronic Acid **145**		EtOAc		-
	1. $BF_3 \cdot Et_2O$	10 min		0 °C	
	2. Diacetate **72**	1 h[a]		0 °C → rt	
4	Diacetate **72**		CH_2Cl_2		-
	1. $TsOH \cdot H_2O$	30 + 30min[c]		-41 °C → rt	
	2. Boronic Acid **145**	18 h		rt	
5	Diacetate **72**		MeCN,		-
	1. $TsOH \cdot H_2O$	30 + 30 min[c]	+ $CHCl_3$(1:5)	0 °C → rt	
	2. Boronic Acid **145**	1 h		rt	
6	Diacetate **72**		CH_2Cl_2		-
	1. Boronic acid **145**	1 h[a]		0 °C → rt	

[a] Reaction was left at room temperature for 1 hour after removal from cooling bath. [b] Reaction was left at room temperature for 120 minutes after removal from cooling bath. [c] Reaction was left at room temperature for 30 minutes after removal from cooling bath.

The initial conditions used provided the iodonium salt in poor yield. Attempts to improve the yield by tuning reaction conditions were unsuccessful. Lowering the temperature and changing the order of addition of reagents produced no product (entry 2). Changing the solvent to ethyl acetate was also unsuccessful (entry 3). Furthermore, reaction directly with the diacetate (entry 6) or with *in situ* produced Koser reagent **73** gave no iodonium salt product (entries 4 and 5).

Previous synthesis of iodonium salts had proceeded well using aryl stannanes. Therefore, the appropriate aryl stannane was produced for utility in the synthesis of diaryliodonium salt **166** (Scheme 12).
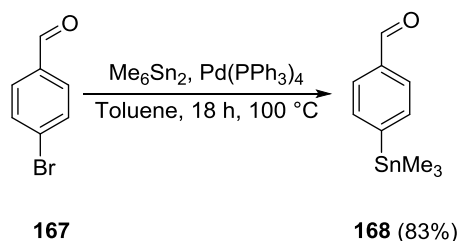
Scheme 12 – Synthesis of aryl stannane 168

Aryl stannane **168** was produced using a procedure recently reported in a patent by Liu *et al.* in good yield.[13] However, reactions with *in situ* produced Koser again failed to produce the iodonium salt **166(Br)** (Scheme 13).
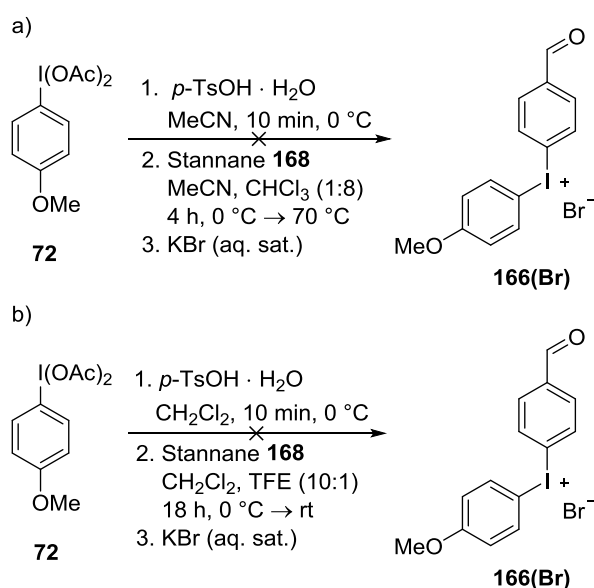
Scheme 13 – Attempted reactions for the production of iodonium salt 166(Br) from aryl stannane 168

Due to the difficulties in synthesising the desired precursors for [^{18}F]FBA production, investigation moved on to synthesising precursors for the second target; [^{18}F]4-fluorophenol (Figure 7).

Precursors for [^{18}F]4-fluorophenol production

As well as the solid supported precursor **164(Br),** compounds **169(Br)** and **170(Br)** were targeted. This would allow comparison of the supported method with precursor formation and fluorination in solution phase.
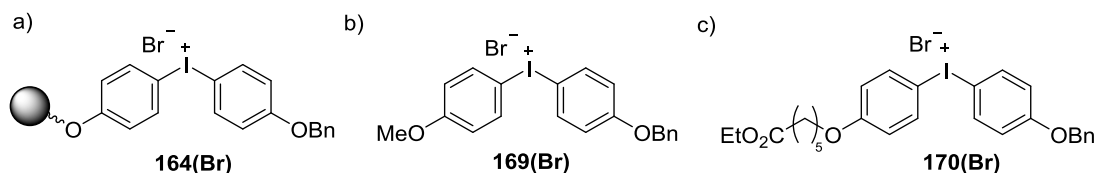
Figure 7 – Proposed precursors for the production of *O*-benzyl [^{18}F]4-fluorophenol. a) Solid supported precursor 164(Br). b) Anisole derived solution phase precursor 169(Br). c) Linker derived solution phase precursor 170(Br).

Iodonium salt **170(Br)** was targeted first to probe the reactivity of the linker moiety. Furthermore, subsequent transformation would provide a carboxylic acid for linkage to the amino methyl resin (Scheme 14). The initial synthesis route is shown below.
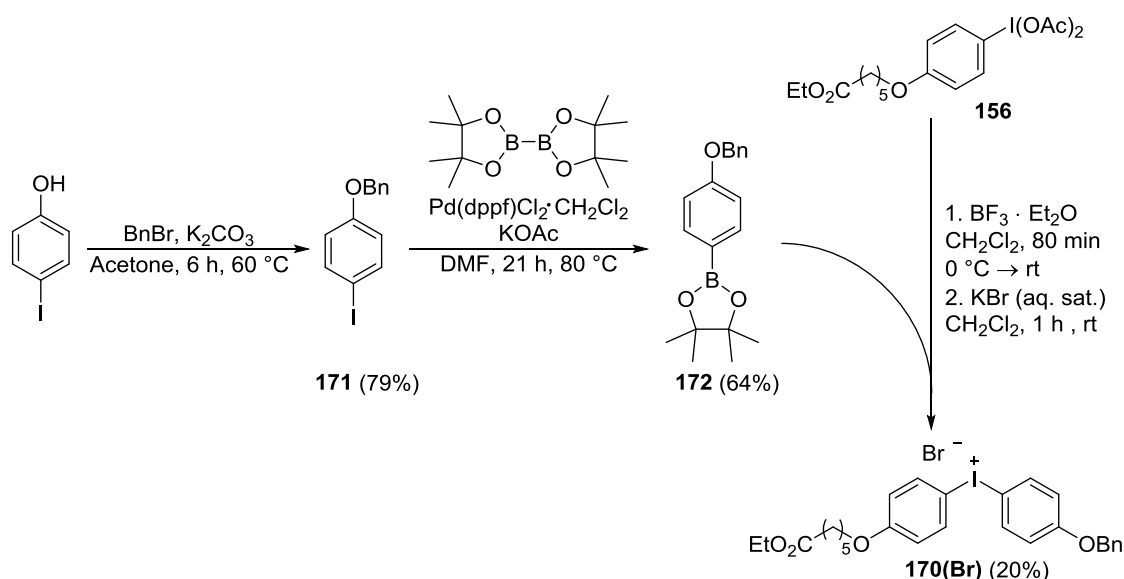
Scheme 14 – Synthesis of iodonium salt 170(Br) via Aryl BPin moiety 172

Firstly, aryl BPin moiety **172** was synthesised by benzyl protection of 4-iodophenol and subsequent coupling reaction with bis(pinocolato)diboron. Subsequent reaction with diacetate **156** produced the desired product but with poor yields so an alternative approach was investigated.

Improved synthesis

It was found that significant improvements to the yield could be made by using a slightly altered synthetic strategy (Scheme 15).
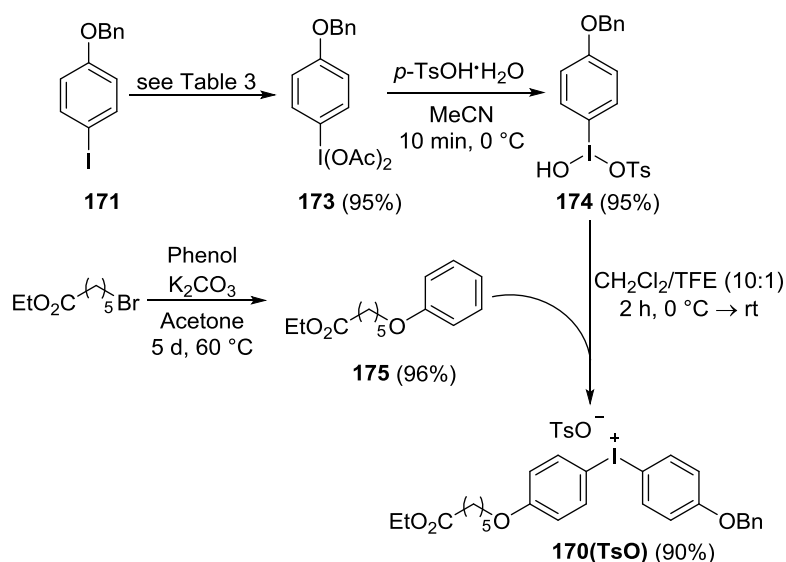
Scheme 15 – Synthesis of iodonium salt precursor 170(TsO) via diacetate 173

Rather than oxidation of iodophenol ether **152**, oxidation of the *O*-benzyl 4-iodophenol **171** was conducted. Optimisation for the oxidation of aryl iodide **171** is shown in Table 3.

Table 3 – Conditions explored for the formation of diacetate 173

Entry	Reagents and Solvent	Time (h)	Temp. (°C)	Yield (%)
1	$NaIO_4$, NaOAc, AcOH, Ac_2O	2	120	Impure
2	$NaIO_4$, NaOAc, AcOH, Ac_2O	24	80	48
3	AcOOH, CH_2Cl_2	2	rt	0
4	Selectfluor®, AcOH, MeCN	5	rt	95

The use of Selectfluor® as an oxidant in acetonitrile and acetic acid proved optimal, giving quantitative yield of the corresponding diacetate.

Conversion of the diacetate to the Koser derivative **174** followed by reaction with electron rich aromatic **175** gave the desired iodonium tosylate **170(TsO)** in excellent yields. The iodonium salt **170(TsO)** could then be hydrolysed using TFA in water. Coupling to the solid support was then possible using the standard conditions (Scheme 16).
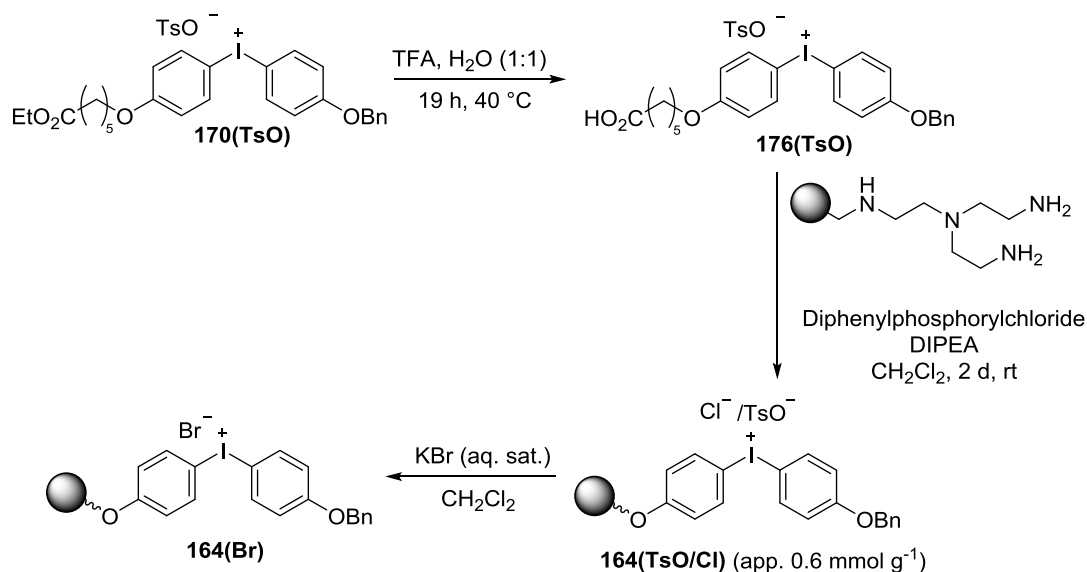
Scheme 16 – Synthesis of solid supported precursor 164(Br)

Synthesis of the solution phase iodonium bromides was also successful (Scheme 17). Iodonium tosylate **169(TsO)** could be produced using an analogous procedure for reaction with anisole. The isolated iodonium tosylates **169(TsO)** and **170(TsO)** were then converted to their respective iodonium bromides **169(Br)** and **170(Br)** by washing with aqueous KBr (sat.).
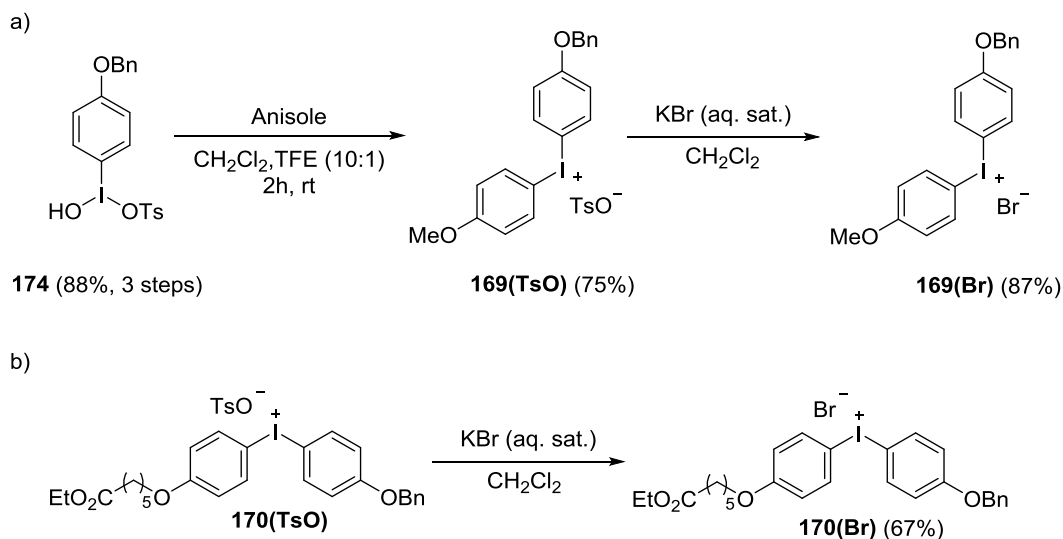
Scheme 17 – Production of iodonium bromides 169(Br) and 170(Br)

Fluorination of iodonium salt precursors

After the synthesis of iodonium precursors **169(Br)** and **170(Br),** it was important to test their efficacy in the fluorination reaction. Optimisation was conducted using iodonium salt **169(Br)** with TMAF as the source of nucleophilic fluoride (Table 4).

Table 4 – Fluorination of solution phase iodonium salt precursor 169(Br)
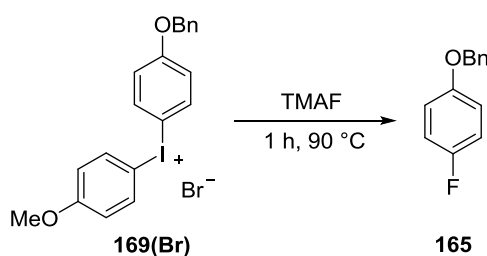
Entry	Solvent	Conc. of 166(Br) [mol dm^{-3}]	TMAF (Equiv)	Yield (%)[a]
1	MeCN	0.05	1	13
2	DMF	0.05	1	7
3	DMSO	0.05	1	8
4	MeCN	0.025	1	5
5	MeCN	0.0125	1	5
6	MeCN	0.05	2	20
7	MeCN	0.05	4	22

[a] Yields determined using GC analysis

Optimal conditions were found using GC analysis of the reaction mixture subsequent to the thermal breakdown. Of the solvents tested acetonitrile gave the best result giving a 13% yield. When performed in DMF or DMSO the yields obtained dropped to 7% and 8% respectively. Decreasing the concentration of the iodonium bromide **169(Br)** was detrimental to the reaction. Yields could be improved by increasing the equivalents of TMAF; 2 equivalents increasing the yield to 20% and 4 equivalents giving 22%.

When performing the optimised fluorination reaction with precursor **170(Br)** the yields improved to 30% of the desired fluorinated product **165** (Scheme 18).
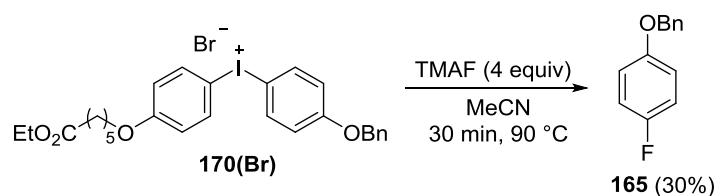
Scheme 18 – Fluorination of linker derived iodonium salt precursor 170(Br)

This showed that the linker moiety was beneficial for the fluorination reaction. The solid supported precursor was now investigated.

Fluorination of the solid supported precursor

Fluorination of the solid supported precursor was successful giving yields between 22% and 24% depending on the scale of the reaction (Table 5). The results show that the reaction is reproducible and scalable.

Table 5 – Fluorination of solid supported iodonium salt precursor 164(Br)
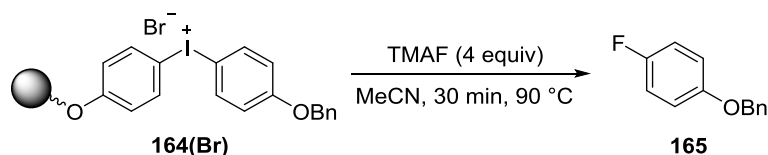
Entry	Scale (mmol resin)	Yield (%)ᵃ
1	0.013	22
2	0.06	24

ᵃ Yields determined using GC analysis

The high number of equivalents used for the cold fluorination reactions mean that conditions are far from emulating those used for the 'hot' fluorination. Testing of the solid supported precursor under radiofluorination conditions needs to be conducted as this application is where such a precursor would be of greatest value.

1.3   Conclusion

A number of synthetically relevant iodonium salt precursors have been synthesised on a solid support. The utility of these compounds has been shown for the production of ^{19}F bearing aromatics as well as for the production of [^{18}F]fluorobenzene **[^{18}F]77**. The successful radiofluorination shows a proof of concept for the production of valuable ^{18}F labelled synthons / prosthetic groups using this method. Furthermore, the importance of the resin functionality has been demonstrated. Limitations of amino methyl functionalised resin for amide linkage were discovered. The problem was addressed by the use of a resin with improved amine availability for a much improved loading via amide bond formation.

The production of a resin bound precursor for [^{18}F]FBA **[^{18}F]38** production could not be realised using the linker strategy investigated here. However, the production of such a precursor with an alternative linker seems a promising area of investigation. A proposed synthesis using Wang resin is outlined below (Scheme 19). It is envisaged that the

electronics of the hypervalent species **180** will be more suitable for iodonium salt formation, as seen in the solution phase (Chapter 2, Pg. 122, Scheme 50).
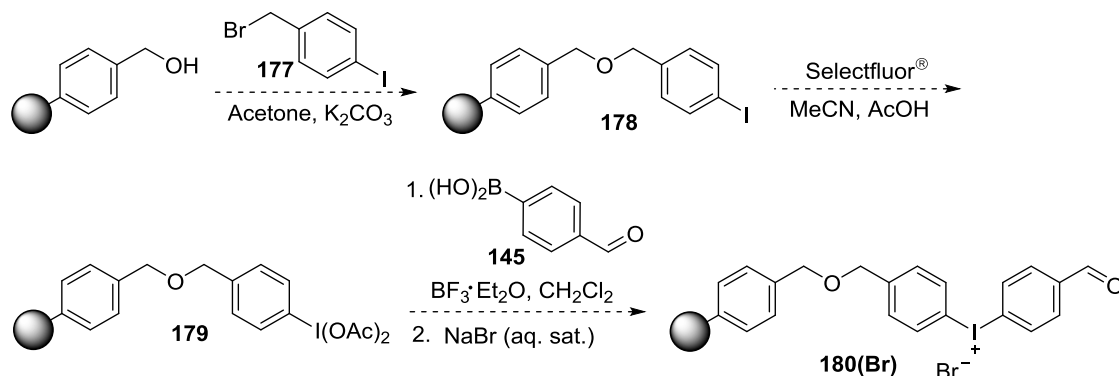
Scheme 19 – Proposed synthesis of alternative solid supported precursor for [^{18}F]FBA

Production of a solid supported precursor for *O*-benzyl 4-fluorophenol was successful. An efficient route via diacetate **173** was established for the synthesis of the resin bound iodonium salt and proceeded with excellent yields. This method provides a promising alternative strategy to those previously reported for the synthesis of resin bound iodonium salts. Fluorination of the precursor was successful providing moderate yields of the fluorinated product **165**. Adaption of this procedure for the incorporation of [^{18}F]fluoride would provide a suitable method for the production of a valuable PET synthon.

1.4   References

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Experimental

Contents

General Description:

All chemicals were purchased from Sigma Aldrich, Alfa Aesar, Apollo, Fluorochem and ABX and used without further purification unless otherwise stated. Tetramethylammonium fluoride (TMAF) was used in a glove box under inert conditions. Dry solvents were obtained from an MBRAUN SPS-800 solvent purification system. Acetonitrile-d_3 was stored under argon over molecular sieves. All reactions involving air- or moisture- sensitive reagents were carried out under an argon atmosphere using oven-dried glasswear. ^{13}C and ^1H NMR spectra were recorded on Bruker DPX 250, Bruker DPX 400 or Bruker DPX 500 spectrometers. ^{19}F NMR spectra were recorded on an Oxford 300 spectrometer. Chemical shifts were referenced to the residual proton solvent peaks (^1H: CDCl$_3$, δ 7.26; MeOD, δ 3.31; CD$_3$CN, δ 1.94; (CD$_3$)SO, δ 2.50), solvent ^{13}C signals (CDCl$_3$, δ 77.16; MeOD, δ 49.00; CD$_3$CN, δ 118.26; (CD$_3$)$_2$SO, δ 39.52). Signals were reported in ppm, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad), coupling constant in Hz, integration. Infrared specta were recorded using a Perkin Elmer, Spectrum 100, FT-IR spectrometer. Selected peaks were reported in cm^{-1}. Mass spectra were recorded by the EPSRC National Mass Spectrometry Facility in Swansea. High resolution mass spectra (HRMS) were recorded using positive electrospray ionisation (ESI) or atmospheric pressure chemical ionisation (APCI). GC analysis was carried out on an Agilent 7890A GC system using an Agilent19091J413 (30 m $\times$ 320 μm $\times$ 0.25 μm) column and helium as the carrier gas with a constant column flow of 2.26 mL/min. The injector temperature was held constant at 220 ℃ and the GC oven temperature program was: 60 ℃ hold 10 min, ramp 2 ℃/min to 75 ℃, then ramp 20 ℃/min to 220 ℃. Elemental analysis was carried out by Medac Ltd. Reactions were monitored using thin layer chromatography (TLC) carried out on Merck Kieselgel 60 F$_{254}$ plates. HPLC analysis was performed using an AGILENT Technology 1200 Series System.

General Procedures ('Cold' Chemistry)

General procedure for the formation of diaryl iodonium salts suitable for [^{18}F]F-DOPA production from diacetate (GP1)

To a stirred suspension of either 2-(diacetoxy)iodothiophene **87** or 4-(diacetoxy)iodoanisole **72** (0.44 mmol) in acetonitrile (5 mL) at 0 °C was added *p*-TsOH·H$_2$O (84 mg, 0.44 mmol) before immediate dilution with chloroform (25 mL). The appropriate protected 6-(trimethylstannyl)-L-DOPA reagent (**82**, **104**, **111** or **141**) (0.29 mmol) in chloroform (5 mL) was added dropwise. The reaction mixture was stirred for 18 h at 50 °C for **72** and reflux for **87**. The reaction mixture was cooled to room temperature and the solvent was removed under reduced pressure. The residue was dissolved in CH$_2$Cl$_2$ (40 mL) and washed with water / saturated KX (X = TfO, Br, or I) solution (3 × 40 mL). The organic layer was passed through a phase separator and concentrated under reduced pressure to give the crude product as a yellow oil. The product was triturated with hexane from a minimum amount of CH$_2$Cl$_2$ and diethyl ether (1:1). The precipitate was collected on a Telos® phase separator and washed with hexane. The collected precipitate was removed from the phase separator with CH$_2$Cl$_2$. The CH$_2$Cl$_2$ was removed before the product was triturated once more with hexane from a minimum amount of CH$_2$Cl$_2$ and diethyl ether (1:1). Removal of the solvent under reduced pressure gave the product as a colourless solid.

General procedure for the formation of diaryl iodonium salts suitable for [^{18}F]F-DOPA production from hydroxyl(*p*-tosyloxy)iodoarenes (GP2)

73 or **88** (0.44 mmol) was added to acetonitrile (5 mL) at 0 °C before immediate dilution with chloroform (25 mL). Boc protected 6-(trimethylstannyl)- L -DOPA ethyl ester **82** (200 mg, 0.29 mmol) in chloroform (5 mL) was added dropwise. The reaction mixture was heated to 50 °C and stirred for 18 h. The reaction mixture was cooled to room temperature and the solvent was removed under reduced pressure. The residue was dissolved in CH$_2$Cl$_2$ (40 mL) and washed with water / saturated KX (X = TfO, Br, or I) solution (3 × 40 mL). The organic layer was passed through a phase separator and concentrated under reduced pressure to give the crude product as a yellow oil. The product was triturated with hexane from a minimum amount of CH$_2$Cl$_2$ / diethyl ether (1:1). The precipitate was collected on a Telos® phase separator and washed with hexane. The collected precipitate was removed from the phase separator with CH$_2$Cl$_2$. The CH$_2$Cl$_2$ was removed before the product was triturated once more with hexane from

a minimum amount of CH_2Cl_2 / diethyl ether (1:1). Removal of the solvent under reduced pressure gave the product as a colourless solid.

Cold Fluorinations

General Procedure for cold fluorination in acetonitrile, DMF and DMSO (GP3)

In a glove box tetramethylammonium fluoride (TMAF) (3.9 mg, 0.04 mmol) was added to a NMR tube before it was sealed with a rubber septum and removed from the glove box. Iodonium salt precursor (0.04 mmol) was dissolved in the appropriate dry deuterated solvent (1 mL) and added to the TMAF by injecting the solution through the septum equipped with an argon balloon. The reaction mixture was heated in a silicon oil bath at 120 °C for 30 min before being removed and cooled to room temperature. The reaction was monitored by ^{19}F NMR and HPLC.

General Procedure for cold fluorination in toluene (GP4)

In a glove box tetramethylammonium fluoride (TMAF) (3.9 mg, 0.04 mmol) was added to a NMR tube before it was sealed with a rubber septum and removed from the glove box. Iodonium salt precursor (0.04 mmol) was dissolved in dry d_3-MeCN (1 mL) and added to the TMAF by injecting the solution through the septum equipped with an argon balloon. The acetonitrile was removed under vacuum and before addition of dry toluene (1 mL). The reaction mixture was heated in a silicon oil bath at 120 °C for 30 min before being removed and cooled to room temperature. The reaction was monitored by ^{19}F NMR and HPLC.

General procedure for the fluorination of solution phase iodonium salt precursors at 90 °C (GP5)

In a glove box tetramethylammonium fluoride (TMAF) was added to a NMR tube before it was sealed with a rubber septum and removed from the glove box. Iodonium salt precursor was dissolved in the appropriate dry deuterated solvent and added to the TMAF by injecting the solution through the septum equipped with an argon balloon. The reaction mixture was heated in a silicon oil bath at 90 °C for 1 h before being removed and cooled to room temperature. The reaction was monitored by ^{19}F NMR and GC.

General procedure for the fluorination of solid-supported iodonium salt precursors (GP6)

In a glove box tetramethylammonium fluoride (TMAF) was added to a reaction vessel containing supported iodonium salt before it was sealed with a rubber septum and removed from the glove box. The appropriate dry deuterated solvent was added to the TMAF and precursor by injection through the septum equipped with an argon balloon. The reaction mixture was heated in a silicon oil bath at 90 °C for 1 h before being removed and cooled to room temperature. The reaction was monitored by ^{19}F NMR and GC.

Calculation of yields for solid supported compounds

<u>Amide coupling</u>

Tris(aminoethyl)amino resin was purchased with an N loading of 3.5 – 5.0 mmolg^{-1} equating to an amine functionality of 1.75 – 2.5 mmolg^{-1}. Yields for the loading of the support were calculated by the gain in weight of the solid support and given as a percentage of the maximum possible gain in weight (2.5 mmol of functionalization).

$$\text{mmol loading} = \Delta\text{Mass}/\Delta\text{Mr}$$

$$\text{Yield} = \text{mmol loading}/2.5 \text{ mmolg}^{-1}$$

For certain experiments the support was submitted for elemental analysis to show that the gain in weight was accurate in calculating the loading with regards to iodine (Table S1).

Table S1:

Reaction	Calculated I%	EA I%
T$_3$P Coupling (Chapter 4, Table 1, Entry 10)	13.54	12.32
DPPC Coupling (Chapter 4, Table 1, Entry 11)	13.69	13.60

<u>Oxidation</u>

Yields for the loading of the support were calculated by the gain in weight of the solid support and given as a percentage of the maximum possible gain in weight (mmol of functionalisation calculated for the previous step).

<u>Iodonium salt formation</u>

Yields for the loading of the support were calculated by the gain in weight of the solid support and given as a percentage of the maximum possible gain in weight (mmol of functionalisation calculated for the previous step).

Radiochemistry

Materials and Methods

All solvents and reagents were commercially available and used without further purification unless otherwise stated. Dry solvents were purchased from Sigma Aldrich. HPLC grade acetonitrile was purchased from Fisher Scientific. $H_2^{18}O$ was purchased from Nukem. QMA-light Sep-Pak cartridges, Sep-Pak alumina cartridges and Sep-Pak C18 cartridges were purchased from Waters. QMA-light Sep-Pak cartridges were pre-treated with sodium bicarbonate solution (8.4 wt.%, 5 mL) and sterile water (5 mL) before use. Alumina cartridges were pre-treated with sterile water (10 mL). Sep-Pak C18 cartridges were pre-treated with ethanol (10 mL) and sterile water (10 mL). Radio TLC was carried out on Macherey-Nagel pre-coated TLC-sheets POLYGRAM® SIL G (0.2 mm silica gel) using 100% acetonitrile as the mobile phase. Radio HPLC analysis was performed using an AGILENT Technology 1200 Series System. Manipulations were carried out using an Eckert and Ziegler Modular-Lab automated radiochemistry synthesis platform. Nitrogen was used as a pressurizing gas during automated manipulations. $[^{18}F]$Fluoride was produced by $^{18}O(p,n)^{18}F$ reaction with $H_2^{18}O$ as the target using an IBA Cyclone 18/9 cyclotron. Reactions were performed with a starting activity of approximately 2 GBq (aqueous $[^{18}F]$fluoride).

General Procedures ('Hot' Chemistry)

General procedure for n.c.a. $[^{18}F]$fluoride incorporation using iodonium salts (GP7)

$[^{18}F]$Fluoride delivered from the cyclotron as an aqueous solution (≈2 GBq) was trapped on a pre-treated QMA cartridge to remove the ^{18}O enriched water. The $[^{18}F]$fluoride was eluted with a kryptofix carbonate solution (0.6 mL) (0.3 mL MeCN, 0.3 mL H_2O, 22.8 mg Kryptofix 2.2.2, 8.4 mg K_2CO_3) into a 5 mL V-shaped vial. The mixture was dried under a flow of nitrogen and reduced pressure at 120 °C for 440 seconds. The residue was azeotropically dried twice with the addition of acetonitrile (2 × 1 mL). Distillation was achieved by heating at 120 °C under a flow of nitrogen for 440 seconds. To the dried $[^{18}F]$KF • Kryptofix 222 • K_2CO_3 salt was added iodonium precursor and (2,2,6,6-tetramethylpiperidin-1-yl)oxy (TEMPO) (0.7 equiv) in the described solvent(s). The reaction was heated at the described temperature for 30 min before being cooled to room temperature. The reaction mixture was ejected into a sterile vial and the activity

was measured in a well counter to calculate the radiochemical recovery (RCR). The reaction mixture was analysed using radio HPLC and radio TLC.

Definitions

Radiochemical Yield (RCY)

Radiochemical yield refers to the percentage of total radioactivity incorporated into the radiolabelled compound being synthesised. This is given as a decay corrected value.

Radiochemical Conversion (RCC)

Radiochemical conversion refers to the conversion of the starting material ($[^{18}F]$fluoride) to radiolabelled product. This is given as a percentage of the total radioactivity of these components.

Radiochemical Recovery (RCR)

Radiochemical recovery refers to the percentage of the total starting radioactivity that is recovered from the reaction in the product vial. This is given as a decay corrected value.

Measurements of Radiochemical Yield (RCY)

Isolated Compounds

The decay corrected radiochemical yields were calculated by measurement of the isolated ^{18}F-labelled product in a Campitec CRC-25PET well counter. The activity present was divided by the decay corrected activity of $[^{18}F]$fluoride delivered by the cyclotron and converted to a percentage.

Unisolated Compounds

Radiochemical yield for unisolated compounds were calculated by TLC conversion whilst taking into account the radiochemical purity found using HPLC analysis.

Ethyl (*S*) 2-((di-*tert*-butoxycarbonyl)amino)-3-(2-4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl-4,5-dimethoxyphenyl)propanoate (32)
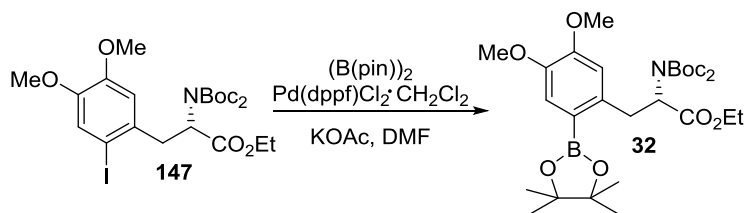
Bis(pinacolato)diboron (109 mg, 0.43 mmol), Pd(dppf)Cl$_2$·CH$_2$Cl$_2$ (16 mg, 0.02 mmol) and KOAc (115 mg, 1.17 mmol) were added to a round bottom flask under nitrogen. Dry DMF was added and the mixture was purged with nitrogen for 15 min. IodoDOPA compound **147** (227 mg, 0.39 mmol) in dry DMF was added and the mixture was heated to 80 °C and stirred for 18 h. The reaction mixture was allowed to cool to room temperature and brine was added before extraction with Et$_2$O. The combined organic extracts were washed with brine, dried over MgSO$_4$ and concentrated in vacuo. The crude product was purified by column chromatography (10% - 25% EtOAc in hexane) to give the product **32** as a colourless solid (141 mg, 62%, m.p. 67-78 °C (lit. 58-60 °C)).[1]

^{1}H NMR (400 MHz, CDCl$_3$) δ ppm: 7.26 (s, 1H), 6.57 (s, 1H), 5.25 (dd, *J* = 11.2, 3.9 Hz, 2H), 4.28 – 4.17 (m, 2H), 4.02 (dd, *J* = 13.5, 3.9 Hz, 1H), 3.88 (s, 3H), 3.85 (s, 3H), 3.11 – 3.04 (ABX system, bm, 2H), 1.34 (s, 18H), 1.33 (s, 6H), 1.31 (s, 6H), 1.30 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (126 MHz, CDCl$_3$) δ ppm: 170.5, 152.0, 150.8, 146.9, 138.8, 118.6, 114.3, 83.4, 82.3, 61.0, 60.2, 56.1, 55.6, 35.2, 27.8, 24.9, 24.8, 14.3; ^{11}B NMR (161 MHz, CD$_3$Cl) δ ppm: 31 (bs). In accordance with literature data.[1]

[^{18}F]4-Fluorobenzaldehyde ([^{18}F]FBA) ([^{18}F]38)
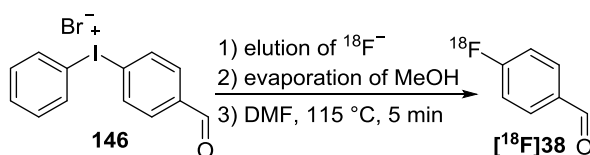
The reaction was performed according to literature procedure.[2] [^{18}F]Fluoride delivered from the cyclotron as an aqueous solution was trapped on a pre-treated QMA cartridge (from the male side) to remove the ^{18}O enriched water. The cartridge was washed with MeOH (1 mL) before elution of the [^{18}F]fluoride into a reaction vial with a solution **146** (5 mg, 0.013 mmol) in MeOH (500 µL). Methanol was evaporated under reduced

pressure at 70 °C for 3 min. After cooling to room temperature, DMF (500 µL) was added. The reaction mixture was heated at 115 °C for 5 min. The mixture was cooled down to room temperatureand water (4 mL) was added before elution of the mixture into a sterile vial. The reaction was analysed by radio HPLC and radio TLC.

Production of protected [^{18}F]4-fluorobenzaldehyde [^{18}F]38 was confirmed by comparison with a cold standard.
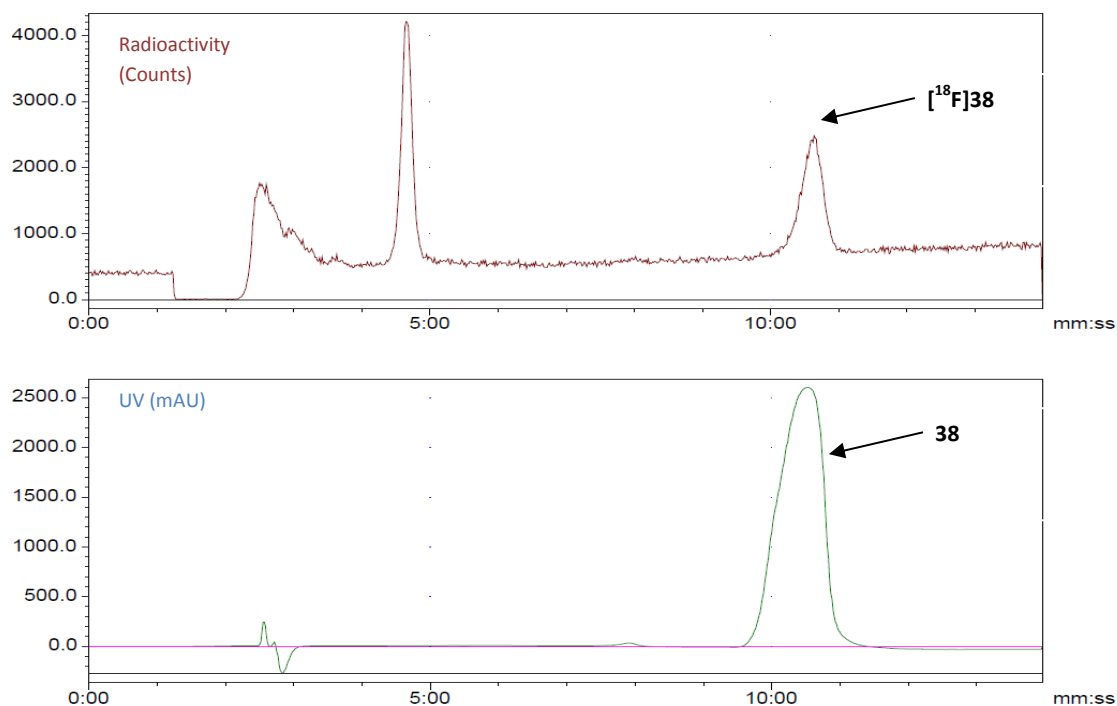
Analytical HPLC Conditions

Column: Analytical Phenomenex Synergi 4 µm Hydro-RP 80 C-18 4.6 × 250 mm column

Gradient: 70% MeCN in H$_2$O (0.01% TFA)

Flow Rate: 1 mL/min

Benzene (4-methoxyphenyl) iodonium trifluoroacetate (71(TFA))
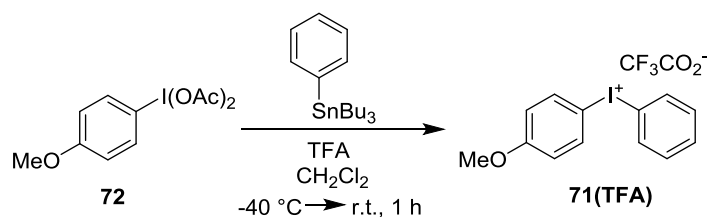
4-diacetoxyiodoanisoloe (1.0 g, 2.8 mmol) in CH_2Cl_2 (10 mL), was cooled to -40 °C and treated with tri-*n*-butylbhenyltin (0.96 mL, 2.9 mmol) and trifluoroacetic acid (0.45 mL, 5.88 mmol). The reaction was stirred for 1 h whilst it was allowed to warm to room temperature. The reaction was concentrated under vacuum before being triturated in diethylether to produce the salt as a fluffy white solid (0.76 g, 63%, m.p. 160-161 °C (lit. 146-148 °C)).[3]

^{1}H NMR (250 MHz, MeOD) δ ppm: 8.04 – 8.16 (m, 4H), 7.68 (t, J = 7.44 Hz, 1H), 7.52 (t, J = 7.7 Hz, 2H), 7.07 (d, J = 9.1 Hz, 2H), 3.85 (s, 3H); ^{13}C NMR (63 MHz, MeOD) δ ppm: 164.5, 138.6, 136.0, 133.5, 133.1, 118.9, 116.7, 104.6, 56.4; ^{19}F NMR (300 MHz, MeOD) δ ppm: -79.3. In accordance with literature data.[3]

Benzene (4-methoxyphenyl) iodonium tosylate (71(TsO))
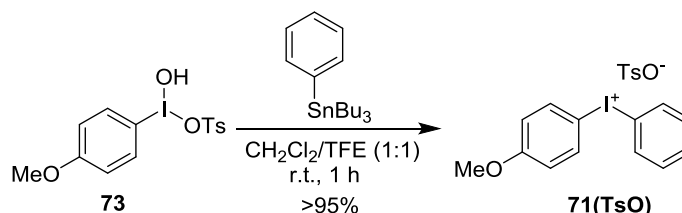
To a stirred solution of 4-methoxy Koser reagent (0.13 g, 0.31 mmol) in CH_2Cl_2 (3 mL) and TFE (3 mL) was added tri-*n*-butylphenyltin (0.084 mol, 0.26 mmol) to give an orange / pink solution. The reaction was stirred at room temperature for 2 h before being concentrated under vacuum. The product was triturated in diethyl ether to produce the salt as a fluffy white solid (0.13 g, 0.26 mmol, 100%, 155-157 °C (lit. 143-146 °C)).

^{1}H NMR (250 MHz, MeOD) δ ppm: 8.03 – 8.22 (m, 4H), 7.61 – 7.79 (m, 3H), 7.54 (t, J = 7.85 Hz, 2H), 7.25 (d, J = 8.5 Hz, 2H), 7.09 (d, J = 9.2 Hz, 2H) 3.87 (s, 3H), 2.39 (s, 3H); ^{13}C NMR (63 MHz, MeOD) δ ppm: 164.1, 143.6, 141.5, 138.5, 135.9, 133.2, 132.9, 129.8, 126.9, 118.7, 116.5, 104.5, 56.3, 21.3. In accordance with literature data.[4]

(4-phenyl)(4-methoxyphenyl)iodonium hexafluorophosphate (71(PF$_6$))
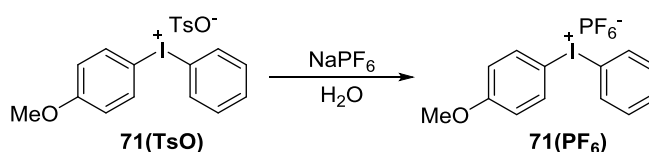
Iodonium tosylate **71(TsO)** (0.10 g, 0.21 mmol) was dissolved in water (25 mL). $NaPF_6$ (0.11 g, 0.63 mmol) was added to the solution. The product crystallised as a white solid (81 mg, 85%, m.p. 111-114 °C).

^{1}H NMR (400 MHz, CD_3CN) δ ppm: 7.96 – 8.07 (m, 4H), 7.70 (t, *J* = 7.5 Hz, 1H), 7.53 (t, *J* = 7.9 Hz, 2H), 7.06 (d, *J* = 9.2 Hz, 2H), 3.83 (s, 3H); ^{13}C NMR (125 MHz, CD_3CN) δ ppm: 164.6, 138.8, 135.9, 134.0, 133.5, 119.4, 115.0, 102.2, 56.8; ^{19}F NMR (300 MHz, CD_3CN) δ ppm: -72.7 (d, $^1J_{P-F}$ = 707.3 Hz). In accordance with literature data.[5]

4-(Diacetoxy)iodoanisole (72)
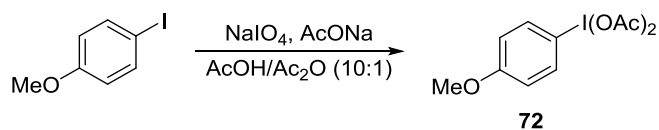
72 was synthesized according to a literature procedure.[6] $NaIO_4$ (2.20 g, 10.3 mmol) and $AcONa·3H_2O$ (2.90 g, 22 mmol) were suspended in a stirred mixture of AcOH and Ac_2O (16.5 mL) (10:1). 4-Iodoanisole (2.34 g, 10 mmol) was added, and the mixture was stirred at reflux for 2 h, cooled to room temperature and poured into water (40 mL). The oily residue was extracted with CH_2Cl_2 (3 × 40 mL). The organic extracts were washed with water, dried over $MgSO_4$ and concentrated under vacuum to give a pale yellow solid. Trituration with diethyl ether gave the product as a white solid (2.97 g, 84%, m.p. 90-92 °C (lit. 92-96 °C).[6]

^{1}H NMR (250 MHz, $CDCl_3$) δ ppm: 8.01 (d, *J* = 9.1 Hz, 2H), 6.96 (d, *J* = 9.1 Hz, 2H), 3.86 (s, 3H), 2.00 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 176.3, 162.1, 137.1, 116.6, 111.5, 55.5, 20.3. In accordance with literature data.[6]

Hydroxy(*p*-tosyloxy)iodo-4-methoxybenzene (73)
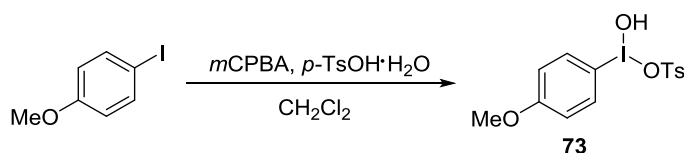
Hydroxy(*p*-tosyloxy)iodo-4-methoxybenzene **73** was synthesised according to the literature.[8] 4-iodoanisole (0.50 g, 2.14 mmol) was dissolved in CH_2Cl_2 (3 mL) and treated with *m*CPBA (0.77%) (0.48 g, 2.14 mmol) followed by *p*-TsOH•H_2O (0.41 g, 2.14 mmol). The solution was stirred at room temperature for 10 min before addition of diethyl ether to precipitate the product. The product was isolated by filtration and dried

briefly under suction to give the product as a colourless powder (0.61 g, 67%, m.p. decomposition at room temperature).[7]

^{1}H NMR (250 MHz, MeOD) δ ppm: 8.31 (d, *J* = 9.1 Hz, 2H), 7.69 (d, *J* = 8.2 Hz, 2H), 7.35-7.07 (m, 4H), 3.94 (s, 3H), 2.37 (s, 3H); ^{13}C NMR (63 MHz, MeOD) δ ppm: 165.2, 142.8, 141.8, 139.9, 129.7, 126.8, 118.1, 111.7, 56.4, 21.2. In accordance with the literature.[7]

Benzene (1,3,5-methoxyphenyl) iodonium tosylate (74(TsO))
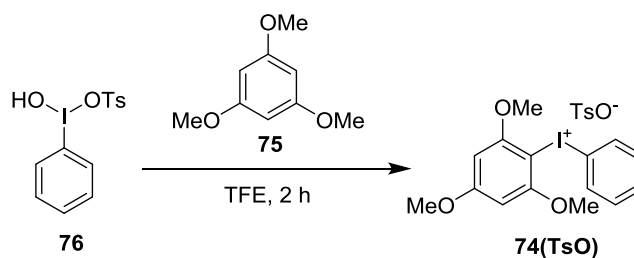
To a stirred solution of 1,3,5-trimethoxybenzene in TFE (4.5 mL) was added Koser reagent (**76**). The reaction mixture was stirred for 2 h at room temperature. MeOH was added to the reaction mixture and the solvents were removed under vacuum. Trituration in diethyl ether gave the pure product as a pale brown solid (0.42 g, 87%, 178-181 °C (Lit. 178-180 °C)).[8]

^{1}H NMR (250 MHz, MeOD) δ ppm: 7.95 (d, *J* = 8.4 Hz, 2H), 7.70 (t, *J* = 8.2 Hz, 1H), 7.62 (t, *J* = 7.5 Hz, 1H), 7.46 (t, *J* = 7.6 Hz, 2H), 7.23 (d, *J* = 7.4 Hz, 2H), 3.98 (s, 6H), 3.89 (s, 3H), 2.37 (s, 3H); ^{13}C NMR (63 MHz, MeOD) δ ppm: 168.7, 161.4, 143.6, 141.6, 136.1, 135.7, 133.0, 132.7, 129.8, 126.9, 115.9, 92.8, 86.1, 57.7, 56.7, 21.3. In accordance with literature data.[8]

1,3,5-methoxybenzene (75)
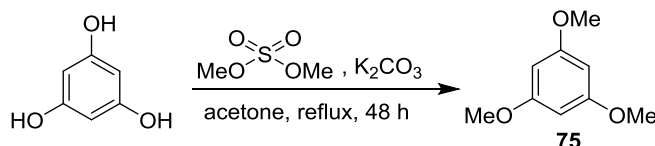
Phloroglucinol (2.0 g, 12.34 mmol) and K_2CO_3 (5.97 g, 43.19 mmol) were dissolved in acetone (20 mL). Dimethylsulfate (5.85 mL, 61.7 mmol) was added and the reaction mixture was stirred at reflux under nitrogen for 48 h. The reaction mixture was concentrated under vacuum and partitioned between diethyl ether and water. The ether

layer was washed with NaOH (1 N) and brine, dried over MgSO$_4$ and concentrated under vacuum. Trituration in hexane gave the product as a pale yellow solid (1.94 g, 93%, 50-53 °C (lit. 51-53 °C)).[9]

^{1}H NMR (250 MHz, CDCl$_3$) δ ppm: 6.09 (s, 3H), 3.77 (s, 9H). In accordance with literature data.[10]

Koser reagent (76)
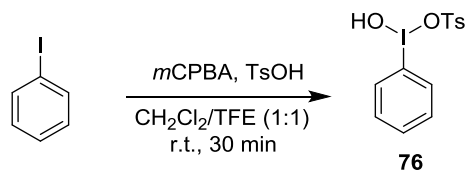
76 was synthesised according to a literature procedure.[7] To a stirred solution of iodobenzene (2.0 g, 9.80 mmol) in CH$_2$Cl$_2$ (6 mL) and TFE (6 mL) was added *m*CPBA (1.69 g, 9.80 mmol). The reaction was left for 10 min before the addition of TsOH.H$_2$O (1.87 g, 9.80 mmol). The solution was stirred at room temperature for 30 min before being concentrated under a stream of nitrogen. The product was triturated in diethyl ether, filtered and dried under vacuum to afford the product as a fluffy white solid (3.39 g, 88%, 133-136 °C (Lit. 139-140 °C)).[11]

^{1}H NMR (250 MHz, MeOD) δ ppm: 8.36 (d, *J* = 7.4 Hz, 2H), 7.85 (t, *J* = 7.5 Hz, 1H), 7.73 − 7.67 (m, 4H), 7.23 (d, *J* = 8.4 Hz, 2H), 2.37 (s, 3H); ^{13}C NMR (125 MHz, (CD$_3$)$_2$SO) δ ppm: 144.9, 138.1, 134.5, 132.4, 131.1, 128.22, 125.5, 123.6, 20.8.

Procedure for n.c.a. [^{18}F]fluoride incorporation using resin bound iodonium salt 161(TFA) for the production of [^{18}F]fluorobenzene ([18F]77)

[^{18}F]Fluoride delivered from the cyclotron as an aqueous solution was trapped on a pre-treated QMA cartridge to remove the ^{18}O enriched water. The [^{18}F]fluoride was eluted with a Kryptofix 2.2.2 carbonate solution (0.6 mL) (0.3 mL MeCN, 0.3 mL H$_2$O, 22.8 mg Kr-2.2.2, 8.4 mg K$_2$CO$_3$) into a 5 mL V-shaped vial. The mixture was dried under a flow of nitrogen and reduced pressure at 120 °C for 440 seconds. The residue was azeotropically dried twice with the addition of acetonitrile (2 × 1 mL). Distillation was

achieved by heating at 120 °C under a flow of nitrogen for 440 seconds. The dried [^{18}F]KF•Kr222•K$_2$CO$_3$ salt was re-dissolved in acetonitrile and to a sealed vial containing the supported iodonium precursor **161(TFA)** (0.103 g, 0.12 mmol, 1.16mmol g^{-1}) and TEMPO (6.56 mg, 0.042 mmol). The reaction mixture was then heated at 90 °C for 15 min on a hot plate. The product solution was removed from the support by filtration. Analysis with radio TLC showed a RCC of 3%. Product identity was confirmed by radio HPLC.

Radio HPLC of reaction mixture

Analytical HPLC Conditions

Column: Analytical Phenomenex Synergi 4 µm Hydro-RP 80 C-18 4.6 × 250 mm column

Gradient: 30% MeCN in H$_2$O (0.01% TFA) to 70% MeCN in H$_2$O (0.01% TFA) over 14 min

Flow Rate: 1 mL/min

Radio TLC of reaction mixture (Mobile phase: 100% MeCN):

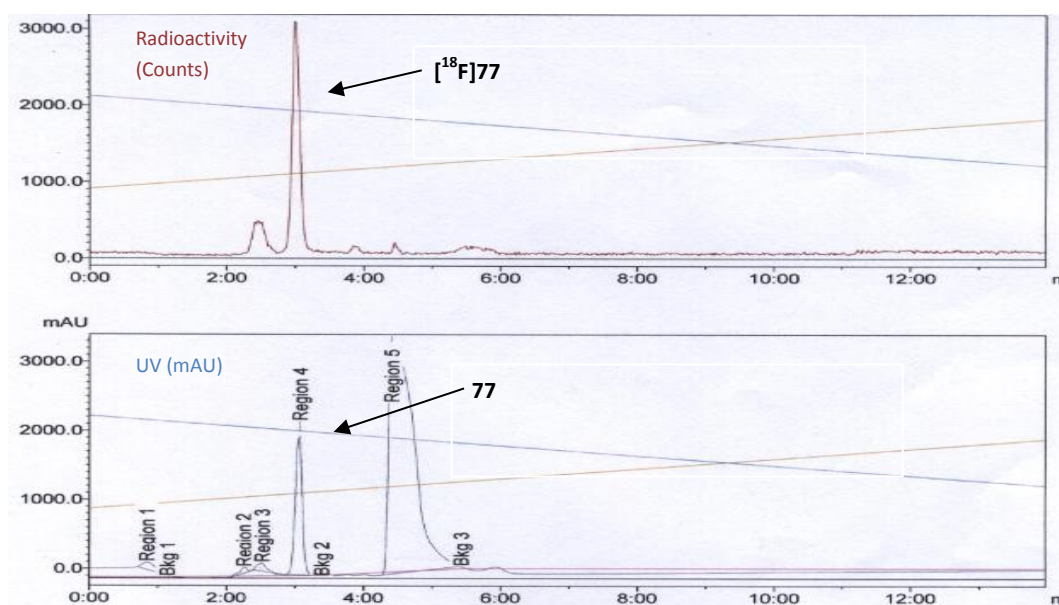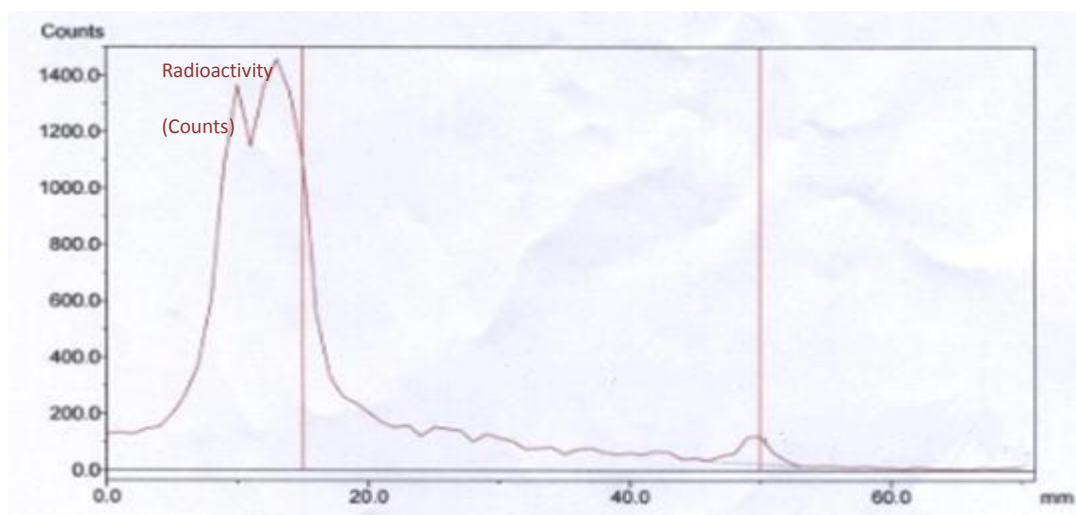## Procedure for n.c.a. [18F]fluoride incorporation using solution phase iodonium salts for the production of [18F]fluorobenzene ([18F]77)
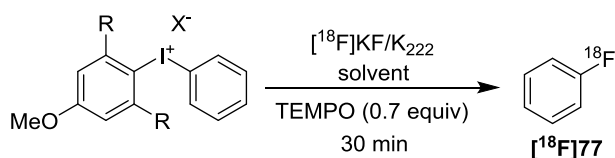
[^{18}F]Fluoride delivered from the cyclotron as an aqueous solution was trapped on a pre-treated QMA cartridge to remove the ^{18}O enriched water. The [^{18}F]fluoride was eluted with a Kryptofix 2.2.2 carbonate solution (0.6 mL) (0.3 mL MeCN, 0.3 mL H$_2$O, 22.8 mg Kr-2.2.2, 8.4 mg K$_2$CO$_3$) into a 5 mL V-shaped vial. The mixture was dried under a flow of nitrogen and reduced pressure at 120 °C for 440 seconds. The residue was azeotropically dried twice with the addition of acetonitrile (2 × 1 mL). Distillation was achieved by heating at 120 °C under a flow of nitrogen for 440 seconds. The iodonium salt precursor in the appropriate solvent(s) was added to the dried [^{18}F]KF•Kr222•K$_2$CO$_3$. The reaction was heated at the described temperature for 30 min before elution into a sterile vial. The reaction was analysed by radio HPLC and radio TLC.

Radio HPLC of reaction mixture
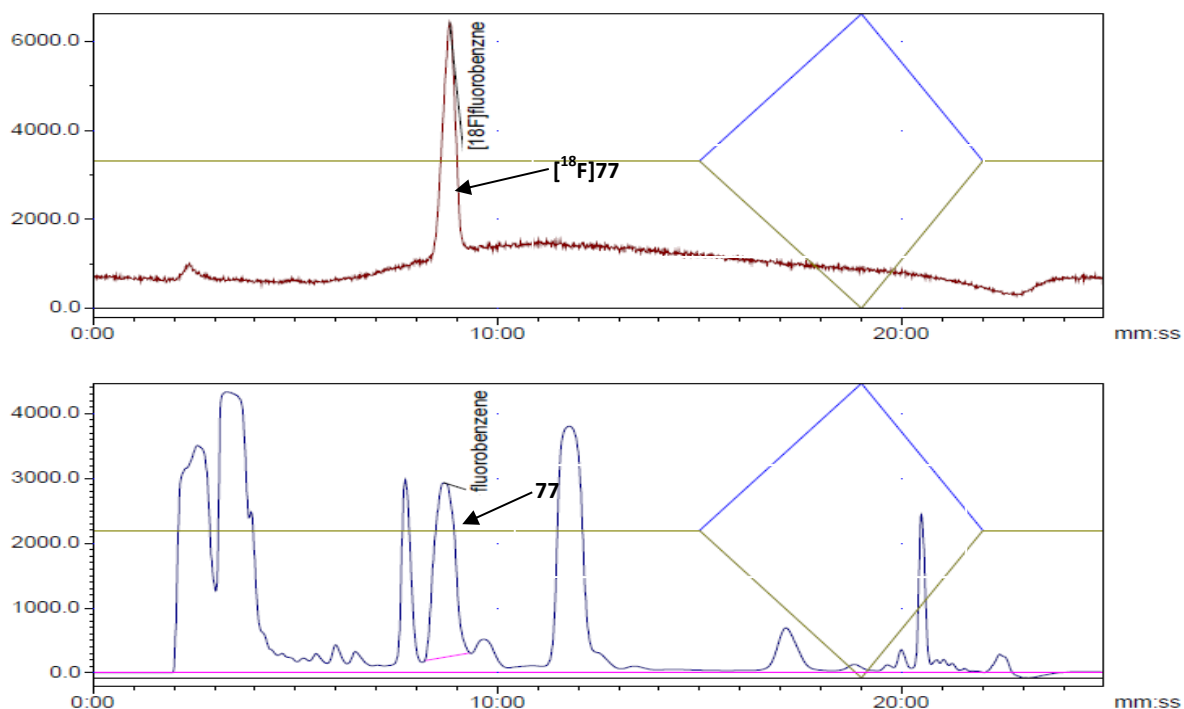
Analytical HPLC Conditions

Column: Analytical Phenomenex Synergi 4 μm Hydro-RP 80 C-18 4.6 × 250 mm column

Gradient: 50% MeCN in H_2O (0.01% TFA) Isocratic 15 min, linear increase from 50% to 100% MeCN in H_2O (0.01% TFA) 4 min, linear decrease from 100% to 50% MeCN in H_2O (0.01% TFA) 4 min, 50% MeCN in H_2O (0.01% TFA) Isocratic 3 min.

Flow Rate: 1 mL/min

2-iodo-1,3,5-methoxybenzene (78)
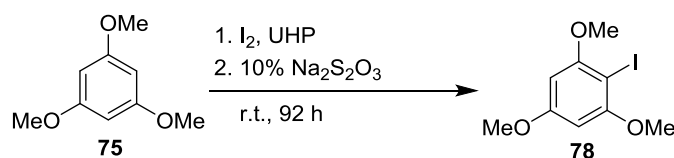
78 was synthesised according to a literature procedure.[13] 1,3,5-trimethoxybenzene, I_2 and UHP were all separately finely powdered in a mortar. 1,3,5-trimethoxybenzene **75** (1.0 g, 5.94 mmol) and I_2 (0.76 g, 2.98 mmol) were added to a 25 mL RBF and shaken vigorously befor addition of UHP (0.335 g, 3.56 mmol). The reaction mixture was agitated at 45 °C for 92 h. Saturated NaS_2O_3 solution (90 mL) was added and the

resulting precipitate was stirred at room temperature for 1 h before filtration. The crude product containing starting material was purified by column chromatography (9 : 1; Pet Ether : EtOAc) to give the pure product as white crystals (1.02 g, 59%, 118-120 °C (Lit. 120-122 °C)).[13]

^{1}H NMR (250 MHz, MeOD) δ ppm: 6.18 (s, 2H), 3.90 (s, 6H), 3.86 (s, 3H); ^{13}C NMR (125 MHz, (CD$_3$)$_2$SO) δ ppm: 161.9, 159.3, 91.6, 66.3, 56.4, 55.5. In accordance with literature data.[13]

[*N*-(*tert*-Butoxycarbonyl)-3,4-di(*tert*-butoxycarbonyloxy)- L -phenylalanine ethyl ester]-6-(4-anisyl)iodonium tosylate (81(TsO))

81(TsO)
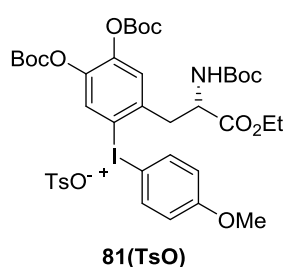
Using GP1 the product was obtained as a colourless solid (159 mg, 60%, m.p. 84-90 °C).

IR ν_{max} (cm^{-1}; neat) 1767, 1705, 1485, 1369, 1250, 1240, 1150, 1119, 1007, 820, 681; ^{1}H NMR (400 MHz; CDCl$_3$) δ ppm: 7.85 (d, *J* = 9.1 Hz, 2H), 7.79 (s, 1H), 7.45 (d, *J* = 8.2 Hz, 2H), 7.33 (s, 1H), 7.03 (d, *J* = 7.9 Hz, 2H), 6.84 (d, *J* = 9.2 Hz, 2H), 5.98-5.79 (bm, 1H), 4.74-4.43 (bm, 1H), 4.28-4.09 (m, 2H), 3.80 (s, 3H), 3.43-3.35 (ABX system, bm, 2H), 2.31 (s, 3H), 1.53 (s, 9H), 1.52 (s, 9H), 1.35 (s, 9H), 1.25 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, CDCl$_3$) δ ppm: 171.3, 162.1, 149.7, 149.6, 145.2, 142.2, 142.2, 139.2, 138.7, 136.8, 131.4, 128.4, 125.8, 125.2, 117.4, 115.7, 104.4, 84.4, 79.6, 61.7, 55.5, 53.1, 39.0, 28.1, 27.5, 27.5, 21.1, 14.0; HRMS (ESI) [M-TsO]$^+$ found 758.2026 calc. 758.2032 [C$_{33}$H$_{45}$INO$_{11}$]$^+$.

[*N*-(*tert*-Butoxycarbonyl)-3,4-di(*tert*-butoxycarbonyloxy)- L -phenylalanine ethyl ester]-6-(4-anisyl)iodonium bromide (81(Br))

81(Br)
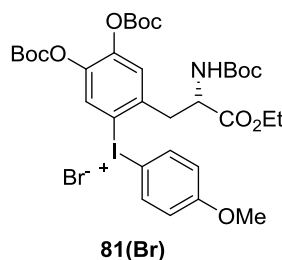
Iodonium tosylate **81(TsO)** (63 mg, 0.068 mmol) was dissolved in CH_2Cl_2 50 mL and washed with aqueous KBr (0.2 M, 3×50 mL) and the organic layer was passed through a phase separator. The solvent was removed before the product was triturated with hexane from a minimum amount of CH_2Cl_2 and diethyl ether (1:1). Removal of the solvent under reduced pressure gave the product as a colourless solid (57 mg, 100%, m.p. 92-102 °C).

IR ν_{max} (cm^{-1}; neat) 2980, 1769, 1711, 1487, 1370, 1250, 1154, 1123, 822; ^{1}H NMR (400 MHz; CDCl$_3$) δ ppm: 7.90 (d, *J* = 9.2 Hz, 2H), 7.74 (s, 1H), 7.31 (s, 1H), 6.87 (d, *J* = 9.2 Hz, 2H), 5.30-5.17 (bm, 1H), 4.72-4.62 (bm, 1H), 4.31-4.17 (m, 2H), 3.81 (s, 3H), 3.47 − 3.22 (ABX system, bm, 2H), 1.52 (s, 18H), 1.39 (s, 9H), 1.28 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, CDCl$_3$) δ ppm: 171.2, 161.7, 149.8, 149.6, 144.9, 142.4, 137.8, 135.9, 131.0, 125.5, 121.0, 117.4, 110.1, 84.5, 84.4, 80.0, 61.8, 55.5, 53.3, 39.4, 28.2, 27.5, 27.5, 14.1; HRMS (ESI) [M-Br]$^+$ found 758.2023 calc. 758.2032 [$C_{33}H_{45}INO_{11}$]$^+$.

**[*N*-(*tert*-Butoxycarbonyl)-3,4-di(*tert*-butoxycarbonyloxy)- L -phenylalanine ethyl ester]-6-(4-anisyl)iodonium triflate 81(TfO)**

81(TfO)
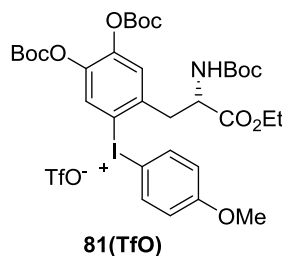
Iodonium tosylate **81(TsO)** (0.136 mg, 0.146 mmol) was dissolved in CH_2Cl_2 50 mL and washed with aqueous KOTf (0.2 M, 3×50 mL) and the organic layer was passed through a phase separator. The solvent was removed before the product was triturated with hexane from a minimum amount of CH_2Cl_2 and diethyl ether (1:1). Removal of the

solvent under reduced pressure gave the product as a white solid (128 mg, 97%, m.p. 78-80°C).

IR ν_{max} (cm^{-1}; neat) 1771, 1707, 1572, 1487, 1371, 1248, 1152, 1123, 1026, 637; ^{1}H NMR (400 MHz; CDCl$_3$) δ ppm: 7.92 (d, J = 9.2 Hz, 2H), 7.71 (s, 1H), 7.44 (s, 1H), 6.96 (d, J = 9.2 Hz, 2H), 5.59-5.45 (m, 1H), 4.65-4.51 (m, 1H), 4.33-4.14 (m, 2H), 3.85 (s, 3H), 3.52 -3.24 (ABX system, bm, 2H), 1.53 (s, 9H), 1.52 (s, 9H), 1.41 (s, 9H), 1.28 (t, J = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, CDCl$_3$) δ ppm: 171.2, 163.0, 155.4, 149.5, 149.4, 145.7, 142.8, 138.6, 137.4, 130.8, 125.9, 120.2 (q, J = 320.2 Hz, 1C), 118.1, 113.9, 102.3, 84.9, 84.8, 80.4, 62.2, 55.6, 53.8, 40.1, 28.1, 27.4, 27.4, 13.8; ^{19}F NMR (300 MHz, CDCl$_3$) δ ppm: −78.3; HRMS (ESI) [M-TfO]$^+$ found 758.2028 calc. 758.2032 [C$_{33}$H$_{45}$INO$_{11}$]$^+$.

[N-($tert$-Butoxycarbonyl)-3,4-di($tert$-butoxycarbonyloxy)- L -phenylalanine ethyl ester]-6-(4-anisyl)iodonium iodide 81(I)

81(I)
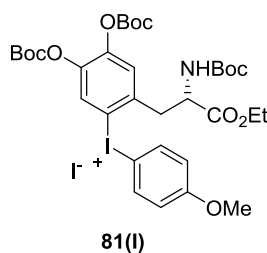
Iodonium tosylate **81(TsO)** (66 mg, 0.071 mmol) was dissolved in CH$_2$Cl$_2$ (50 mL) and washed with aqueous KI (0.2 M, 3 × 50 mL) and the organic layer was passed through a phase separator. The solvent was removed before the product was triturated with hexane from a minimum amount of CH$_2$Cl$_2$ / diethyl ether (1:1). Removal of the solvent under reduced pressure gave the product as a pale yellow solid (59 mg, 94%, m.p. 82-85 °C). The iodonium iodide is unstable during the work up and should be isolated as quickly as possible. If left to precipitate too long, a pink solution indicates the decomposition of the salt.

IR ν_{max} (cm^{-1}; neat) 2980, 1767, 1709, 1572, 1487, 1369, 1252, 1150, 1121, 1020, 824; ^{1}H NMR (500 MHz, CDCl$_3$) δ ppm: 7.92 (d, J = 9.0 Hz, 2H), 7.84 (s, 1H), 7.31 (s, 1H), 6.88 (d, J = 9.0 Hz, 2H), 5.36-5.23 (bm, 1H), 4.72-4.54 (bm, 1H), 4.31-4.10 (bm, 2H), 3.81 (s, 3H), 3.48-3.32 (ABX system, bm, 2H), 1.52 (s, 9H), 1.52 (s, 9H), 1.40 (s, 9H), 1.26 (t, J = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, CDCl$_3$) δ ppm: 171.1, 162.1, 155.2, 149.8, 149.6, 145.0, 142.6, 137.4, 136.6, 130.6, 125.7, 120.4, 117.8, 109.0, 84.7, 84.6,

80.5, 62.3, 55.6, 53.6, 40.0, 28.3, 27.6, 27.5, 14.2; HRMS (ESI) [M-I]$^+$ found 758.2025 calc. 758.2032 $[C_{33}H_{45}INO_{11}]^+$.

N-(tert-Butoxycarbonyl)-3,4-di(tert-butoxycarbonyloxy)-6-trimethylstannyl- L -phenylalanine ethyl ester (82)
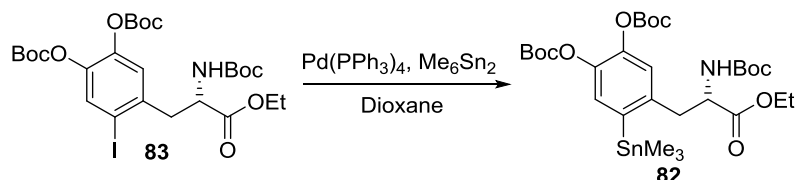
82 was synthesised according to the literature.[14] To a solution of triboc-6-iodo-L-DOPA ethyl ester **83** (1.00 g, 1.54 mmol) in anhydrous dioxane (25 mL) under argon and protected from light was added tetrakis triphenylphosphine palladium (0.089 g, 0.077 mmol) and hexamethylditin (0.93 g, 2.85 mmol, 0.59 mL). The mixture was stirred at reflux for 6 h before being cooled to room temperature and filtered. The filtrate was diluted with EtOAc, washed with water and brine, dried over MgSO$_4$ and concentrated to dryness. The residue was purified by flash chromatography (hexane/ethyl acetate, 21:5) to give the product as a colourless solid (0.525 g, 50%, m.p. 41-45 °C). The data were consistent with those reported in the literature measured in CD$_2$Cl$_2$.[14]

^{1}H NMR (400 MHz, CDCl$_3$) δ ppm: 7.26 (s, with tin satellites J^3_{Sn-H} = 47.7 Hz, 1H), 7.12 (s, with tin satellites J^4_{Sn-H} = 15.4 Hz, 1H), 4.88 (bd, J = 8.8 Hz, 1H), 4.48 (bdd, J = 15.0, 8.0 Hz, 1H), 4.16 (q, J = 7.2 Hz, 2H), 3.10-2.99 (ABX system, bm, 2H), 1.54 (s, 9H), 1.53 (s, 9H), 1.39 (s, 9H), 1.20 (t, J = 7.0 Hz, 3H), 0.35 (s, with tin satellites J^2_{Sn-H} = 54.8 Hz, 9H); ^{13}C NMR (126 MHz, CDCl$_3$) δ ppm: 171.9, 155.0, 150.7, 150.5, 142.5, 141.3, 141.4, 140.7, 130.0 (s, with tin satellites J^2_{Sn-C} = 39.2 Hz, 1C), 123.3 (s, with tin satellites J^2_{Sn-C} = 42.2 Hz, 1C), 83.4, 79.8, 61.3, 54.3, 40.3, 28.1, 27.5, 27.5, 13.9, -8.0 (s, with tin satellites J^1_{Sn-C} = 355.3 Hz, 3C).

N-(tert-Butoxycarbonyl)-3,4-di(tert-butoxycarbonyloxy)-6-iodo-L-phenylalanine ethyl ester (83)

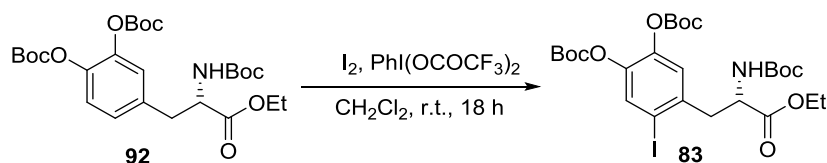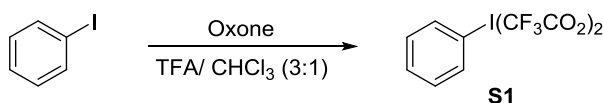**83** was synthesised according to the literature.[15] To a round bottom flask containing I_2 (1.46 g, 5.80 mmol) and $PhI(CF_3CO_2)_2$ (3.09 g, 6.96 mmol) under argon was added freshly distilled CH_2Cl_2 (40 mL). The mixture was stirred at 0 °C for 15 min before addition of tribocDOPA ethyl ester (3.0 g, 5.8 mmol) in CH_2Cl_2 (10 mL). The reaction was kept at 0 °C for 15 min before being stirred at room temperature overnight. Following dilution with CH_2Cl_2 (40 mL) the reaction mixture was washed with 1 M $Na_2S_2O_3$ (2 × 50 mL), water, brine and being dried over $MgSO_4$. The solvent was removed under vacuum and the product was purified by column chromatography (hexane/ethyl acetate, 5:1) to give **83** as a colourless solid (1.64 g, 43%, m.p. 43-48 °C). The data were consistent with those reported in the literature measured in CD_2Cl_2.[15]

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.72 (s, 1H), 7.13 (s, 1H), 5.06 (bd, J = 9.2 Hz, 1H), 4.58 (bdd, J = 15.0, 7.8 Hz, 1H), 4.23-4.09 (m, 2H), 3.32-3.03 (ABX system, bm, 2H), 1.54 (s, 18H), 1.40 (s, 9H), 1.21 (t, J = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm: 171.6, 155.0, 150.2, 150.2, 142.6, 141.5, 138.2, 133.4, 124.2, 95.4, 84.1, 84.0, 79.9, 61.6, 53.5, 42.5, 28.3, 27.6, 14.0.

Bis(trifluoroacetoxy)iodobenzene (S1)

Bis(trifluoroacetoxy)iodobenzene **S1** was synthesised according to the literature.[16] To a solution of iodobenzene (5.0 g, 24.5 mmol, 2.7 mL) in TFA (75 mL) and chloroform (25 mL) was added Oxone® (5.6 g, 36.8 mmol) with stirring at room temperature. The reaction mixture was stirred at room temperature for 2 h. The solvent was evaporated under vacuum and the residue was treated with chloroform. The mixture was filtered and the filtrate was evaporated under reduced pressure to give the product as a pale yellow solid. Recrystallisation from chloroform and hexane gave the product as a white solid (6.4 g, 55% (90% purity), m.p. 110-114 °C (lit. 121-125 °C)).[16]

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 8.26-8.10 (m, 2H), 7.81-7.70 (m, 1H), 7.65-7.60 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 161.1 (q, J = 41.2 Hz, 2C), 135.1, 133.7, 132.0, 122.7, 112.8 (q, J = 288.5 Hz, 2C).

2-(Diacetoxy)iodothiophene (87)
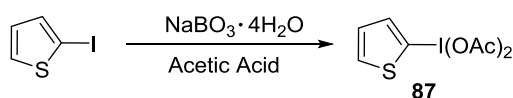
2-(Diacetoxy)iodothiophene **87** was synthesised according to the literature.[17] Sodium perborate tetrahydrate (29.23 g, 190 mmol) was added portion wise over 30 min to a solution of 2-iodothiophene (4.0 g, 19 mmol, 2.1 mL) in acetic acid (150 mL). The temperature was raised to 50 °C and the mixture stirred for 6 h. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The product was extracted in CH_2Cl_2 and washed with water before being dried over $MgSO_4$ and concentrated under vacuum. Trituration in diethyl ether gave the product as a colourless solid (2.9 g, 40% (85% purity), m.p. 118-112 °C (lit. 120-122 °C)).[17]

^{1}H NMR (250 MHz, CDCl$_3$) δ ppm: 7.78 (dd, J = 3.8, 1.2 Hz, 1H), 7.64 (dd, J = 5.4, 1.2 Hz, 1H), 7.13 (dd, J = 5.4, 3.8 Hz, 1H), 2.02 (s, 6H); ^{13}C NMR (100 MHz, CDCl$_3$) δ ppm: 176.9, 139.0, 134.8, 128.5, 106.1, 20.3.

Hydroxy(p-tosyloxy)iodo-2-thiophene (88)
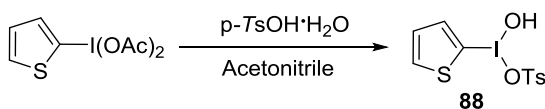
88 was synthesised according to the literature.[18] To a suspension of 2-(diacetoxy)iodothiophene (200 mg, 0.61 mmol) in acetonitrile (5 mL) was added *p*-TsOH·H$_2$O (116 mg, 0.61 mmol). The mixture was stirred at room temperature for 1 h before addition of diethyl ether and ethyl acetate (2:1) (15 mL) to precipitate the product. The product was isolated by filtration and dried briefly under suction to give the product as a white powder (0.2 g, 82%, m.p. decomposition at room temperature).[18]
^{1}H NMR (250 MHz, MeOD) δ ppm: 8.24 (dd, J = 3.9, 1.2 Hz, 1H), 8.10 (dd, J = 5.3, 1.2 Hz, 1H), 7.70 (d, J = 8.3 Hz, 2H), 7.37 (dd, J = 5.3, 3.9 Hz, 1H), 7.23 (d, J = 8.5 Hz, 2H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, MeOD) δ ppm: 144.5, 142.8, 141.8, 140.6, 130.8, 129.7, 126.7, 107.6, 21.2. In accordance with the literature data.[18]

[*N*-(*tert*-Butoxycarbonyl)-3,4-di(*tert*-butoxycarbonyloxy)-L-phenylalanine ethyl ester]-6-(2-thienyl)iodonium tosylate (89(TsO))

89(TsO)
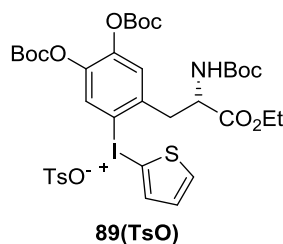
Using GP1 the product was obtained as a white solid (116 mg, 44%, m.p. 80-84 °C).

IR ν_{max} (cm^{-1}; neat) 1769, 1707, 1487, 1369, 1252, 1152, 1121, 1030, 1007, 679; ^{1}H NMR (500 MHz; CDCl$_3$) δ ppm: 7.95 (s, 1H), 7.75 (dd, J = 3.8, 0.9 Hz, 1H), 7.50 (dd, J = 5.3, 1.1 Hz, 1H), 7.28 (s, 1H), 7.25 (d, J = 8.9 Hz, 2H), 7.00 (d, J = 8.1 Hz, 2H), 6.95 (dd, J = 5.3, 3.9 Hz, 1H), 6.12-5.89 (bm, 1H), 4.66-4.49 (bm, 1H), 4.27-4.10 (bm, 2H), 3.64-3.34 (ABX system, bm, 2H), 2.29 (s, 3H), 1.51 (s, 9H), 1.51 (s, 9H), 1.33 (s, 9H), 1.23 (t, J = 7.1 Hz, 1H); ^{13}C NMR (126 MHz, CDCl$_3$) δ ppm 171.3, 155.7, 149.7, 149.5, 145.4, 142.2, 141.6, 139.6, 139.5, 138.4, 135.3, 131.5, 129.3, 128.6, 125.7, 125.0, 118.6, 99.7, 84.5, 84.5, 79.6, 61.7, 53.0, 39.1, 28.2, 27.5, 27.5, 21.2, 14.0; HRMS (ESI) [M-TsO]$^+$ found 734.1483 calc. 734.1490 [C$_{30}$H$_{41}$INO$_{10}$S]$^+$.

[*N*-(*tert*-Butoxycarbonyl)-3,4-di(*tert*-butoxycarbonyloxy)-L-phenylalanine ethyl ester]-6-(2-thienyl)iodonium bromide 89(Br)

89(Br)
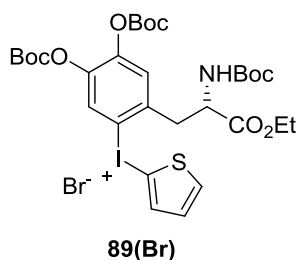
Iodonium tosylate **89(TsO)** (62 mg, 0.069 mmol) was dissolved in CH$_2$Cl$_2$ (50 mL) and washed with aqueous KBr (0.2 M, 3 × 50 mL) and the organic layer was passed through a phase separator. The solvent was removed before the product was triturated with hexane from a minimum amount of CH$_2$Cl$_2$ and diethyl ether (1:1). Removal of the solvent under reduced pressure gave the product as a colourless solid (55 mg, 99%, m.p. 84-94 °C).

IR ν_{max} (cm^{-1}; neat) 1767, 1713, 1489, 1370, 1252, 1154, 1123, 1019, 802; ^{1}H NMR (400 MHz; CDCl$_3$) δ ppm: 8.05 (s, 1H), 7.70 (dd, J = 3.8, 1.2 Hz, 1H), 7.53 (dd, J =

5.3, 1.2 Hz, 1H), 7.34 (s, 1H), 7.01 (dd, J = 5.2, 3.8 Hz, 1H), 5.55-5.28 (bm, 1H), 4.85-4.62 (bm, 1H), 4.29-4.13 (bm, 2H), 3.62-3.43 (ABX system, bm, 2H), 1.53 (s, 9H), 1.52 (s, 9H), 1.40 (s, 1H), 1.25 (t, J = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, CDCl$_3$) δ ppm: 171.2, 155.4, 149.7, 149.5, 145.1, 142.5, 137.5, 137.5, 134.0, 131.2, 129.0, 125.3, 123.0, 107.2, 84.5, 84.4, 79.9, 61.8, 53.2, 39.5, 28.2, 27.5, 27.5, 14.1; HRMS (ESI) [M-Br]$^+$ found 734.1485 calc. 734.1490 [C$_{30}$H$_{41}$INO$_{10}$S]$^+$.

[*N*-(*tert*-Butoxycarbonyl)-3,4-di(*tert*-butoxycarbonyloxy)-L-phenylalanine ethyl ester]-6-(2-thienyl)iodonium iodide 89(I)
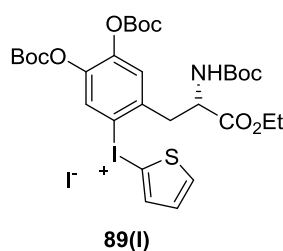

89(I)

Iodonium tosylate **89(TsO)** (42 mg, 0.046 mmol) was dissolved in CH$_2$Cl$_2$ (50 mL) and washed with aqueous KI (0.2 M, 3 × 50 mL) and the organic layer was passed through a phase separator. The solvent was removed before the product was triturated with hexane from a minimum amount of CH$_2$Cl$_2$ and diethyl ether (1:1). Removal of the solvent under reduced pressure gave the product as a yellow solid (35 mg, 90%).

^{1}H NMR (250 MHz; CDCl$_3$) δ ppm: 8.43 (s, 1H), 8.03 (dd, J = 3.8, 1.3 Hz, 1H), 7.91 (dd, J = 5.4, 1.2 Hz, 1H), 7.50 (s, 1H), 7.20 (dd, J = 5.3, 3.9 Hz, 1H), 4.54 − 4.39 (m, 1H), 4.22 (q, J = 7.1 Hz, 2H), 3.65 − 3.18 (ABX system, bm, 2H), 1.53 (s, 9H), 1.52 (s, 9H), 1.40 (s, 9H), 1.26 (t, J = 7.2 Hz, 3H).

[*N*-(*tert*-Butoxycarbonyl)-3,4-di(*tert*-butoxycarbonyloxy)-L-phenylalanine ethyl ester]-6-(2-thienyl)iodonium perchlorate 89(ClO$_4$)

89(ClO$_4$)
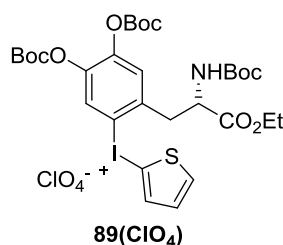
Counter ion exchange was achieved using a method reported in the literature.[20] Iodonium tosylate **89(TsO)** (55 mg, 0.061 mmol) was absorbed onto a Biotage® KP-C18-HS 12 g SNAP cartridge in a minimum amount of acetonitrile. The RP column was eluted with aqueous KClO$_4$ (0.1%, 50 mL) followed by elution with water (50 mL). The

salt was then eluted from the column using a gradient of acetonitrile in water (20% - 90%). The acetonitrile was removed under reduced pressure before the water was removed by lyophilisation to give the product as a fluffy colourless solid (15 mg, 30%, m.p. 96-107 °C).

IR ν_{max} (cm^{-1}; neat) 1765, 1707, 1686, 1491, 1372, 1252, 1150, 1123, 1094, 621; ^{1}H NMR (400 MHz; CDCl$_3$) δ ppm: 7.99 (dd, J = 3.9, 1.2 Hz, 1H), 7.85 (s, 1H), 7.72 (dd, J = 5.4, 1.2 Hz, 1H), 7.48 (s, 1H), 7.16 (dd, J = 5.4, 3.9 Hz, 1H), 5.62 (d, J = 8.1 Hz, 1H), 4.66-4.50 (bm, 1H), 4.38-4.08 (bm, 2H), 3.65 − 3.31 (ABX system, bm, 2H), 1.53 (s, 9H), 1.53 (s, 9H), 1.42 (s, 9H), 1.29 (t, J = 7.2 Hz, 3H); HRMS (ESI) [M-ClO$_4$]$^+$ found 734.1485 calc. 734.1490 [C$_{30}$H$_{41}$INO$_{10}$S]$^+$.

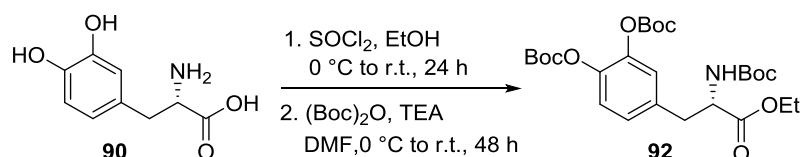### *N*-(*tert*-Butoxycarbonyl)-3,4-di(*tert*-butoxycarbonyloxy)-L-phenylalanine ethyl ester 92

92 was synthesised according to the literature.[14] To a suspension of 3,4-dihydroxy-L-phenylalanine (2.5 g, 12.7 mmol) in ethanol (15 mL), cooled to 0 °C, was added SOCl$_2$ (7.55 g, 4.6 mL, 63.5 mmol) dropwise over 30 min. The reaction was stirred at 0 °C for 2 h before being left to warm to room temperature overnight. The reaction was concentrated under vacuum, dissolved in ethyl acetate and washed with 10% aq Na$_2$CO$_3$, water and brine before being dried over MgSO$_4$. The solvent was removed to give the crude the 3,4-dihydroxy-L-phenylalanine ethyl ester (hydrochloride salt) as a yellow oil. The product could be isolated as a solid by addition of CH$_2$Cl$_2$ followed by removal of the solvent to give the product as a pale yellow solid (1.64 g, 55%, m.p. 84-85 °C). The data were consistent with those reported in the literature measured in CDCl$_3$.[14] However it was found that the solidified product was more soluble and gave better spectra in MeOD.

### 3,4-Dihydroxy-L-phenylalanine ethyl ester (hydrochloride salt)

^{1}H NMR (400 MHz, MeOD) δ ppm: 6.68 (d, J = 8.0 Hz, 1H), 6.61 (d, J = 2.1 Hz, 1H), 6.49 (dd, J = 8.0, 2.1 Hz, 1H), 4.13 (q, J = 7.1 Hz, 1H), 3.61 (t, J = 6.5 Hz, 1H), 2.87-2.76 (ABX system, m, 2H), 1.22 (t, J = 7.1 Hz, 1H); ^{13}C NMR (63 MHz, MeOD) δ ppm: 176.0, 146.4, 145.4, 129.5, 121.7, 117.4, 116.4, 62.0, 56.8, 41.2, 14.5.

To a solution of L-DOPA ethyl ester (hydrochloride salt) (1.07 g, 4.58 mmol) in DMF (10 mL), cooled to 0 °C, was added triethylamine (1.58 g, 15.61 mmol, 2.18 mL) followed by di-*tert*-butyldicarbonate (3.61 g, 16.55 mmol, 3.8 mL) in DMF (3 mL). The reaction was stirred at 0 °C for 2 h followed by 48 h at room temperature. The solution was diluted with ethyl acetate and washed with water and brine before being dried over $MgSO_4$. Removal of the solvents gave the crude triboc L-DOPA ethyl ester which was purified by column chromatography (hexane:ethyl acetate, 5:1) to give the pure product as a colourless foam (2.09 g, 87%). The data were consistent with those reported in the literature measured in CD_2Cl_2.[14]

^{1}H NMR (400 MHz, CDCl$_3$) δ ppm: 7.23-6.95 (m, 3H), 5.01 (bd, *J* = 8.1 Hz, 1H), 4.54 (bdd, *J* = 14.0, 6.4 Hz, 1H), 4.15 (q, *J* = 7.2 Hz, 2H), 3.08 (bd, *J* = 5.9 Hz, 2H), 1.54 (s, 18H), 1.42 (s, 9H), 1.22 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ ppm: 171.4, 155.0, 150.6, 150.5, 142.2, 141.4, 134.7, 127.1, 123.9, 122.9, 83.6, 79.9, 61.4, 54.2, 37.5, 28.2, 27.5, 27.3, 14.0.

N-(*tert*-Butoxycarbonyl)-3,4-di(*tert*-butoxycarbonyloxy)-6-fluoro-L-phenylalanine ethyl ester (95)
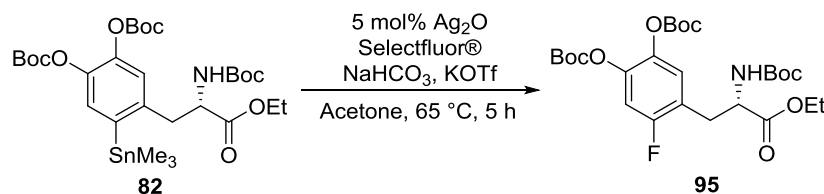
95 was synthesised using a literature procedure.[20] To triboc-6-(trimethylstannyl)-L-DOPA ethyl ester **82** (500 mg, 0.727 mmol) in acetone (14 mL) at room temperature was added Ag$_2$O (8.34 mg, 0.036 mmol), NaHCO$_3$ (122 mg, 1.45 mmol), KOTf (136 mg, 0.727 mmol) and selectfluor$^®$ (387 mg, 1.09 mmol). The reaction mixture was stirred for 5 h at 65 °C in a sealed vial. After cooling to room temperature the reaction mixture was filtered through a pad of celite, eluted with CH$_2$Cl$_2$ and the filtrate was concentrated *in vacuo*. The residue was purified by chromatography (hexane:EtOAc, 5:1), to give the product as a colourless oil (87 mg, 22%). The data were consistent with those reported in the literature measured in CD_2Cl_2.[20,21]

^{1}H NMR (500 MHz, CDCl$_3$) δ ppm: 7.06 (d, *J*$^4_{F-H}$ = 7.1 Hz, 1H), 7.00 (d, *J*$^3_{F-H}$ = 9.6 Hz, 1H), 5.08 (bd, *J* = 7.6 Hz, 1H), 4.52 (bm, 1H), 4.15 (q, *J* = 7.1 Hz, 2H), 3.16-3.03 (ABX system, bm, 2H), 1.52 (s, 9H), 1.52 (s, 9H), 1.40 (s, 9H), 1.21 (t, *J* = 7.2 Hz, 3H);

^{13}C NMR (126 MHz, CDCl$_3$) δ ppm: 171.3, 158.0 (d, $J_{F\text{-}C}$ = 245.9 Hz, 1C), 150.1, 141.9 (d, $J_{F\text{-}C}$ = 11.3 Hz, 1C), 138.5, 125.2 (d, $J_{F\text{-}C}$ = 5.7 Hz, 1C), 121.4 (d, $J_{F\text{-}C}$ = 18.3 Hz, 1C), 110.6 (d, $J_{F\text{-}C}$ = 27.1 Hz, 1C), 84.1, 83.8, 79.9, 61.6, 53.4, 31.4, 28.2, 27.5, 13.9; ^{19}F NMR (300 MHz, CDCl$_3$) δ ppm: −117.4; HRMS (ESI) [M+NH$_4$]$^+$ found 561.2806 calc. 561.2818 [C$_{26}$H$_{38}$FNO$_{10}$+NH$_4$]$^+$.

[^{18}F]*N*-(*tert*-Butoxycarbonyl)-3,4-di(*tert*-butoxycarbonyloxy)-6-fluoro-L-phenylalanine ethyl ester ([^{18}F]95)
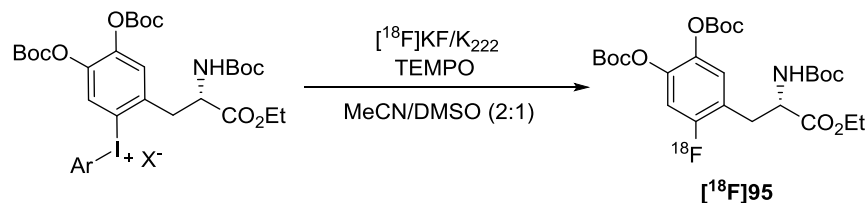
Radiofluorination was achieved using GP7. The reaction was analysed using radio HPLC and radio TLC. For purification, the reaction mixture was loaded onto the HPLC sample loop. Reverse phase purification was performed using a semi-prep Agilent 1200 column (4 mL/min, 70% MeCN in H$_2$O containing 0.01% formic acid). The gamma peak was collected (retention: 7.5 min − 8.5 min) and the activity of the isolated product was measured using a Campitec CRC-25PET well counter. A 100 μL sample was taken for HPLC analysis to confirm the product as the protected [^{18}F]F-DOPA.

Alternatively, the reaction mixture could be directly eluted though a Sep-Pak alumina cartridge (prewashed with distilled water (10 mL)) into the product vial. The alumina cartridge was then eluted with acetonitrile (2 mL) to provide the partially purified product. Further purification could be achieved by elution of this mixture on to a Sep-Pak C18 cartridge followed by elution of the product **[^{18}F]95** with ethanol (2 mL).

HPLC of crude reaction mixture shows [¹⁸F]95 co-eluted with cold standard 95
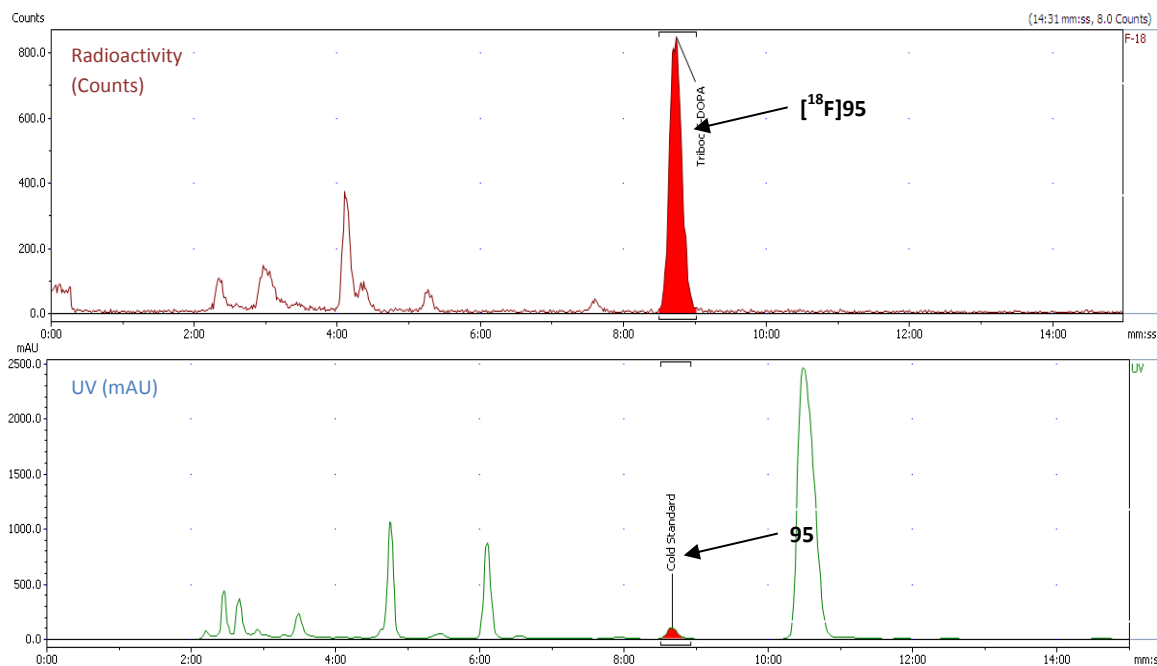
HPLC of purified [¹⁸F]95*
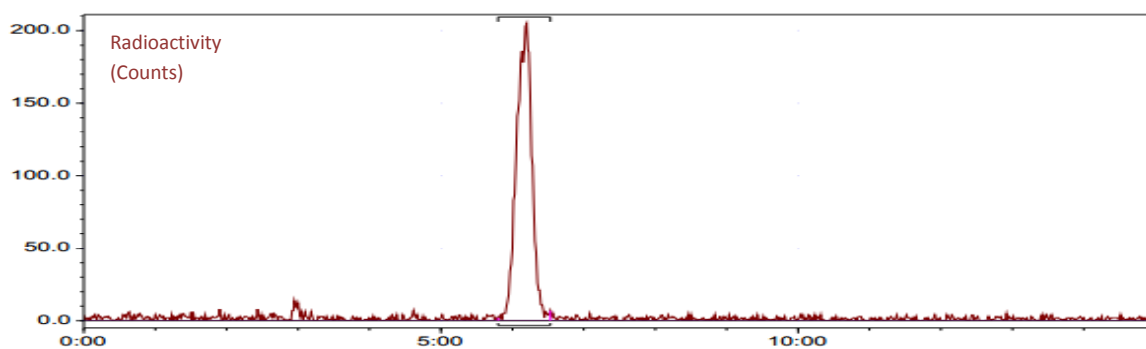
*Retention time differs from that above due to ageing of the column, having been performed months apart.

<u>Analytical HPLC Conditions</u>

Column: Analytical Phenomenex Synergi 4 μm Hydro-RP 80 C-18 4.6 × 250 mm column

Gradient: 80% MeCN in H_2O (0.01% TFA)

Flow Rate: 1 mL/min

<u>Purification HPLC conditions:</u>

Column: Semi-prep Phenomenex Synergi 4 μm Hydro-RP 80 C-18 10 × 250 mm column

Gradient: 70% MeCN in H_2O (0.01% TFA)

Flow Rate: 4 mL/min

TLC: [^{18}F]96 after Sep-Pak alumina cartridge

HPLC: [^{18}F]95 after Sep-Pak alumina cartridge

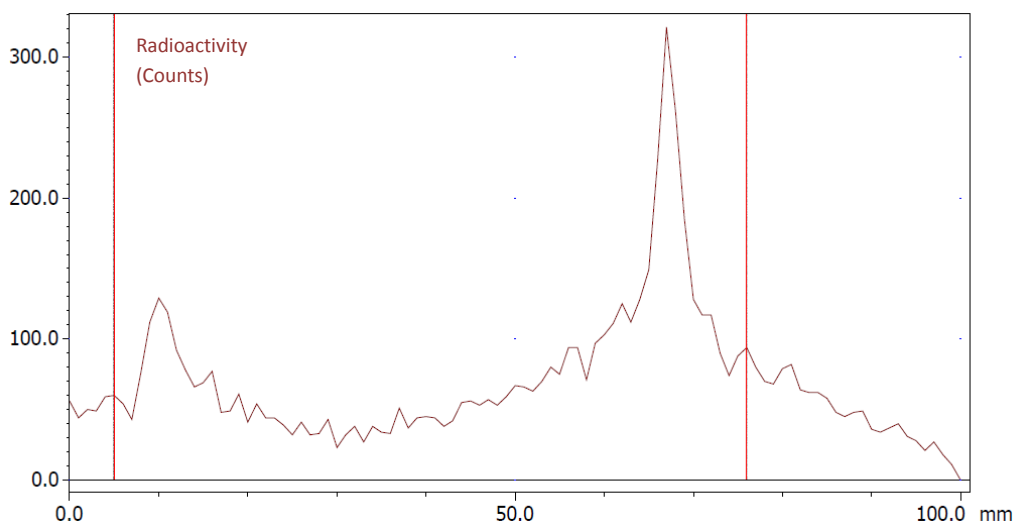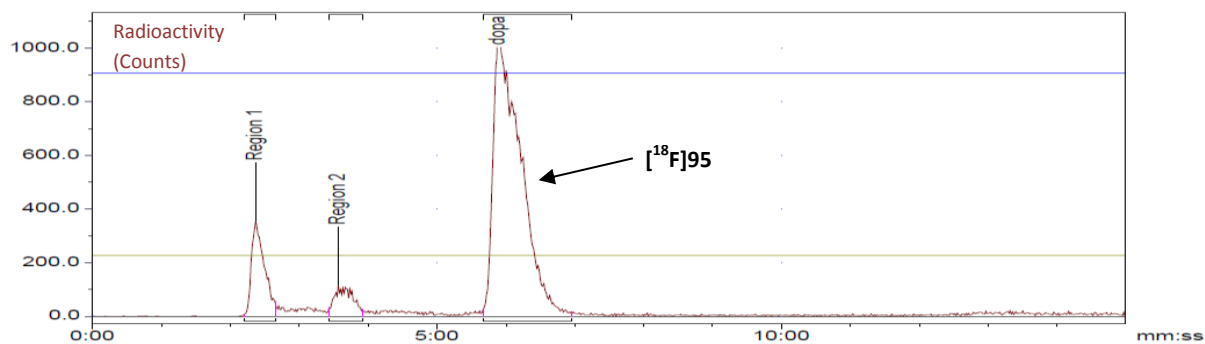*HPLC: [^{18}F]95 after Sep-Pak C-18 cartridge*
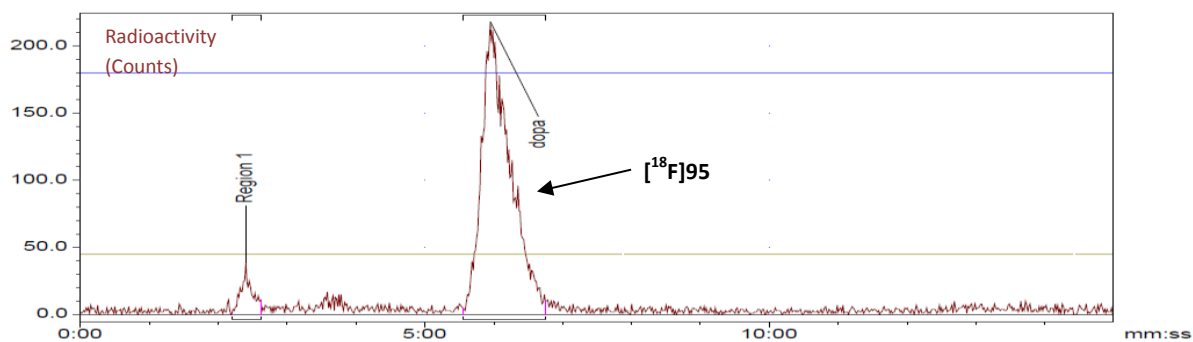
Analytical HPLC Conditions

Column: Analytical Phenomenex Synergi 4 μm Hydro-RP 80 C-18 4.6 × 250 mm column

Gradient: 80% MeCN in aqueous ammonium formate (50mM)

Flow Rate: 1 mL/min

Phenyl(thiophen-2-yl)iodonium triflate (96(TfO))
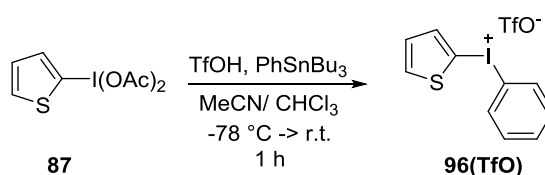
Trifluoromethanesulfonic acid (54 μL, 92 mg, 0.61 mmol) was added to a solution of 2-(diacetoxy)iodo thiophene **87** (0.2 g, 0.61 mmol) in MeCN (2.5 mL) at -40 °C with stirring. The solution was diluted with chloroform (15 mL) and tributylphenyltin (0.2 mL, 0.22 g, 0.6 mmol) in chloroform (5 mL) was added portion wise. The mixture was allowed to warm to room temperature before being stirred for 1 h. The volatiles were removed under a stream of nitrogen. Trituration with Et$_2$O gave the product as a beige powder (0.233 g, 89%).

^{1}H NMR (250 MHz, MeOD) δ ppm: 8.16 (d, J = 7.4 Hz, 2H), 8.01 (dd, J = 3.8, 1.2 Hz, 1H), 7.89 (dd, J = 5.4, 1.2 Hz, 1H), 7.69 (t, J = 7.5 Hz, 1H), 7.54 (t, J = 7.7 Hz, 1H), 7.18 (dd, J = 5.4, 3.9 Hz, 1H). In accordance with literature data.[22]

[*N*-(*tert*-Butoxycarbonyl)-3,4-di(*tert*-butoxycarbonyloxy)-L-phenylalanine ethyl ester]-6-(4-tolyl)iodonium tosylate (97(TfO))
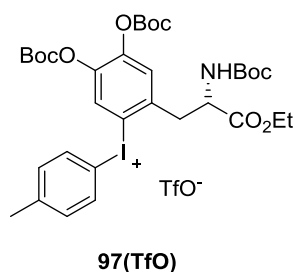
Using GP1 (on a 0.16 mmol scale, with KOTf wash) the product was obtained as a white solid (85 mg, 59%, m.p. 78-81 °C).

^{1}H NMR (500 MHz; CDCl$_3$) δ ppm: 7.86 (d, J = 8.4 Hz, 2H), 7.76 (s, 1H), 7.45 (s, 1H), 7.27 (d, J = 8.6 Hz, 2H), 5.56 (d, J = 7.6 Hz, 1H), 4.57 (d, J = 7.2 Hz, 1H), 4.34 – 4.11 (m, 2H), 3.50 – 3.23 (ABX system, bm, 2H), 2.42 (s, 3H), 1.53 (s, 9H), 1.52 (s, 9H), 1.40 (s, 9H), 1.28 (t, J = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, CDCl$_3$) δ ppm: 171.3, 155.6, 149.8, 149.7, 146.0, 144.0, 143.1, 139.0, 135.3, 133.3, 131.3, 126.3, 120.4 (q, J = 320.0 Hz, 1C), 113.6, 110.6, 85.1, 85.2, 80.7, 62.5, 54.02, 40.5, 28.3, 27.6, 21.5, 14.1; HRMS (ESI) [M-TfO]$^+$ found 742.2069 calc. 742.2083 [C$_{33}$H$_{45}$INO$_{10}$]$^+$.

[N-di-($tert$-Butoxycarbonyl)-3,4-di($tert$-butoxycarbonyloxy)-L-phenylalanine ethyl ester]-6-(2-thienyl)iodonium bromide (100(Br))
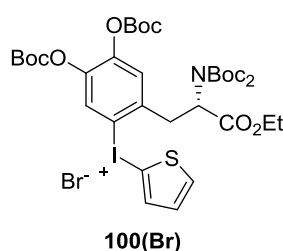
100(Br)

Iodonium bromide **100(Br)** was produced by washing the crude iodonium tosylate **100(TsO)** in CH$_2$Cl$_2$ with aqueous KBr (0.2 M, 3 × 50 mL). The organic layer was passed through a phase separator. The solvent was removed before the product was triturated with hexane from a minimum amount of CH$_2$Cl$_2$ / diethyl ether (1:1). The precipitate was collected on a Telos$^®$ phase separator and washed with hexane. The collected precipitate was removed from the phase separator with CH$_2$Cl$_2$. The CH$_2$Cl$_2$ was removed before the product was triturated once more with hexane from a minimum amount of CH$_2$Cl$_2$ and diethyl ether (1:1). Removal of the solvent under reduced pressure gave the product as a colourless solid (64 mg, 20%, m.p. 107-110 °C).

^{1}H NMR (400 MHz, MeOD) δ ppm: 8.30 (s, 1H), 8.05 (dd, J = 3.8, 1.1 Hz, 1H), 7.95 (dd, J = 5.3, 1.0 Hz, 1H), 7.48 (s, 1H), 7.22 (dd, J = 5.3, 4.0 Hz, 1H), 5.23 (dd, J = 8.4, 6.0 Hz, 1H), 4.26 (q, J = 6.9 Hz, 2H), 3.90-3.45 (m, 2H), 1.53 (s, 18H), 1.46 (s, 18H), 1.31 (t, J = 7.1, Hz, 3H); HRMS (ESI) [M-Br]$^+$ found 834.2023 calc. 834.2015 [C$_{35}$H$_{49}$INO$_{12}$]$^+$.
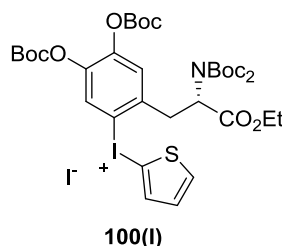
[*N*-di-(*tert*-Butoxycarbonyl)-3,4-di(*tert*-butoxycarbonyloxy)-ʟ-phenylalanine ethyl ester]-6-(2-thienyl)iodonium iodide (100(I))

100(I)

Iodonium iodide **100(I)** was produced by washing the crude iodonium tosylate **100(TsO)** in CH_2Cl_2 with aqueous KI (0.2 M, 3 × 50 mL). The organic layer was passed through a phase separator. The solvent was removed before the product was triturated with hexane from a minimum amount of CH_2Cl_2 / diethyl ether (1:1). The precipitate was collected on a Telos® phase separator and washed with hexane. The collected precipitate was removed from the phase separator with CH_2Cl_2. The CH_2Cl_2 was removed before the product was triturated once more with hexane from a minimum amount of CH_2Cl_2 and diethyl ether (1:1). Removal of the solvent under reduced pressure gave the product as a yellow solid (122 mg, 29%, m.p. 84-88 °C).

^{1}H NMR (250 MHz, MeOD) δ ppm: 8.30 (s, 1H), 8.04 (dd, J = 3.9, 1.3 Hz, 1H), 7.92 (dd, J = 5.5, 1.2 Hz, 1H), 7.47 (s, 1H), 7.21 (dd, J = 5.4, 3.9 Hz, 1H), 5.31 − 5.14 (m, 1H), 4.26 (q, J = 6.9 Hz, 2H), 3.90 − 3.44 (ABX system, bm, 2H), 1.53 (s, 9H), 1.52 (s, 9H), 1.46 (s, 18H), 1.31 (t, J = 7.1 Hz, 3H).

(Diacetox) iodotoluene (102)

102
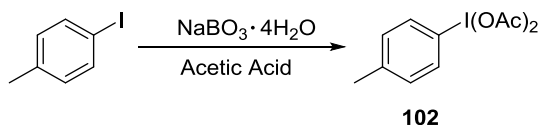
102 was synthesised according to the literature.[17] Sodium perborate tetrahydate (10.6 g, 69 mmol) was added portion wise over 30 min to a solution of 4-iodotoluene (1.5 g, 6.9 mmol) in acetic acid (50 mL). The temperature was raised to 50 °C and the mixture stirred for 6 h. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The product was extracted in CH_2Cl_2 and washed with water before being dried over $MgSO_4$ and concentrated under vacuum. Trituration in diethyl ether gave the product as a colourless solid (1.34 g, 46% (79% purity)).

^{1}H NMR (250 MHz, CDCl$_3$) δ ppm: 7.97 (d, J = 8.4 Hz, 2H), 7.29 (d, J = 8.2 Hz, 2H), 2.44 (s, 3H), 2.00 (s, 6H); ^{13}C NMR (100 MHz, CDCl$_3$) δ ppm: 176.5, 142.8, 135.1, 131.9, 118.4, 21.7, 20.5. In accordance with literature data.[23]

(Diacetox) iodomesitylene (103)

103
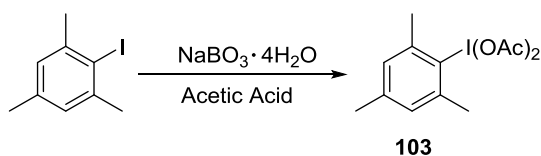
103 was synthesised according to the literature.[17] Sodium perborate tetrahydate (6.7 g, 43 mmol) was added portion wise over 30 min to a solution of 2-iodomesitylene (1.06 g, 4.3 mmol) in acetic acid (30 mL). The temperature was raised to 50 °C and the mixture stirred for 6 h. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The product was extracted in CH$_2$Cl$_2$ and washed with water before being dried over MgSO$_4$ and concentrated under vacuum. Trituration in diethyl ether gave the product as a colourless solid (1.08 g, 66% (95% purity), m.p. 155-157 °C (lit. 160-163 °C)).[24]

^{1}H NMR (250 MHz, CDCl$_3$) δ ppm: 7.45 (s, 1H), 3.05 (s, 3H), 2.70 (s, 1H), 2.32 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ ppm: 176.7, 143.4, 141.5, 129.6, 129.1, 26.9, 21.4, 20.3. In accordance with literature data.[24]

N-di-(*tert*-Butoxycarbonyl)-3,4-di(*tert*-butoxycarbonyloxy)-6-trimethylstannyl-ʟ-phenylalanine ethyl ester (104)
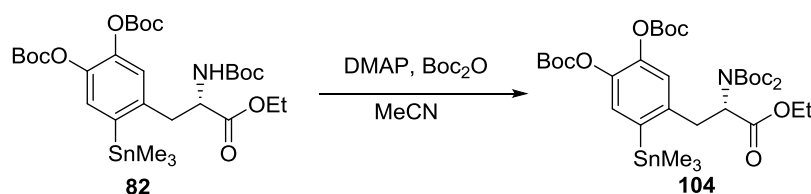
To a solution of triboc-6-(trimethylstannyl)-ʟ-DOPA ethyl ester **84** (0.50 g, 0.73 mmol) in dry acetonitrile (12 mL) under argon was added 4-dimethylaminopyridine (DMAP) (35.7 mg, 0.29 mmol) in dry acetonitrile (5 mL) and di-*tert*-butyl dicarbonate (0.32 g, 1.46 mmol, 0.34 mL) in dry acetonitrile (5 mL). The reaction was stirred at room temperature overnight before being concentrated under vacuum and purified by column chromatography (hexane/ethyl acetate, 21:5) to give the product **104** as a colourless solid (0.54 g, 94%, m.p. 117-119 °C).

IR ν_{max} (cm^{-1}; neat) 2984, 2972, 1773, 1767, 1757, 1736, 1697, 1478, 1458, 1367, 1248, 1134, 1020, 758; ^{1}H NMR (250 MHz, CDCl$_3$) δ ppm: 7.24 (s, with tin satellites J^3_{Sn-H} = 49.3 Hz, 1H), 7.03 (s, with tin satellites J^4_{Sn-H} = 16.2 Hz, 1H), 5.03 (bdd, J = 10.1, 4.7 Hz, 1H), 4.34-4.09 (m, 2H), 3.45-3.27 (ABX system, bm, 2H), 1.54 (s, 9H), 1.52 (s, 9H), 1.39 (s, 18H), 1.28 (t, J = 7.1 Hz, 3H), 0.33 (s, with tin satellites J^2_{Sn-H} = 54.9 Hz, 9H); ^{13}C NMR (126 MHz, CDCl$_3$) δ ppm: 169.9, 151.9, 150.7, 150.5, 143.0, 142.4, 141.1, 140.5, 129.9 (s, with tin satellites J^2_{Sn-C} = 40.5 Hz, 1C), 123.7 (s, with tin satellites J^2_{Sn-C} = 42.3 Hz , 1C), 83.3, 83.2, 83.0, 61.3, 59.3, 37.8, 27.8, 27.6, 14.1, -8.2 (s, with tin satellites J^1_{Sn-C} = 354.0 Hz, 3C); HRMS (ESI) [M+NH$_4$]$^+$ found 799.3122 calc. 799.3111 [C$_{34}$H$_{55}$NO$_{12}$Sn+NH$_4$]$^+$.

[N-di-($tert$-Butoxycarbonyl)-3,4-di(tert-butoxycarbonyloxy)-L-phenylalanine ethyl ester]-6-(4-anisyl)iodonium tosylate (106(TsO))

106(TsO)
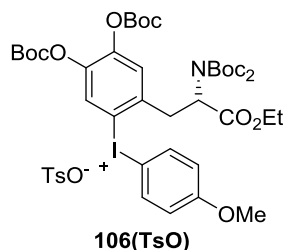
Using GP1 the product was obtained as a colourless solid (78 mg, 28%, m.p. 75-77 °C). IR ν_{max} (cm^{-1}; neat) 1771, 1734, 1572, 1491, 1368, 1250, 1142, 1119, 1007, 777, 679; ^{1}H NMR (400 MHz; CDCl$_3$) δ ppm: 7.92 (d, J = 9.2 Hz, 2H), 7.63 (s, 1H), 7.59 (d, J = 8.2 Hz, 2H), 7.36 (s, 1H), 7.04 (d, J = 7.9 Hz, 2H), 6.83 (d, J = 9.2 Hz, 2H), 5.12 (dd, J = 8.2, 6.72Hz, 1H), 4.21 (q, J = 7.2 Hz, 2H), 3.80 (s, 3H), 3.67 − 3.30 (ABX system, bm, 2H), 2.30 (s, 3H), 1.52 (s, 9H), 1.51 (s, 9H), 1.47 (s, 18H), 1.28 (t, J = 7.2 Hz, 3H); ^{13}C NMR (126 MHz, CDCl$_3$) δ ppm: 169.6, 162.4, 151.8, 149.7, 149.5, 145.2, 142.9, 142.6, 139.0, 138.7, 137.0, 130.6, 128.3, 126.1, 126.0, 117.6, 115.4, 105.3, 84.9, 84.8, 84.3, 62.2, 58.1, 55.5, 38.8, 27.9, 27.4, 21.2, 14.0; HRMS (ESI) [M-TsO]$^+$ found 858.2542 calc. 858.2556 [C$_{38}$H$_{53}$INO$_{13}$]$^+$.

[*N*-di-(*tert*-Butoxycarbonyl)-3,4-di(*tert*-butoxycarbonyloxy)-L-phenylalanine ethyl ester]-6-(4-anisyl)iodonium bromide (106(Br))

106(Br)
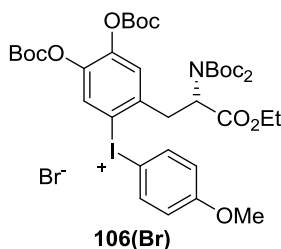
Iodonium tosylate **106(TsO)** (65 mg, 0.063 mmol) was dissolved in CH_2Cl_2 (50 mL) and washed with aqueous KBr (0.2 M, 3 × 50 mL) and the organic layer was passed through a phase separator. The solvent was removed before the product was triturated with hexane from a minimum amount of CH_2Cl_2 and diethyl ether (1:1). Removal of the solvent under reduced pressure gave the product as a white solid (59 mg, 100%, m.p. 85-88 °C).

IR v_{max} (cm^{-1}; neat) 1766, 1737, 1573, 1487, 1368, 1250, 1152, 1138, 1120, 820, 736; ^{1}H NMR (400 MHz, CDCl$_3$) δ ppm: 7.95 (d, J = 9.2 Hz, 2H), 7.56 (s, 1H), 7.31 (s, 1H), 6.87 (d, J = 9.2 Hz, 2H), 5.18 (t, J = 7.7 Hz, 1H), 4.27 − 4.17 (m, 2H), 3.81 (s, 3H), 3.73-3.26 (ABX system, 2m, 2H), 1.52 (s, 9H), 1.51 (s, 9H), 1.46 (s, 18H), 1.29 (t, J = 7.2 Hz, 3H); ^{13}C NMR (126 MHz, CDCl$_3$) δ ppm: 169.5, 161.9, 151.9, 149.8, 149.6, 144.7, 142.5, 138.1, 136.4, 129.9, 126.1, 122.2, 117.5, 109.5, 84.7, 84.5, 84.1, 62.1, 58.1, 55.6, 38.4, 27.9 (, 27.5 (, 14.1; HRMS (ESI) [M-Br]$^+$ found 858.2546 calc. 858.2556 [C$_{38}$H$_{53}$INO$_{13}$]$^+$.

N-Phthalimide-3,4-di(*tert*-butoxycarbonyloxy)-L-phenylalanine methyl ester 109

109
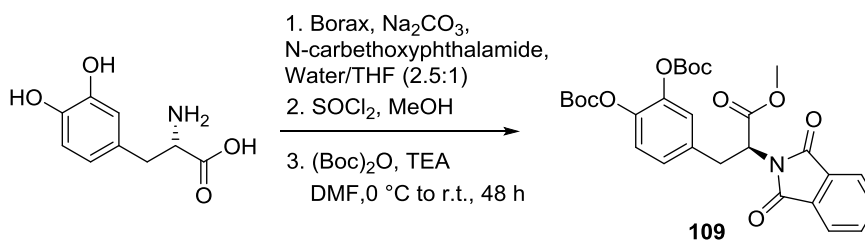
N-Phthalimide-3,4-dihydroxy-L-phenylalanine methyl ester **107** was synthesised according to the literature.[25]To a round bottom flask was added borax (1.0 g, 5.0 mmol), water (25 mL) and a stirrer bar. The mixture was degassed with argon for 30 min. The L-DOPA (1.97 g, 10 mmol) was added followed by Na$_2$CO$_3$ (1.06 g, 10 mmol) and N-carbethoxyphthalimide (2.66 g, 12.1 mmol) in THF (10 mL). The mixture was stirred overnight at room temperature and then acidified to pH 1-2 with 1 M HCl

solution. The THF was removed by rotary evaporation and the mixture was extracted with EtOAc before being washed with water and dried over MgSO$_4$. The solvent was removed to give the crude *N*-phthalimide-3,4-dihydroxy-L-phenylalanine **107** as a grey gum (3.7 g).

Without further purification the crude *N*-phthalimide-3,4-dihydroxy-L-phenylalanine (3.7 g, 10 mmol) was dissolved in methanol (25 mL) and cooled to -41 °C in an acetonitrile/ dry ice bath. Thionyl chloride (2.39 g, 20 mmol, 1.46 mL) was added drop wise over 5 min. The reaction mixture was allowed to warm to room temperature before being stirred overnight. Volatile reagents were removed by rotary evaporation and the residue was dissolved in chloroform before being triturated with hexane. The mixture was left in a refrigerator overnight and the liquid was decanted. Remaining solvent was removed under vacuum to give the crude product **108** as a pink/brown solid (2.5 g, 73% (impure)).

^{1}H NMR (250 MHz, CDCl$_3$) δ ppm: 7.87-7.63 (m, 4H), 6.72-6.52 (m, 3H), 5.10 (dd, *J* = 10.9, 5.7 Hz, 1H), 3.77 (s, 3H), 3.54-3.36 (ABX system, bm, 2H); ^{13}C NMR (100 MHz, CDCl$_3$) δ ppm: 169.5, 167.7, 143.6, 142.7, 134.2, 131.4, 129.0, 123.5, 121.2, 115.7, 115.3, 53.4, 53.0, 33.9.

Without further purification the crude phthalimide-L-DOPA methyl ester (1.0 g, 2.9 mmol) was dissolved in anhydrous DMF (10 mL) and cooled to 0 °C. Triethylamine (0.68 g, 6.7 mmol, 0.94 mL) was added followed by di-*tert*-butyldicarbonate (1.59 g, 7.3 mmol, 1.68 mL) in DMF (3 mL). The reaction was stirred at 0 °C for 2 h followed by 48 h at room temperature. The solution was diluted with ethyl acetate and washed with water and brine before being dried over MgSO$_4$. Removal of the solvents gave the crude diboc-phthalimide-L-DOPA methyl ester, which was purified by column chromatography (hexane/ethyl acetate, 3:1) to give the pure product **109** as a colourless solid (1.2 g, 77%, m.p. 55-61 °C).

IR ν$_{max}$ (cm^{-1}; neat) 2980, 2365, 1763, 1713, 1508, 1385, 1246, 1148, 1111, 720; ^{1}H NMR (250 MHz, CDCl$_3$) δ ppm: 7.96-7.59 (m, 4H), 7.16-7.01 (m, 3H), 5.14 (dd, *J* = 10.3, 6.2 Hz, 1H), 3.77 (s, 3H), 3.66-3.42 (ABX system, bm, 2H), 1.49 (s, 9H), 1.48 (s, 9H); ^{13}C NMR (126 MHz, CDCl$_3$) δ ppm: 169.0, 167.4, 150.5, 150.4, 142.2, 141.3, 135.2, 134.0, 131.5, 126.5, 123.5, 123.5, 123.0, 83.5, 83.5, 52.9, 52.8, 34.0, 27.5 (6C); HRMS (ESI) [M+NH$_4$]$^+$ found 559.2276 calc. 559.2286 [C$_{28}$H$_{31}$NO$_{10}$+NH$_4$]$^+$.

N-Phthalimide-3,4-di(*tert*-butoxycarbonyloxy)-6-iodo-L-phenylalanine methyl ester (110)
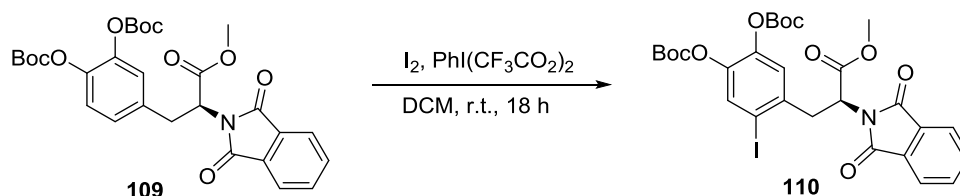
To a round bottom flask containing I_2 (0.56 g, 2.20 mmol) and $PhI(CF_3CO_2)_2$ (1.24 g, 2.70 mmol) under argon was added freshly distilled CH_2Cl_2 (10 mL). The mixture was stirred at 0 °C for 15 min before addition of diboc-Phth-L-DOPA methyl ester **109** (1.2 g, 2.2 mmol) in CH_2Cl_2 (10 mL). The reaction was kept at 0 °C for 15 min before being stirred at room temperature overnight. Following dilution with CH_2Cl_2 the reaction was washed with 1 M $Na_2S_2O_3$ (2 x 10 mL), water and brine before being dried over $MgSO_4$. The solvent was removed under vacuum and the product was purified by column chromatography (hexane/ethyl acetate, 3:1) to give the pure product as a colourless foam (0.64 g, 43%, m.p. 61-64 °C).

IR ν_{max} (cm^{-1}; neat) 1769, 1713, 1483, 1385, 1244, 1150, 1121, 718; ^{1}H NMR (250 MHz, CDCl$_3$) δ ppm: 7.81-7.70 (bm, 5H), 6.98 (s, 1H), 5.33 (dd, J = 10.9, 5.3 Hz, 1H), 3.79 (s, 3H), 3.75-3.55 (ABX system, bm, 2H), 1.48 (s, 9H), 1.41 (s, 9H); ^{13}C NMR (100 MHz, CDCl$_3$) δ ppm: 168.8, 167.4, 150.0, 149.8, 142.3, 141.5, 137.7, 134.0, 133.5, 131.6, 124.7, 123.6, 94.6, 84.1, 83.9, 53.0, 50.9, 38.9, 27.5, 27.4; HRMS (ESI) [M+NH$_4$]$^+$ found 685.1243 calc. 685.1253 [C$_{28}$H$_{30}$INO$_{10}$+NH$_4$]$^+$.

N-Phthalimide-3,4-di(*tert*-butoxycarbonyloxy)-6- trimethylstannyl-L-phenylalanine methyl ester (111)
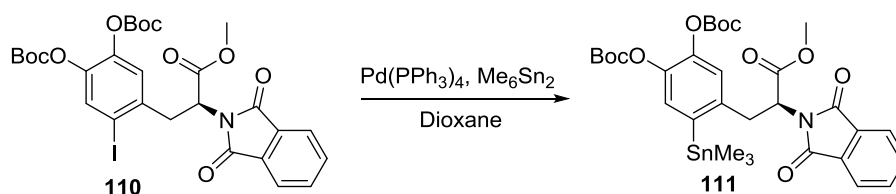
To a solution of diboc-phthalimide-6-iodo-L-DOPA methyl ester **110** (1.29 g, 1.93 mmol) in anhydrous dioxane (30 mL) under argon and protected from light was added tetrakis triphenylphosphine palladium (0.112 g, 0.097 mmol) and hexamethylditin (1.17 g, 3.57 mmol, 0.74 mL). The mixture was stirred at reflux for 6 h before being cooled to room temperature and filtered. The filtrate was diluted with EtOAc, washed with water and brine, dried over $MgSO_4$ and concentrated to dryness. The residue was purified by

flash chromatography (hexane/ethyl acetate, 3:1) to give the product **111** as a colourless foam (0.68 g, 50%, m.p. 58-61 °C).

IR ν_{max} (cm^{-1}; neat) 1765, 1715, 1385, 1370, 1246, 1152, 1121, 772, 718; ^{1}H NMR (400 MHz, CDCl$_3$) δ ppm: 7.83-7.65 (m, 4H), 7.23 (s, with tin satellites J^3_{Sn-H} = 48.8 Hz, 1H), 6.94 (s, with tin satellites J^4_{Sn-H} = 16.1 Hz, 1H), 5.07 (dd, J = 11.1, 5.1 Hz, 1H), 3.77 (s, 3H), 3.71-3.52 (ABX system, bm, 2H), 1.49 (s, 9H), 1.40 (s, 9H), 0.40 (s, with tin satellites J^2_{Sn-H} = 54.9 Hz, 9H); ^{13}C NMR (126 MHz, CDCl$_3$) δ ppm: 169.1, 167.6, 150.7, 150.4, 142.4, 141.8, 141.2, 140.6, 134.0, 131.8, 130.3 (s, with tin satellites J^2_{Sn-C} = 39.1 Hz, 1C), 123.6, 123.0 (s, with tin satellites J^2_{Sn-C} = 41.3 Hz, 1C), 83.5, 83.3, 53.0, 52.8, 36.4, 27.6, 27.5, -8.00 (s, with tin satellites J^1_{Sn-C} = 347.0 Hz, 3C); HRMS (ESI) [M+NH$_4$]$^+$ found 715.1971 calc. 715.1960 [C$_{31}$H$_{39}$NO$_{10}$Sn+NH$_4$]$^+$.

[*N*-Phthalimide-3,4-di(*tert*-butoxycarbonyloxy)-L-phenylalanine methyl ester]-6-(4-anisyl)iodonium tosylate (113(TsO))

113(TsO)
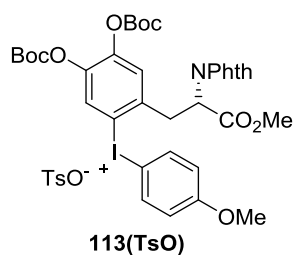
Using GP1 (on a 0.213 mmol scale) the product was obtained as a colourless solid (59 mg, 29%, m.p. 105-108 °C).

IR ν_{max} (cm^{-1}; neat) 1767, 1750, 1718, 1489, 1385, 1250, 1150, 1123, 1007, 820, 679; ^{1}H NMR (400 MHz; CDCl$_3$) δ ppm: 7.94 (d, J = 9.2 Hz, 2H), 7.85-7.70 (m, 5H), 7.63 (d, J = 8.2 Hz, 2H), 7.25 (s, 1H), 7.08 (d, J = 7.9 Hz, 2H), 6.88 (d, J = 9.2 Hz, 2H), 5.04 (dd, J = 8.7, 6.7 Hz, 1H), 3.82 (s, 3H), 3.78 (s, 3H), 3.70-3.44 (m, 2H), 2.32 (s, 3H), 1.49 (s, 9H), 1.45 (s, 9H); ^{13}C NMR (126 MHz, CDCl$_3$) δ ppm: 168.4, 167.3, 162.3, 149.4, 149.4, 145.2, 142.6, 142.4, 139.1, 137.8, 136.9, 134.2, 131.7, 131.5, 128.3, 125.9, 125.0, 123.7, 117.5, 115.1, 104.9, 84.6, 84.5, 55.5, 53.3, 51.5, 37.1, 27.4, 27.3, 21.1; HRMS (ESI) [M-TsO]$^+$ found 774.1394 calc. 774.1406 [C$_{35}$H$_{37}$INO$_{11}$]$^+$.

[*N*-Phthalimide-3,4-di(*tert*-butoxycarbonyloxy)- L-phenylalanine methyl ester]-6-(4-anisyl)iodonium bromide (113(Br))

113(Br)
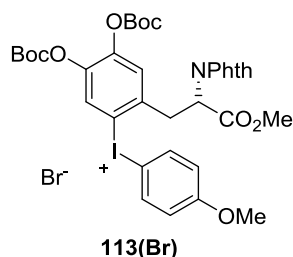
Iodonium tosylate **113(TsO)** (50 mg, 0.053 mmol) was dissolved in CH_2Cl_2 (50 mL) and washed with aqueous KBr (0.2 M, 3×50 mL) and the organic layer was passed through a phase separator. The solvent was removed before the product was triturated with hexane from a minimum amount of CH_2Cl_2 and diethyl ether (1:1). Removal of the solvent under reduced pressure gave the product as a colourless solid (45 mg, 100%, m.p. 107-110 °C).

IR ν_{max} (cm^{-1}; neat) 1771, 1717, 1489, 1389, 1372, 1150, 1256, 1153, 1127, 1087, 720; ^{1}H NMR (400 MHz, CDCl$_3$) δ ppm: 7.98 (d, J = 9.2 Hz, 2H), 7.85 − 7.77 (m, 2H), 7.76 (s, 1H), 7.75 − 7.67 (m, 2H), 7.17 (s, 1H), 6.88 (d, J = 9.2 Hz, 2H), 5.04 (dd, J = 9.9, 5.9 Hz, 1H), 3.81 (s, 3H), 3.80 (s, 3H), 3.91-3.56 (ABX system, bm, 2H), 1.48 (s, 9H), 1.42 (s, 9H); ^{13}C NMR (126 MHz, CDCl$_3$) δ ppm: 168.4, 167.3, 161.8, 149.6, 149.5, 144.8, 142.4, 137.2, 136.2, 134.1, 131.6, 131.2, 125.0, 123.7, 121.0, 117.4, 110.2, 84.5, 84.3, 55.5, 53.3, 51.7, 36.8, 27.5, 27.4; HRMS (ESI) [M-Br]$^+$ found 774.1401 calc. 774.1406 [C$_{35}$H$_{37}$INO$_{11}$]$^+$.

N-**Phthalimide-3,4-di(trifluoroacetoxy)-L-phenylalanine methyl ester (115)**
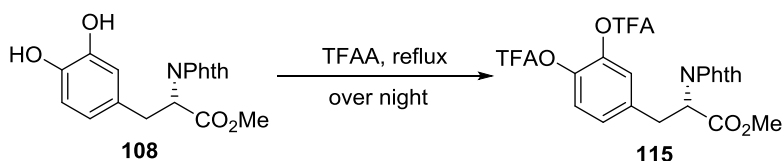
Under inert conditions trifluoroacetic anhydride (1.66 mL, 2.47 g, 11.8 mmol) was added to a flask containing **108** (0.5 g, 1.5 mmol) equipped with a stirrer bar and a condenser. The reaction was refluxed for 1 h before being stirred at room temperature for 18 h. The volatiles were removed under a flow of nitrogen to yield the product as a pale orange oil (0.69 g, 88%).

^{1}H NMR (250 MHz, CDCl$_3$) δ ppm: 7.85 – 7.70 (m, 4H), 7.30 – 7.14 (m, 3H), 5.15 (dd, J = 10.7, 6.0 Hz, 1H), 3.79 (s, 3H), 3.72 – 3.53 (ABX system, bm, 2H); ^{19}F NMR (300 MHz, CDCl$_3$) δ ppm: -74.4.

(4-(*O*-Boc)phenyl)(thienyl)iodonium tosylate (117(TsO))
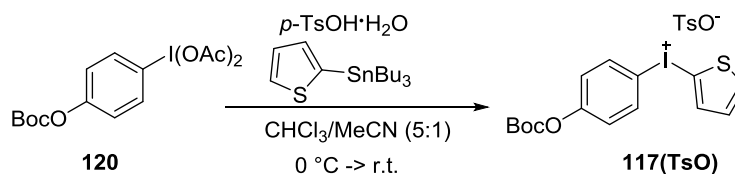
To a stirred suspension of *O*-Boc 4-(diacetoxy)iodophenol **120** (0.85 g, 1.94 mmol) in acetonitrile (15 mL) at 0 °C was added *p*-TsOH·H$_2$O (369 mg, 1.94 mmol) before immediate dilution with chloroform (70 mL). 2-(Tributylstannyl)thiophene (0.616 mL, 0.724 g, 1.94 mmol) was added dropwise. The reaction mixture was stirred for 18 h at room temperature before the solvents were removed under reduced pressure. The residue was dissolved in CH$_2$Cl$_2$ (40 mL) and washed with water. The organic layer was passed through a phase separator and concentrated under reduced pressure to give the crude product as a yellow oil. Trituration with Et$_2$O gave the product as a colourless solid (1.10 g, 98%, m.p. 144-145 °C).

^{1}H NMR (250 MHz, CDCl$_3$) δ ppm: 7.95 (d, J = 9.0 Hz, 2H), 7.75 (dd, J = 3.8, 1.2 Hz, 1H), 7.59 (dd, J = 5.3, 1.2 Hz, 1H), 7.52 (d, J = 8.2 Hz, 2H), 7.17 (d, J = 9.1 Hz, 2H), 7.11 – 7.00 (m, 3H), 2.32 (s, 3H), 1.54 (s, 9H); ^{13}C NMR (125 MHz, CDCl$_3$) δ ppm: 153.6, 150.9, 142.2, 140.7, 139.8, 136.1, 135.9, 129.7, 128.7, 126.1, 124.5, 114.1, 99.7, 84.7, 27.8, 21.4; HRMS (ESI) [M-TsO]$^+$ found 402.9852 calc. 402.9859 [C$_{15}$H$_{16}$ISO$_3$]$^+$.

(4-(*O*-Boc)phenyl)(thienyl)iodonium bromide (117(Br))
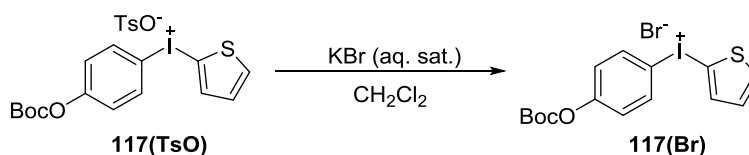
Iodonium tosylate **117(TsO)** (676 mg, 1.18 mmol) was dissolved in CH$_2$Cl$_2$ (50 mL) and washed with aqueous KBr (0.2 M, 3 × 50 mL) and the organic layer was passed through a phase separator. The solvent was removed before the product was triturated with diethyl ether from a minimum amount of CH$_2$Cl$_2$. Filtration gave the product as a colourless solid (528 mg, 93%, m.p. 154-156 °C).

^{1}H NMR (250 MHz, CDCl$_3$) δ ppm: 8.03 (d, J = 9.0 Hz, 2H), 7.70 (dd, J = 3.7, 1.2 Hz, 1H), 7.54 (dd, J = 5.3, 1.2 Hz, 1H), 7.19 (d, J = 9.0 Hz, 2H), 7.01 (dd, J = 5.3, 3.7 Hz, 1H), 1.54 (s, 9H); ^{13}C NMR (125 MHz, (CD$_3$)$_2$SO) δ ppm: 152.4, 150.5, 138.8, 136.1, 135.8, 129.1, 124.4, 118.1, 106.6, 84.0, 27.1; HRMS (ESI) [M-Br]$^+$ found 402.9850 calc. 402.9859 [C$_{15}$H$_{16}$ISO$_3$]$^+$.

O-Boc 4-iodophenol (119)
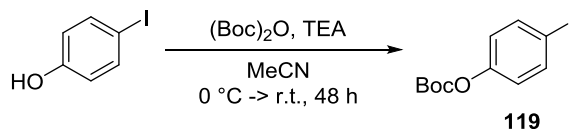
To a solution of 4-iodophenol (10.0 g, 45.5 mmol) in acetonitrile (17 mL), cooled to 0 °C, was added triethylamine (6.98 mL, 5.06 g, 49.9 mmol) followed by di-*tert*-butyldicarbonate (10.5 mL, 9.93 g, 45.5 mmol) in acetonitrile (17 mL). The reaction was stirred at 0 °C for 2 h followed by 48 h at room temperature. The solution was diluted with ethyl acetate and washed with water and brine before being dried over MgSO$_4$. Removal of the solvents gave the crude *O*-Boc 4-iodophenol which was purified by column chromatography (hexane:ethyl acetate, 10:1) to give the pure product as a colourless solid (13.5 g, 93%, m.p. 39-42 °C (lit. 116-118 °C).[26]

^{1}H NMR (250 MHz, CDCl$_3$) δ ppm: 7.69 (d, J = 8.9 Hz, 2H), 6.94 (d, J = 8.9 Hz, 2H), 1.55 (s, 9H); ^{13}C NMR (100 MHz, CDCl$_3$) δ ppm: 151.5, 151.0, 138.5, 123.4, 89.8, 84.1, 27.7. In accordance with literature data.[26]

O-Boc 4-(Diacetoxy)iodophenol (120)
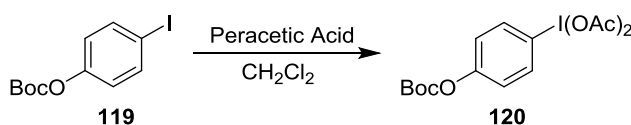
O-Boc 4-iodophenol (217 mg, 0.625 mmol) in CH$_2$Cl$_2$ (3 mL) at 0 °C, was treated with peracetic acid (1 mL, 39%). The reaction was stirred at 0 °C for 8 h. The reaction was then partitioned between CH$_2$Cl$_2$ (40 mL) and water (2 × 40 mL). The CH$_2$Cl$_2$ layer was separated, dried over MgSO$_4$ and concentrated under vacuum to give a pale yellow oil. The crude was triturated with hexane to give a white solid (162 mg, 59%, m.p. 138-141 °C).

^{1}H NMR (250 MHz, CDCl$_3$) δ ppm: 8.08 (d, J = 9.0 Hz, 2H), 7.31 (d, J = 9.0 Hz, 2H), 2.01 (s, 6H), 1.57 (s, 9H); ^{13}C NMR (125 MHz, CDCl$_3$) δ ppm: 176.6, 153.6, 151.1, 136.7, 124.1, 117.4, 84.8, 27.8, 20.5 (2C); HRMS (APCI) [M-OAc]$^+$ found 379.0035 calc. 379.0037 [C$_{13}$H$_{16}$IO$_5$]$^+$.

O-Boc 4-fluorophenol (121)

To a solution of 4-fluorophenol (2.0 g, 17.8 mmol) in acetonitrile (3 mL), cooled to 0 °C, was added triethylamine (2.73 mL, 1.98 g, 19.58 mmol) followed by di-*tert*-butyldicarbonate (4.91 mL, 4.66 g, 21.36 mmol) in acetonitrile (3 mL). The reaction was stirred at 0 °C for 2 h followed by 48 h at room temperature. The solution was diluted with ethyl acetate and washed with water and brine before being dried over MgSO$_4$. Removal of the solvents gave the crude *O*-Boc 4-iodophenol which was purified by column chromatography (hexane:ethyl acetate, 10:1) to give the pure product as a colourless solid (3.75 g, 99%, m.p. 43-45 °C (lit. 38-39 °C)).

^{1}H NMR (250 MHz, CDCl$_3$) δ ppm: 7.20 – 6.92 (m, 4H), 1.56 (s, 9H); ^{13}C NMR (63 MHz, CDCl$_3$) δ ppm: 160.3 (d, J = 244.1 Hz), 152.0, 147.1 (d, J = 2.9 Hz), 122.8 (d, J = 8.5 Hz, 2C), 116.1 (d, J = 23.5 Hz, 2C), 83.9, 27.8; ^{19}F NMR (300 MHz, CDCl$_3$) δ ppm: -117.0. In accordance with previous literature data.[1]

[^{18}F]*O*-Boc 4-fluorophenol ([^{18}F]121)
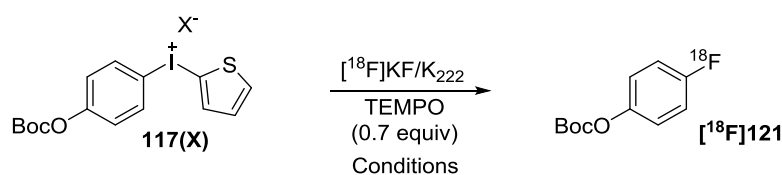
Radiofluorination was achieved using GP7. The reaction was analysed using radio HPLC and radio TLC.

Radio HPLC of the crude reaction mixture
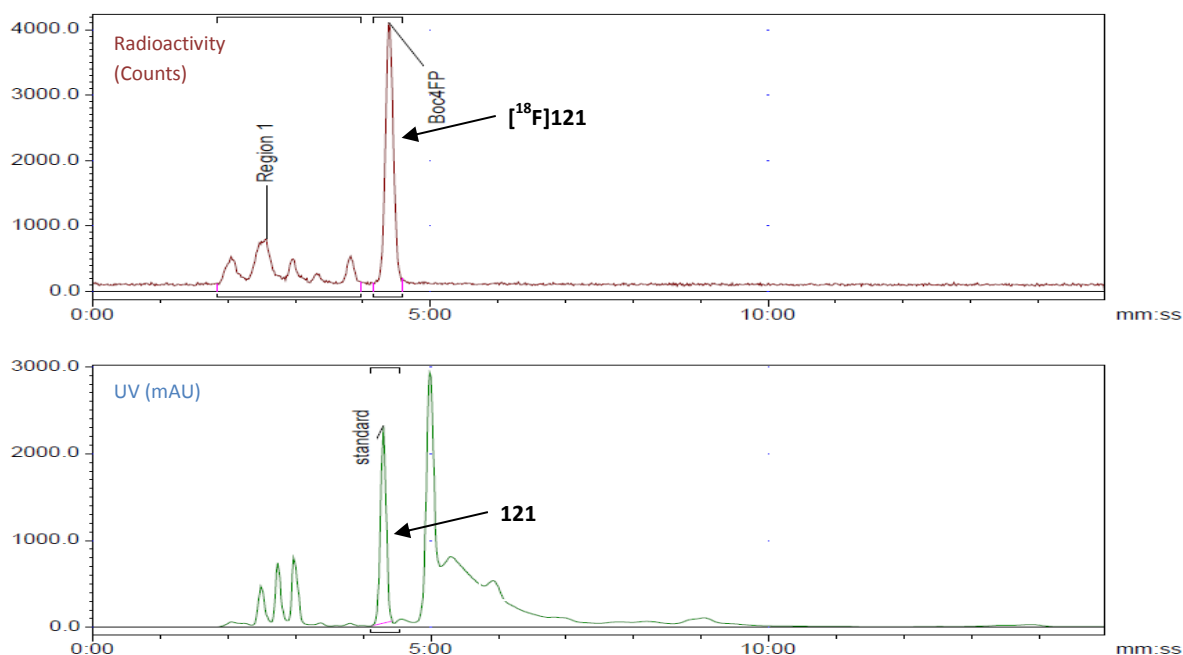
Analytical HPLC Conditions

Column: Analytical Phenomenex Synergi 4 µm Hydro-RP 80 C-18 4.6×250 mm column

Gradient: 80% MeCN in H_2O (0.01% TFA)

Flow Rate: 1 mL/min

4-iodophenyl 2,2,2-trifluoroacetate (122)
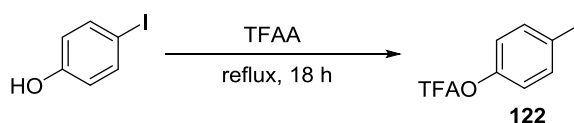
Under inert conditions trifluoroacetic anhydride (11.3 mL, 16.8 g, 80 mmol) was added to a flask containing 4-iodophenol (2.2 g, 10 mmol) equipped with a stirrer bar and a condenser. The reaction was refluxed for 1 h before being stirred at room temperature for 18 h. The volatiles were removed under a flow of nitrogen to yield the product as a pale orange oil (2.65 g, 84%).

^{1}H NMR (250 MHz, CDCl$_3$) δ ppm: 7.77 (d, $J = 8.9$ Hz, 2H), 7.00 (d, $J = 8.9$ Hz, 2H); ^{13}C NMR (100 MHz, CDCl$_3$) δ ppm: 149.3, 139.2, 122.7, 114.6 (q, $J = 285.7$ Hz,1C), 91.8; ^{19}F NMR (300 MHz, CDCl$_3$) δ ppm: -74.6.

(4-hydroxyphenyl)(thiophen-2-yl)iodonium Tosylate (125)
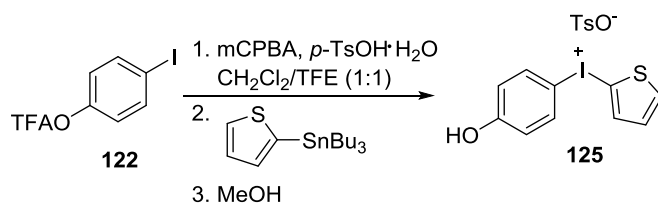
To a stirred solution of **122** (0.5 g, 1.58 mmol) in CH_2Cl_2/TFE (1:1) (16 mL) was added *m*CPBA (77 wt.%, 354 mg, 1.58 mmol) followed by *p*-TsOH·H_2O (301 mg, 1.58 mmol). The resulting solution was stirred for 30 min before being concentrated under nitrogen. Signs of decomposition were observed. Therefore, CH_2Cl_2/TFE (1:1) (16 mL) was added to give a stable suspension. Addition of 2-(tributylstannyl)thiophene resulted in a dark orange solution. The solution was stirred for 1.5 h before being concentrated under a flow of nitrogen to give an orange gum. Resolubilisation in a minimum amount of methanol resulted in a green solution. Trituration with Et_2O gave the 4-hydroxy phenyl product as a brown green powder (194 mg, 26%, m.p. 159-165 °C).

^{1}H NMR (250 MHz, MeOD) δ ppm: 8.05 – 7.91 (m, 3H), 7.86 (dd, *J* = 5.4, 1.2 Hz, 1H), 7.70 (d, *J* = 8.2 Hz, 2H), 7.23 (d, *J* = 7.9 Hz, 2H), 7.15 (dd, *J* = 5.4, 3.8 Hz, 1H), 6.95 – 6.80 (d, *J* = 9.1 Hz, 2H), 5.50 (s, 1H), 2.37 (s, 3H); HRMS (ESI) [M-TsO]$^+$ found 302.9338 calc. 302.9346 [$C_{10}H_8ISO$]$^+$.

Production of dimethyldioxirane (DMDO)
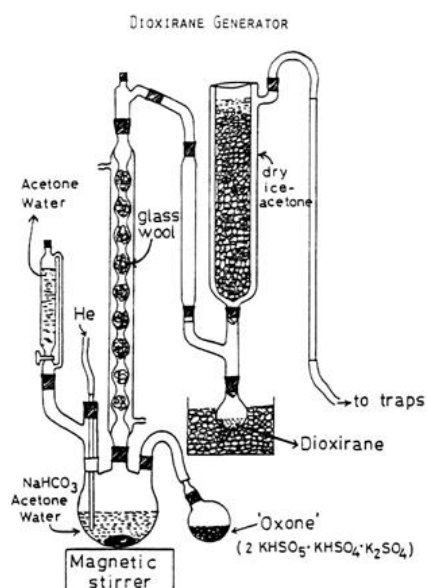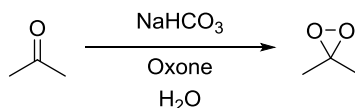
DMDO was produced according to a literature procedure.[27] A round bottom flask containing a mixture of water (40 mL), acetone (25 mL, 0.34 mol), and sodium bicarbonate (48 g, 0.57 mol), was equipped with a magnetic stir bar and a pressure equalizing addition funnel containing water (30 mL) and acetone (30 mL, 0.41 mol). A round bottom flask containing Oxone (90 g, 0.15 mol) was attached to the reaction vessel via a rubber tube and glass adaptors. A condenser was attached to the reaction vessel. The outlet of the condenser was connected to a dry ice cooled condenser, connected to a round bottom flask cooled in a dry ice-acetone bath. A stream of nitrogen gas was bubbled through the reaction mixture as the Oxone® was added in portions. The acetone-water mixture was simultaneously added dropwise. The reaction mixture was stirred vigorously throughout the addition of reagents (30 min). A pale yellow solution of dimethyldioxirane in acetone collected in the receiving flask. Vigorous stirring was continued for an additional 15 min while a slight vacuum was applied to the cold trap. The dioxirane solution was dried over Na_2SO_4 before being filtered and stored in a freezer (-25 °C) over Na_2SO_4 ($\approx$50 mL, 60 mM).

The concentration of dimethyldioxirane in acetone was assessed by oxidation of thioanisole to the corresponding sulfoxide and determined by ^{1}H NMR integration of the different phenyl protons according to the literature.[28] A solution of DMDO (0.50 mL) was reacted with thioanisole (0.10 mL, 0.7 M in acetone-d$_6$) at 10 °C for 10 min. The reaction mixture was directly transferred to an NMR tube for ^{1}H NMR. The concentration of DMDO in acetone was established by integration of the thioanisole protons and the sulphoxide phenyl protons.

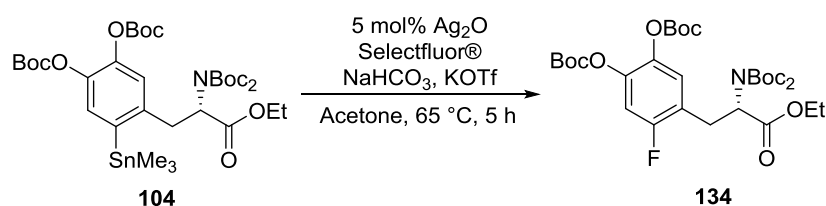### *N*-Phthalimide-3,4-di(*tert*-butoxycarbonyloxy)-6-iodyl-L-phenylalanine methyl ester (131)
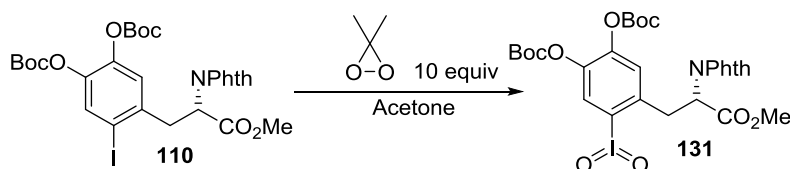
131 was synthesised adapting a literature procedure.[29] IodoDOPA compound **110** (67 mg, 0.1 mmol) was dissolved in anhydrous acetone (3 mL) and cooled to 0 °C in an ice bath. DMDO (17 mL, 60 mM, 1.0 mmol) was added dropwise and the reaction was

stirred for 1 h. The solvent was then removed under reduced pressure. The residue was dissolved in chloroform and washed with water. The organic layer was dried over $MgSO_4$ and filtered before removal of the solvent under reduced pressure to give the product as a white solid (69 mg, 99%, m.p. 112-113 °C).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 8.07 (s, 1H), 7.93 – 7.67 (m, 4H), 7.27 (s, 1H), 5.03 (dd, J = 9.8, 4.3 Hz, 1H), 4.10 (dd, J = 14.8, 9.9 Hz, 1H), 3.71 (s, 1H), 3.34 (dd, J = 14.8, 4.3 Hz, 1H), 1.52 (s, 2H), 1.48 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 170.3, 167.1, 149.9, 149.6, 145.9, 142.5, 137.8, 134.3, 131.7, 125.5, 124.0, 121.5, 184.3, 53.6, 52.5, 39.0, 27.6, 27.5; HRMS (ESI) [M+NH$_4$]$^+$ found 717.1155 calc. 717.1151 $[C_{28}H_{30}INO_{12}NH_4]^+$.

N-di-(*tert*-Butoxycarbonyl)-3,4-di(*tert*-butoxycarbonyloxy)-6-fluoro-L-phenylalanine ethyl ester (134)

N-di-(*tert*-Butoxycarbonyl)-3,4-di(*tert*-butoxycarbonyloxy)-6-fluoro-L-phenylalanine ethyl ester **134** was synthesised adapting a literature procedure.[20] To tetraboc-6-(trimethylstannyl)-L-DOPA ethyl ester **104** (305 mg, 0.39 mmol) in acetone (7 mL) at room temperature was added Ag_2O (4.4 mg, 0.019 mmol), $NaHCO_3$ (65 mg, 0.77 mmol), KOTf (73 mg, 0.39 mmol) and selectfluor$^®$ (205 mg, 0.58 mmol). The reaction mixture was stirred for 5 h at 65 °C in a sealed vial. After cooling to room temperature the reaction mixture was filtered through a pad of celite, eluted with CH_2Cl_2 and the filtrate was concentrated *in vacuo*. The residue was purified by chromatography (hexane:EtOAc, 6:1), to give the product as a colourless solid (149 mg, 60%).

IR ν$_{max}$ (cm^{-1}; neat) 2982, 2936, 2361, 2342, 1767, 1740, 1697, 1368, 1250, 1142, 1109, 841; ^{1}H NMR (250 MHz, $CDCl_3$) δ ppm: 7.08 (d, J^4_{F-H} = 7.2 Hz, 1H), 6.99 (d, J^3_{F-H} = 9.6 Hz, 1H), 5.18 (dd, J = 10.3, 5.1 Hz, 1H), 4.20 (q, J = 7.2 Hz, 2H), 3.51-3.19 (ABX system, bm, 2H), 1.53 (s, 18H), 1.41 (s, 18H), 1.27 (t, J = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm: 169.9, 158.1 (d, J_{F-C} = 246.1 Hz, 1C), 151.6, 150.5, 150.1, 141.7 (d, J_{F-C} = 11.5 Hz, 1C), 138.4 (d, J_{F-C} = 3.4 Hz, 1C), 125.3 (d, J_{F-C} = 6.0 Hz, 1C), 122.8 (d, J_{F-C} = 17.6 Hz, 1C), 110.4 (d, J_{F-C} = 27.1 Hz, 1C), 84.0, 83.7, 83.1, 61.4, 57.8, 29.3,

27.8 (, 27.5, 27.5, 14.1; ^{19}F NMR (300 MHz, CDCl$_3$) δ ppm: −117.6; HRMS (ESI) [M+NH$_4$]$^+$ found 661.3343 calc. 661.3342 [C$_{31}$H$_{46}$FNO$_{12}$+NH$_4$]$^+$.

[^{18}F]N-di-(*tert*-Butoxycarbonyl)-3,4-di(*tert*-butoxycarbonyloxy)-6-fluoro-L-phenylalanine ethyl ester ([^{18}F]134)

Radiofluorination was achieved using GP7 at 90 °C using 0.03 mmol precursor **106(Br)**. The reaction was analysed using radio HPLC and radio TLC.
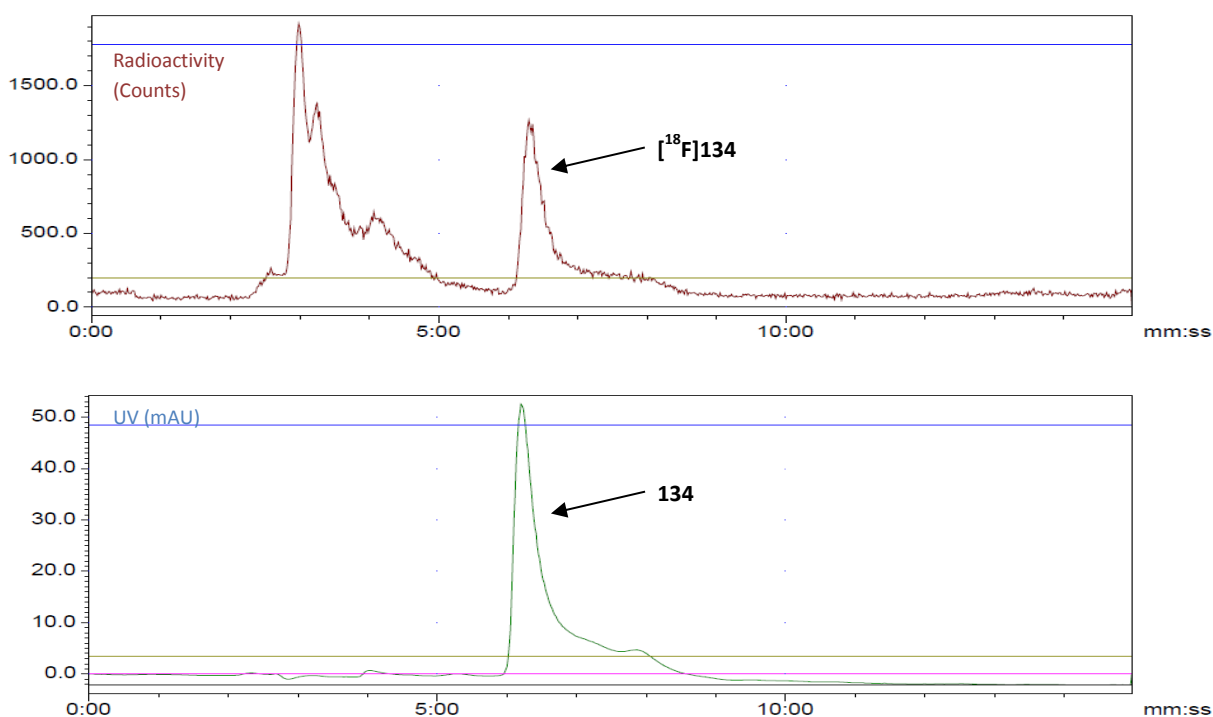
Analytical HPLC Conditions

Column: Analytical Phenomenex Synergi 4 μm Hydro-RP 80 C-18 4.6 × 250 mm column

Gradient: 90% MeCN in H$_2$O (0.01% TFA)

Flow Rate: 1 mL/min

N-Phthalimide-3,4-di(*tert*-butoxycarbonyloxy)-6-fluoro-L-phenylalanine methyl ester (136)
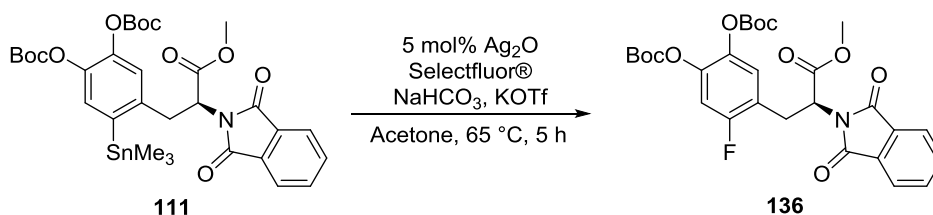
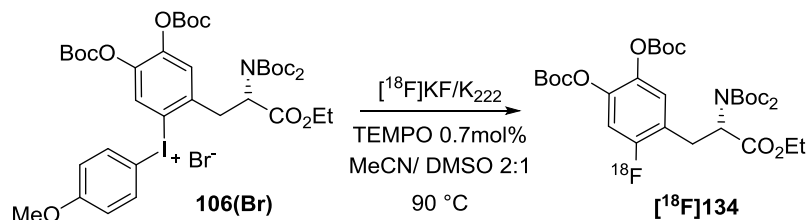*N*-Phthalimide-3,4-di(*tert*-butoxycarbonyloxy)-6-fluoro-L-phenylalanine methyl ester **136** was synthesised adapting a literature procedure.[20] To *N*-phthalimide diboc-6-(trimethylstannyl)-L-DOPA methyl ester **111** (258 mg, 0.37 mmol) in acetone (7 mL) at room temperature was added Ag$_2$O (4.2 mg, 0.018 mmol), NaHCO$_3$ (62 mg, 0.73 mmol), KOTf (69 mg, 0.37 mmol) and selectfluor® (195 mg, 0.55 mmol).The reaction mixture was stirred for 5 h at 65 °C in a sealed vial. After cooling to room temperature the reaction mixture was filtered through a pad of celite, eluted with CH$_2$Cl$_2$ and the filtrate was concentrated *in vacuo*. The residue purified by chromatography (hexane:EtOAc, 4:1), to give the product **136** as a colourless oil (69 mg, 34%).

IR ν_{max} (cm^{-1}; neat) 2982, 2934, 2361, 2342, 1765, 1751, 1715, 1508, 1387, 1372, 1273, 1248, 1140, 1109, 719; ^{1}H NMR (250 MHz, CDCl$_3$) δ ppm: 7.81-7.68 (bm, 4H), 7.00 (d, J^4_{F-H} = 7.0 Hz, 1H), 6.97 (d, J^3_{F-H} = 9.7 Hz, 1H), 5.18 (dd, J = 11.1, 5.0 Hz, 1H), 3.77 (s, 3H), 3.76-3.34 (ABX system, bm, 2H), 1.49 (s, 9H), 1.45 (s, 9H); ^{13}C NMR (126 MHz, CDCl$_3$) δ ppm: 168.9, 167.4, 158.1 (d, J_{F-C} = 246.5 Hz, 1C), 150.4, 150.0, 142.1 (d, J_{F-C} = 11.6 Hz, 1C), 138.5 (d, J_{F-C} = 3.4 Hz, 1C), 134.1, 131.7, 125.0 (d, J_{F-C} = 5.9 Hz, 1C), 123.6, 121.8 (d, J_{F-C} = 17.4 Hz, 1C), 110.7 (d, J_{F-C} = 26.9 Hz, 1C), 84.1, 83.8, 53.0, 51.5, 28.6, 27.6, 27.5; ^{19}F NMR (300 MHz, CDCl$_3$) δ ppm: −117.7; HRMS (ESI) [M+NH$_4$]$^+$ found 577.2187 calc. 577.2192 [C$_{28}$H$_{30}$FNO$_{10}$+NH$_4$]$^+$.

[*N*-(*tert*-Butoxycarbonyl)-3,4-(dimethoxy)-L-phenylalanine ethyl ester]-6-(4-anisyl)iodonium tosylate 137(TsO)

137(TsO)
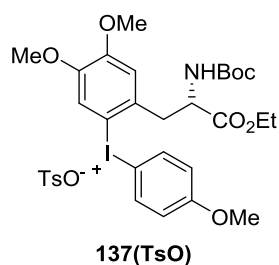
Using GP1 (on a 0.41 mmol scale) the product was obtained as a colourless solid (244 mg, 79%, m.p. 102-103 °C).

^{1}H NMR (400 MHz; CDCl$_3$) δ ppm: 7.81 (d, J = 9.0 Hz, 2H), 7.50 (d, J = 8.2 Hz, 2H), 7.39 (s, 1H), 7.03 (d, J = 7.9 Hz, 2H), 6.87 (s, 1H), 6.85 (d, J = 9.2 Hz, 2H), 5.95 (s, 1H), 4.60 (s, 1H), 4.26-4.14 (m, 2H), 3.87 (s, 3H), 3.79 (s, 3H), 3.78 (s, 3H), 3.36 (d, J = 7.2 Hz, 2H), 2.31 (s, 3H), 1.35 (s, 9H), 1.26 (t, J = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, CDCl$_3$) δ ppm: 171.6, 161.9, 152.0, 149.1, 142.6, 139.1, 136.4, 133.5, 128.2, 125.8, 119.8 , 117.1, 112.6 , 109.3, 104.1, 79.4, 61.5, 56.4, 55.9, 55.4, 53.5, 39.1, 28.2, 21.1, 14.0; HRMS (ESI) [M-TsO]$^+$ found 586.1302 calc. 586.1296 [C$_{25}$H$_{33}$INO$_7$]$^+$.

[*N*-(*tert*-Butoxycarbonyl)-3,4-(dimethoxy)-L-phenylalanine ethyl ester]-6-(4-anisyl)iodonium bromide 137(Br)

137(Br)
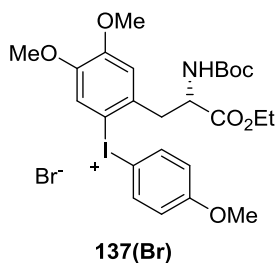
Iodonium tosylate **137(TsO)** (140 mg, 0.184 mmol) was dissolved in CH$_2$Cl$_2$ (50 mL) and washed with aqueous KBr (0.2 M, 3 × 50 mL) and the organic layer was passed through a phase separator. The solvent was removed before the product was triturated with hexane from a minimum amount of CH$_2$Cl$_2$ and diethyl ether (1:1). Removal of the solvent under reduced pressure gave the product as a colourless solid (120 mg, 98%, m.p. 111-112 °C).

^{1}H NMR (400 MHz; CDCl$_3$) δ ppm: 7.88 (d, J = 7.3 Hz, 2H), 7.60 (s, 1H), 6.78 (s, 1H), 6.66 (d, J = 7.8 Hz, 2H), 5.45 (s, 1H), 4.68 (s, 1H), 4.28-4.08 (m, 2H), 3.77 (s, 3H), 3.69 (s, 3H), 3.55 (s, 3H), 3.47-3.30 (m, 2H), 1.29 (s, 9H), 1.22 (t, J = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, CDCl$_3$) δ ppm: 171.8, 161.3, 155.7, 151.2, 148.9, 138.2, 136.4, 131.7, 119.4, 166.4, 115.6, 111.4, 79.6, 61.4, 57.2, 55.9, 55.2, 53.2, 39.0, 28.3, 14.2; HRMS (ESI) [M-Br]$^+$ found 586.1302 calc. 586.1296 [C$_{25}$H$_{33}$INO$_7$]$^+$.

N-(*tert*-Butoxycarbonyl)-3,4-(dimethoxy)-L-phenylalanine ethyl ester (139)
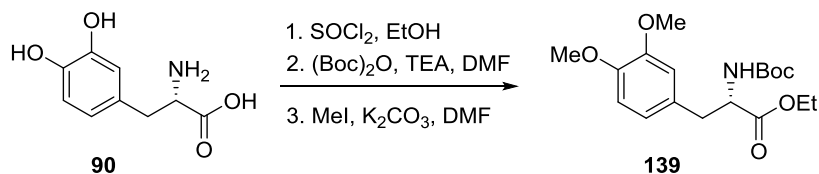
N-(*tert*-Butoxycarbonyl)-3,4-(dimethoxy)-L-phenylalanine ethyl ester was synthesised according to the literature.[21] To a suspension of 3,4-dihydroxy-L-phenylalanine (4.9 g, 25.0 mmol) in dry ethanol (125 mL), under argon, cooled to 0 °C, was added $SOCl_2$ (5.1 g, 3.1 mL, 42.0 mmol) dropwise over 30 min. The reaction was heated at reflux for 20 h before being cooled to room temperature and concentrated under reduced pressure. Toluene was added and the mixture was concentrated under reduced pressure to give the crude 3,4-dihydroxy-L-phenylalanine ethyl ester (hydrochloride salt) as an off white gum (6.05 g).

Without further purification the crude 3,4-dihydroxy-L-phenylalanine ethyl ester (hydrochloride salt) (3.30 g, 12.6 mmol) was dissolved in ethanol (55 mL) and treated with triethylamine (1.31 g, 12.9 mmol, 1.8 mL) followed by di-*tert*-butyldicarbonate (2.90 g, 13.3 mmol). The reaction was stirred at room temperature for 2 h before the solvent was removed under reduced pressure. The mixture was acidified with 1M HCl at 0 °C and extracted with ethyl acetate (3 × 20 mL). The extracts were dried over $MgSO_4$ and concentrated under reduced pressure to give the crude N-(*tert*-butoxycarbonyl)-3,4-(dihydroxy)-L-phenylalanine ethyl ester, which was purified by column chromatography (15 – 50% ethyl acetate/hexane) to give the pure product as a colourless oil (3.17 g, 77%).

^{1}H NMR (250 MHz, CDCl$_3$) δ ppm: 6.76 - 6.51 (m, 3H), 6.08 (bs, 2H), 5.06 (d, *J* = 8.3 Hz, 1H), 4.48 (dd, *J* = 14.5, 6.4 Hz, 1H), 4.17 (q, *J* = 7.1 Hz, 2H), 3.07-2.83 (ABX system, bm, 2H), 1.42 (s, 9H), 1.24 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (63 MHz, CDCl$_3$) δ ppm: 172.4, 155.6, 144.0, 143.1, 128.1, 121.4, 116.1, 115.2, 80.5, 61.6, 54.7, 37.8, 28.3, 14.1.

N-(*tert*-butoxycarbonyl)-3,4-(dihydroxy)-L-phenylalanine ethyl ester (3.13 g, 9.62 mmol) was dissolved in anhydrous DMF (20 mL) followed by addition of K_2CO_3 (11.97 g, 86.6 mmol). MeI (6.15 g, 2.7 mL, 43.3 mmol) was added and the reaction was stirred at room temperature in the dark for 24 h. The reaction was diluted with water and

the pH was adjusted to 1-2 using 1 M HCl before extraction with diethyl ether. The combined extracts were washed with brine and dried over MgSO₄. Removal of the solvent under reduced pressure gave the crude *N*-(*tert*-butoxycarbonyl)-3,4-(dimethoxy)-ʟ-phenylalanine ethyl ester. The crude was purified by column chromatography (5 – 30% ethyl acetate/hexane) to give the pure *N*-(*tert*-butoxycarbonyl)-3,4-(dimethoxy)-ʟ-phenylalanine ethyl ester as a white solid (3.09 g, 91%, m.p. 75-76 °C (lit. 62-63 °C)).[30]

^{1}H NMR (400 MHz, CDCl₃) δ ppm: 6.79 (d, *J* = 8.1 Hz, 1H), 6.71-6.61 (m, 2H), 4.97 (d, *J* = 7.6 Hz, 1H), 4.53 (dd, *J* = 14.0, 6.0 Hz, 1H), 4.17 (q, *J* = 7.1 Hz, 2H), 3.86 (s, 6H), 3.10-2.96 (ABX system, bm, 2H), 1.42 (s, 9H), 1.25 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, CDCl₃) δ ppm: 171.9, 155.1, 148.9, 148.2, 128.6, 121.5, 112.6, 111.3, 79.9, 61.3, 55.9, 55.8, 54.6, 37.9, 28.3, 14.2. In accordance with literature data.[21]

N-(*tert*-Butoxycarbonyl)-3,4-(dimethoxy)-6-iodo-ʟ-phenylalanine ethyl ester (140)
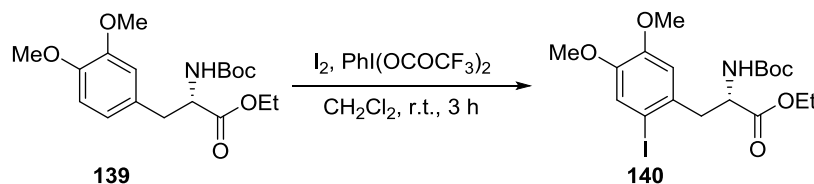
N-(*tert*-Butoxycarbonyl)-3,4-(dimethoxy)-6-iodo-ʟ-phenylalanine ethyl ester was synthesised according to the literature.[21] To a round bottom flask containing I₂ (1.45 g, 5.70 mmol) and PhI(CF₃CO₂)₂ (2.94 g, 6.84 mmol) under argon was added freshly distilled CH₂Cl₂ (30 mL). The mixture was stirred at 0 °C for 15 min before addition of *N*-(*tert*-Butoxycarbonyl)-3,4-(dimethoxy)-ʟ-phenylalanine ethyl ester (2.0 g, 5.70 mmol) in CH₂Cl₂ (10 mL). The reaction was kept at 0 °C for 15 min before being stirred at room temperature for 3 h. Following dilution with CH₂Cl₂ the reaction was washed with 1 M Na₂S₂O₃ (2 x 40 mL), water and brine before being dried over MgSO₄. The solvent was removed under vacuum and the product was purified by column chromatography (15% - 30% EtOAc in hexane) to give the pure product as a colourless solid (1.01 g, 37%, m.p. 108-111 °C).

^{1}H NMR (250 MHz, CDCl₃) δ ppm: 7.21 (s, 1H), 6.72 (s, 1H), 5.06 (d, *J* = 9.1 Hz, 1H), 4.58 (dd, *J* = 14.4, 8.3 Hz, 1H), 4.28-4.11 (m, 2H), 3.84 (s, 6H), 3.25-2.98 (ABX system, bm, 2H), 1.39 (s, 9H), 1.23 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, CDCl₃) δ

ppm: 171.8, 154.9, 149.1, 148.3, 131.7, 121.5, 112.7, 88.9, 79.8, 61.4, 56.0, 55.8, 53.7, 42.6, 28.2, 14.0. In accordance with literature data.[21]

N-(*tert*-Butoxycarbonyl)-3,4-(dimethoxy)-6- trimethylstannyl-L-phenylalanine methyl ester (141)
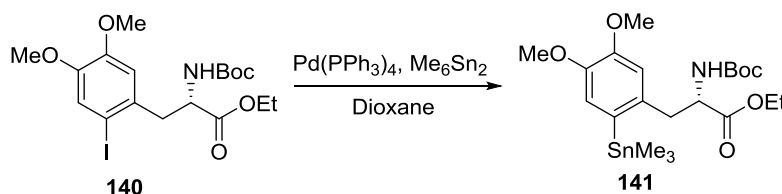

N-(tert-Butoxycarbonyl)-3,4-(dimethoxy)-6-(trimethylstannyl)-L-phenylalanine methyl ester was synthesised adapting a literature procedure.[15] To a solution of *N*-(*tert*-butoxycarbonyl)-3,4-(dimethoxy)-6-iodo-L-phenylalanine ethyl ester (0.79 g, 1.65 mmol) in anhydrous dioxane (25 mL) under argon and protected from light was added tetrakis triphenylphosphine palladium (0.095 mg, 0.082 mmol) and hexamethylditin (1.00 g, 3.05 mmol, 0.63 mL). The mixture was stirred at reflux for 6 h before being cooled to room temperature and filtered. The filtrate was diluted with EtOAc, washed with water and brine, dried over $MgSO_4$ and concentrated to dryness. The residue was purified by flash chromatography (10% - 25% EtOAc in hexane) to give the product as a colourless oil (0.483 g, 57%).

^{1}H NMR (400 MHz, CDCl3) δ ppm: 6.89 (s, with tin satellites J^3_{Sn-H} = 49.4 Hz, 1H), 6.71 (s, with tin satellites J^4_{Sn-H} = 17.4 Hz, 1H), 4.86 (d, *J* = 8.5 Hz, 1H), 4.56 − 4.44 (m, 1H), 4.18 (q, *J* = 7.2 Hz, 2H), 3.87 (s, 3H), 3.85 (s, 3H), 3.16 − 2.83 (ABX system, bm, 2H), 1.38 (s, 9H), 1.24 (t, *J* = 7.2 Hz, 3H), 0.34 (s, with tin satellites J^2_{Sn-H} = 53.2 Hz, 9H); ^{13}C NMR (126 MHz, CDCl3) δ ppm: 172.3, 155.1, 149.4, 147.5 (s, with tin satellites J^2_{Sn-C} = 47.3 Hz, 1C), 135.9, 133.2, 118.9, 112.6 (s, with tin satellites J^2_{Sn-C} = 51.4 Hz, 1C), 79.6, 61.1, 55.9, 55.6, 54.7, 40.6, 28.2, 14.0, -7.9 (s, with tin satellites J^1_{Sn-C} = 349.7 Hz, 1C); HRMS (APCI) [M+H]+ found 518.1557 calc. 518.1563 $[C_{21}H_{35}NO_6SnH]^+$.

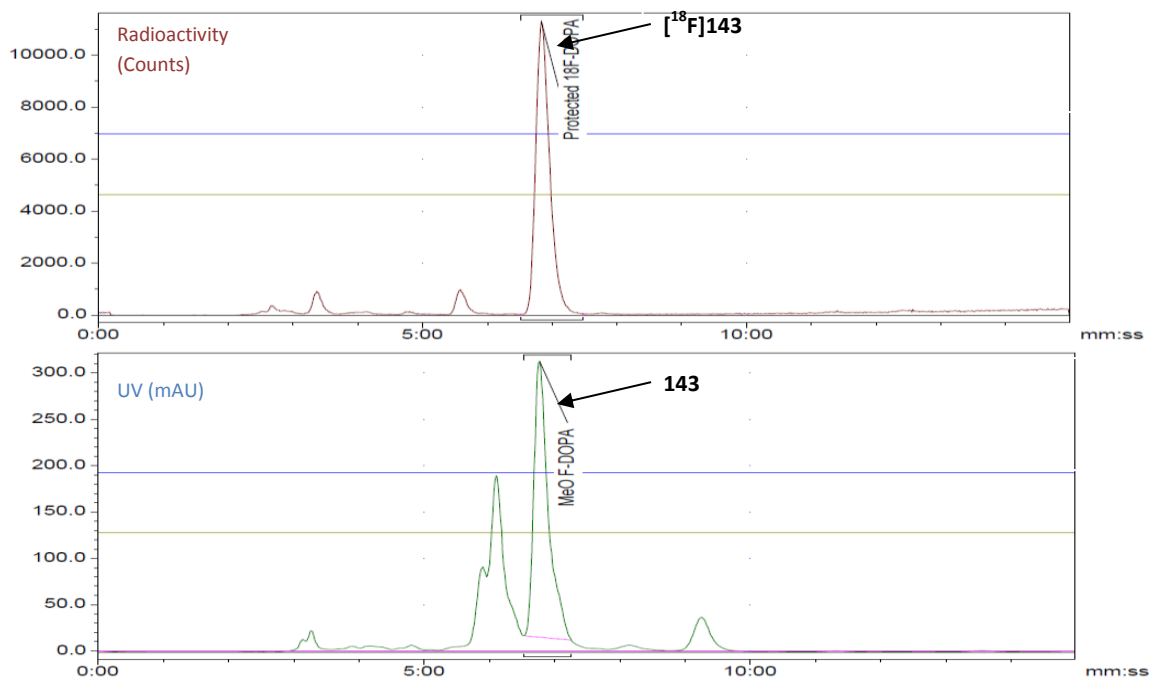### N-(tert-Butoxycarbonyl)-3,4-(dimethoxy)-6-fluoro-ʟ-phenylalanine ethyl ester (143)

N-(tert-Butoxycarbonyl)-3,4-(dimethoxy)-6-fluoro-ʟ-phenylalanine ethyl ester **143** was synthesised adapting a literature procedure.[20] To N-(tert-Butoxycarbonyl)-3,4-(dimethoxy)-6-(trimethylstannyl)-ʟ-phenylalanine ethyl ester **141** (85 mg, 0.17 mmol) in acetone (3.5 mL) at room temperature was added Ag_2O (1.9 mg, 0.008 mmol), $NaHCO_3$ (28 mg, 0.33 mmol), KOTf (31 mg, 0.17 mmol) and selectfluor® (88 mg, 0.25 mmol).The reaction mixture was stirred for 5 h at 65 °C in a sealed vial. After cooling to room temperature the reaction mixture was filtered through a pad of celite, eluted with CH_2Cl_2 and the filtrate was concentrated *in vacuo*. The residue was partially purified by chromatography (hexane:EtOAc, 4:1), to give the impure product as a colourless gum (32 mg, 71% purity, 34%, 72-79 °C (lit. 89-90 °C)).[1]

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 6.68 – 6.51 (m, 2H), 5.07 (d, J = 8.2 Hz, 1H), 4.60 – 4.43 (m, 1H), 4.24 – 4.08 (m, 2H), 3.84 (s, 3H), 3.83 (s, 3H), 3.14 – 2.87 (ABX system, bm, 2H), 1.41 (s, 9H), 1.25 (t, J = 7.2 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm: 171.9, 155.6 (d, J_{F-C} = 238.4 Hz, 1C), 155.2, 149.0 (d, J_{F-C} = 9.9 Hz, 1C), 145.7, 113.8 (d, J_{F-C} = 6.0 Hz, 1C), 113.6 (d, J_{F-C} = 17.5 Hz, 1C), 100.1 (d, J_{F-C} = 28.5 Hz, 1C), 79.9, 61.6, 56.6, 56.2, 53.9, 31.6, 28.4, 14.2; ^{19}F NMR (300 MHz, $CDCl_3$) δ ppm: −124.7. In accordance with literature data.[1]

[18F]N-(tert-Butoxycarbonyl)-3,4-(dimethoxy)-6-fluoro-ʟ-phenylalanine ethyl ester (143)
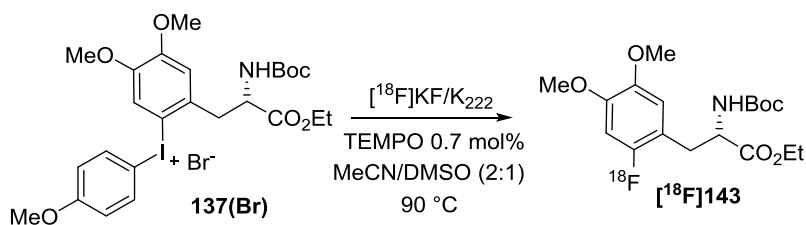
Radiofluorination was achieved using GP7 at 90 °C using 0.03 mmol precursor **137(Br)**. The reaction was analysed using radio HPLC and radio TLC.

Production of protected [¹⁸F]4-fluorobenzaldehyde [¹⁸F]143 was confirmed by comparison with a cold standard.

Analytical HPLC Conditions

Column: Analytical Phenomenex Synergi 4μ Hydro-RP80 C-18 4.6×250 mm column

Gradient: 60% MeCN in aqueous ammonium formate (50mM) (Isocratic)

Flow Rate: 1 mL/min

Synthesis of [¹⁸F]N-(tert-Butoxycarbonyl)-3,4-(dimethoxy)-6-fluoro-ʟ-phenylalanine ethyl ester (143) using Boronic Ester Precursor (32)
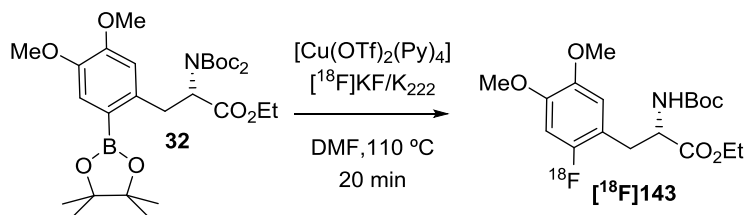
[¹⁸F]143 was produced according to literature procedure.[1]   [¹⁸F]Fluoride delivered from the cyclotron as an aqueous solution was trapped on a pre-treated QMA cartridge to remove the ¹⁸O enriched water. The [¹⁸F]fluoride was eluted with a Kryptofix 2.2.2 carbonate solution (0.6 mL) (0.3 mL MeCN, 0.3 mL H_2O, 22.8 mg Kr-2.2.2, 8.4 mg K_2CO_3) into a 5 mL V-shaped vial. The mixture was dried under a flow of nitrogen and reduced pressure at 120 °C for 440 seconds. The residue was azeotropically dried twice

with the addition of acetonitrile (2 × 1 mL). Distillation was achieved by heating at 120 °C under a flow of nitrogen for 440 seconds. The dried [^{18}F]KF • Kryptofix 222 • K_2CO_3 salt was redissolved in anhydrous acetonitrile (0.5 mL). The reaction vial was then purged with air, followed by addition of **32** (35 mg, 0.06 mmol) and tetrakis(pyridine)copper(II) triflate (15 mg, 0.022 mmol) in DMF (300 μL). The reaction was heated at 110 °C for 20 min and then eluted into a product vial. The radioactivity recovered was measured in a well counter before a sample was taken for radio TLC analysis. Radio TLC showed a radiochemical conversion of 34%.

Radio TLC of reaction mixture (100% MeCN)
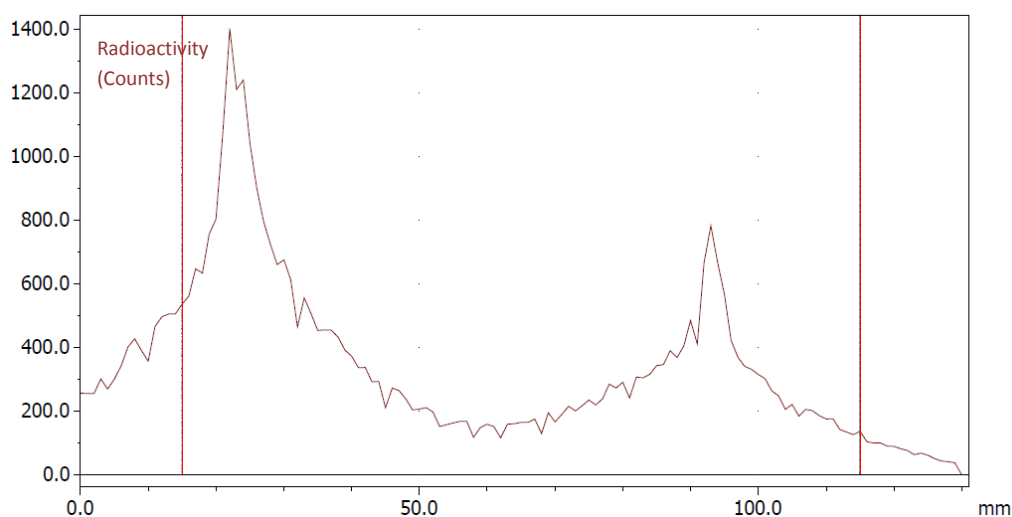
(4-formylphenyl)(phenyl)iodonium bromide (146)
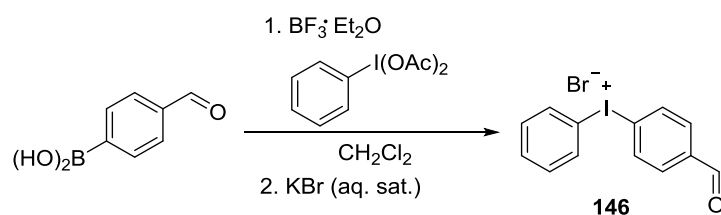
BF$_3$·Et$_2$O (0.8 mL, 0.98 g, 6.3 mmol) was added dropwise to an ice-cold solution of 4-formylphenylboronic acid (480 mg, 3.2 mmol) in anhydrous CH_2Cl_2 (15 mL) under argon and the resulting mixture was stirred for 10 min. Diacetoxy iodobenzene (1.03 g, 3.2 mmol) was added and the cooling bath was removed. The mixture was stirred at room temperature for 1 h. The solvent was removed under reduced pressure before resolution in CH_2Cl_2 (25 mL) and vigorous stirring with aqueous saturated NaBr (25

mL). The product was filtered and washed with water and diethyl ether to give the product as an off white solid (1.16 g, 93%).

^{1}H NMR (400 MHz, (CD$_3$)$_2$SO) δ ppm: 10.07 (s, 1H), 8.48 (d, J = 8.3 Hz, 2H), 8.31 (dd, J = 8.3, 1.0 Hz, 2H), 8.02 (d, J = 8.4 Hz, 2H), 7.70 (t, J = 7.4 Hz, 1H), 7.57 (t, J = 7.9, 2H); ^{13}C NMR (100 MHz, (CD$_3$)$_2$SO) δ ppm: 192.6, 137.5, 135.6, 135.1, 131.7, 131.6, 125.7, 119.7. In accordance with literature data.[31]

N-di-(*tert*-Butoxycarbonyl)-3,4-(dimethoxy)-6-iodo-L-phenylalanine ethyl ester (147)
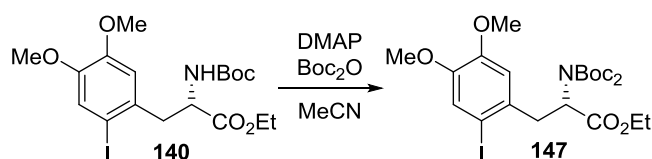
To a solution of **140** (250 mg, 0.52 mmol) in dry acetonitrile (5 mL) under argon was added 4-dimethylaminopyridine (DMAP) (26 mg, 0.21 mmol) in dry acetonitrile (5 mL) and di-*tert*-butyl dicarbonate (228 mg, 1.04 mmol) in dry acetonitrile (5 mL). The reaction was stirred at room temperature overnight before being concentrated under vacuum and purified by column chromatography (10% - 25% EtOAc in hexane) to give the product **147** as a colourless solid (227 mg, 75%).

^{1}H NMR (250 MHz, CDCl$_3$) δ ppm: 7.19 (s, 1H), 6.63 (s, 1H), 5.17 (dd, J = 11.1, 4.2 Hz, 1H), 4.23 (q, J = 7.1 Hz, 2H), 3.82 (s, 6H), 3.75-3.24 (ABX system, bm, 2H), 1.38 (s, 18H), 1.30 (t, J = 7.1 Hz, 3H); ^{13}C NMR (63 MHz, CDCl$_3$) δ ppm: 170.2, 151.9, 149.2, 148.4, 132.9, 121.5, 113.7, 89.0, 83.0, 61.6, 58.0, 56.3, 55.9, 40.2, 28.0 (, 14.3.

6-(4-Iodophenoxy)hexanoic acid (150)
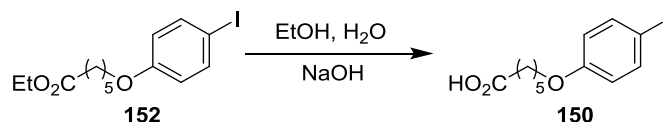
150 was synthesised according to a literature procedure.[32] Ethyl 6-(4-iodophenoxy)hexanoate (2.17 g, 6.0 mmol) in ethanol (20 mL), and water (20 mL) was treated with sodium hydroxide (0.6 g, 15 mmol), and the reaction was stirred under reflux for 3 h. The reaction was then allowed to cool and concentrated to a white solid under vacuum before being treated with ethyl acetate (2 × 35 mL) and 1 M hydrochloric acid (2 × 35 mL). The ethyl acetate layer was separated, dried over sodium sulphate and concentrated under vacuum to give a white solid (1.98 g, 99%, m.p. 95-97 °C).

IR v_{max} (cm^{-1}; KBr) 2943, 1708, 1581, 1488, 1471, 1243, 1174, 826; ^{1}H NMR (500 MHz, CDCl$_3$) δ ppm: 7.45 (d, J = 9.0 Hz, 2H), 6.57 (d, J = 9.0 Hz, 2H), 3.83 (t, J = 6.4 Hz, 2H), 2.31 (t, J = 7.4 Hz, 2H), 1.71-1.43 (m, 6H); ^{13}C NMR (126 MHz, CDCl$_3$) δ ppm: 179.9, 158.9, 138.1, 116.9, 82.5, 67.7, 33.9, 28.8, 25.5, 24.3. In accordance with data provided in patent literature.[32]

Ethyl-6-(4-iodophenoxy)hexanoate (152)
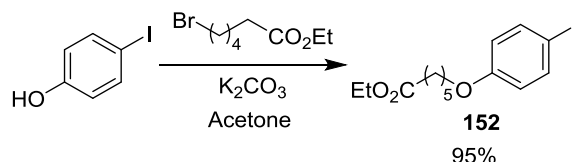
152 was synthesised according to a literature procedure.[32] Ethyl 6-bromohexanoate (1.39 g, 6.25 mmol) in acetone (25 mL) was treated with 4-iodophenol (1.38 g, 6.25 mmol) and potassium carbonate (1.73 g, 12.5 mmol) in a round bottom flask. The reaction mixture was stirred and heated under reflux for 60 h. The reaction was then allowed to cool to room temperature before being concentrated under vacuum to a beige gum and oil. The reaction was then partitioned in ethyl acetate (25 mL) and water (5 × 25 mL). The ethyl acetate layer was separated, and dried over MgSO$_4$ before being concentrated under vacuum to give the crude as a yellow oil. The crude was purified by chromatography (Petroleum Ether:EtOAc, 30:1) to give the product as a colourless oil (2.15 g, 95%).

IR v_{max} (cm^{-1}; KBr) 2939, 2868, 1732, 1586, 1572, 1486, 1470, 1243, 1175, 820; ^{1}H NMR (500 MHz, CDCl$_3$) δ ppm: 7.52 (d, J = 8.9 Hz, 2H), 6.65 (d, J = 8.9 Hz, 2H), 4.13 (q, J = 7.1 Hz, 2H), 3.91 (t, J = 6.4 Hz, 2H), 2.32 (t, J = 7.4 Hz, 2H), 1.81-1.46 (m, 6H) 1.25 (t, J = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, CDCl$_3$) δ ppm: 173.3, 158.8, 138.0, 116.8, 82.4, 67.7, 60.1, 34.1, 28.7, 25.5, 24.6, 14.2. In accordance with data provided in patent literature.[32]
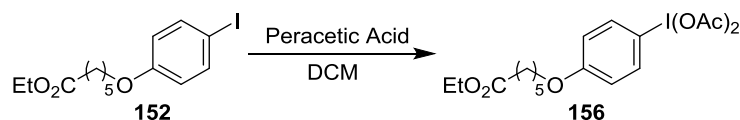
Ethyl-6-(4-diacetoxyiodophenoxy)hexanoate (156)

156 was synthesised according to a literature procedure.[32] Ethyl 6-(4-iodophenoxy)hexanoate 152 (1 g, 2.76 mmol), was treated with peracetic acid (5 mL, 39

wt.%) and CH_2Cl_2 (15 mL) in an ice bath with stirring to give a pink coloured reaction mixture. The reaction was allowed to warm to room temperature over 2 h to give a yellow solution. The reaction was then partitioned between CH_2Cl_2 (40 mL) and water (2 × 40 mL). The CH_2Cl_2 layer was separated, dried over $MgSO_4$ and concentrated under vacuum to give a yellow oil. The crude was triturated with hexane to give a pale yellow oil (82% product 18% starting material) (0.65 g, 40%).

^{1}H NMR (500 MHz, CDCl$_3$) δ ppm: 7.99 (d, J = 9.1 Hz, 2H), 6.93 (d, J = 9.1 Hz, 2H), 4.13 (q, J = 7.1 Hz, 2H), 4.00 (t, J = 6.3 Hz, 2H), 2.34 (t, J = 7.5 Hz, 2H), 1.99 (s, 6H), 1.93-1.42 (m, 6H), 1.26 (t, J = 7.1 Hz, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ ppm: 176.4, 173.6, 159.1, 138.3, 117.2, 117.1, 68.0, 60.4, 34.3, 28.9, 25.7, 24.8, 20.5, 14.4. In accordance with data provided in patent literature.[32]

6-(4-Iodophenoxy)-N-phenylhexanamide (158)
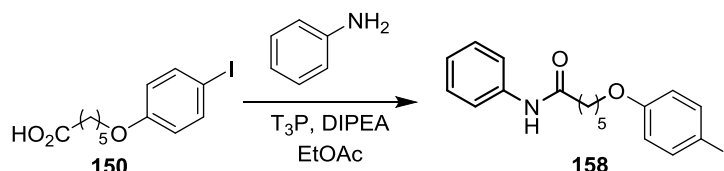
To a solution of 6-(4-iodophenoxy)hexanoic acid **150** (0.4 g, 1.2 mmol) in ethylacetate (7 mL), T$_3$P (50% in EtOAc, 1.44 mmol, 0.85 mL), diisopropylethylamine (0.31 g, 2.4 mmol, 0.45 mL) and aniline (0.11 g, 1.2 mmol, 0.11 mL) were added at 0 °C. After being stirred for 20 min at 0 °C, the reaction was allowed to warm to room temperature and stirred overnight. The reaction was then quenched with water and neutralised with HCl (1 N). The ethyl acetate layer was washed with water and dried over $MgSO_4$. The solvent was evapourated under vacuum to give the product as an off white powder (0.448 g, 91%, m.p. 107 – 108 °C).

IR ν$_{max}$ (cm^{-1}; neat) 3287, 2940, 1655, 1599, 1519, 1484, 1251, 1174, 974, 814, 758, ^{1}H NMR (400 MHz; CDCl$_3$) δ ppm: 7.58 – 7.46 (m, 4H), 7.32 (t, J = 7.9 Hz, 2H), 7.11 (t, J = 7.4 Hz, 1H), 6.66 (d, J = 8.9 Hz, 2H), 3.98 – 3.99 (m, 2H), 2.39 (t, J = 7.4 Hz, 2H), 1.86-1.46 (m, 6H); ^{13}C NMR (126 MHz, CDCl$_3$) δ ppm: 171.0, 158.91, 138.2, 137.8, 129.0, 124.3, 119.8, 117.0, 82.5, 67.8, 37.6, 28.82, 25.6, 25.2.

6-(4-Iodophenoxy)hexanoic acid – tris(2-aminoethyl)amine polystyrene resin amide (159)
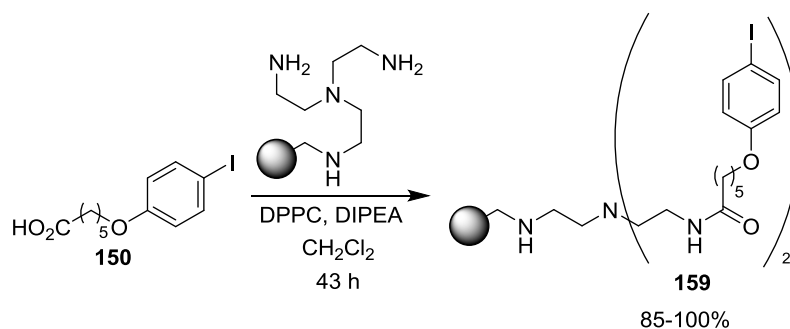
Under argon tris(2-aminoethyl)amine-polymer resin (0.25 g, 0.88 mmol) in freshly distilled CH_2Cl_2 (7 mL) was treated with 6-(4-iodophenoxy)hexanoic acid (0.39 g, 1.17 mmol), diisopropylethylamine (0.34 g, 2.63 mmol) and diphenylphosphorylchloride (0.31 g, 1.17 mmol). The reaction was kept under agitation for 43 h. The reaction was then filtered and washed thoroughly with CH_2Cl_2 (100 mL) and 20% water in methanol (100 mL). The resin was then dried under vacuum to give a beige sand like product (0.47 g, 1.73 mmolg^{-1}, 85%). Found C 68.12%, H 6.34%, N 3.57%, I 13.6%.

6-(4-Diacetoxyiodophenoxy)hexanoic acid – tris(2-aminoethyl)amine polystyrene resin amide (160)
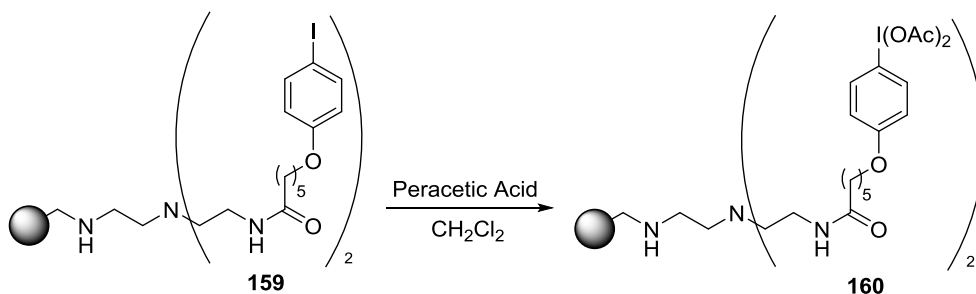
6-(4-iodophenoxy)hexanoic acid - tris(2-aminoethyl)amine-polymer resin amide (0.25 g, 0.52 mmol) in CH_2Cl_2 (7 mL) was treated with peracetic acid (2 mL, 39 wt.%). The reaction was agitated at room temperature for 18 h before the reaction was filtered and washed with CH_2Cl_2. The resin was then dried under vacuum to give a sand like solid (0.284 g, 1.16 mmolg^{-1}, 55%). Found C 66.34%, H 6.62%, N 3.67%, I 9.53%.

6-(4-Phenyliodoniumphenoxy)hexanoic acid – tris(2-aminoethyl)amine polystyrene amide trifluoroacetate salt (161(TFA))
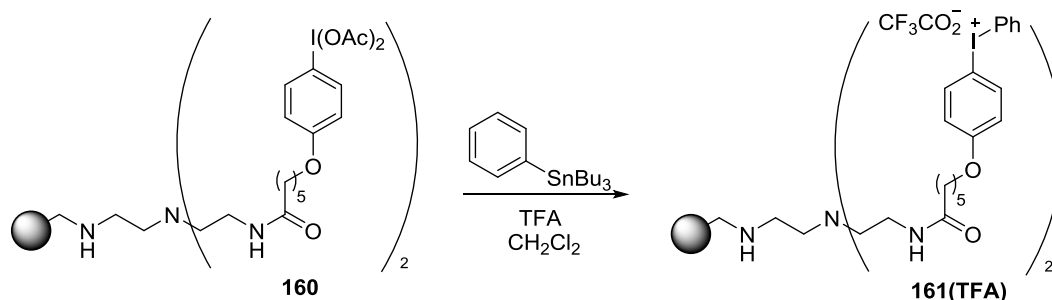
161(TFA) was produced adapting a literature procedure.[32] 6-(4-iodophenoxy)hexanoic acid - aminomethyl polystyrene resin amide (0.15 g, 0.174 mmol) in CH_2Cl_2 (5 mL) was cooled in a acetonitrile and dry ice bath to – 41 °C and treated with tri-n-butylphenyl tin (128 mg, 0.348 mmol). The reaction was agitated and treated with trifluoroacetic acid (79 mg, 0.696 mmol) and allowed to warm to room temperature over 2 h. The resin was then washed with CH_2Cl_2 to give a beige sand like solid (0.244 g, 1.16 mmolg^{-1}, 100%). Found C 62.55%, H 6.16%, N 3.29%, I 9.97%, F 5.99%.
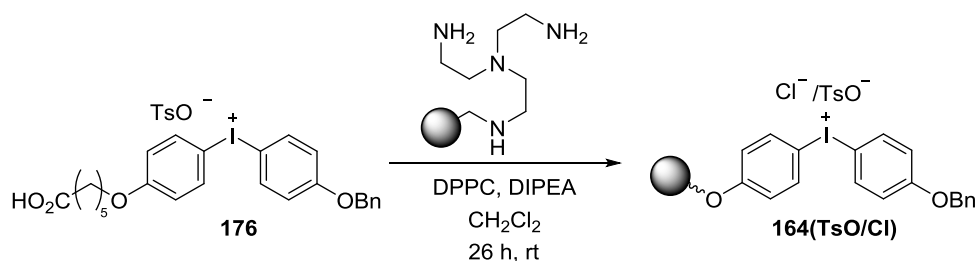
6-(4-(4-Phenoxyphenyl)iodoniumphenoxy)hexanoic acid – tris(2-aminoethyl)amine polystyrene amide tosylate salt (164(TsO/Cl))

Under argon tris(2-aminoethyl)amine-polymer resin (224 mg, 0.75 mmol) in freshly distilled CH_2Cl_2 (7 mL) was treated with **176** (516 mg, 0.75 mmol), diisopropylethylamine (218 mg, 1.69 mmol) and diphenylphosphorylchloride (201 mg, 0.75 mmol). The reaction was kept under agitation for 26 h. The reaction was then filtered and washed thoroughly with CH_2Cl_2 (100 mL) and 20% water in methanol (100 mL). The resin was then dried under vacuum to give a beige sand like product (375 mg, 0.60 mmolg^{-1}, 40%).

6-(4-(4-Phenoxyphenyl)iodoniumphenoxy)hexanoic acid – tris(2-aminoethyl)amine polystyrene amide bromide salt (164(Br))
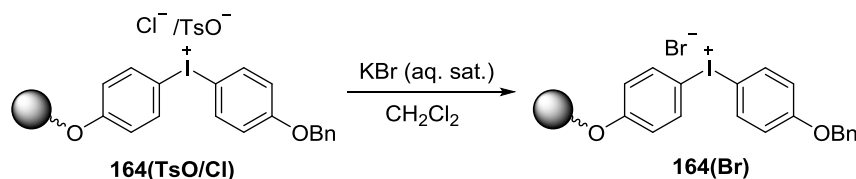
164(TsO/Cl)   **164(Br)**

6-(4-(4-phenoxyphenyl)iodoniumphenoxy)hexanoic acid – tris(2-aminoethyl)amine polystyrene amide tosylate salt **164(TsO/Cl)** (250 mg, 0.6 mmolg$^{-1}$, 0.15 mmol) was agitated in a mixture of CH$_2$Cl$_2$ (3 mL) and aqueous saturated KBr (3 mL) overnight. The reaction was then filtered and washed thoroughly with CH$_2$Cl$_2$ (100 mL) and 20% water in methanol (100 mL). The resin was then dried under vacuum to give a beige sand like product (238 mg, 0.60 mmolg^{-1}, 100%). Found C 68.48%, H 6.24%, N 3.27%, Br 10.83%, I 8.45%, S <0.3% (none detectable).

1-(Benzyloxy)-4-fluorobenzene (165)

165
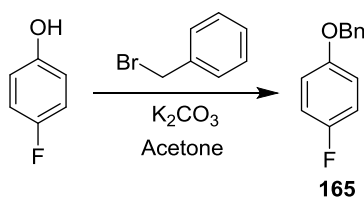
To a solution of 4-fluorophenol (112 mg, 1.0 mmol) in acetone (5 mL) was added K$_2$CO$_3$ (166 mg, 1.2 mmol) and benzylbromide (180 mg, 0.13 mL, 1.05 mmol) at room temperature. The reaction mixture was refluxed for 6 h. After cooling the reaction mixture was filtered and the insoluble material was rinsed with acetone. The filtrate was concentrated under reduced pressure and the residue was purified by chromatography (Hexane, EtOAc, 20:1) to give the product as a white solid (190 mg, 94%, m.p. 55-56 °C (lit. 56 °C)).[33]

^{1}H NMR (400 MHz, CDCl$_3$) δ ppm: 7.45 - 7.37 (m, 4H), 7.36 - 7.31 (m, 1H), 7.02 - 6.94 (m, 2H), 6.94 - 6.88 (m, 2H), 5.03 (s, 2H); ^{13}C NMR (100 MHz, CDCl$_3$) δ ppm: 157.4 (d, J_{F-C} = 238.3 Hz, 1C), 155.0 (d, J_{F-C} = 2.2 Hz, C$_{Ar}$), 136.9, 128.7, 128.2, 127.6, 116.0 (d, J_{F-C} = 7.0 Hz, 2C), 115.9 (d, J_{F-C} = 8.0 Hz, 2C), 70.7; ^{19}F NMR (300 MHz, CDCl$_3$) δ ppm: -123.6 (d, J = 15.0). In accordance with previous literature.[33]

(4-Formylphenyl)(4-methoxyphenyl)iodonium bromide (166(Br))
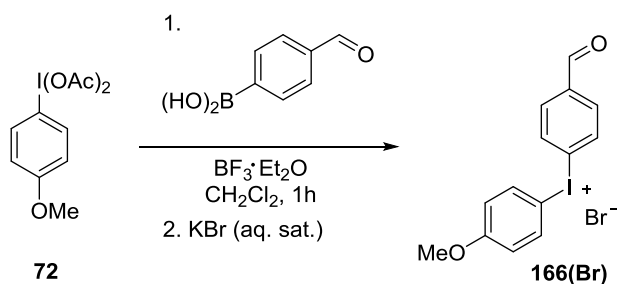
BF$_3$·Et$_2$O (170 mg, 148 µl, 1.2 mmol) was added dropwise to a solution of 4-formylphenylboronic acid (90 mg, 0.6 mmol) in anhydrous CH$_2$Cl$_2$ (3 mL) under argon at 0 °C and the mixture was stirred for 10 min. (Diacetoxy)iodoanisole (211 mg, 0.6 mmol) was added and the cooling bath was removed. The mixture was stirred for 15 min before addition of aqueous KBr (sat.) (3 mL). The aqueous layer was extracted with chloroform (3 × 3 mL) and the solvents were removed *in vacuo* to give a brown residue. Trituration with Et$_2$O followed by recrystallisation from CH$_2$Cl$_2$ /Et$_2$O gave the product as a brown solid (45 mg, 18%).

^{1}H NMR (400 MHz, CDCl$_3$) δ ppm: 9.95 (s, 1H) 8.18 (d, *J* = 8.2 Hz, 2H), 7.94 (d, *J* = 8.8 Hz, 2H), 7.74 (d, *J* = 8.2 Hz, 2H), 6.82 (d, *J* = 8.8 Hz, 2H) 3.78 (s, 3H); HRMS (ESI) [M-Br]$^+$ found 338.9876 calc. 338.9876 [C$_{13}$H$_{11}$IO$_2$]$^+$.

4-(Trimethylstannyl)benzaldehyde (168)
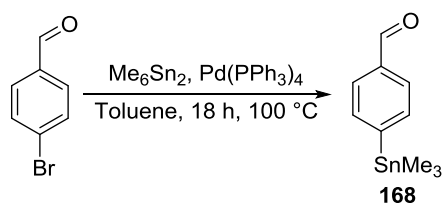
To a solution of 4-bromobenzaldehyde (434 mg, 2.34 mmol) in dry toluene under argon was added Pd(PPh$_3$)$_4$ (135 mg, 0.117 mmol) and hexamethylditin (1 g, 3.05 mmol). The reaction was heated overnight at 100 °C. The reaction mixture was allowed to cool and then passed through a pad of celite before removal of the volatiles under reduced pressure. The crude was purified by chromatography (Hexane:EtOAc, 19:1) to give the product as a colorless oil (519 mg, 83%).

^{1}H NMR (400 MHz, CDCl$_3$) δ ppm: 10.00 (s, 1 H) 7.81 (d, *J* = 7.92 Hz, 2H), 7.68 (d, *J* = 8.2 Hz, 2H), 3.78 (s, with tin satellites J^2_{Sn-H} = 54.7 Hz, 9H). In accordance with previous literature.[34]

(4-(Benzyloxy)phenyl)(4-methoxyphenyl)iodonium tosylate (169(TsO))
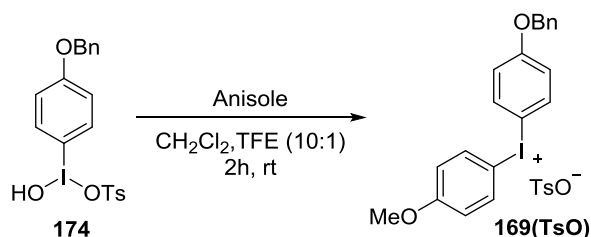
Koser reagent **174** (200 mg, 0.401 mmol) was dissolved in dichloromethane (3 mL) and cooled to 0 °C before addition of anisole (43.8 mg, 0.405 mmol). TFE (0.3 mL) was added to the solution and the reaction was allowed to warm to room temperature over 2 h. The solvents were removed *in vacuo* and the product was triturated with Et$_2$O. Filtration gives the iodonium salt which may be recrystallized from dichloromethane and Et$_2$O if necessary (59 mg, 87%, m.p. 140-141 °C).

^{1}H NMR (400 MHz, CDCl$_3$) δ ppm: 7.85 (d, J = 8.9 Hz, 4H), 7.50 (d, J = 8.1 Hz, 2H), 7.41 - 7.30 (m, 5H), 7.00 (d, J = 7.9 Hz, 2H), 6.86 (d, J = 8.9 Hz, 2H), 6.78 (d, J = 9.0 Hz, 2H); ^{13}C NMR (100 MHz, CDCl$_3$) δ ppm: 162.4, 161.5, 139.4, 137.0 (3C), 135.9, 128.9, 128.6, 128.5, 127.6, 126.2, 118.3, 117.5, 104.8, 104.4, 70.5, 55.7, 21.4; HRMS (ESI) [M-TsO]$^+$ found 417.0350 calc. 417.0346 [C$_{20}$H$_{18}$IO$_2$]$^+$.

(4-(Benzyloxy)phenyl)(4-methoxyphenyl)iodonium bromide (169(Br))
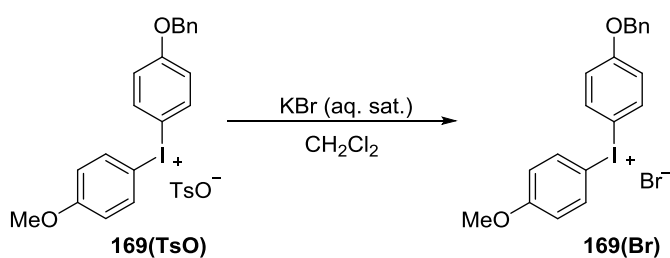
To a solution of iodonium tosylate **169(TsO)** (80 mg, 0.136 mmol) in CH$_2$Cl$_2$ (1.5 mL) was added an aqueous solution of KBr (sat.) (1.5 mL). The mixture was stirred for 1 h at room temperature. The precipitated iodonium bromide was filtered off and washed with CH$_2$Cl$_2$. The aqueous layer was extracted with ethyl acetate and the combined organic extracts were evaporated to yield more iodonium bromide as a white solid. The combined iodonium bromides were isolated as a white solid (59 mg, 87%, m.p. 204-205 °C).

^{1}H NMR (400 MHz, MeOD) δ ppm: 8.08 – 8.01 (m, 4H), 7.44 - 7.28 (m, 5H), 7.11 (d, J = 9.0 Hz, 2H), 7.04 (d, J = 9.0 Hz, 2H), 5.15 (s, 2H), 3.84 (s, 3H); ^{13}C NMR (126 MHz, MeOD) δ ppm: 164.4, 163.4, 138.1, 138.0, 137.5, 129.6, 129.2, 128.7, 19.7, 118.7, 105.7, 105.5, 71.5, 56.4.

(4-(Benzyloxy)phenyl)(4-((6-ethoxy-6-oxohexyl)oxy)phenyl)iodonium tosylate (170(TsO))

Koser reagent **174** (150 mg, 0.30 mmol) was dissolved in dichloromethane (2 mL) and cooled to 0 °C before addition of **175** (716mg, 0.303 mmol). TFE (0.2 mL) was added to the solution and the reaction was allowed to warm to room temperature over 2 h. The solvents were removed in vacuo and the product was triturated with Et$_2$O. Filtration gives the iodonium salt which may be recry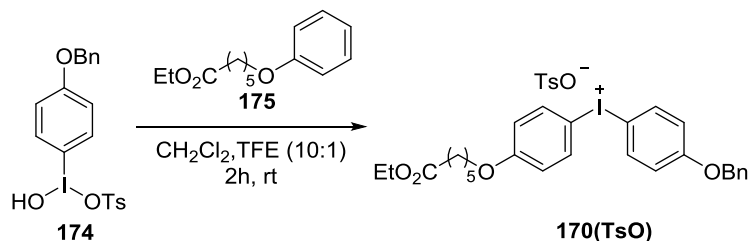stallized from dichloromethane and Et$_2$O if necessary to give the product as an off white solid (193 mg, 90%, m.p. 138-139 °C).

^{1}H NMR (400 MHz, CDCl$_3$) δ ppm: 7.87 - 7.77 (m, 4H), 7.56 (d, J = 8.1 Hz, 2H), 7.42 – 7.29 (m, 5H), 7.04 (d, J = 7.9 Hz, 2H), 6.90 (d, J = 9.1 Hz, 2H), 6.80 (d, J = 9.1 Hz, 2H, 5.04 (s, 2H), 4.12 (q, J = 7.3 Hz, 2H), 3.93 (t, J = 6.3 Hz, 2H), 2.39 - 2.26 (m, 5H), 1.90 - 1.57 (m, 4H), 1.54 - 1.29 (m, 2H), 1.25 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ ppm: 173.7, 161.8, 161.4, 142.9, 139.4, 137.0, 136.8, 135.8, 128.9, 128.6, 128.5, 127.6, 126.1, 118.2, 117.9, 104.7, 104.0, 70.44, 68.2, 60.4, 34.3, 28.8, 25.7, 24.7, 21.5, 14.2; HRMS (ESI) [M-TSO]$^+$ found 545.1183 calc. 545.1183 [C$_{27}$H$_{30}$IO$_4$]$^+$.

(4-(Benzyloxy)phenyl)(4-((6-ethoxy-6-oxohexyl)oxy)phenyl)iodonium bromide (170(Br))
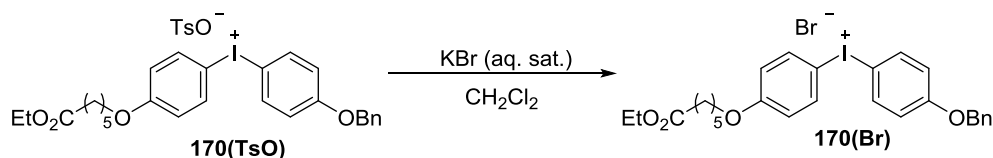
To a solution of iodonium tosylate **170(TsO)** (200 mg, 0.419 mmol) in CH$_2$Cl$_2$ (3.0 mL) was added an aqueous solution of KBr (sat.) (3.0 mL). The mixture was stirred for 1 h at room temperature. The precipitated iodonium bromide was filtered off and washed with CH$_2$Cl$_2$. The aqueous layer was extracted with ethyl acetate and the combined organic extracts were evaporated to yield more iodonium bromide as a white solid. The

combined iodonium bromides were isolated as a white solid (174 mg, 67%, m.p. 130-132 °C).

^{1}H NMR (400 MHz, MeOD): δ ppm: 8.06 - 7.97 (m, 4H), 7.44 - 7.28 (m, 5H), 7.12 (d, J = 9.1 Hz, 2H), 7.03 (d, J = 9.1 Hz, 2H), 5.15 (s, 2H), 4.10 (q, J = 7.1 Hz, 2H), 4.03 (t, J = 6.3 Hz, 2H), 2.34 (t, J = 7.3 Hz, 2H), 1.87 − 1.73 (m, 2H), 1.71 − 1.60 (m, 2H), 1.55 − 1.42 (m, 2H), 1.22 (t, J = 7.1 Hz, 3H).

1-(Benzyloxy)-4-iodobenzene (171)

171
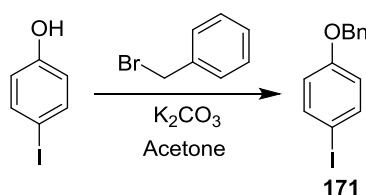
To a solution of 4-iodophenol (7.70 g, 35 mmol) in acetone (80 mL) was added K_2CO_3 (5.81 g, 42 mmol) and benzylbromide (5.99 g, 4.16 mL, 35 mmol) at room temperature. The reaction mixture was refluxed for 6 h. After cooling the reaction mixture was filtered and the insoluble material was rinsed with acetone. The filtrate was concentrated under reduced pressure and the residue was purified by chromatography (Hexane, EtOAc, 95:5) to give the product as a white solid (8.58 g, 79%, m.p. 61 °C (lit. 62-63 °C)).[35]

^{1}H NMR (400 MHz, CDCl₃) δ ppm: 7.56 (d, J = 9.0 Hz, 2H), 7.44 - 7.29 (m, 5H), 6.75 (d, J = 9.0 Hz, 2H), 5.03 (s, 2H); ^{13}C NMR (100 MHz, CDCl₃) δ ppm: 158.7, 138.4, 136.6, 128.8, 128.3, 127.6, 117.4, 83.2, 70.2. In accordance with previous literature.[35]

2-(4-(Benzyloxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (172)

171   **172**
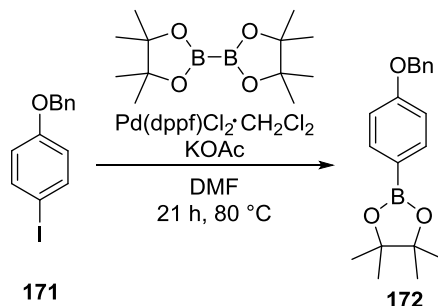
Bis(pinocolato)diboron (838 mg, 3.3 mmol), Pd(dppf)Cl₂· CH₂Cl₂ (123 mg, 0.15 mmol) and KOAc (1.24 g, 9.0 mmol) were added to a round bottom flask under nitrogen atmosphere. Anhydrous DMF (15 mL) was added and the mixture was stirred for 15

min to give a dark red solution. 1-(benzyloxy)-4-iodobenzene (935 mg, 3.0 mmol) was added and the mixture was heated to 80 °C and stirred for 21 h. The reaction was allowed to cool to room temperature before addition of brine (15 mL) was added followed by extraction with Et$_2$O (3×30 mL). The combined organic extracts were dried over Mg$_2$SO$_4$ and concentrated *in vacuo*. The crude product was purified using chromatography to give the product as a white solid (598 mg, 64%).

^{1}H NMR (400 MHz, CDCl$_3$) δ ppm: 7.75 (d, J = 8.7 Hz, 2H), 7.45 - 7.29 (m, 5H), 6.98 (d, J = 8.7 Hz, 2H), 5.09 (s, 2H), 1.33 (s, 12H); ^{13}C NMR (100 MHz, CDCl$_3$) δ ppm: 161.4, 136.9, 136.6, 128.7, 128.1, 127.6, 114.3, 83.7, 69.8, 25.0 ppm. In accordance with previous literature.[36]

1-(Benzyloxy)-4-(diacetoxy)iodobenzene (173)

A solution of *O*-benzyl 4-iodophenol **171** (1.55 g, 5.0 mmol) and selectfluor® (8.86 g, 25.0 mmol) in MeCN/AcOH (3:1) (200 mL) was stirred for 5 h at room temperature. The acetonitrile was evaporated *in vacuo* and water was added to the residue before extraction with dichloromethane. The combined organic layers were washed with water and dried over MgSO$_4$. Removal of the solvent gave the crude product as a yellow solid. Trituration with hexane gave the pure product as a white solid (2.13 g, 95%, m.p. 61-62 °C).

^{1}H NMR (400 MHz, CDCl$_3$) δ ppm: 8.01 (d, J = 8.9 Hz, 2H), 7.45 - 7.32 (m, 5H), 7.04 (d, J = 9.0 Hz, 2H), 5.11 (s, 2H), 2.00 (s, 6H); ^{13}C NMR (100 MHz, CDCl$_3$) δ ppm: 176.5, 161.4, 137.3, 135.8, 128.9, 128.6, 127.6, 117.5, 111.8, 70.5, 20.6. In accordance with previous literature.[37]

Hydroxy(*p*-tosyloxy)iodo-4-benzyloxybenzene (174)
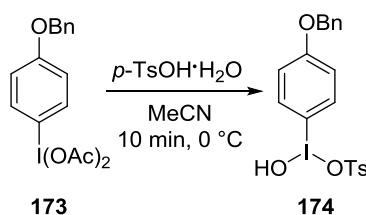
Diacetate **173** (1.9 g, 4.44 mmol) was dissolved in MeCN (50 mL) and cooled to 0 °C before the addition of *p*-TsOH·H_2O (843 mg, 44 mmol). The product began to precipitate immediately. After 10 min Et_2O was added to the slurry and the product was filtered off and washed with Et_2O. The pure product was dried under a flow of nitrogen to give the product as a pale yellow solid (2.09 g, 95%). The compound was stored under nitrogen at -20 °C. If the compound was submitted to high vacuum it decomposed to a brown solid.

^{1}H NMR (400 MHz, MeOD) δ ppm: 8.30 (d, *J* = 8.9 Hz, 2H), 7.69 (d, *J* = 8.1 Hz, 2H), 7.49 - 7.31 (m, 5H), 7.27 (d, *J* = 8.9 Hz, 2H), 7.23 (d, *J* = 8.0 Hz, 2H), 5.25 (s, 2H), 2.37 (s, 4H); ^{13}C NMR (100 MHz, MeOD) δ ppm: 164.7, 143.3, 141.8, 140.3, 137.4, 129.8, 129.7, 129.4, 128.8, 126.9, 119.3, 71.6, 21.3.

Ethyl 6-phenoxyhexanoate (175)
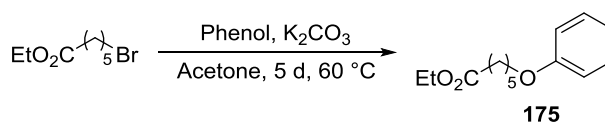
Ethyl 6-bromohexanoate (3.50 g, 2.79 mL, 15 mmol) in acetone (60 mL) was treated with phenol (1.41 g, 15 mmol) and potassium carbonate (4.15 g, 30 mmol) in a round bottom flask. The reaction mixture was stirred and heated under reflux for 60 h. The reaction was then allowed to cool to room temperature before being concentrated under vacuum to a beige gum and oil. The reaction was then partitioned in ethyl acetate (60 mL) and water (5 × 60 mL). The ethyl acetate layer was separated, and dried over $MgSO_4$ before being concentrated under vacuum to give the crude as a yellow oil. The crude was purified by chromatography (Petroleum Ether:EtOAc, 15:1) to give the product as a colourless oil (3.39 g, 96%).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.27 (t, *J* = 7.2 Hz, 2H), 6.98 - 6.84 (m, 3H), 4.13 (q, *J* = 7.1 Hz, 2H) 3.96 (t, *J* = 6.4 Hz, 2H), 2.34 (t, *J* = 7.5 Hz, 2H), 1.94 - 1.77 (m, 2H), 1.76 - 1.59 (m, 2H), 1.57 - 1.43 (m, 2H), 1.26 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 173.7, 159.1, 129.4, 120.6, 114.5, 67.5, 60.3, 34.3, 29.0, 25.8, 24.9, 14.4; HRMS (ESI) [M+H]$^+$ found 237.1483 calc. 237.1485 [$C_{14}H_{21}O_3$]$^+$.

(4-(Benzyloxy)phenyl)(4-((5-carboxypentyl)oxy)phenyl)iodonium tosylate (176(TsO))
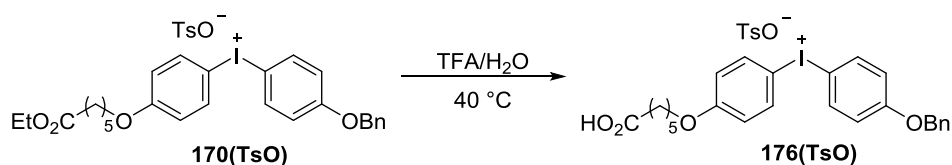
Iodonium tosylate **170(TsO)** (1.47 g, 1.6 mmol) in trifluoroacetic acid and water (1:1) (1 mL) was stirred for 19 h at 40 °C. Subsequently the solvent was removed and the yellow oil was triturated with Et$_2$O to give a grey gum. Recrystalisation from CH$_2$Cl$_2$/Et$_2$O gave the product as a white solid (1.01 g, 92%, m.p.124-125 °C)

^{1}H NMR (400 MHz, CDCl$_3$) δ ppm: 8.08 – 7.94 (m, 1H), 7.70 (d, J = 8.1 Hz, 2H), 7.47 – 7.27 (m, 2H), 7.23 (d, J = 8.0 Hz, 2H), 7.11 (d, J = 9.0 Hz, 2H), 7.03 (d, J = 9.0 Hz, 2H), 5.14 (s, 2H), 4.03 (t, J = 6.3 Hz, 2H), 2.37 (s, 3H), 2.31 (t, J = 7.3 Hz, 2H), 1.88 – 1.74 (m, 2H), 1.71 – 1.59 (m, 2H), 1.56 – 1.43 (m, 2H); ^{13}C NMR (100 MHz, MeOD) δ ppm: 177.4, 163.8, 163.3, 143.5, 141.6, 138.1 (2C), 137.5, 129.8, 129.6, 129.3, 128.7, 126.9, 119.6, 119.1, 105.4, 104.9, 71.4, 69.5, 34.8, 29.8, 26.6, 25.7, 21.3; HRMS (ESI) [M-TsO]$^+$ found 517.0858 calc. 517.0870 [C$_{25}$H$_{26}$IO$_4$]$^+$.

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