NEW METHODS FOR THE CONSTRUCTION OF C-^{18}F BONDS

A thesis submitted to the Board of the Faculty of Physical Sciences
in partial fulfillment of the requirements for the degree of
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Author's Declaration

The work presented in this thesis was conducted at the Chemistry Research Laboratory, Oxford University, Durham University and Turku PET Centre (Finland) between Michaelmas Term 2009 and Michaelmas Term 2013, under the supervision of Professor Véronique Gouverneur. All of the work is my own, except where stated otherwise, and has not been submitted for any other degree at this or any university.

Ida Sofia Refsholt Stenhagen
November 2013

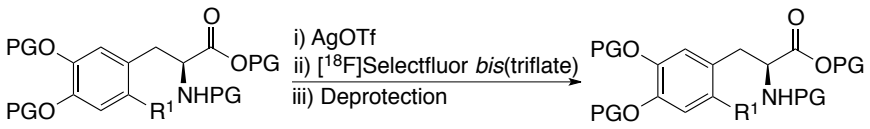
Construction of C-^{18}F Bonds Using Novel Electrophilic N-^{18}F Reagents

Ida Sofia Refsholt Stenhagen D.Phil
Lady Margaret Hall Michaelmas Term 2013

The main electrophilic source used in radiolabelling is [^{18}F]F_2, which is highly reactive, toxic and requires specialist equipment for safe handling. The Gouverneur group has initiated a research programme focused on the preparation of new stable and easy-to-handle N-^{18}F reagents. In the development of [^{18}F]radiolabelling reactions it would be extremely valuable to develop a library of selective N-^{18}F reagents possessing reactivity tailored to the desired chemical transformation. The aim of this thesis is to further assess the scope of electrophilic N-^{18}F reagents in new transformations for the construction of C-^{18}F bonds.

Chapter 1 provides a general introduction to fluorine-18 radiochemistry and summarises the aims and objectives of the thesis.

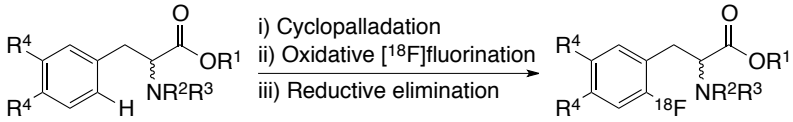
The application of [^{18}F]Selectfluor *bis*(triflate) in a silver-mediated fluorination methodology for the preparation of 6-[^{18}F]fluoro-L-DOPA was studied in **Chapter 2**. Both arylstannane and aryl boronic acid derivative precursors were successfully employed (Scheme i).



R^1 = $Sn(alkyl)_3$ or $B(OR^2)_2$
R^2 = H or alkyl
PG = protecting group

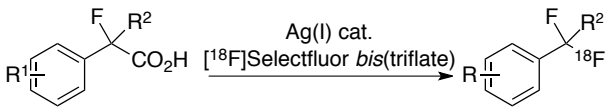
Scheme i. Preparation of 6-[^{18}F]fluoro-L-DOPA using [^{18}F]Selectfluor *bis*(triflate).

In **Chapter 3**, the feasibility of a palladium-mediated C-H activation [^{18}F]fluorination reaction for the preparation of 6-[^{18}F]fluoro-L-DOPA was investigated (Scheme ii). Studies towards the preparation of new N-^{18}F reagents for the use in transition metal catalysis were also carried out.



Scheme ii. Synthesis of 6-[^{18}F]fluoro-L-DOPA *via* a palladium-mediated C-H activation approach.

General and robust routes for the preparation of [^{18}F]trifluoromethylated arenes are highly sought after. In **Chapter 4** a silver-catalysed fluorodecarboxylation approach was developed for the synthesis of [^{18}F]tri- and [^{18}F]difluoromethylated arenes (Scheme iii). [^{18}F]Selectfluor *bis*(triflate) was found to be a superior labelling reagent to [^{18}F]F_2.



R^1 = alkyl, aryl, EDG, EWG
R^2 = F or H

Scheme iii. Preparation of [^{18}F]tri- and [^{18}F]difluoromethylated arenes.

Chapter 5 gives full experimental procedures and characterisation data for all compounds.

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Du ska få en dag i mårå som rein og ubrukt står,
med blanke ark og farjestifter tel,
og da kan du rette oppatt alle feil ifrå i går,
og da får du det så godt i mårå kveld.

Alf Prøysen

Til Mimmi og Beste, verdens beste besteforeldre.

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Abbreviations and Acronyms

[^{11}C]	Carbon-11 label
[^{11}C]DTBZ	(+)-[^{11}C]-dihydrotetrabenazine
[β-^{11}C]-L-DOPA	[beta-^{11}C]labelled-L-3,4-dihydroxyphenylalanine
6-fluoro-[β-^{11}C]-L-DOPA	6-fluoro-[beta-^{11}C]-L-3,4-dihydroxyphenylalanine
[^{11}C]Nomifensine	1,2,3,4-tetrahydro-2-[^{11}C]methyl-4-phenyl-8-isoquinolinamine
[^{18}F]	Fluorine-18 label
[^{18}F]Altanserin	3-[2-[4-(4-[^{18}F]fluorobenzoyl)piperidin-1-yl]ethyl]-2-sulfanylidene-1*H*-quinazolin-4-one
[^{18}F]AV-133	[^{18}F]-9-fluoropropyl-(+)-dihydrotetrabenazine
[^{18}F]CFT	2β-carbomethoxy-3β-(4-[^{18}F-fluorophenyl)tropane
[^{18}F]EF3	[^{18}F]-2-(2-Nitroimidazol-1-yl)-*N*-(3,3,3-trifluoropropyl)-acetamide
[^{18}F]EF5	2-(2-Nitro-1H-imidazol-1-yl)-*N*-(2,2,3,3,3-[^{18}F]pentafluoropropyl) acetamide
[^{18}F]FACBC	(*anti*-1-amino-3-[^{18}F]fluorocyclobutane-1-carboxylic acid
[^{18}F]FBR	*N*-[^{18}F]fluoroacetyl-*N*-(2,5-dimethoxybenzyl)-2-phenoxyaniline
[^{18}F]FCWAY	[^{18}F]-*trans*-4-fluoro-*N*-2-[4-(2-methoxyphenyl)piperazin-1-yl]ethyl-*N*-(2-pyridyl)cyclohexane carboxamide
[^{18}F]FDG	2-Deoxy-2-[^{18}F]fluoro-D-glucose
[^{18}F]FET	[^{18}F]fluoro- ethyl-L-tyrosine
[^{18}F]FLT	3'-deoxy-3'-[^{18}F]fluorothymidine
6-[^{18}F]fluoro-L-DOPA	6-[^{18}F]fluoro-L-3,4-dihydroxyphenylalanine
[^{18}F]MeNER-d_2	(*S,S*)-2-(α-(2-[^{18}F]fluoro[$^{2}H_2$]methoxyphenoxy)-phenoxy)benzyl)morpholine
[^{18}F]FMISO	1H-1-(3-[^{18}F]fluoro-2-hydroxy-propyl)-2-nitroimidazole
[^{18}F]TFMISO	[1-(2-nitro-1H-imidazol-1-yl)-3-(2,2,2-[^{18}F]trifluoroethoxy)propan-2-ol]
[^{18}F]MTEB	[^{18}F]3-fluoro-5-[2-methyl-1,3-thiazol-4-yl)ethynyl]benzonitrile
[^{18}F]SP203	3-fluoro-5-(2-(2-[^{18}F](fluoromethyl)-thiazol-4-yl)athynyl)benzonitrile
[^{18}F]SPA-RQ	Substance P antagonist receptor quantifier
+*I*	Positive inductive effect
+*M*	Positive mesomeric effect
α	Alpha particle, helium nucleus
$[\alpha]_D^{25}$	Specific rotation
δ	Chemical Shift
$\Delta G^{\ddagger}$	Gibbs free energy of activation
^{o}C	Degrees Celsius
[^{13}N]	Nitrogen-13
[^{15}O]	Oxygen-15
2D	2-dimensional
5-HT_{1D}/5-HT_{1B}	5-hydroxytryptamine receptors 1D or 1B
18-crown-6	1,4,7,10,13,16-hexaoxacyclooctadecane
β^+	positron
Å	Ångström (10^{-10} metres)
Ac	Acetyl
AADC	Aromatic L-amino acid decarboxylase
aq	Aqueous
Ar	Arene
BBB	Blood brain barrier
BDE	Bond dissociation energy

Bn	Benzyl
Boc	*t*-Butyloxycarbonyl
Bq	Becquerel (s^{-1})
br	Broad
BrettPhos	2-(Dicyclohexylphosphino)3,6-dimethoxy-2′,4′,6′-triisopropyl-1,1′-biphenyl
Bu	Butyl
Cat.	Catalytic
cm^{-1}	Wavenumber
Ci	Curie
CNS	Central Nervous System
CO_2	Carbon dioxide
COD	1,5-Cyclooctadiene
COMT	Catechol-*O*-methyltransferase
COSY	Correlation Spectroscopy
CT	Computer tomography
CV	Cyclic voltammetry
d	Deuterated
d	Doublet
d.c.	Decay-corrected
D2	Type of dopamine receptor
DA	Dopamine
DABCO	Diazoniabicyclo[2.2.2]octane
DAM	Di(*p*-anisyl)methyl
DAST	Diethylaminosulfur trifluoride
DAT	Dopamine active transporter
dba	Dibenzylideneacetone
DBH	1,3-dibromo-5,5-dimethylhydantoin
DCE	1,2-Dichloroethane
DFT	Density functional theory
Deoxofluor	*bis*(2-Methoxyethyl)- aminosulfur trifluoride
DMAC	Dimethylacetamide
DME	1,2-Dimethoxyethane
DMF	*N*,*N*-Dimethylformamide
DMSO	Dimethyl sulfoxide
dppf	1,1'- *Bis*(diphenylphosphino) ferrocene
E	Entgegen, opposite side
E^0	Standard electrode potential
Equiv.	Equivalents
ESI	Electrospray ionisation
Et	Ethyl
Et_2O	Diethyl ether
eV	Electron volts
F^-	Nucleophilic fluorine, fluoride
F^+	Electrophilic fluorine
F^+ reagent	Electrophilic fluorinating reagent
F_2	Elemental fluorine
$FClO_3$	Perchloryl fluoride
FDG	Fluorodeoxyglucose
g	Gram
GABA	4-aminobutanoic acid
GBq	Gigabequerel
GC	Gas chromatography
GP	General procedure
h	Hour(s)

HCl	Hydrochloric acid
Hippuric acid	Benzoylaminoethanoic acid
HIV	Human immunodeficiency virus
HMDS	*bis*(Trimethylsilyl)amide
HPLC	High pressure liquid chromatography
HRMS	High resolution mass spectrometry
$h\nu$	Light
Hz	Hertz
i	Iso
IC_{50}	Inhibitory concentration
IR	Infrared (Spectroscopy)
J	Coupling constant
K_{222}	Kryptofix 222, 1,10-Diaza-4,7,13,16,21,24-hexaoxabicyclo[8.8.8]hexacosane
Kcal	Kilocalorie
kJ	Kilojoule
kV	Kilovolts
L	Neutral ligand
L	Litre
LDA	Lithium diisopropylamine
LG	Leaving group
L-DOPA	L-3,4-dihydroxyphenylalanine
Lit.	Literature (value)
Log*p*	Partition coefficient
LUMO	Lowest unoccupied molecular orbital
M	Moles per cubic decimetre ($moldm^{-3}$)
m	*Meta*
M	Metal
M	Molecular mass
m	Multiplet
MAO	Monoamine oxidase
MBq	Megabequerel
Me	methyl
mg	Milligram(s)
min	Minute(s)
µL	Microlitre(s)
mL	Millilitre(s)
mm	Millimetre
mol	Mole(s)
MOM	Methoxymethyl
µmol	micromol
mmol	millimol
Mp	Melting point
m/z	Mass/charge ratio
MCR	Multicomponent reaction
MRI	Magnetic resonance imaging
MS	Mass spectroscopy
MS	Molecular sieves
ν	Neutrino
n	Normal (unbranched)
n	Neutron
N-F reagent	Nitrogen-containing electrophilic fluorinating reagent, N-F bond
N-^{18}F reagent	[^{18}F]labelled nitrogen-containing electrophilic fluorinating reagent, N-F bond
NBS	*N*-bromosuccinimide

NFSI	*N*-Fluorobenzenesulfonimide
NHC	*N*-Heterocyclic Carbene
NK_1	Neurokinin 1 receptor
nm	Nanometre(s)
NMP	*N*-Methyl-2-pyrrolidone
NMR	Nuclear Magnetic Resonance Spectroscopy
Ns	Nosyl, *ortho*-toluenesulfonyl
p	*Para*
P	Proton
PET	Positron Emission Tomography
Pet. Ether	Petroleum Ether
PG	Protecting group
Ph	Phenyl
pH	$-\log_{10}[H^+]$
Phen	1,10-phenanthroline
PIDA	Phenyliodine diacetate
PIFA	Phenyliodine *bis*(trifluoroacetate)
pK_a	Acid dissociation constant
pK_aH	Acid dissociation constant of the conjugate acid
ppm	Parts per million
Pr	Propyl
Prec.	Precursor
PTC	Phase transfer catalyst
PTFE	Polytetrafluoroethylene
Py	Pyridine
R	Rictus, meaning clockwise
γ-rays	Gamma rays
RCY	Radiochemical yield
Red P	Red phosphorus
Ref.	Reference
rt	Room temperature
S	Sinister, meaning anti-clockwise
s	Singlet
s	Seconds
SA	Specific activity
SAR	Structure-Activity Relationship
SCE	Saturated calomel electrode
S_EAr	Electrophilic Aromatic Substitution
Selectfluor	1-Chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane
Selectfluor™	1-Chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate)
SET	Single Electron Transfer
S_N2	Bimolecular nucleophilic substitution
S_NAr	Nucleophilic Aromatic Substitution
SOMO	Singly occupied molecular orbital
SPECT	Single Photon Emission Computed Tomography
t	Tertiary
t	Triplet
$t_{1/2}$	Half life
TBAF	Tetra-*n*-butylammonium fluoride
TBDPS	*tert*-Butyldiphenylsilyl
TBS	*tert*-Butyldimethylsilyl
TDAE	Tetrakis(dimethylamino)ethylene

t-BuBrettphos	2-(Di(*tert*-butyl)phosphino)3,6-dimethoxy-2′,4′,6′-triisopropyl-1,1′-biphenyl
t-BuXPhos	2-Di-*tert*-butylphosphino-2′,4′,6′-triisopropylbiphenyl
Temp.	Temperature
TES	Triethylsilane
TH	Tyrosine hydroxylase
THF	Tetrahydrofuran
Tf	Trifluoromethanesulfonyl (Triflyl)
TFA	Trifluoroacetic acid
TFAA	Trifluoroacetic anhydride
TLC	Thin Layer Chromatography
TMEDA	*N,N,N′,N′*-Tetramethylethylenediamine
TMAF	tetramethylammonium fluoride
TMP	Tetramethylpiperidine
TMS	Trimethylsilyl
TREAT-HF	Triethylamine trihydrofluoride
Ts	*para*-Toluenesulfonyl (Tosyl)
UV	Ultraviolet
V	Volt(s)
Veratrole	1,2-Dimethoxybenzene
VMAT	Vesicular monoamine transporter
v/v	Volume for volume
vs	Versus
XanthPhos	4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene
Z	Zusammen, same side, together

Chapter 1. General Introduction

1.1 Introduction to Positron Emission Tomography (PET)

Positron emission tomography (PET) is a functional imaging technique, which aids in the detection of diseases at an early stage of their development and pharmaceutical drug evaluation. In comparison to MRI, CT, and X-ray, which provide structural anatomical imaging, PET imaging provides information on molecular events and metabolism. The use of two imaging techniques in combination is advantageous as both physiological and anatomical details are obtained.[1]

Exogenous probes labelled with positron (β^+) emitting short-lived radioisotopes, such as carbon-11, nitrogen-13, oxygen-15 and fluorine-18, have been designed to bind to specific targets without interfering with their biological activity (Table 1.1).[2]

Radioisotope	Half-life (min)	Nuclear reaction	Decay product
^{11}C	20.38	$^{14}N(p,\alpha)^{11}C$	^{11}B
^{13}N	9.97	$^{16}O(p,\alpha)^{13}N$	^{13}C
^{15}O	2.04	$^{15}N(d,n)^{15}O$	^{15}N
^{18}F	109.77	$^{18}O(p,n)^{18}F$ $^{20}Ne(d,\alpha)^{18}F$	^{18}O

Table 1.1. Radionuclides commonly used in PET imaging.

The relatively short half-life of these isotopes necessitates the preparation of the labelled imaging agents close to the site of isotope production and use. As a general rule, the total synthesis time must be less than three half-lives.

Shortly after injection of the labelled compound into the subject, an annihilation event occurs between the positron emitted from the decaying isotope and a surrounding electron, causing two coincident gamma rays to be emitted in opposite directions. As fluorine-18 decays, it forms an oxygen-18 atom in addition to a positron and neutrino (Figure 1.1).[4]

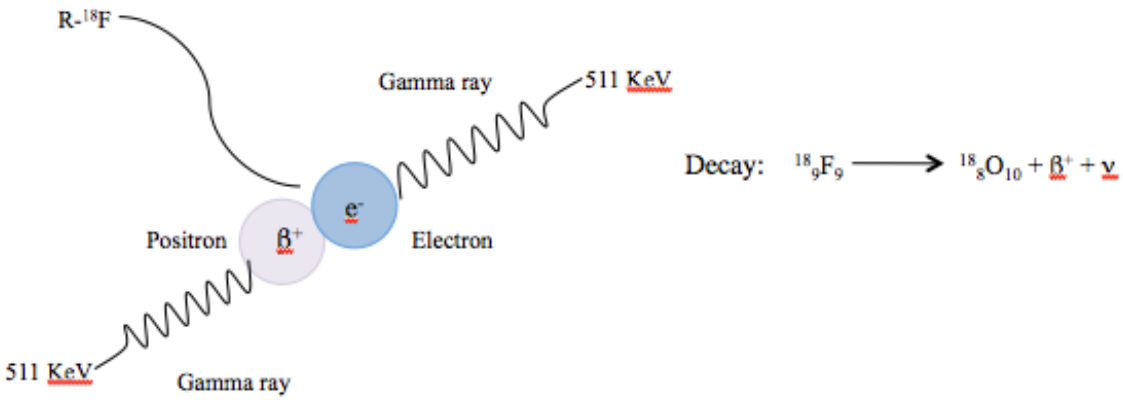


Figure 1.1. Illustration of the decay of fluorine-18 and the subsequent annihilation event.

Detection of the total amount of radiation provides a detailed image of a specific target or biochemical process. A ring of high sensitivity detectors are placed around the subject and the simultaneously detected gamma rays are first converted into visible light and second into an electrical signal using a photo-multiplier. Mathematical algorithms translate the signal into a 2D or 3D image (Figure 1.2).

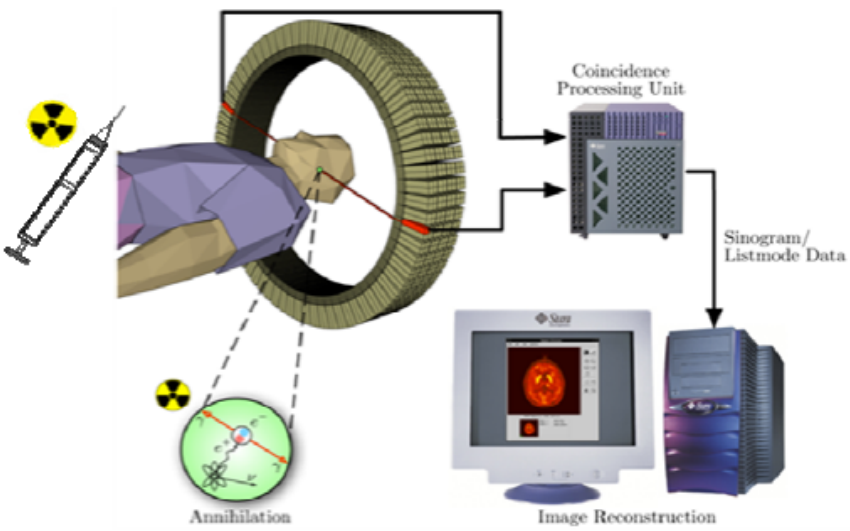


Figure 1.2. Principles of PET (The figure is provided by Jens Langner and used with permission from its author).

The resolution of the PET image depends on the average distance travelled by a positron before annihilation, which in turn depends on its energy. The low positron energy of fluorine-18 (511 keV) allows the positron to travel approximately 2.4 mm before colliding with an electron. This allows for images of higher resolution by

pinpointing the site of annihilation more precisely, compared to the other PET isotopes with higher maximum positron energies (Table 1.2).[2]

Radionuclide	Decay process	Maximum β^+ energy (keV)	Range in water (mm)
^{11}C	99.8% β^+	960	4.1
^{13}N	100% β^+	1190	5.4
^{15}O	99.9% β^+	1720	8.2
^{18}F	97% β^+	635	2.4

Table 1.2. Decay process, maximum positron energy and range in water for common PET isotopes.[2]

PET images detail the spatial distribution and kinetic profile of the radioisotope *in vivo* and have been used in the diagnosis of a wide range of fields including oncology, neurological diseases such as Alzheimer's and Parkinson's Disease[3] and cardiovascular disorders.[4] Furthermore, this imaging technique has been found to be very valuable in drug discovery and development, by providing a non-invasive and quantitative assay of normal and abnormal chemistry in living man at an early stage of the drug discovery process. By allowing optimisation of drug dosing regimens, the investigation of biodistribution, metabolism and receptor/enzyme occupancy studies, PET will aid in the selection of promising drug candidates at an early stage of the drug development.[5]

1.2 Production of Fluorine-18

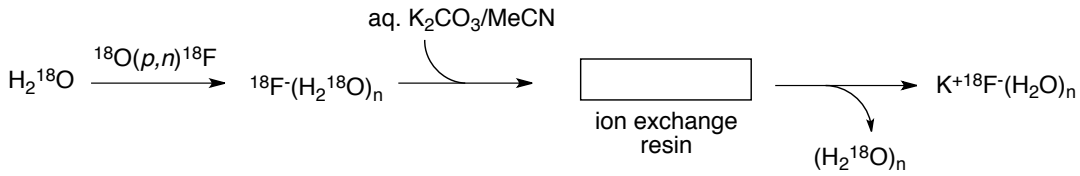
1.2.1 General considerations

It is important to take notice of the environmental and safety implications inherent to working with ionising radiation. Furthermore, the labelling of organic compounds with short half-life radioisotopes such as fluorine-18 raises significant challenges not encountered in conventional organic synthesis. The relatively long half-life of fluorine-18 (~110 min) allows for transport of the isotope to radiochemistry facilities several hours away, preparation of the imaging agent *via* multistep protocols and subsequent biodistribution studies. However, it is important to employ rapid and simple chemical transformations in order to minimise the decay of the positron emitter prior to the PET scan. As such, synthetic routes towards PET radiotracers that incorporate the fluorine at as late a stage as possible are preferred while the [^{18}F]radiofluorination reactions themselves should be clean and rapid processes

(typically ≤ 30 minutes). In addition, purification of the labelled tracer from the crude reaction mixture should be fast and operationally simple.

1.2.2 Preparation of Nucleophilic [^{18}F]Fluoride

The fluorine-18 isotope can be prepared with medical cyclotrons (10-18 MeV).[6] The most common route for the production of fluorine-18 as nucleophilic [^{18}F]fluoride is by proton irradiation of oxygen-18 enriched water, $^{18}O(p,n)^{18}F$.[7] Before it is ready for labelling reactions, oxygen-18 enriched water is removed from the [^{18}F]fluoride by adsorbing the solution onto an ion exchange resin (QMA cartridge). After separation from the solvent, the [^{18}F]fluoride is eluted by aqueous K_2CO_3 and MeCN. The excess water is removed by successive azeotropic drying with MeCN in the presence of a phase transfer catalyst, typically Kryptofix$_{222}$ (Scheme 1.1).



Scheme 1.1. Preparation of [^{18}F]fluoride from [^{18}O]water.

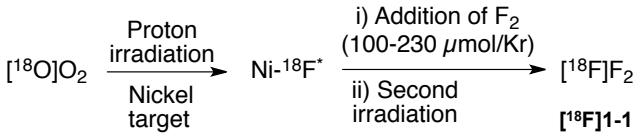
The loss of water and formation of the [cryptand-K^+] [^{18}F]fluoride complex greatly increases the nucleophilicity of [^{18}F]fluoride for both aromatic and aliphatic nucleophilic substitution reactions in polar aprotic solvents.

1.2.3 Preparation of [^{18}F]F_2

Electrophilic fluorine-18 is routinely produced as [^{18}F]F_2 **[^{18}F]1-1** by two nuclear reactions; the first involved irradiation of neon in the $^{20}Ne(d,\alpha)^{18}F$ nuclear reaction. After bombardment of the gas for 1-2 hours with 8-9 MeV deuterons, less than 37 MBq of [^{18}F]F_2 was produced with very low specific activity (0.37-0.74 MBq/μmol).[8]

Conversely, a "double shoot" method was developed for the production of [^{18}F]F_2 in the $^{18}O(p,n)^{18}F$ nuclear reaction using [^{18}O]O_2 gas and a metal target.[9] Firstly, the nickel or aluminium target filled with [^{18}O]O_2 is irradiated by the proton beam. The excited $^{18}F^*$ atoms produced rapidly adhere to the walls of the target. The isotope is

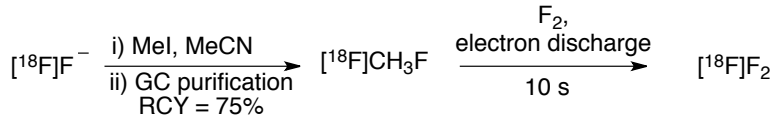
released upon the introduction of carrier F_2 gas (~0.1% in Ne or Kr) and a second irradiation. This promotes isotopic exchange between the $^{18}F^*$ atoms and F_2 to afford $[^{18}F]F_2$ in 3.1-4.1 GBq/μA (Scheme 1.2).[10]



Scheme 1.2. Preparation of $[^{18}F]F_2$ from $[^{18}O]O_2$.

This approach relies on large amounts of carrier F_2 to release the radioactivity from the target, which has a detrimental effect on the specific activity (< 0.4 GBq/μmol). This is a disadvantage in the imaging of receptor targets often present in very low densities. If the labelled probe is only available in low specific activity, i.e, most of it is 'cold' fluorine-19, more must be injected to obtain an image. This may in turn cause physiological effects and extensive toxicological testing.

Bergman and Solin reported a 'post-target' method for the production of high-specific activity **$[^{18}F]$1-1** (up to ~55 GBq/μmol) from $[^{18}F]$fluoride.[11] High specific activity $[^{18}F]$fluoromethane was produced by nucleophilic substitution of methyl iodide with $[^{18}F]$fluoride. $[^{18}F]F_2$ was then prepared in the $^{18}F/^{19}F$ exchange reaction between $[^{18}F]$fluoromethane and a low amount of the F_2 carrier (~ 1 μmol) in an electrical discharge chamber. The specific activity of the labelled product could be increased from less than 0.4 GBq/μmol to 10–20 GBq/μmol with high specific activity $[^{18}F]F_2$ (Scheme 1.3).



Scheme 1.3. Preparation of high specific activity $[^{18}F]$1-1.

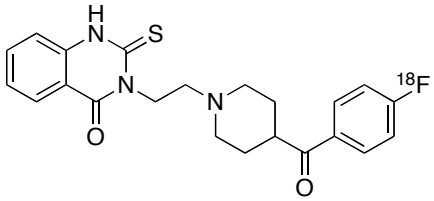
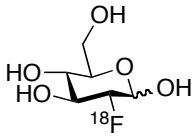
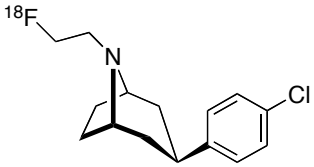
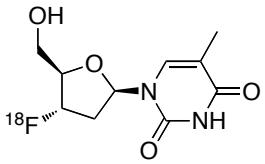
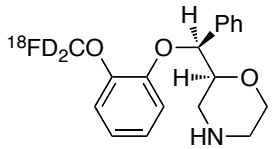
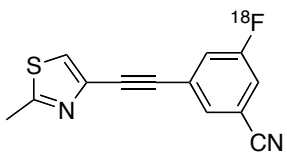
The specific activities achieved with the described labelling methods and the variation in the amount of the tracer injected are summarised in Table 1.3.

Labelling Method (^{18}F)	Specific Activity (GBq/µmol)	Mass injected (µg)
Nucleophilic labelling	37-1000	0.06-1.5
High SA electrophilic labelling	3.7-25	2.2-15
Electrophilic labelling	0.037-0.75	74-1500

Table 1.3. Labelling methods and the variation in mass required to achieve an injection of 185 MBq of radioactivity of a radiotracer (mw = 300 g/mol).

1.3 Radiochemistry – Preparation of [^{18}F]Radiopharmaceuticals

There is a growing interest in preparing [^{18}F]radiopharmaceuticals to monitor molecular targets for ***proliferation, angiogenesis, apoptosis, receptor expression, metastasis*** and ***hypoxia.*** A selection of radiotracers prepared for clinical PET imaging or preclinical microPET studies are highlighted in Table 1.4.

Radiotracer	Structure	Application
[^{18}F]Altanserin **[^{18}F]1-2**[12]		Brain 5-HT$_2$ receptors
[^{18}F]FDG **[^{18}F]1-3**[13], [14]		Glucose metabolism
[^{18}F]FECNT **[^{18}F]1-4**[15]		Brain dopamine transporters
[^{18}F]FLT **[^{18}F]1-5**[16]		Cellular proliferation
[^{18}F]FMeNERd_2 **[^{18}F]1-6**[17]		Noradrenaline transport
[^{18}F]FMTEB **[^{18}F]1-7**[18]		Brain mGluR5 receptors

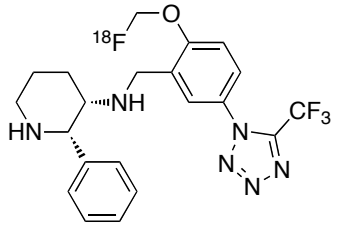
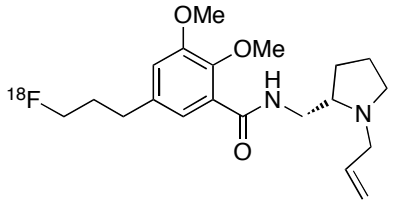
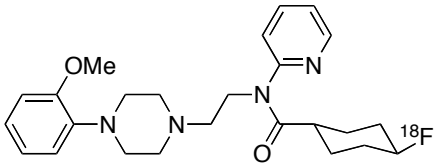
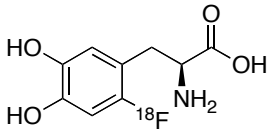
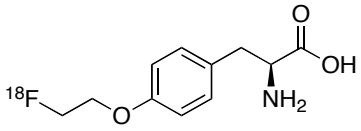
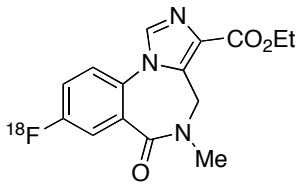
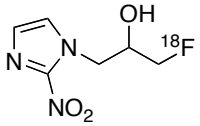
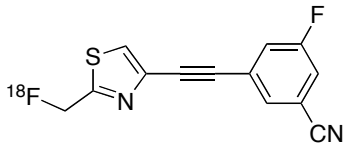
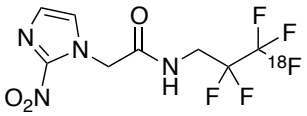
[^{18}F]SPA-RQ **[^{18}F]1-8**[19]		Brain neurokinin type-1-receptors
[^{18}F]Fallypride **[^{18}F]1-9**[20]		Brain D_2 receptors
[^{18}F]FCWAY **[^{18}F]1-10**[21]		Brain 5-HT_{1A} receptors
6-[^{18}F]fluoro-L-DOPA **[^{18}F]1-11**[22]		Brain dopamine metabolism
[^{18}F]FET **[^{18}F]1-12**[23]		Tumor location
[^{18}F]Flumazenil **[^{18}F]1-13**[24]		Brain benzodiazepine receptors
[^{18}F]FMISO **[^{18}F]1-14**[25]		Hypoxia
[^{18}F]SP203 **[^{18}F]1-15**[26]		Brain mGluR5 receptors
[^{18}F]EF5 **[^{18}F]1-16**[27]		Hypoxia

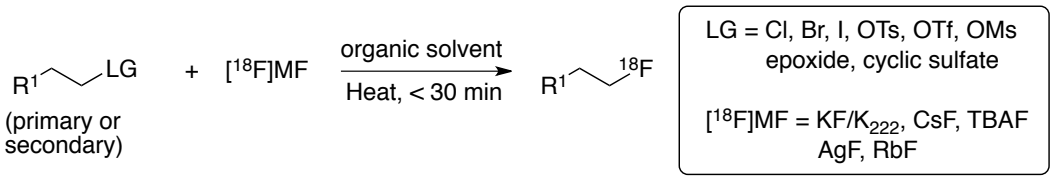
Table 1.4. A selection of radiotracers prepared for clinical PET imaging or preclinical microPET studies.

1.3.1 Radiolabelling with [^{18}F]fluoride

Metal fluorides (such as [^{18}F]KF and [^{18}F]CsF) and tetra-*n*-butylammonium [^{18}F]fluoride ([^{18}F]TBAF) are the most widely used fluorine-18 precursor in aliphatic and aromatic substitution reactions.

1.3.1.1 Nucleophilic aliphatic [^{18}F]fluorination

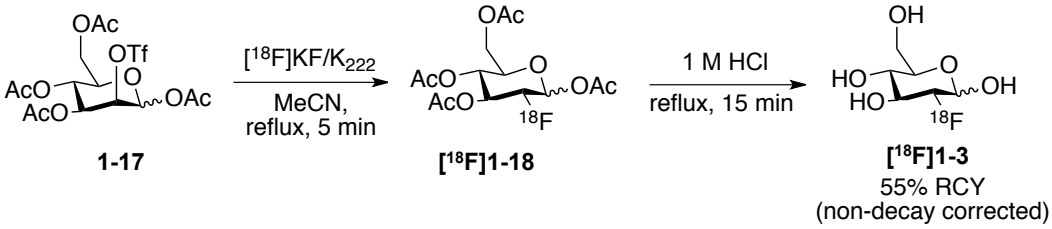
Direct nucleophilic aliphatic [^{18}F]fluorination is an applicable strategy for preparing labelled molecules with high specific activity (100 GBq/μmol).[28] The substrate must contain a suitable leaving group, for example a halide (I, Br) or a sulfonate (Tf, Ts, Ms, Ns), whilst S_N2-type ring-opening of cyclic sulfates and epoxides has also been demonstrated. The reactivity of the substrate for [^{18}F]fluoride substitution increases in the order: tertiary < secondary < primary sulfonates/halides, as expected for S_N2 reactions. The choice of leaving groups mostly depends on the availability and stability of the precursor and the ease of separation of the labelled product from the other components of the reaction mixture, rather than the yield. Protic functional groups (acid, alcohol, amine) that can react with fluoride must be protected, which add a deprotection step to the synthetic sequence and increases synthesis time (Scheme 1.4).



Scheme 1.4. S_N2 nucleophilic [^{18}F]radiofluorination of aliphatic substrates.

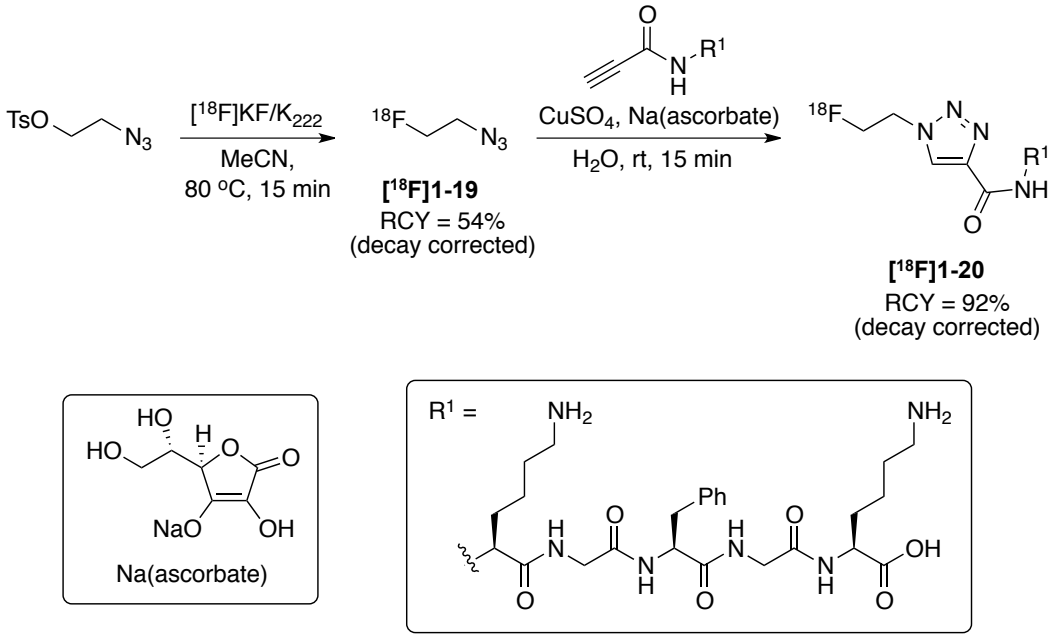
The most established PET tracer to date is 2-deoxy-2-[^{18}F]fluoro-D-glucose ([^{18}F]FDG, **[^{18}F]1-3**). This imaging agent is an analogue of D-glucose and it is used widely in diagnostic medicine in fields such as oncology and neurology and acts by studying glucose metabolism *in vivo*. In cancerous cells the glucose intake is highly increased, and once [^{18}F]FDG is taken up by the cell a phosphorylation reaction occurs. Due to the presence of the fluorine atom at the C2-position, not a hydroxyl group, further metabolism is inhibited and [^{18}F]FDG remains trapped in the cell, allowing the cell to be visualised in a PET image.[12]

[^{18}F]1-3 is routinely prepared in PET centres by nucleophilic substitution of a triflate leaving group on a globally protected D-glucose precursor **1-17** using [^{18}F]KF. The acetate protecting groups of the labelled intermediate **[^{18}F]1-18** are removed under acidic conditions and **[^{18}F]1-3** is afforded in 55% non-decay corrected yield (Scheme 1.5).[12]



Scheme 1.5. Preparation of [^{18}F]FDG.[12]

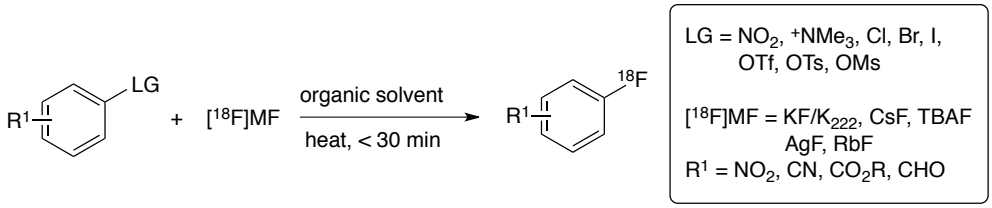
Although S_N2 nucelophilic aliphatic substitution is the method of choice for the [^{18}F]radiolabelling of many radiotracers, the conditions required for C(sp^3)-^{18}F fluorination to occur may not be compatible with sensitive substrates. The high temperature and organic solvent required for direct [^{18}F]fluorination is not compatible with many biomolecules, and proteins and peptides would undergo denaturation. An alternative indirect strategy, relying on the use of intermediate [^{18}F]radiolabelled prosthetic groups has therefore been devised.[29],[30] The labelled prosthetic group is prepared according to the conventional nucleophilic [^{18}F]fluorination conditions (either S_N2 or S_NAr) and then purified before it is attached to the biomolecule in a rapid and mild ligation step. Popular coupling strategies include the condensation of [^{18}F]labelled benzaldehyde prosthetic groups (see Section 1.3.1.2) with peptide *N*-termini and the Huisgen 1,3-dipolar cycloaddition of terminal alkynes with 2-[^{18}F]fluoroethylazide **[^{18}F]1-19**. This 'click' reaction was employed by Årstad and co-workers to efficiently prepare the [^{18}F]labelled peptide **[^{18}F]1-20** in 92% decay corrected RCY. After the synthesis of the prosthetic group, the ligation step was complete within 15 minutes at room temperature (Scheme 1.6).[31]



Scheme 1.6. Indirect radiolabelling of a peptide fragment using a 'click' reaction.[31]

1.3.1.2 Aromatic nucleophilic [^{18}F]fluorination

Fluorinated aromatics are an important motif in pharmaceuticals and have as a result become common in radiotracers. [^{18}F]Fluoride is typically introduced by aromatic nucleophilic substitution *via* an addition-elimination mechanism (Scheme 1.7).



Scheme 1.7. Nucleophilic aromatic [^{18}F]radiofluorination of aromatic substrates.

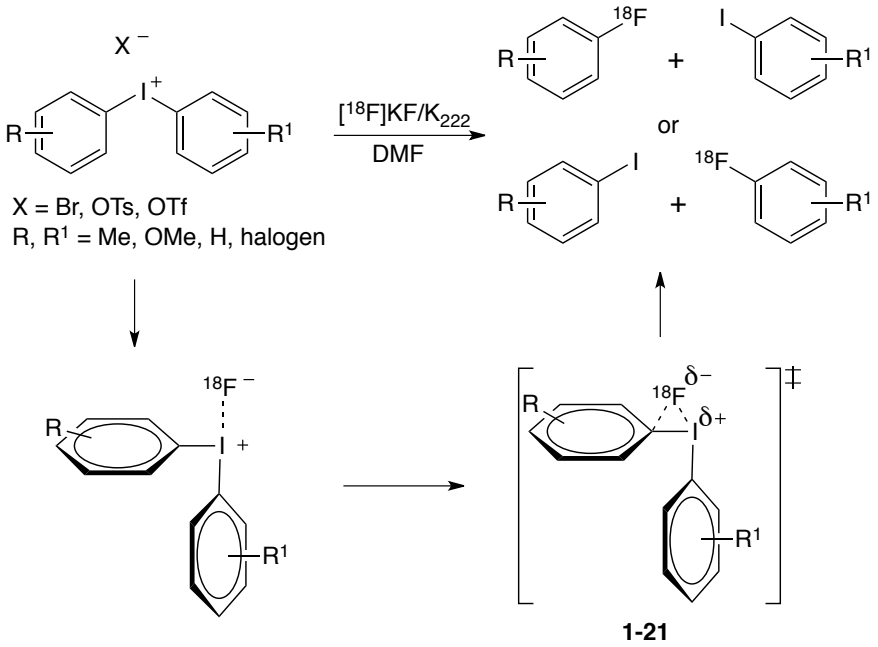
This class of S_NAr reactions with non-carrier-added [^{18}F]fluoride are often highly efficient processes, delivering [^{18}F]radiolabelled arenes in good radiochemical yields within 30 minutes.[32] The RCYs of the [^{18}F]radiolabelled products varied depending on the nature of the leaving group, and were found to be highest with arenes bearing nitro- or trimethylammonium salt leaving groups, although aromatic halides and sulfonyl esters have also been successfully employed.[33] The choice of leaving group may also impact the purification of the [^{18}F]radiolabelled product.

Trimethylammonium salt precursors has the added advantage of facile separation of the [^{18}F]radiolabelled products from the unreacted starting materials, while nitro- and haloarene precursors often possess similar chromatographic properties to the [^{18}F]fluoroaromatic products making purification challenging.

The scope of this [^{18}F]fluorination is limited, as to enable the reaction to proceed within a reasonable timescale, the substrates must be able to stabilise the negative charge created by the attack of [^{18}F]fluoride. This requires the presence of at least one electron-withdrawing group in the *ortho*- or *para*-positions on the arene.

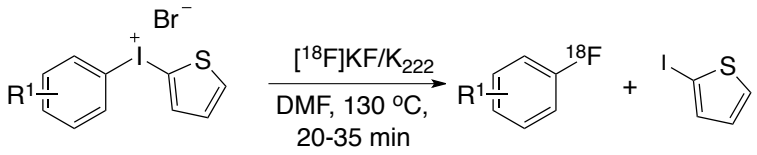
1.3.1.3 [^{18}F]Fluorination of iodonium salts

As a result of the limitations discussed, effort has been devoted to developing nucleophilic protocols for the labelling of electron-neutral and electron-rich arenes. In 1995, Pike and Aigbirhio demonstrated this using iodonium salts (Scheme 1.8).[34] When symmetrical arene substitutents were used, a mixture of products was obtained. The mechanism was postulated to proceed *via* transition state **1-21** and the reaction is driven by the reduction of the iodine centre with the entropically favoured elimination of iodobenzene.[35]



Scheme 1.8. Nucleophilic [^{18}F]fluorination via iodonium salts.

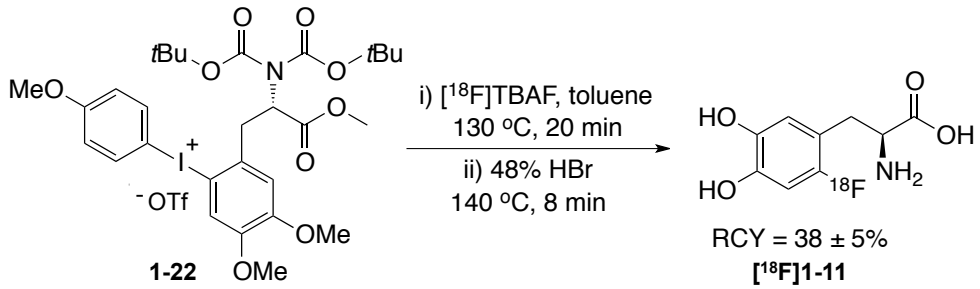
The positively-charged iodonium group removes electron density from the arene ring as well as acting as the leaving group, thereby activating it towards nucleophilic attack. The distribution of [^{18}F]fluorinated products was found to be highly dependent on the electronic character of the aryl groups of the salt. As expected, the most electron deficient ring is preferentially attacked by [^{18}F]fluoride. In 2007, Coenen and co-workers successfully prepared a range of [^{18}F]fluorinated arenes upon by using asymmetric iodonium salts.[36] Iodine(III) reagents bearing one thiophene substituent and one aryl group were treated with [^{18}F]KF/K_{222} in DMF at 130 ^{o}C. The reaction was successful with substrates bearing electron-neutral and electron-donating substituents on the arene ring. The *para*-methyl and *para*-methoxy substituted arenes were afforded in 32 ± 2% and 29 ± 3% RCY (Scheme 1.9).



R^1 = H RCY = 64 ± 4%
R^1 = *para*-Me RCY = 32 ± 2%
R^1 = *para*-OMe RCY = 29 ± 3%
R^1 = *meta*-OMe RCY = 20 ± 3%
(all decay corrected)

Scheme 1.9. [^{18}F]Fluorination using asymmetric iodonium salts.

The application of this methodology towards more complicated substrates has proved challenging, but recently DiMagno and co-workers published a patent reporting the preparation of 6-[^{18}F]fluoro-L-DOPA **[^{18}F]1-11** from the iodonium salt precursor **1-22** (Scheme 1.10).[37]



1-22

RCY = 38 ± 5%
[^{18}F]1-11

Scheme 1.10. Synthesis of [^{18}F]1-11 from a diaryliodonium salt precursor.

1.3.1.4 Oxidative [^{18}F]fluorination of phenols

[^{18}F]Radiolabelled pharmaceuticals with 4-[^{18}F]fluorophenol or 4-[^{18}F]fluorocatechol motifs have found increasing clinical applications in PET, such as 6-[^{18}F]fluoro-L-DOPA **[^{18}F]1-11**, 6-[^{18}F]fluoro-L-*m*-tyrosine **[^{18}F]1-23**[38] and (1*R*,2*S*)-6-[^{18}F]fluorometaraminol **[^{18}F]1-24**[39] (Figure 1.3). This has stimulated an interest in developing new strategies for robust synthesis of these motifs with high efficiency.

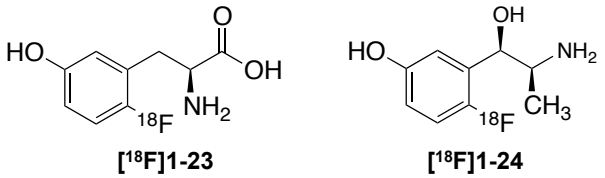
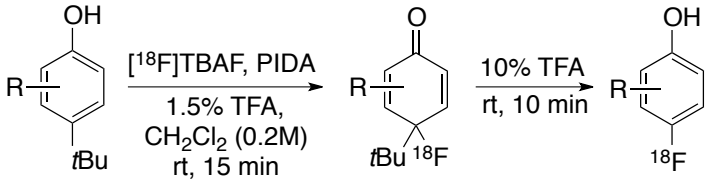


Figure 1.3. Selected PET radiopharmaceuticals containing the 4-[^{18}F]fluorophenol or 4-[^{18}F]fluorocatechol motif.

Recently, an umpolung strategy for the direct nucleophilic [^{18}F]fluorination of electron-rich phenols was reported by Gouverneur and co-workers.[40] In the presence of a two-electron oxidant, various substituted 4-*tert*-butylphenols were oxidised to the corresponding cationic intermediate cyclohexadien-1-one, amenable to nucleophilic attack by [^{18}F]fluoride. After cleavage of the *tert*-butyl group and rearomatisation in the presence of a catalytic amount of acid, the [^{18}F]radiolabelled arenes were obtained in 11 to 32% RCY (Scheme 1.11).



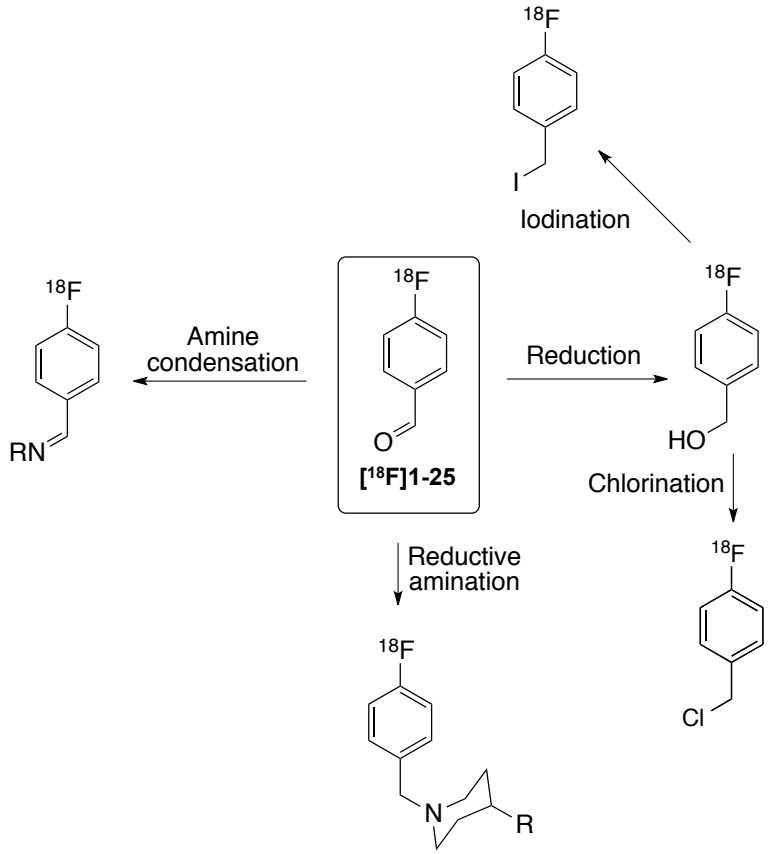
R = H	RCY = 15% (*n* = 5)
R = 2-Me	RCY = 15% (*n* = 8)
R = 2-*t*Bu	RCY = 32% (*n* = 5)
R = 2-COPh	RCY = 11% (*n* = 6)
R = 2-Br	RCY = 16% (*n* = 11)
R = 3-Me	RCY = 13% (*n* = 7)

Scheme 1.11. Oxidative [^{18}F]fluorination of phenols.[40]

1.3.1.5 [^{18}F]Fluorination using prosthetic groups

Despite recent developments, the nucleophilic [^{18}F]fluorination of both electron-poor and electron-rich aromatic substrates remains relatively limited in scope. As a result,

the preparation of imaging agents for PET heavily relies on indirect labelling strategies employing [^{18}F]radiolabelled prosthetic groups, such as 4-[^{18}F]fluorobenzaldehyde **[^{18}F]1-26**, which can be further converted into a versatile range of radiolabelled building blocks (Scheme 1.12).[41] This strategy forces the introduction of the isotope at an early stage of a multi-step synthetic sequence, which results in substantial decay before the imaging agent is ready for injection.

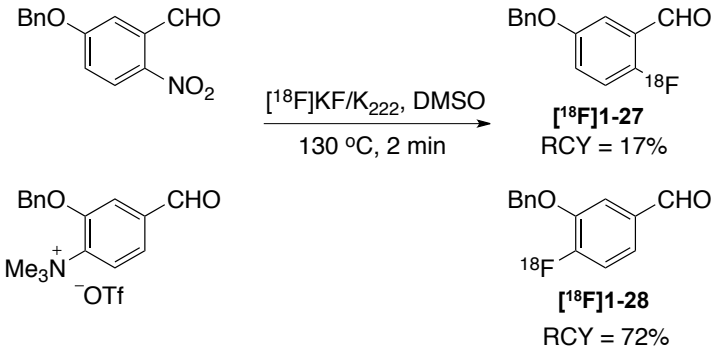


Scheme 1.12. Selected modifications of 4-[^{18}F]fluorobenzaldehyde [^{18}F]1-25 as a prosthetic group.

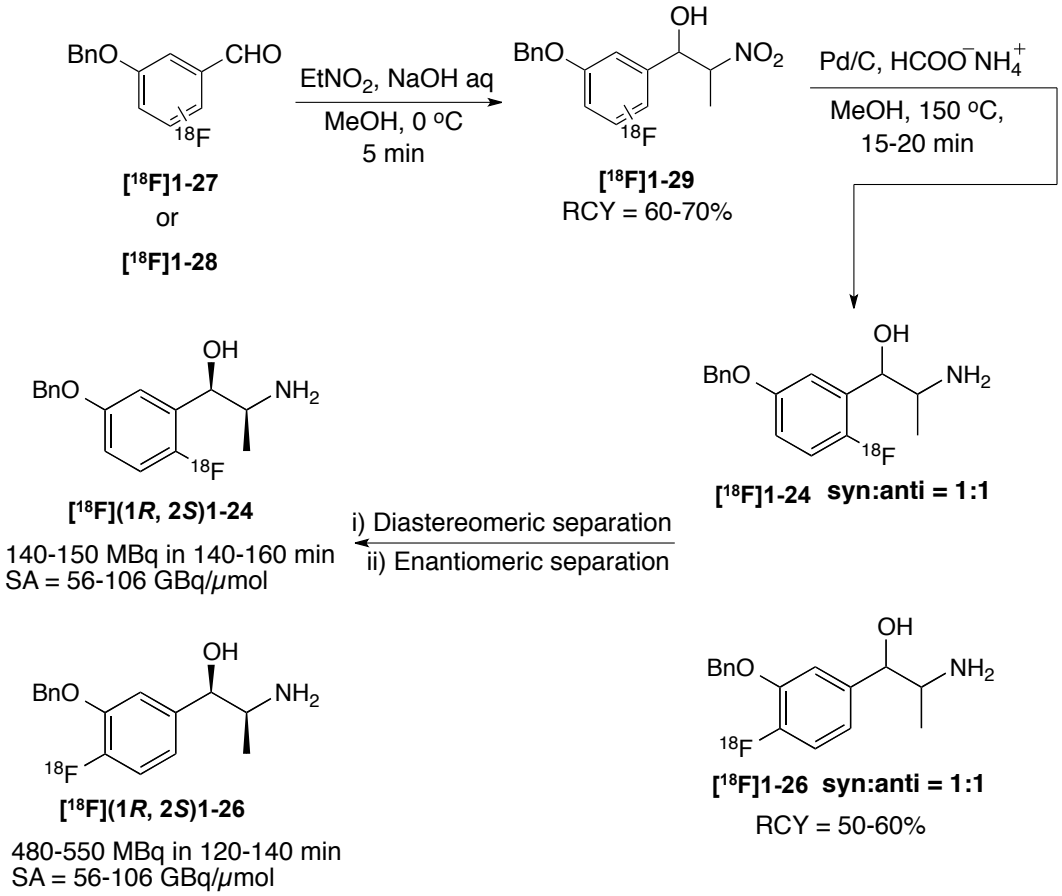
Despite this limitation, key PET imaging agents have been prepared by this approach. The preparation of (1*R*, 2*S*)-6-[^{18}F]fluorometaraminol **[^{18}F](1*R*, 2*S*)1-24** and (1*R*, 2*S*)-4-[^{18}F]fluorometaraminol **[^{18}F](1*R*, 2*S*)1-26**, relies on the nucleophilic addition of nitroethane to *O*-benzyl protected [^{18}F]labelled benzaldehyde **[^{18}F]1-27** or **[^{18}F]1-28**, respectively, followed by deprotection of the benzyl group and simultaneous reduction of the nitro group with Pd/C-ammonium formate. Optically pure **[^{18}F](1*R*, 2*S*)1-24** could be obtained in 140 – 150 MBq (specific activity 56 – 106 GBq/μmol) within a total synthetic time of 140 – 160 min (including diastereomeric separation

and enantiomeric separation *via* HPLC). **[^{18}F](1*R*, 2*S*)1-26** could be obtained within 120 – 140 min *via* an analogous method (Scheme 1.13).[42]

Preparation of [^{18}F]1-27 and [^{18}F]1-28.



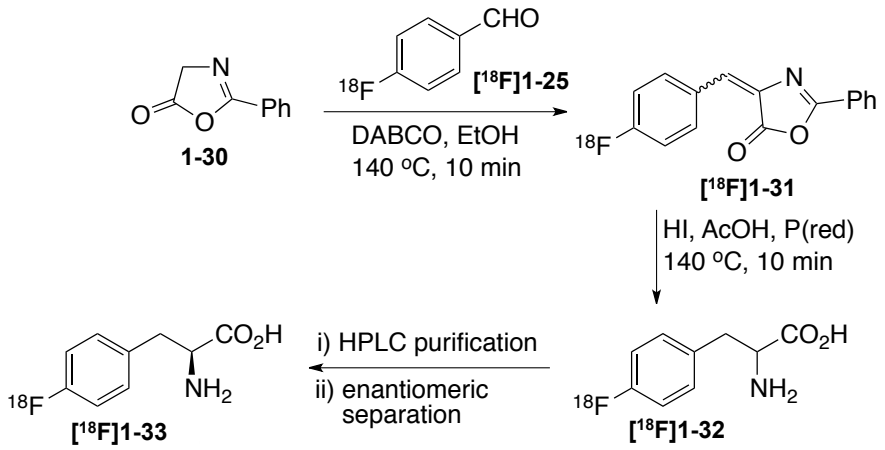
Preparation of [^{18}F](1*R*, 2*S*)1-25 and [^{18}F](1*R*, 2*S*)1-2.



Scheme 1.13. Preparation of optically pure [^{18}F](1*R*, 2*S*)1-24 and [^{18}F](1*R*, 2*S*)1-26.[42]

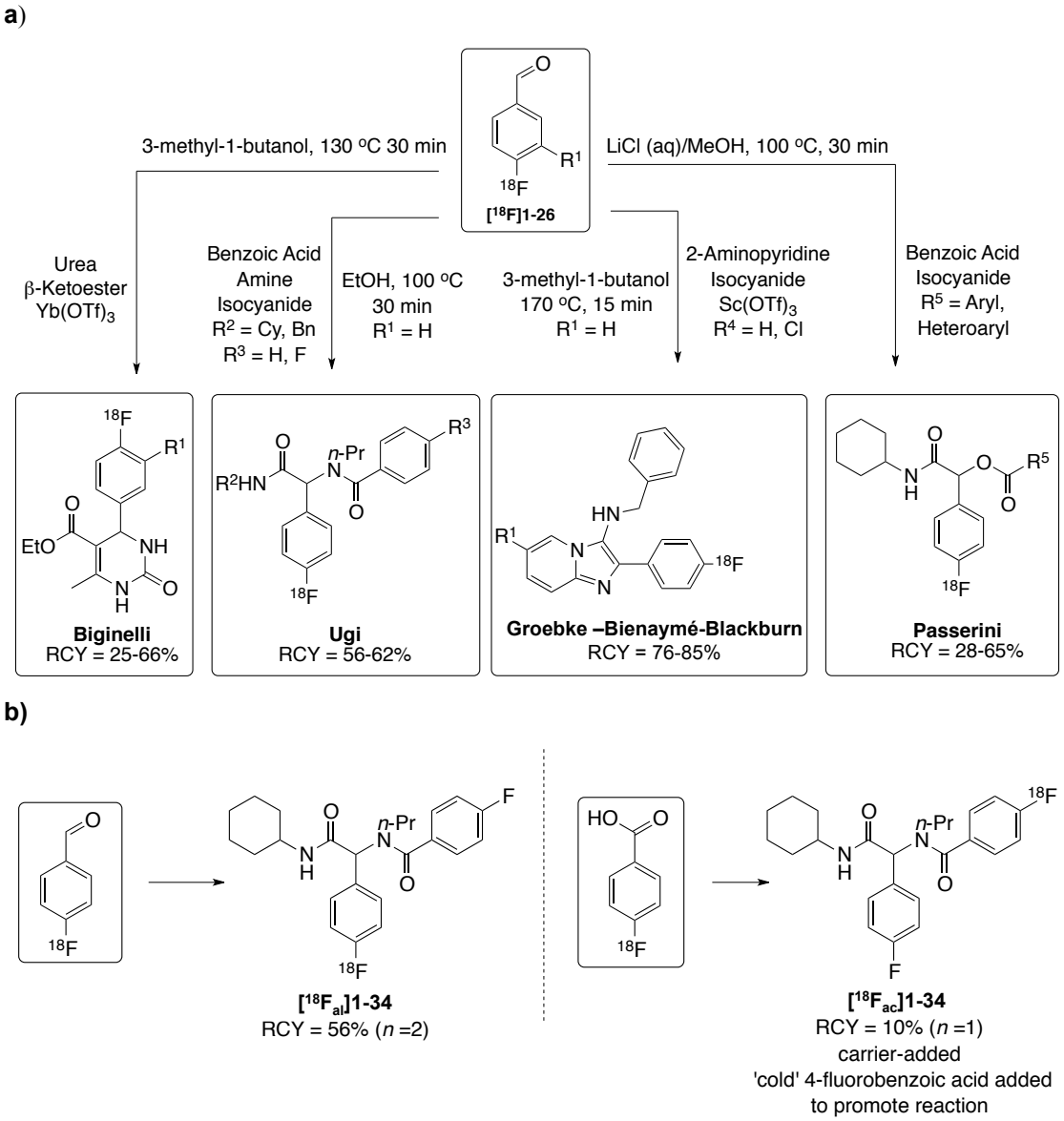
4-[^{18}F]Fluorobenzaldehyde **[^{18}F]1-25** has been used in radiochemistry as the carbonyl component in a range of base-mediated condensations with C-H acidic compounds. The radiosynthesis of 6-[^{18}F]fluoro-L-phenylalanine **[^{18}F]1-33** is an early example of

this strategy.[43] The Knoevenagel condensation between **[^{18}F]1-25** and 2-phenyl-5-oxazolone **1-30** is the key step in the synthetic sequence. Following acidic hydrolysis, HPLC purification and enantiomeric separation on a chiral stationary phase, the desired radiolabelled product **[^{18}F]1-33** was obtained in 5% RCY (non-decay corrected) (Scheme 1.14).



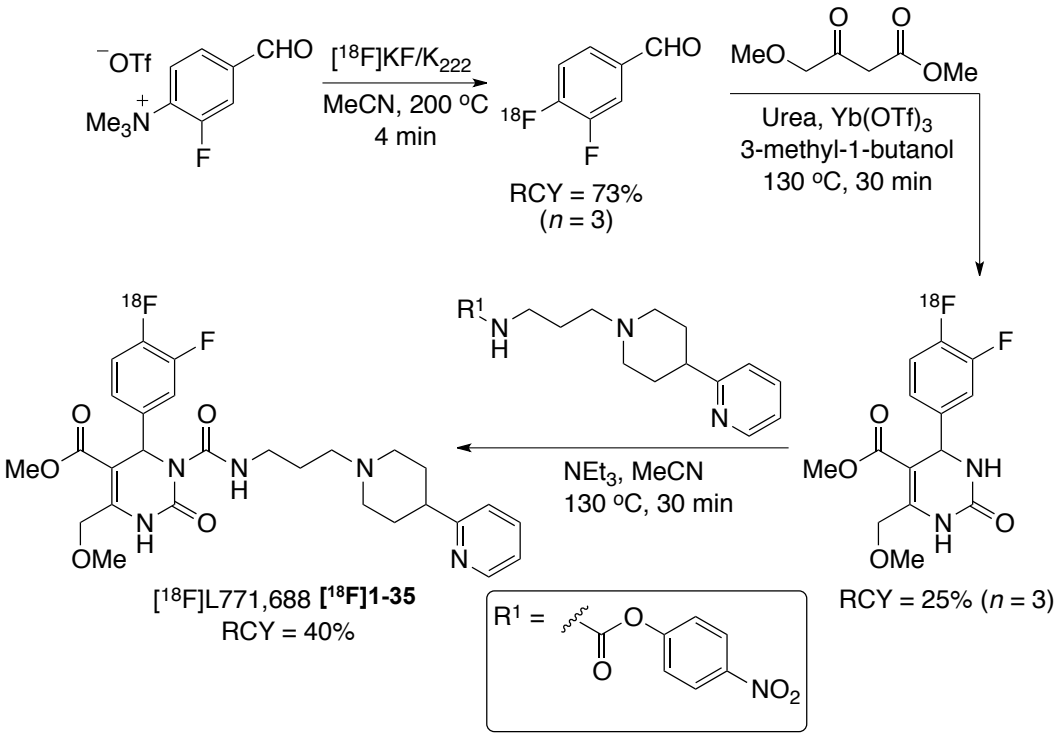
Scheme 1.14. Synthesis of 4-[^{18}F]fluoro-L-phenylalanine [^{18}F]1-33.

Gouverneur and co-workers have also demonstrated that 4-[^{18}F]fluorobenzaldehyde **[^{18}F]1-25** or 4-[^{18}F]fluorobenzoic acid can act as building blocks in a multicomponent reaction (MCR) affording complex fluoroaromatic compounds in one-pot. MCR reactions such as the Biginelli[44], Ugi[45], Passerini[46] and Groebke-Bienaymé-Blackburn[47] were explored, and a selection of peptides and heterocyclic compounds featuring electron-rich motifs were [^{18}F]radiolabelled in two steps, in moderate to good radiochemical yields, using [^{18}F]KF/K_{222} as the [^{18}F]fluoride source (Scheme 1.15a).[48] Using each class of MCR reaction, a variety of complex [^{18}F]labelled compounds could be obtained using a single set of optimised conditions. Only minor differences in the efficiency of the reactions were observed on variation of the non-radioactive components. Interestingly, the Ugi coupling product **[^{18}F]1-34** could be [^{18}F]radiolabelled using either the benzaldehyde or benzoic acid component labelled with fluorine-18, thereby affording the desired product with the label at two different positions (Scheme 1.15b).



Scheme 1.15. a) MCR reactions for the preparation of [^{18}F]Fluoroaromatics. b) Labelling of the Ugi Product [^{18}F]1-34 at two different positions using different protecting groups.

The potential of multicomponent reactions in the preparation of radiopharmaceuticals have been illustrated by the efficient synthesis of the α_{1A} adrenoceptor agonist [^{18}F]L881,668 **[^{18}F]1-35**. The key synthetic step relies on a three-component Biginelli reaction (Scheme 1.16).[49]



Scheme 1.16. Convergent radiosynthesis of [^{18}F]1-35.

1.4 Electrophilic [^{18}F]Radiolabelling

Radiochemists are often hesitant to employ electrophilic fluorination protocols in the development of new radiotracers. There are many reasons for this: (1) [^{18}F]radiolabelled products can only be delivered with low specific activity because the production of [^{18}F]F_2 require the addition of F_2 as a carrier; (2) the high reactivity of [^{18}F]F_2 requires special equipment for handling; (3) reactions utilising [^{18}F]F_2 often suffer from low selectivity and can result in a mixture of [^{18}F]labelled products and (4) the inherent disadvantage of the capped maximum RCY of 50%.

Synthetic routes avoiding the need for carrier gas have not yet been realised, but the 'post-target' protocol employed at the Turku PET Centre for the preparation of high specific activity [^{18}F]F_2 has been applied to the routine production of several radiotracers, such as 6-[^{18}F]fluoro-L-DOPA **[^{18}F]1-11**[50] and [^{18}F]EF5 **[^{18}F]1-16**[27],[51]. Dihydroxyboryl-2-[^{18}F]fluorophenylalanine **[^{18}F]1-36** was prepared for the use in boron neutron capture therapy.[52] Fluorine is arguably the most reactive element in the periodic table, as it combines with all other elements (except the lighter noble gases, He, Ne and Ar).[53] The high reactivity is caused by the very weak F-F bond (38 kcal, 159 kJ mol^{-1}) and the strong bonds fluorine form upon reaction with

other atoms (C-F, 552 kJ mol^{-1}; O-F 222 ± 17 kJ mol^{-1}; N-F 283 kJ mol^{-1}).[54] Specialist equipment is therefore required to make the use of fluorine gas practical and safe.

Despite these limitations, there is continued interest in electrophilic [^{18}F]fluorination for the preparation of electron-rich systems inaccessible or more challenging to access *via* nucleophilic fluorination. Rather than resorting to complex multi-step syntheses where the isotope is introduced early in the sequence of steps, it would be highly beneficial to employ an electrophilic strategy.

1.4.1 [^{18}F]Fluorination using [^{18}F]F_2

Conversely to the advances made with nucleophilic [^{18}F]fluoride, only a small selection of imaging agents have been prepared *via* direct radiofluorination using [^{18}F]F_2 (Table 1.5).

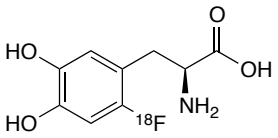
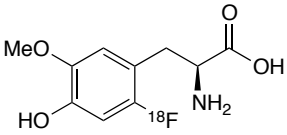
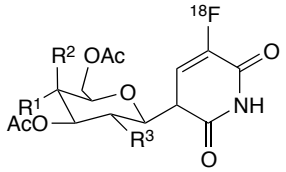
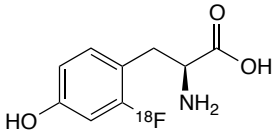
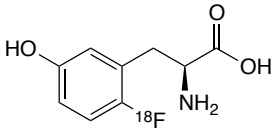
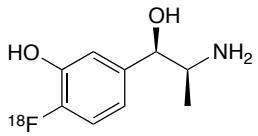
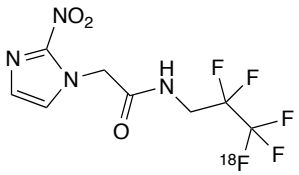
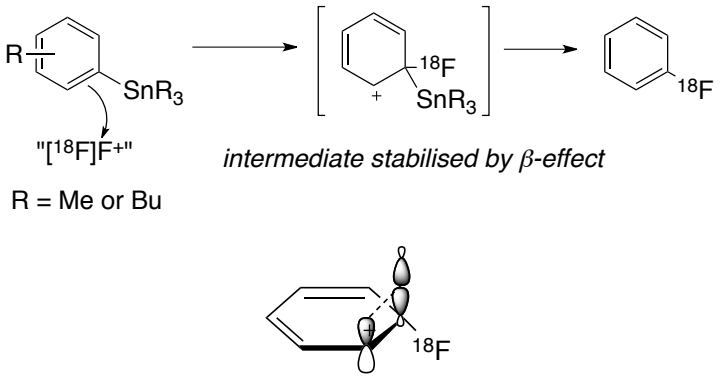
Imaging agent	Structure	Application
6-[^{18}F]Fluoro-L-DOPA **[^{18}F]1-11**[55]		Brain dopamine metabolism
3-*O*-Me-6-[^{18}F]Fluoro-L-DOPA **[^{18}F]1-37**[56]		Amino acid transport
Nucleoside analogues **[^{18}F]1-38**[57]	 R^1, R^2, R^3 = H, OAc, OH	Nucleoside transport, and therapy response
2-[^{18}F]Fluoro-L-tyrosine **[^{18}F]1-39**[58]		Protein metabolism
2-[^{18}F]Fluoro-L-*m*-tyrosine **[^{18}F]1-23**		Brain dopamine metabolism
(1*R*, 2*S*)-4-[^{18}F]Fluoro-metaraminol **[^{18}F]1-26**[59]		Cardiac sympathetic innervation
[^{18}F]EF5 **[^{18}F]1-16**[27]		Tissue hypoxia

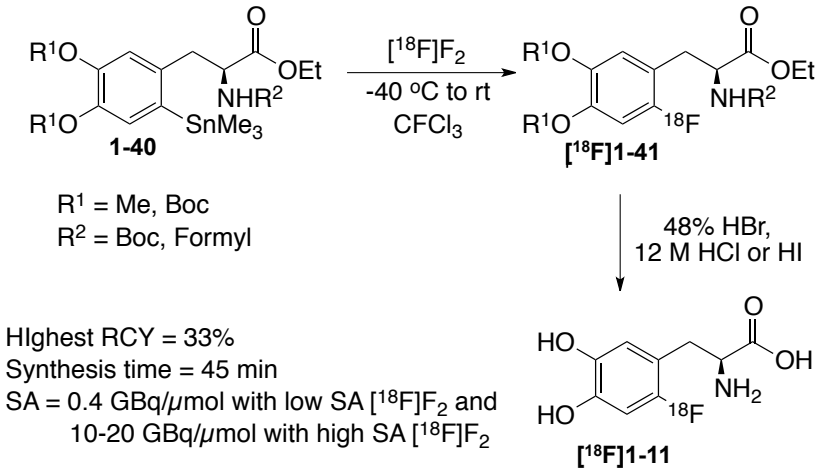
Table 1.5. Selection of PET radiotracers prepared using [^{18}F]F_2.

Apart from **[^{18}F]1-16** and **[^{18}F]1-38**, which were prepared by addition of [^{18}F]F_2 to an perfluorinated alkene and direct [^{18}F]fluorination of an alkene, respectively, these imaging agents are prepared by [^{18}F]fluorodemetallation, commonly on precursors substituted with an trialkyltin species. This transformation proceeds *via* a selective electrophilic *ipso* substitution promoted by the hyperconjugation of the carbon-tin σ-bond into the empty p-orbital of carbon atom in the *ortho* position of the cationic Wheland intermediate (Scheme 1.17).[60] The relative reactivities of compounds of the general structure $C_6H_5MEt_3$ towards electrophiles as M changes follow the trend: benzene 1, Si 5 x 10^4, Ge x 10^6, Sn 5 x 10^{11}, Pb 10^{20}.[61]



Scheme 1.17. Mechanism of [^{18}F]fluorodestannylation.

The classic example of this transformation is the preparation of 6-[^{18}F]Fluoro-L-DOPA **[^{18}F]1-11** (Scheme 1.18). A globally protected arylstannane precursor **1-40** undergoes [^{18}F]fluorodemetallation in the presence of [^{18}F]F_2 and following acidic deprotection of intermediate **[^{18}F]1-41**, 6-[^{18}F]fluoro-L-DOPA **[^{18}F]1-11** was afforded in 33% RCY.[62] Using high specific activity [^{18}F]F_2 increases the SA from 0.4 GBq/μmol to 10 GBq/μmol.[50] The preparation of **[^{18}F]1-11** will be discussed in detail in Chapter 2.



Scheme 1.18. Traditional route for the preparation of [^{18}F]1-11.[62]

1.4.2 Alternative sources of electrophilic fluorine-18

As a result of the limitations associated with [^{18}F]F_2, several attempts have been made to tame the extremely reactive nature of fluorine gas by the preparation of secondary

radiolabelling reagents. These reagents can be divided into three classes according to the nucleophile [^{18}F]fluoride reacts with: O-F, Xe-F and N-F reagents (Table 1.6).

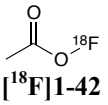
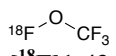
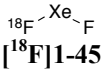
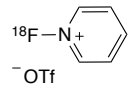
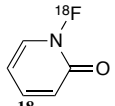
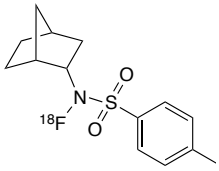
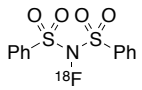
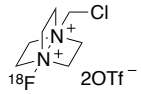
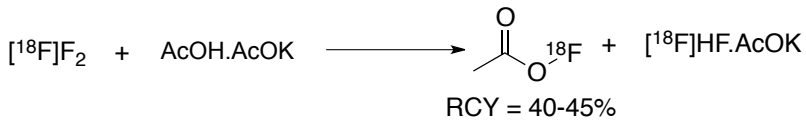
Class	Reagent	Name	Preparation	RCY (%)	Applications	Ref
O-F	 **[^{18}F]1-42**	[^{18}F]Acetyl hypofluorite	Gas-solid phase reaction with [^{18}F]F_2	40-45	[^{18}F]fluorodopamine, [^{18}F]1-24, [^{18}F]5-fluorouracil	[55]
	 **[^{18}F]1-43**	[^{18}F]Trifluoro-methyl hypofluorite	Direct reaction of CsF, F_2 and carbonyl fluoride with bound ^{18}F in target	33	-	[63]
	 **[^{18}F]1-44**	[^{18}F]Perchloryl fluoride	[^{18}F]F_2 is passed through column of $KClO_3$ maintained at 90 °C	23	2-[^{18}F]fluoroaniline, 2-[^{18}F]fluoroanisole	[64]
Xe-F	 **[^{18}F]1-45**	[^{18}F]Xenon difluoride	Direct reaction with [^{18}F]F_2 or exchange between XeF_2 and [^{18}F]F^-	< 90% highly varia-ble	[^{18}F]FDG, [^{18}F]1-24	[65]
N-F	 **[^{18}F]1-46**	[^{18}F]*N*-fluoropyridinium triflate	Direct reaction of *N*-trimethylsilyl-pyridinium trilfate with [^{18}F]F_2	46	Transfer of F-18 to sp^2C *via* grignards and other carbanions	[66]
	 **[^{18}F]1-47**	[^{18}F]*N*-fluoro-2-pyridone	Direct reaction with [^{18}F]F_2	40-49	F-18/metal exchange with organometallic compounds	[67]
	 **[^{18}F]1-48**	[^{18}F]*N*-fluoro-*N*-alkylsulfonamides	Direct reaction with [^{18}F]F_2	45	Fluorination of carbanions by fluorine transfer from nitrogen	[68]
	 **[^{18}F]1-49**	[^{18}F]NFSI	Direct reaction with [^{18}F]F_2	40	[^{18}F]Fluorination of silyl enol ethers and allylsilanes	[69]
	 **[^{18}F]1-50**	[^{18}F]Selectfluor *bis*(triflate)	Direct reaction with [^{18}F]F_2		[^{18}F]Fluorination of silyl enol ethers and arylstannanes	[70]

Table 1.6. Alternative electrophilic fluorine-18 sources.

1.4.2.1 [^{18}F]Acetyl hypofluorite

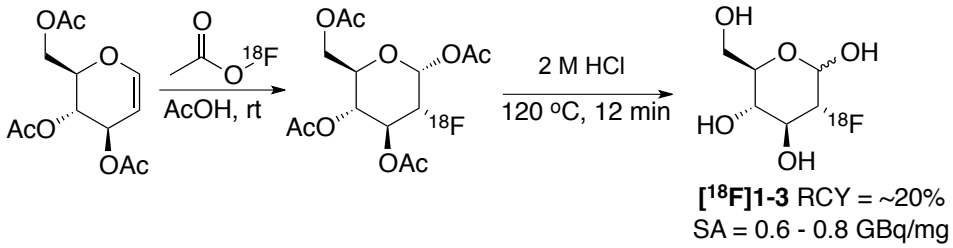
The secondary electrophilic reagent [^{18}F]acetyl hypofluorite **[^{18}F]1-42** is most widely used in radiochemistry after [^{18}F]F_2, as it has a lower reactivity profile and allow for the selective introduction of fluorine-18 into a wide range of compounds. Its

preparation relies on a gas-solid phase reaction.[55],[71] [^{18}F]F_2 is eluted through a column containing an alkali metal/acetic acid complex. The afforded reagent **[^{18}F]1-42** is trapped on the column but can be released by elution with an aqueous wash (Scheme 1.19).



Scheme 1.19. Preparation of [^{18}F]acetyl hypofluorite.[72]

[^{18}F]Acetyl hypofluorite has been used to prepare 6-[^{18}F]fluoro-L-DOPA **[^{18}F]1-11** (See Chapter 2) and other [^{18}F]labelled aromatics using the selective fluorodemetallation approach[73],[74], but was also used for the early routine production of [^{18}F]FDG (Scheme 1.20).[75]

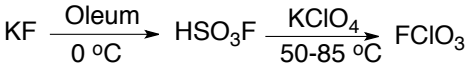


Scheme 1.20. Preparation of [^{18}F]FDG using [^{18}F]acetyl hypofluorite.[75]

1.4.2.2 [^{18}F]Perchloryl fluoride

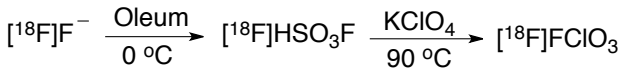
Perchloryl fluoride was the first electrophilic fluorinating reagent shown to have industrial relevance. In the 1960s it was used prepare fluorinated steroids.[76] However, it is a challenging reagent to employ in selective fluorination reactions due to its high oxidation potential. This results in a constant threat of explosion upon contact with organic solvents. In particular, if this reagent is allowed to come into contact with alcohols, extremely shock-sensitive alkyl perchlorates are formed. Its high reactivity arises from the fact that the fluorine atom is bound to a chlorine atom in its highest oxidation state. These limitations prevent the widespread use of this reagent in organic synthesis and radiochemistry, and it was quickly abandoned in favour of reagents that were more selective and easier to handle.

Interestingly, 'cold' perchloryl fluoride **1-52** is the only electrophilic fluorinating reagent to be successfully prepared from fluoride. The product was obtained by collecting the gas in a trap cooled by liquid nitrogen (Scheme 1.21).[77]



Scheme 1.21. Preparation of 'cold' perchloryl fluoride.

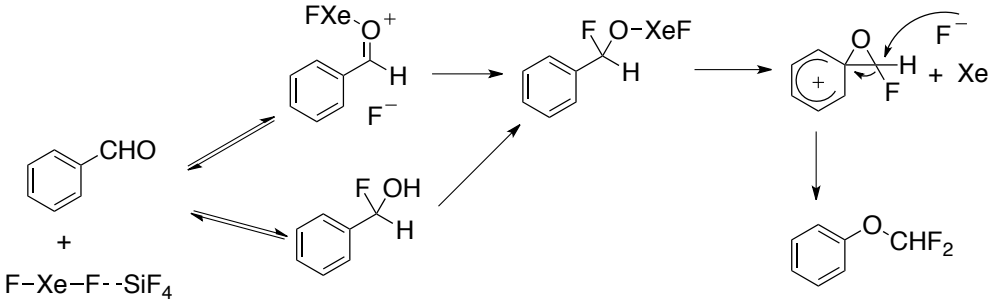
Attempts have been made to modify this protocol for the preparation of a radiolabelled analogue.[78] Non carrier added **[^{18}F]1-45** was synthesised upon the addition of superacidic media, e.g. oleum (fuming sulfuric acid), to either [^{18}F]HF or [^{18}F]KF in the presence of anhydrous $HClO_4$ (Scheme 1.22.). Unfortunately, this protocol suffered from poor reducibility and low RCYs (1 – 6%), illustrating the need for an alternative method for the production of electrophilic sources of fluorine-18 from [^{18}F]fluoride.



Scheme 1.22. Preparation of [^{18}F]1-45 from [^{18}F]fluoride.

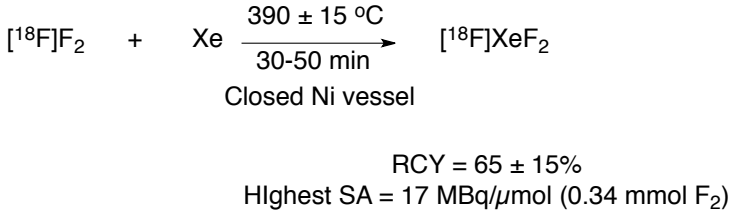
1.4.2.3 [^{18}F]Xenon Difluoride

Xenon difluoride is a powerful fluorinating reagent, but as a solid is easy to handle.[79] Another benefit is that it can be used in combination with solvents that are relatively inert to oxidation, such as MeCN and CH_2Cl_2. This reagent enables selective fluorination of arenes[80], Hunsdiecker-like fluorodecarboxylation of carboxylic acids[81] (see Chapter 4) and fluorinative rearrangements of carbonyl compounds to form difluoromethyl ethers[82],[83] (Scheme 1.23).



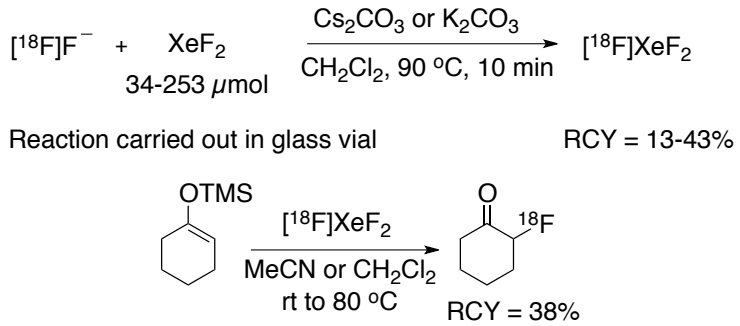
Scheme 1.23. Fluorinative rearrangements of carbonyl compounds to form difluoromethyl ethers.[82],[83]

In radiochemistry, [^{18}F]XeF_2 has been used in the [^{18}F]radiolabelling of [^{18}F]FDG[84] and 6-[^{18}F]fluoro-L-DOPA **[^{18}F]1-11**[85] (see Chapter 2). Its electrophilic preparation relies on the direct reaction between [^{18}F]F_2 and xenon under high pressure and high temperature (Scheme 1.24). The solid reagent is isolated by vacuum sublimation.



Scheme 1.24. Preparation of [^{18}F]1-46 from the reaction between Xe and [^{18}F]F_2.

Recently, a nucleophilic route was also devised for the preparation of **[^{18}F]1-45**, by the exchange between XeF_2 and [^{18}F]fluoride (Scheme 1.25).[65] The yield was found to increase when larger amounts of 'cold' XeF_2 were used. The reagent was also found to successfully radiolabel model substrates.[86]



Scheme 1.25. Nucleophilic preparation of [^{18}F]1-45.

In order to ensure an efficient exchange reaction, several aspects of the experimental design must be optimised, such as the vessel material, solvent and cation used upon the production of [^{18}F]XeF_2. Glass vials aid in the ionization of XeF_2 and afforded the reagent in higher RCY compared to polypropylene vials. The use of potassium or caesium cations in combination with Kryptofix$_{222}$ in the production of [^{18}F]fluoride, also promoted the ionisation of XeF_2 by acting as a Lewis acid. In terms of solvent, the reaction was found to be most efficient in CH_2Cl_2, as the reactivity of the cation/cryptand/[^{18}F]fluoride complex was higher than in MeCN. The preparation of **[^{18}F]1-45** could also be carried out in a microreactor, where smaller amounts of XeF_2 (~ 4 μmol) could be used compared to the vial strategy. This had a positive effect on the specific activity obtained (< 1 GBq/μmol).[86]

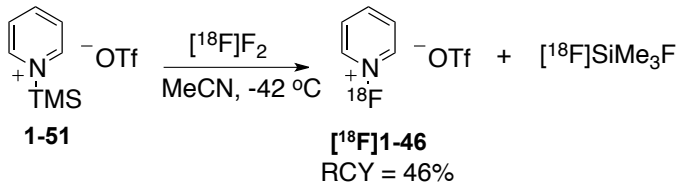
1.4.2.4 N-^{18}F reagents

Electrophilic N-F fluorinating reagents have become important in organic synthesis for the preparation of fluorinated molecules. Interest in this class of reagents began in the 1980s and compounds such as *N*-fluorobis(trifluoromethanesulfonyl)imide[87], *N*-fluoro-N-alkyl-sulfonamides[88], dihydro-*N*-fluoro-2-pyridone[89] and *N*-fluoropyridinium triflate[90] were found to be stable, easy-to-handle, solid fluorinating reagents. Following the preparation of *N*-fluorodibenzenesulfonamide (NFSI) [91] and Selectfluor™[92] in the early 1990s, less attention has been devoted to the original N-F reagents. However, the use of pyridine based N-F reagents has recently flourished in the field of transition metal-mediated fluorinations (see Chapter 3). Commonly, these fluorinating reagents are normally prepared by the direct fluorination of a neutral base [93] or salt[94] with fluorine gas.

1.4.2.4.1 N-^{18}F reagents prepared between 1980-1990.

In contrast, there are only limited examples of the applications of N-F reagents to [^{18}F]radiochemistry. *N*-[^{18}F]fluoropyridinium triflate **[^{18}F]1-46**[66], [^{18}F]-1-fluoro-2-pyridone **[^{18}F]1-47**[67] and a selection of [^{18}F]-*N*-fluoro-*N*-alkyl-sulfonamides **[^{18}F]1-48**[68] have been prepared and investigated under radiochemical conditions.

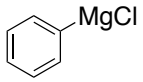
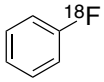
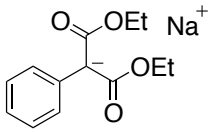
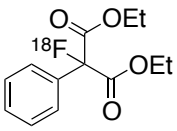
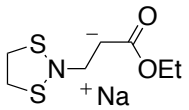
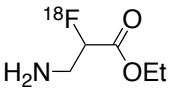
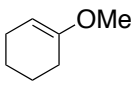
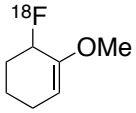
The preparation of *N*-[^{18}F]fluoropyridinium triflate **[^{18}F]1-46** was reported in 1988 by Oberdorfer and co-workers, by direct [^{18}F]fluorination of *N*-trimethylsilylpyridinium triflate with [^{18}F]F_2 (Scheme 1.26).[66]



Scheme 1.26. Preparation of [^{18}F]1-46.[66]

The [^{18}F]radiolabelled reagent could not be identified by HPLC or TLC and instead the decayed reaction mixture was analysed by ^{19}F NMR and MS to confirm the preparation of **[^{18}F]1-46**. In order to prevent decomposition of the reagent, it was imperative to remove all traces of free pyridine after the preparation of the starting material **1-51**. Furthermore, it was established that the reaction required almost equimolar amounts of the 'cold' reagents, preferably a ratio of 0.75-0.9 of starting material and F_2, which greatly impacts the specific activity of the reagent.

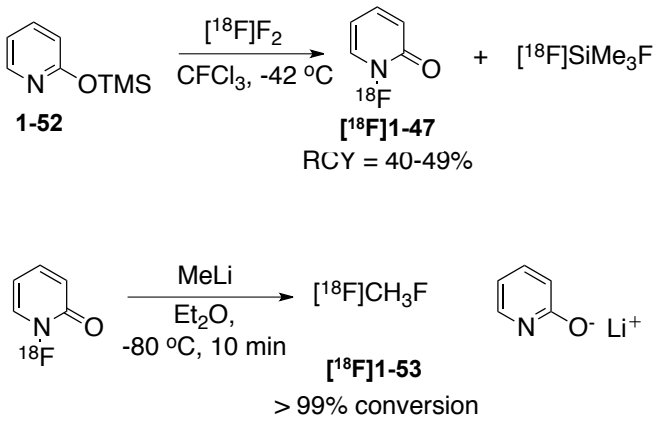
The [^{18}F]reagent was shown to successfully radiolabel sp^2-carbons in a range of compounds within a radiochemical time scale and under mild reaction conditions (Table 1.7). Further studies into the preparation and applications of this reagent have not been reported.

Compound[a]	Solvent	Reaction		Product	Yield[b] (%)
		°C	min		
	THF	5	10		62
$CH_3(CH_2)_6MgCl$	Et_2O	5	15	$CH_3(CH_2)_6{}^{18}F$	78
MeLi	Et_2O	-78	-	No reaction	
	THF	0	10		58*
	THF	25	60		23*
	CH_2Cl_2	reflux	40		67

[a] Equimolar amounts of reagents; 0.7 mM of *N*-fluoropyridinium triflate spiked with 1.85 x 10^8 Bq of the labelled compound; [b] Determined by HPLC or, when indicated by an asterix; ^{19}F NMR.

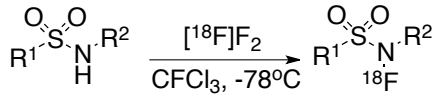
Table 1.7. Reaction of [^{18}F]1-46 with a selection of substrates.

Oberdorfer also reported the [^{18}F]radiolabelling of 1-[^{18}F]fluoro-2-pyridone **[^{18}F]1-47** by fluorination of the 2-(trimethylsiloxy)pyridine **1-52** with [^{18}F]F_2 (Scheme 1.27).[67] The reactivity of this reagent has only been studied in the reaction with methyl lithium and the desired [^{18}F]fluoromethane **[^{18}F]1-53** was obtained with virtually quantitative conversion.



Scheme 1.27. Preparation of [^{18}F]1-47 and its reaction with MeLi.

The [^{18}F]-*N*-fluoro-*N*-alkyl-sulfonamides **[^{18}F]1-48a-h**[68] reported by Satyamurthy and co-workers were also prepared by direct [^{18}F]fluorination of the free *N*-alkylsulfonamides with [^{18}F]F_2 in good yields (Table 1.8).



1-54a-h **[18F]1-48a-h**

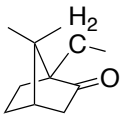
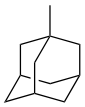
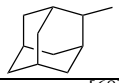
Compound	R^1	R^2	RCY (%)
[18F]1-48a	4-$CH_3C_6H_4$	CH_3	42
[18F]1-48b	4-$CH_3C_6H_4$	$CH_2C(CH_3)_3$	25
[18F]1-48c	4-$CH_3C_6H_4$	$C(CH_3)_2CH_2CH_3$	23
[18F]1-48d	4-$CH_3C_6H_4$		45
[18F]1-48e	4-$CH_3C_6H_4$		43
[18F]1-48f		$C(CH_3)_3$	21
[18F]1-48g	CH_3		13
[18F]1-48h	CH_3		23

Table 1.8. Preparation of [18F]1-48a-h.[68]

[18F]-*N*-fluoro-*N*-endo-norbornyl(*p*-tolyl)sulfonamide **[18F]1-48d** was found to be the highest yielding reagent for the [18F]radiolabelling of organometallic compounds. Phenylmagnesium bromide and 1-naphthylmagnesium bromide underwent [18F]fluorination in 58% and 61% RCY, respectively.

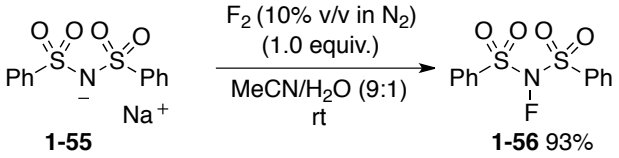
These three N-18F reagents have been shown to be potentially promising reagents for electrophilic [18F]radiolabelling reaction, but beyond their initial preparation no further applications have been investigated.

1.4.2.4.2 [18F]NFSI and [18F]Selectfluor *bis*(triflate).

Gouverneur and co-workers have shown a continued interest in developing reactions for selective electrophilic fluorinations and saw the potential for further explorations in this field of [18F]fluorination. Currently, the two most popular N-F reagents are NFSI and Selectfluor™, and it was postulated that preparation of these reagents under radiochemical conditions would address this gap in the transfer of synthetic chemistry to radiolabelling.

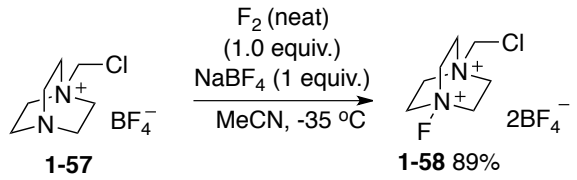
Preparation and Reactivity of NFSI and Selectfluor™

For NFSI **1-56**, the sodium salt of dibenzenesulfonimide **1-55** is used as the precursor. This species is highly insoluble in organic solvents and was therefore dissolved in a 10% mixture of H_2O in MeCN. Following fluorination with 1 equivalent of F_2 at room temperature, **1-56** was obtained in 93% yield (Scheme 1.28).[69]



Scheme 1.28. Preparation of NFSI.

The Selectfluor precursor **1-57** was directly fluorinated using neat F_2 in the presence of 1 equivalent of sodium tetrafluoroborate, affording the desired reagent **1-58** in 89% yield (Scheme 1.29).[94]



Scheme 1.29. Preparation of Selectfluor™.

The reactivity of N-F reagents have been assessed based on their success in particular fluorination reactions, but also the reduction potential, i.e. how easily the fluorine atom is transferred in the reaction and the reagent itself becomes reduced, will provide a measure of reactivity. In an electrochemical studies by Gilicinski the reduction potentials of NFSI and Selectfluor were measured using cyclic voltammetry.[95] NFSI is a less reactive electrophilic reagent as seen by its reduction potential (-0.78 V *vs*. SCE) compared to Selectfluor (-0.04 V *vs*. SCE).

NFSI is capable of introducing fluorine into neutral and carbanionic nucleophiles (Table 1.9).

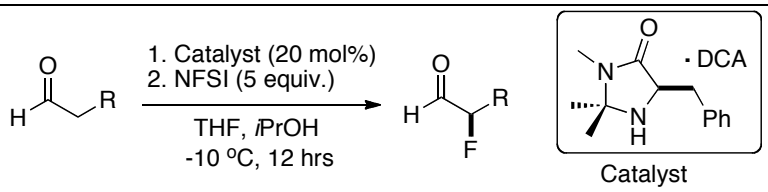
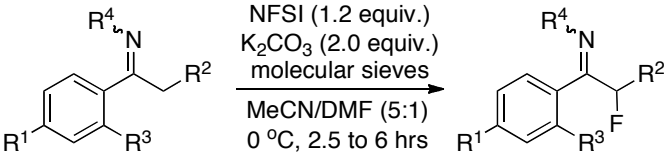
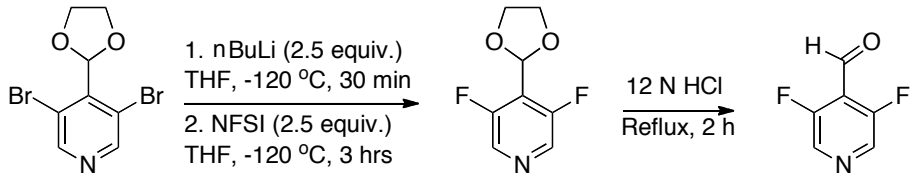
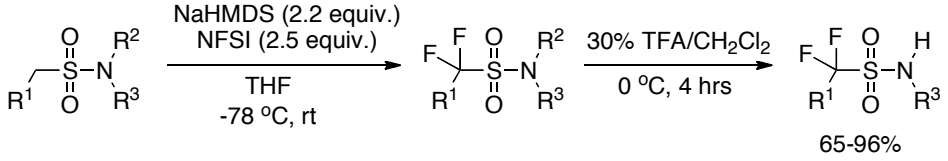
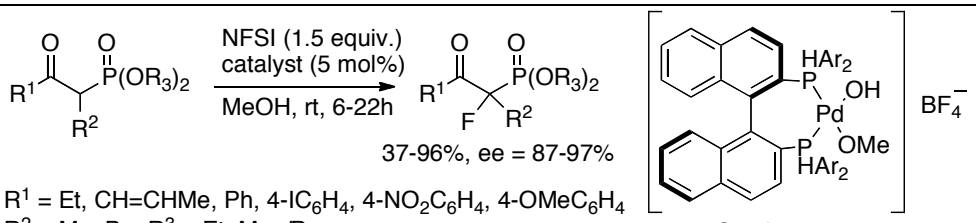
Reaction	Ref
 9 examples, R = alkyl, phenyl, benzyl yield = 54-96, ee = 91-99%	[96]
 R^1 = H or Cl, R^2 = H or alkyl, R^3 = H or alkyl, R^4 = alkyl 7 examples 37-92%	[97]
 76% 90%	[98]
 65-96% R^1 = Ph, 4-BrC_6H_4, 4-IC_6H_4, R^2 = DMB R^3 = Ph, Me, H	[99]
 37-96%, ee = 87-97% R^1 = Et, CH=CHMe, Ph, 4-IC_6H_4, 4-$NO_2C_6H_4$, 4-$OMeC_6H_4$ R^2 = Me, Bn; R^3 = Et, Me, *i*Pr	[100]

Table 1.9. Reactivity of NFSI.

A vast multitude of literature detailing the reactivity of Selectfluor has been reported, illustrating its capability of providing access to a vast range of fluorinated building blocks. This field has been extensively reviewed[92],[101] and hence only a selection will be highlighted here. Selectfluor is able to fluorinate silyl enol ethers, alkenes and enolates. Furthermore, arenes activated with electron-donating groups (*+I, +M*) groups, can be accessed (Table 1.10).

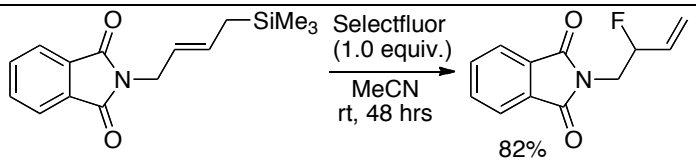
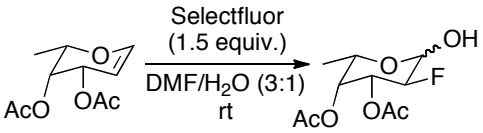
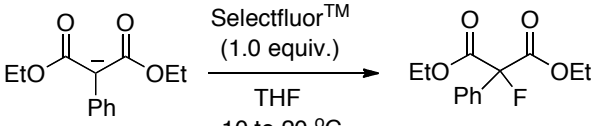
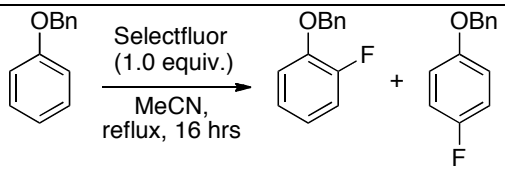
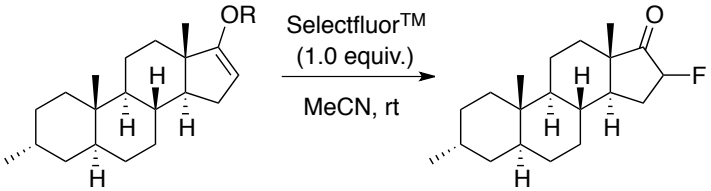
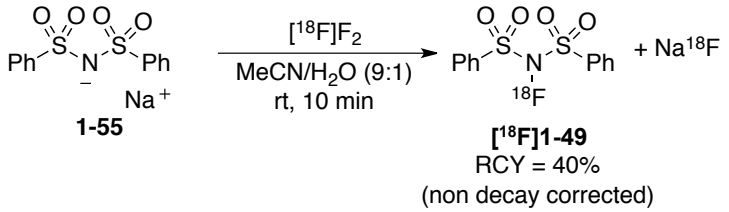
Reaction	Ref
	[102]
	[103]
	[104]
	[104]
	[105]

Table 1.10. Reactivity of Selectfluor™.

The applications of Selectfluor are much more extensive than described herein, but the examples give a good indication of the versatility of this reagent.

Preparation of [^{18}F]NFSI

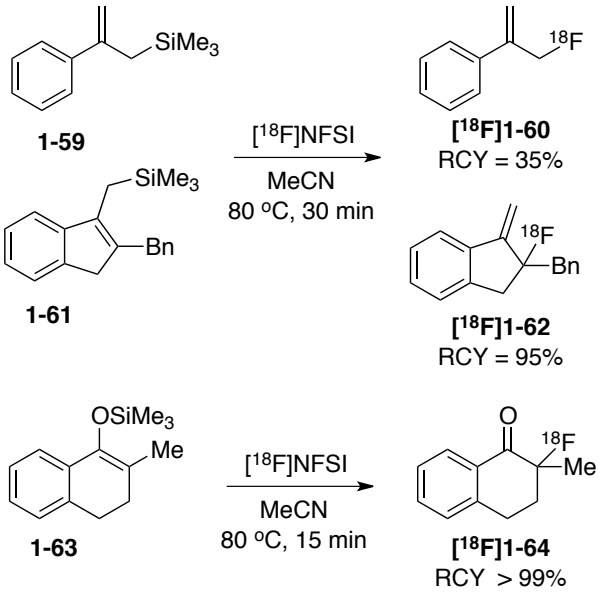
[^{18}F]F_2 is accessible *via* several nuclear reactions, so adaptation of the 'cold' methodology for the preparation of N-F reagents for radiochemistry is viable. NFSI was prepared using analogous conditions to 'cold' mode. The [^{18}F]F_2 was prepared *via* the ^{18}O(*p,n*)^{18}F nuclear using enriched [^{18}O]O_2 with 0.2% F_2 added (Scheme 1.30).[69]



Scheme 1.30. Preparation of [^{18}F]NFSI [^{18}F]1-49.[69]

NFSI contains a UV-active chromophore so is easily identified by HPLC. This allows for identification of reagent **[^{18}F]1-49** upon co-elution with the 'cold' NFSI reference compound. **[^{18}F]1-49** was obtained in 40% RCY (non decay corrected) and only traces of [^{18}F]F_2 were recorded after the labelling reaction, indicating almost maximum theoretical formation of [^{18}F]NFSI.[69]

The stock of **[^{18}F]1-49** in a mixture of 10% H_2O in MeCN was subjected to azeotropic drying to remove all traces of H_2O, before anhydrous MeCN was added and aliquots the stock of **[^{18}F]1-49** were used in labelling reactions (Scheme 1.31).

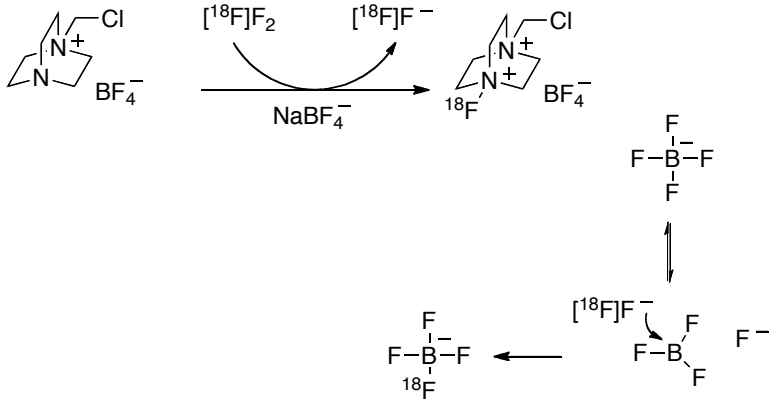


Scheme 1.31. Radiolabelling with [^{18}F]1-50.[69]

After heating at 80 °C for 30 minutes, allylsilanes **1-59** and **1-61** were successfully radiolabelled in 35% and 95% RCY, respectively. Furthermore, the [^{18}F]fluorodesilylation of the more reactive silyl enol ether **1-63** was amenable to a shorter reaction time of 15 minutes.

Preparation and reactivity of [^{18}F]Selectfluor *bis*(triflate)

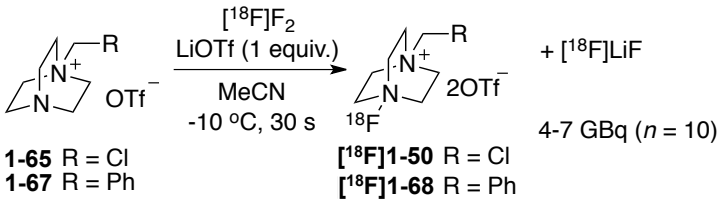
With a view to designing a suitable [^{18}F]Selectfluor reagent, the nature of the counterion must be considered. The tetrafluoroborate salt in the commercially available Selectfluor^{TM} **1-58** introduces the possibility of isotopic exchange between ^{18}F and ^{19}F (Scheme 1.32). This would lead to a significant decrease in the specific activity.



Scheme 1.32. Proposed mechanism for isotopic exchange.

Instead it was deemed pertinent to prepare [^{18}F]Selectfluor *bis*(triflate) **[^{18}F]1-50**. Studies have shown very small differences in reactivity between **1-58** and Selectfluor *bis*(triflate) **1-66**, with any differences favouring the triflate analogue.[104] Isotopic exchange reaction between the CF_3 of the triflate anion and [^{18}F]fluoride cannot be ruled out as isotopic substitution reactions have been observed on substrates containing fluorine atoms α to the leaving group.[106] However, S_N2 nucleophilic substitution on α-fluorinated substrates is discouraged by the increased energy barrier of the process due to the electrostatic repulsion between the fluorine atoms and the incoming nucleophile compared to the non-fluorinated analogue.[107] This trend will be further explained in Chapter 4, in the context of trifluoromethylation.

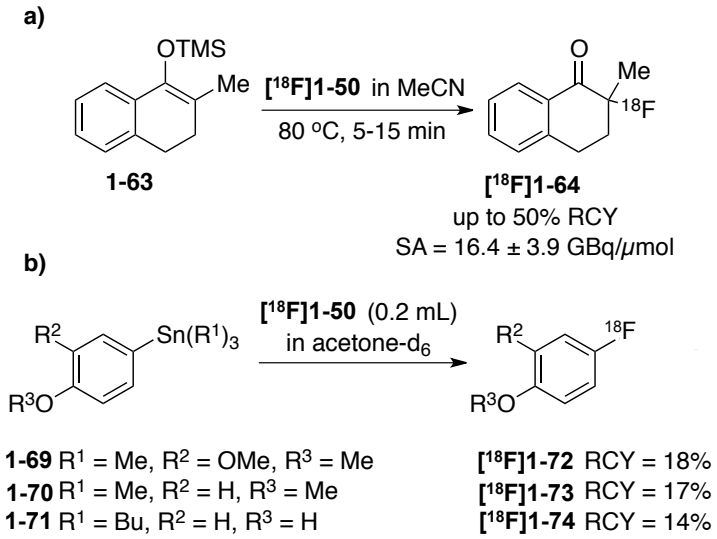
The radiolabelling of Selectfluor precursor **1-65** was achieved in the presence of high specific activity (> 1 GBq/μmol) [^{18}F]F_2 and 1 equivalent of lithium triflate as the counter ion. After 30 second at -10 ^{o}C, the stock solution of **[^{18}F]1-50** in acetonitrile was ready for use (Scheme 1.33).[70]



Scheme 1.33. Preparation of [^{18}F]1-50 and [^{18}F]1-68.[70]

The analysis of **[^{18}F]1-50** proved challenging. HPLC is the most common tool used for analysis and purification in radiochemistry, but as a non-UV active and doubly charged species, finding suitable HPLC columns and eluents for **[^{18}F]1-50** was not trivial. To aid characterisation, [^{18}F]Benzylselectfluor *bis*(triflate) **[^{18}F]1-68** was prepared. The chloromethyl derivative **[^{18}F]1-50** could be identified by radio-HPLC, but the reagent co-elutes with [^{18}F]fluoride. Further analysis was carried out on the benzyl substituted **[^{18}F]1-68**. Radio-HPLC showed that **[^{18}F]1-68** co-eluted with the 'cold' reference sample. In addition, the decayed sample of **[^{18}F]1-68** was analysed by ^{19}F NMR and the N-F peak was observed at +52.6 ppm ($CFCl_3$ = internal standard) and the triflate salt was observed at -76.6 ppm. This was in agreement with the data for the 'cold' reagent.[70]

Further evidence for the formation of **[^{18}F]1-50** was afforded by the successful [^{18}F]fluorination of a silyl enol ether **1-63** (Scheme 1.34a) and electron-rich arenes in a silver-mediated fluorination reaction (Scheme 1.34b).[70],[108]



Scheme 1.34. [^{18}F]fluorination of a silyl enol ether and electron-rich arylstannanes using [^{18}F]Selectfluor *bis*(triflate).[70]

[^{18}F]Fluoro-2-methyl tetralone **[^{18}F]1-64** could be obtained in excellent RCY in the presence of [^{18}F]Selectfluor *bis*(triflate)under similar conditions employed with [^{18}F]NFSI. Using high specific activity [^{18}F]F_2, the SA achieved was increased to ~16 GBq/μmol (Scheme 1.44a). Pleasingly, in the presence of silver triflate, three electron-rich arenes were successfully radiolabelled by [^{18}F]Selectfluor *bis*(triflate).[70] 4-[^{18}F]fluoroveratrole **[^{18}F]1-72** was obtained in 18% RCY following semi-preparative purification by HPLC, while the less electron rich substrate **1-70** was [^{18}F]fluorinated in 17% RCY. Finally, 4-[^{18}F]fluorophenol **[^{18}F]1-74** was also accessible by [^{18}F]fluorodestannylation in 14% RCY. This transformation was unsuccessful when [^{18}F]Selectfluor *bis*(triflate) was replaced by [^{18}F]NFSI, both highlighting the value of developing a collection of [^{18}F]N-F reagents with tailored reactivity and emphasising the need to further study their reactivity in new radiochemical transformations.

1.5 Outline of this thesis

As mentioned in this Chapter, the main electrophilic source used in radiolabelling is $[^{18}F]F_2$, which is highly reactive, toxic and requires specialist equipment for safe handling. The Gouverneur group has initiated a research programme focused on the preparation of new stable and easy-to-handle [^{18}F]labelled N-^{18}F reagents with tailored reactivity. In the development of [^{18}F]radiolabelling reactions it would be extremely valuable to develop a library of selective N-^{18}F reagents possessing reactivity tailored to the desired chemical transformation.

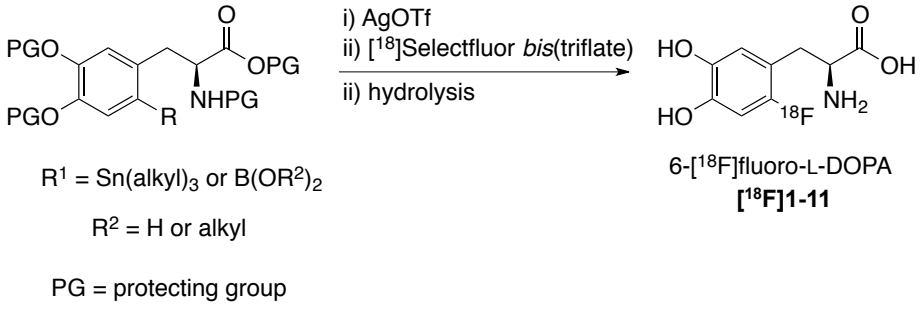
The aim of this thesis is to further assess the scope of these electrophilic N-^{18}F reagents in new transformations for the construction of C-^{18}F bonds:

- Chapter 2: The recently developed N-^{18}F reagents [^{18}F]Selectfluor *bis*(triflate) and [^{18}F]NFSI have so far only been explored in the radiolabelling of simple electron-rich arenes. Their value and application in the preparation of a complex imaging agent will therefore be investigated.
- Chapter 3: Recently, the interest in the preparation of C-F bonds by transition metal catalysis has flourished, but application in radiochemistry is still limited. The development of new palladium-mediated [^{18}F]fluorination methodologies, relying on the use of N-^{18}F reagents, will be investigated as this will offer an alternative strategy for the preparation radiolabelled arenes.
- Chapter 4: Trifluoromethylated compounds have been found to be important motifs in pharmaceuticals and agrochemicals. PET is an important tool for drug discovery and development, but the development of general and robust strategies for [^{18}F]trifluoromethylation have proved challenging. It was therefore decided to investigate the potential of N-^{18}F reagents as the source of fluorine-18 in the preparation of [^{18}F]trifluoromethylated arenes *via* a fluorodecarboxylation approach.

Chapter 2: Application of [^{18}F]Selectfluor *bis*(triflate) in the silver-mediated synthesis of 6-[^{18}F]fluoro-L-DOPA.

2.1 Aims

With the success of the N-^{18}F reagents [^{18}F]NFSI and [^{18}F]Selectfluor *bis*(triflate) in the [^{18}F]fluorination of silyl enol ethers and allylsilanes, and silver-mediated [^{18}F]radiolabelling of electron-rich arenes, it was decided to further probe the application of [^{18}F]Selectfluor *bis*(triflate) in the preparation of an established PET imaging agent. The amino acid-based tracer 6-[^{18}F]fluoro-L-DOPA was selected as a suitable target for this purpose. In the following introduction, the mode of action and applications of 6-[^{18}F]fluoro-L-DOPA will be highlighted, in addition to the electrophilic and nucleophilic routes reported for its preparation. Furthermore, the recent silver-mediated approaches employed in the fluorination of electron-rich arenes will be discussed in detail. In the results and discussion, the silver-mediated fluorination of arylstannane and arylboronic acid derivative model substrates will be carried out to validate the strategy, before L-DOPA precursors are explored in the fluorination reaction. Under radiochemical conditions, the arylstannnane L-DOPA precursor will first be investigated to compare this strategy with the current electrophilic route for the preparation of 6-[^{18}F]fluoro-L-DOPA. Secondly, a novel arylboronic acid derivative L-DOPA precursor will be studied.



Scheme 2.1. Aim of this chapter.

2.2 Introduction to 6-[^{18}F]fluoro-L-DOPA

Since the 1980s, 6-[^{18}F]fluoro-L-DOPA **[^{18}F]1-11** was reported as a tracer for the imaging of pre-synaptic dopaminergic function.[109] Much effort has since been focused on developing fast, simple and automated synthetic routes for the preparation of this imaging agent. 6-[^{18}F]Fluoro-L-DOPA was traditionally used for the imaging of Parkinson's Disease (PD),[110] but its use has extended into the fields of oncology[111] and congenital disorders.[112]

2.2.1 Dopamine and the presynaptic dopaminergic system

Dopamine is one of many neurotransmitters that carry signals from one neuron to a target cell across a synapse.[113] These transmitters are produced and stored in presynaptic vesicles called vesicular monoamine transporters (VMATs) until they are released in response to an electrical signal. This subsequently induces postsynaptic effects in the target cells, followed by rapid inactivation of the neurotransmitter in question by reuptake into the presynaptic terminal by the high-affinity dopamine transporter (DAT) or low-affinity transporter plasma membrane monoamine transporter (PMAT) (Figure 2.1).[114]

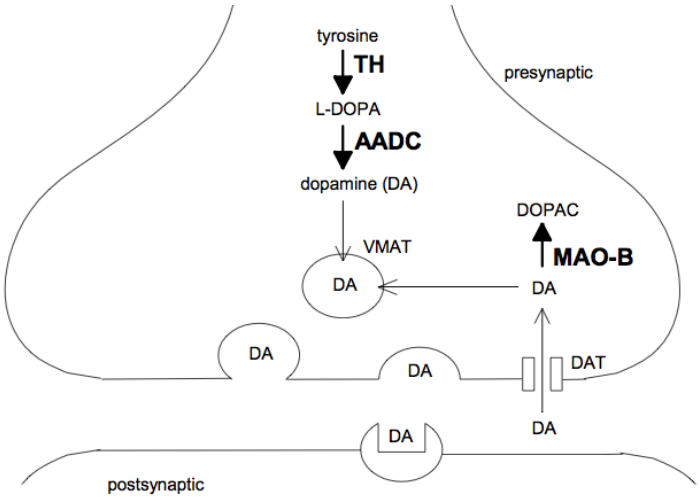
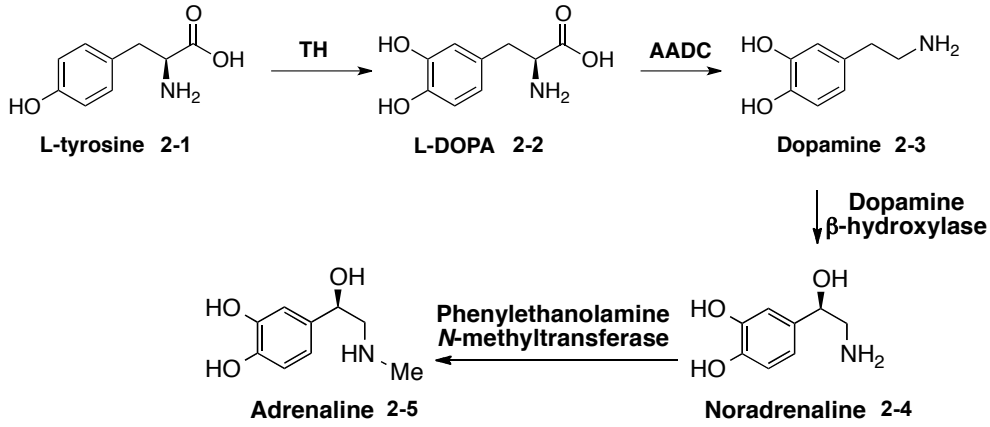


Figure 2.1. The dopaminergic presynaptic terminal.[115]

Dopamine is produced in a two-step process by aromatic hydroxylation of tyrosine by tyrosine hydroxylase (TH) **2-1** to form L-3,4-dihydroxyphenylalanine (L-DOPA) **2-2**. The following decarboxylation by aromatic L-amino acid decarboxylase (AADC) yields dopamine **2-3**, which can be further converted to noradrenaline **2-4** and finally

adrenaline **2-5** (Scheme 2.1). AADC is present both inside and outside of the CNS, and in the treatment of PD AADC inhibitors such as carbidopa are administered to prevent metabolism of L-DOPA peripherally before it is able to cross the blood brain barrier (BBB) *via* amino acid transporters. This increases the bioavailability of L-DOPA in the brain and may relieve symptoms temporarily.[116]



Scheme 2.1. Biosynthesis of adrenaline.

The four main dopaminergic pathways that transport the neutrotransmitter within the CNS are illustrated in figure 2.2.[114]

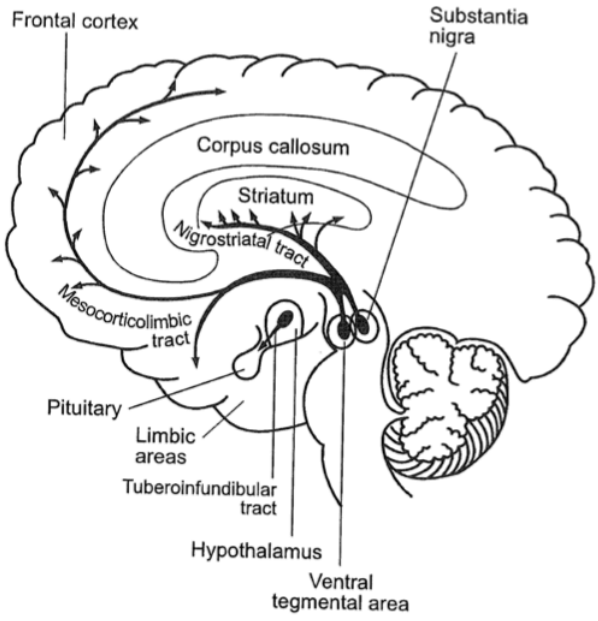


Figure 2.2. Illustration of the main dopaminergic pathways in the brain (Figure modified from [114], used with permission from Science.

- **Tuberoinfundibular pathway:** connects the hypothalamus to the pituitary gland.
- **Nigrostriatal pathway:** runs from the substantia nigra to the neostriatum.
- The **mesocortical** and **mesolimbic** pathways both originate in the ventral tegmental area and project to areas of the frontal cortex, the septum and the olfactory bulb, or to the nucleus accumbens *via* the amygdala and hippocampus, respectively.

Abnormal activities in the mesocortical and mesolimbic systems are known to be associated with psychiatric diseases, and the loss of dopaminergic neurons in the nigrastriatal pathway is known to be the main cause of Parkinson's Disease. Dopaminergic synapses also play a role in peripheral neuroendocrine tumours and pancreatic ß-cells.[114]

PET has been a useful tool in investigating overall dopaminergic function by imaging L-DOPA synthesis, vesicle transport and transport from the synaptic cleft. A wide variety of molecular imaging agents have been designed for this purpose and they can be divided into three classes based on their target (Figure 2.3).

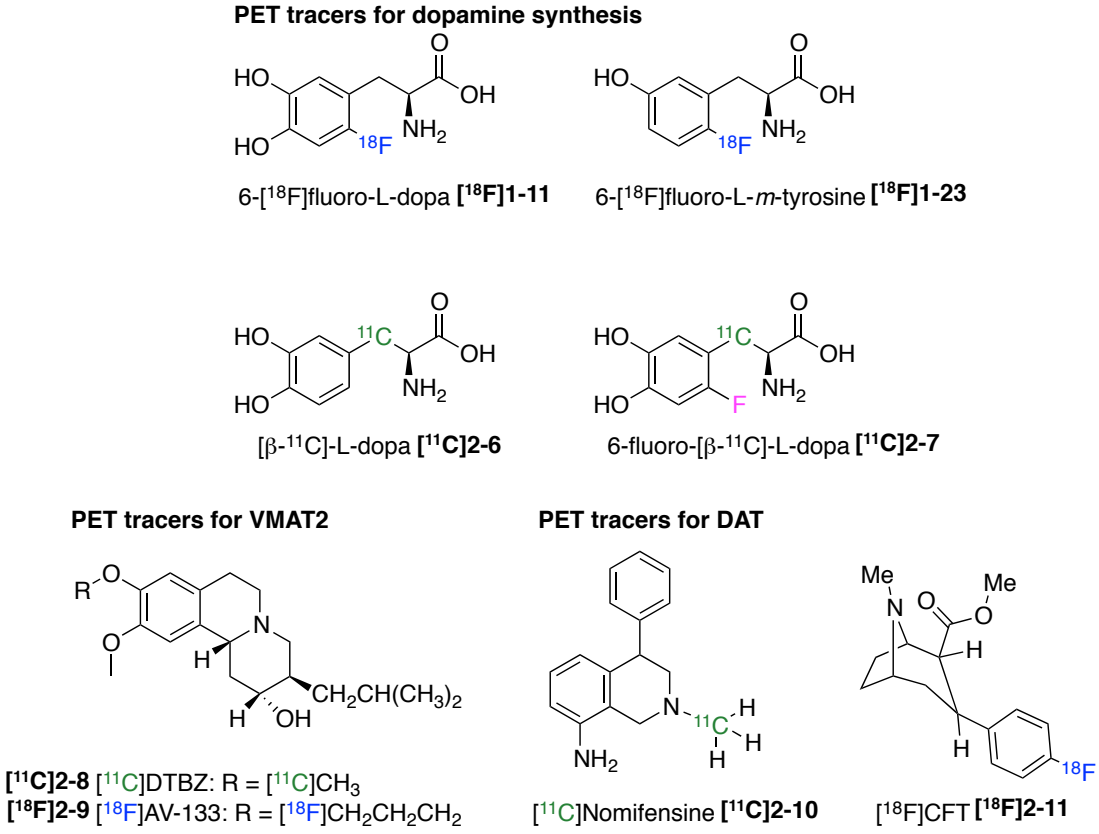


Figure 2.3. PET agents for the dopaminergic system.

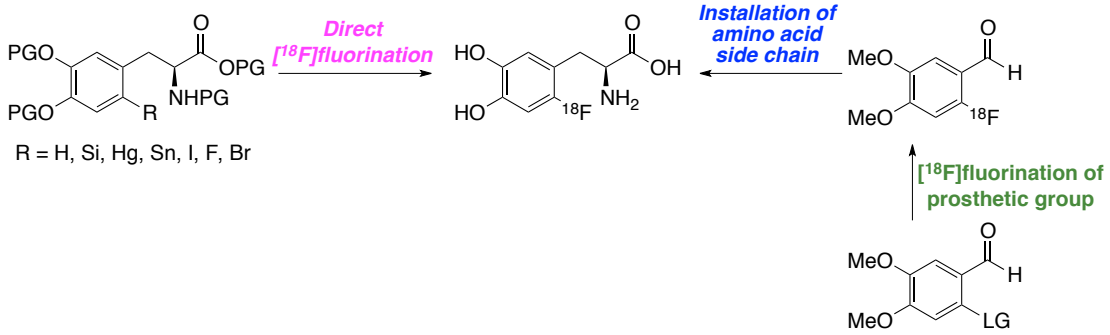
In the class targeting dopamine synthesis, the most popular choice is 6-[^{18}F]fluoro-L-DOPA **[^{18}F]1-11**, a fluorinated analogue of the L-DOPA intermediate in the dopamine synthesis. Accumulation of 6-[^{18}F]fluoro-L-DOPAin the striatum signifies the transport of the imaging agent into nigrostriatal nerve terminals, activity of AADC, storage of [^{18}F]fluorodopamine within the vesicles and the number of functioning nerve terminals. Although other carbon-11 analogues have since been investigated, the rate of decarboxylation of both [β-^{11}C]-L-DOPA **[^{11}C]2-6** and 6-fluoro-[β-^{11}C]-L-DOPA **[^{11}C]2-7** is significantly slower than that of 6-[^{18}F]fluoro-L-DOPA, which discourages their use in PET. Furthermore, their radiosynthesis is complex and time-consuming.[117],[118] Rather than targeting central dopamine biosynthetic pathways, 6-[^{18}F]fluoro-L-*m*-tyrosine **[^{18}F]1-23** is a substrate for the AADC enzyme. As a result, it has a simpler metabolic profile than **[^{18}F]1-11**, which is beneficial for PET imaging, however relatively little has been reported regarding brain uptake values in normal human subjects.[119],[120]

Development of agents for vesicle transport has focused on the VMAT2 isoform. Carbon-11 and fluorine-18 labelled dihydrotetrabenazine ([^{11}C]DTBZ[121] **[^{11}C]2-8** and [^{18}F]AV-133[122] **[^{18}F]2-9**) may both be used to map VMAT2 concentrations in monoaminergic neurons. A further application of [^{11}C]DTBZ is the indirect measurement of the loss of β-pancreatic cells in diabetes mellitus.[123]

Many imaging agents, of different chemical classes, have been designed for the investigation of the pharmacology and physiology of DAT.[124],[125] The first to be employed in *in vivo* imaging was [^{11}C]Nomifensine **[^{11}C]2-10**[126], but the focus subsequently moved to phenyltropane analogues of cocaine, like [^{18}F]CFT **[^{18}F]2-11**.[127] The carbon-11 analogues exhibited shorter half-life for the binding equilibrium, so fluorine-18 became the isotope of choice.

2.2.2 Routes to 6-[^{18}F]fluoro-L-DOPA

In order to prepare 6-[^{18}F]fluoro-L-DOPA, a [^{18}F]C-F bond must be installed. Two main pathways are available for its preparation: Direct [^{18}F]fluorination of a L-DOPA precursor or nucleophilic [^{18}F]fluorination of a prosthetic group followed by installation of the amino acid side chain (Scheme 2.2).

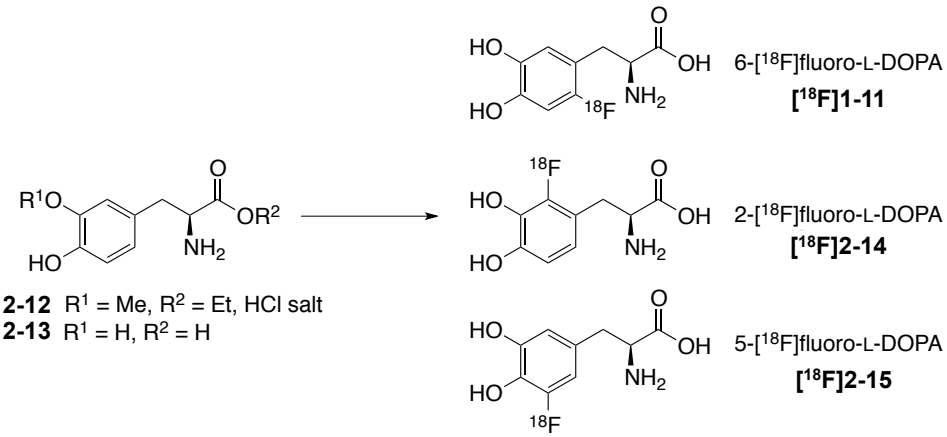


Scheme 2.2. Routes for the preparation of 6-[^{18}F]fluoro-L-DOPA.

The direct [^{18}F]fluorination pathway primarily relies on the use of an electrophilic source of [^{18}F]fluorine reacting with a nucleophilic L-DOPA precursor, but the few examples using nucleophilic [^{18}F]fluoride will also be discussed. Conversely, nucleophilic [^{18}F]fluoride is required in the prosthetic group strategy to install the radiolabel by the displacement of the leaving group in a S_NAr reaction.

2.2.2.1 Direct [^{18}F]fluorination of L-DOPA precursors.

Preliminary efforts focussed on the preparation 6-[^{18}F]fluoro-L-DOPA from the partially protected or unprotected L-DOPA amino acid precursors **2-12** and **2-13**. Direct fluorination was carried out using either [^{18}F]xenon difluoride, [^{18}F]acetyl hypofluorite or elemental [^{18}F]fluorine (Table 2.1). [128]

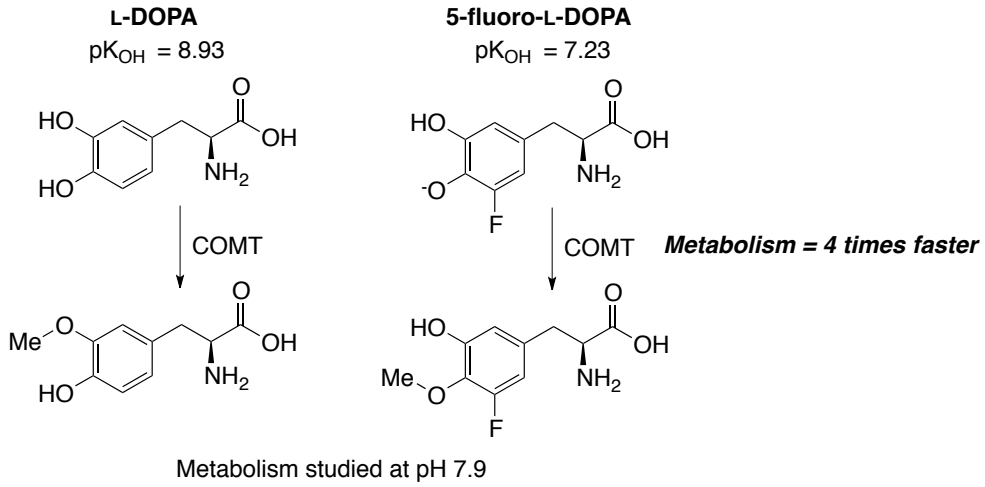


Entry	R	[^{18}F]fluorination conditions	Synthesis time (min)	Regioselectivity (%) (6 : 2 : 5 isomer)	RCY (%)	Ref
1	**2-12**	i) [^{18}F]XeF_2 in HF, -60 ^{o}C, 10 min. ii) 48% HBr, 140 ^{o}C, 15 min.	240	100 : 0 : 0	< 1	[129]
2	**2-12**	i) [^{18}F]AcOF in AcOH, rt, 20 min. ii) 48% HBr, 148 ^{o}C, 15 min.	180	64 : 21 : 14	4	[130]
3	**2-13**	[^{18}F]F_2 in HF at -65 ^{o}C,	60	59 : 5 : 35	1.5	[131]
4	**2-13**	[^{18}F]F_2 in HF with BF_3, -70 ^{o}C, 30 min	120	60 : 35 : 5	18	[132]

Table 2.1. Direct [^{18}F]fluorination of L-DOPA precursors.

The disadvantages associated with this approach were the use of highly reactive hazardous reagents, low radiochemical yields, long reaction times and poor regioselectivity. All three possible isomers, 2-[^{18}F]fluoro-L-DOPA, 5-[^{18}F]fluoro-L-DOPA and 6-[^{18}F]fluoro-L-DOPA, were formed in varying ratios. The highest RCY was obtained when the Lewis acid, BF_3, was added (Table 2.1, Entry 4). It was postulated that boron trifluoride acts as a fluoride acceptor and thereby increases the acidity of the solvent, allowing the phenol moieties of L-DOPA to be protonated. This retards the electrophilic aromatic substitution, but was found to promote the radiolabelling at the least hindered 6-position on the ring in favour of the other isomers. Conversely, the use of polar solvent (MeCN and water) in the presence of BF_3, increased the yield of the 2- and 5-isomers.[132]

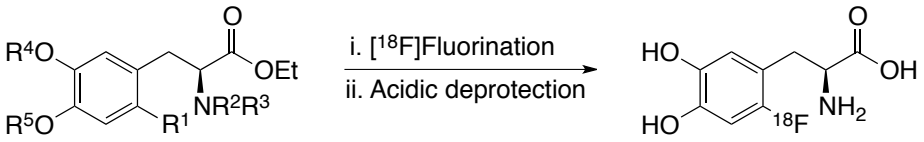
Chirakal and co-workers, carried out a detailed comparative study to determine the distribution and metabolic fate of all three isomers in the human brain. After injection, 6-[^{18}F]fluoro-L-DOPA was found to accumulate in the striata whereas poor accumulation was observed upon the injection of 2-[^{18}F]fluoro-L-DOPA and 5-[^{18}F]fluoro-L-DOPA. In further studies, it became evident that 2-[^{18}F]fluoro-L-DOPA is unable to cross the blood brain barrier using amino acid transport.[22] Alternative studies, using rat models pre-treated with carbidopa (an inhibitor of AADC), showed that 2-[^{18}F]fluoro-L-DOPA is not a substrate for AADC and is rapidly metabolised by catechol-*O*-methyl transferase (COMT) (in comparison with L-DOPA). In contrast, 5-[^{18}F]fluoro-L-DOPA crosses the blood-brain barrier in a similar extent to L-DOPA, but is not retained in the striatum as its affinity for COMT was comparable to 2-[^{18}F]fluoro-L-DOPA. The increased metabolism of these two isomers is credited to the fluorine being positioned *ortho* to the hydroxy groups. The result of metabolism by COMT is normally *O*-methylation on the phenol in the 3-position in the case of L-DOPA. It has been argued that fluorination of the 2- or 5-positions of the arene in L-DOPA increasing the nucleophilicity of the adjacent phenol moiety by increasing ionisation, and hence increases the propensity for methylation of the *ortho*-hydroxyl. This was studied on 5-fluoro-L-DOPA (Scheme 2.3).[22] The presence of the fluorine atom increased ionisation of the hydroxyl moiety in the 4-position (ionised:unionised = 4.86:1 *vs.* 0.085:1 for L-DOPA). The resulting metabolism was found to be 4 times faster for 5-fluoro-L-DOPA.



Scheme 2.3. Difference in rate of metabolism between L-DOPA and 5-fluoro-L-DOPA.

To this end, 6-[^{18}F]fluoro-L-DOPA readily crosses the BBB using amino acid tranporters and has the most similar affinity for COMT and AADC to endogenous L-DOPA, so it became evident that continued efforts to selectively and rapidly synthesise 6-[^{18}F]fluoro-L-DOPA in high RCY and SA would be valuable. In order to circumvent the formation of several regioisomers and with the aim of increasing the RCY, the attention turned to the development of a regioselective methodology.

Regioselective cleavage of an aryl-M bond (where M = Si, Hg or Sn) has been reported with the use of [^{18}F]F_2 and [^{18}F]AcOF for the preparation of aryl fluorides (Chapter 1, Scheme 1.17). Investigations were therefore initiated for the application of this strategy to 6-[^{18}F]fluoro-L-DOPA (Table 2.2).



2-16 R^1 = $SiMe_3$, R^2 = R^3 = C=HAr, R^4 = R^5 = Me
2-17 R^1 = $HgOCOCF_3$, R^2 = H, R^3 = $COCF_3$, R^4 = R^5 = Me
2-18 R^1 = $SnMe_3$, R^2 = H, R^3 = Boc, R^4 = R^5 = Boc
2-19 R^1 = $SnMe_3$, R^2 = H, R^3 = CHO, R^4 = R^5 = Boc

[^{18}F]1-11

Entry	R	[^{18}F]fluorination conditions	Synthesis time (min)	RCY (%)	Ref
1	**2-16**	i) [^{18}F]F_2 $CFCl_3$/CCl_4, -60 °C, 10 min. ii) 48% HBr, 135 °C, 35 min.	60	8	[133]
2	**2-17**	i) [^{18}F]AcOF in CCl_4, reflux, 10 min. ii) 55% HI, 130 °C, 10 min.	50	11	[134]
3	**2-18**	i) [^{18}F]F_2 in $CFCl_3$, rt, 10 min, ii) 48% HBr, 130 °C, 10 min	50	26	[135]
4	**2-19**	i) [^{18}F]F_2 in $CFCl_3$, rt, 10 min ii) 48% HBr, 130 °C, 10 min	45-50	25	[55]
5	**2-19**	i) [^{18}F]F_2 in $CFCl_3$, rt, 4 min ii) 48% HBr, 130 °C, 10 min	45	33	[62]
6	**2-19**	i) High SA [^{18}F]F_2 in $CFCl_3$, rt, 5 min ii) 48% HBr, 130 °C, 5 min	45-50	6.4 ± 1.7	[50]

Table 2.2. Regioselective [^{18}F]fluorodemetallation of L-DOPA precursors.

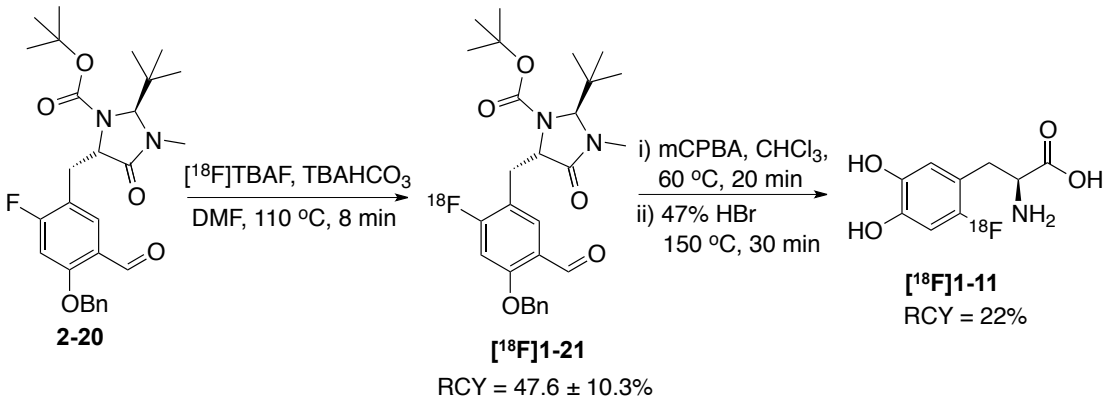
All these protocols relied on the direct [^{18}F]fluorination using either [^{18}F]F_2 or [^{18}F]AcOF (produced by ^{20}Ne(d,α)^{18}F) and afforded 6-[^{18}F]fluoro-L-DOPA within one hour following acidic deprotection. The initial strategy employed a trimethylsilyl group, but preparation of the precursor **2-16** proved challenging as the Grignard

reaction between the arylbromide L-DOPA precursor and trimethylsilyl chloride only proceeded in 5% yield (Table 2.2, Entry 1).[133] Mercury-based precursors **2-17** were investigated next and this approah afforded the desired product **[^{18}F]1-11** in 11% RCY (Table 2.2, Entry 2). In order to improve the quality control of the imaging agent, due to the toxicity of the precursor, an automated solid-supported strategy was also developed.[136],[137] The mercury precursors were rapidly replaced by the stannylated precursors **2-18** and **2-19**, still employed in many PET centres today for the routine production of 6-[^{18}F]fluoro-L-DOPA **[^{18}F]1-11**. Pleasingly, the RCYs of the transformation could be increased by ~ 20% when these trimethylstannane precursors were employed (Table 2.2, Entries 3-5). Precursors **2-18** and **2-19**, only differed in the choice of the protecting group on the amine, and similar RCYs were obtained in both cases, indicating that the reaction was tolerant of different substituents in this position. De Vries and co-workers adapted the protocol to an automated platform, which was immensely beneficial for the routine preparation of the tracer as it avoided the manual handling of radioactivity and also increased the radiochemical yield to 33% (Table 2.2, Entry 5). Solin and co-workers prepared 6-[^{18}F]fluoro-L-DOPA in an analogous semi-automated protocol employing high specific [^{18}F]F_2 (Table 2.2, Entry 6). By reducing the amount of carrier amount of F_2 to ~1 μmol, smaller amounts of precursor and $CFCl_3$ (Freon-11) may be used and this simplified the manipulations and purification of the final product. The obtained specific activity of **[^{18}F]1-11** was 3.7 ± 0.9 GBq/μmol, a significant increase from the previous methods (0.003-0.011 GBq/μmol), which allowed injection of the imaging agent in trace amounts. Importantly, the concentration of tin remaining in the final product ranged from 5.8 to 12.6 μg/L (n = 5) but the majority eluted together with the void volume during the semi-preparative HPLC purification and was not deemed hazardous.[50],[138]

It is important to note that all these electrophilic routes employ the now prohibited solvent Freon-11. Investigations have been carried out by Solin and co-workers and it was established that deuterated solvents such as $CDCl_3$, CD_2Cl_2 and C_3D_6O were suitable alternatives and afforded **[^{18}F]1-11** in improved RCYs (7.5-8.6%).[139] In contrast, low RCYs (< 1%) were obtained when $CHCl_3$ and CH_2Cl_2 were used. These solvents contain amylene as a stabiliser and it was postulated that [^{18}F]F_2 reacts with the double bond of this compound to afford volatile radioactive side products, which

as a consequence reduce the RCY of **[^{18}F]1-11**. At the Turku PET centre the preparation of **[^{18}F]1-11** for patients is now carried out in $CDCl_3$.

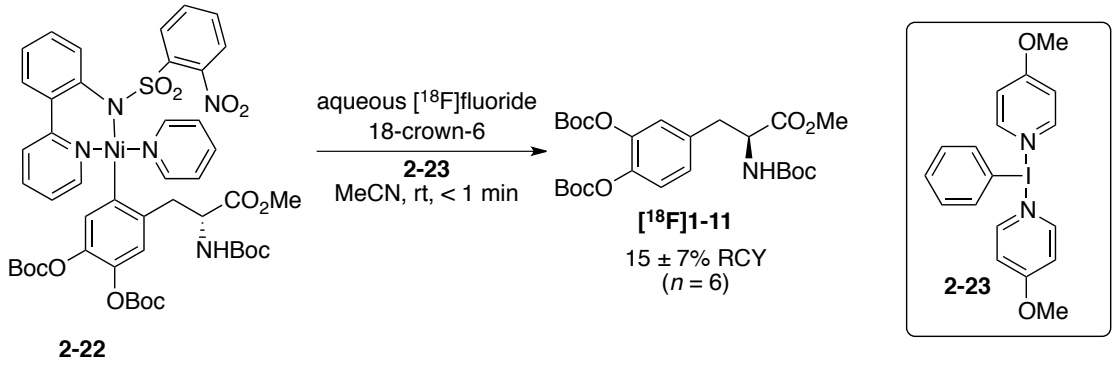
As described in Chapter 1, attempts have been made to directly [^{18}F]fluorinate L-DOPA using [^{18}F]fluoride in order to achieve SA in higher amounts. Recently, DiMagno reported a patent detailing a novel strategy affording **[^{18}F]1-11** upon the nucleophilic [^{18}F]fluorination of a diaryliodonium salt precursor (Scheme 1.10). This is a very exciting development and it will be interesting to see the full studies upon publication. In the same vein, Coenen and co-workers devised a direct nucleophilic [^{18}F]fluorination approach relying on isotopic exchange (Scheme 2.4).[140]



Scheme 2.4. Preparation of 6-[^{18}F]fluoro-L-DOPA by isotopic exchange.[140]

The precursor **2-20** was [^{18}F]fluorinated in the presence of [^{18}F]TBAF within 20 minutes. The [^{18}F]radiolabelled intermediate **[^{18}F]2-21** was afforded in 47.6 ± 10.3% RCY and subsequently converted to **[^{18}F]1-11** by a Baeyer-Villiger oxidation and acidic deprotection in a one-pot reaction. 6-[^{18}F]Fluoro-L-DOPA was afforded in 22% RCY and in >96 % ee within 105 minutes, after semi-preparative HPLC purification.

Ritter and co-workers recently reported an alternative late-stage nickel-mediated oxidative synthesis of 6-[^{18}F]fluoro-L-DOPA, employing a hypervalent iodide oxidant and aqueous [^{18}F]fluoride.[141] The nickel complex **2-22** was prepared in two steps and upon reaction with oxidant **2-23**, 18-crown-6 and aqueous [^{18}F]fluoride, 6-[^{18}F]fluoro-L-DOPA was afforded in 15 ± 7% RCY in < 1 minute at room temperature (Scheme 2.5). This transformation will be discussed in full detail in chapter 3, section 3.1.3.

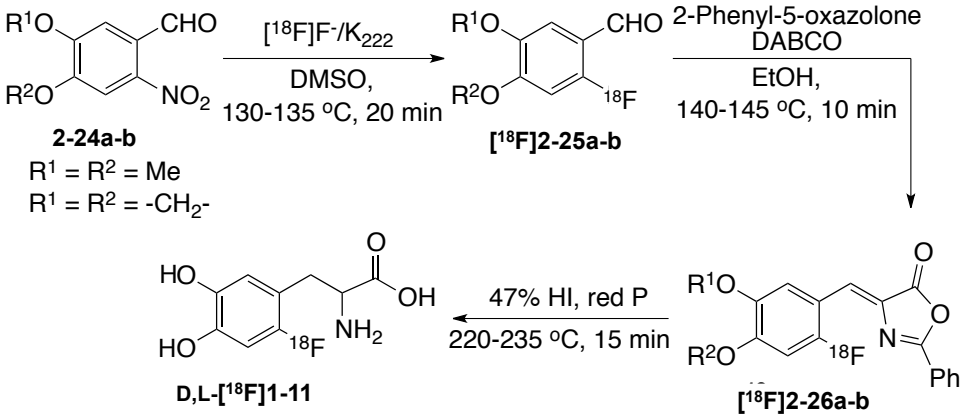


Scheme 2.5. Nickel-mediated oxidative [^{18}F]fluorination for the preparation of 6-[^{18}F]fluoro-L-DOPA.[141]

2.2.2.2 Nucleophilic Routes to 6-[^{18}F]fluoro-L-dopa relying on prosthetic groups.

There has been a continued interest in the preparation of 6-[^{18}F]fluoro-L-DOPA *via* a nucleophilic route. As the direct nucleophilic fluorination of L-DOPA precursors containing a leaving group require the presence of at least one electron-withdrawing group to activate the arene towards nuclophilic attack, prosthetic group strategies have been extensively explored as suitable alternatives.

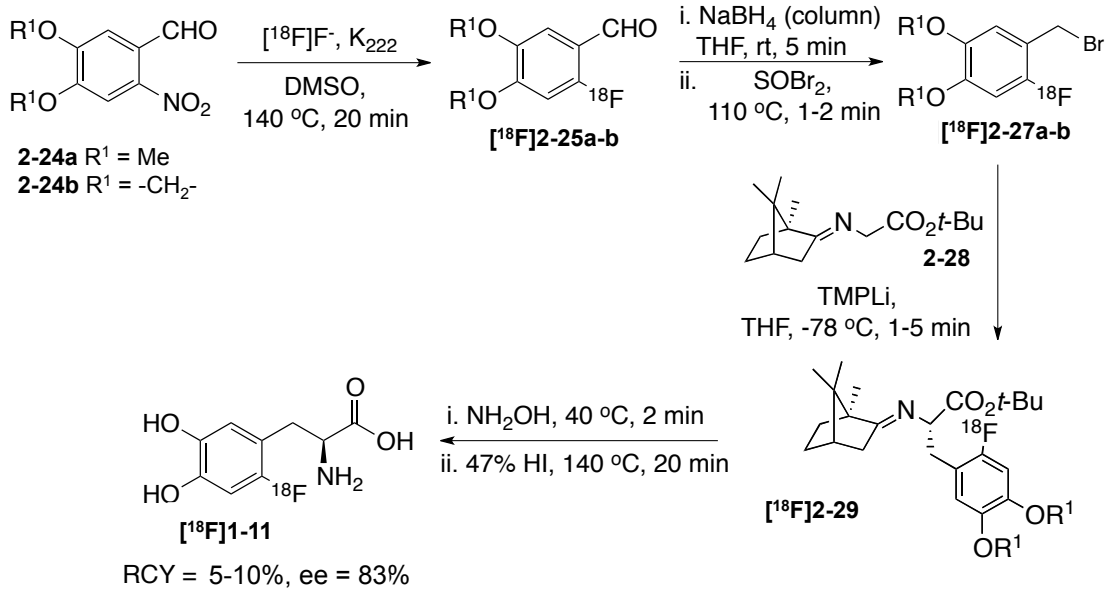
In the early 1990s, the research groups of Lemaire and Reddy reported the synthesis of 6-[^{18}F]fluoro-L-DOPA upon the initial [^{18}F]fluorination of 6-nitroveratraldehyde **2-24a** or 6-nitropiperonal **2-24b** (Scheme 2.6).[142],[143] The [^{18}F]radiolabelled intermediates **[^{18}F]2-25a-b** were reacted with 2-phenyl-5-oxazolone in the presence of base to install the amino acid side-chain. The final reductive hydrolysis of **[^{18}F]2-26a-b** in the presence of 47% hydriodic acid and phosphorus red afforded a racemic mixture of the D- and L-isomer of **[^{18}F]1-11**. Chiral HPLC was implemented to separate the two enantiomers. The final obtained RCYs of **[^{18}F]1-11** were 3-5%[142] and 10%, respectively.[143] The total synthesis time was approximately two hours, and as the reaction was not stereoselective for the L-enantiomer, a time-consuming chiral HPLC separation was required.



Scheme 2.6. Nucleophilic synthesis of [^{18}F]1-11 using oxazolone as the amino acid protecting group.[142],[143]

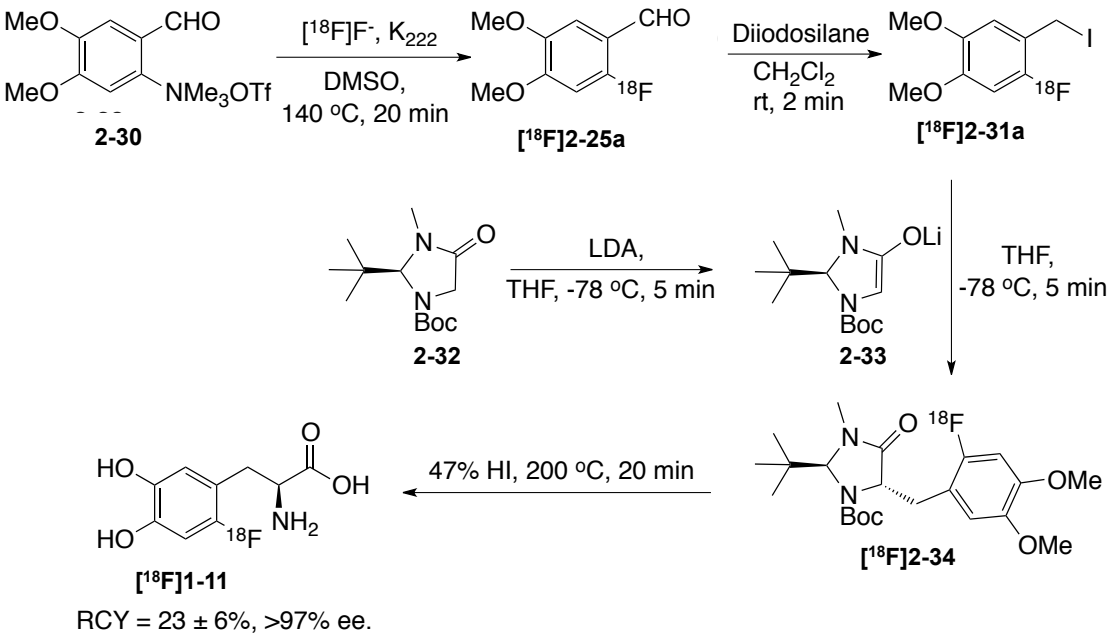
Several attempts have been made to improve the RCY of this process using the same initial prosthetic groups but different enantioselective strategies for the installation of the amino acid functionality.

Following the initial S_NAr reaction, Lemaire[144] and Najafi[145] converted the [^{18}F]radiolabelled intermediates **[^{18}F]2-25a-b** into the corresponding [^{18}F]fluorobenzyl bromides **[^{18}F]2-27a-b** by reduction of the aldehyde functionality to the alcohol in the presence of sodium borohydride and bromination upon the reaction with $SOBr_2$. A chiral agent, 1-(*S*)-(-)camphorimine of *tert*-butylglycinate **2-28** was then coupled with **[^{18}F]2-27a-b** in the presence of base. Following cleavage of the amine-protecting group in the presence of hydroxylamine and final global acidic deprotection, **[^{18}F]1-11** was afforded in 5-10% RCY (Scheme 2.7). The total synthesis time was 120 minutes and this approach afforded the product with an improved enantiomeric excess of 83%.



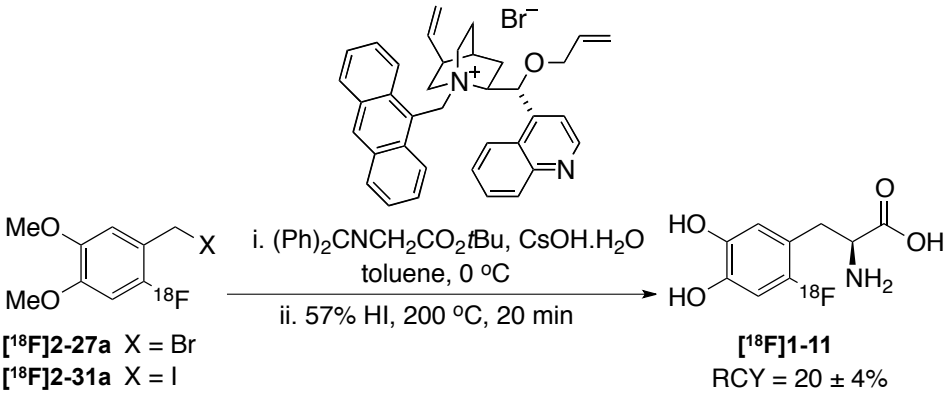
Scheme 2.7. Asymmetric nucleophilic route to [^{18}F]1-11 using 2-28 as the chiral agent.[145]

The enantioselectivity of this strategy was improved by employing (*S*)-(-)-1-Boc-2-*tert*-butyl-3-methyl-4-imdazolidinone **2-32** as the chiral counter part in the alkylation reaction and 6-[^{18}F]fluoro-L-DOPA **[^{18}F]1-11** was afforded in 96% ee after 110 minutes.[146] The RCYs obtained were disappointing (5-10%) and as a result Lemaire and co-workers investigated [^{18}F]fluorobenzyl iodide **[^{18}F]2-31a** as a suitable alternative prosthetic group (Scheme 2.8). Pleasingly, the RCY of the process was increased to 23 ± 6% within a reasonably short synthesis time (90 min) and **[^{18}F]1-11** was afforded in >97% ee. Although this protocol was used to routinely prepare 6-[^{18}F]fluoro-L-DOPA, automation proved challenging due to the requirement of a strong base under anhydrous reaction conditions in the alkylation step.[147]



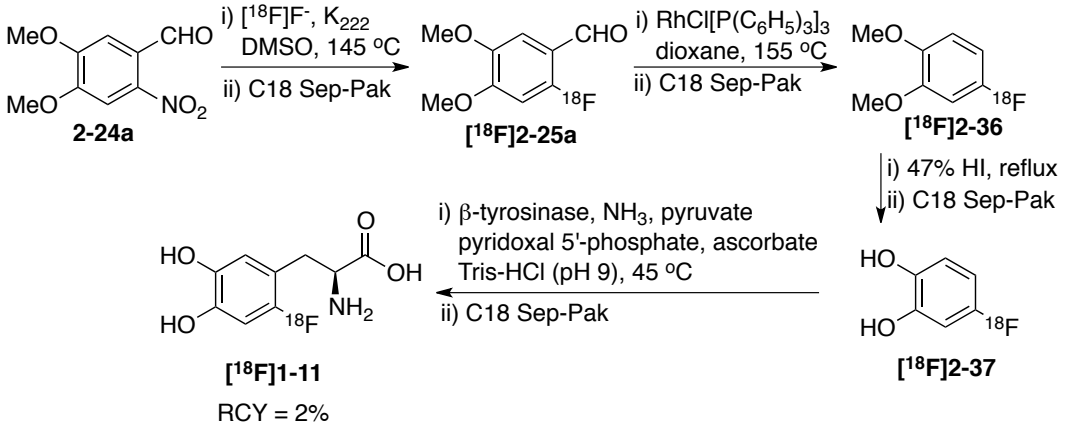
Scheme 2.8. Asymmetric route to [^{18}F]1-11 using 2-32 to install stereocentre.[147]

To develop a protocol compatible with automation, the chiral agent in the alkyation step was redesigned. Instead, a chiral phase-transfer catalyst (PTC) derived from a cinchona alkaloid was employed (Scheme 2.9).[148] *O*-allyl-*N*-(9-anthracenylmethyl)cinchonidium **2-35** catalysed the enantioselective alkylation between either **[^{18}F]2-27a** or **[^{18}F]2-31a** and *N*-(diphenylmethylene)glycine *tert*-butyl ester. Compared to previous strategies, low temperatures and chiral separations were avoided. An automated PTC-based synthesis devise was prepared and enantioselectively pure **[^{18}F]1-11** was afforded in 20 ± 4% RCY and with a SA of 50 GBq/µmol within 120 minutes.[149] Another PTC strategy for the preparation of **[^{18}F]1-11** has also been investigated. An achiral Ni(II) complex of (*S*)-*O*-[(*N*-benzylpropyl)amino]benzophenone and glycine (NiPBPGly) was employed as the catalytic system and underwent alkylation in the presence of **[^{18}F]2-27a**. However, the reaction time, purification and RCY were not significantly improved. [150]



Scheme 2.9 Preparation of 6-[^{18}F]fluoro-L-DOPA [^{18}F]1-11 using PTC 2-35.[148]

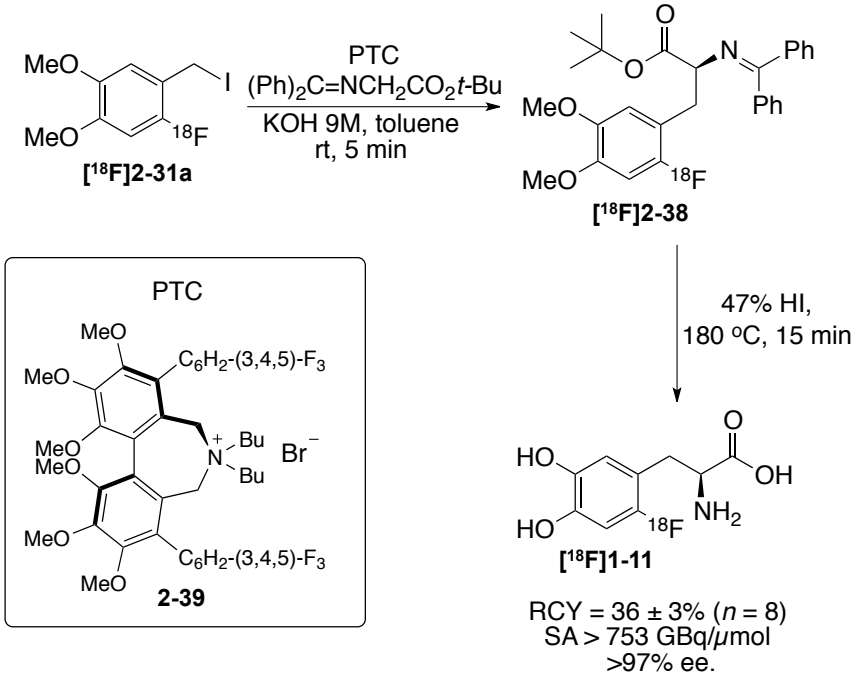
An alternative strategy relied on enzymatic action to install the amino acid side chain (Scheme 2.10).[151] Enzymatic reactions have the added benefit of proceeding under mild conditions with high selectivity and efficiency. 4-[^{18}F]Fluorocatechol **[^{18}F]2-37** was prepared in three steps from **2-24a**. This [^{18}F]radiolabelled compound was a substrate for β-tyrosinase and the reaction afforded 6-[^{18}F]fluoro-L-DOPA after a total synthesis time of 150 minutes. Compared to previous routes this approach was not an improvement as the RCY obtained was only 2%. However, it does illustrate the versatility of the prosthetic group strategy.



Scheme 2.10 Enzymatic route to [^{18}F]1-11.[151]

The many nucleophilic routes to 6-[^{18}F]fluoro-L-DOPA **[^{18}F]1-11** commonly suffer from complex synthetic protocols and long reaction times, which have prevented widespread implementation. Despite these limitations, the attraction of preparing **[^{18}F]1-11** *via* a nucleophilic route and hence benefiting from the increased specific activity and activity, is still generating a significant amount of interest. In addition to

the direct [^{18}F]fluorination of L-DOPA precursors described previously, Lemaire and co-workers recently reported the improved nucleophilic synthesis of **[^{18}F]1-11**, compatible with a commercially available synthesis module (Scheme 2.11).[152]



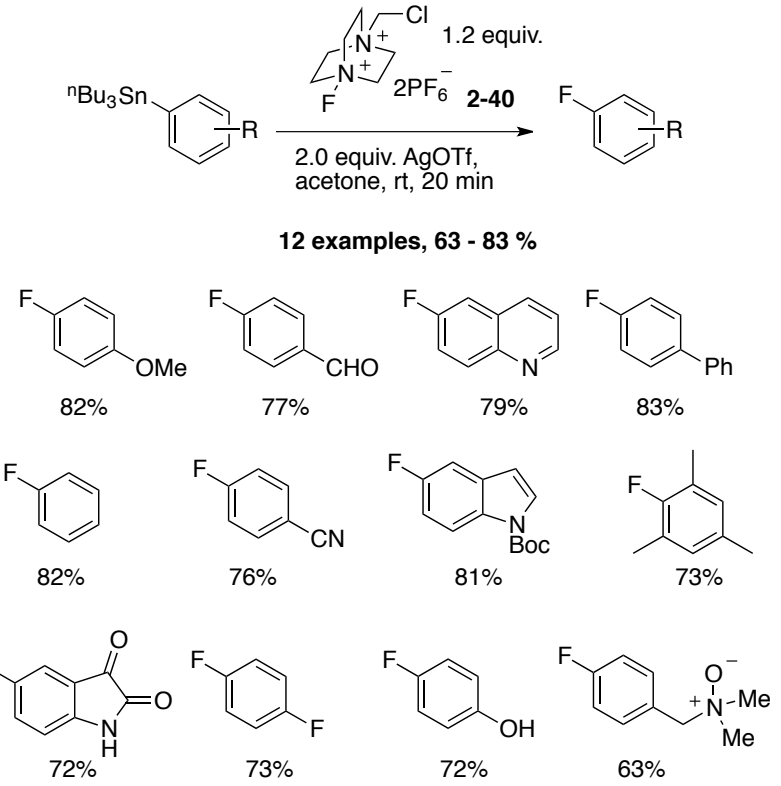
Scheme 2.11. Improved and automated PTC nucleophilic preparation of [^{18}F]1-11.[152]

The [^{18}F]fluorobenzyl iodide **[^{18}F]2-31a** was used to alkylate a Schiff base in the presence of phase-transfer catalyst (PTC) **2-39** within 5 minutes to afford the [^{18}F]labelled intermediate **[^{18}F]2-38**. Upon acidic deprotection, enantiomerically pure 6-[^{18}F]fluoro-L-DOPA **[^{18}F]1-11** was obtained in an improved RCY of 36 ± 3% within 65 minutes under automation. The level of SA was also significantly improved to 753 GBq/μmol. This route offers an attractive nucleophilic strategy for the routine production of 6-[^{18}F]fluoro-L-DOPA.[152]

2.2.3 Recent advances in silver-mediated electrophilic fluorination strategies

As described in Chapter 1 (Scheme 1.34), [^{18}F]Selectfluor *bis*(triflate) can be used to [^{18}F]radiolabel simple electron rich arylstannanes, which are more challenging to obtain under nucleophilic fluorination reaction conditions.[70] The radiochemistry protocol was adopted from a pioneering procedure reported by Ritter and co-workers, where it was established that rapid and selective fluorination was achievable in the

presence of a supramolar amount of silver triflate and Selectfluor *bis*(hexafluorophosphate) **2-40** (Scheme 2.12).[108]

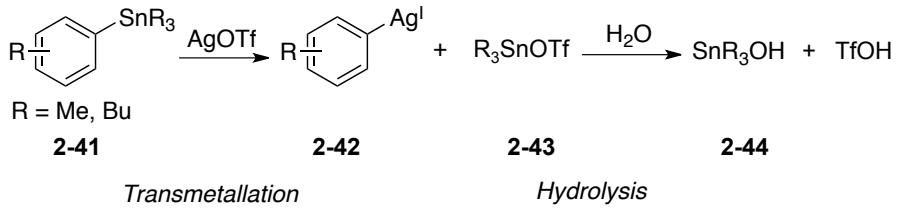


Scheme 2.12. Silver mediated fluorination of arylstannanes.[108]

A wide variety of electron-poor and electron-rich aryl tributylstannanes were prepared and fluorinated in excellent yields at room temperature within 20 minutes in the presence of 2.0 equivalents of silver triflate and 1.2 equivalents of Selectfluor *bis*(hexafluorophosphate) **2-40** in a one-pot reaction. It was found that **2-40** was a superior reagent compared to commercial Selectfluor *bis*(tetrafluoroborate) and afforded the fluorinated product in higher yields. It was proposed that Selectfluor™ was less efficient due to arylation of the tetrafluoroborate anion by the arylstannanes, and thereby affording aryl borates as a side-product.[153]

In addition to the desired fluorinated product, the formation of significant amounts of the protonated product, as a result of protodestannylation, was observed. This side-reaction, where a proton rather than a fluorine atom is installed, has been widely studied in a variety of systems, including allyl, vinyl, allenyl, alkyl and aryl.[154],[155] This transformation requires acid to be present in the reaction mixture, which competes with Selectfluor. It is thought that triflic acid is formed *in situ* by the

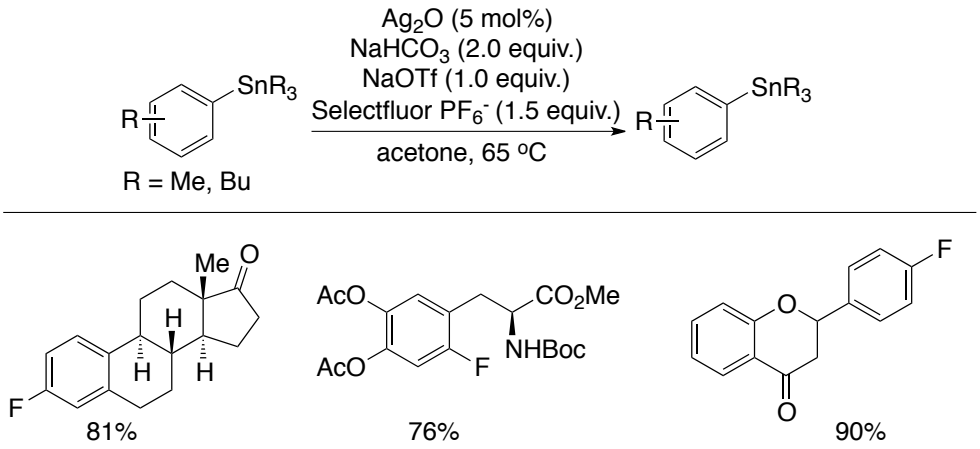
hydrolysis of trialkyltin triflate, formed upon transmetallation between silver(I) triflate and arylstannanes (Scheme 2.13).[156]



Scheme 2.13. Proposed mechanism for formation of triflic acid *in situ*.

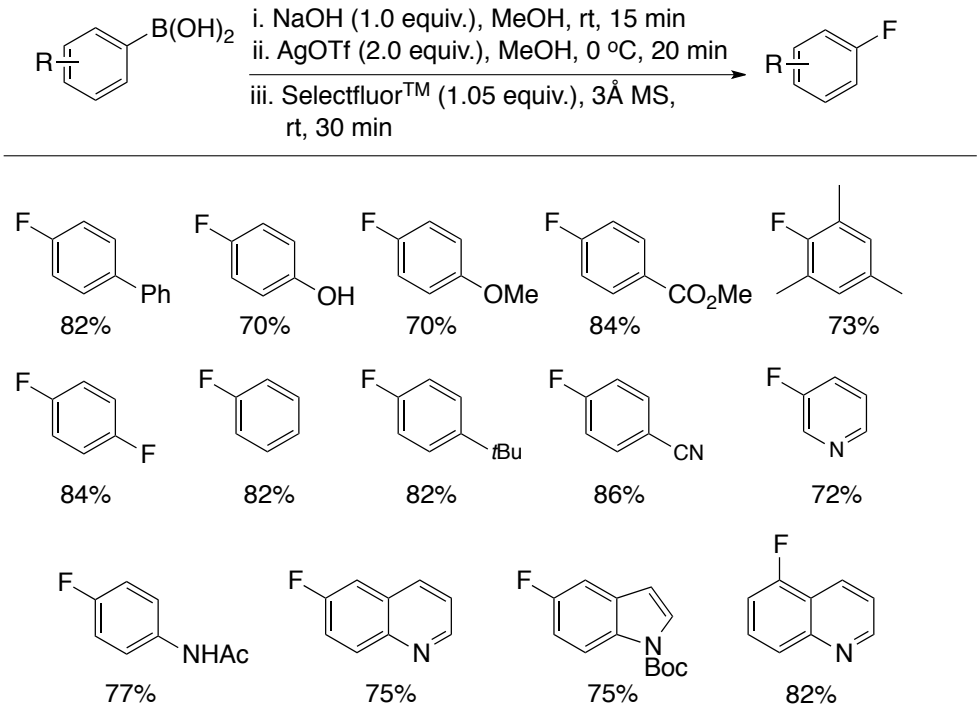
A transmetallation reaction was reported as the first step of Ritter's fluorination protocol, and results in the formation of a silver(I) aryl complex **2-42** and trialkyltin triflate **2-43**. Acetone was used as the solvent and it is notoriously challenging to dry this solvent to eliminate all traces of water. It is therefore postulated that the water present in the solvent causesd hydrolysis of the trialkyltin triflate species to afford trialkyltin hydroxide **2-44** and triflic acid *in situ*. The acid then reacts with the arylsilver complex **2-42** in an electrophilic aromatic substitution reaction to afford the protodestannylated product. Further evidence in favour of this process was obtained by Ritter, as it was shown that fluorination of purified arylsilver complexes, not containing trialkyltin triflate, did not afford the protodestannylated side-product.[108]

In an attempt to inhibit the undesired protodestannylation process, a catalytic variant of the previous reaction was developed and sodium bicarbonate was added to neutralise the acid formed *in situ*.[157] Using a combination of 10% of silver(I) oxide and 1 equivalent of sodium triflate in the presence of 2 equivalents of sodium bicarbonate, a range of diverse arenes could be fluorinated in high yields with the undesired side-product obtained in < 10% in all cases (Scheme 2.14).



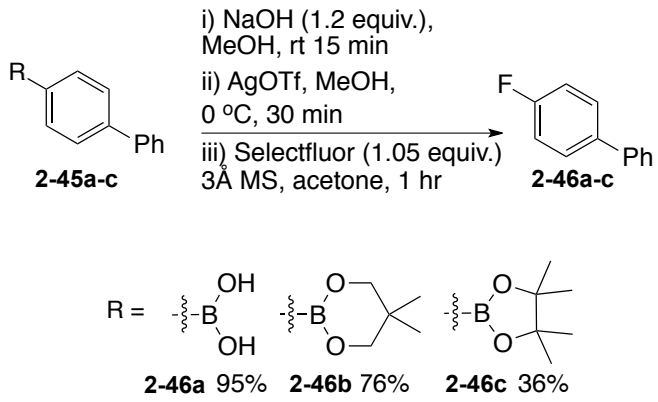
Scheme 2.14. Catalytic fluorination of complex arenes.[157]

Ritter also reported an analogous procedure employing boronic acids, thereby avoiding the use of the toxic stannane functional group.[158] Boronic acids are often commercially available, stable to a range of functional groups and virtually non-toxic. The arylboronic acids were activated in the presence of 1 equivalent of sodium hydroxide in methanol and the subsequent transmetallation with 2 equivalents of silver triflate, afforded the corresponding arylsilver complex intermediates. After removal of the methanol, fluorination was carried out in the presence of 1.05 equivalents of Selectfluor™ and 3 Å MS in acetone. The reaction was complete within 30 minutes at room temperature and amenable to a wide substrate scope (Scheme 2.15).



Scheme 2.15. Silver-mediated fluorination of arylboronic acids.

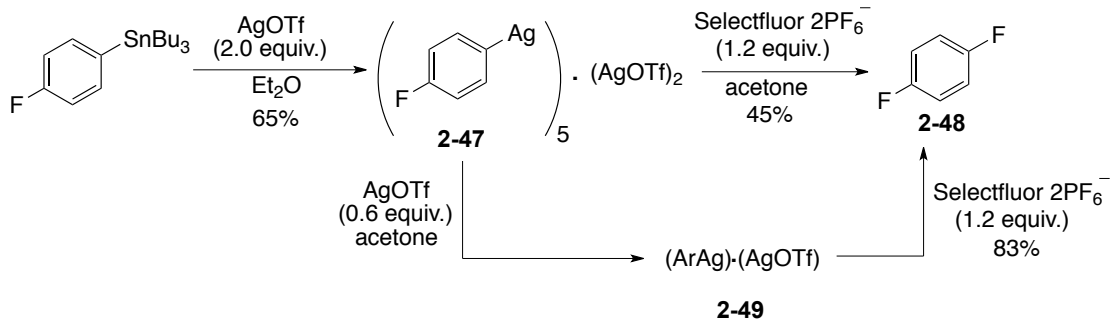
It was also established that arylboronic esters were suitable precursors for this methodology and could be directly activated and transmetallated, without the requirement of initial hydrolysis. This widens the range of substrates compatible with this fluorination reaction (Scheme 2.16).[158]



Scheme 2.16. Silver-mediated fluorination of arylboronic acid and esters.

2.2.3.1. Proposed mechanism for the silver(I)-mediated fluorination of arylstannanes and arylboronic acid derivatives

The presence of the silver(I) catalyst is essential for the success of this reaction. Vinyl stannanes are known to undergo direct fluorination using XeF_2, but the rate of reaction is greatly increased in the presence of a silver(I) catalyst.[159],[160] Simple aryl stannanes may be directly fluorinated in the presence of highly reactive electrophilic fluorine sources, but with increasingly electron-rich arenes the reaction becomes unselective. Ritter and co-workers carried out preliminary mechanistic studies on 4-fluorophenyltributyltin to elucidate the mechanism of reaction (Scheme 2.17).[108] The intermediate **2-47**, formed upon transmetallation between silver triflate and arylstannanes, was isolated and is also well characterised in the literature.[161] Addition of reagent Selectfluor *bis*(hexafluorophosphate) **2-40** to this complex only afforded the fluorinated product **2-48** in 45% yield. When 0.6 equivalents of silver triflate were added, the ratio of silver to arene was adjusted to equal 2:1, and the yield of the reaction was improved to 83%. The postulated bimetallic silver intermediate **2-49** was observed in NMR studies but not isolated (Scheme 2.17).

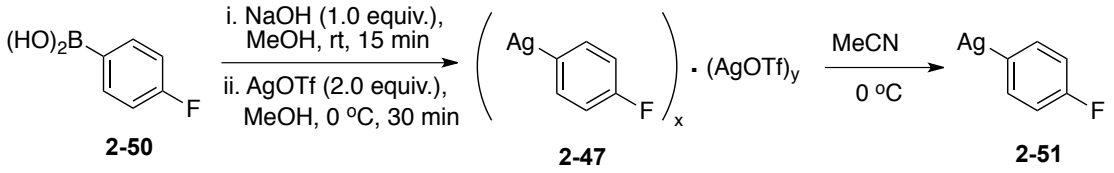


Scheme 2.17. Proposed mechanism of silver(I)-mediated fluorination of electron-rich arenes.

Further studies were carried out to confirm the requirement of a supramolecular amount of silver triflate. The fluorination of purified arylsilver complex **2-47**, required the addition of an additional equivalent of silver triflate to achieve a yield of 84%. Investigating a catalytic system using 10 mol% of silver triflate and two equivalents of sodium triflate, while adding the arylstannane slowly, increased the yield to 53%, compared to when only 10% of silver triflate was added to the system (36%, 3.6 turnovers). However, in order to obtain high yields, the addition of two equivalents of

silver triflate are required, meaning a 1:1 ratio of ArAg to AgOTf is required for optimal yields of the fluorinated products.

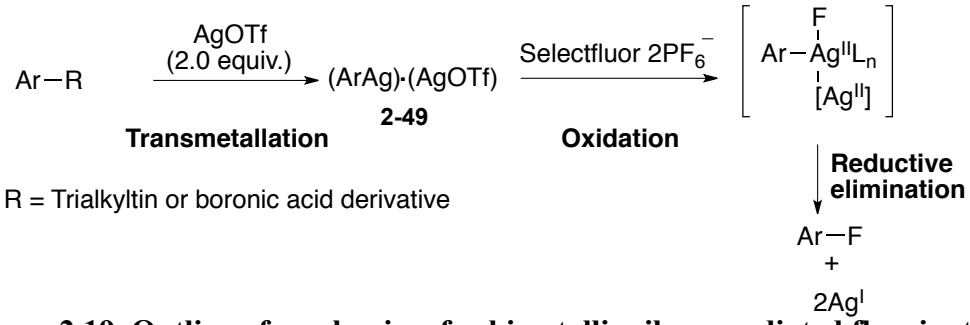
Ritter reported further evidence for the operation of a bimetallic silver(I/II) mechanism in the fluorination reaction of arylboronic acids.[158] Upon activation of 4-fluorophenyl boronic acid **2-50** in the presence of sodium hydroxide and the subsequent transmetallation, the resulting intermediate **2-47** was obtained. The ratio of 4-fluorophenylsilver product **2-51** to silver triflate in intermediate **2-47** was variable and irreproducible, but the 4-fluorophenylsilver compound **2-51** could be purified and isolated upon washing with acetonitrile (Scheme 2.18). Similar complexes to **2-47** have also been studied and characterised in the literature.[161]



Scheme 2.18. Isolation of arylsilver intermediates 2-47 and 2-51.

Furthermore, in Ritter's optimisation studies, the yield obtained in the fluorination of 4-biphenylboronic acid increased from 43% to 95% when the amount of silver triflate was increased from 1 to 3 equivalents.[158] This requirement of superstoichiometric amounts of silver triflate is consistent with the previous proposed silver bimetallic mechanism.[108]

It was therefore postulated that the first step of the fluorination reaction is transmetallation between the arylstannane or arylboronic acid derivative and the silver catalyst affording a silver(I) bimetallic complex **2-49**, which is subsequently oxidised upon the addition of Selectfluor *bis*(hexafluorophosphate) **2-40**. This affords a fluorinated bimetallic silver(II) complex which undergoes a final reductive elimination to yield the corresponding arylfluorides (Scheme 2.19).



Scheme 2.19. Outline of mechanism for bimetallic silver-mediated fluorination.

2.4 Results and Discussion

The 'cold' fluorination studies on the boronic acid derivatives were carried out in collaboration with Dr. Charlotte Grube Jørgensen.

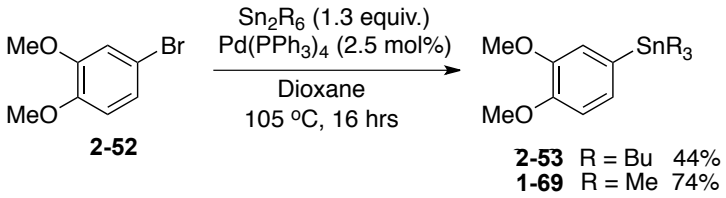
2.4.1 Fluorination optimisation studies of arylstannane and arylboronic acid derivative model substrates

2.4.1.1 Fluorination of 4-trialkyltinveratrole

In the original protocol reported by Ritter for the silver-mediated fluorination of arylstannanes and previous studies within the Gouverneur research group, formation of a significant amount of side-product, as a result of protodestannylation, was observed in addition to the fluorinated arenes.[108] It was therefore decided to optimise the reaction conditions in an attempt to minimise the protodestannylation process.

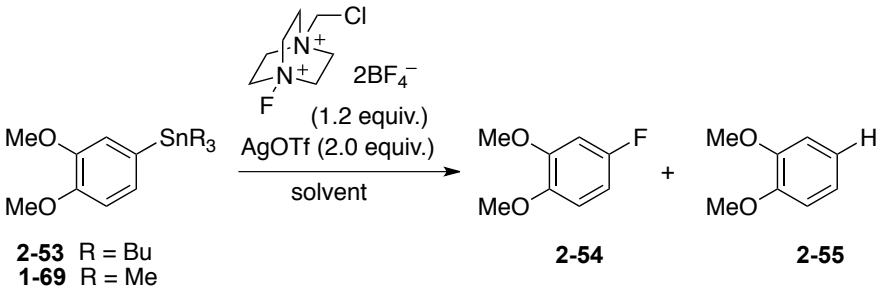
Veratrole, 1,2-dimethoxybenzene, containing the catechol functionality also present in L-DOPA, have been previously studied in this silver-mediated fluorination reaction.[70] Hence, it was chosen as a model substrate for L-DOPA and preliminary optimisation studies of the fluorination reaction was carried out using this substrate for both the arylstannane and arylboronic acid derivatives.

The veratrole trialkyltin compounds **2-53** and **1-69** were prepared in a palladium-catalysed stannylation of 4-bromoveratrole **2-52** in the presence of hexabutyl- or hexamethylditin and Tetrakis(triphenylphosphine)palladium(0) (Scheme 2.20). 4-Tributyl- **2-53** and 4-trimethyltin veratrole **1-69** were obtained in 44% and 74% yield, respectively.



Scheme 2.20. Synthesis of 4-trialkyltin veratrole 2-53 and 1-69.

The arylstannanes **2-53** and **1-69** were reacted with to 1.2 equivalents of Selectfluor™ and 2 equivalents of silver(I) triflate to achieve the one-pot transmetallation/fluorination reaction (Table 2.3).



Entry	Compound	Solvent	Temperature (°C)	Time (min)	Yield 2-54:2-55 (%)[a]	Ratio 2-54:2-55 (%)[b]
1	**2-53**	MeCN	rt	30	-	50:50
2	**2-53**	Acetone	rt	30	17:17	50:50
3	**1-68**	Acetone	rt	30	28:28	50:50
4	**1-68**	Acetone-d_6	rt	60	-	42:58
5	**1-68**	Acetone-d_6	rt	240	-	36:64
6	**1-68**	Acetone-d_6	0	30	-	48:52
7	**1-68**	Acetone-d_6	60	20	-	36:64
8[c]	**1-68**	Acetone-d_6	rt	30	-	42:58
9[d]	**1-68**	Acetone-d_6	rt	30	-	42:58
10[e]	**1-68**	Acetone-d_6	rt	30	-	43:57

[a]Isolated yields of **2-54** and **2-55** as a mixture. [b]Ratio determined from the ^{1}H NMR spectrum. [c]Molecular sieves (3Å) were added, [d]10 equivalents of Selectfluor™ was added. [e]$NaHCO_3$ (1.1 equiv.) was added.

Table 2.3. Optimisation of fluorination of 4-trialkyltin veratrole.

Despite extensive efforts to reduce the protodestannylation, this process could not be avoided. Reactions in acetonitrile afforded the two products, as confirmed by ^{1}H NMR analysis, but isolation was not possible as the two products were only present in trace amounts (Table 2.3, Entry 1).

The oxidation power of a silver(I)-catalyst is greatly dependent on the solvent of the reaction.[163],[164] Trogler and co-workers measured this using cyclic voltammetry in order to obtain the reduction potentials of silver(I) trifluoroacetate in a variety of solvents (Table 2.4).

Entry	Solvent	(E^o')
1	CH_2Cl_2	0.65
2	THF	0.41
3	acetone	0.18
4	MeCN	0.04

Table 2.4. Reduction potential (E^o') of Silver (I) trifluoroacetate in different solvents.[164]

It was found that the reduction potential of silver(I) trifluoroacetate decreased in the order of CH_2Cl_2 > THF > acetone > MeCN. These results show that oxidation of silver(I) trifluoroacetate is most thermodynamically favoured in CH_2Cl_2 and the least in MeCN. This suggested that the silver(I) salt may not undergo oxidation in the presence of Selectfluor to form the bimetallic silver(II) species **2-49** under these reaction conditions (Scheme 2.18). Furthermore, silver(I) is also thought to be stabilised in MeCN because the silver(I) cation reacts with the solvent to form a $[Ag(MeCN)_4]^+$ complex.[164] This would prevent the transmetallation reaction between the aryl stannane and the silver(I) salt (Scheme 2.19).[108]

In acetone, the products were obtained in an improved yield and in a ratio of 50:50 (**2-54:2-55**) (Table 2.3, Entries 2 and 3). Since the yield of 4-fluorovetraole was higher when the trimethylstannyl-substituted compound **1-69** was used compared to the tributyl equivalent **2-53,** the latter was not further explored in the fluorination studies. Further optimisation studies (Table 2.3, Entries 4-10) were conducted as NMR experiments to obtain the ratios by ^{1}H NMR directly. When cooled to 0 ^{o}C, the amount of **2-55** was reduced in comparison to heating (Table 2.3, Entries 6 and 7). This indicated that the protodestannylation process could be temperature dependent. Removal of any water present in the reaction mixture by the addition of molecular sieves, in an attempt to prevent the protodestannylation process, did not diminish the amount of side-product **2-55** (Table 2.3, Entry 8). It was proposed that an excess of Selectfluor (10 equivalents) could promote fluorination over protodestannylation, but the ratio of **2-54** to **2-55** was not improved (Table 2.3, Entry 9). Finally, it was found

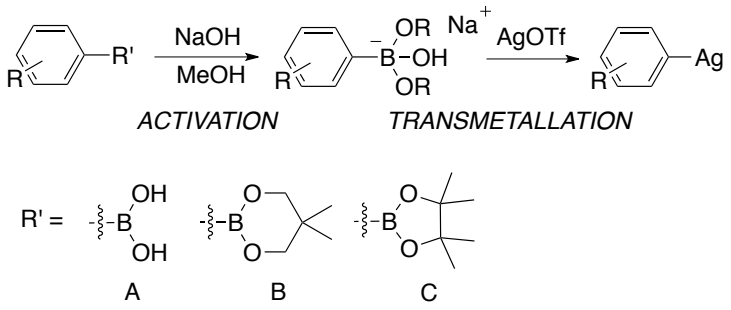
that addition of 1 equivalent of $NaHCO_3$, in an attempt to neutralise the acid formed in the reaction, did not diminish the formation of **2-55** (Table 2.3, Entry 10).

2.4.1.2 Literature regarding the choice of boronic moieties for the fluorination of veratrole boronic acid derivatives

It was decided to also study the veratrole model substrate for the fluorination of arylboronic acid derivatives, in order to easily compare the results obtained with those afforded when the arylstannane analogues **2-53** and **1-68** were investigated. Firstly, a suitable boronic moiety for the fluorination reaction was identified.

In the original study by Ritter, using the optimised reaction conditions, it was found that the yield of the fluorinated products **2-46a-c** depended on the nature of the boron moiety (Scheme 2.16).[158] The yields of the fluorinated products **2-46a-c** decreased according to the following trend: boronic acid (95%) > neopentylglycol boronic ester (76%) > pinacol boronic ester (36%).

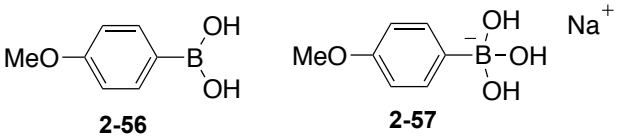
It is not explained by Ritter whether the formation of side-products is observed in addition to the desired product, or if only unreacted starting material is recovered. The reaction time for the activation step in this protocol is relatively short (15 min) so the reason for this observed trend could be explained by the varying reactivity of different boronic acid derivatives towards sodium hydroxide to form the corresponding hydroxyboronate anion, prior to transmetallation (Scheme 2.21).[158]



Scheme 2.21. Activation of boronic acid derivatives and transmetallation.

The requirement of activation by the addition of base prior to participation in transmetallation reactions, can be reasoned by comparing the differences in the B-C

and B-O bond lengths before and after activation. The B-C and B-O bond lengths of 4-methoxyphenylboronic acid are summarised in Table 2.5.[165]



2-56 **2-57**

Compound	B-C (Å)	B-O[1] (Å)	B-O[2] (Å)
2-56	1.568	1.378	1.362
2-57	1.631	1.492	1.487

Table 2.5. Comparison of bond lengths of 2-56 before and after activation.[165]

The addition of a hydroxide anion into the vacant *p* orbital of the boron changes its level of hybridisation from sp^2 to sp^3 and increases the bond lengths of both B-O bonds and the C-B bond. In essence the bonds are elongated by approximately 0.10 Å.[165] As a result, the energy barrier for cleavage of the C-B bond is lowered and the subsequent transmetallation with a transition metal is postulated to proceed more readily. Formation of the tetrahedral hydroxyboronate anion **2-57** also allows the boronic derivative to depart from the aryl group as a stable 3-coordinate species ($B(OH)_3$).[166]

The rate of activation depends on the nature of the boronic acid derivative, and is for boronic esters measured by the rate of attack of water, i.e. formation of the corresponding tetrahedral hydrate. [166] Simple acyclic boronic esters are hydrated at a rate comparable to boronic acids.[167],[168] However, in the case of cyclic substituted boronic esters, the rate of activation depends on two factors: 1) the increase of steric effects on neighboring atoms upon formation of the hydrated complex, and 2) the concomitant release of angle strain upon going from a planar configuration to the tetracoordinate hydrated form with tetrahedral B and O atoms.[166]

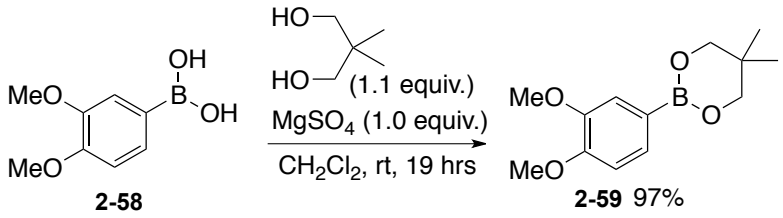
To this end, the rate of activation would follow the trend: boronic acid > 5-membered boronic ester > 6-membered boronic ester.[166] In reference to Ritter's study, this does not explain the trend in the obtained yields (Scheme 2.16). It is postulated that in the case of the extremely hindered pinacol boronic ester **2-46c**, factor 2) has less effect compared to the increase in steric hindrance according to factor 1), therefore six-membered boronic ester **2-46b** was activated to a greater extent within the 15 minute

reaction time and in return afforded the desired fluorinated product in a greater yield (76% *vs*. 36%).[158]

From these studies it became clear that the reaction conditions for the fluorination of arylboronic acid derivatives, most importantly in terms of amount of base and reaction time, should be tailored to the choice of boronic moiety. In order to design suitable reaction conditions for the systems studied herein, the activation step was studied in detail for a variety of veratrole boronic acid derivatives prior to investigations using L-DOPA precursors.

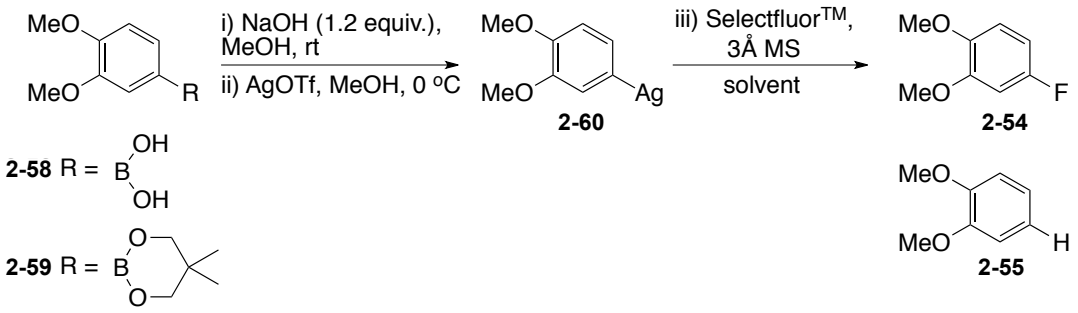
2.4.1.3 Fluorination of veratrole boronic acid derivatives

The veratrole boronic ester 2-(3,4-dimethoxyphenyl)-5,5-dimethyl-1,3,2-dioxaborinane **2-59** was prepared from the commercially available 3,4-dimethoxyphenylboronic acid **2-58** by dehydration with neopentyl glycol in the presence of anhydrous magnesium sulfate (Scheme 2.22).[169]



Scheme 2.22. Preparation of 2-59.

Optimisation of the activation, transmetallation and fluorination steps was carried out by Dr. Charlotte Grube Jørgensen (Table 2.6). 1.2 equivalents of sodium hydroxide was added to substrate **2-58** or **2-59** in methanol and stirred at room temperature before the reaction mixture was cooled to 0 ^{o}C. Upon the addition of silver triflate, the reaction mixture turned bright orange signalling that transmetallation occurred. The methanol was evaporated and replaced with acetone, before Selectfluor^{TM} and molecular sieves were added. After the required time, the reaction was worked up and the ratio of the fluorodeboronated and protodeboronated compounds, **2-54** and **2-55**, was determined by ^{1}H NMR spectroscopy. Purification by column chromatography to afforded **2-54** and **2-55** as a mixture.



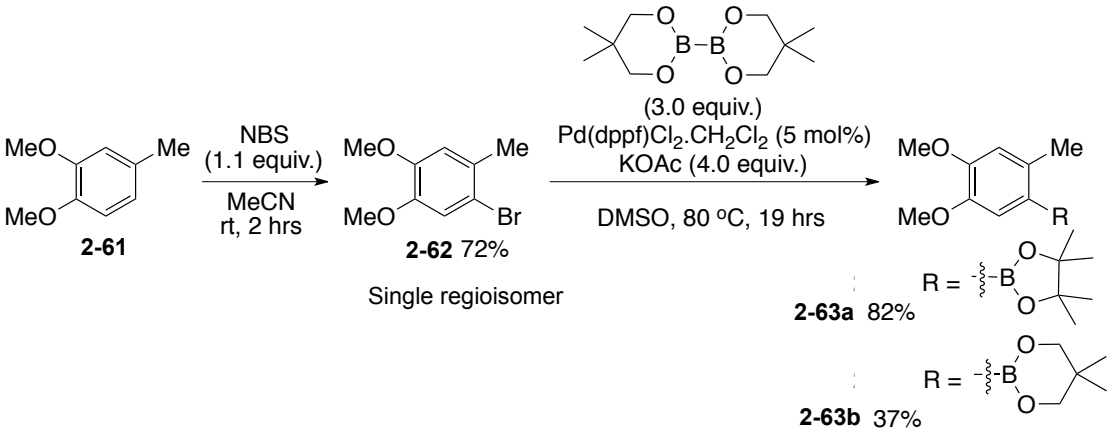
Entry	Prec.	Time (min) i)/ii)	AgOTf (equiv.)	SF (equiv.)	Solvent step iii)	Time (min)	Yield 2-54:2-55 (%)[a]	Ratio (2-54:2-55) (%)[b]
1	**2-58**	15/30	3	1.05	acetone	60	13:3	80:20
2	**2-58**	50/30	3	1.05	acetone	60	19:18	51:49
3	**2-58**	50/30	6	3	THF	120	31:11	73:27
4	**2-59**	15/30	6	3	THF	90	17:2	90:10
5	**2-59**	180/30	3	1.05	acetone	30	27:11	76:24

[a]Concentration = 0.1M. [b]Ratio measured by ^{1}H NMR. [c]Yield of **2-54** and **2-55** isolated as a mixture.

Table 2.6. Optimisation of fluorination of precursors 2-58 and 2-59 (by Dr. CGJ).

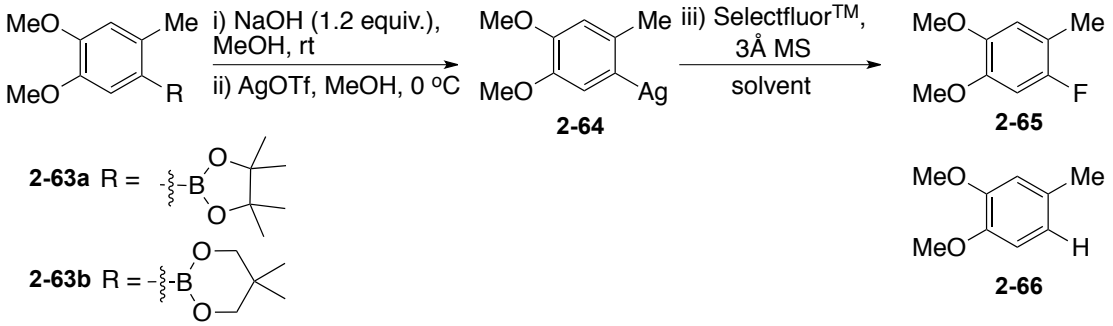
Ritter reported that a significant benefit of using boron over tin was the eradication of the unfavoured protodemetallation process.[158] However, in these studies it became apparent that protodeboronation occurred when the veratrole substrates **2-58** and **2-59** were used (Table 2.6). Even when the optimised conditions used by Ritter were employed, a mixture of the two products **2-54** and **2-55** were afforded in a 1:1 ratio (Table 2.6, Entry 1). Increasing the reaction time for the activation step had no significant positive effect on the yield and afforded **2-55** as the major product (Table 2.6, Entry 2). Garg and co-workers modified the protocol by Ritter for the fluorination of ibuprofen, by increasing the amount of silver triflate and Selectfluor to 6 and 3 equivalents, respectively. In the same studies, acetone was replaced by THF in the fluorination step and the reaction time was increased from 30 minutes to 2 hours.[170] Under these conditions, the amount of protodeboronated side-product was greatly reduced to only 29% and the fluorinated product was afforded in 28% yield (Table 2.6, Entry 3). When the boronic ester **2-59** was investigated using the reaction conditions reported by Garg,[170] the two products **2-54** and **2-55** were obtained in a 90:10 ratio in a combined yield of 19% (Table 2.6, Entry 4). The activation time was extended to 180 minutes to ensure full activation of the boronic ester, and after fluorination using 1.05 equivalents of Selectfluor™, the expected mixture of **2-54** and **2-55** was obtained in a combined yield of 38% and in a 74:26 ratio (Table 2.6, Entry 5).

The effect of increasing the steric hindrance in the position *ortho* to the boronic ester by installing a methyl group was subsequently investigated. This was an attempt to more closely mimic the L-DOPA substrate, which contains the amino acid chain in that position. 1-Bromo-4,5-dimethoxy-2-methylbenzene **2-62** was prepared upon the reaction of 2-methylveratrole **2-61** with NBS in 72% yield, before the boronic esters **2-63a** and **2-63b** were obtained by palladium-catalysed boronylation in 82% and 37% yields, respectively (Scheme 2.23).



Scheme 2.23. Preparation of boronic esters 2-63a and 2-63b.

Optimisation studies, carried out by Dr. Charlotte G. Jørgensen, using similar reaction conditions to the previous study, confirmed the requirement of longer activation reaction times for hindered boronic esters (Table 2.



Entry	Prec.	Time (min) i)/ii)	AgOTf (equiv.)	SF (equiv.)	Solvent step iii)	Time (min) step iii)	Yield 2-65:2-66 (%)[a]	Ratio (2-65:2-66) (%)[b]
1	**2-63a**	25/30	6	3	THF	50	13:3	80:20
2	**2-63a**	180/30	3	1.05	acetone	30	19:18	51:49
3	**2-63b**	180/30	3	1.05	acetone	30	31:11	73:27

[a]Yield of **2-65**:**2-66** as a mixture. [b]Ratio measured by ^{1}H NMR.

Table 2.7. Fluorination of 2-63a and 2-63b (Dr. CGJ).

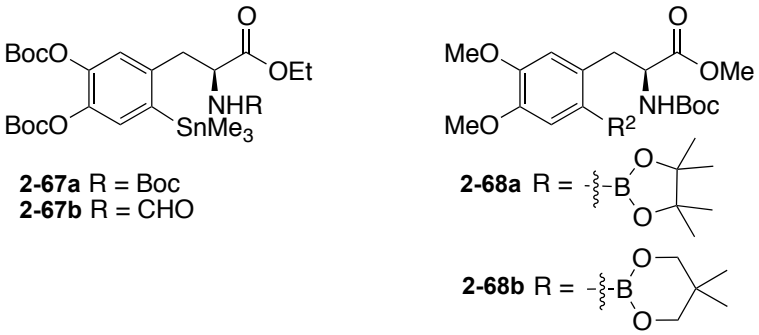
When pinacol boronic ester **2-63a** was subjected to activation conditions for only 25 minutes and subsequently transmetallated and fluorinated in the presence of 6 equivalents of silver triflate and 3 equivalents of Selectfluor^{TM}, respectively, the fluorodeboronated **2-65** and protodeboronated **2-66** products were obtained in a combined yield of 16% and in a ratio of 80:20 (Table 2.7, Entry 1). Increasing the length of the activation step to 180 minutes and employing Ritter's optimised reaction conditions in the fluorination step, increased the yield of the two products to 37%, respectively, but the ratio of **2-65** and **2-66** worsened (Table 2.7, Entry 2). Studying the six-membered neopentyl boronic ester under identical reactions afforded the mixture of products in a significantly improved yield (42%) and product distribution (73:27%) (Table 2.7, Entry 3).

The study of the different model substrates containing different boronic acid derivatives showed that protodeboronation was unavoidable under the reaction conditions studied. The boronic acid **2-58** required a shorter reaction time for the activation step to afford the mixture of **2-54** and **2-55** in yields ranging from 26% to 42%. In comparison, the boronic esters required longer activation prior to transmetallation and fluorination, and afforded the two products in similar yields and ratios. Pleasingly, the fluorination of the more sterically hindered veratrole boronic esters **2-63a-b** was also successful.

The optimisation studies showed that this fluorination reaction was consistently competing with protodemetallation. However, the reaction time was suitable for a radiochemical timescale and the two compounds were separable by HPLC. Further optimisation of the fluorination reaction was optimised directly on L-DOPA precursors.

2.4.2 Preparation of arylstannane and arylboronic ester L-DOPA precursors

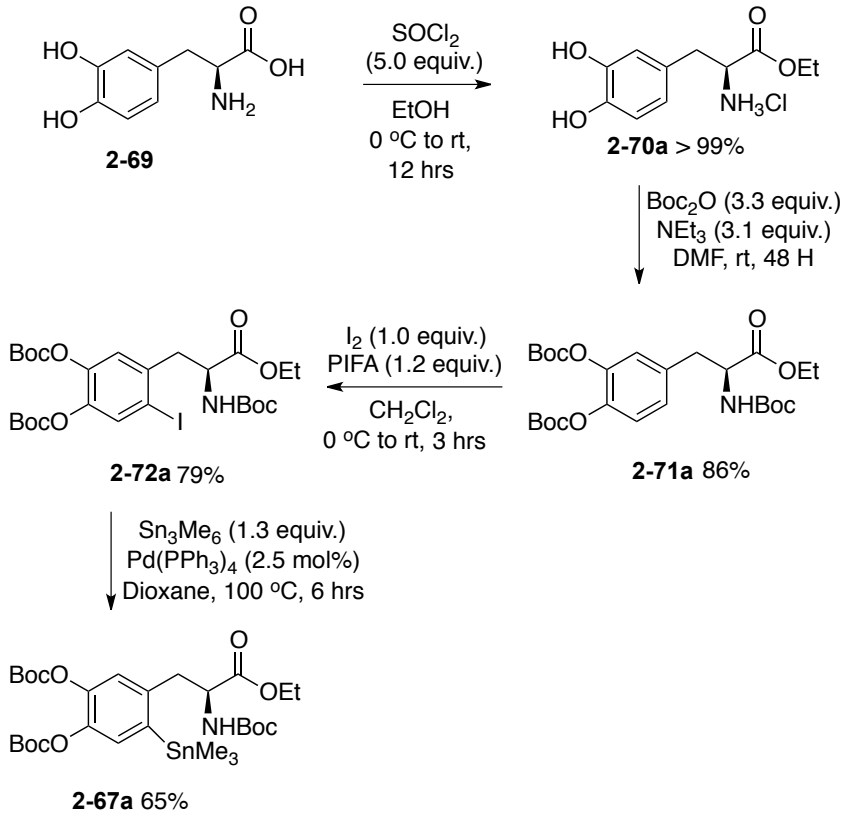
Having studied the veratrole model substrates in detail, we explored the fluorination of arylstannane L-DOPA precursors **2-67a-b** and arylboronic ester L-DOPA precursors **2-68a-b** (Scheme 2.24).



Scheme 2.24. L-DOPA precursors investigated under 'cold' fluorination reaction conditions.

In order to investigate if the nature of the amine protecting group, which is in close proximity to the site of fluorination, two L-DOPA precursors with different substituents on the amine functionality was prepared and investigated in the fluorination reaction. The protected trimethylstannyl L-DOPA precursor **2-67a**, was globally protected with di-*tert*-butyl dicarbonate, and in the commercially available precursor **2-67b**, the amine was protected with a formyl group. Precursor **2-67b** is commonly used in the routine electrophilic production of 6-[^{18}F]fluoro-L-DOPA **[^{18}F]1-11**.[55],[50]

The protected trimethylstannyl L-DOPA precursor **2-67a** was synthesised according to literature procedures (Scheme 2.25).[135]



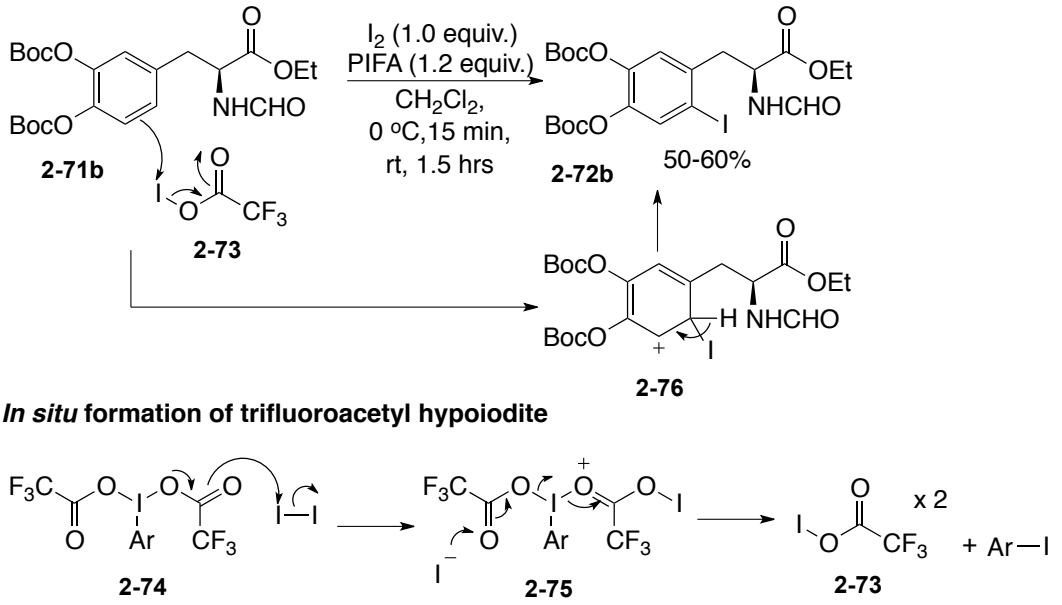
Scheme 2.25. Preparation of L-DOPA precursor 2-67a.

Fischer esterification of L-DOPA **2-69** using thionyl chloride in ethanol, followed by global protection of both alcohols and the amine using di-*tert*-butyl dicarbonate, gave **2-71a** in 86% yield over two steps.

Iodine is insufficiently electrophilic to undergo direct aromatic substitution and require oxidation to the corresponding iodonium species (I^+) prior to the iodination reaction. In the synthetic route to trimethylstannyl L-DOPA precursor **2-67b** designed by Namavari and co-workers, iodine was used in the presence of silver(I) trifluoroacetate as the oxidant. The desired iodinated product was obtained in 12% yield after 24 hours.[55]

The direct electrophilic iodination of L-DOPA precursor **2-71b** has been optimised by Füchtner and co-workers, by using [bis(trifluoroacetoxy)iodo]benzene (PIFA) as the oxidant.[171] Iodine reacts with PIFA to yield trifluoroacetyl hypoiodite **2-73** which is the reactive source of iodine in the S_NAr reaction. Füchtner found that in the presence

of 1 equivalent of iodine and 1.2 equivalents of PIFA, the desired product 2-72b was obtained in 50-60% yield after 1.5 hours (Scheme 2.26).



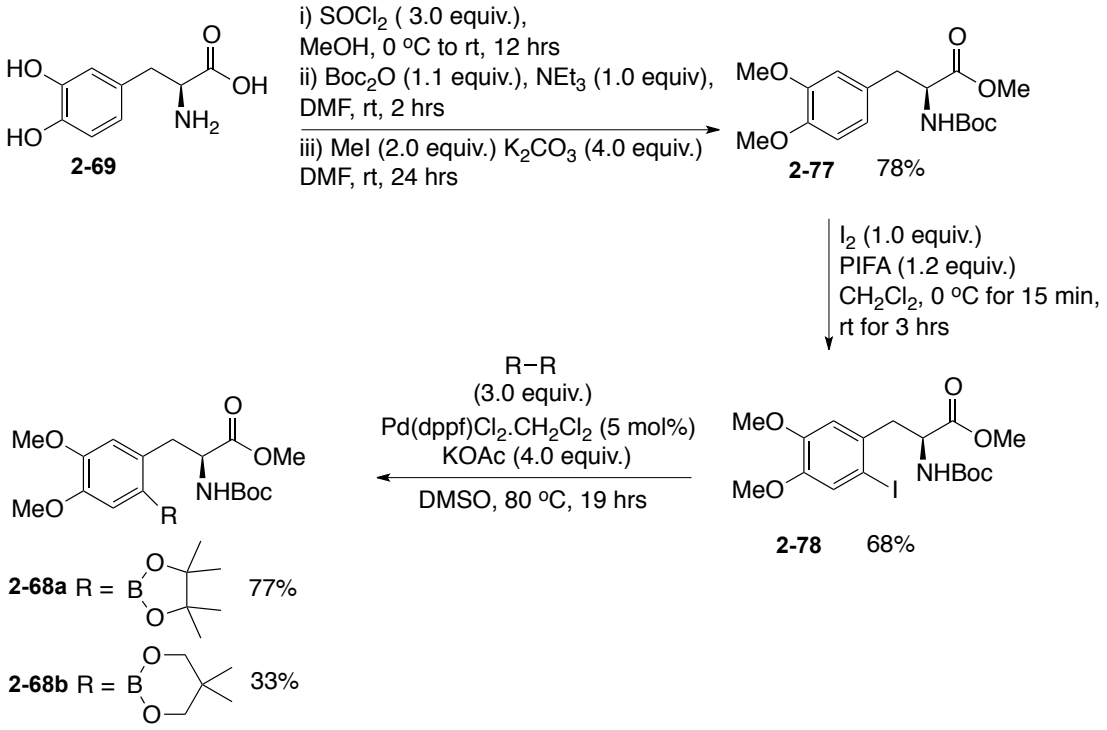
Scheme 2.26. Optimisation of iodination and mechanism of iodination with iodine and PIFA (Füchtner).[171]

In the preparation of the corresponding compound **2-72a**, it was found that the yield could be increased to 79% by extending the reaction time to 3 hours (Scheme 2.25). The regioselectivity of the iodination reaction was confirmed by the presence of two singlets in the aromatic region of the ^{1}H NMR spectrum (7.75 and 7.15 ppm).

The final palladium-catalysed stannylation, using $Pd(PPh_3)_4$ and hexamethylditin, proceeded smoothly to yield **2-67a** in 65% yield.

The boronic ester L-DOPA precursors **2-68a-b** were prepared in five steps from L-DOPA **2-69** according to literature procedures analogous to the trimethylstannane L-DOPA precursors **2-67a-b**. Global protection was achieved in three steps by formation of the methyl ester, protection of the amine functionality using di-*tert*-butyl dicarbonate and protection of the catechol functionality as the methyl ethers, affording precursor **2-77** in 78% yield. Direct electrophilic iodination using the previously optimised conditions (Scheme 2.25) afforded **2-78** in 68% yield. The boronic esters were installed by palladium-catalysed borylation using either *bis*(pinacolato)diboron or

bis(neopentyl glycolato)diboron affording **2-68a** and **2-68b** in 77% and 33% yields, respectively (Scheme 2.27).

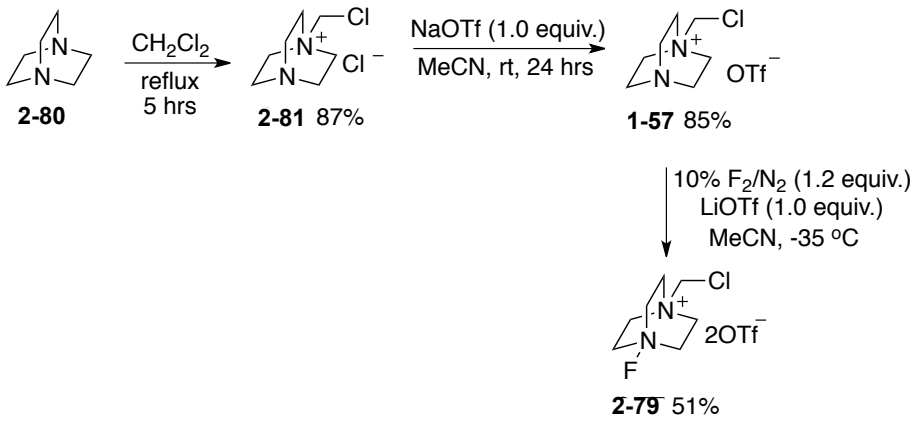


Scheme 2.27. Preparation of boronic ester precursors 2-63a and **2-63b.**

2.4.3 Fluorination of arylstannane and arylboronic ester L-DOPA precursors

The fluorination of **2-67a-b** and **2-68a-b** was studied using both Selectfluor™ **1-58** and Selectfluor *bis*(triflate) **2-79** to investigate whether the difference in counterion influenced the outcome of the reaction. Furthermore, [^{18}F]Selectfluor *bis*(triflate) **[^{18}F]1-51** will be employed in the radiochemical studies so it is valuable to explore its reactivity in the 'cold' fluorination studies. As **2-79** is no longer commercially available, it was prepared according to a literature procedure.[94] DABCO **2-80** was chloromethylated in dichloromethane under reflux to afford the chloromethylated intermediate **2-81** in 87% yield. Counterion exchange to introduce the triflate anion into **1-57** was performed in the presence of sodium triflate (Scheme 2.28). The success of the counterion exchange reaction was measured by analysis of the ^{19}F NMR spectrum of the reaction by addition of fluorobenzene (1 equivalent) as an internal reference standard to 1 equivalent of **2-82** in MeCN-d_3. Two peaks were observed at -79.3 ppm and -124.9 ppm, in a 3 to 1 ratio, corresponding to the triflate and

fluorobenzene, respectively. This confirmed that the counterion exchange was complete.



Scheme 2.28. Preparation of Selectfluor *bis*(triflate) 2-79.

The final fluorination, using fluorine gas, to prepare Selectfluor *bis*(triflate) was carried out in the laboratory of Professor Graham Sandford at Durham University (Scheme 2.28).The specialist equipment for handling F_2 is shown in Figure 2.4. The solution of precursor **1-57** and 1 equivalent of sodium triflate in acetonitrile was placed in a PTFE reaction vessel (**A**) containing a stirrer bar and fitted with PTFE tubing to create an inlet (**B**) and an outlet (**C**). The vessel was placed in an acetone and dry ice bath at a temperature of -35 ^{o}C. First, the system was purged with nitrogen gas for a minimum of 5 minutes to eliminate air from the system. The PFTE inlet (**A**) was designed such that it nearly touches the rapidly stirring magnetic follower, i.e. the gas was released into the middle of the solution to ensure most efficient reaction. The flow rate was controlled by a flow meter (**D**) at 15.0 mL/min. The F_2 gas (10% in nitrogen gas) was allowed to bubble through the system for a time corresponding to 1.2 equiv. of F_2, while the temperature was kept at -35 ^{o}C. After the reaction, the reaction mixture was allowed to warm up to room temperature while nitrogen gas was bubbled through for 10 minutes to purge the system. The outlet (**C**) goes into a soda-lime scrubber. Following work up and recrystallisation, Selectfluor *bis*(triflate) **2-79** was obtained in 51% yield.

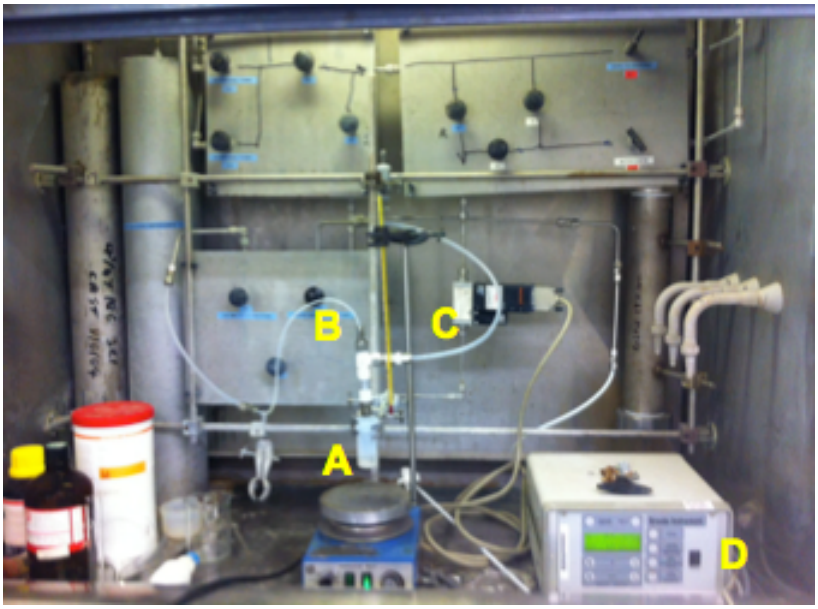
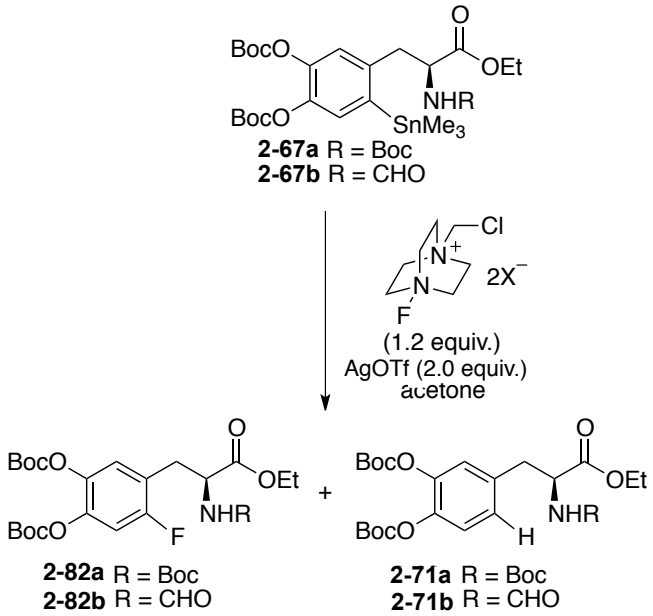


Figure 2.4. Equipment for F_2 chemistry.

With both fluorinating reagents in hand, the fluorination of **2-67a-b** was studied first. In the presence of either Selectfluor™ or Selectfluor *bis*(triflate) and 2 equivalents of silver triflate in acetone or acetonitrile, the desired fluorinated products **2-82a-b** were obtained within 30 minutes at room temperature in good yields and with a lower amount of the protodestannylated product being observed compared to the veratrole system (Table 2.8). Optimisation studies were carried out in attempt to minimise the protodestannylation process.



Entry	Prec.	X	Solvent	Temperature (^{o}C)	Time (min)	Yield (%)[a] 2-82a-b: 2-71a-b	Ratio (%)[b] 2-82a-b: 2-71a-b
1	**2-67a**	BF_4^-	actone	rt	30	50:12	81:19
2	**2-67a**	BF_4^-	MeCN	rt	30	35:18	65:35
3[c]	**2-67a**	BF_4^-	actone	rt	30	44:18	73:27
4[d]	**2-67a**	BF_4^-	actone	rt	30	41:17	71:29
5[e]	**2-67a**	BF_4^-	actone	rt	25	2.6:3.7	41:59
6	**2-67a**	OTf^-	actone	rt	25	45:15	74:26
7	**2-67b**	BF_4^-	actone	rt	25	43:23	65:35
8	**2-67b**	OTf^-	actone	rt	25	44:22	67:33
9[d]	**2-67b**	OTf^-	actone	60	20	42:17	71:29

[a]Yields of **2-82a** and **2-71a** or **2-82b** and **2-71b** were calculated from mixtures of the two compounds. [b]Ratio measured by ^{1}H NMR. [c]3Å MS added. [d] $NaHCO_3$ (1.2 equiv.) added. [e]AgOTf (20 mol%).

Table 2.8. Optimisation of fluorination of precursors 2-67a and 2-67b.

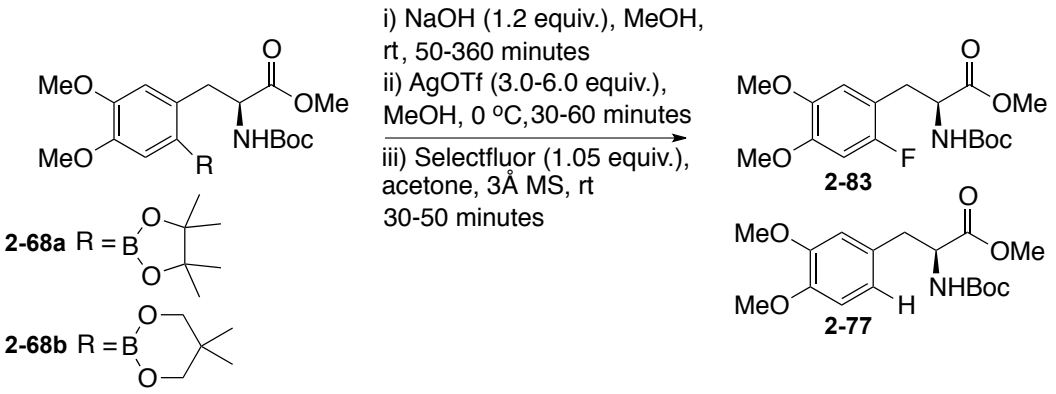
Fluorination of trimethylstannane precursor **2-67a** at room temperature was carried out using the optimised conditions for veratrole **1-68** and afforded the mixture of **2-82a** and **2-71a** in 67% yield (Table 2.8, Entry 1). Furthermore, only 19% of the protodestannylated product was observed. Interestingly, the reaction proceeded with greater success in acetonitrile than veratrole trimethylstannane **1-68** (Table 2.8, Entry 2). However, the yields obtained for **2-82a** and **2-71a** were variable, and ranged from 37-69% (average = 53%, *n* = 2). Conversely, the ratio of the two products did not change significantly when the reaction was repeated (66:34 to 62:38, average = 65:35, *n* = 2) (Table 2.8, Entry 2). Adding 3Å molecular sieves or base did not improve the ratio of products (Table 2.8, Entries 3 and 4). $NaHCO_3$ was selected as the base since it was found to reduce the amount of protodestannylated product in Ritter's silver(I)

oxide catalysed fluorination of arenes (Scheme 2.14).[157] When the L-DOPA precursor was exposed to 20 mol % AgOTf, this increased the amount of protodestannylated product **2-71a** to 59% and decreased the yield to 6% (Table 2.8, Entry 5). Finally, when Selectfluor *bis*(triflate) was explored as the electrophilic source of fluorine, the ratio of **2-82a** to **2-71a** was comparable to that afforded by Selectfluor™ (Table 2.8, Entry 6).

Fluorination of the commercial L-DOPA precursor **2-67b** afforded similar ratios and yields of the two expected products, **2-82b** and **2-71b**, to L-DOPA precursor **2-67a**. There was no significant difference in the product ratio when either Selectfluor™ or Selectfluor *bis*(triflate) was used (65:35 *vs* 67:33) (Table 2.8, Entries 7 and 8). Upon heating and, in the presence of base and Selectfluor™, the two products **2-82b** and **2-71b** were afforded in 59% yield and a 71:29 ratio (Table 2.8, Entry 9).

In summary, the use of two different trimethylstannane L-DOPA precursors **2-67a** and **2-67b** did not significantly affect the ratio of the two products, implying that modifying the amine-protecting group does not affect the fluorination reaction. Selectfluor™ and Selectfluor *bis*(triflate) afforded the two products in similar yield and ratio. Moreover, the reaction reached completion within 30 minutes at room temperature and the products could be easily separated by HPLC. These reaction conditions are ideal for extension to a radiochemical setting.

The previous optimisation studies on the fluorination of veratrole boronic acid derivatives revealed that activation of boronic esters is slower than for boronic acids (Tables 2.6 and 2.7). As a result, it was decided to optimise the activation step for arylboronic ester L-DOPA precursors **2-68a** and **2-68b** in order to maximise the yield of the fluorination reaction. Both Ritter[158] and Garg's[170] optimised fluorination conditions were investigated (Table 2.9).



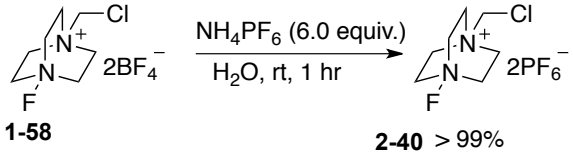
Entry[a]	Prec.	Time (min) Step i)/ii)	AgOTf (equiv.)	SF (eq.)	Solvent step iii)	Time (min) Step iii)	Yield (%)[b] (2-83:2-77)	Ratio (%)[c] (2-83:2-77)
1	**2-68a**	50/60	6	3	THF	50	-	67:7
2	**2-68a**	180/30	3	1.05	acetone	30	7:7	50:50
3	**2-68b**	180/30	6	3	THF	30	18:7	71:29
4	**2-68b**	180/30	3	1.05	acetone	30	30:7	82:18
5[d]	**2-68b**	80/30	6	3	THF	30	11:12	47:53
6	**2-68b**	360/30	3	1.05	acetone	30	21:6	77:23

[a]Reactions in entries 1-3, 5 and 6 were carried out by Dr. Charlotte G. Jørgensen. [b]Yields of **2-83** and **2-77** were calculated from mixtures of the two compounds. [c]Ratio measured by ^{1}H NMR. [d]Heated at 45 °C.

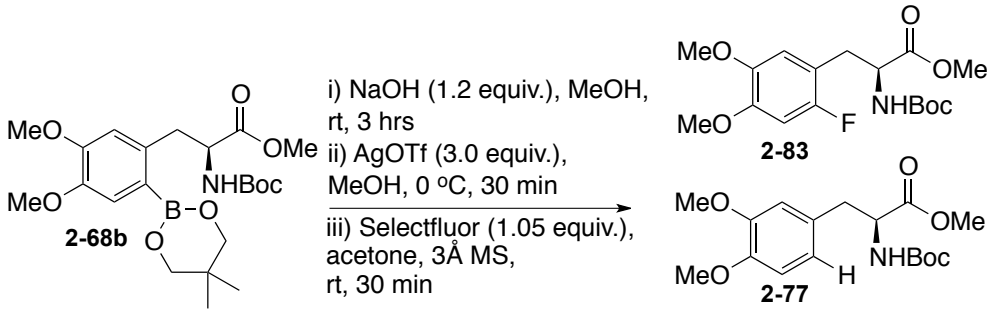
Table 2.9. Fluorination of arylboronic ester L-DOPA precursors 2-68a and 2-68b.

The fluorination of arylboronic pinacol ester L-DOPA precursor **2-68a** was challenging. Under short activation conditions and in the presence of a large excess of silver triflate and Selectfluor™, the obtained ratio of the fluorodeboronated **2-83** and protodeboronated **2-77** products was 69% to 5%, respectively. Precursor **2-68a** was recovered in 26% yield (Table 2.9, Entry 1). When the activation step was extended to 3 hours and Ritter's optimised reaction conditions were employed, the two expected products **2-83** and **2-77** were obtained in a disappointing 14% yield, in a 1:1 ratio (Table 2.9, Entry 2). The arylboronic neopentylglycol ester L-DOPA precursor **2-68b** was found to be more amenable to fluorination. In the presence of Garg or Ritter's fluorination conditions, the mixture of **2-83** and **2-77** was obtained in improved yields of 25% and 37%, respectively. This was further reflected in the improved product ratios: 71:29 and 82:18 of **2-83** and **2-77** (Table 2.9, Entry 3 and 4). Further attempts at improving the outcome of the reaction, by heating the reaction mixture at 45 °C during the activation step or extending the reaction time of this step to 6 hours, failed to significantly increase the yield of **2-83** and **2-77** (Table 2.9, Entry 5 and 6).

From these studies arylboronic neopentylglycol ester L-DOPA precursor **2-68b** was identified as the best candidate for radiolabelling studies, both in terms of yield and ratio obtained for the fluorodeboronated **2-83** and protodeboronated **2-77** products. The optimisation studies in Table 2.9 were carried out with the commercially available Selectfluor™ **1-58**, so prior to the radiolabelling studies, the fluorination reaction was also repeated with Selectfluor *bis*(triflate) **2-79** and Selectfluor *bis*(hexafluorophosphate) **2-40** (Table 2.10). Selectfluor *bis*(hexafluorophosphate) **2-40** was prepared according to a literature procedure from Selectfluor™ in >99% yield (Scheme 2.29).[108]



Scheme 2.29. Preparation of Selectfluor *bis*(hexafluorophosphate) 2-40.



Entry	Selectfluor Counterion	Ratio (2-83:2-77)[a]	Yield (%)[b] (2-83:2-77)
1	OTf	91:9	45:4
2	PF_6	85:15	36:6
3	BF_4	82:18	31:6

[a] Ratio measured by ^{1}H NMR. [b]Yields of **2-83** and **2-77** were calculated from mixtures of the two compounds.

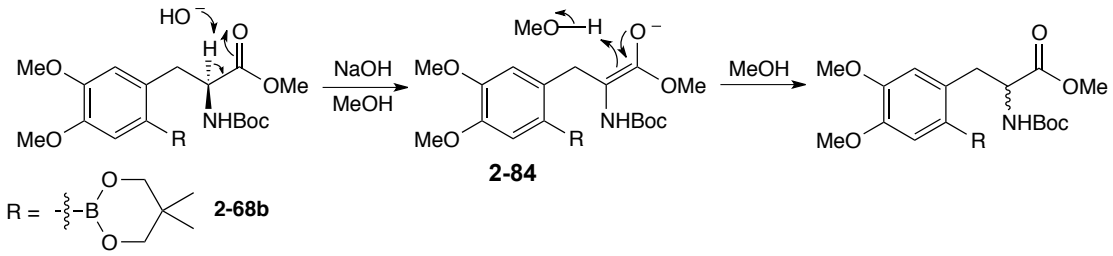
Table 2.10. Effect of varying the Selectfluor counterion on yield and ratio of 2-83 and 2-77.

After the activation and transmetallation according to the optimised reaction conditions (Table 2.9 Entry 4), the fluorination of **2-68b** was carried out with Selectfluor containing tetrafluoroborate, triflate or hexafluorophosphate as the counterion. It was found that Selectfluor *bis*(triflate) afforded the mixture of products **2-83** and **2-77** in the highest yield of 49% in a 91:9 ratio (Table 2.10, Entry 1).

Selectfluor containing either hexafluorophosphate or tetrafluoroborate counterions afforded the products in a lower yield and with increased amount of protodeboronation (Table 2.10, Entries 2 and 3). These results are encouraging for radiolabelling where [^{18}F]Selectfluor *bis*(triflate) is the reagent of choice.

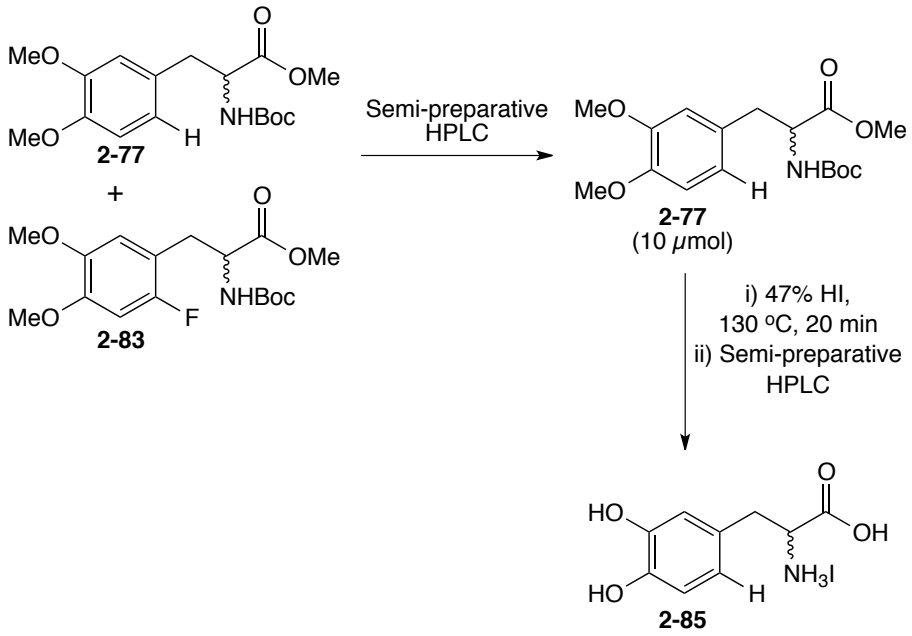
2.4.4 Investigation into the racemisation of arylboronic acid ester L-DOPA precursor 2-68b during the fluorination reaction

The first step of the fluorination reaction developed herein, is activation of the arylboronic ester L-DOPA precursors **2-68a** and **2-68b** in the reaction with sodium hydroxide in methanol for 3 hours at room temperature. Although an unlikely process under these reaction conditions, [172] racemisation of the amino acid functionality of **2-68a** and **2-68b** *via* an enolate intermediate **2-84** may be possible (Scheme 2.30).



Scheme 2.30. Mechanism of possible racemisation of 2-68b.

As a result, it was decided to investigate the enantiomeric purity of the fluoro- and protodeboronated products **2-83** and **2-77,** obtained after fluorination of enantiopure (> 98% ee) arylboronic ester L-DOPA precursor **2-68b**. *N*-(*tert*-Butoxycarbonyl)-3,4-di(*tert*-butoxycarbonyloxy)-L-phenylalanine methyl ester **2-77** was obtained upon semi-preparative HPLC purification of the isolated mixture of the fluoro- and protodeboronated products **2-83** and **2-77**. Global deprotection was successful in the presence of a solution of 47% HI at 130 ^{o}C for 20 minutes and the HI salt of unprotected DOPA **2-85** was afforded after semi-preparative HPLC purification (Scheme 2.31). Analysis of **2-85**, using a chiral Crownpak (+) HPLC column showed that the enatiomeric excess of 6-fluoro-L-DOPA was 91.6%, confirming that a relatively small extent of racemisation occurred during the activation of arylboronic ester L-DOPA precursor **2-68b** (Figure 2.5).



Scheme 2.31. Deprotection of 2-77 for determination of ee.

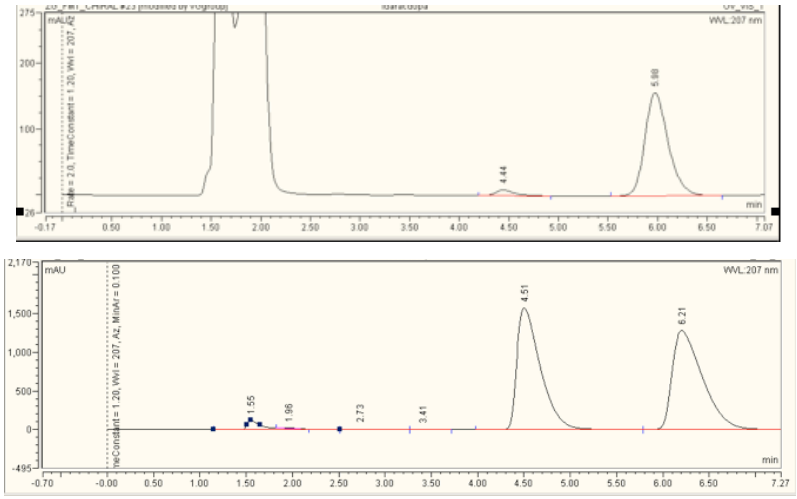
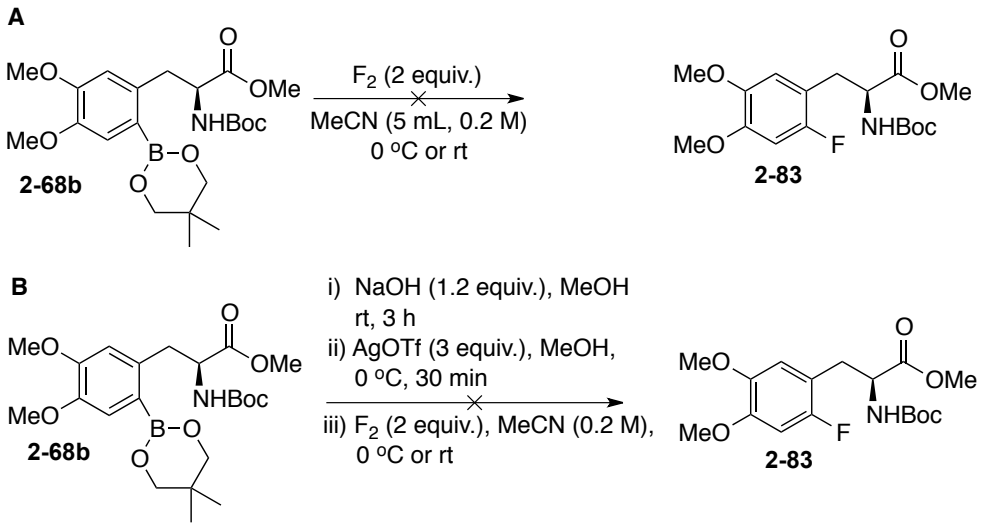


Figure 2.5. Determination of ee of L- DOPA. Top: L-DOPA from reaction mixture (minor D-DOPA, 4.44 min = 4.2%, major L- DOPA, 5.98 min = 95.8%). Bottom: Authentic racemic DL- DOPA (D-DOPA, 4.51 min, L- DOPA, 6.21 min).

2.4.5 Fluorination of boronic ester L-DOPA precursor 2-68b using fluorine gas

Considering the success of the reaction with Selectfluor *bis*(triflate), we wanted to investigate the potential of fluorine gas as an alternative reagent. Studies were again carried out in Prof. Graham Sandford's Laboratory at Durham University using the same equipment as described above (Section 2.4.3). We first investigated the direct fluorination of the arylboronic ester L-DOPA precursor **2-68b**, in an attempt to mimic

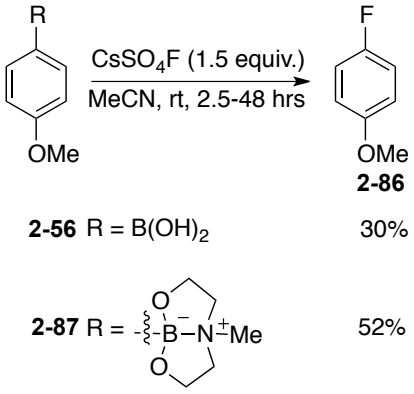
the direct fluorination of trimethylstannyl L-DOPA precursor **2-67b** with fluorine gas (Scheme 2.32A), before investigating the silver(I)-catalysed strategy (Scheme 2.32B).



Scheme 2.32. Fluorination of boronic esters using F_2.

In the presence of 2 equivalents of F_2, at either 0 °C or room temperature, no peaks in the aromatic region of the ^{19}F NMR were observed upon the fluorination of **2-68b** (Scheme 2.32A). The only peak in the spectrum corresponded and the internal reference (1-fluoro-3-nitrobenzene). Starting material was recovered in 85% yield.

Upon consulting the literature it was discovered that direct fluorination of 4-methoxyphenylboronic acid **2-56** may be achieved in the presence of cesium fluoroxysulfate, a more selective reagent with comparable reactivity to XeF_2. Clough and co-workers found that in the presence of 1.5 equivalents of $CsSO_4F$, 30% of the desired product **2-86** was obtained after 2 hours at room temperature (Scheme 2.33).[173] Optimisation studies by the same research group showed that protection of the boronic acid as the diethanolamine ester **2-87** increased the yield of **2-86** to 52%.[174] It was postulated that the increased electron density on boron in **2-87** by the formation of the tetracoordinate complex, in turn improved the nucleophilicity of the arene. In either case, no unselective fluorination of the aromatic moiety was observed. An analogous reaction for the direct fluorination of arylboronic acids was reported employing Selectfluor™ as the fluorine source, but a reaction time of 24 hours was required at room temperature.[175]



Scheme 2.33. Direct fluorination of 4-methoxyphenyl boronic acid derivatives 2-56 and 2-87 by Clough.[173],[174]

In the studies in this thesis, 2 equivalents of F_2 were bubbled through the reaction mixture at 0 ^oC or room temperature, which equals a reaction time of 7.5 minutes. It was postulated that these reactions conditions were not forcing enough to allow, what appears to be a quite a challenging transformation to proceed, even in the presence of F_2.

When the arylsilver complex was prepared and subjected to fluorination in acetonitrile, no fluorination was achieved and 61% starting material was recovered (Scheme 2.32B). This result may be explained by the choice of solvent for the reaction. As explained in section 2.4.1.1, silver(I) salts react with acetontrile to form $[Ag(MeCN)_4]^+$ which may prevent the oxidation step from occurring.[164]

The reaction conditions required for successful fluorination with F_2 are very restrictive due to the high reactivity of the reagent. Less reactive reagents like [^{18}F]Selectfluor *bis*(triflate) are compatible with a wider range of transformations. This set of experiments illustrates the benefit of having electrophilic N-F reagents with tailored reactivity, which allow the preparation of complex targets using transformations incompatible with F_2 .

2.4.6 Radiochemistry

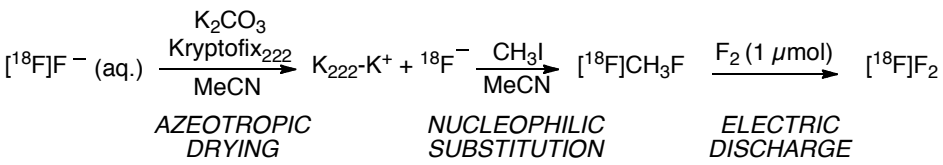
The optimisation studies suggested that both silver(I)-mediated fluorination of arylstannane and arylboronic ester L-DOPA precursors had the potential to be extended to radiolabelling. The [^{18}F]fluorination of both the commercially available L-

DOPA trimethylstannane precursor **2-67b** and the boronic ester L-DOPA precursor **2-68b** using [^{18}F]Selectfluor *bis*(triflate) **[^{18}F]1-51** was investigated. The radiolabelling studies were carried out at Turku PET Centre under the supervision of Professor Olof Solin.

2.4.6.1 Preparation of [^{18}F]Selectfluor *bis*(triflate) [^{18}F]1-50

It was decided to optimise the original method for the preparation of [^{18}F]Selectfluor *bis*(triflate) **[^{18}F]1-50**, which employed a large excess of the Selectfluor precursor **1-57** (48μmol) and acetonitrile as the solvent. [^{18}F]Selectfluor *bis*(triflate) **[^{18}F]1-50** was prepared directly in acetone-d_6 in the radiolabelling of both **2-67b** and **2-68b** in order to avoid an additional evaporation step prior to the subsequent [^{18}F]fluorination reactions. It was also investigated whether [^{18}F]Selectfluor *bis*(triflate) could be prepared using greatly reduced amounts of Selectfluor precursor (7.5–2.0 μmol). Such reaction conditions would afford more efficient and cleaner subsequent labelling reactions.

The research group of Professor Solin has devised a "post-target" method for the preparation of high specific activity [^{18}F]F_2 (Scheme 2.34).[11]

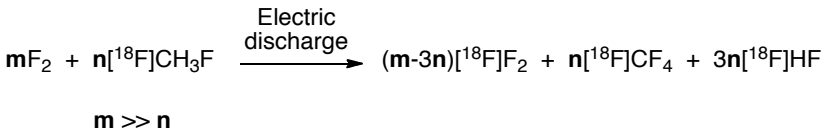


Scheme 2.34. Preparation of [^{18}F]F_2.

[^{18}F]fluoride was prepared *via* the ^{18}O(*p*,*n*)^{18}F nuclear reaction following irradiation of the ^{18}O-enriched water target for either 30 (precursor **2-67b**) or 15 minutes (precursor **2-68b**) with a beam current of 35 μA. The aqueous [^{18}F]fluoride was subsequently passed through an ion-exchange resin with the effect of separating the [^{18}F]fluoride from the ^{18}O-enriched water. The [^{18}F]fluoride was then delivered to the hot cell as a solution in MeCN into a reaction vessel containing $Kryptofix_{222}$ and K_2CO_3.

Azeotropic drying to remove water from the system and synthesis of [^{18}F]F_2 was carried out using a specially designed automated device controlled by a touch screen.

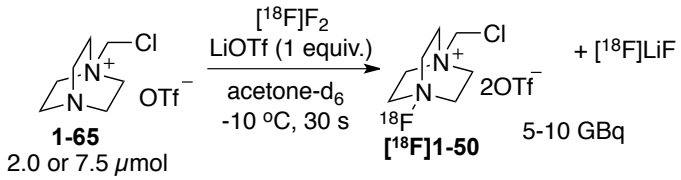
The MeCN/H_2O solution containing the mixture of Kryptofix$_{222}$/K^+/[^{18}F]fluoride was evaporated to dryness under reduced pressure and a stream of helium at 90 ^oC. After 2 minutes, anhydrous MeCN was added and the drying step repeated. The reaction vial was allowed to cool down before CH_3I was added to the dry cryptate. The nucelophilic substitution step took place at 90 ^oC within 1 minute. The radioactive gases and flushing neon gas were transferred to a syringe and injected onto the GC column. The radioactive products were eluted with neon at room temperature and the desired [^{18}F]fluoromethane [^{18}F]**1-54** fraction was trapped in a steel loop placed in a Dewer containing liquid nitrogen. The elution of [^{18}F]**1-54** was monitored by a detector placed adjacent to the steel loop and once trapped, the steel loop was allowed to warm up for 30 seconds before the contents were transferred into the electric discharge chamber using neon. This chamber contains a known amount of carrier fluorine gas (approximately 1 μmol). [^{18}F]Fluoromethane [^{18}F]**1-54** and F_2 were allowed to react under electric discharge for 10 seconds. Electric discharge occurs when an electric current flows through a gaseous medium. This causes the chemical bonds of the content to break and reassemble. In this case this results in an interchange between a ^{19}F and ^{18}F atom. Assuming that all bonds are broken, the product distribution depended on the amount of [^{18}F]fluoromethane and F_2 used. When an excess of F_2 was used (m>>n), the distribution may be described by the following equation (Scheme 2.35).[11]



Scheme 2.35. 'Post-target' electric discharge method for the preparation of [^{18}F]F_2.

The equation demonstrates that when an excess of F_2 was added, the major product formed was [^{18}F]F_2 while the predicted side-products ([^{18}F]CF_4 and [^{18}F]HF) were present in negligible amounts. Despite requiring an excess of F_2 carrier gas, the amount added was much less than in the other "in-target" protocols (1 μmol vs 100-200 μmol).[176] Following the electric discharge process, the [^{18}F]F_2 was ready for use in the preparation of [^{18}F]Selectfluor *bis*(triflate).

A Wheton vial containing a solution of Selectfluor precursor **1-65** (2.0 or 7.5 μmol) and 1 equivalent of lithium triflate in acetone-d_6 (0.75 mL) was cooled in an ice/salt bath at -10 °C before the [^{18}F]F_2 was bubbled through for 30 seconds (Scheme 2.36).



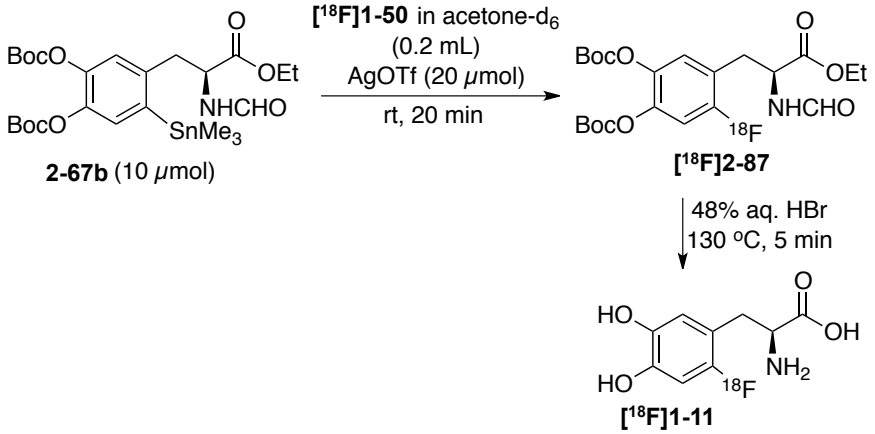
Scheme 2.36. Preparation of [^{18}F]Selectfluor *bis*(triflate).

The activity of the crude stock solution in acetone-d_6 ranged from 5 to 10 GBq, depending on the target irradiation time. Aliquots of the **[^{18}F]1-50** stock were used directly in the subsequent labelling reactions.

2.4.6.2 Synthesis of 6-[^{18}F]fluoro-L-DOPA

The radiochemistry was first validated on trimethylstannane L-DOPA precursor **2-67b** to directly compare the [^{18}F]Selectfluor *bis*(triflate) methodology to the [^{18}F]F_2 route currently employed for patient PET studies at the Turku PET Centre, before studies were carried out on veratrole boronic ester **2-59** and arylboronic ester L-DOPA precursor **2-68b**.

An aliquot of the [^{18}F]Selectfluor *bis*(triflate) stock (0.2 mL) prepared using either 7.5 or 2.0 μmol of Selectfluor precursor **1-65** was added to the trimethylstannane L-DOPA precursor **2-67b** (10 μmol) and 2 equivalents of silver triflate. The reaction mixture was stirred for 20 minutes at room temperature before the acetone-d_6 was evaporated under a stream of nitrogen. A solution of 48% hydrobromic acid was added and after heating at 130 °C for 5 minutes, global deprotection was complete and 6-[^{18}F]fluoro-L-DOPA was obtained (Scheme 2.37).



Scheme 2.37. Radiolabelling of trimethylstannane L-DOPA precursor 2-67b.

The radiolabelling reaction was repeated six times each with [^{18}F]Selectfluor *bis*(triflate) containing either 2.0 and 7.5 μmol of Selectfluor precursor **1-65**. The results are summarised in Table 2.11.

Entry	SF prec. 1-65 (μmol)[a]/ LiOTf (μmol)	Available activity (%)	RCY of [^{18}F]2-87 (%)[d]	RCY of [^{18}F]1-11 (%)[e]	SA (GBq/μmol)
1	2.0/2.0	27	14	15	3.23
2	2.0/2.0	31	14	17	3.40
3	2.0/2.0	49	13	13	3.38
4	2.0/2.0	56	25	10	3.45
5	2.0/2.0	60	22	7	3.46
6[b]	2.0/2.0	39	20	10	3.47
Mean	-	43.7	17.7	12.1	3.40
Std. Dev.	-	13.5	5.1	3.7	0.10
7	7.5/7.5	19	9	4	3.36
8[c]	7.5/7.5	25	11	7	3.34
9[b]	7.5/7.5	35	17	9	3.31
10[c]	7.5/7.5	34	16	6	2.94
11[b]	7.5/7.5	38	9	9	2.85
12	7.5/7.5	35	6	6	2.75
Mean	-	31.0	11.4	6.8	3.09
Std. Dev.	-	7.3	4.1	1.8	0.30

[a]**[^{18}F]1-50** concentration: Entries 1-6 = 0.003 M, Entries 7-12 = 0.01M. [b]$NaHCO_3$(1 equiv.) added. [c] $NaHCO_3$ (1 equiv.), MeOH (10 μL) added. [d]Proportion collected (%) of the radioactivity detected following analytical HPLC of protected 6-[^{18}F]fluoro-L-DOPA intermediate (decay-corrected). [e] Proportion collected (%) of the radioactivity detected following semi-preparative HPLC of 6-[^{18}F]fluoro-L-DOPA multiplied by the available activity (decay-corrected).

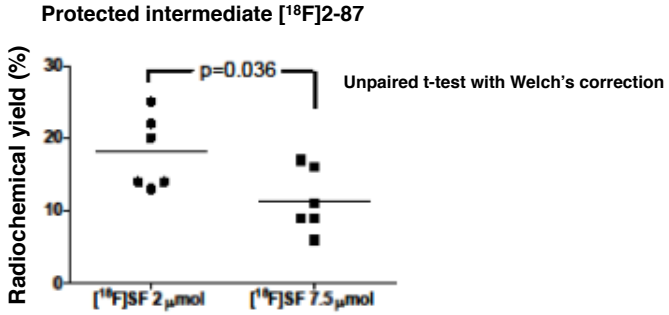
Table 2.11. [^{18}F]fluorination of trimethylstannane L-DOPA precursor 2-67b.

The radiochemical yield of the [^{18}F]labelled protected intermediate **[^{18}F]2-87** was calculated by injecting an aliquot of the reaction mixture of known radioactivity into the HPLC system. The peak corresponding to **[^{18}F]2-87** was collected and its activity measured. The RCY was calculated as the fraction of the activity of the product peak over the total activity of the original aliquot and reported as a percentage. During the acidic deprotection of **[^{18}F]2-87**, unreacted [^{18}F]fluoride is lost as gaseous [^{18}F]HF and the final RCY of 6-[^{18}F]fluoro-L-DOPA **[^{18}F]1-11** must be corrected for this. After the [^{18}F]labelling step, the total radioactivity of the reaction vial was measured and acetone-d_6 was evaporated under nitrogen. A solution of 48% aqueous HBr was added to the reaction mixture and once the deprotection was complete, the activity of the reaction vial was recorded again. This allows the loss of activity in the deprotection step to be measured and the radioactivity remaining is termed 'available activity' (%). The same procedure as above was then carried out to calculate the RCY as a fraction of the total amount of activity injected into the HPLC (%). This result was lastly multiplied with the 'available activity' to afford the corrected RCY (%) of 6-[^{18}F]fluoro-L-DOPA. All RCYs were decay-corrected to the E.O.S of the original [^{18}F]Selectfluor *bis*(triflate) stock.

The success of this reaction showed that the preparation of [^{18}F]Selectfluor *bis*(triflate) in alternative solvents to acetonitrile was possible. When 2.0 μmol of Selectfluor precursor **1-65** was used to prepare **[^{18}F]1-50**, the mean RCY of the protected intermediate **[^{18}F]2-87** was 17.7 ± 5.1%, while 6-[^{18}F]fluoro-L-DOPA **[^{18}F]1-11** was obtained in 12.1 ± 3.7% RCY following acidic deprotection (Table 2.11, Entries 1-6). When the amount of Selectfluor precursor in the [^{18}F]Selectfluor *bis*(triflate) stock was increased to 7.5 μmol, the yields of the protected intermediate **[^{18}F]2-87** and 6-[^{18}F]fluoro-L-DOPA **[^{18}F]1-11** were decreased to 11.4 ± 4.1% and 6.8 ± 1.8%, respectively (Table 2.11, Entries 7-12).

Statistical analysis was carried out by M. Haaparanta using Prism v 5.01 (Graphpad) to determine whether the difference in the RCYs were significantly different. An unpaired t-test was used to compare the mean RCYs obtained for both the protected intermediate **[^{18}F]2-87** (Figure 2.5A) and 6-[^{18}F]fluoro-L-DOPA **[^{18}F]1-11** (Figure 2.5B) when 7.5 or 2.0 μmol of Selectfluor precursor **1-57** was used. The mean RCYs were considered to be significantly different when the p value < 0.05.

A



B

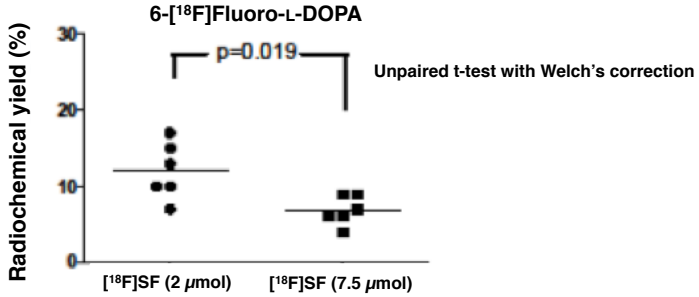


Figure 2.5. Statistical analysis for the comparison of RCY. A) protected intermediate [^{18}F]2-87 B) 6-[^{18}F]fluoro-L-DOPA [^{18}F]1-11.

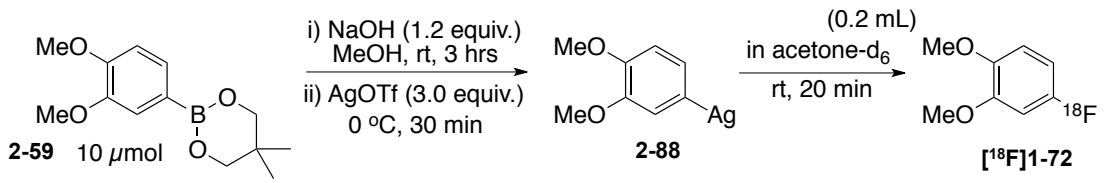
For the protected intermediate **[^{18}F]2-87** the p value = 0.036, which is less than 0.05 and this means that there was a significant difference in the mean RCY of **[^{18}F]2-87** obtained when two different amounts of the Selectfluor precursor **1-65** were used (Figure 2.5A). The same result (p value = 0.019) was obtained when the mean RCYs of the final product 6-[^{18}F]fluoro-L-DOPA **[^{18}F]1-11** were compared at different Selectfluor precursor amounts (Figure 2.5B). When the amount of Selectfluor precursor was decreased from 7.5 µmol to 2.0 µmol, the yield of **[^{18}F]1-11** increased from 6.8 ± 1.8% to 12.1 ± 3.7% RCY. This study shows that it was not necessary to use such a large excess of Selecftluor precursor **1-65** to increase the radiochemical yield of the subsequent labelling reaction.

The radiochemical yield corresponded well to the values currently obtained at the Turku PET Centre (6.4 ± 1.7%).[50] This showcases the potential of the use of [^{18}F]Selectfluor *bis*(triflate) in the radiolabelling of complex targets.

All specific activities were calculated using the calibration system developed for the clinical production of 6-[^{18}F]fluoro-L-DOPA at Turku PET Centre. The SAs obtained in this study were all in the same range, at 3.40 ± 0.10 to 3.09 ± 0.30 GBq/μmol, independent of the reaction conditions. These values were an 8-fold increase compared to the values obtained in the preparation of **[^{18}F]1-11** using low SA [^{18}F]F_2.[55] Furthermore, the values correspond well to those currently obtained in the clinical production of 6-[^{18}F]fluoro-L-DOPA at Turku PET Centre (3.7 ± 0.9 GBq/μmol).[50]

The preparation of 6-[^{18}F]fluoro-L-DOPA **[^{18}F]1-11** from arylstannane precursor **2-67b** was successful, but as nothing is known regarding the use of boronic acid derivatives under radiochemical conditions, veratrole boronic ester precursor **2-59** was investigated prior to arylboronic ester L-DOPA precursor **2-68b** in an attempt to optimise the reaction conditions.

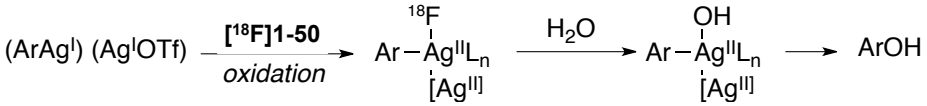
The [^{18}F]Selectfluor *bis*(triflate) was prepared as explained above (Scheme 2.34) using 2.0 μmol of Selectfluor precursor **2-82**. The silver(I) complex **2-88** was prepared from veratrole boronic ester **2-59** immediately prior to the radiolabelling studies by the activation of the boronic ester with 1.2 equivalents of sodium hydroxide in methanol and transmetallation with 3 equivalents of silver triflate. The reaction mixture was divided into three equal batches and the methanol was subsequently removed under reduced pressure. The reaction vessels containing the silver(I) precursor **2-88** were stored at -20 °C for a maximum of one hour before an aliquot of [^{18}F]Selectfluor *bis*(triflate) was added and the reaction was stirred for 20 minutes at room temperature (Scheme 2.37).



Scheme 2.37. Radiolabelling of veratrole boronic ester precursor 2-59 using [^{18}F]Selectfluor *bis*(triflate).

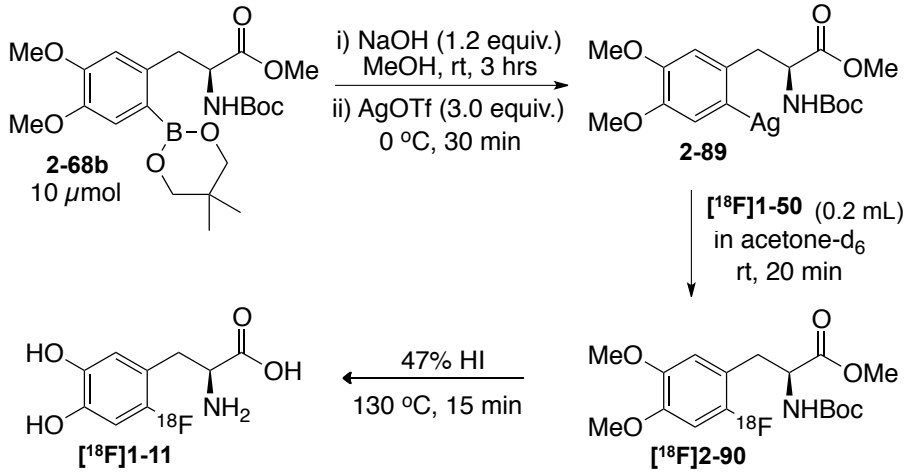
Following injection of the reaction mixture into the radio-HPLC system, no radioactive peaks, besides [^{18}F]fluoride, were observed. The reaction was repeated, but

the best result obtained was 0.5% RCY of the desired [^{18}F]labeled compound **[^{18}F]1-72**. It is challenging to elucidate the reason for the failure of the radiolabelling of this substrate as the 'cold' fluorination proceeded in good yields (Table 2.6). A possibility is that the silver(I)-intermediate **2-88** decomposed either during storage in the freezer or during the reaction. In the 'cold' studies, powdered molecular sieves were added to aid removal of water from the solvent. This was not feasible under radiochemical conditions, as the silicon component of the molecular sieves could undergo fluorination in the presence of [^{18}F]fluoride. As a result it was challenging to expel moisture from the system. Therefore, it is possible that the corresponding phenol was formed in the presence of water, by C-O reductive elimination from the bimetallic Ag(II) centre (Scheme 2.38), but this was not conclusively confirmed by HPLC analysis.[158] No further studies were carried out with this substrate.



Scheme 2.38. Proposed formation of phenol by C-O reductive elimination.

The [^{18}F]fluorination arylboronic ester L-DOPA precursor **2-68b** was studied next. The activation and transmetallation of the boronic ester was carried out using identical reaction conditions as for the veratrole model substrate and divided equally into three reaction vessels. [^{18}F]Selectfluor *bis*(triflate) [^{18}F]**1-50**, prepared using 2.0 of μmol precursor **2-82** was employed as this afforded 6-[^{18}F]fluoro-L-DOPA in the highest RCY with the arylstannane L-DOPA precursor. After drying, [^{18}F]**1-50** in acetone-d_6 (0.2 mL) was added and the resulting reaction mixture was stirred at room temperature for 20 minutes. During this time the reaction changed colour from bright orange to pale yellow. Hydrobromic acid (48%, aq.) (pKa = -8) was not a sufficiently strong acid to deprotect the methyl ether functional groups on the arene. Several peaks were observed by HPLC, suggesting only partial deprotection. By using a solution of 47% hydroiodic acid instead (pKa = -10) and extending the reaction time, full deprotection was achieved to afford 6-[^{18}F]fluoro-L-DOPA **[^{18}F]1-11** (Scheme 2.39).



Scheme 2.39. Radiolabelling of boronic ester precursor 2-68b using [^{18}F]Selectfluor *bis*(triflate).

Entry	SF prec. 1-57 (μmol)/ LiOTf (μmol)[a]	Available activity (%)	RCY of [^{18}F]2-90 (%)[b]	RCY of [^{18}F]1-11 (%)[c]	SA (GBq/μmol)
1	2.0/2.0	37	7	9	2.73
2	2.0/2.0	53	17	16	2.85
3	2.0/2.0	35	17	12	2.80
4	2.0/2.0	75	27	40	2.16
5	2.0/2.0	58	9	18	2.25
Mean	-	51.6	15.3	19.0	2.56
Std. Dev.	-	16.4	7.9	12.2	0.33

[a] **[^{18}F]1-50** concentration: Entries 1-5 = 0.003M. [b] Proportion collected (%) of the radioactivity detected following analytical HPLC of protected 6-[^{18}F]fluoro-L-DOPA intermediate (decay-corrected). [c] Proportion collected (%) of the radioactivity detected following semi-preparative HPLC of 6-[^{18}F]fluoro-L-DOPA multiplied by the available activity (decay-corrected).

Table 2.12. Summary of RCYs obtained using boronic ester precursor 2-68b.

6-[^{18}F]Fluoro-L-DOPA **[^{18}F]1-11** was obtained in a RCY of 19.0 ± 12.2% and SA of 2.6 ± 0.3 GBq/μmol. This reaction represents the first direct [^{18}F]fluorination of an arylboronic acid derivative.

The identity of the desired product 6-[^{18}F]fluoro-L-DOPA was confirmed by spiking the Radio-HPLC sample with the 'cold' 6-fluoro-L-DOPA reference material (Figure 2.6).

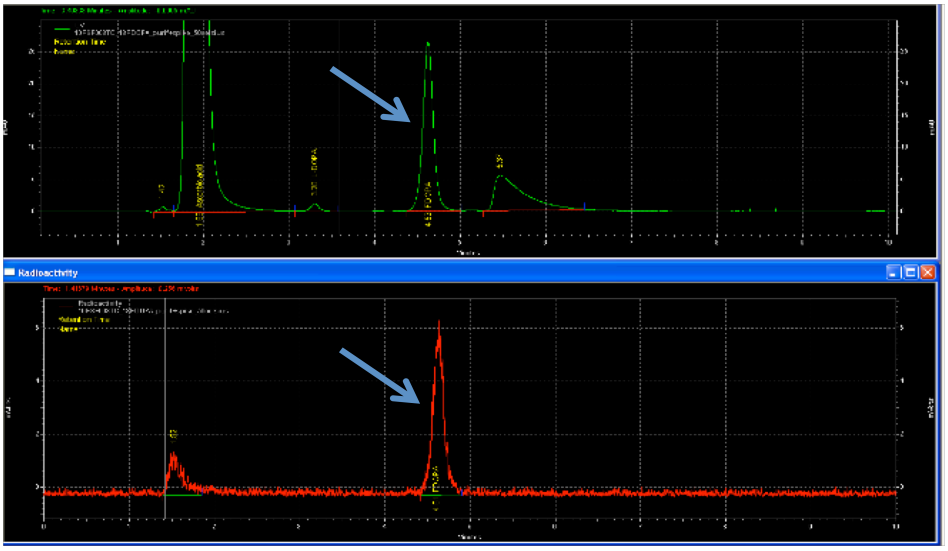


Figure 2.6. 6-[^{18}F]-Fluoro-L-DOPA after preparative HPLC separation, co-injected with authentic 6-Fluoro-L-DOPA (shown by blue arrows). Top: UV-chromatogram, Bottom: Radioactivity-chromatogram.

The RCYs were calculated according to the method described for the radiolabelling of trimethylstannane precursor **2-67b**. The results are summarised in Table 2.12. All RCYs were decay-corrected to the end of synthesis of the original [^{18}F]Selectfluor *bis*(triflate) stock.

Finally, statistical analysis was carried out to compare the mean RCYs of 6-[^{18}F]Fluoro-L-DOPA **[^{18}F]1-11** obtained in the silver(I)-mediated [^{18}F]fluorination of trimethylstannane L-DOPA precursor **2-67b** and arylboronic ester L-DOPA **2-68b** using [^{18}F]Selectfluor *bis*(triflate) (Figure 2.7).

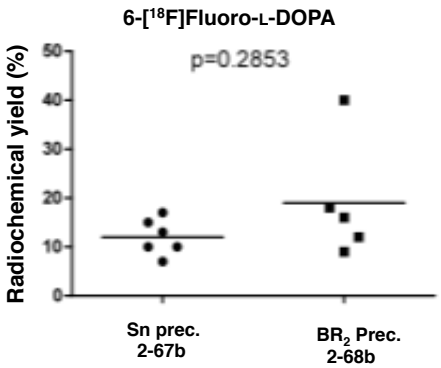


Figure 2.7. Comparison of mean RCY of [^{18}F]1-11 from precursor 2-67b or 2-68b.

The t-test gave a p value of 0.2853, which means that there is no significant statistical difference between the RCYs obtained in the [^{18}F]fluorination of arylstannane L-DOPA precursor **2-67b** or arylboronic ester L-DOPA precursor **2-68b,** i.e the mean RCYs of 12.1 ± 3.7% and 19.0 ± 12.2%, respectively, are comparable. This cements the use of boronic acid derivatives as a suitable alternative functional group to trialkylstannanes in the radiolabelling of complex arenes for the use in PET. As a result, a wider range of imaging agents of interest may be accessed.

2.5 Conclusion

The aim of this chapter was to further develop the application of the [^{18}F]N-F reagent [^{18}F]Selectfluor *bis*(triflate) by exploring its use in the preparation of the imaging agent 6-[^{18}F]fluoro-L-DOPA, in a silver(I)-mediated [^{18}F]fluorination of arylstannanes and arylboronic ester precursors. Pleasingly, [^{18}F]Selectfluor *bis*(triflate) was found to yield 6-[^{18}F]fluoro-L-DOPA in 12.1 ± 3.7% RCY in a one-pot reaction with silver triflate and a commercially available arylstannane L-DOPA precursor used routinely in the preparation of this tracer. A novel arylboronic ester L-DOPA precursor was prepared and found to be amenable to the [^{18}F]fluorination reaction after activation and transmetallation of the boronic ester moiety. Using this strategy, 6-[^{18}F]Fluoro-L-DOPA was afforded in 19.1 ± 12.2% RCY. Statistical analysis confirmed that the RCYs obtained in these two approaches were comparable and within the same range. The specific activities for these radiolabelling reactions varied from 2.6 to 3.4 GBq/μmol, depending on the initial target irradiation time.

Boronic acid derivatives are virtually non-toxic and offer an attractive alternative to the use of tin compounds. A plethora of boronic acid derivatives may now be accessed through the use of this novel transformation. These studies also suggested that F_2 may not be a suitable alternative to Selectfluor *bis*(triflate) in the fluorination of arylboronic acid derivatives, and showcases the benefit of developing a range of electrophilic N-^{18}F with tailored reactivity for the exploration of new radiolabelling methods.

Chapter 3. Preparation of [^{18}F]labelled arenes by palladium-mediated C-H activation

3.1 Aims

The development of palladium-mediated cross coupling reaction revolutionised the field of organic synthesis, illustrated by the Nobel Prize in Chemistry being awarded to Heck, Negishi and Suzuki in 2010 for their pioneering work in this field.[177] Although efforts primarily focused on the preparation of C-C bonds, interest in the use of transition metal catalysis to access carbon-heteroatom bonds have flourished in recent years.

Compared to other palladium-catalysed strategies, methodologies allowing for the preparation of C-F bonds remained elusive for a long time and it wasn't until 2006 that a successful protocol for this transformation was reported.[178] C-F and C-CF_3 moieties are extremely valuable in a wide range of industries[179] and several research groups focus on the design of efficient and versatile routes to these functional groups *via* transition metal catalysis.[180],[181] Today a small library of palladium-catalysed fluorination reaction is readily at hand for chemists, and successful transferral of a select few of these methodologies to radiochemistry has also been achieved.[141],[182]

The palladium species may be incorporated into desired targets in two general approaches. Preactivated precursors (substituted with a halide, boron or stannane functional group) react with a palladium catalyst in a transmetallation reaction, while unactivated precursors substituted with a directing group allow selective introduction of the palladium catalyst by C-H activation. The first approach often relies on complex and time-consuming protocols for the preparation of the required preactivated precursors while the latter offers a much more elegant and simplified strategy for the preparation of C-F bonds.

In the previous chapter, the imaging agent 6-[^{18}F]fluoro-L-DOPA was successfully prepared in a silver-mediated fluorination of preactivated arylstannane and aryl boronic ester precursors using [^{18}F]Selectfluor *bis*(triflate). It was therefore

hypothesised that the preparation of this imaging agent could be achieved using a palladium-mediated C-H activation approach, relying on a hypervalent palladium(IV) intermediate, in the presence of [^{18}F]N-F reagents. If successful, this would advance the synthesis of this compound to a new level and offer the first example of a direct conversion of a C-H bond to a C-^{18}F moiety.

The introduction to this chapter will focus on the challenges facing the preparation of C-F bonds compared to other C-heteroatom bonds and the methodologies available in the literature for C-F bond formation will be discussed together with the application to [^{18}F]radiolabelling.

Based on these existing protocols for palladium-mediated fluorination, a stoichiometric palladium-mediated strategy for C-H activation and subsequent fluorination of arenes was devised. The stoichiometric C-H activation-fluorination reaction was optimised on L-phenylalanine as a model substrate before the optimised reaction was applied to L-DOPA. Radiolabelling studies using [^{18}F]N-F reagents were also carried out. Furthermore, it was decided to study known leading palladium-mediated C-F bond forming reactions in the literature, relying on the use of alternative reagents to Selectfluor^{TM} and NFSI, with the aim of developing new [^{18}F]N-F reagents.

3.2 Introduction

3.2.1 Palladium-mediated formation of Csp^2-F bonds

The development of carbon-heteroatom bond-formation has flourished with the advent of transition metal catalysis, in particular palladium. Several palladium-mediated protocols for the synthesis of aryl C-O, C-N, C-S and C-P bonds have been reported and reviewed.[183]

A tremendous amount of effort has been undertaken in the last decades to prepare Csp^2-F bonds by transition metal catalysis using either nucleophilic or electrophilic fluorine, but the development of this field has been considerably slower. An idealised general catalytic cycle of palladium(II)-mediated nucleophilic fluorination for the synthesis of C_{aryl}-F bonds is shown in Figure 3.1. Three steps must be satisfied for successful fluorination. First, oxidative addition occurs between an aryl triflate or

halide and a palladium(0) source to afford a palladium(II) complex. Fluoride is introduced to the system by ligand exchange to form the corresponding aryl palladium(II) fluoride complex and finally reductive elimination is required to yield the desired product.

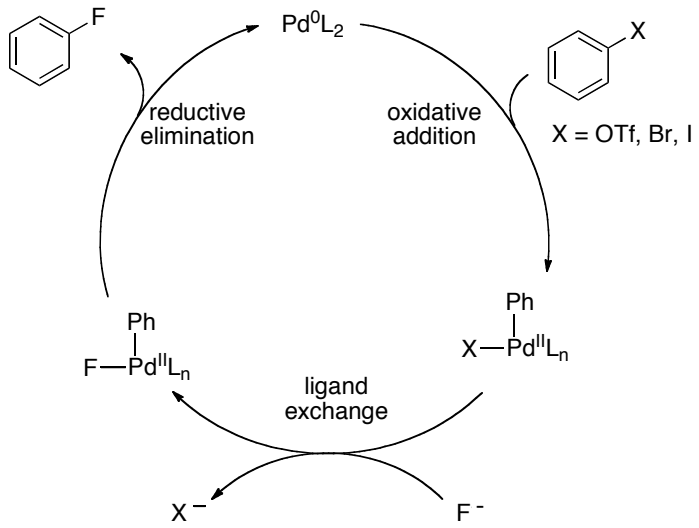
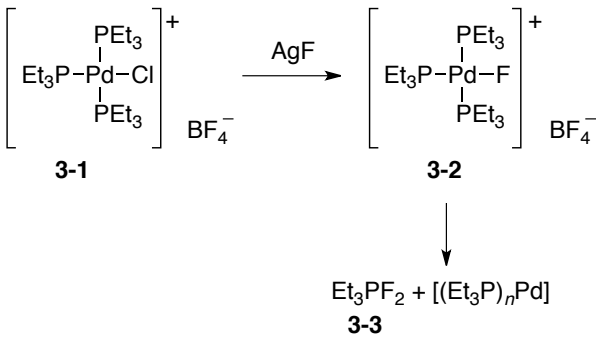


Figure 3.1. Pd-mediated C*aryl*-F Bond Formation: General Catalytic Cycle.

The oxidative addition of aryl halides to palladium(0) species is well-documented and established in a wide range of transition metal catalysed transformations.[184] In contrast, the ligand exchange process required for the preparation of aryl palladium(II) fluoride complexes is more challenging and was not achieved until recently.

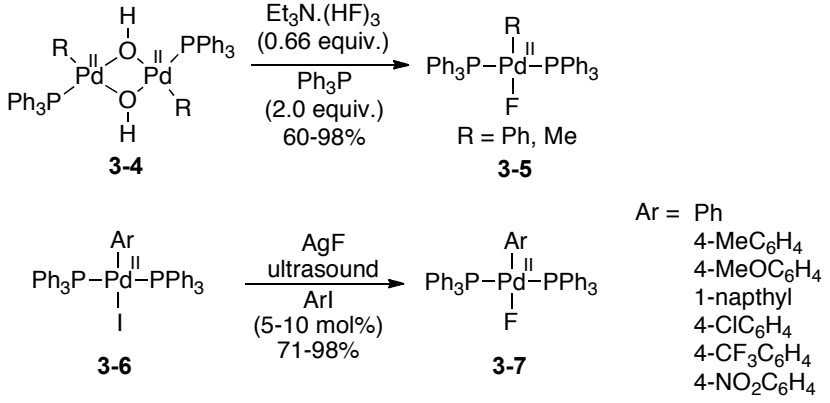
Early attempts to prepare monomeric Pd-F complexes failed due to the weak interaction between the hard fluoride ion and the soft Pd^{II} metal centre, instead only yielding dimerisation or decomposition products (Scheme 3.1).[185-187]



Scheme 3.1. Palladium(II) fluoride complex in solution.[185]

McFarland and co-workers reported the formation of fluoride complex **3-2** from the corresponding chloride complex upon reaction with silver fluoride **3-1**. The complex was observed in solution during ^{19}F NMR studies, but all attempts at isolating the complex failed. Further investigations showed that complex **3-2** rapidly decomposed to afford dimerisation products and Et_3PF_2 **3-3**.[185]

Grushin reported two stable palladium fluoride(II) complexes, thereby proving that the ligand exchange is viable. The reaction of the dimeric organopalladium complex **3-4** bridged by hydroxides with triethylamine trihydrofluoride (TREAT-HF) in the presence of free phosphine afforded mononuclear fluoride complexes **3-5** (Scheme 3.2, top).[187] An alternative route is preparation of aryl palladium(II) complex **3-7** by I/F ligand exchange with AgF in the presence of a catalytic amount of ArI (Scheme 3.2, bottom).[189] Complex **3-7** could be prepared with a range of electron-rich and electron-poor arenes.

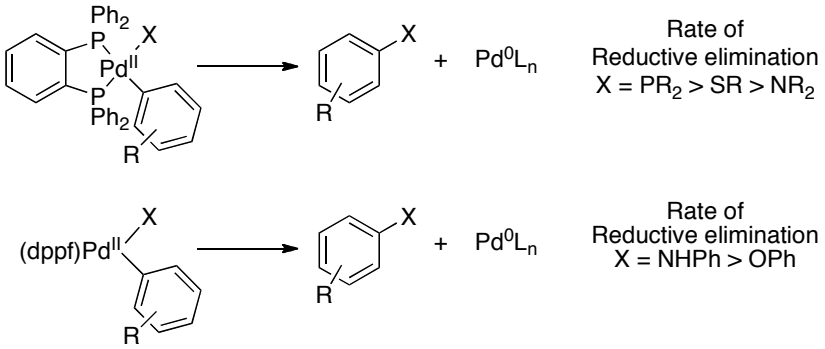


Scheme 3.2. Isolation of the first stable palladium fluoride.[189]

The final challenge is the reductive elimination of palladium(II) fluoride complexes to afford fluorinated arenes. Palladium(II) complexes, with d^8 configuration, are square planar and reductively eliminate *via* one of three possible mechanisms: dissociative, non-dissociative and associative. Irrespective of which mechanism is in operation, the two leaving groups must be *cis* to one another for concerted reductive elimination to occur. It is known that reductive elimination is faster from three-coordinated complexes compared to a related four-coordinate species.[190],[191] The rate of reductive elimination is increased if sterically hindered ligands with large bite angles are

employed, as the two leaving groups are forced closer together.[192] In this section palladium(II) complexes of both coordination modes are discussed.

Hartwig and co-workers carried out a comprehensive study, which revealed that reductive elimination to form C-X bonds occurs more rapidly from complexes with more nucleophilic heteroatoms. The rate of elimination from arylpalladium(II) amido, alkoxo, thiolato and phosphido complexes complexes containing similar substituents on the heteroatom proceed in the order of C-P > C-S > C-N > C-O bond formation (Scheme 3.3).[192]



Scheme 3.3. Rate of C-X reductive elimination as a function of the heteroatom.[192]

The positive relationship between increasing nucleophilicity and faster reductive elimination is due to a more favourable attack of the electron pair onto the *ipso* carbon of the aryl group in the transition state (π effect) (Figure 3.2).[193]

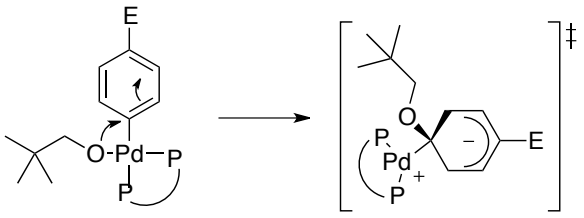
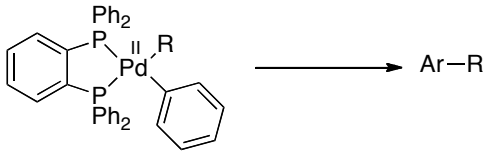


Figure 3.2. Attack of electron pair on *ipso* carbon –Transition State.[193]

An alternative reasoning is that a decrease in polarity may be the cause of faster reductive elimination, due to reduction of the strength of the M-X bond. Disregarding steric and mesomeric effects, the increase in polarity of the M-X bond may lead to increased bond strength due to the stronger ionic contribution to the bond energy (σ effect). The rate of reductive elimination from arylpalladium alkyl complexes

containing different functional groups on the alkyl carbon atom helps to clarify the potential contribution of the σ and π effect (Scheme 3.4).



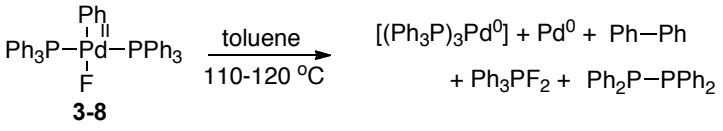
	k_{rel} (110 °C)
R = Me	> 600
R = Bn	> 250
R = $CH_2C(O)Ar$	31
R = CH_2CF_3	1.7
R = CH_2CN	1
R = CF_3	no reaction

Scheme 3.4. Electronic effect on the rate of C-C reductive elimination.[194]

The rate of reductive elimination in these complexes is retarded as the electron withdrawing nature of the R group on the arylpalladium alkyl complexes increases. This is illustrated by prevention of reductive elimination when R = CF_3. These complexes do not contain available lone pair electrons on the alkyl carbon bound to the metal, therefore the predominant σ effect need only be taken into account.[194]

Fluorine is the most electronegative element in the periodic table, which in turn results in M-F bond energies with a large ionic contribution causing the rate of reductive elimination to be slowed down. Additionally, in terms of electronegativity, fluorine is considered to be the least nucleophilic atom in the series of anions: C, N, O, F.[195] Both of these properties explain why C-F bond formation is so challenging compared to the formations of alternative C-X bonds.

The complexes prepared by Grushin in Scheme 3.4 are stable in the solid state and in anhydrous solvent, but water may potentially cleave the Pd-F bond.[196] This ionisation may pose a problem for synchronous C-F reductive elimination. Initial attempts to induce reductive elimination by heating the alternative palladium(II) fluoride complex **3-8** to 110 °C in anhydrous toluene were unsuccessful. Disappointingly, only C-C, P-P and F-P bond formation was observed in the initial studies (Scheme 3.5).[197]

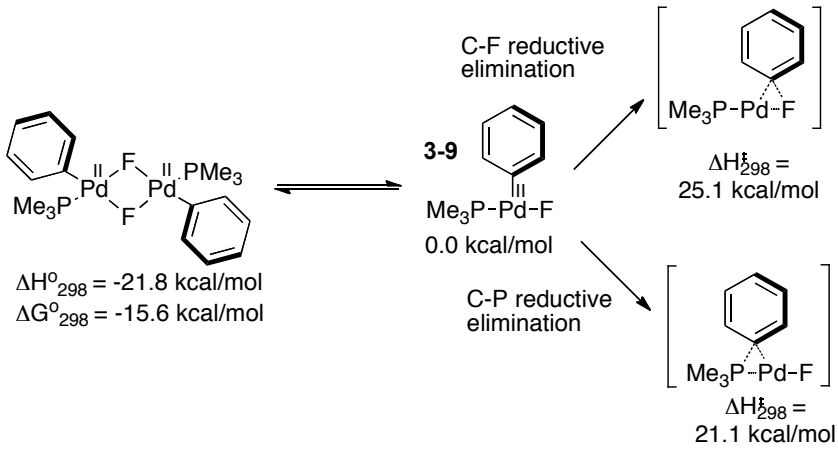


3-8

Scheme 3.5. Initial reductive elimination attempts.[197]

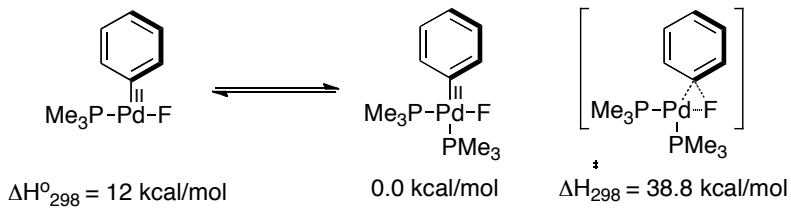
In complex **3-8** in scheme 3.5, the preferred angle between the two phosphine ligands is 180°. When the ligands were replaced by the bidentate ligand XanthPhos, the rigid heteroaromatic backbone enforced a bite angle of approximately 110°. This distorts the spatial arrangement the substituents bound to the palladium centre. The aryl and fluoride substituents are forced spatially closer together and this increases the likelihood of the favoured C-F formation. Unfortunately, in the case of complex **3-8**, these reaction conditions led only to the disfavoured P-F bond formation.[198]

Yandulov and co-workers carried out computational analysis of C-F reductive elimination from arylpalladium(II) fluorides, with both N-heterocyclic carbenes and phosphines as ligands.[199],[200] Reductive elimination from the T-shaped intermediate **3-9** containing phosphines was computed. The activation enthalpy for Ar-F bond formation was 25.1 kcal/mol, while migration of the phenyl group onto the phosphine ligand (P-C bond formation) was predicted to be slightly lower at 21.1 kcal/mol. Furthermore, the study revealed that dimerisation of monomeric complex **3-9** was a highly feasible process and it was found to be exothermic by 21.8 kcal/mol. (Scheme 3.6).



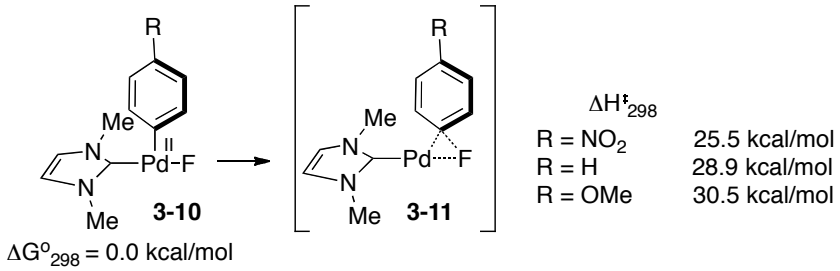
Scheme 3.6. Computational studies of C-F reductive elimination.[199],[200]

A four-coordinate complex would avoid dimer formation. However, the activation enthalpy for C-F reductive elimination from this type of complex was measured to be 38.8 kcal/mol (Scheme 3.7).



Scheme 3.7. Potential reductive elimination for four-coordinate complex.

Yandulov carried out additional studies wherein calculations showed that, in the related NHC complexes, reductive elimination becomes more facile for aryl groups with electron-withdrawing substituents (Scheme 3.8).[195],[201]



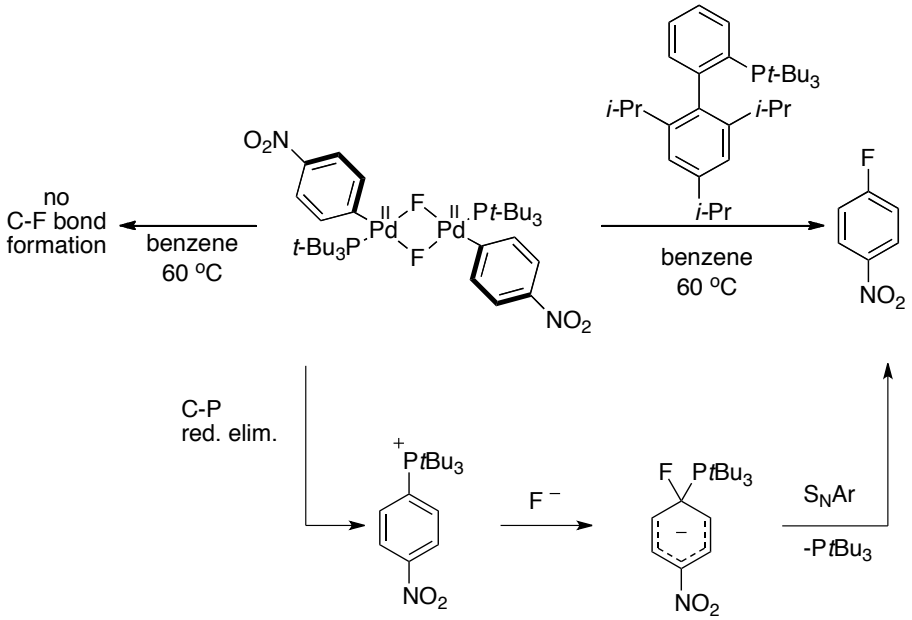
Scheme 3.8. Effect of electron-withdrawing substituents on the rate of reductive elimination.[195],[201]

The presence of a hydrogen donor, such as hydrogen fluoride, was found to stabilise the starting material more than the transition state, thereby increasing the activation barrier.[194]

Yandulov's studies indicated that complexes with NHC ligands would undergo undesired C-C reductive elimination instead of C-F bond formation. Additionally, related complexes with phosphine ligands would have lower activation barriers than those with NHC ligands. The activation barrier for C-F reductive elimination from palladium phosphine complexes is relatively high. Electron-withdrawing groups on the arene reduce the transition state energy while addition of hydrogen bond donors would increase the barrier of activation.[194]

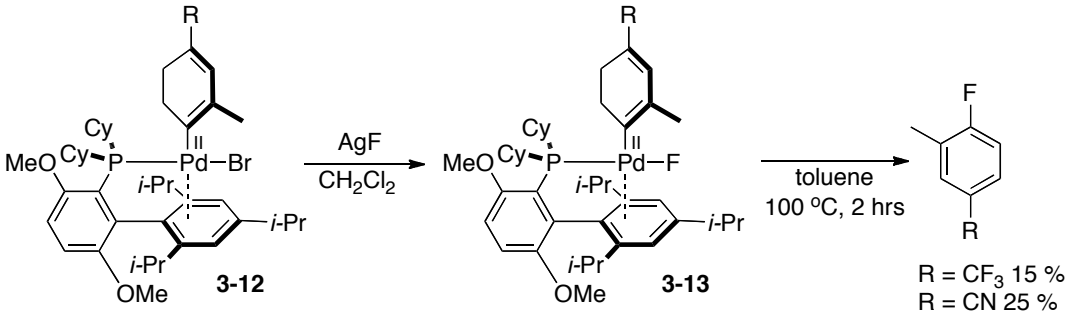
In order to overcome the challenges highlighted by Yandulov, it was proposed that destabilisation of a palladium dimer by bulky ligands would be likely to increase the concentration of the three-coordinate arylpalladium(II) fluoride complex, which would in turn undergo reductive elimination. A complex containing an electron-withdrawing

aryl group and the bulky ligand tri-*tert*-butylphosphine failed to undergo C-F reductive elimination upon heating in benzene at 60 °C. Conversely, addition of the bulky phosphine ligand *t*-BuXPhos afforded the desired product by C-F bond formation in *ca.* 10 % yield (Scheme 3.9). The elucidation of the mechanism has proved challenging, but Grushin has proposed C-P reductive elimination followed by nucleophilic aromatic fluorination as a possibility.[202]



Scheme 3.9. First observation of C-F bond formation from an aryl palladium complex.[202]

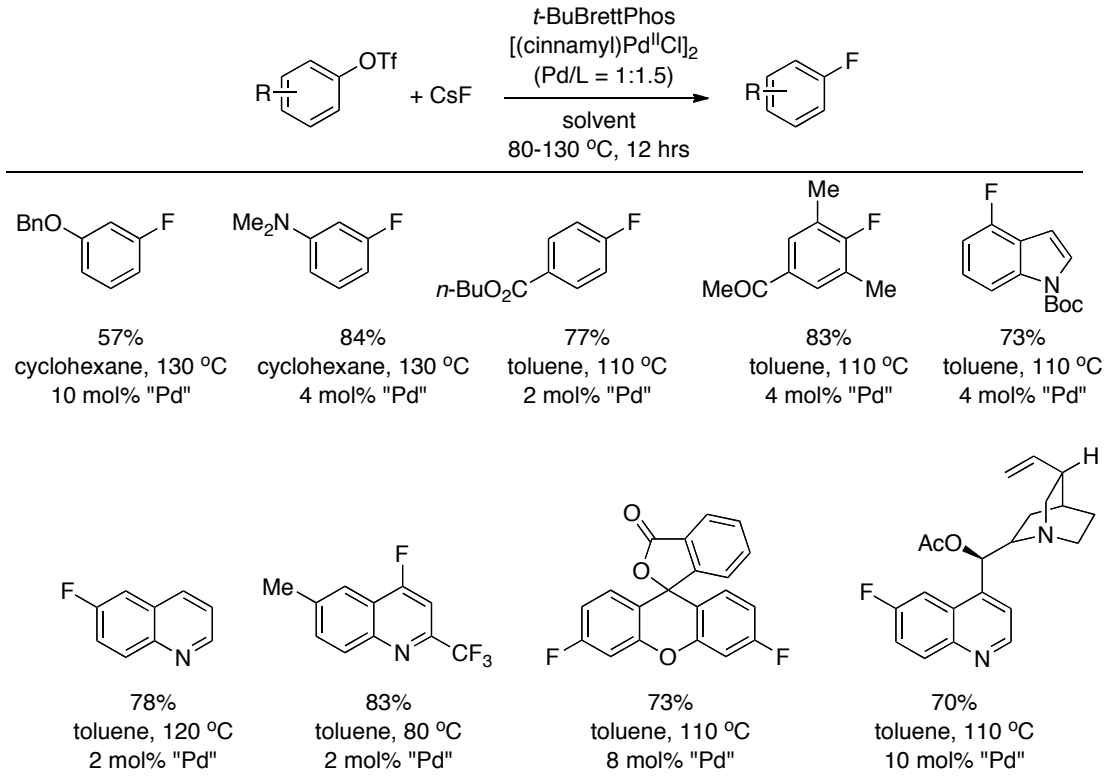
The first palladium-catalysed nucleophilic aromatic fluorination was reported by Buchwald in 2009, and also showed that C-F reductive elimination was feasible from a palladium(II) complex.[203] BrettPhos and *t*-BuBrettPhos, bulky monodentate phosphine ligands, were essential for the formation of mononuclear T-shaped tricoordinate palladium(II) complexes. The fourth coordination site was occupied by the biphenyl moiety of the phosphine ligand (Scheme 3.10). When complex **3-12** was treated with AgF to form the intermediate **3-13**, which was heated in toluene at 100 °C for two hours, fluorinated aromatics were obtained in 15-25% yield.



Scheme 3.10. C-F reductive elimination from T-shaped three-coordinate complex 3-13.[203]

It was speculated that the *trans* relationship between the fluoride and the bidentate phosphine ligand might be responsible for the successful reductive elimination step over the competing P-F reductive elimination, which was commonly observed in alternative palladium(II) fluoride complexes containing monophosphines.[204]

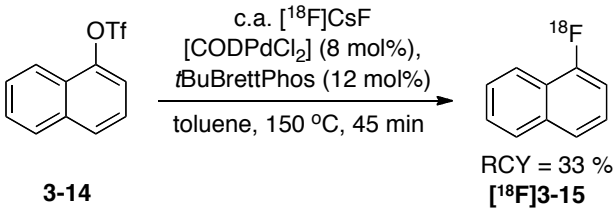
The development of a catalytic variant was possible by employing aryl triflates, 6 mol% of *t*-BuBrettPhos, 2 mol% of $[(\text{cinnamyl})\text{Pd}^{\text{II}}\text{Cl}]_2$ and 2.0 equivalents of CsF as the fluoride source. Electron-poor, electron-rich, *ortho,ortho*-disubstituted arenes and hereocycles were compatible with the reaction conditions. Due to the high basicity of fluoride, protic functional groups were not tolerated. Additionally, it was important to exclude moisture from the system (Scheme 3.11).[203]



Scheme 3.11. Substrate of Buchwald's catalytic variant.[203]

Although Buchwald's work was a significant achievement in synthetic catalysis, the long reaction times, need for anhydrous reaction environments and excess fluoride source mean that this methodology is not easily applicable to radiochemistry.

Recently, Coenen and co-workers carried out preliminary investigations into a radiochemical variant of the reaction reported by Buchwald, but their efforts were met with limited success.[205] The main challenge was the insolubility of the reagents, especially CsF, in non-polar solvents required for the reaction to proceed. A specific reaction vessel made of glassy carbon was designed to aid solvation. The catalyst used in Buchwald's original study was replaced by [(COD)$PdCl_2$]. The best result was obtained when 1-naphtyltriflate **3-14** was reacted with *t*BuBrettPhos, CsF, [^{18}F]CsF and [(COD)$PdCl_2$] in toluene at 150 °C for 45 minutes to yield 1-[^{18}F]fluoronaphtyl **[^{18}F]3-15** (Scheme 3.12).



20 μmol CsF was added to 25 μmol of precursor

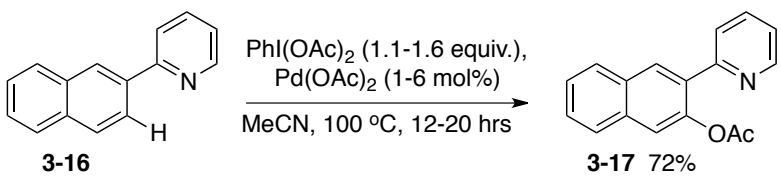
Scheme 3.12. [^{18}F]Fluorination of 1-napthyltriflate under modified Buchwald conditions.[205]

Under the described reaction conditions, the desired product **[^{18}F]3-15** was obtained in 33% RCY. The addition of almost one equivalent of 'cold' CsF relative to the amount of precursor was required for the reaction to proceed and as a result this protocol is only amenable for the preparation of radiotracers with low specific radioactivity (the exact SA is not given in the publication).[205]

3.2.2 Palladium-mediated electrophilic fluorination

The previous section highlights how palladium(0)/palladium(II) systems have been extensively studied for the formation of aryl fluorides. This transformation was challenging to implement, but the with the development of sterically hindered ligands, Buchwald succeeded in achieving the elusive C-F reductive elimination.

In contrast, it is known that transition metal catalysis under oxidising conditions may encourage bond forming reaction challenging under Pd(0)/Pd(II) systems as higher oxidation states are less stable (Pt(IV) > Pd(IV) > Ni(IV)). Sanford and co-workers explored this in a C-H activation/acetoxylation with PIDA as an oxidant and postulated that the reaction proceeded *via* a hypervalent palladium(IV) intermediate (Scheme 3.13).[206]



Scheme 3.13. Acetoxylation *via* Pd(IV) intermediate.

Recently, a lot of attention has focused on the development of palladium(II)/palladium(IV) catalytic systems for novel bond forming reactions on arenes. Two substrate classes are amenable for this strategy, preactivated M-arenes (M = SnR_3 or $B(OH)_2$) or unactivated arenes containing a directing group. The catalytic cycle for both strategies are shown in Figure 3.3.

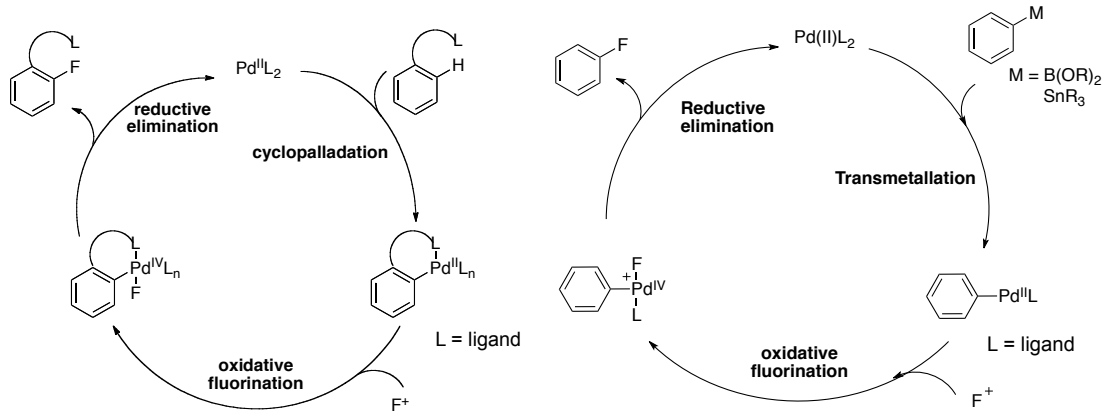


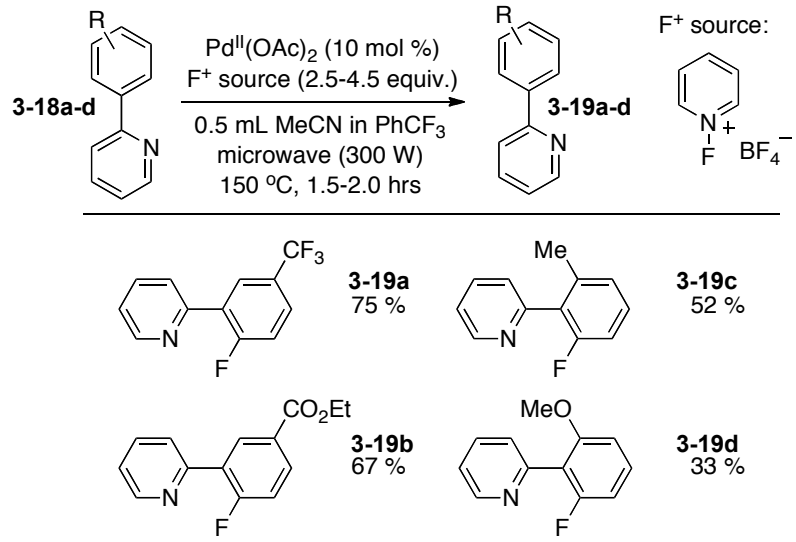
Figure 3.3. General catalytic cycles:
Left: **unactivated substrates, *Right*: preactivated substrates.**

The use of unactivated substrates (Figure 3.3, left) requires a Lewis basic directing group to ensure regiospecificity in the C-H activation/cyclopalladation step. Electrophilic fluorinating reagents promote oxidation of the Pd(II) arylcomplex to a Pd(IV) complex with a simultaneous formation of a Pd-F bond, before reductive elimination is postulated to occur to afford the fluorinated arene.

In contrast, preactivated substrates, such as arylstannanes and arylboronic acid derivatives, undergo transmetallation in the presence of a palladium catalyst. The fluorination and oxidation to the corresponding palladium(IV) intermediate is postulated to proceed in a oxidative fluorination step followed by reductive elimination. However, direct electrophilic cleavage of the palladium-carbon bond with the electrophilic fluorinating reagent may also be possible. Advances in the preparation of aryl fluorides using both strategies will be discussed.

3.2.2.1 Palladium-mediated electrophilic fluorination of unactivated arenes

Sanford exploited this principle and demonstrated the pioneering palladium catalysed electrophilic fluorination in 2006. A variety of N-F reagents were investigated in this $Pd(OAc)_2$ catalysed fluorination of phenylpyridines and quinolines (Scheme 3.14).[178]

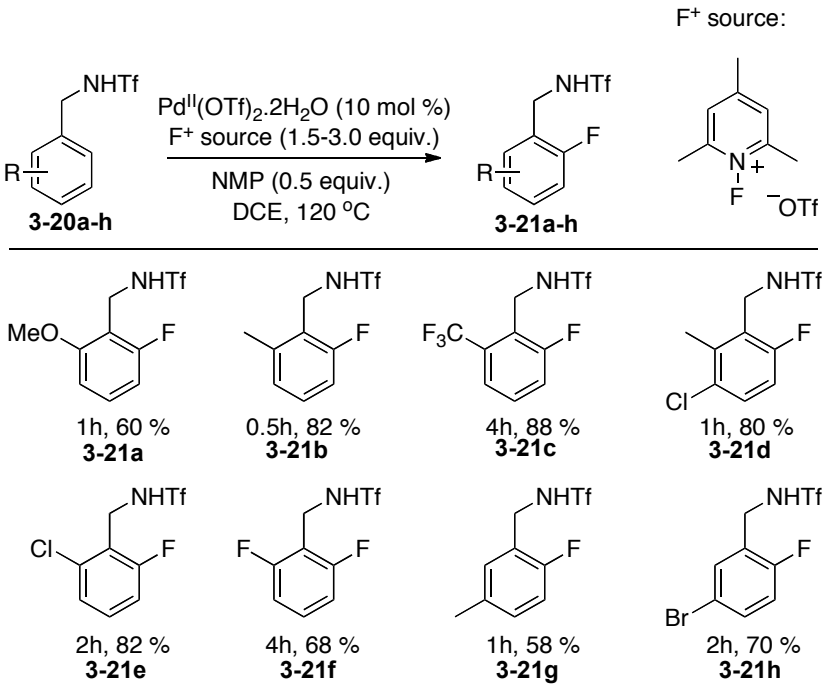


Scheme 3.14. Pd^{IV} catalysed fluorination of phenylpyridines.

Precursors containing electron-poor or electron-rich arenes **3-18a-d** were fluorinated in the presence of 10 mol% $Pd(OAc)_2$ and *N*-fluoropyridinium tetrafluoroborate in 33-75% yield when using microwave irradiation.

The limitations of this approach were the harsh reaction conditions, the need to block the *ortho*-position on the fluorinated aromatic ring, in order to avoid difluorination, and the requirement of substrates containing an *ortho*-directing pyridine group to promote the initial cyclopalladation step.

Yu also explored a similar route where a wide range of protected benzylamines **3-20a-h** were fluorinated in the presence of catalytic $Pd(OTf)_2.2H_2O$, *N*-fluoro-2,4,6-trimethylpyridinium triflate and NMP as a promoter (Scheme 3.15).[207]

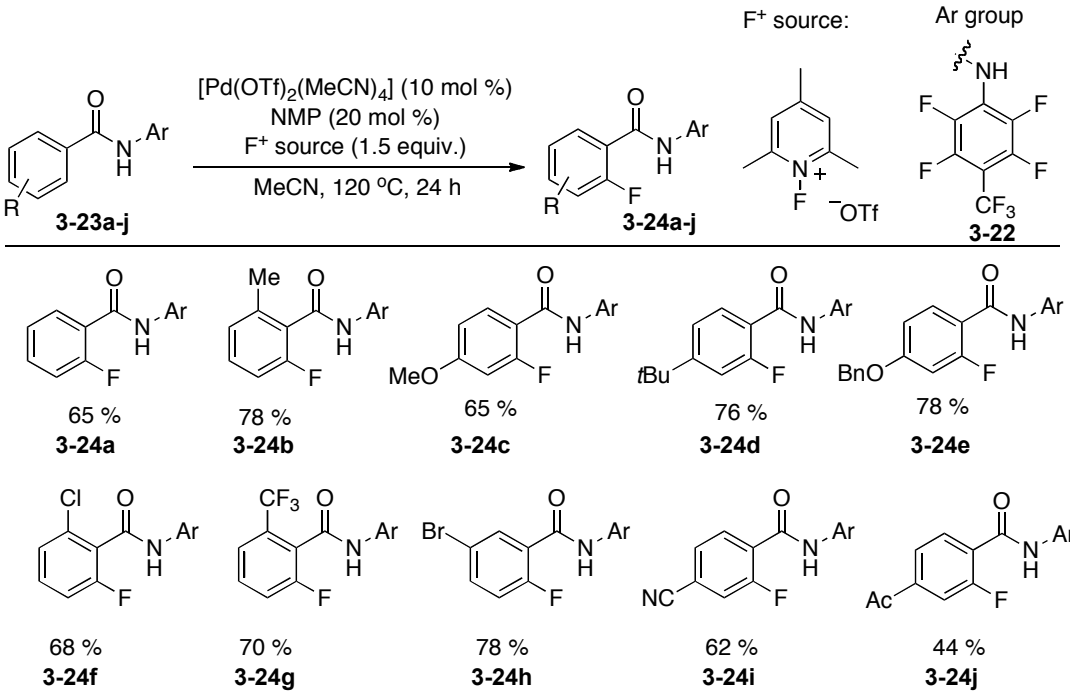


Scheme 3.15. Pd-catalysed *ortho*-fluorination of triflamide protected benzylamides.

This protocol is amenable to slightly milder reaction conditions and the triflamide directing group can be easily converted in a variety of other functional groups. The replacement of $Pd(OAc)_2$ with $Pd(OTf)_2.2H_2O$ prevents competitive acetyloxylation and carbonylative lactamisation. However, the requirement for an *ortho*- or *meta*-blocking group remains. After the formation of the monofluorinated product, its detachment from the palladium(II) centre is thought to be relatively slow, allowing a second C-H activation and fluorination to occur before the product is released. This has also been found to be the case with strongly coordinating ligands such as pyridine.[178]

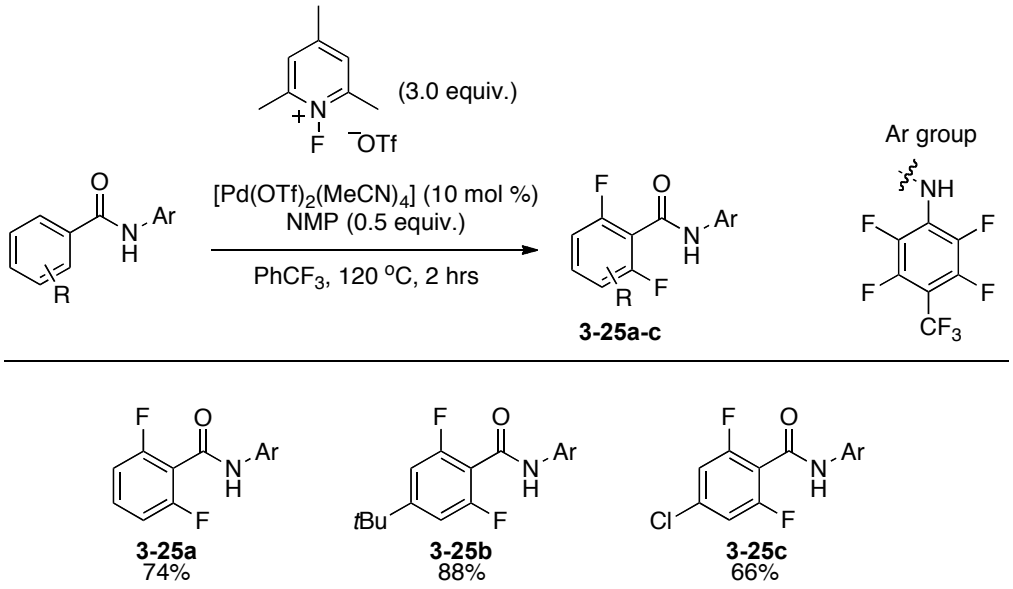
In order to address the need for a blocking group to avoid difluorination, Yu developed an alternative system using benzoic acid substrates protected as a readily removable amide.[208] By using a highly acidic perfluorinated arene **3-22** as the protecting group, Yu postulated that selective monofluorination would be possible. This weakly coordinating ligand should ensure rapid displacement of the monofluorinated product from the from the Pd(II) intermediate and avoid a second fluorination reaction. In the presence of $Pd(OTf)_2.(MeCN)_4$, NMP, *N*-fluoro-2,4,6-trimethylpyridinium triflate, a

range of benzamides **3-23a-j** with different functional groups were fluorinated in varying yields **3-24a-j** (Scheme 3.16).



Scheme 3.16. Monofluorination of *N*-arylbenzamides

Electron-rich arenes required shorter reaction times to reach completion than electron-withdrawing arenes. Only traces of difluorinated products were observed. However, by increasing the amount of NMP and *N*-fluoro-2,4,6-trimethylpyridinium triflate, the formation of difluorinated species **3-25a-c** was possible in excellent yield (Scheme 3.17).[208]



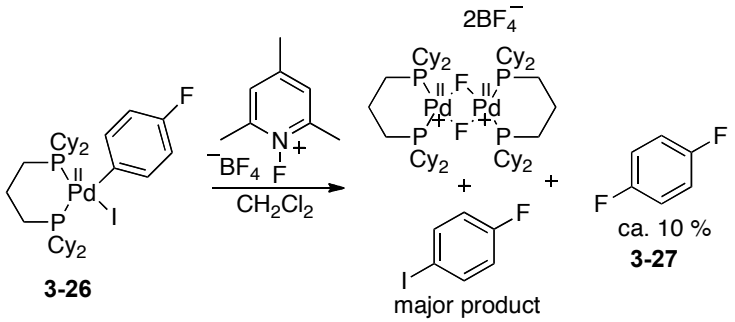
Scheme 3.17. Selective difluorination.

In both of Yu's protocols the addition of a catalytic amount of NMP appears to be crucial for the success of the reaction. Although the precise role of NMP is yet to be elucidated, it is thought to acts as a labile ligand. Several research groups have provided evidence for the formation of a palladium(IV) intermediate (Section 3.1.2.2).[209],[180] Yu and Vigalok proposed the formation of Pd(IV) cationic pentacoordinated complexes by oxidation using the F^+ source according to the mechanism highlighted in the catalytic cycle in Figure 3.3.[208],[210]

However, a redox-neutral Pd^{II}/ Pd^{II} catalytic pathway could be operating in the case of substrates containing weakly coordinating directing groups. This means that the Pd(II) catalyst undergoes C-H activation with the arene without coordinating to the nitrogen directing group and still remains a Pd(II) species. The fluorination subsequently occurs by electrophilic cleavage of the Pd-C bond by the F^+ source. Yu also does not exclude the existence palladium(III) species. The field of palladium(III) catalysis is underdeveloped as few complexes of this nature has been characterised, but Ritter has recently carried out extensive studies to elucidate the role of dinuclear palladium(III) complexes in reactions thought to proceed *via* a mononuclear Pd(II)/Pd(IV) mechanism. [211]

3.2.2.2 Palladium-mediated electrophilic fluorination of preactivated arenes

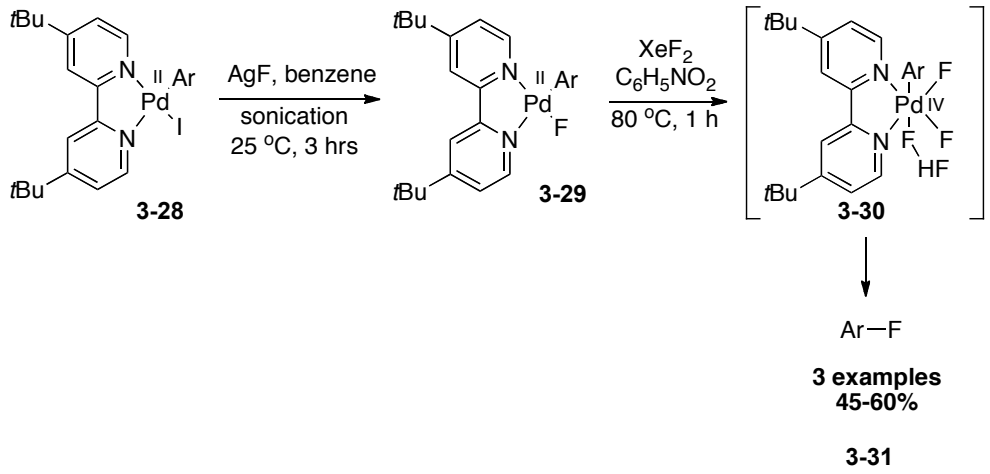
Vigalok investigated the outcome of the reaction between palladium(II) halide complexes and electrophilic fluorinating reagents. The starting palladium Treatment of a palladium(II) complex **3-26** containing a η^1 aryl group, with *N*-fluoro-2,4,6-trimethylpyridinium tetrafluoroborate afforded the aryl fluoride **3-27** in *ca.* 10 % yield. The major product was the iodinated arene resulting from C-I reductive elimination (Scheme 3.18).[210]



Scheme 3.18. C-F bond formation in the presence of an electrophilic fluorinating reagent.

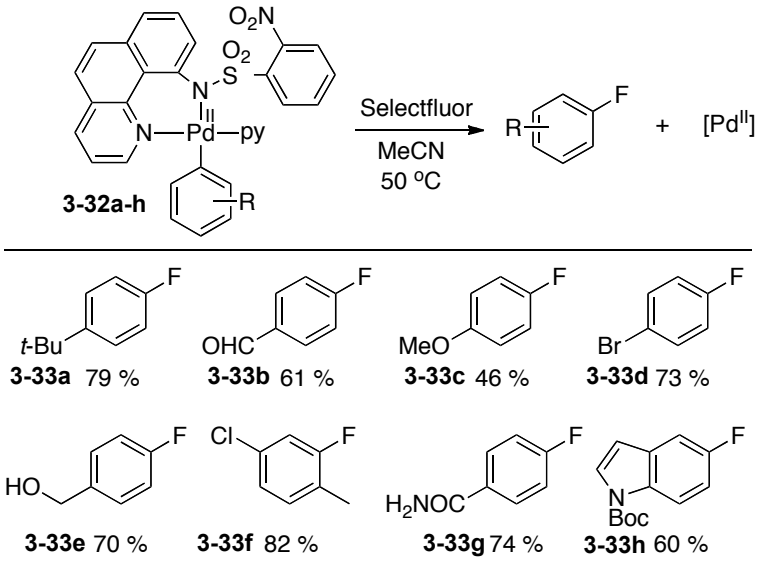
Two alternative strategies are proposed for C-F bond formation: electrophilic cleavage of the C-Pd bond with the electrophilic fluorinating reagent or C-F reductive elimination from a palladium(IV) complex. Much attention has been devoted to the elucidation of the mechanism of the formation of the C-F bond.

Sanford designed an arylpalladium(II) complex **3-28** stabilised by a bipyridine ligand, which afforded the Pd-F bond by reaction with AgF in an I/F exchange reaction. The subsequent oxidation of **3-29** to the hexavalent Pd(IV) intermediate **3-30** was successful in the presence of XeF_2, NBS or NFSI. The reductive elimination occurred within 1 hour and afforded a range of aryl fluorides **3-31a-c** in good yields. Most importantly, the Pd(IV) intermediate could be trapped and analysed, providing substantial evidence for the proposed Pd(II)/Pd(IV) mechanism (Scheme 3.19).[180]



Scheme 3.19. Reductive elimination from a Pd^{IV} complex to afford aryl fluorides 3-31a-c.

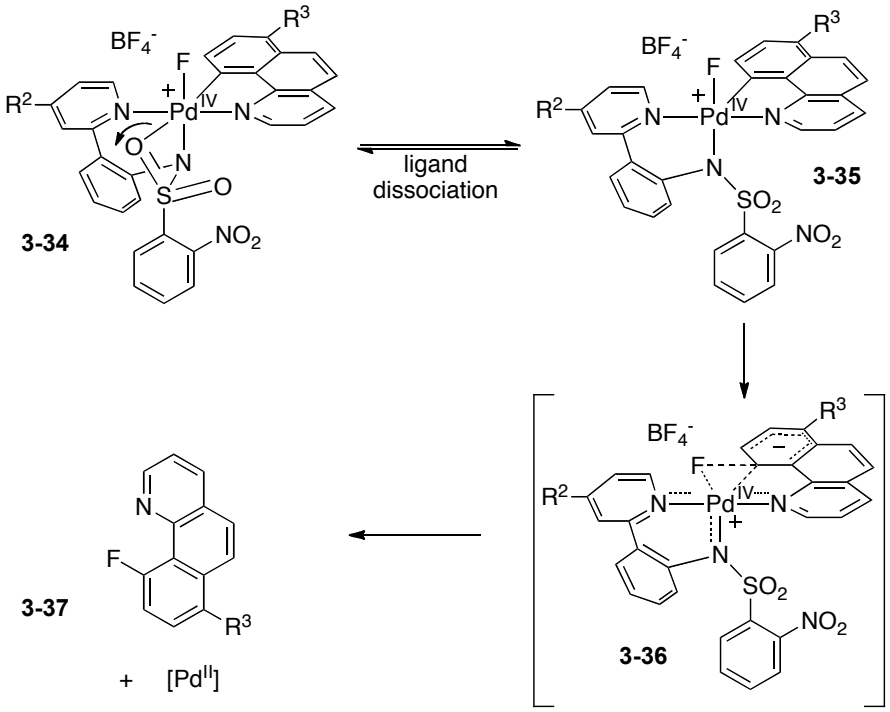
A stoichiometric procedure to form aryl fluorides **3-33a-h** from aryl boronic acids using Selectfluor™ and a benzoquinoline-based palladium(II) complexes **3-32a-h**, was reported by Ritter in 2008 (Scheme 3.20).[181]



Scheme 3.20. Fluorination of aryl boronic acid mediated by palladium.

The choice of the pyridine-sulfonamide ligand proved essential to the stabilisation of the high-valent palladium intermediate. It is proposed that one of the oxygen atoms of the sulfonyl functionality coordinates to the palladium in this high-valent state, offering additional stabilisation. Further evidence was provided by mechanistic studies using the more rigid pyridyl-sulfonamide palladium(IV) complex **3-34**, which is

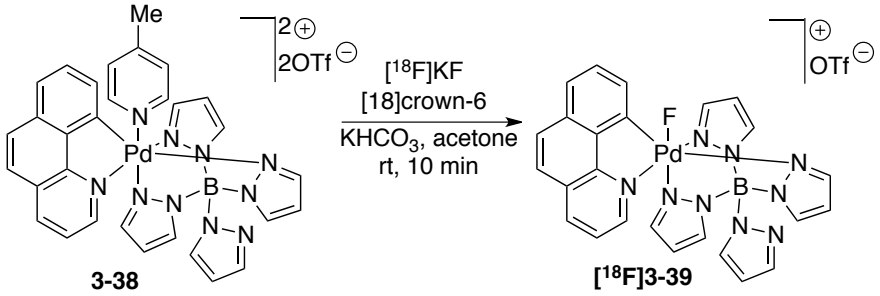
stabilised by the tridentate coordination mode. The reductive elimination step is initiated by the dissociation of the hemilable sulfonamide oxygen (Scheme 3.21).[209]



Scheme 3.21. Proposed dissociative mechanism for C-F reductive elimination.

3.2.3 Transition metal-mediated [^{18}F]fluorination strategies

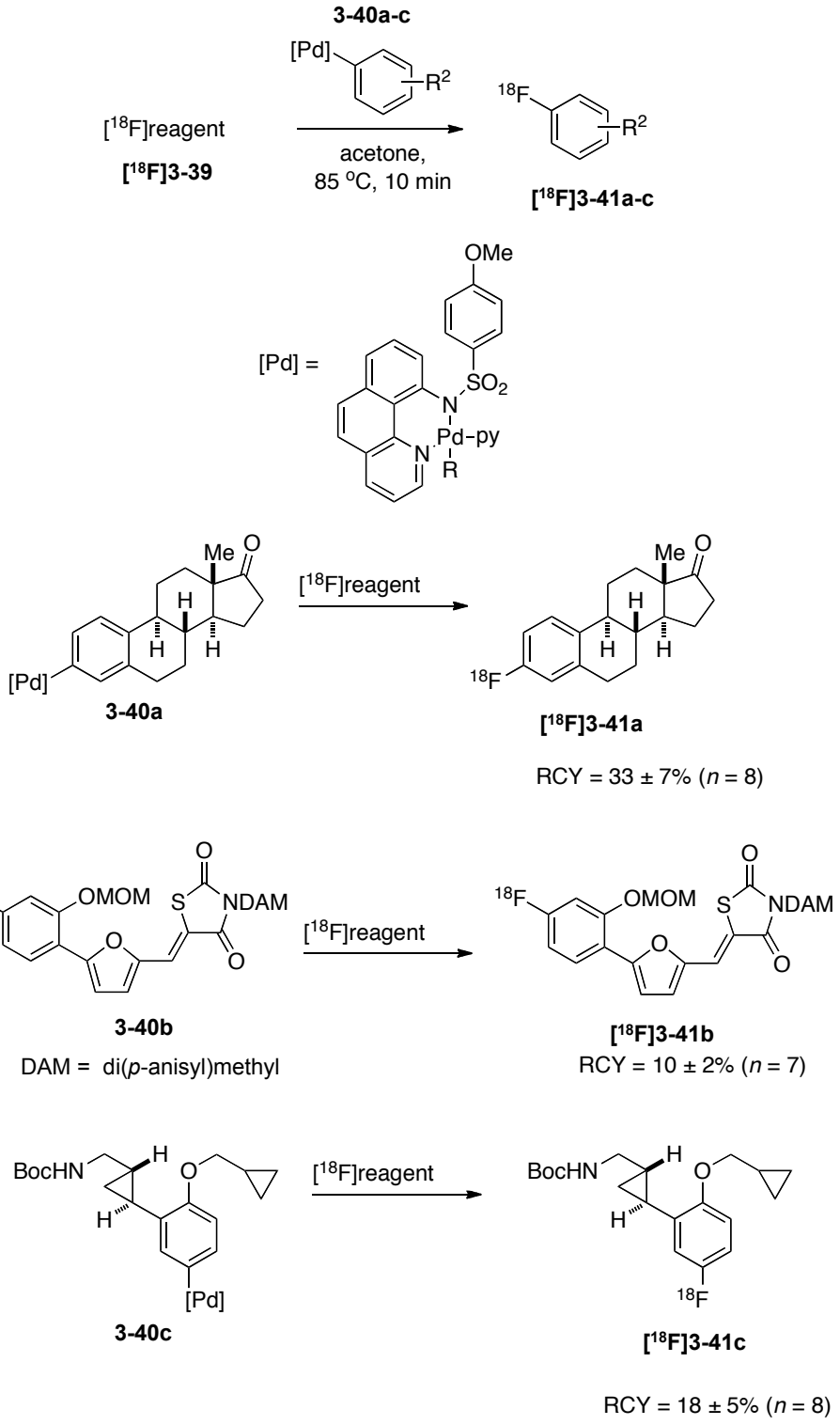
Ritter reported the first palladium mediated electrophilic ^{18}F-fluorination of arenes using a palladium-fluorine source derived from [^{18}F]fluoride.[182] This approach circumvents the use of [^{18}F]F_2 and makes electrophilic fluorination more accessible. The fluorophilic palladium(IV) **[^{18}F]3-39** species was generated *in situ* by reaction of complex **3-38** with [^{18}F]KF within 10 minutes at room temperature. (Scheme 3.22).



Scheme 3.22. Preparation of [^{18}F]reagent 3-39.

The palladium(IV) complex **3-38** was designed to carry three formal positive charges in order to encourage nucleophilic attack by fluoride in solution. This is of particular importance under radiochemical conditions when the concentration of fluoride is very low. The oxidation state of the palladium centre in complexes **3-38** and **[^{18}F]3-39** is +IV which enables them to act as an oxidant and transfer a ligand to a nucleophile while being reduced.[182] The multidentate benzo[*h*]guinolyl and tetrapyrazole borate ligands ensure the stability of the complexes to prevent the undesired C-F bond reductive elimination side-reaction with the benzo[*h*]quinolyl ligand. Additionally, the octahedral structure of the complexes avoids undesired nucleophilic attack at the palladium centre as the required orbitals are relatively high in energy. All these factors enable the radiolabelled complex **[^{18}F]3-39** to act as an electrophilic [^{18}F]reagent.

Following filtration over a polymer-supported resin, the Pd^{IV} complex **[^{18}F]3-39** was reacted with Pd(II) complexes **3-40a-c** upon heating for 10 minutes to afford the radiolabelled compounds **[^{18}F]41a-c** (Scheme 3.23).

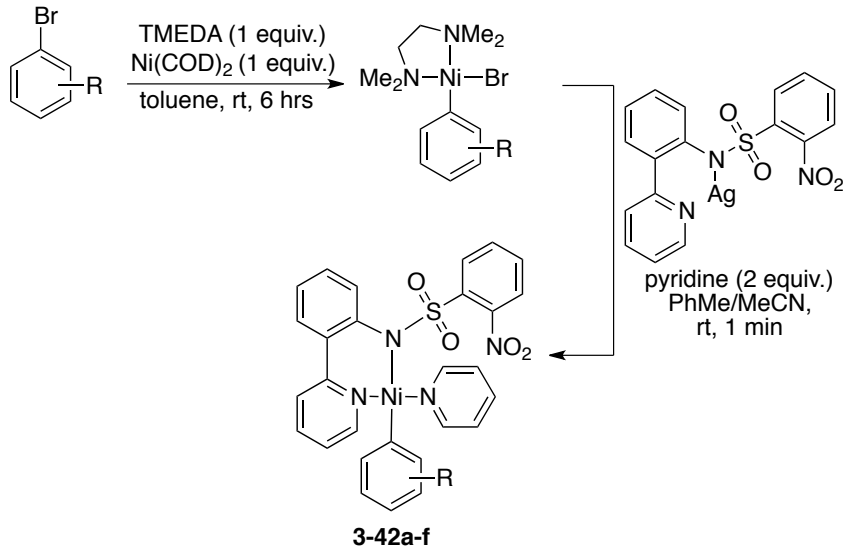


Scheme 3.23. Late-stage fluorination using [^{18}F]reagent 3-39.

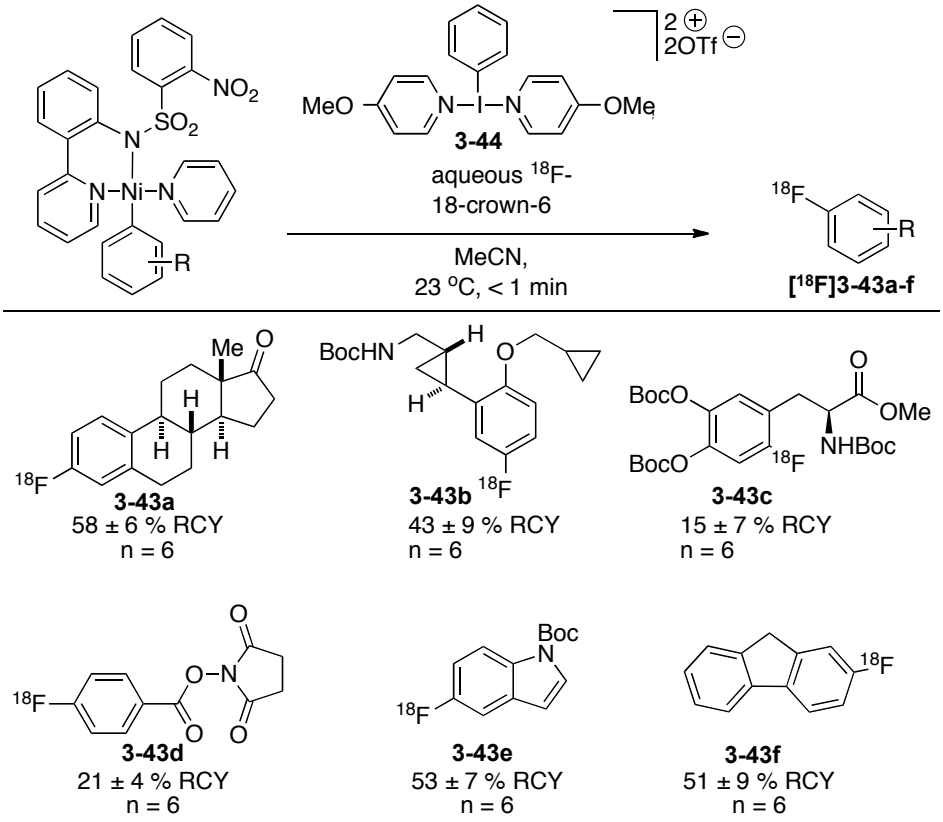
[^{18}F]fluorodeoxyestrone **[^{18}F]41a** was afforded in 33 ± 7% RCY. Two other [^{18}F]labelled arenes, bearing a variety of functional groups, could be obtained in RCYs superior to 10%. This electrophilic strategy represents a significant step towards accessing functionally diverse imaging agents synthesised from [^{18}F]fluoride. The

methodology was recently extended to preliminary non-human primate baboon PET imaging.[212]

Recently, Ritter developed a one-step oxidative fluorination for C-F bond formation using nickel complexes, an hypervalent iodine oxidant and aqueous [^{18}F]fluoride.[141] In comparison to the palladium strategy, the reaction is simplified and does not require the laborious drying of the [^{18}F]fluoride. The nickel(II) aryl complexes **3-42a-f** were prepared in two steps from the corresponding aryl bromides (Scheme 3.24).[141] A variety of complex biomolecules were successfully labelled using this strategy (Scheme 3.25).



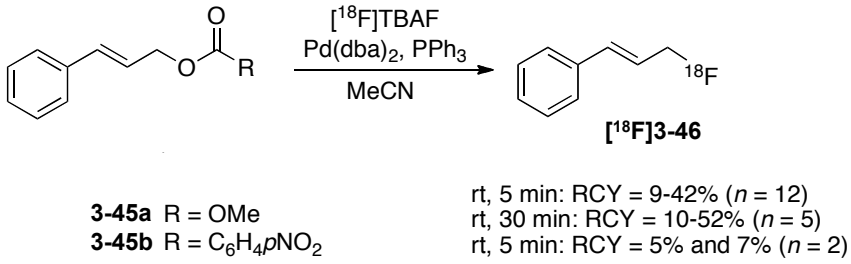
Scheme 3.24. Preparation of nickel(II) aryl complexes 3-42a-f.



Scheme 3.25. Nickel-mediated oxidative fluorination for PET.

The complexes were successfully radiolabelled in less than 1 minute in the presence of the hypervalent iodide oxidant **3-44**. A wide range of complex arenes could be successfully labelled with [^{18}F]fluoride **3-43a-f** in good RCYs. The benefits of this strategy compared to the corresponding palladium approach are the use of less starting material, no strenuous drying step and speed of the labelling step.

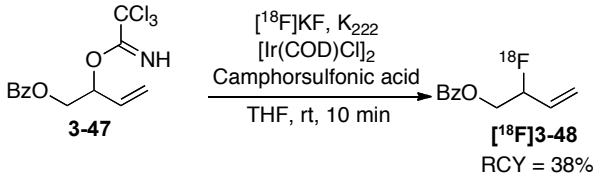
[^{18}F]Radiolabelling of allylic moieties have also been recently reported.[213],[214] The allylic precursors **3-45a** and **3-45b** substituted with carbonate or *para*-nitrobenzoate leaving groups successfully underwent fluorination in the presence of a palladium catalyst and [^{18}F]TBAF (Scheme 3.26).[214]



Scheme 3.26. Palladium mediated synthesis of allylic [^{18}F]fluorides.

The choice of leaving group proved to affect the RCY of the reaction. In the case of carbamate **3-45a**, the desired [^{18}F]cinnamyl fluoride **[^{18}F]46** was obtained in 9-42% after 5 minutes. Extending the reaction time did not significantly improve the yield of the reaction. When **3-45b** was investigated under the same reaction conditions, the yield of **[^{18}F]3-46** was reduced to 5%. This work demonstrated that C-^{18}F bond formation was feasible using a mild and rapid palladium-based protocol.[214]

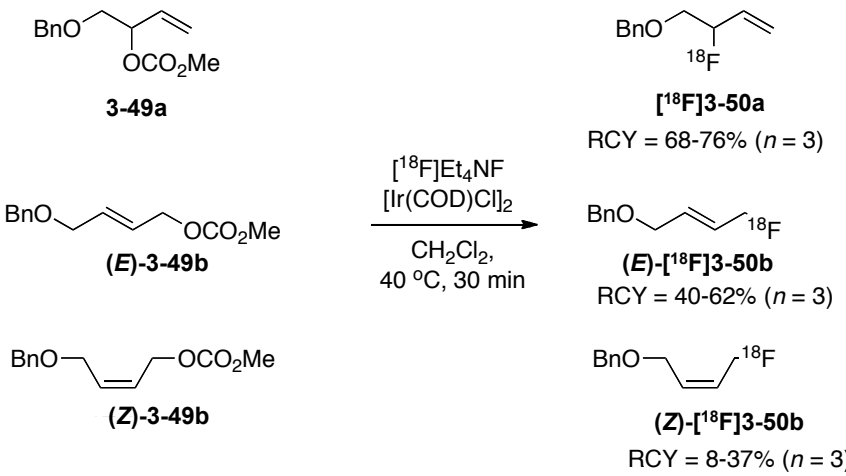
Preparation of allylic [^{18}F]fluorides have also been demonstrated under iridium catalysis.[213] Nguyen and co-workers studied the fluorination of allylic imidates and found that in the presence of $[Ir(COD)Cl]_2$ and triethylamine-HF complex as the fluoride source, a range of branched allylic fluorides could be obtained at room temperature within 1 hour from branched starting materials. This protocol was amenable to radiolabelling using [^{18}F]KF and $[Ir(COD)Cl]_2$. The radiolabelling of **3-47** afforded **[^{18}F]3-48** in 38% RCY within 10 minutes at room temperature (Scheme 3.27).



Scheme 3.27. [^{18}F]fluorination of allylic imidates under iridium catalysis.

Recent work from Gouverneur and co-workers described the successful [^{18}F]fluorination of allylic carbonates within 30 minutes at 40 °C using [^{18}F]Et_4NF as the fluoride source (Scheme 3.28).[213b] [^{18}F]KF was found to be an inferior labelling reagent to [^{18}F]Et_4NF under these reaction conditions. The RCYs obtained were higher in the case of the branched product **[^{18}F]3-50a** compared to the linear products (*E*)-

[^{18}F]3-50b and (*Z*)- **[^{18}F]3-50b**, with the (*E*)-isomer being the most efficient of the two. The amount of iridium catalyst added was approximately 0.4 mol%, but control experiments confirmed that no [^{18}F]fluorination occurred in the absence of iridium.

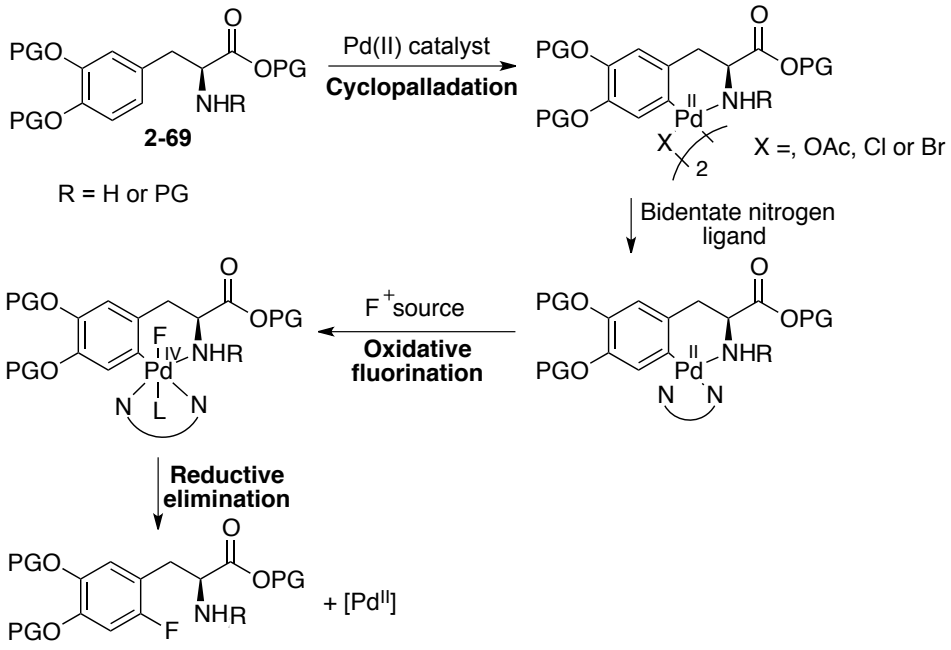


Scheme 3.28. [^{18}F]fluorination of allyl carbonates under iridium catalysis.

3.2.4 Factors to consider in the design of L-DOPA precursors for palladium-mediated fluorination reactions

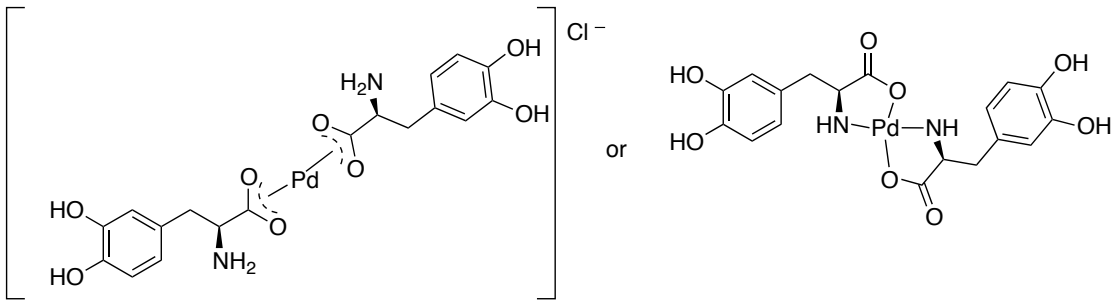
The success of each palladium-mediated fluorination protocol discussed in the introduction relies on a distinct set of reaction conditions. The right choice of palladium catalyst, ligand, solvent, reaction temperature, precursor and fluorine source must be made, in order to ensure an efficient fluorination reaction. All these factors must therefore be assessed for the development a set of optimum reaction conditions for the C-H activation-fluorination of L-DOPA.

The success of the palladium-mediated fluorination of L-3,4-dihydroxyphenylalanine **2-69** by reductive elimination depends on several steps: cyclopalladation, installation of the ligand and the oxidative fluorination (Scheme 3.29). In order to allow for the design of an optimal set of reaction conditions, each step must be considered in detail.



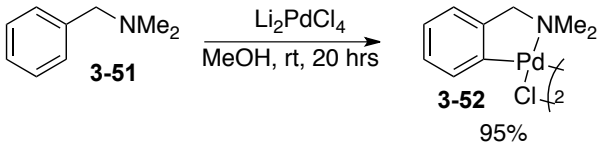
Scheme 3.29. Steps for successful Pd-mediated fluorination of L-DOPA.

The L-DOPA scaffold needed to be modified before cyclopalladation could take place. The carboxylic acid functionality is a good coordination site for palladium and must be protected to ensure reactivity at the C-H bond instead (Scheme 3.30).[215]



Scheme 3.30. Possible unfavoured palladium coordination modes.

The aim is to achieve selective C-H activation in the 6-position of L-DOPA. To promote this process, the amine coordinates to the metal catalyst and allows selective elctrophilic attack by the arene onto the metal, generating the palladacycle. [216] Cope and co-workers reported an early example of this by the cyclopalladation of *N*,*N*-dimethylbenzylamine **3-51** using lithium tetrachloropalladate(II) in methanol at room temperature (Scheme 3.31).[217] The cyclopalladated product **3-52** was obtained in 96% yield and analysed by NMR.

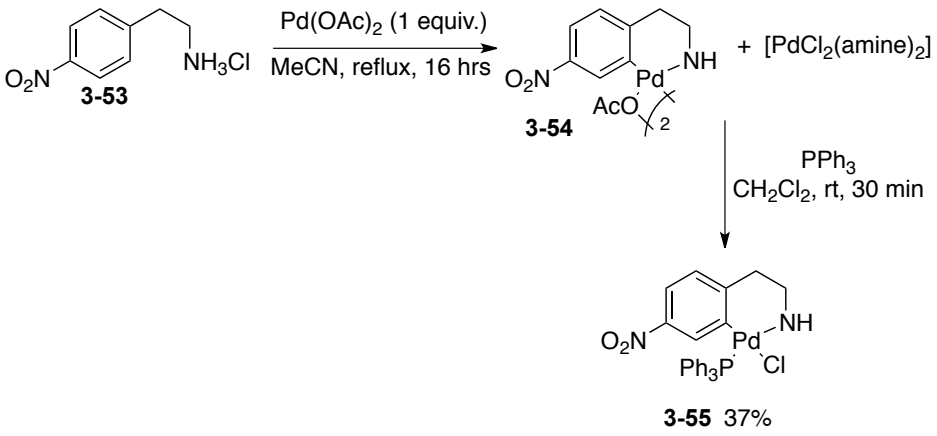


Scheme 3.31. Cyclopalladation of tertiary amines.

However, Cope and Friedrich carried out preliminary studies on *ortho*-palladation of other aliphatic amines and concluded that the process failed when the arene was substituted with electron-withdrawing groups, when primary amines were used and when a six-membered palladacycle was required. Cope speculated that the six-membered palladacycles were too unstable and that electron-poor arenes were too deactivated to undergo C-H activation. The primary amines were predicted to bind too strongly to the palladium centre and as two equivalents of amine were used in this protocol, the energy barrier for displacement of one amine to allow attack on the metal was considered to be too high to overcome under these reaction conditions. In these cases the complex $[PdCl_2(amine)_2]$ was isolated instead.[217]

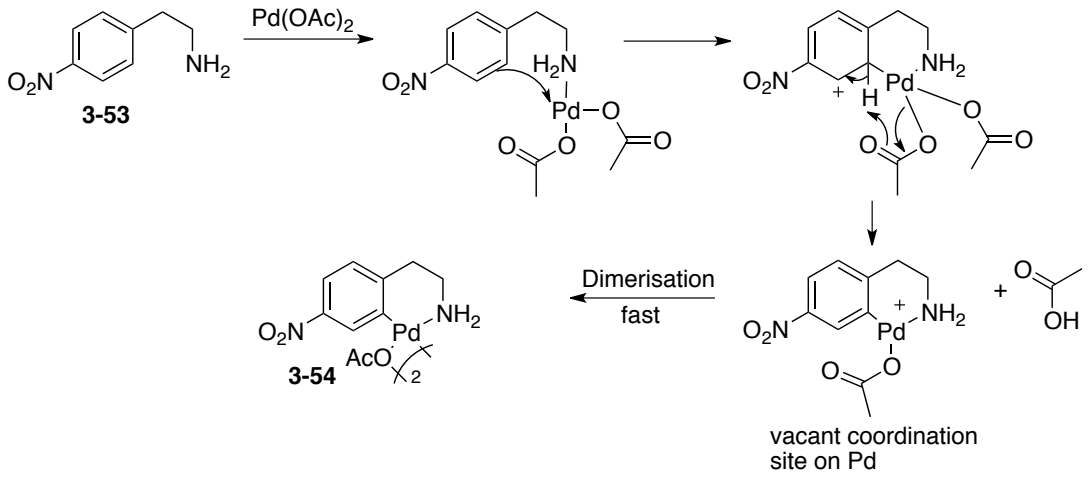
Conversely, Vicente and co-workers have reported several protocols dispelling these limitations by preparing six-membered palladacycles using a primary amine as the directing group to promote selective C-H activation of electron-poor arenes.[218],[219] [220]

4-Nitrophenethylamine hydrochloride **3-53** successfully underwent cyclopalladation to afford the aceto-bridged dimer **3-54** in the presence of palladium(II) acetate in acetonitrile at reflux (Scheme 3.31). The side-product $[PdCl_2(amine)_2]$ was also observed, indicating that the C-H activation is not selective. However, upon the addition of triphenylphosphine, the monomeric compound **3-55** was obtained in 37% yield. The structure of this class of 6-membered complexes was confirmed by NMR and x-ray spectroscopy (Scheme 3.32). The successful cyclopalladation of **3-53** was a very important achievement as it overcomes all three limits imposed by Cope and Friedrich.



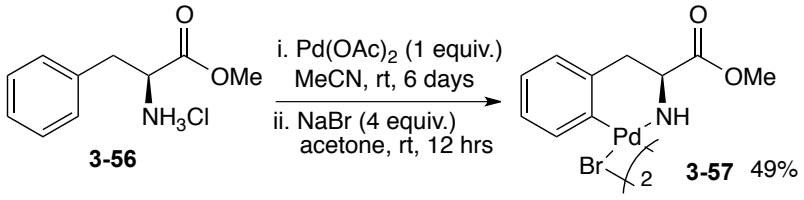
Scheme 3.32. *Ortho*-palladation of 3-53.

The proposed mechanism involves coordination of palladium acetate to the amine-directing group of **3-53** followed by nucleophilic attack of the arene onto the palladium metal. Rearomatisation is promoted by the protonation of one of the acetate groups to afford a three-coordinated intermediate with a vacant coordination site and acetic acid. The dimerisation of the three-coordinate species is fast as this process generates the stable square planar palladium(II) species **3-54** (Scheme 3.33). Evidence for dimerisation was obtained by x-ray crystallography and ^{1}H NMR. Only two acetate peaks were observed, one for the external acetate not associated with the palladium and one for the two bridged acetates, indicating that they are in a similar environment.[221]



Scheme 3.33. Mechanism for cyclopalladation.

Vicente extended this methodology to the cyclopalladation of amino acids.[222] L-Phenylalanine hydrochloride **3-56** was *ortho*-palladated using similar reaction conditions as for the cyclopalladation of compound **3-53**. After stirring **3-56** in the presence of palladium acetate in acetonitrile at room temperature for 6 days, the desired chloro-bridged palladium dimer was afforded as a mixture of several unidentifiable species, which proved challenging to purify. Anion exchange with sodium bromide allowed the isolation of the pure bromide-bridged dimer **3-57** in 49% yield (Scheme 3.34).



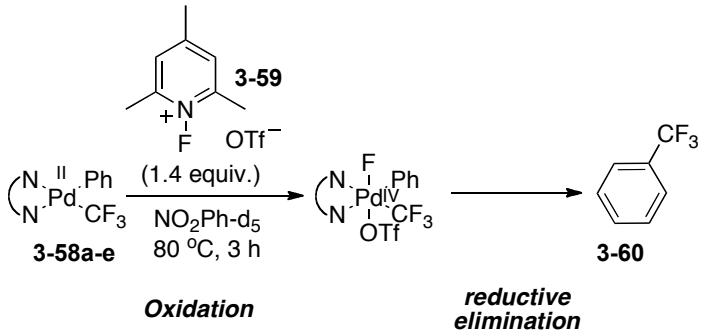
Scheme 3.34. *Ortho*-palladation of L-Phenylalanine hydrochloride.

This protocol shows the potential for successful *ortho*-palladation of L-DOPA, but in preliminary studies the cyclopalladation of L-phenylalanine will also be investigated in order to compare the outcome of the L-DOPA cyclopalladation reaction to a more studied system.

The next step for considering is the installation of an appropriate ligand. This can be achieved by the direct nucleophilic attack of the desired ligand on the dimeric complex and thereby generating the corresponding mononuclear ligand-substituted analogue. As described in the previous section, phosphorus-based ligands commonly promote P-F reductive elimination and will not be explored in these studies. The high-yielding palladium-mediated fluorination reactions reported in the literature, relied on the use of palladium(IV) complexes substituted with bidentate nitrogen ligands.[180],[181] Bidentate nitrogen ligands have found extensive use in the field of organometallic chemistry. These ligands are good σ donors and easily coordinate to transition metals.[223] Furthermore, these ligands also provide kinetic stabilisation of hypervalent palladium(IV) complexes.[224],[225]

Sanford carried out investigations into the effect of using different bidentate nitrogen ligands in a palladium trifluoromethylation reaction.[226] It was shown in section 3.2.1 (Scheme 3.4) that C-CF_3 reductive elimination is a challenging process, similarly to C-F bond formation, due to the low nucleophilicity of the CF_3 moiety. Although, studies by Grushin have shown that in related complexes, C-CF_3 bond formation require milder conditions than the corresponding C-F bond formation (discussed in detail in the introduction), it was proposed that the study reported by Sanford would provide reasoning for the choice of appropriate ligands, in order to successfully encourage challenging reductive elimination reactions to proceed.[198]

Arylpalladium(II) trifluoromethyl complexes **3-58a-e** was prepared in two steps from the corresponding aryl iodide followed by introduction of the trifluoromethyl moiety using $TMSCF_3$. Oxidation of the palladium(II) complexes **3-58a-e** in nitrobenzene at 80 ^oC was achieved by addition of *N*-fluoro-2,4,6-trimethylpyridinium triflate **3-59**. Subsequent reductive elimination afforded the trifluoromethylated compound **3-60** (Table 3.1).



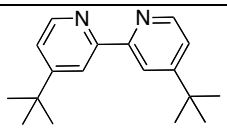
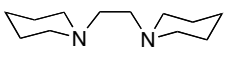
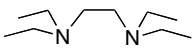
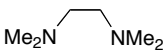
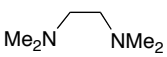
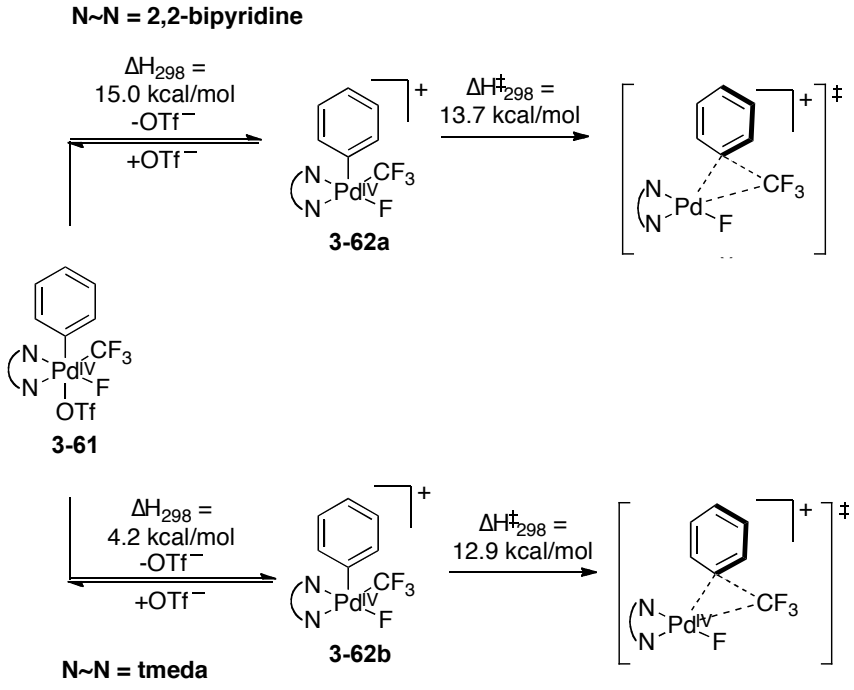
Entry	Compound	N-N	Temperature (^oC)	Yield (%)
1	**3-58a**		80	66
2	**3-58b**		80	99
3	**3-58c**		80	40
4	**3-58d**		80	90
5	**3-58e**		23	83

Table 3.1. Effect of the nature of the bidentate ligand.

Sanford showed that both sp^2 and sp^3 nitrogen bidentate ligands encouraged the reaction to proceed. When the complex was substituted with 4,4'-di-*tert*-butyl-2,2'-bipyridine **3-58a**, the desired product was obtained in 66% yield (Table 3.1, Entry 1). Compounds **3-58b** and **3-58c** substituted with sp^3 ligands, afforded the product **3-60** in yields ranging from 40-99% and illustrated the potential of this class of ligands (Table 3.1, Entry 2 and 3). Pleasingly, compound **3-58d**, containing the readily available TMEDA ligand, was highly successful under the reaction conditions (Table 3.1, Entry 4). Furthermore, complex **3-58e** underwent reductive elimination at room temperature in 83% yield. These are extremely mild conditions for a transition metal-mediated trifluoromethylation and showcase the benefit of employing nitrogen bidenate ligands.

DFT studies were also carried out to study the C-CF_3 reductive elimination from complexes substituted with different ligands (Scheme 3.35).[226]



Scheme 3.35. DFT calculations – enthalpies for reductive elimination.

Mechanistic studies showed that reductive elimination occurred form a five-coordinate cationic intermediate **3-62a-b**; the first step was the loss of the triflate anion from complex **3-61**. It was calculated that the energy barrier for dissociation of the anion was 10.8 kcal/mol lower for the TMEDA complex **3-62b** than the corresponding

bipyridine complex **3-62a**. However, the difference in the activation energy for the reductive elimination step was predicted to be only 0.8 kcal/mol lower for the TMEDA complex **3-62b**. This suggested that reductive elimination for C-CF_3 bond formation would be equally feasible from each complex under similar reaction conditions.
These results support and offer evidence for the benefit of using nitrogen bidentate ligands palladium-mediated fluorination reaction. As a result different bidentate ligands will be studied for the C-F bond formation.

Having chosen an appropriate bidentate nitrogen ligand for the palladium(II) complex, the subsequent step is introduction of the fluorine substituent and resulting oxidation of the palladium(II) centre by oxidative fluorination. Several electrophilic fluorinating reagents have been explored in the reported palladium-mediated fluorination reactions. The catalytic variants reported by Yu employ pyridine-based N-F reagents, while in the stoichiometric protocols Ritter and Sanford found Selectfluor and XeF_2 to yield the desired fluorinated product. It is difficult to predict which source of fluorine will be appropriate for the C-F reductive elimination in the L-DOPA substrates, and hence a range of electrophilic fluorine sources will be investigated.

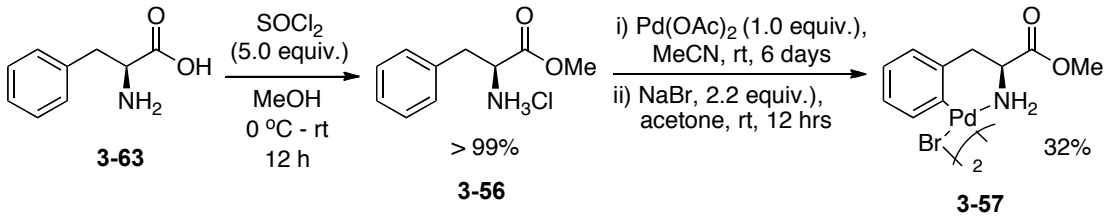
In summary, all of these experimental aspects must act in concert in order to culminate in successful reductive elimination and C-F bond formation.

3.3 Results and Discussion

3.3.1 Studies towards palladium-mediated C-H activation for the preparation of 6-[^{18}F]fluoro-L-DOPA

The *ortho*-palladation of L-DOPA has not been reported in the literature. Therefore, it was decided to preliminarily investigate the C-H activation and fluorination reaction using L-phenylalanine. If successful fluorination reaction conditions can be obtained, the methodology will be extended to L-DOPA.

The carboxylic acid functionality of L-phenylalanine was protected as the methyl ester **3-63** in the presence of thionyl chloride in methanol in quantitative yield. The *ortho*-palladation of **3-56** was carried out following the reaction conditions developed by Vicente.[222] Upon reaction of **3-56** with 1 equivalent of palladium acetate in acetonitrile at room temperature, followed by halogen exchange by NaBr, the desired dimeric palladacycle **3-57** was afforded in 32% yield (Scheme 3.36).[222]

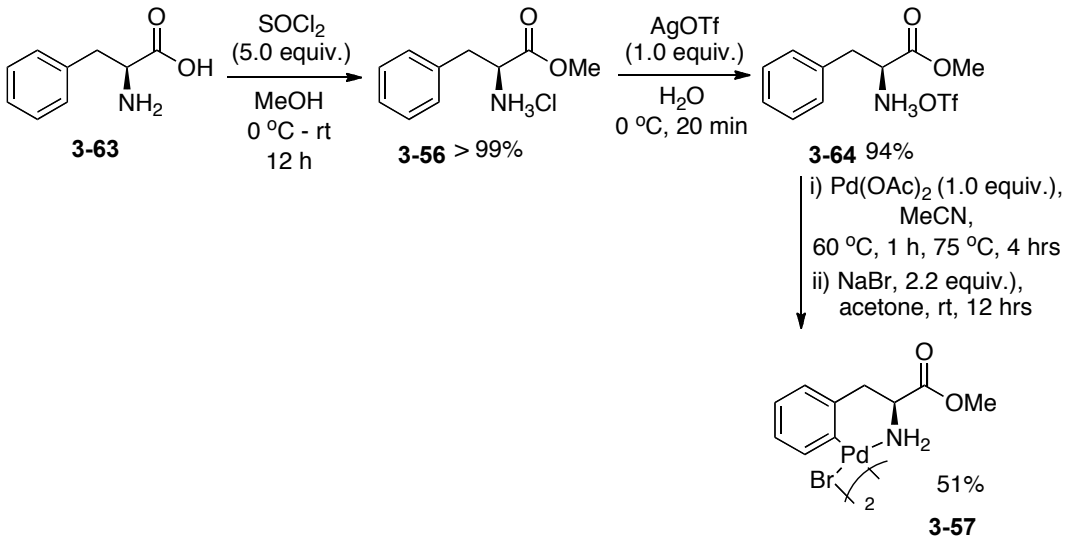


Scheme 3.36. Ortho-palladation of L-phenylalanine.

The halide exchange of the bridging chloride for bromide was required because of the presence of a mixture of inseparable species in the crude product mixture following the initial cyclopalladation step. By replacing the chloride, the desired product **3-57** could be purified by recrystallisation. It has been explained that this class of cyclopalladation reaction afford the products as dimers (Scheme 3.33) and Vicente confirmed the formation of **3-57** by x-ray crystallography in addition to characterisation by ^{1}H and ^{13}C NMR.[222] In these studies **3-57** was only analysed by ^{1}H and ^{13}C NMR spectroscopy. The data obtained corresponded to those reported in the literature. Only four aromatic protons were observed in the ^{1}H NMR and the carbon bonded to palladium was deshielded compared to the corresponding carbon in the starting material in the ^{13}C NMR (140.5 ppm *vs.* 129.1 ppm). It was postulated that **3-57** was

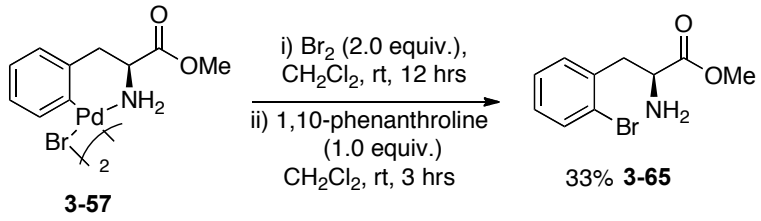
obtained as the dimer confirmation due to identical reaction conditions to Vicente's being employed.

The reaction time for the cyclopalladation of **3-57** was long (6 days) and attempts to reduce it by heating to 60 ^{o}C for 4 hours resulted in the precipitation of palladium black, and thereby afforded **3-57** in a significantly reduced yield (14%). Vicente recently reported an updated protocol, using the triflate amine salt instead of the hydrochloride equivalent, employing a significantly shorter reaction time.[227] In this study, L-phenylalanine methyl ester hydrochloride **3-56** was reacted with silver triflate to form the triflate salt **3-64** in 94% yield. In this case, it was found that the cyclopalladation reaction was amenable to heating. After heating the reaction mixture for 1 hour at 60 ^{o}C and then for a further 4 hours at 75 ^{o}C, the desired palladacycle **3-57** was obtained in an improved yield of 51% and in a much shorter reaction time (Scheme 3.37).



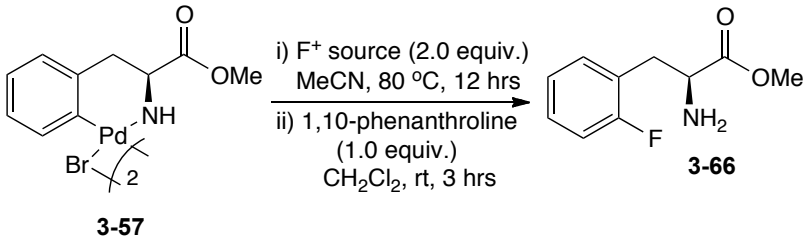
Scheme 3.37. Formation of 3-57 using Vicente's updated conditions.

In Vicente's original publication, it was shown that complex **3-57** underwent selective halogenation in the presence of iodine or bromine.[222] Using Vicente's reported conditions, 6-bromo-L-phenylalanine **3-65** could be obtained in 33% yield (Scheme 3.38).



Scheme 3.38. Bromination of complex 3-57.

With this encouraging result in hand, it was investigated whether an analogous reaction would proceed with electrophilic fluorinating reagents (Table 3.2). 1-Fluoro-3-nitrobenzene was added as an internal reference standard to determine the yield of the fluorinated product 6-fluoro-L-phenylalanine methyl ester **3-66** by ^{19}F NMR spectroscopy.



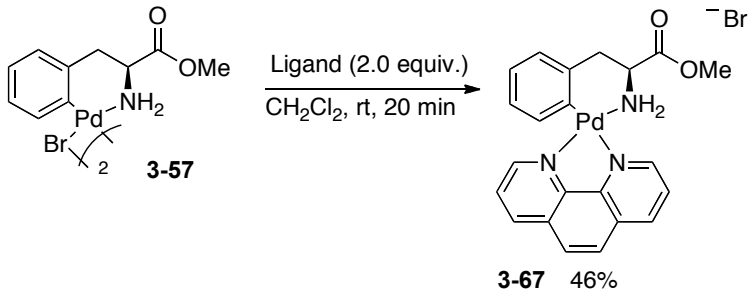
Entry	F^+ source	Yield (%)
1	Selectfluor™	0
2	NFSi	0
3	*N*-fluoro-2,4,6-trimethylpyridinium triflate	0

Table 3.2. Fluorination of complex 3-58.

In all cases, the reaction between complex **3-57** with Selectfluor, NFSI or *N*-fluoro-2,4,6-trimethylpyridinium triflate in acetonitrile at 80 °C, did not afford the fluorinated L-phenylalanine **3-66** (Table 3.2). In all cases the brominated compound **3-65** was identified by mass spectroscopy. In addition, the starting material was recovered with small amounts of palladium black precipitating out of the reaction mixture.

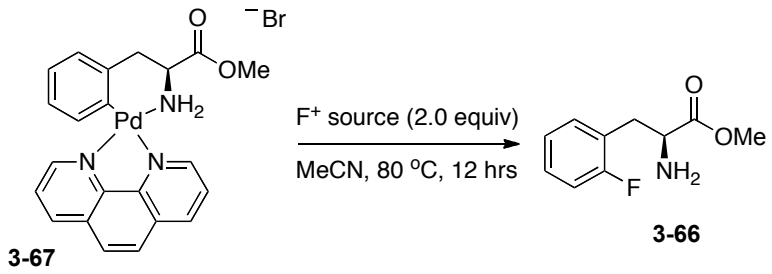
The failure of C-F bond formation under these reaction conditions prompted investigations into suitable nitrogen bidentate ligands.

It was decided to first investigate, 1,10-phenanthroline. Sanford found that, 4,4'-di-*tert*-butyl-2,2'-bipyridine, is a suitable ligand in the palladium-mediated fluorination of aryl iodides using XeF_2 (Scheme 3.20).[180] Palladium complex **3-57** was reacted with two equivalents of 1,10-phenanthroline in CH_2Cl_2 and this results in displacement of the two bridging bromine atoms by nucleophilic substitution. The resulting stable monomeric palladium complex **3-67** substituted with 1,10-phenanthroline was obtained in 46% yield (Scheme 3.39). All efforts to recrystallise complex **3-67** and obtain a structure by x-ray crystallography were unsuccessful. Detailed characterisation of the structure of **3-67** by NMR spectroscopy proved challenging. However, the complex could be characterised by elemental analysis (Expected: C = 48.51%, H = 3.70%, N = 7.71%; Found: C = 49.44%, H = 3.84%, N = 7.22%).



Scheme 3.39. Preparation of monomeric phenanthroline palladium(II) complex.

The complex **3-67** was subsequently heated in the presence of 2 equivalents either Selectfluor™, NFSi or *N*-fluoro-2,4,6-trimethylpyridinium triflate. 1-Fluoro-3-nitrobenzene was added as an internal reference standard to determine the yield of **3-68** by ^{19}F NMR (Table 3.3).

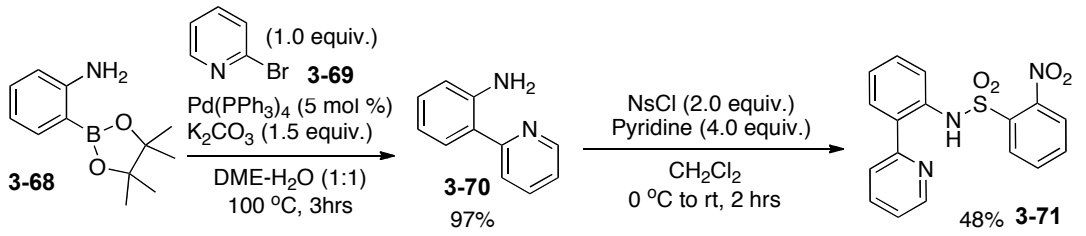


Entry	F^+ source	Yield (%)
1	Selectfluor™	0
2	NFSi	0
3	*N*-fluoro-2,4,6-trimethylpyridinium triflate	0

Table 3.3. Fluorination of complex 3-67.

Upon addition of Selectfluor the reaction mixture turned deep red and paled to orange over of 30 minutes (Table 3.3, Entry 1). After 12 hours, a significant amount of palladium black had precipitated from the reaction mixture, signalling reduction of the palladium(II) complex. Disappointingly, no fluorinated product was observed by ^{19}F NMR analysis in the expected range for C-F bonds in aromatic amino acids (~ -110 to -130 ppm), although peaks corresponding to the un-fluorinated Selectfluor species **2-72** were observed in the ^{1}H NMR spectrum, suggesting that the fluorine atom had been transferred. The ^{1}H NMR spectrum showed that 48% of the starting complex **3-67** remained in the reaction mixture. A complex mixture of other species appeared to be present, but these could not be separated or identified. No fluorinated product was observed when NFSi or *N*-fluoro-2,4,6-trimethylpyridinium triflate were investigated (Table 3.3, Entries 2-3). In both cases, only a complex mixture of aromatic peaks was found in the ^{1}H NMR spectrum and none of the diagnostic peaks of the starting complex could be identified. Furthermore, no peaks were observed in the ^{19}F NMR in the expected region for fluorinated aromatic amino acids.

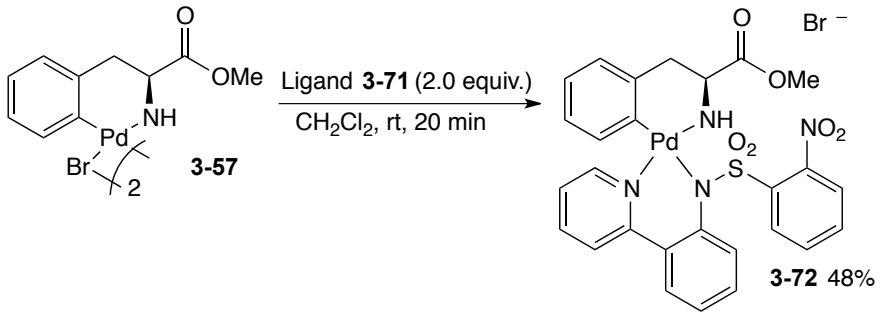
This encouraged the investigation of 2-(2-pyridinyl)phenyl-2-nitrobenzenesulfonamide ligand **3-71**, used in Ritter's studies, as it was shown to successfully stabilise Pd(IV) intermediates through the SO_2 moiety of the sulfonamide component of the nosyl protecting group. Ligand **3-71** was prepared in two steps according to the procedure reported by Ritter (Scheme 3.40).[228]



Scheme 3.40. Preparation of 2-(2-pyridinyl)phenyl-2-nitrobenzenesulfonamide ligand 3-71.

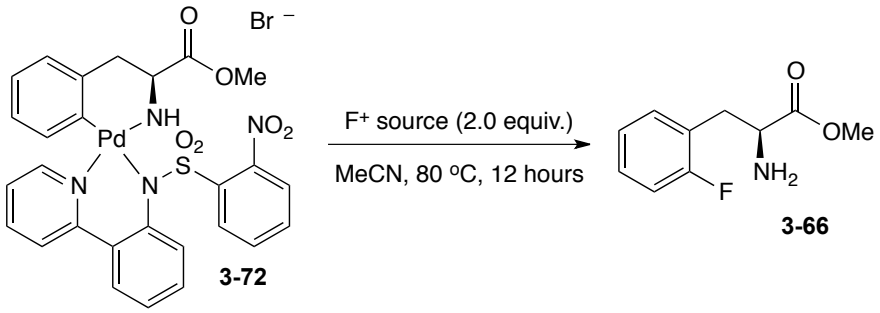
The Suzuki coupling of 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline **3-68** and 2-bromopyridine **3-69** proceeded in excellent yield. Aniline **3-70** was subsequently protected with *o*-nitrobenzenesulfonyl chloride, using pyridine as the base, to afford **3-71** in 48% yield.

Upon the addition of two equivalents of ligand **3-71** in CH_2Cl_2, the bromo-bridge of the dimeric palladium(II) L-phenylalanine complex **3-57** was split into the corresponding monomer by ligand exchange, affording the desired monomeric complex **3-72** in 54% yield (Scheme 3.41). Owing to its insolubility in all common deuterated solvents, NMR analysis of this compound was unsuccessful. However, the complex could be characterised by elemental analysis (Expected: C = 45.95%, H = 3.44%, N = 7.65%; Found: C = 45.79%, H = 3.50%, N = 7.69%).



Scheme 3.41. Preparation of complex 3-72 with ligand 3-71.

The complex was subsequently heated to 80 °C in the presence of a range of electrophilic N-F reagents to investigate the propensity for C-F bond formation from complex **3-72** (Table 3.4).



Entry	F^+ source	Yield (%)
1	*N*-fluoro-2,4,6-trimethylpyridinium triflate	0
2	NFSi	0
3	Selectfluor™	trace

Table 3.4. Fluorination of complex 3-72.

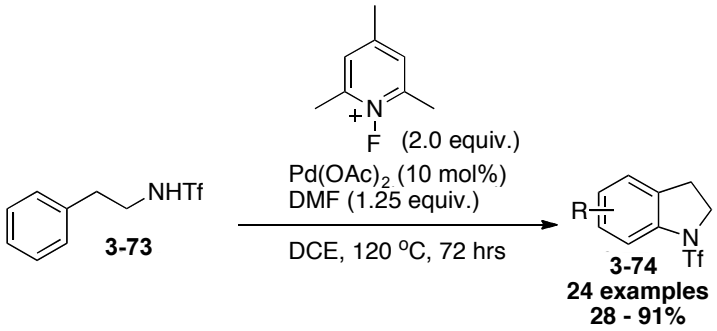
In the presence of NFSi and *N*-fluoro-2,4,6-trimethylpyridinium triflate, no peaks corresponding to aromatic C-F bonds were observed in the ^{19}F NMR spectrum (Table 3.3, Entries 1 and 2). However, in the presence of Selectfluor, 60% of the starting material was recovered and a trace amount of a fluorinated product was observed (Table 3.3, Entry 3). A peak at -124.5 ppm was observed in the ^{19}F NMR spectrum, but present in a too small amount of be characterised by ^{1}H NMR spectroscopy due to the other species present in the reaction mixture. Electrospray ionisation mass spectrometry revealed a peak at 220.0759 m/z, which corresponds to fluorinated L-phenylalanine and a sodium cation (calc. 220.0750 $[C_{10}H_{12}FNO_2 + Na]^+$). However, the regioselectivity of the product cannot be confirmed, as direct unselective fluorination of L-phenylalanine may be possible. The other components of the reaction mixture proved challenging to identify, due to the presence of a complex mixture of peaks in the ^{1}H NMR spectrum.

These preliminary optimisation studies suggest that L-phenylalanine is not a suitable substrate for palladium-mediated fluorination under these reaction conditions.

A significant difference between a six-membered palladium(II) complex, such as **3-72** and the five-membered equivalent is that intramolecular C-N reductive elimination is a competitive side-reaction. As explained in the introduction to this chapter, carbon-heteroatom reductive elimination is more facile the more nucleophilic the heteroatom

is. In terms of nucleophilicity, nitrogen is a better nucleophile than fluorine. In a reaction system where both processes are in competition, C-N reductive elimination is predicted to be favoured.

Yu reported a method for the preparation of indolines **3-74** from triflamide protected 2-phenethylamines **3-73** using the electrophilic N-F reagent *N*-fluoro-2,4,6-trimethylpyridinium triflate as a two-electron oxidant (Scheme 3.42).[229]



Scheme 3.42. Yu's protocol for C-N reductive elimination in the presence of an F^+ reagent.[229]

In the presence of two equivalents of *N*-fluoro-2,4,6-trimethylpyridinium triflate, $Pd(OAc)_2$ and DMF, a wide variety of indolines were prepared in poor to excellent yields.[229] This process is predicted to proceed *via* a C-N reductive elimination following a Pd(II)/Pd(IV) pathway and hence could be a viable side-reaction of the fluorination reaction attempted to develop herein.

It was attempted to identify indoline **3-75** (Figure 3.4) by mass spectroscopy analysis of the reaction mixtures obtained by fluorination of complexes **3-67** and **3-72** in Tables 3.3 and 3.4. However, no peaks corresponding to indoline **3-75** was observed.

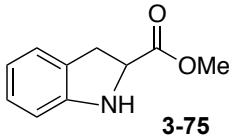


Figure 3.4. Indoline 3-75 – potential side-product from C-N reductive elimination.

The conditions required for the amination to proceed in the protocol developed by Yu are extremely forcing (120 °C, 72 hrs). Furthermore, Yu reported that the presence of

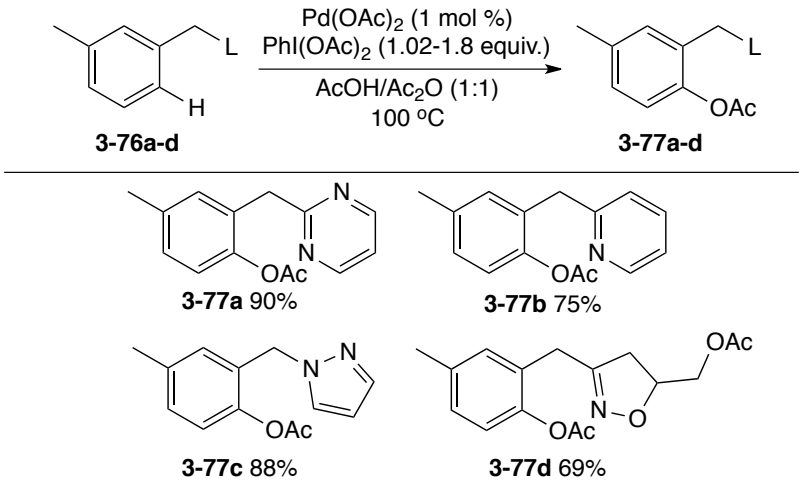
DMF was crucial for the process to succeed, by perhaps acting as a labile ligand on the palladium.[229]

It is likely that C-N reductive elimination is not feasible under the alternative fluorination conditions employed in herein (80 ^{o}C, 12 hrs) and that other alternative side-reactions proceed instead.

3.3.2 Palladium-mediated fluorination of L-phenylalanine using sp^2 directing groups

The previous studies focussing on the palladium-mediated fluorination on L-phenylalanine precursors, with the free sp^3 amine functionality as the directing group, did not encourage C-F bond formation. In most cases, recovery of the starting material or formation of palladium black was observed, suggesting that these precursors are not suitable substrates for this transformation. It was therefore decided to redesign the amino acid precursor.

In the pioneering palladium-mediated fluorination, Sanford and co-workers illustrated the potential of sp^2 pyridine functional groups as directing groups (Scheme 3.14).[178] This research group further showcased the utility of a range of heterocycles as directing groups in a palladium acetoxylation reaction (Scheme 3.43).[230]



Scheme 3.43. Heterocycles as directing groups.

It was therefore decided investigate alternative sp^2 nitrogen directing groups for the palladium-mediated C-H activation-fluorination of L-phenylalanine.

Albert and co-workers have reported the successful cyclopalladation of L-phenylalanine using aryl imines as directing groups.[231],[232] However, when unsubstituted aryl imines are employed, the formation of two different regioisomers is possible (Figure 3.5).

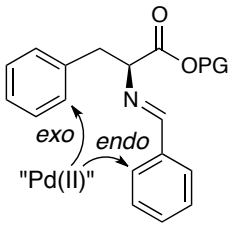
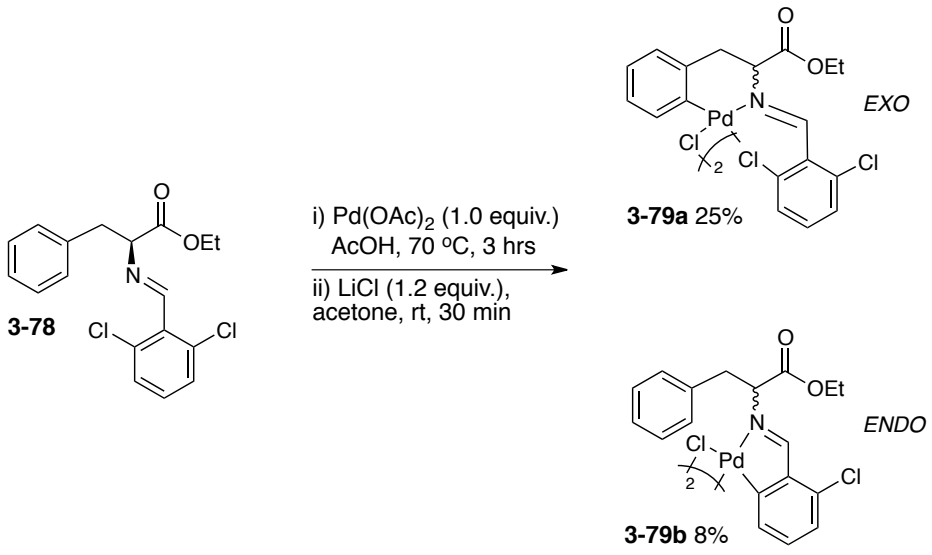


Figure 3.5. *Exo vs. endo* palladacycle.

The six-membered *exo* palladacycle is afforded by C-H activation of the benzylic arene, while the five-membered *endo* is obtained by C-H activation of the 2-position of the aryl imine. It has been widely reported in the literature that when both regioisomers are possible, the five-membered *endo* palladacycle is kinetically favoured and obtained as the major product.[233],[234]

Albert attempted to increase regioselectivity for the *exo* palladacycle by blocking the 2- and 6-position of the aryl imine with chlorine atoms (Scheme 3.44).[231]



Scheme 3.44. Cyclopalladation of aryl imines by Albert.[231]

In Albert's studies, the desired *exo* palladacycle **3-79a**, afforded by C-H activation on the benzylic arene, was afforded in 25% yield as the major regioisomer upon the reaction between L-phenylalanine aryl imine **3-78** and palladium(II) acetate in acetic acid. Conversely, the undesired five-membered *endo* palladacycle **3-79b** was obtained in 8% yield, upon activation of the aryl imine by insertion of the palladium catalyst into the C-Cl bond. Albert and co-workers found that the regioisomers could be separated by column chromatography. [231]

In the study herein, the starting imine compound **3-78** was prepared in >99% yield upon the condensation reaction between L-phenylalanine ethyl ester and 2,6-dichlorobenzaldehyde, in the presence of $MgSO_4$. However, the cyclopalladation reaction, using the conditions reported by Albert, led to a mixture of products that were inseparable by flash column chromatography. Albert also found that the stereocentre of the amino acid underwent complete racemisation during cyclopalladation reactions.[231] The limitations of this protocol prompted further investigations into alternative sp^2 nitrogen directing groups.

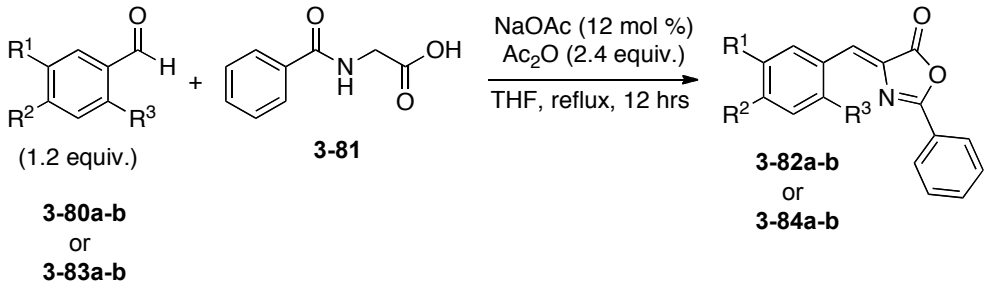
3.3.2.1 Oxazolone as an amino acid protecting group

The classic Erlenmeyer reaction for the synthesis of amino acids uses an oxazolone as a protecting group of the amino acid functionality that can be readily cleaved under reduction conditions.[235] This reaction traditionally consists of a three-component condensation between benzaldehyde, *N*-benzoylglycine and a catalytic amount of base (sodium acetate) in excess acetic acid.

This heterocycle contains an sp^2 nitrogen directing group and this protecting group was therefore proposed as a suitable alternative in the cyclopalladation of L-phenylalanine and L-DOPA.

The Erlenmeyer reaction afforded unsaturated (*Z*)-2-aryl-4-arylidene-5(4H)-oxazolones **3-82a-b** in a single step. Hippuric acid **3-81** self-condenses in the presence of acetic anhydride before reacting with benzaldehyde **3-80a** or 3,4-dimethoxybenzaldehyde **3-80b** and sodium acetate (Table 3.5). Carey and co-workers carried out Raman spectroscopy studies on *E* and *Z* unsaturated 5(4H)-oxazolones, and showed that the Ehrlenmeyer reaction proceeds stereoselectively to afford the more

thermodynamically stable *Z* isomer as the only product.[236] The *Z*-configuration has also been confirmed by X-ray crystallography.[237]



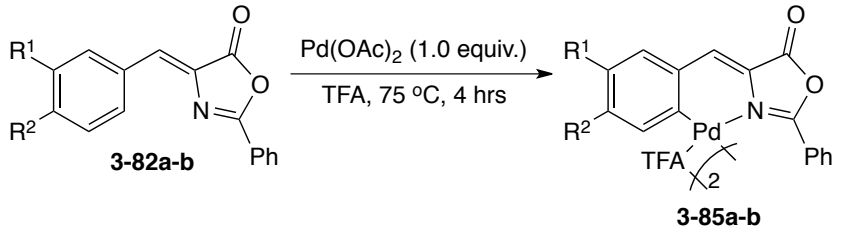
Compound	R^1	R^2	R^3	Yield (%)
3-82a	H	H	H	58
3-82b	OMe	OMe	H	96
3-84a	H	H	F	79
3-84b	OMe	OMe	F	66

Table 3.5. Preparation of (*Z*)-2-aryl-4-arylidene-5(4H)-oxazolones

The DL-phenylalanine **3-82a** and DL-DOPA **3-82b** oxazolone compounds were prepared in 58% and 96% yield, respectively. In order to ease the identification of the desired fluorinated products by ^{19}F NMR, the fluorinated reference compounds **3-84a-b** were also independently prepared, using the corresponding 2-fluorobenzaldehydes **3-83a-b**, in 79% and 66% yield respectively.

The Urriolabeitia research group have recently carried out extensive studies into the *ortho*-metallation of unsaturated 5(*4H*)-oxazolones.[238],[237] They found that heating oxazolones, in the presence of $Pd(OAc)_2$ in acetic or trifluoroacetic acid, afforded the six-membered palladacycles in high yields. Only the cyclopalladation compounds of highly electron-rich substrates were attainable in acetic acid, while both electron-neutral and electron-poor oxazolones also underwent *ortho*-palladated in TFA.[237]

In the studies herein, oxazolones **3-82a** and **3-82b** were cyclopalladated in the presence of 1 equivalent of $Pd(OAc)_2$ in TFA upon heating at 75 ºC for 4 hours. The bridged-TFA dimers **3-85a** and **3-85b** were prepared in 56% and 51% yield, respectively (Table 3.6).



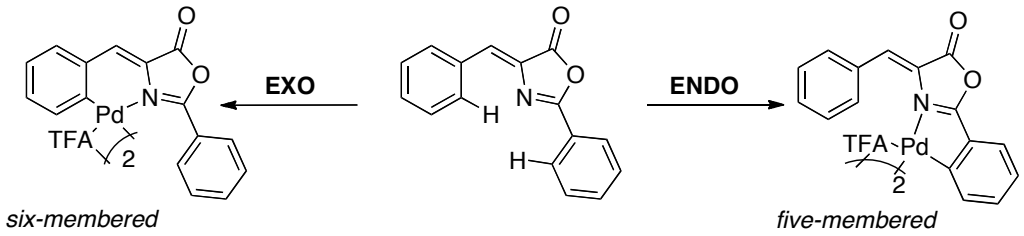
Compound	R^1	R^2	Yield (%)
3-85a	H	H	56
3-85b	OMe	OMe	51

Table 3.6. Preparation of palladacycles.

Urriolabeitia carried out x-ray crystallography studies to confirm the structure of the cyclopalladated oxazolones **3-85a** and **3-85b** as TFA-bridged open-book dimers.[237] Complexes **3-85a** and **3-85b** were also characterised by NMR. The data obtained herein corresponded to those reported in the literature. Upon cyclopalladation the diagnostic benzylidene proton became deshielded (for **3-85a**: 7.29 ppm to 7.56 ppm, for **3-85b**: 7.27 ppm to 7.42 ppm). Only one TFA peak was observed in the ^{19}F NMR spectra of **3-85a** and **3-85b** (-75.2 ppm and -74.8 ppm, respectively), indicating that the TFA species must exist in a similar environment. These results indicate that the cyclopalladation reaction occurred and that the expected dimeric complexes were obtained. The dimeric complexes **3-85a** and **3-85b** were found to be stable for a minimum of 2 months at room temperature under argon.

3.3.2.2 Literature studies regarding the regioselectivity of complexes 3-85a-b

As explained previously, it is known that the formation of five-membered palladacycles is favoured over the corresponding six-membered rings when both are facile. However, in this case, the six-membered palladacycle appeared to be most stable and was formed regioselectively. ^1H and ^{13}C NMR spectroscopy supported the formation of the *exo* palladacycle and the structure was confirmed by x-ray crystallography.[238] The five-membered *endo* equivalent was never observed, even in minor quantities (Scheme 3.45).



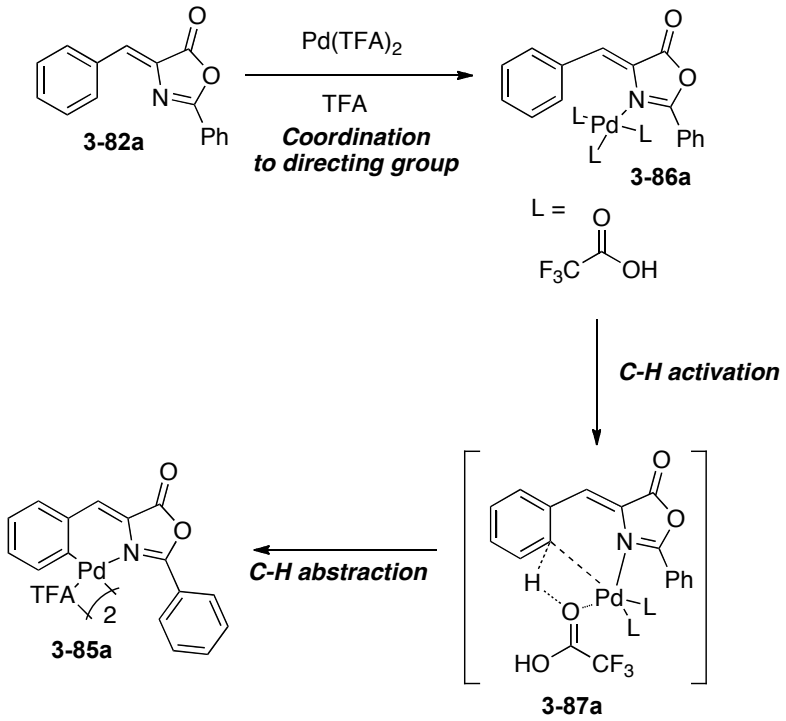
Scheme 3.45. Endo *vs.* exo palladacycles.

The regioselectivity was shown to be independent of the nature of the substituents on the arylidene ring. The presence of either strongly electron-donating or electron-withdrawing groups did not alter the regioselectivity or significantly alter the yield. This is difficult to justify on the basis of an electrophilic aromatic substitution mechanism.[237]

Urriolabeitia postulated this was due to a combination of effects including sterics, planarity of the cycle and metalloaromaticity.[237] Extensive kinetic and thermodynamic studies were carried out to elucidate the reason for the observed regioselectivity. X-ray crystallography studies on these complexes confirmed that the benzylidene moiety existed in a Z-configuration[239] as shown in scheme 3.45. This configuration forces the entire molecule to adopt a planar arrangement.[238],[237] This was an unusual situation but increased the likelihood of forming a six-membered palladacycle.

The studies revealed that the preference for 6-membered palladacyles is mainly governed by kinetic control, ie. the activation energy barriers. A small thermodynamic preference was also observed, as the relative energy of the final *ortho*-palladated product is lower for the six-membered complex **3-85a** relative to the five-membered equivalent (Scheme 3.45).

The kinetic preference is best explained schematically (Scheme 3.46).



Scheme 3.46. Ambiphilic mechanism for the formation of six-membered palladacycle 3-85a.

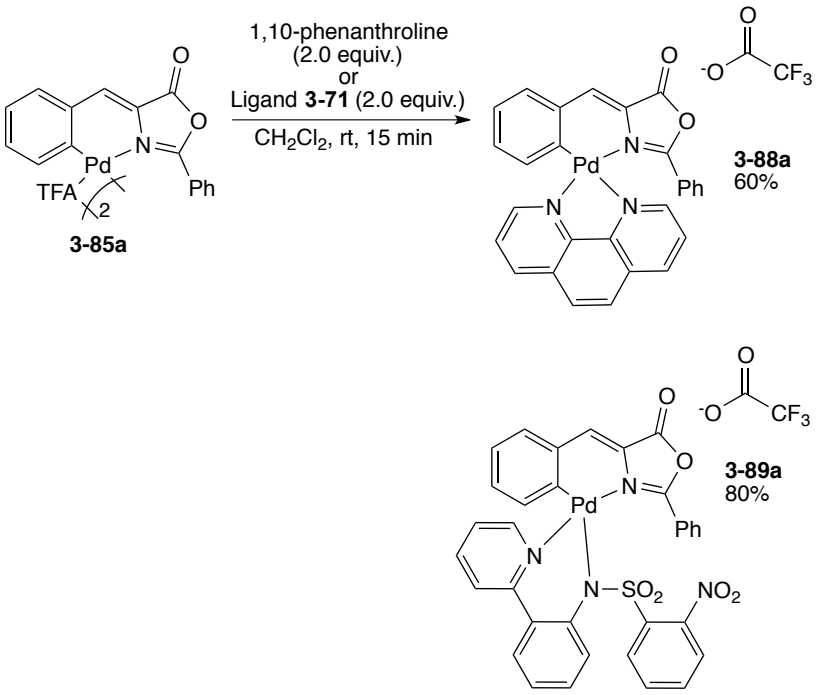
The extent of the preference for the six-membered transition state is dependent on whether trifluoroaetic or acetic acid is used as the solvent. The first step in both cases is the coordination of the palladium catalyst to the nitrogen atom of the oxazolone functional group. In TFA, the acetate ligands on the palladium catalyst are exchanged for TFA ligands. The next step involves an agostic interaction between the C-H bond and the carbonyl group of the TFA ligand (C-H activation). In the case of acetic acid this is the rate-limiting step as the acetic acid ligand binds strongly to the palladium centre. In TFA this step is fast, as the TFA ligand is protonated and therefore bind weakly to the palladium centre. The bond lengths in the transition state were calculated to be longer in TFA than in acetic acid. The opposite is true for the next step where the C-H is broken and the protonated TFA ligand departs (C-H abstraction). The activation energy of this step remains constant but is lower in TFA due to the TFA ligand being bound more weakly. The overall mechanism for this C-H activation process, where an electron-deficient late transition metal centre and a basic ligand act in concert to break a C-H bond, has been named an ambiphilic mechanism.[237]

DFT calculations showed that the energy barrier for the formation of the six-membered ring was lower than for the corresponding five-membered alternative in both acetic and trifuoroacetic acid, but the difference was greater in the latter. The difference was related to the preorganisation of the acid ligand as the hydrogen acceptor in the agostic interaction. In TFA, the energy required for prearrangement of the oxazolone and acid ligand for the formation of the five-membered ring is 20 kJ/mol higher than in the six-membered equivalent. Increased steric hindrance is thought to influence this.

The lower energy barriers, due to the longer bond lengths in the transition state for the desired cyclopalladation reaction, also explain why the reaction is accelerated in TFA.[237]

3.3.2.3 Preparation of monomeric oxazolone complexes and subsequent fluorination studies

The TFA dimer palladium(II) complex **3-85a** was easily split into the monomeric form by associative ligand substitution in the presence of two equivalents of 1,10-phenathroline or ligand **3-71** in CH_2Cl_2 at room temperature (Scheme 3.47).



Scheme 3.47. Preparation of monomeric oxazolone complexes.

The oxazolone complexes ligated by either 1,10-phenanthroline **3-88a** or 2-(2-pyridinyl)phenyl-2-nitrobenzenesulfonamide **3-89a** were afforded in 60% and 80% yield, respectively. Both of these complexes were very insoluble in most organic solvents. Complex **3-88a** was insoluble in chlorinated solvents, but soluble enough in acetone to allow full characterisation by both ^{1}H NMR and ^{13}C NMR. Complex **3-89a** was only partially soluble in chloroform and acetone, but a ^{1}H NMR spectrum was obtained showing all 22 protons (Figure 3.6). The highly insoluble complex **3-89a** consists of only aromatic protons, making it challenging to confirm each peaks' identity by COSY experiments. It was attempted to increase the solubility of the NMR sample of complex **3-89a** by heating the sample prior to analysis, but the level detail of the COSY experiments was not improved. However, the diagnostic benzylidene peak (a singlet) was identified and it was evident that installation of the ligand further deshielded the proton in this position from 7.56 ppm to 7.75 ppm. Elemental analysis was also successfully carried out for complex **3-89a**. The expected values were C: 51.14%, H: 2.70%, N: 6.82%, and the values found were C: 52.31%, H: 2.62%, N: 6.51%. Complex **3-89a** was stable at room temperature under air for a minimum of 3 months.

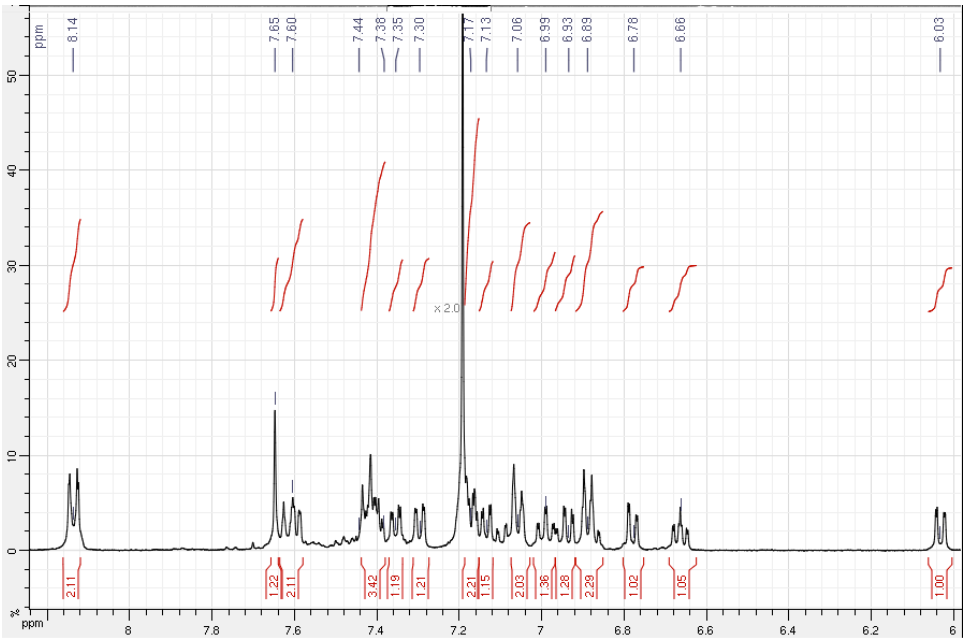
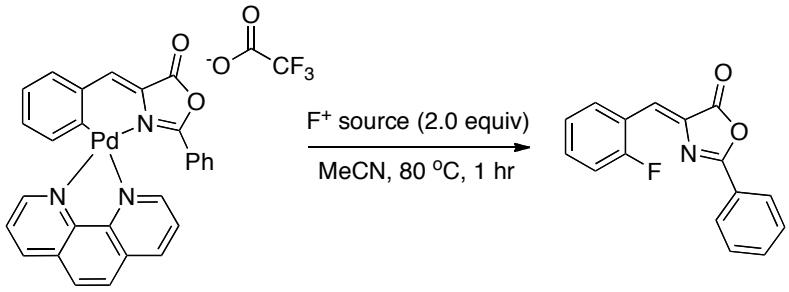


Figure 3.6. Close up of aromatic region of ^{1}H NMR spectrum of 3-89a.

Complexes **3-88a** and **3-89a** were subsequently subjected to fluorination conditions. Complex **3-88a** was fluorinated in the presence of 2 equivalents of different electrophilic fluorinating reagents (Table 3.7). After heating at 80 ^{o}C for 12 hours, 1 equivalent of 1-fluoro-3-nitrobenzene was added as added as an internal reference standard to allow determination of the yield of fluorinated product **3-84a** by ^{19}F NMR.

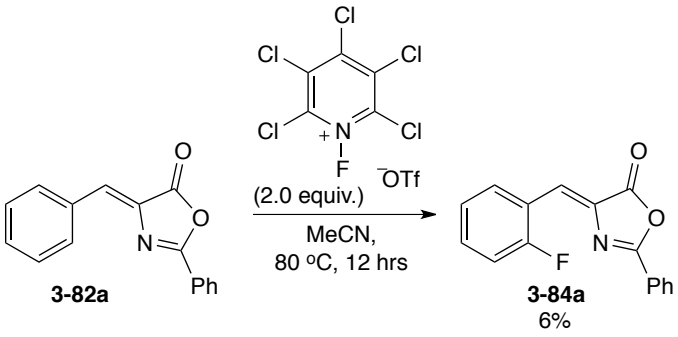


Entry	F^+ reagent	Solvent	Time (hrs)	Yield (%)
1	Selectfluor^{TM}	MeCN-d_3	12	-
2	NFSi	MeCN-d_3	12	-
3	*N*-fluoro-*2*,3,4,5,6-pentachloropyridinium triflate	MeCN-d_3	12	46

Table 3.7. Fluorination of complex 3-89a.

After 12 hours at 80 ^{o}C, no reaction was observed in the presence of Selectfluor^{TM} and NFSi, with only the starting complex being recovered (Table 3.7, Entries 1 and 2). In the presence of the highly reactive *N*-fluoro-2,3,4,5,6-pentachloropyridinium triflate reagent, a 46% yield of the desired fluorinated product was afforded (Table, 3.7, Entry 3).

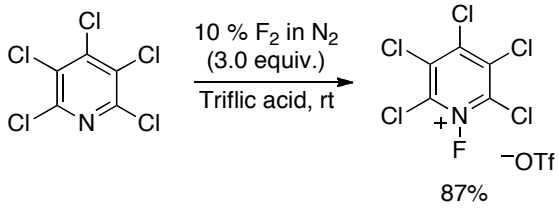
The direct fluorination of oxazolone **3-82a** with *N*-fluoro-2,3,4,5,6-pentachloropyridinium triflate showed that background reaction occurred and a 6% yield of the fluorinated product **3-84a** was obtained (Scheme 3.48). The identity of **3-84a** was confirmed by comparison of the NMR data of independently prepared **3-84a** (^{19}F NMR = -116.3 ppm) (Table 3.5).



Scheme 3.48. Control reaction: direct fluorination of 3-82a.

The fluorination of complex **3-88a** using *N*-fluoro-2,3,4,5,6-pentachloropyridinium triflate represents the first successful example of a palladium-mediated fluorination of DL-phenylalanine *via* a C-H activation strategy. Furthermore, this positive result indicates that the choice of this sp^2 leaving group was promising. It was therefore investigated whether the preparation of *N*-fluoro-2,3,4,5,6-pentachloropyridinium triflate could be extended to radiochemistry.

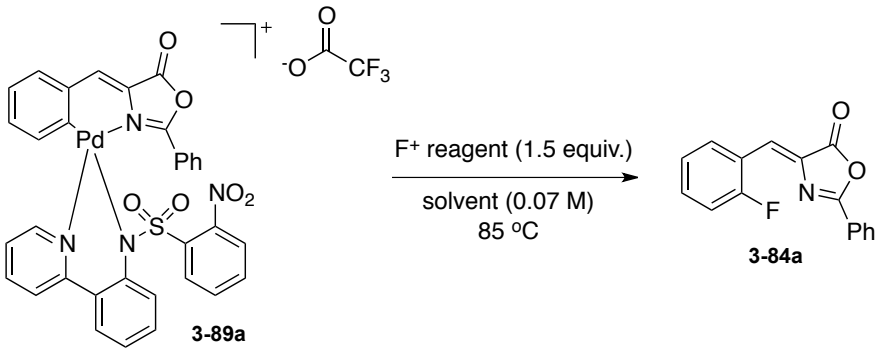
Umemoto and co-workers have extensively studied the preparation of pyridine based N-F reagents by direct fluorination with F_2 and found that *N*-fluoro-2,3,4,5,6-pentachloropyridinium triflate could be prepared at room temperature using an excess amount of F_2 in triflic acid as the solvent (Scheme 3.49).[240],[241]

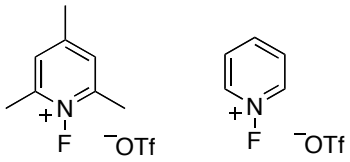


Scheme 3.49. Preparation of *N*-fluoro-2,3,4,5,6-pentachloropyridinium triflate by Umemoto.[241]

Although the fluorination of **3-88a** was successful when *N*-fluoro-*2*,3,4,5,6-pentachloropyridinium triflate was used, the reaction conditions required for its preparation may be problematic under radiochemical conditions. The triflic acid would need to be evaporated and replaced with acetonitrile. Changing the solvent of a N-^{18}F reagent is known to be nontrivial and may impact the reactivity of the reagent.

Further fluorination studies were next carried out on complex **3-89a** substituted with ligand **3-72**. This ligand contains a sulfonamide group which has been shown to stabilise the palladium(IV) intermediate by coordination to the palladium centre and might therefore promote C-F bond formation compared to 1,10-phenathroline. Similarly to complex **3-88a,** a range of electrophilic fluorinating reagents was investigated (Table 3.8). After heating at 85 ^{o}C for 12 hours, 1 equivalent of 1-fluoro-3-nitrobenzene was added as an internal reference standard to allow determination of the yield of fluorinated product **3-84a** by ^{19}F NMR.





A **B**

Entry	F^+ reagent	Solvent	Time (hrs)	Yield (%)
1	Selectfluor™	MeCN-d_3	12	21
2	NFSI	MeCN-d_3	12	32
3	A	MeCN-d_3	1	Trace
4	B	MeCN-d_3	1	5
5[a]	XeF_2	CH_2Cl_2	0.5	0
6[b]	XeF_2	CH_2Cl_2	1	0
7[c]	Selectfluor™	MeCN-d_3	12	0
8[c]	NFSI	MeCN-d_3	12	15
9	NFSI	MeCN-d_3	6	31
10	**NFSI**	**MeCN-d_3**	**3**	**39**
11	NFSI	MeCN-d_3	1	32
12[d]	NFSI	MeCN-d_3	1	21
13	NFSI	DMF	12	5
14	NFSI	DCE	12	17
15	NFSI	$CHCl_3$	1	18
16	NFSI	EtOH	1	0
17	NFSI	Dioxane	1	8
18	NFSI	Toluene-d_8	1	0
19[e]	NFSI	MeCN-d_3	1	30
20[f]	NFSI	MeCN-d_3	1	35
21[g]	NFSI	MeCN-d_3	1	0
22[h]	NFSI	MeCN-d_3	1	14

[a]Fluorination reaction run at 0 °C. [b]Fluorination reaction run at room temperature. [c]3.0 equiv. of F^+ reagent was used. [d]0.5 equiv. of NFSi was used. [e]Concentration of reaction = 0.03 M. [g]MeCN-d_3 evaporated and replaced with $CDCl_3$.[h]Reaction run at 60 °C. [i]NMP (0.5 equiv.) was added.

Table 3.8. Fluorination optimisation studies on complex 3-89a.

Pleasingly, the fluorination of complex **3-89a** was successful with both Selectfluor™ and NFSI. In the optimisation studies, NFSI was found to be a superior reagent, compared to Selectfluor at 85 °C in MeCN-d_3 by affording **8-34a** in 32% over 21%

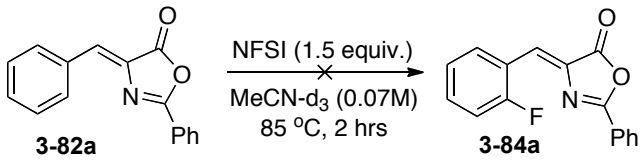
yield (Table 3.8, Entries 1-2). Neither *N*-fluoro-2,4,6-trimethylpyridinium triflate nor *N*-fluoro-pyridinium triflate afforded the desired product (Table 3.8, Entries 3 and 4). The highly reactive reagent XeF_2 was also investigated, at both 0 ^oC and room temperature, but full recovery of starting material **3-89a** was observed (Table 3.8, Entries 5 and 6). Attempts to increase the yield by increasing the amount of F^+ source had a detrimental effect. In the case of Selectfluor, when the amount was increased to three equivalents, no fluorinated product **3-84a** was observed (Table 3.8, Entry 7). Conversely, the reaction still proceeded in the presence of 3 equivalents of NFSi, but the yield was reduced from 32% to 15% (Table 3.8, Entry 8). Further optimisation was therefore carried out with NFSI as this reagent has previously been prepared under radiochemical conditions.[69] This indicated that transferral of this palladium-mediated methodology to radiochemistry would be possible.

A reaction time of 12 hours was clearly outside a radiochemical timescale. Pleasingly, it was found that reducing the reaction time from 12 hours to 1 hour did not have a detrimental effect on the yield of the reaction (Table 3.8, Entries 9 to 11). To mimic a radiochemical setting, the amount of NFSI was decreased to 0.5 equivalents and in this case a 21% yield of the desired product was observed (Table 3.8, Entry 12). This showed that the reaction still proceeded when a substoichiometric amount of fluorine was added. Alternative solvents met with limited success. DMF reduced the yield to 5% (Table 3.8, Entry 13). $CHCl_3$ and CH_2Cl_2 aided the solubility of the starting material at 85 ^oC, but the yield of the final product was decreased to 17% and 18%, respectively (Table 3.8, Entries 14 and 15). Ethanol, a protic solvent, inhibited the reaction completely (Table 3.8, Entry 16). The use of non-polar solvents also severely inhibited the reaction (Table 3.8, Entries 17 and 18).

As mentioned previously, the starting complex **3-89a** was found to be highly insoluble in common organic solvents. In the fluorination reactions using acetonitrile, the reaction mixture was never homogenous, even at 85 ^oC. When the concentration was reduced from 0.07 M to 0.03 M, to aid solvation, no increase in the yield was observed (Table 3.8 Entry 19). The independently prepared fluorinated oxazolone reference **3-84a** was shown to be significantly less soluble in acetonitrile than chloroform, and this could have impacted the measurement of the yield by NMR. Therefore, the reaction was carried out in acetonitrile, but the solvent was removed by evaporation and

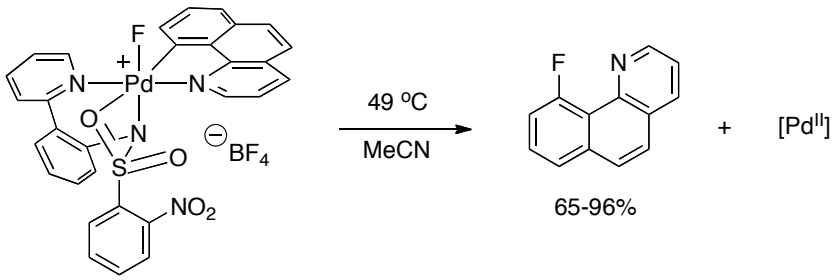
replaced with $CDCl_3$ before the yield was measured (Table 3.8, Entry 20). No significant change in the yield was observed. Reducing the temperature to 60 ^oC did not promote the fluorination reaction (Table 3.8, Entry 21). Yu and co-workers found that a catalytic amount of NMP was essential for the success of the fluorination reaction of benzyltriflamides (Scheme 3.16). [207] When 0.5 equivalents of NMP were added to the reaction mixture, no increase in the yield of **3-84a** was observed (Table 3.8, Entry 22).

Direct fluorination of oxazolone **3-82a** using NFSI failed to afford the fluorinated product and confirmed that fluorination of complex **3-89a** is palladium mediated (Scheme 3.50).



Scheme 3.50. Control reaction in the absence of palladium.

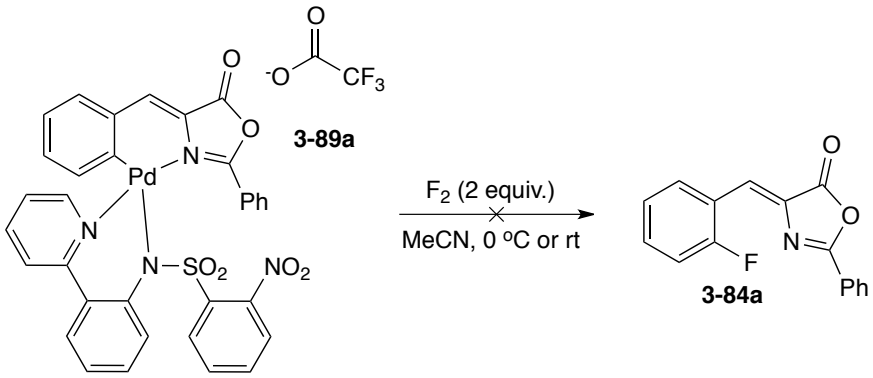
When the fluorination studies detailed in table 3.7 were carried out, the reaction mixture was a bright yellow suspension before the colour gradually became more orange over the course of one hour. When the reaction mixture was filtered and washed repeatedly with acetonitrile, a yellow filtrate and an orange solid were obtained. The filtrate contained the fluorinated product and traces of other species. Identification of the orange solid proved challenging as it was completely insoluble in NMR solvents even when heated. Analysis by TLC showed no elution from the baseline, even using EtOAc:MeOH mixtures as eluents, perhaps suggesting a salt. In Ritter's extensive mechanistic studies of his similar systems, he only reported an unidentified Pd(II) species in addition to the desired product (Scheme 3.51).[209]



Scheme 3.51. Ritter's thermal decomposition of Pd(IV) complexes with ligand 3-72.

Elemental analysis was carried out and confirmed that the solid side product was not the starting complex **3-89a**. The expected values were C: 51.14%, H: 2.70%, N: 6.82%, and the values found were C: 42.15%, H: 1.97%, N: 9.62%. Unfortunately, all other attempts to identify the unknown species have been unsuccessful.

In an attempt to improve the efficiency of the fluorination reaction, F_2 was investigated as an alternative source of electrophilic fluorine (Scheme 3.52).



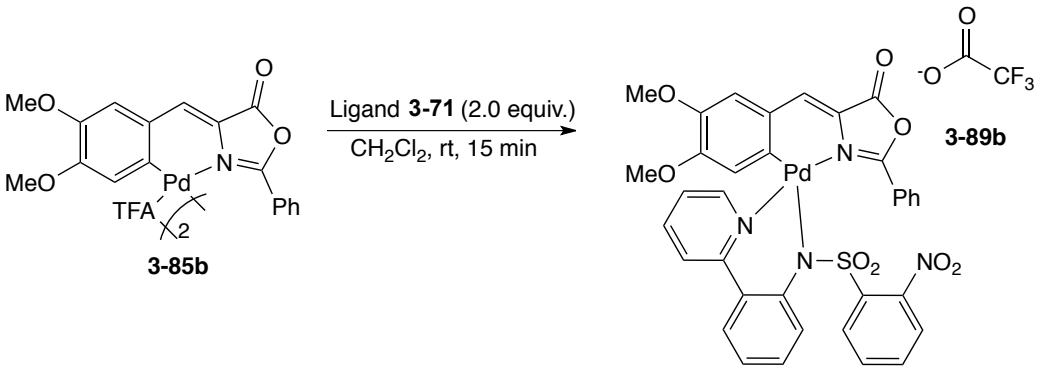
Scheme 3.52. Fluorination of complex 3-89a using F_2.

These studies were carried out in the laboratory of Prof. Graham Sandford at Durham University following the same experimental procedures described in Chapter 2. The oxazolone complex **3-89a** was added to MeCN in the PTFE reaction vessel and the system was purged with nitrogen gas to eliminate the presence of air. The F_2 gas (10% F_2 in N_2) was bubbled through at a constant flow rate (15 mL/min) as the reaction mixture was stirred vigorously. Following the required reaction time (to equal 2 equivalents of F_2), the reaction was purged with nitrogen gas and analysed by ^{19}F NMR (using 1-fluoro-3-nitrobenzene as an internal reference standard). Unfortunately,

the desired fluorinated compound **3-84a** was not obtained at 0 °C nor room temperature and only recovery of starting material was observed.

The oxazolone complex **3-89a** exhibits limited solubility in acetonitrile during the fluorination reaction with NFSI at 85 °C. It is therefore not surprising that the solubility in this solvent at lower temperatures is worsened. The F_2 chemistry employed herein occurs at the gas-liquid interphase. When the two phases are brought into contact, mass transfer between the phases and a subsequent chemical reaction occurs. The Chambers and Sandford research groups have extensively studied its application in fluorine chemistry.[242],[243],[244] Its success relies on the formation of bubbles of F_2 gas, formed by rapid stirring of the reaction mixture, which can react with the desired compound in solution. Due to the limited solubility of complex **3-89a** in acetonitrile it was postulated that the reaction failed due to the small amount present in solution, available to react with F_2.

With the success of the DL-phenylalanine oxazolone **3-89b** in the desired fluorination reaction, it was decided to further explore the fluorination reaction on the L-DOPA oxazolone substrate (Table 3.5). The monomeric DOPA oxazolone complex **3-89b**, substituted with the 2-(2-pyridinyl)phenyl-2-nitrobenzenesulfonamide ligand **3-71** was prepared from the L-DOPA oxazolone TFA dimer **3-85b** as previously described (Scheme 3.53).

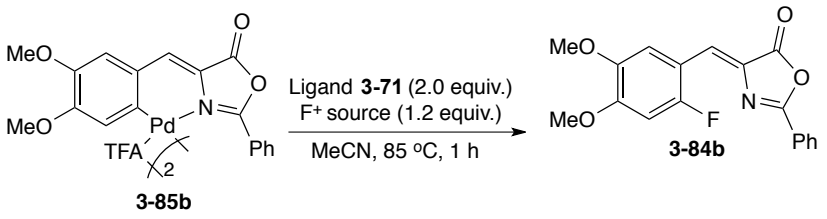


Scheme 3.53. Formation of monomeric DOPA complex 3-89b.

The starting TFA dimer **3-85b** and 2.0 equivalents of 2-(2-pyridinyl)phenyl-2-nitrobenzenesulfonamide **3-71** were added to CH_2Cl_2 and stirred at room temperature

for 15 minutes. The solution changed from clear yellow to a thick dark red suspension. Upon filtration, a grey/orange powder was obtained. Analysis of the reaction mixture by NMR spectroscopy showed that the complex was not stable at room temperature and had undergone decomposition. Free ligand **3-71** and oxazolone **3-82b** were identified. In an attempt to overcome this, the reaction was repeated at -10 ^{o}C, but the same result was observed.

One-pot reactions were carried out to investigate whether the complex could be formed and fluorinated *in situ* (Table 3.9).



3-85b **3-84b**

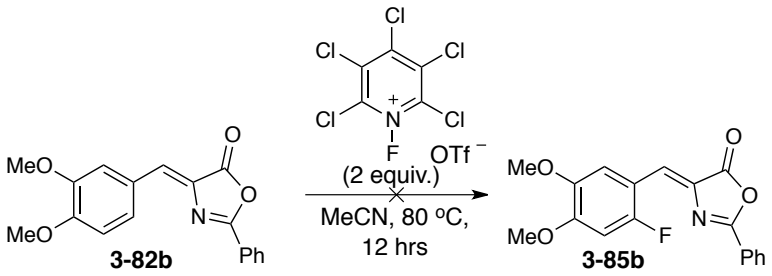
Entry	F^+ reagent	Yield (%)
1	Selectfluor^{TM}	-
2	NFSi	-
3	*N*-fluoro-*2*,3,4,5,6-pentachloropyridinium triflate	34

Table 3.9. One-pot formation and fluorination of complex 3-89b.

In the presence of either Selectfluor or NFSi, no reaction was observed and the starting complex **3-85b** could be recovered (Table, 3.9, Entries 1 and 2). This was disappointing, given the successful fluorination of the DL-phenylalanine oxazolone complex **3-89a** with NFSi, *vide supra*. As previously described in Table 3.6, *N*-fluoro-2,3,4,5,6-pentachloropyridinium triflate encouraged fluorination on these oxazolone systems. In the one-pot fluorination reaction with complex **3-85b**, the desired product was afforded in 34% yield (Table 3.9, Entry 3).

However, the direct fluorination of the free L-DOPA oxazolone **3-82b** using *N*-fluoro-2,3,4,5,6-pentachloropyridinium triflate in the absence of palladium, afforded the desired product **3-84b** in 12% yield (Scheme 3.54). The identity of **3-84b** was

confirmed by comparison of the NMR data of independently prepared **3-84b** (^{19}F NMR = -118.9 ppm) (Table 3.5).



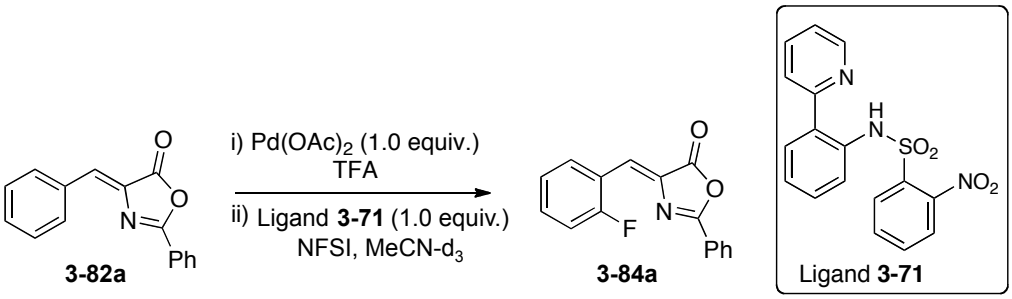
Scheme 3.54. Control reaction: direct fluorination of oxazolone 3-82b.

When *N*-fluoro-2,3,4,5,6-pentachloropyridinium triflate is used as the source of fluorine, a significant background reaction is occurring. The aforementioned concerns about the use of *N*-fluoro-2,3,4,5,6-pentachloropyridinium triflate in radiochemistry also apply here, hence further optimisation using this substrate was not carried out at this stage.

3.3.2.4 Development of a one-pot reaction

For the radiochemistry experiments, a one-pot approach where the cyclopalladation by C-H activation, ligand exchange and fluorination all occur in one step, would be attractive. This would allow that oxazolone complex **3-82a** to be directly converted to **3-84a**, without the need for preparation and isolation of **3-89a** prior to radiolabelling studies.

Subsequently, the *in situ* formation of the TFA dimer **3-85a** was investigated, followed by the monomer formation and fluorination. The original 4 hour reaction time for the palladacycle formation in the preformed complex was considered to be inconvenient for a radiochemical protocol and it was investigated whether the reaction time for this step could be shortened. The temperature and time of the fluorination step was also optimised (Table 3.10). The yield of the reaction was measured by ^{19}F NMR using 1-fluoro-3-nitrobenzene as an internal reference standard.



Entry	Reaction conditions	F^+ reagent	Amount of F^+ reagent (equiv.)	Yield of 3-84a (%)
1	A	NFSi	1.2	25
2	B	NFSi	1.2	20
3	C	NFSi	1.2	21
4	C	NFSi	0.6	14
5	D	NFSi	1.2	19
6	E	NFSi	1.2	23
7	F	NFSi	1.2	28
8	G	NFSi	1.2	0
9	C	Selectfluor	1.2	6
10	C	Selectfluor	0.6	5

A = Step i). TFA, 75 ^oC, 4 h. Step ii). MeCN-d_3, 85 ^oC, 1 h.
B = Step i). TFA, 75 ^oC, 1 h. Step ii). MeCN-d_3, 85 ^oC, 1 h.
C = Step i). TFA, 75 ^oC, 1 h. Step ii). MeCN-d_3, 85 ^oC, 30 min.
D = Step i). TFA, 90 ^oC, 30 min. Step ii). MeCN-d_3, 85 ^oC, 1 h.
E = Step i). TFA, 75 ^oC, 30 min. Step ii). MeCN-d_3, 85 ^oC, 30 min.
F = Step i). TFA, 90 ^oC, 30 min. Step ii). MeCN-d_3, 85 ^oC, 30 min.
G = Step i). TFA, 75 ^oC, 1 h. Step ii). TFA, 85 ^oC, 1 h.

Table 3.10. Optimisation of one-pot fluorination reaction.

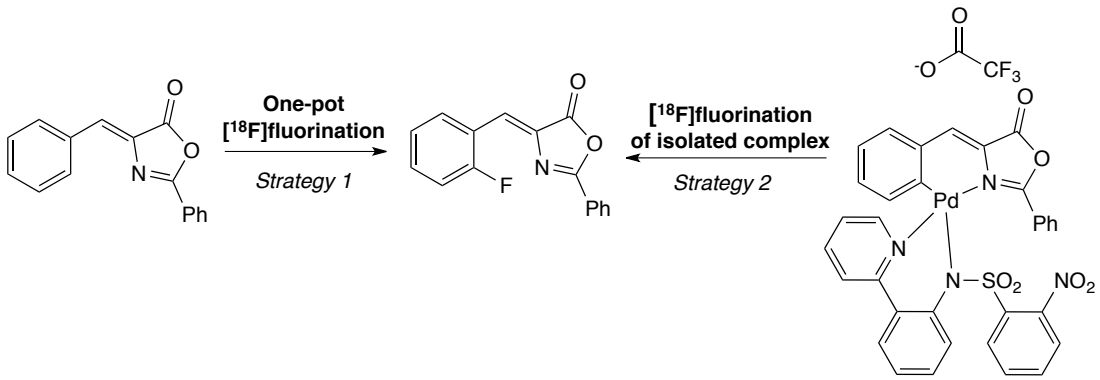
TFA and one equivalent of $Pd(OAc)_2$ were added to the oxazolone and heated at 75 ^oC for 4 hours. The TFA was evaporated under a stream of argon to complete dryness (30 min), before one equivalent of the 2-(2-pyridinyl)phenyl-2-nitrobenzenesulfonamide ligand **3-71** and 1.2 equivalents of NFSI and MeCN-d_3 were added and the reaction mixture stirred at 85 ^oC for one hour. Pleasingly, the desired product **3-84a** was obtained in 25% yield (Reaction conditions **A**, Table, 3.10 Entry 1). When the reaction time of the cyclopalladation step was reduced to 1 hour and the same fluorination conditions were employed, the fluorinated product was obtained in 20% yield (Reaction conditions **B**, Table, 3.10 Entry 1). Although the overall reaction time was reduced, the yield of **3-84a** only slightly decreased compared yield obtained with the preformed complex (39%) (Table 3.8). Therefore, attempts were made to further optimise the reaction conditions. First, the effect of reducing the fluorination step to 30

minutes was investigated, while the reaction time for the complex-formation time was kept constant and this afforded the desired fluorinated oxazolone **3-84a** in a similar yield to entry 1 (Reaction conditions **C**, Table, 3.10, Entry 2). The amount of NFSi was also reduced to 0.6 equivalents under these conditions and a 14% yield of the product was obtained (Reaction conditions **C**, Table, 3.10, Entry 3). Furthermore, reaction time of the cyclopalladation step was reduced to 30 minutes and the temperature increased to 90 ^{o}C. After 1 hour of fluorination, a 19% yield of the product was obtained (Reaction conditions **D**, Table 3.10, Entry 4). When both steps were shortened to 30 minutes, the yield of the final product **3-84a** was 23% (Reaction conditions **E**, Table, 3.10, Entry 5). These reaction conditions would be amenable for use in radiochemistry, as neither step was too time consuming. The effect of increasing the temperature of the cyclopalladation to 90 ^{o}C was also investigated and it was found that the overall yield of **3-84a** was increased to 28% (Reaction conditions **F**, Table 3.10, Entry 6). When both the cyclopalladation and fluorination steps were performed in deuterated TFA, the reaction did not proceed, confirming need for a solvent change prior to the fluorination step (Reaction conditions **G**, Table 3.10, Entry 7). Under reactions conditions **C**, Selectfluor was shown to be inferior to NFSI and only afforded the product in 6% and 5% yield at 1.2 and 0.6 equivalents of the reagent, respectively (Table 3.10, Entries 8 and 9).

The optimisation studies in this chapter revealed that an oxazolone is a suitable protecting group for the amino acid functionality and is capable of undergoing selective cyclopalladation in the presence of palladium acetate. It was also found that the correct choice of ligand is imperative for the success of the fluorination reaction. The 2-(2-pyridinyl)phenyl-2-nitrobenzenesulfonamide ligand **3-71**, containing a sulfonamide group proposed to be capable of stabilising the palladium(IV) intermediate, was found to afford the desired fluorinated product in the highest yield. Pleasingly, NFSI was found to be the optimal source of fluorine for the fluorination in these studies and this was beneficial for transferral of this methodology to radiochemistry, as the radiochemical synthesis of this N-F reagent has already been reported.

3.3.3 Radiolabelling of a DL-phenylalanine oxazolone 3-89a complex with [^{18}F]NFSI

Two approaches for the palladium-mediated C-H activation-fluorination of DL-phenylalanine oxazolone complexes have been developed. Direct fluorination of the readily prepared and isolated complex, or an alternative strategy where the cyclopalladation, ligand exchange and fluorination all occur in a one-pot reaction. The [^{18}F]fluorination of the DL-phenylalanine oxazolone complex with [^{18}F]NFSI will be investigated using both of these strategies (Scheme 3.55).



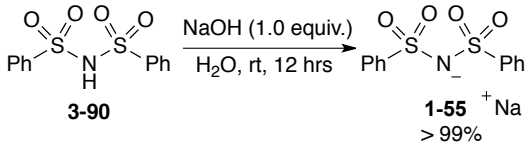
Scheme 3.55. Outline of the two strategies for [^{18}F]fluorination.

3.3.3.1 Preparation of [^{18}F]NFSI

The radiochemistry studies were carried out at Turku PET Centre under the supervision of Prof. Olof Solin.

Gouverneur and co-workers previously reported the radiosynthesis of [^{18}F]NFSI and explored the application of this reagent in the [^{18}F]fluorination of silyl enol ethers and allyl silanes (Schemes 1.30 and 1.31).[69] These studies were carried out at the GE Healthcare site at Hammersmith hospital, using low specific activity [^{18}F]F_2. As the investigations in this study were carried out using a different experimental set-up, the preparation of [^{18}F]NFSI was optimised.

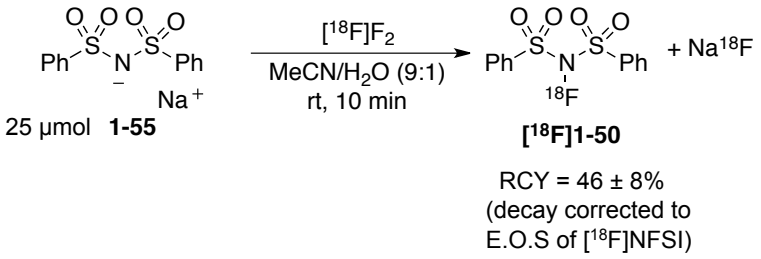
The NFSI sodium salt precursor **1-55** was prepared upon the deprotonation of *N*-(phenylsulfonyl)benzenesulfonamide **3-90** in the presence of sodium hydroxide in water at room temperature (Scheme 3.56). The precursor **1-55** was afforded in a quantitative yield.



Scheme 3.56. Preparation of NFSI precursor 3-91.

The NFSI precursor **1-55** was subsequently directly fluorinated with high specific activity $[^{18}F]F_2$. The same methods for the preparation of $[^{18}F]$fluoride (target irradiation time = 5 min) and $[^{18}F]F_2$ were used as detailed in Chapter 2, section 2.4.6.

In the studies herein, the amount of NFSI precursor **1-55** in the preparation of $[^{18}F]$NFSI was reduced to 25 µmol, compared to the 50 µmol employed in the original protocol.[69] The precursor **1-55** was dissolved in a mixture of water and acetonitrile (1:9, 1 mL) and the $[^{18}F]F_2$ gas was bubbled through the solution for 30 seconds at room temperature (Scheme 3.57). Prior the subsequent radiolabelling studies, water present in the stock solution was removed. This was carried out by heating the $[^{18}F]$NFSI stock solution at 60 ^{o}C under a stream of helium. This drying step was repeated before 0.5 mL of anhydrous acetonitrile was added. Aliquots of this $[^{18}F]$NFSI stock solution solution was used directly in the subsequent labelling studies without further purification.



Scheme 3.57. Optimised preparation of $[^{18}F]$NFSI 1-50.

As this N-F reagent contains a UV active chromophore, the identity of $[^{18}F]$NFSI could be confirmed by HPLC (Figure 3.7). The NFSI precursor **1-55** eluted first at 5.46 min. $[^{18}F]$NFSI was found to be the major radioactive product and eluted with a reaction time of 14.8 minutes. The radiochemical yield of $[^{18}F]$NFSI was calculated as the fraction of the injected activity that corresponded to $[^{18}F]$NFSI and given as a percentage. The mean RCY of $[^{18}F]$NFSI = 46 ± 8% (decay corrected to E.O.S of

[^{18}F]NFSI). Taking into consideration that the maximum RCY of this transformation using [^{18}F]F_2 is 50%, the optimised synthesis of [^{18}F]NFSI was very successful. The specific activity of this transformation was calculated using the same technique as in Chapter 1. An authentic reference sample of 'cold' NFSI, of known amount and volume, was injected onto the HPLC and the peak area was measured. This was repeated three times and the average peak area was calculated. Separately, the UV peak area of the radioactive product peak obtained upon the HPLC analysis of the reaction mixture was measured. This allows for the determination of the amount of 'cold' NFSI and as the radioactivity of the product peak is known, this allows for the calculation of the SA (radioactivity/amount of 'cold' compound). The SA for the preparation of [^{18}F]NFSI ranged from 0.5 to 1.2 GBq/µmol.

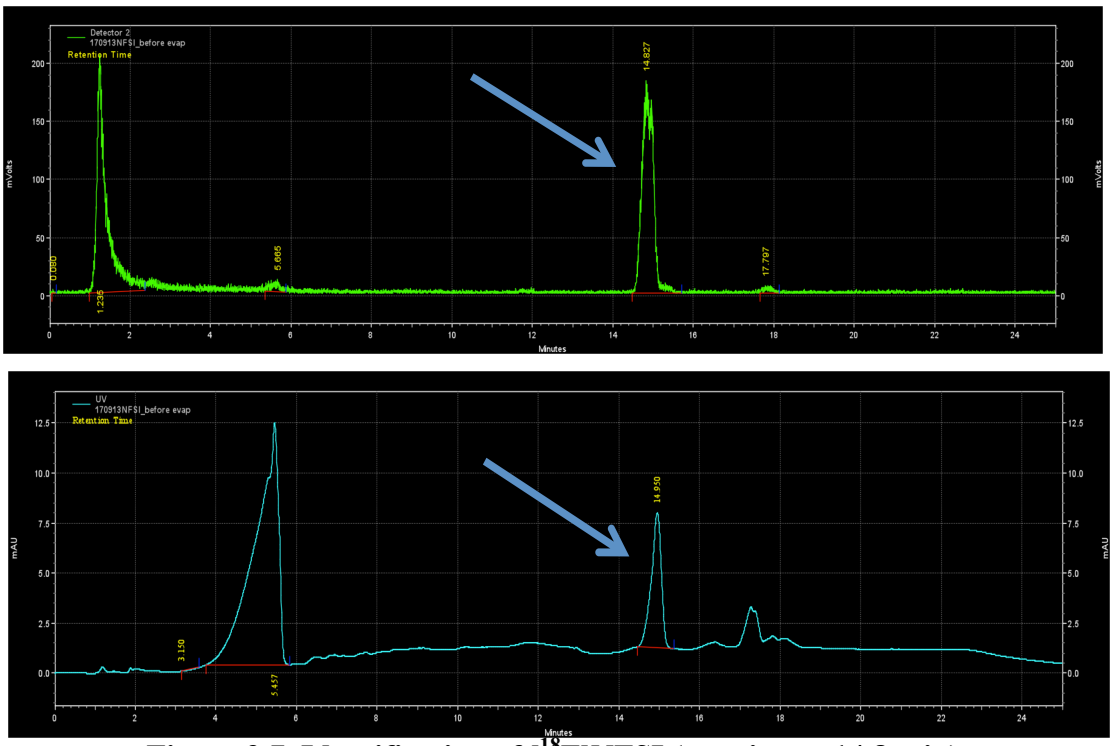
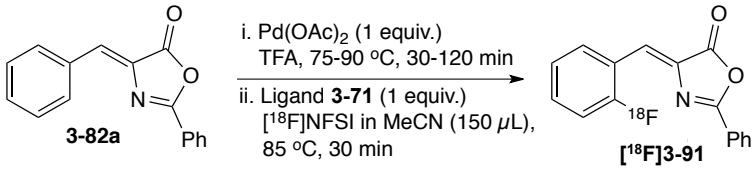


Figure 3.7. Identification of [^{18}F]NFSI (ret. time = 14.8 min).
Top: radio-HPLC chromatogram. Bottom: UV-HPLC trace.

3.3.3.2 Strategy 1: One-pot [^{18}F]fluorination reaction

An analogous one-pot reaction of C-H activation-fluorination reaction to that developed under 'cold' reaction conditions, was explored using [^{18}F]NFSI (Table 3.11).



Entry	Precursor amounts (μmol)	Step i. Temp (°C)/Time (min)	Step ii. Temp (°C)/Time (min)	RCY (%)
1	10	90/30	85/30	6
2	10	75/60	70/30	< 1
3	5	80/90	85/30	8
4	0.5	80/90	85/30	2
5	10	80/120	80/30	5

Table 3.11. One-pot [^{18}F]fluorination

DL-phenylalanine oxazolone precursor **3-82a (**10 μmol) and 1 equivalent of palladium acetate was dissolved in TFA and the reaction was shaken in an Eppendorf mixer at 90 °C for 30 minutes. The solvent was evaporated under argon at room temperature before 1 equivalent of 2-(2-pyridinyl)phenyl-2-nitrobenzenesulfonamide ligand **3-71** and an aliquot of [^{18}F]NFSI in MeCN (150 μL) was added. After heating at 85 °C for 30 min, the reaction mixture was analysed by HPLC. The desired [^{18}F]radiolabelled compound **[^{18}F]3-91** was obtained in 6% RCY (Table 3.11, Entry 1). Several other radioactive peaks were observed in the radio-HPLC chromatogram, suggesting that the one-pot reaction lead to the formation of unknown reactive intermediates during the course of the reaction which subsequently underwent [^{18}F]radiolabelling (Figure 3.8).

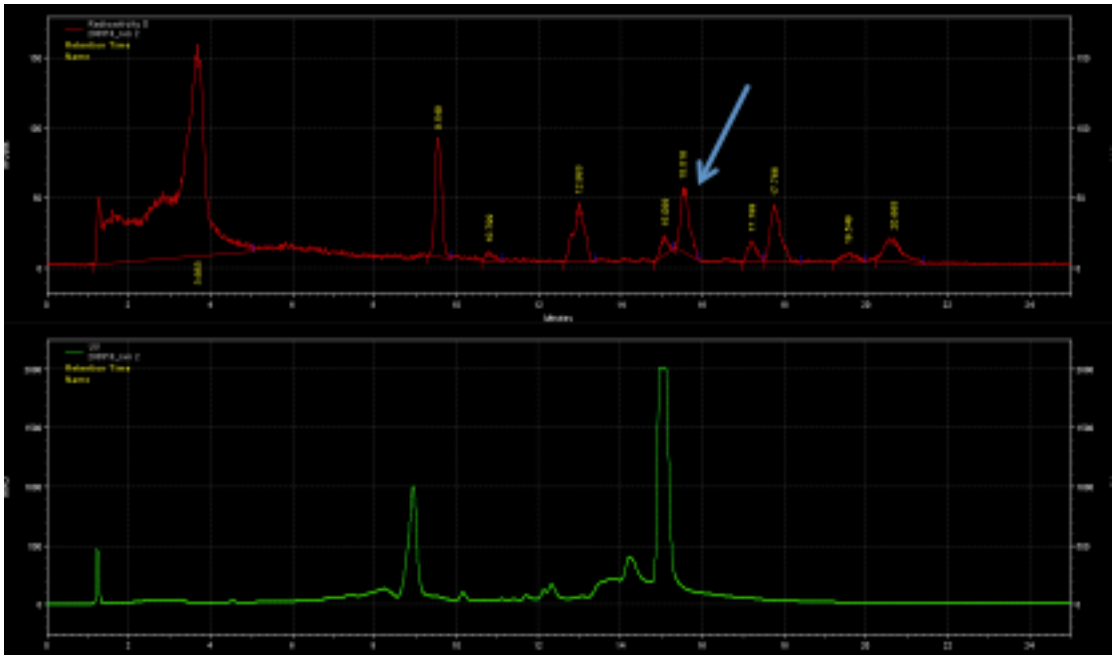


Figure 3.8. HPLC chromatogram of one-pot [^{18}F]fluorination. Top: Radio-HPLC chromatogram (retention time of [^{18}F]3-91 = 15.5 min, highlighted by blue arrow), Bottom: UV-HPLV chromatogram.

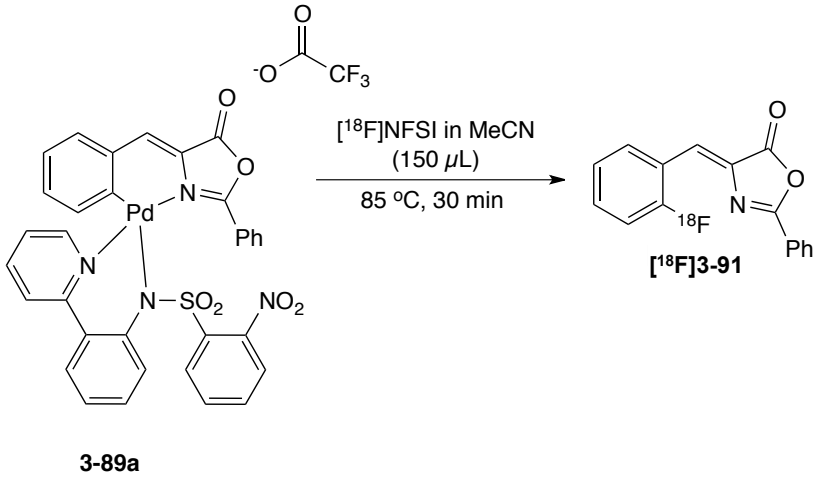
Further attempts to optimise the reaction conditions were unsuccessful. Reducing the temperature of both the cyclopalladation and fluorination step, decreased the RCY of **[^{18}F]3-91** to < 1% (Table 3.11, Entry 2). Decreasing the amount of precursor **3-82a** to 5 and 0.5 µmol in an attempt to improve the selectivity of the reaction was not successful (Table 3.11, Entries 3 and 4). By greatly reducing the amount of precursor to 0.5 µmol, the stoichiometry of the reaction becomes closer to that utilised in the 'cold' reactions (~0.3 µmol of [^{18}F]NFSI to 0.5 µmol of precursor). Extending the reaction time of the cyclopalladation step did not improve the yield of the radiolabelled product **[^{18}F]3-91** (Table 3.11, Entry 5).

Under the reaction conditions investigated for the one-pot palladium-mediated [^{18}F]fluorination of **3-82a,** selective formation of the desired radiolabelled phenylalanine oxazolone **[^{18}F]3-91** was not achieved. It was therefore decided to focus on the direct [^{18}F]fluorination of the preformed complex **3-89a**.

3.3.3.3 Strategy 2: [^{18}F]fluorination of preformed oxazolone complex 3-89a

These studies did not require any chemical manipulations prior to the radiolabelling step. An aliquot of [^{18}F]NFSI (150 µmol) in MeCN was added to an Eppendorf vial

containing DL-phenylalanine oxazolone preformed palladium complex **3-89a (**2.5 μmol) and the reaction mixture was stirred at 85 ^{o}C for 30 minutes, before the reaction mixture was analysed by HPLC (Scheme 3.58).



Scheme 3.58. [^{18}F]fluorination of preformed DL-phenylalanine oxazolone palladium complex 3-89a.

The radiolabelling of the preformed complex **3-89a**, afforded the desired [^{18}F]radiolabelled DL-phenylalanine oxazolone product **[^{18}F]3-91** in significantly improved selectivity. The radio-HPLC chromatogram of the reaction mixture revealed the presence of two minor radioactive impurities, but both are easily separable from the product (Figure 3.9). The RCY of **[^{18}F]3-91** = 19.5 ± 10% (*n* = 3, decay corrected to E.O.S of [^{18}F]NFSI). The RCY was determined as the fraction of the activity injected onto the HPLC corresponding to **[^{18}F]3-91**. The SA of **[^{18}F]3-91** measured to be 0.29 ± 0.02 GBq/μmol and was calculated as described for [^{18}F]NFSI. The SA values obtained for [^{18}F]NFSI and **[^{18}F]3-91** are within the same range (0.5-1.2 to 0.3 GBq/μmol) which is expected as both compounds are prepared from the same batches of [^{18}F]F_2.

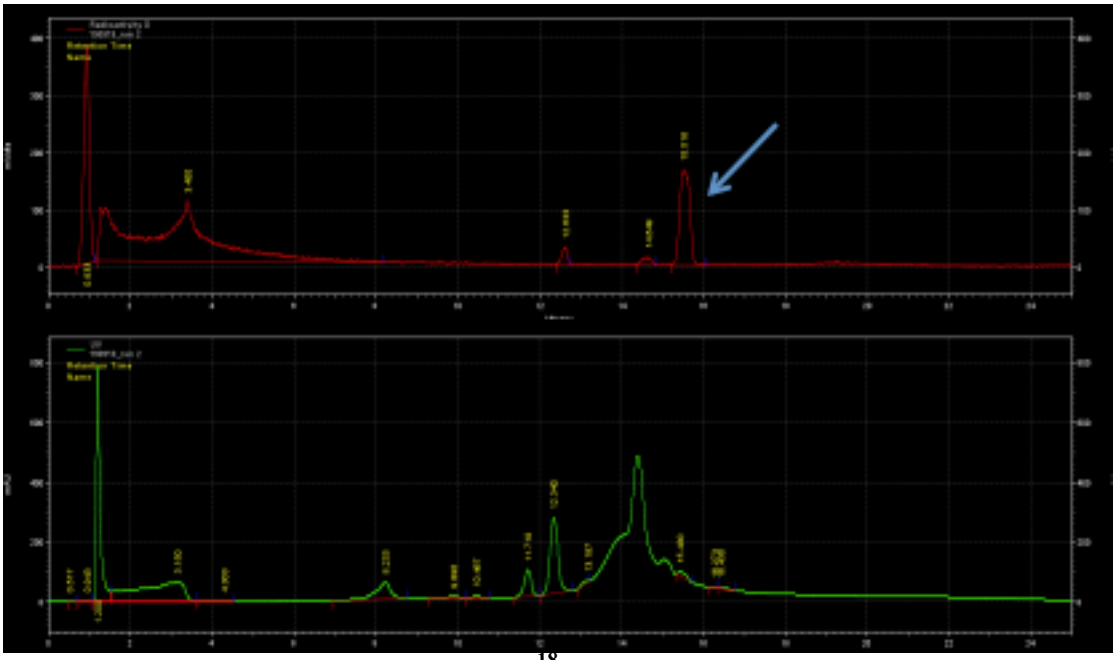


Figure 3.9. HPLC chromatogram of [^{18}F]fluorination of preformed oxazolone complex 3-89a.
Top: Radio-HPLC chromatogram (retention time of [^{18}F]3-91 = 15.5 min, highlighted by blue arrow), Bottom: UV-HPLV chromatogram.

The aim of this study was to design a stoichiometric palladium-mediated C-H activation-[^{18}F]fluorination strategy for the preparation of 6-[^{18}F]fluoro-L-DOPA or related model substrates. After optimisation of the structure of substrate, it was found that the DL-phenylalanine oxazolone compound **3-89a,** substituted with a ligand postulated to be capable of stabilising the palladium(IV) intermediate, successfully promoted C-F bond formation in the presence of the electrophilic fluorinating agent NFSI. This methodology was successfully extended to radiochemistry through the use of [^{18}F]NFSI and the radiolabelled DL-phenylalanine oxazolone product was afforded in 19 ± 10% RCY. This transformation represents the first example of a palladium-mediated [^{18}F]fluorination through selective C-H activation of an unactivated arene.

3.3.4 Towards the preparation of new N-^{18}F reagents employed in palladium mediated fluorination reactions

In the previous section the utility of [^{18}F]NFSI in a palladium-mediated fluorination reaction was demonstrated. However, as highlighted in the introduction to this chapter (section 3.2.2), several leading transition-mediated fluorination approaches employ alternative pyridine-based N-F reagents, which have not been extensively studied under radiochemical conditions. With the aim of expanding the library of selective N-

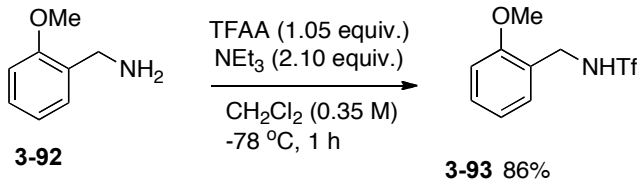
^{18}F reagents, investigations were carried out in an attempt to prepare a new N-^{18}F reagent.

3.3.4.1 Identifying a suitable reaction system

Both Sanford[178] and Yu[207-208] have reported catalytic fluorination methodologies, which would be interesting to investigate for application to radiochemistry. Sanford and co-workers employed 8-methylquinoline and a selection of substituted 2-phenylpyridines as substrates in palladium-mediated microwave fluorination reaction using *N*-fluoropyridinium tetrafluoroborate as the electrophilic fluorinating reagent (Scheme 3.14). However, the reaction conditions for the transformation are harsh and require long reaction times (~12 hours). Furthermore, the substrate scope was relatively limited.

Therefore, it was decided to investigate the fluorination of arenes *via* a triflamide directed *ortho*-palladation, developed by Yu and co-workers, for application to radiochemistry (Scheme 3.15).[207] The methodology has a wide substrate scope, but electron-rich arenes exhibited faster reaction kinetics and underwent fluorination in 30-60 minutes using *N*-fluoro-2,4,6-trimethylpyridinium triflate. This transformation would be amenable to a radiochemical time scale and hence 2-methoxy benzyltriflamide **3-93** was chosen as the model substrate for this study.

2-Methoxy benzyltriflamide **3-93** was prepared in 86% yield from 2-methoxy benzylamine **3-92** by protection of the amine in the presence of trifluoroacetic anhydride and triethylamine (Scheme 3.59).



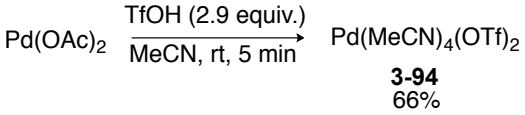
3-92 **3-93** 86%

Scheme 3.59. Synthesis of triflamide precursor 3-93.

In the original publication, Yu and co-workers found $Pd(OTf)_2.2H_2O$ to be a superior catalyst to $Pd(OAc)_2$.[207] However, its preparation required the solvation of palladium

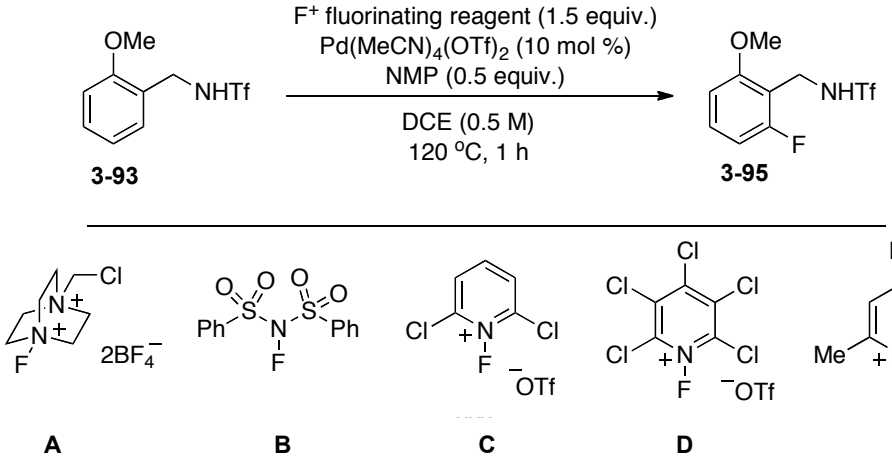
metal in conc. nitric acid. [245] In their optimisation studies, Yu found that $Pd(CH_3CN)_4(OTf)_2$ also showed good results in the preliminary fluorination studies and could be considered an alternative to $Pd(CH_3CN)_4(OTf)_2$.

$Pd(CH_3CN)_4(OTf)_2$ was prepared in the presence of $Pd(OAc)_2$ and trifluoromethanesulfonic acid in acetonitrile in 66% yield (Scheme 3.60).[246] The formation of **3-94** was confirmed by elemental analysis (Expected for $C_{10}H_{12}N_4F_6O_6S_2Pd$: C 21.12%; H 2.13%; N 9.85%. Found: C 22.33%, H 1.89%, N 10.02%.).



Scheme 3.60. Preparation of $Pd(CH_3CN)_4(OTf)_2$.

The palladium-mediated fluorination protocols reported in literature show that different reactions require different electrophilic sources of fluorine to succeed. There is no easy way of predicting which type will afford the desired fluorinated product in the highest yield. The next step was therefore to optimise the reaction conditions with this alternative catalyst by investigating a wide range of N-F reagents (Table 3.12). The results were compared to those obtained with reagents in the optimisation of unsubstituted benzyltriflamide by Yu and co-workers.[207]

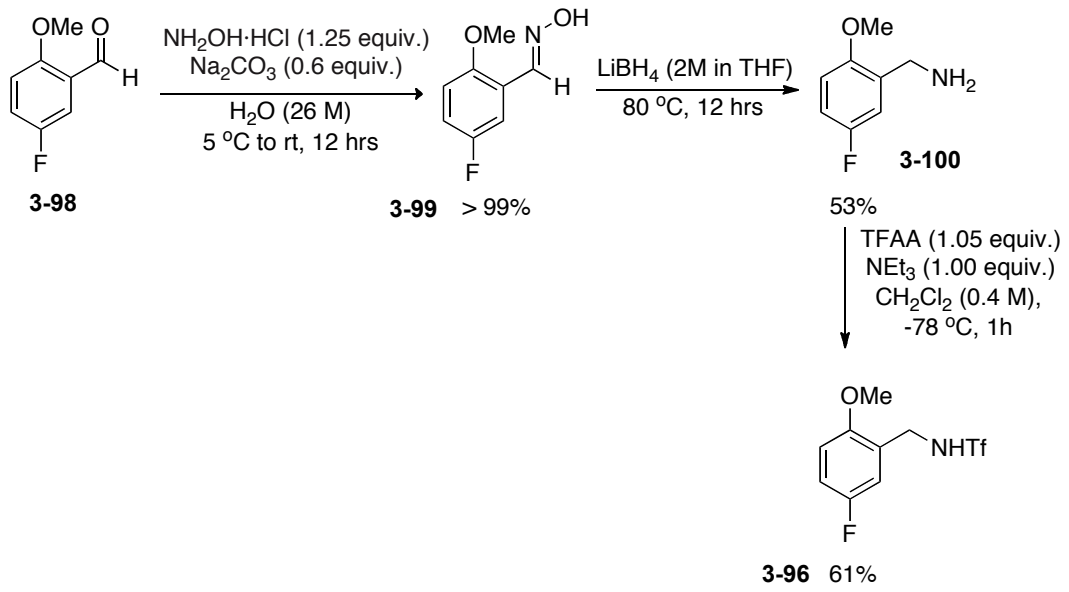


Entry	F+ reagent	Yield (%)	Literature Yield (%)[207]
1	A	23[a]	-
2	A[b]	0	N/A
3	B	-	5
4	B[b]	-	N/A
5	C	34	4
6	D	Trace[a]	N/A
7	D[b]	Trace[a]	N/A
8	E	76	20
9	E[b]	-	N/A
10[c]	E	98	N/A

[a] Trace of other aromatic fluoride peaks observed. [b] Without Pd and NMP. [c] 0.1 equiv. F^+.

Table 3.12. Fluorination of 3-93 using different N-F reagents.

In our studies, Selectfluor™ **A** was found to be a poor fluorinating agent under these reaction conditions and afforded the fluorinated product in 23% yield alongside two side-products in trace amounts (Table 3.12, Entry 1). The low yield is expected as Selectfluor, albeit a relatively good oxidant, has met with limited success as an electrophilic source of fluorine under palladium catalysis. The ^{19}F NMR peaks of the side-products corresponded to -116.8 and -115.0 ppm. By direct electrophilic aromatic fluorination, the favoured products were expected to be 5-fluoro-2-methoxybenzyl triflamide **3-96** or 3-fluoro-2-methoxybenzyl triflamide **3-97**. We therefore independently prepared **3-96** in three steps from 5-fluoro-2-methoxybenzaldehyde in attempt to identify the side-product (Scheme 3.61).



Scheme 3.61. Preparation of 5-fluoro-2-methoxybenzyl triflamide 3-96.

5-Fluoro-2-methoxybenzaldehyde **3-98** was converted to the oxime **3-99** by condensation with hydroxylamine hydrochloride in >99% yield, which was in turn reduced to the amine **3-100** by lithium borohydride in 53% yield. Final protection of the amine afforded the 5-fluoro-2-methoxybenzyl triflamide **3-96** in 61% yield. The ^{19}F NMR peak of the C_{sp}^{2}-F bond of **3-96** was recorded to be -123.4 ppm, which was very similar to the peak of 6-fluoro-2-methoxybenzaldehyde **3-95** at -122.9 ppm but significantly different from the trace side-product peaks. When the reaction with Selectfluor^{TM} was repeated in the absence of the palladium catalyst, no fluorinated peaks were observed in the crude reaction mixture (Table 3.10, Entry 2). This suggested that the side-products were not formed by direct electrophilic fluorination.

No reaction was observed when NFSI **B** was used in the presence or absence of a catalytic amount of palladium (Table 3.12, Entries 3 and 4). Rather than acting as a fluorinating reagent, NFSI has been found to oxidise the palladium(II) catalyst as expected and then subsequently act as an amination reagent under Pd(II)/Pd(IV) catalysis.[247]

N-F reagents with a pyridine core were subsequently investigated as they have been reported as appropriate electrophilic sources of fluorine under palladium catalysis. 2,6-Dichloropyridinium triflate **C** successfully afforded the desired product in 34% yield,

indicating that a pyridine reagent is compatible with the system (Table 3.12, Entry 5). However, when the more reactive reagent *N*-fluoro-*2*,3,4,5,6-pentachloropyridinium triflate **D** was added, an inseparable mixture of several fluorinated products was obtained in trace amounts with ^{19}F NMR peaks ranging from -115.6 to -130.0 ppm. Furthermore, when the reaction was repeated in the absence of palladium the same unidentifiable mixture of C-F bonds was observed (Table 3.12, Entries 6 and 7), which suggests unselective direct fluorination of the arene is occurring. Reagent **D** was shown by Umemoto to be one of the most reactive N-F reagents [241], and was clearly too reactive to allow for selective C-F bond formation in this case.

It was therefore decided to focus the rest of the optimisation studies on the use of the less reactive *N*-fluoro-2,4,6-trimethylpyridinium triflate **E**. When using this reagent, the desired fluorinated product was afforded in 76% yield (Table 3.12, Entry 8). No fluorinated product was observed when the reaction was repeated in the absence of palladaium (Table 3.12, Entry 9). This encouraged further tuning of the reaction conditions for the translation to radiochemistry. Reducing the amount of fluorinating agent to 0.1 equivalents still afforded the fluorinated product in 98% yield, respectively (Table 3.12, Entry 10). This was encouraging for the radiolabelling of this system using a N-^{18}F reagent.

In order to understand more about the different N-F reagents investigated, it was beneficial to look at the reduction potentials of the reagents to understand their reactivity pattern. Evans undertook numerous cyclic voltammetry (CV) experiments to shed light on the reactivity of electrophilic fluorinating reagents (Table 3.13).[248]

Entry	Reagent	$E_{p,f}$/V vs AgRE	n
1	2,6-dichloro-1-fluoropyridinium tetrafluoroborate	-0.260	0.97
2	1-Chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bistetrafluoroborate	-0.296	0.79
3	*N*-fluoropyridinium tetrafluoroborate	-0.814	1.39
4	*N*-fluoro-2,4,6-trimethylpyridinium tetrafluoroborate	-1.068	1.13
5	*N*-fluoro-benzenesulfonimide (NFSI)	-1.441	0.89
6	*N*-methyl-*N*-fluoro-*p*-toluenesulfonamide	< -2.2	

Table 3.13. Peak potential voltages of 6 N-F reagents with the calculated n values

The reactivity of the reagents investigated in Evans' study increase in the following order of reactivity: *N*-methyl-*N*-fluoro-*p*-toluenesulfonamide < *N*-fluoro-benzenesulfonimide (NFSI) < *N*-fluoro-2,4,6-trimethylpyridinium tetrafluoroborate < *N*-fluoropyridinium tetrafluoroborate < 1-Chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bistetrafluoroborate < 2,6-dichloro-1-fluoropyridinium tetrafluoroborate.

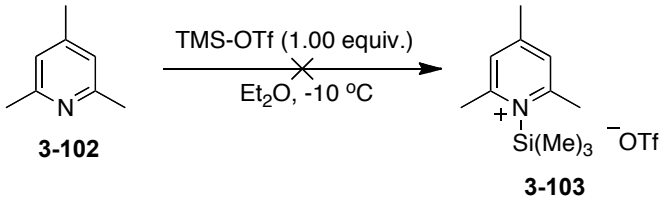
The reactivity pattern elucidated in Evans' study shows that the reactivity of the N-F reagent does not necessarily correlate with their suitability in palladium-mediated fluorination reactions. In the optimisation studies, Selectfluor™ afforded the desired product in a lower yield when compared to *N*-fluoro-2,4,6-trimethylpyridinium triflate (Table 3.12, Entries 1 and 8). This suggested that other influencing factors must be considered in when studying N-F reagents in catalytic palladium-mediated reactions. As highlighted above, competing reactions can be facile such as unselective fluorination and aminations, but it is also possible that the nucleophilic supporting nitrogen of the fluorinating reagents might competitively bind to the palladium centre discouraging C-H activation. Alternatively, the F^+ atom could complex the basic directing group, thereby preventing the required coordination with the palladium catalyst.[208]

3.3.4.2 Towards the preparation of *N*-[^{18}F]fluoro-2,4,6-trimethylpyridinium triflate

The optimisation of the fluorination of 2-methoxy benzyltriflamide **3-93** suggested that *N*-fluoro-2,4,6-trimethylpyridinium triflate **E** could be a suitable reagent for application to radiochemistry.

N-[^{18}F]Fluoropyridinium triflate **[^{18}F]1-47** prepared by Oberdorfer in 1988, remains the only example of a pyridine-based [^{18}F]N-F reagent reported in the literature.[66] It was prepared by fluorination of TMS-protected pyridine **1-52** with [^{18}F]F_2 in MeCN at -42 ^{o}C (Scheme 1.26).

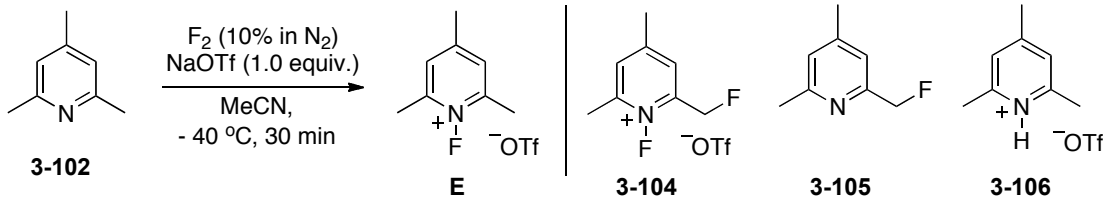
It was investigated whether similar reaction conditions could be employed to prepare *N*-[^{18}F]fluoro-2,4,6-trimethylpyridinium triflate **[^{18}F]3-101**. However, the preparation of *N*-trimethylsilyl-2,4,6-trimethylpyridinium triflate **3-103** from free 2,4,6-trimethylpyridine **3-102**, using TMS triflate was not successful (Scheme 3.62). The only product observed was protonated 2,4,6-trimethylpyridine. The formation *N*-trimethylsilyl-2,4,6-trimethylpyridinium triflate **3-103** may be challenging due to the significant steric hindrance around the nitrogen centre caused by the methyl groups in the 2- and 6-position of **3-103**. In Umemoto's original study the cleavage of the N-TMS bond with F_2 was found to be a highly exothermic process, so further studies with this substrate was abandoned.[241]



Scheme 3.62. Attempts to prepare *N*-trimethylsilyl-2,4,6-trimethylpyridinium triflate 3-103.

Umemoto and co-workers have extensively studied the preparation of a wide range of *N*-fluoropyridinium reagents.[241] Their method for the preparation of *N*-fluoro-2,4,6-trimethylpyridinium triflate **E** is involved the direct fluorination of the free substituted pyridine in the presence of a counterion using an excess amount of F_2 (3 equivalents).

This methodology was subsequently investigated for the preparation of 'cold' *N*-fluoro-2,4,6-trimethylpyridinium triflate **E** (Table 3.14).



Entry	F_2 (equiv.)	Yield (%)[a] **E**	Yield (%)[a] **3-104**	Yield (%)[a] **3-105**	Yield (%)[a] **3-106**
1	3.0	27	3	-	29
2	1.2	51	3	-	32
3	0.5	23	2	-	57
4	0.2	-	-	11	-
5	0.1	-	-	4	-

[a] Yields measured by ^{1}H and ^{19}F NMR (1-fluoro-3-nitrobenzene).

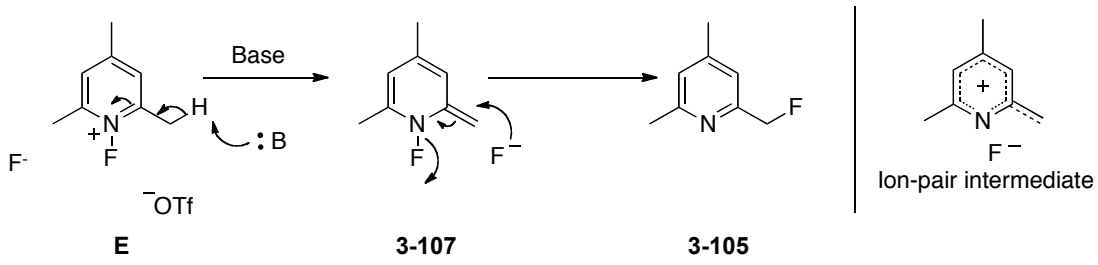
Table 3.14. Fluorination of 2,4,6-trimethylpyridine

These fluorine gas experiments were carried out in the laboratory of Prof. Graham Sandford at Durham University using the equipment described in Chapter 2.

Three equivalents of F_2 was bubbled through a solution of 2,4,6-trimethylpyridine **3-102** and sodium triflate in MeCN at -40 °C. After warming to room temperature and removing NaF by filtration, the reaction mixture was found to contain 27% yield of the desired *N*-fluoro-2,4,6-trimethylpyridinium triflate **E** in addition to two other side-products (Table 3.14, Entry 1). A small amount of the difluorinated product **3-104** was observed in combination with 2,4,6-trimethylpyridinium hydrogen triflate **3-106**. Side-product **3-106** was formed in 29% yield due to protonation by HF present in the reaction mixture.

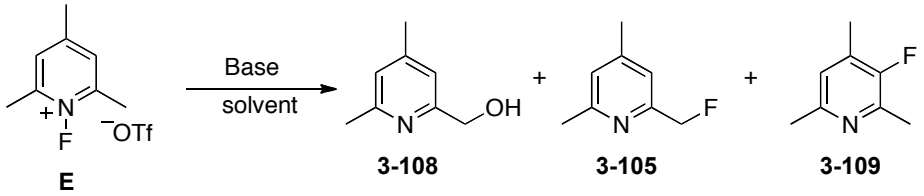
The N-F reagent **E** was obtained in 51 % yield when 1.2 equivalents of F_2 (10 % in N_2) were bubbled through the reaction solution (Table 3.14, Entry 2). The two other side-products **3-104** and **3-106** were obtained in 3% and 32%, respectively. With a view to preparing this reagent in a radiochemical setting, the effect of reducing the amount of F_2 introduced into the system was investigated (Table 3.14, Entries 3-5). Using 0.5 equivalents of F_2 allowed the formation of desired reagent **E** in 23% yield, alongside increased amounts of side-products (Table 3.14, Entry 3). However, further decreasing

the amount of F_2, caused the sole formation of another side-product, 2-fluoromethyl-4,6-dimethylpyridine **3-105**. By reducing the amount of F_2 gas, relative to the amount of the 2,4,6-trimethylpyridine **3-102** (pK_{aH} 7.4), the basicity of the system was increased. It was therefore hypothesised that following formation of the N-F bond, the 2-methyl group of the reagent **E** was deprotonated by the excess **3-102** to form intermediate **3-107**. This species was postulated to undergo a rearrangement to **3-105**. It was proposed that this rearrangement was initiated by attack of fluoride, formed as side-product upon the fluorination with F_2. The rearrangement is suggested to proceed in a similar manner to the Polonovski rearrangement reactions of 2- and 4-methylpyridine *N*-oxides (Scheme 3.63).[249]



Scheme 3.63. Rearrangement of *N*-fluoro-2,4,6-trimethylpyridinium triflate E to 3-105.

Umemoto and co-workers carried out a series of hydrolysis experiments to investigate the stability of *N*-fluoro-2,4,6-trimethylpyridinium triflate **E** in water and under basic conditions (Table 3.15).[241]



Entry	Base	Solvent	yield (%) 3-108	yield (%) 3-105:3-109
1	KOH	Water	24	23
2	NEt_3	THF	-	62[a]
3	NEt_3	CH_2Cl_2	-	63[b]
4	NaH	CH_2Cl_2	-	60[c]

[a] Ratio of **3-105**:**3-109** = 1:1, [b] Ratio of **3-105**:**3-109** = 2:1, [c] Ratio of **3-105**:**3-109** = 8:1.

Table 3.15. Decomposition studies by Umemoto.[241]

Umemoto and co-workers found that the N-F reagent **E** was stable in water for over 30 days at room temperature, but when KOH was added to a solution of **E** in water at room temperature, two decomposition products were obtained and identified as 2-(hydroxymethyl)-4,6-dimethylpyridine **3-108** and 2-(fluoromethyl)-4,6-dimethylpyridine **3-105** in 24% and 23% yield, respectively (Table 3.15, Entry 1). Compounds **3-108** and **3-105** were obtained by rearrangements as explained in Scheme 3.63. With alternative bases in organic solvents, the decomposition of *N*-fluoro-2,4,6-trimethylpyridinium triflate **E** also lead to the formation of **3-105**, alongside 3-fluoro-2,4,6-trimethylpyridine **3-109** in a 1:1 ratio in 62% combined yield (Table 3.15, Entry 2). It was postulated that formation of **3-109** involves deprotonation by triethylamine followed by fluorination by the N-F reagent **E**. By changing the solvent from THF to CH_2Cl_2 and using sodium hydride as the base, the amount of **3-105** could be increased relative to **3-109** (Table 3.15, Entries 3-4).[241]

The result of these studies revealed that in the presence of excess of free 2,4,6-trimethylpyridine, rearrangement processes are favoured over fluorination of the nitrogen centre when F_2 is present in a limiting amount. Therefore, the preparation of N-^{18}F reagent **[^{18}F]3-101** would not be viable under radiochemical reaction conditions.

3.3.4.3 Towards the preparation of alternative N-^{18}F reagents

It was subsequently attempted to identify alternative pyridine-based compounds, which would:

- not undergo rearrangements upon fluorination when a substoichiometric amount of fluorine is used,
- not interfere with the palladium-mediated C-H activation step and
- be amenable to direct fluorination with F_2.

Compounds satisfying these conditions could potentially be candidates for alternative N-^{18}F reagents.

The undesired side-reactions would be discouraged by blocking the β-positions adjacent to the nitrogen centre of the pyridine compounds with alkyl or phenyl substituents (Figure 3.10).

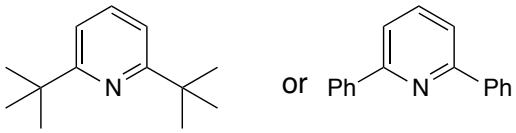
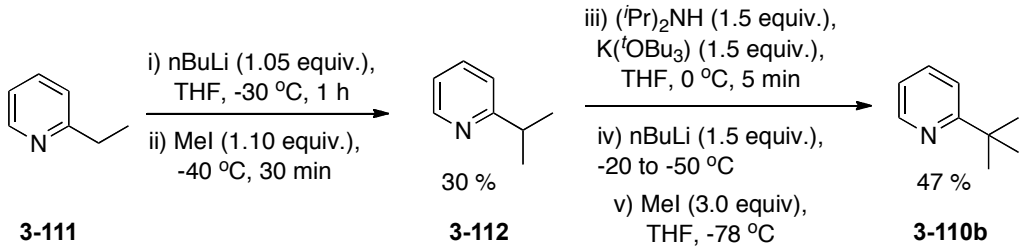


Figure 3.10. Suggested approached for preventing rearrangement side-reactions.

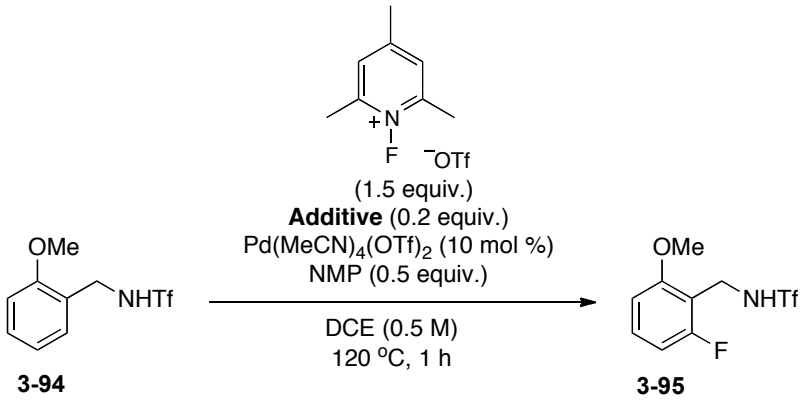
Firstly, a range pyridine-based additives with bulky substituents, **3-102** and **3-110a-g**, was selected. All were commercially available except **3-110b**, which was prepared in two steps from 2-ethylpyridine **3-111** in 47% by sequential deprotonation and alkylation with iodomethane (Scheme 3.64).



Scheme 3.64. Preparation of 2-*tert*butylpyridine.

The effect of adding the free pyridine-based derivatives **3-102** and **3-110a-g** to the palladium-mediated fluorination of 2-methoxybenzyl triflamide **3-91,** studied in Section 3.3.4.1, Table 3.12, was carried out in order to ascertain the success of the reaction in the presence of these additives. The additives allowing the reaction to proceed would finally be considered for preparation with F_2.

The pyridine-based additives, **3-102** and **3-110a-g,** were added to the optimised reaction conditions in 0.2 equivalents (2 equivalents relative to the amount of palladium catalyst). The amount of the product **3-95** was measured by ^{19}F NMR using 1-fluoro-3-nitrobenzene as the internal reference standard (Table 3.16).



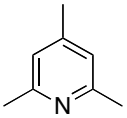
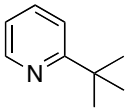
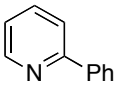
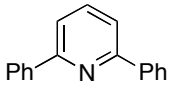
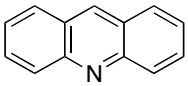
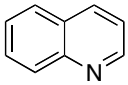
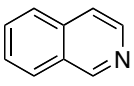
Entry	Additive	pK_{aH}	Yield of 3-95 (%)
1	No additive	-	73
2	 **3-102**	7.43	57
3	 **3-110a**	5.22	Trace
4	 **3-110b**	5.76	6
5	 **3-110c**	5.3	Trace
6	 **3-110d**	-	0
7	 **3-110e**	5.60	Trace
8	 **3-110f**	4.85	25
9	 **3-110g**	5.14	38

Table 3.16. Fluorination in the presence of pyridine additives.

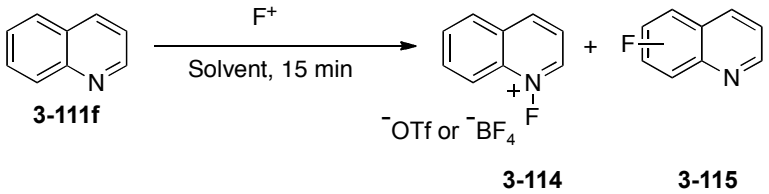
When no pyridine additive was added, the reaction proceeded in 73% yield (Table 3.16, Entry 1). In the case of the corresponding free 2,4,6-trimethylpyridine **3-102**, the desired product was afforded in 57% yield, suggesting that the free base does not significantly interfere with the palladium centre in this case, and still allow the desired

fluorination reaction to proceed (Table 3.16, Entry 2). Unsurprisingly, it was found that introducing an excess of free pyridine into the reaction system prevented the required C-H activation to take place as it competed with the intramolecular directing group (Table 3.16, Entry 3).

2-*tert*-Butylpyridine **3-110b** still impeded the reaction and only afforded a trace amount of the fluorinated product, indicating that this ligand has affinity for the palladium(II) centre (Table 3.16, Entry 4). Increasing the steric bulk by adding either 2- or 2,6-diphenylpyridine still caused full inhibition of the reaction (Table 3.16, Entries 5 and 6). Acridine, was similarly unsuccessful (Table 3.16, Entry 7). Conversely, when changing the additives to quinoline or isoquinoline, some activity of the catalytic system was retained, allowing for the formation of product **3-95** in 25% and 38%, respectively (Table 3.16, Entries 8 and 9). This indicated that these two additives could have potential as novel N-^{18}F reagents for this transformation.

Umemoto previously prepared *N*-fluoroquinolinium triflate **3-114** in 16% yield upon the direct fluorination of quinoline using 3 equivalents of F_2 in the presence of sodium triflate as outlined in Table 3.14, Entry 1.[241]

Preliminary fluorine transfer studies were therefore carried out carried out on quinoline using *N*-fluoro-*2*,3,4,5,6-pentachloropyridinium triflate **D** and Selectfluor^{TM} as fluorinating reagents. The results were analysed by ^{19}F NMR, using 1-fluoro-3-nitrobenzene as the internal reference standard (Table 3.17).



Entry	F^+/equiv.	Solvent	Temp. (^oC)	Yield **3-114** (%)	Yield **3-115** (%)
1	**A**/1.00	MeCN-d_3	0	trace	5[a]
2	**A**/1.00	MeCN-d_3	-35	-	5[a]
3	Selectfluor™/1.00	MeCN-d_3	rt	-	-[c]
4	Selectfluor™/1.00	MeCN-d_3	50	-	20[c]

[a] ^{19}F NMR: -125.1 and -126.1 ppm. [b] ^{19}F NMR: -114.4 ppm. [c] Reaction run for 12 hours.

Table 3.17. Fluorination of quinoline to prepare N-F bond.

The fluorination of quinoline using *N*-fluoro-*2*,3,4,5,6-pentachloropyridinium triflate **D** proved difficult. The reagent **D** was added to a solution of quinoline in MeCN-d_3 at 0 ^oC and stirred for 15 minutes. The reaction mixture was directly analysed by ^{19}F NMR. The N-F bond was only observed in a trace amount at +17 ppm in the ^{19}F NMR spectrum, alongside a variety of other aromatic C-F bonds in a trace amount (Table 3.17, Entry 1). Two other peaks were observed in the ^{19}F NMR spectrum at -125.1 and -126.1 ppm. These peaks correspond to aromatic C-F bonds, indicating that direct unselective fluorination on quinoline had occurred. Attempts to tune the reactivity of the N-F reagent by decreasing the temperature of the system to -35 ^oC still only led to unselective ring fluorination (Table 3.17, Entry 2). When employing the less reactive reagent Selectfluor™ was employed, only starting material was observed after 12 hours room at temperature (Table 3.17, Entry 3). A final attempt to encourage fluorine transfer of quinoline was carried out in the presence of 1 equivalent of Selectfluor by heating the reaction mixture to 50 ^oC. However, no N-F bond was observed in the ^{19}F NMR. Instead a mixture of unidentifiable fluorinated peaks was obtained in 20% (Table 3.17, Entry 3).

This study indicates that the fluorination of quinoline, by fluorine transfer to prepare *N*-fluoroquinolinium triflate **3-114**, is not a viable route. Instead, unselective fluorination of the ring system was favoured due to the high reactivity of *N*-fluoro-*2*,3,4,5,6-pentachloropyridinium triflate. In Umemoto's original study, the *N*-

fluoroquinolinium salt was afforded in a low yield and this could be due to ring fluorination as a side-reaction. Furthermore, the N-F salts of quinoline is thought to be very unstable in the presence of water,[241] which could further decrease the feasibility of the reaction. In radiochemistry, where N-^{18}F reagents are prepared as a stock and used over the course of several hours there is a possibility that this reagent would be too unstable to provide repeatable results, even if successfully obtained.

This study into the preparation of N-^{18}F reagents of pyridine ligands showed that the presence of the free pyridine ligand can have detrimental effect on the success of palladium catalysed fluorination reactions. In addition, the reagents tolerated by the system are very difficult to prepare *via* methods that would be viable for radiochemistry.

3.4. Conclusion

The aim of this project was to develop palladium-mediated C-H activation-fluorination protocols for the application to radiochemistry through the use of N-^{18}F reagents.

A palladium-mediated C-H activation-fluorination protocol was designed for the [^{18}F]radiolabelling of DL-phenylalanine precursors. The optimisation studies showed that the use of a DL-phenylalanine oxazolone precursor complexed with a bidentate nitrogen ligand, with the ability to stabilise the hypervalent palladium intermediate, promoted C-F bond formation in the presence of Selectfluor and NFSI. The [^{18}F]radiolabelling of a DL-phenylalanine oxazolone complex with [^{18}F]NFSI, was found to selectively [^{18}F]label DL-phenylalanine in 19.5 ± 10% RCY. This represents the first example of a palladium-mediated C-H activation-[^{18}F]fluorination protocol. Disappointingly, application of this methodology to the preparation to 6-[^{18}F]fluoro-L-DOPA was unsuccessful. It will be valuable to focus on the development of a palladium-mediated C-H activation-[^{18}F]fluorination protocol compatible with L-DOPA precursors to allow for the synthesis of this imaging agent from unactivated substrates.

Studies were also carried out with the aim of translating a leading palladium mediated C-H activation-fluorination protocol to radiochemistry, by the preparation of new N-

^{18}F reagents. However, this proved extremely challenging due to several factors. First of all, the only reagent compatible with the fluorination of 2-methoxybenzyl triflamide **3-91** was the pyridine-based *N*-fluoro-2,4,6-trimethylpyridinium triflate **E** and attempts to prepare it with a substoichiometric amount of fluorine failed, and instead lead to undesired rearrangement reactions. In a radiochemical setting the electrophilic N-^{18}F reagent will always be the limiting reagent, so the radiochemical preparation of **3-104** may not be possible under these reaction conditions. All attempts to identify and prepare alternative N-F reagents, not capable of undergoing these side-reactions, were unsuccessful. Another important factor to consider is the ability of pyridine-based compounds to bind to the palladium centre, which is likely to inhibit the palladium catalyst from partaking in the C-H activation and cyclopalladation step. In a radiochemical setting there will inherently be an excess amount of free pyridine present, so the possibility of sequestering the palladium catalyst is likely. In order to achieve [^{18}F]radiolabelling of arenes *via* catalytic palladium-mediated C-H activation-[^{18}F]fluorination strategies, further studies should focus on alternative strategies which avoid the use of these reaction conditions for the preparation of pyridine-based [^{18}F]N-F reagents.

Chapter 4: [^{18}F]Radiolabelling of tri- and difluoromethylated arenes with [^{18}F]Selectfluor *bis*(triflate)

4.1 Aims

PET is an important tool in the diagnosis of illnesses and development of the subsequent treatment, but is also a powerful technique for drug discovery and development. Fluorine atoms and trifluoromethyl moieties are common motifs in pharmaceuticals and agrochemicals today and makes *in-vivo* investigation of these compounds possible using PET *via* fluorine-18 labelling. The study of new potential drugs at an early stage of their development allow the non-invasive exploration of the biodistribution of the compounds, and as a result, valuable information is obtainable regarding the drug's metabolic fate, success of the drug's design, tissue kinetics for the drug-dosing regimen and the downstream biochemical effects of the drug's action.[5]

Radiolabelling transformations for the preparation of the important and valuable [^{18}F]CF_3 motif are not trivial and have been significantly less explored compared to the introduction of a simple fluorine-18 atom. The aim of this chapter is therefore to explore a novel 'Hunsdiecker-like' radical [^{18}F]fluorodecarboxylation reaction for the preparation of [^{18}F]trifluoromethylated arenes using [^{18}F]N-F reagents.

In the introduction, the role of fluorinated and trifluoromethylated compounds in medicinal chemistry will be discussed. Furthermore, the application of [^{18}F]trifluoromethylated in PET for drug discovery is highlighted. As the many approaches for preparation of trifluoromethylated compounds have been extensively reviewed, the different strategies will be explained and key examples will be introduced. Next, fluorodecarboxylation using electrophilic fluorinating reagents have received a much attention and a strategy for development of this transformation for trifluoromethylation is discussed in combination with the few approaches for the synthesis of [^{18}F]trifluoromethylated compounds.

4.2 Introduction

4.2.1 Fluorine in Medicinal Chemistry

The presence of a fluorine atom or a trifluoromethyl group has become integral in the synthesis and design of new organic compounds in a multitude of chemical industries. About 25 percent of drugs today contain a fluorine atom, while in the agrochemical sector the number is comparatively high at 17 percent.[250] The US sales and the structure of the top ten best selling fluorine-containing drugs can be seen in table 4.1 and figure 4.1.[251]

Position by sale (2008) relative to all pharmaceuticals	Name	US sales in 2008 ($ x 10^9)
1	Atorvastatin	5.9
4	Fluticasone propionate	3.6
5	Lansoprazole	3.3
11	Cipralex	2.4
17	Rouvastatin	1.7
18	Ezetimibe	1.5
20	Simvastatin	1.5
22	Celecoxib	1.5
28	Levofloxacin	1.2
30	Risperidone	1.2

Table 4.1. US sales of top 10 blockbusters containing fluorine.

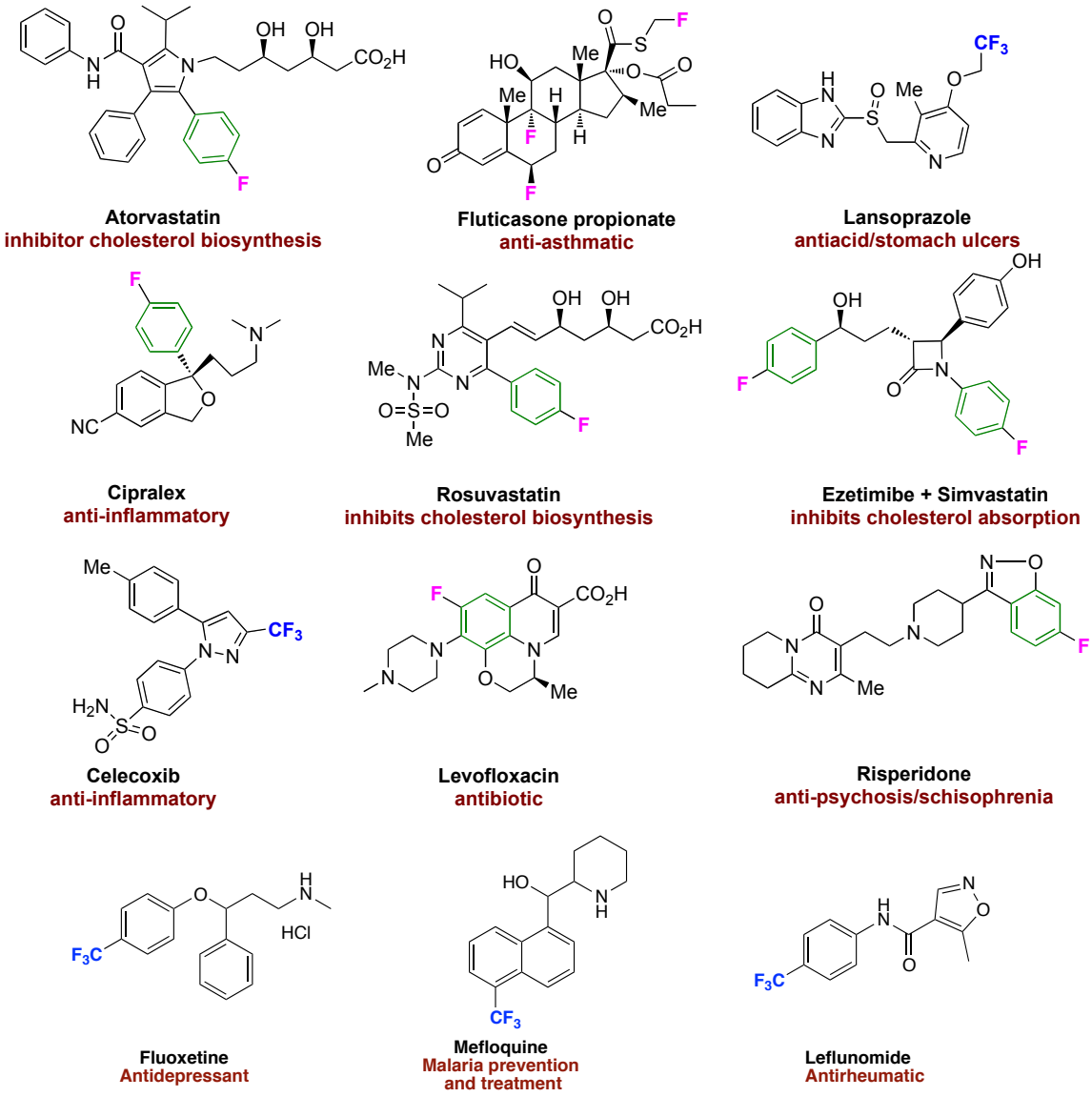


Figure 4.1. Fluorine-containing blockbusters.

This success is mainly due to the fact that selectively fluorinated compounds can exhibit dramatically improved potency when compared to the non-fluorinated analogues. The introduction of a fluorine atom or trifluoromethyl moiety changes the pharmacokinetic properties of a biologically active compound by altering the electronic, lipophilic and steric parameters and can critically increase the intrinsic activity, the chemical and metabolic stability and the bioavailability.[252],[253]

4.2.1.1 Perturbation of pK_a

The alteration of pK_a can greatly affect the binding affinity and pharmacokinetic properties of the biomolecule. As fluorine is the most electronegative element in the

periodic table (Pauling, 3.98) it thus exhibits a strong negative inductive effect on neighbouring reactive groups and may have a marked effect on their basicity and acidity (Table 4.2).

Carboxylic acid	pK_a	Alcohol	pK_a	Amine	pK_b
CH_3C_2OH	4.76	CH_3CH_2OH	15.9	CH_3CH_2NH	10.6
CH_2FCO_2H	2.59	CF_3CH_2OH	12.4	CF_3CH_2OH	5.7
CHF_2CO_2H	1.34	$(CH_3)_3COH$	19.2	$C_6H_5NH_2$	4.6
CF_3CO_2H	0.52	$(CF_3)_3COH$	5.1	$C_6F_5NH_2$	-0.36

Table 4.2. The effect of fluorine substitution on pK_a and pK_b values.

This was observed in a series of piperidinyl and piperazinyl indoles where the perturbation in pK_a reduced the basicity of the amine functionality and resulted in dramatically improved bioavailability (Figure 4.2a). Furthermore, the binding affinity for the target 5-HT_{1D} and 5-HT_{1B} receptors was modulated. Monofluorination of the propyl chain of the propylpiperazines had a small negative effect on 5-HT_{1D} affinity but maintained selectivity over 5-HT_{1B} (Figure 4.2b).[254]

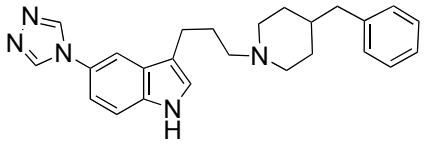
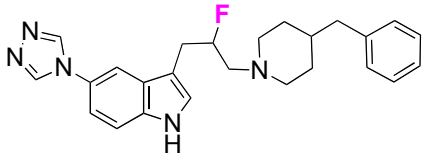
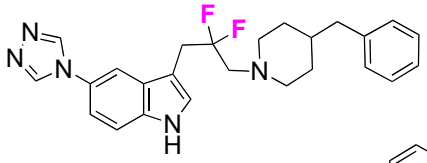
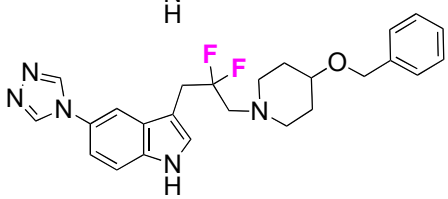
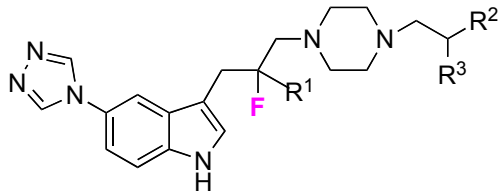
Amine	pK_a	IC_{50} 5-HT_{1D}	Bioavailability
	9.7	0.3	Poor
	8.7	0.9	Good
	6.7	78	–
	5.9	8.5	Good

Figure 4.2a. Basicity and bioavailability of a series of piperidinyl and piperzinyl indoles.[254]



			IC_{50} (nM)		
R^1	R^2	R^3	5-HT_{1D}	5-HT_{1B}	selectivity 1B/1D
H	H	Ph	6.8	930	137
H	H	2-F-Ph	4.7	520	111
H	H	3-F-Ph	3.5	1200	343
H	H	4-F-Ph	5.5	540	98
H	H	3-F-Ph	5.8	680	117
H	H	3-F-Ph	5.1	1000	196
H	CH_3	2-F-Ph	1.0	380	380
H	CH_3	3-F-Ph	0.9	280	311
H	CH_3	4-F-Ph	1.0	310	310
F	H	3-F-Ph	15	1600	107
F	CH_3	Ph	6.2	1800	290
F	CH_3	4-F-Ph	1.8	1000	556

Figure 4.2b. 5-HT Receptor binding affinities of selected 1-(2-fluoropropyl)piperazines and 1-(2,2-difluoropropyl)piperazines.[254]

Efavirenz **4-1** is a non-nucleoside reverse transcriptase inhibitor used for the treatment of HIV.[179] It contains a trifluoromethyl group attached to a tertiary stereocentre in a heteroaliphatic ring and acts by binding to a separate site on the enzyme and thereby altering the conformation of the active site and inhibiting the activity of the enzyme. Through structure-activity relationship studies, the relationship between the chemical structure and bioactivity of a compound, it was found that replacing the methyl group by a trifluoro moiety decreased the pH of the cyclic carbamate by 1.3 pH units (Figure 4.3).[255] This increases the hydrogen bonding interaction between the N-H of the carbamate and the oxygen in the lysine101 residue in the binding site of the enzyme. [256]

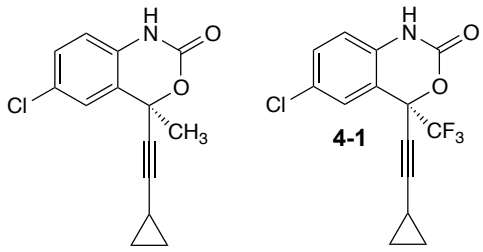


Figure 4.3. Effect of a trifluoromethyl group on the pK_a of Efavirenz.[255]

4.2.1.2 Oxidative metabolism

Another aspect of drug design, is the stability exhibited towards oxidative metabolism caused by cytochrome P450 enzymes, and this class of heme-thiol enzymes present in the liver are known to cause rapid chemical degradation of drugs *in vivo*. The incorporation of fluorine at metabolically labile sites is known to inhibit the required chemical processes necessary for degradation to take place; either by actually blocking the reactive position or perturbing neighbouring functional groups. This strategy was used in the design of Ezetimibe **4-2**, a cholesterol absorption inhibitor (Figure 4.4).[257] In the initial lead structure over 40 possible metabolites can be produced, but the structure was optimised by the introduction of two fluorine atoms and the presence of phenol moieties. This ensured the effect of decreasing "non-productive" metabolism while also pre-activating "productive" metabolism ultimately leading to a 50 fold increase in potency of Ezetimibe over SCH48461.

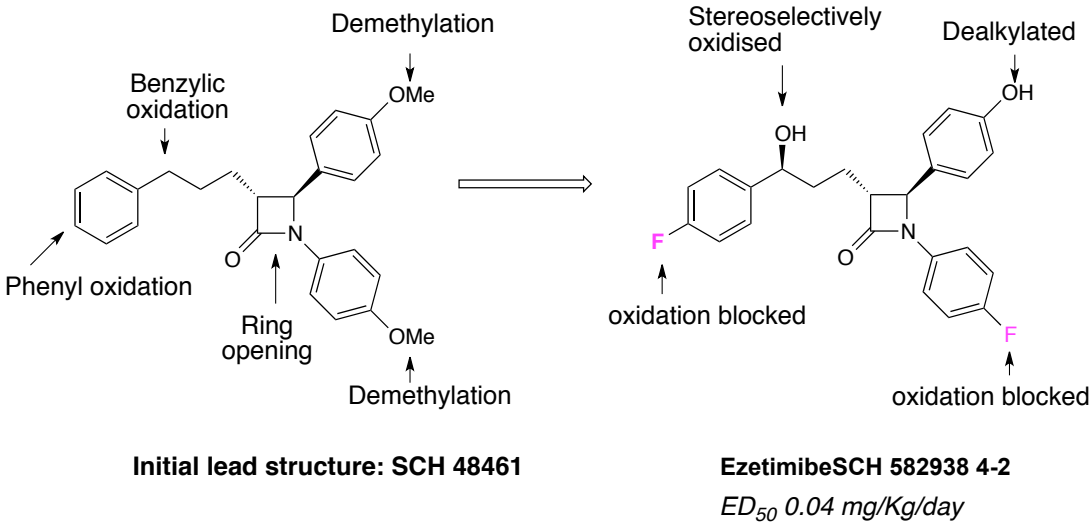


Figure 4.4. Tuning the metabolism of Ezetimibe.[257]

4.2.1.3 Modulation of Lipophilicity

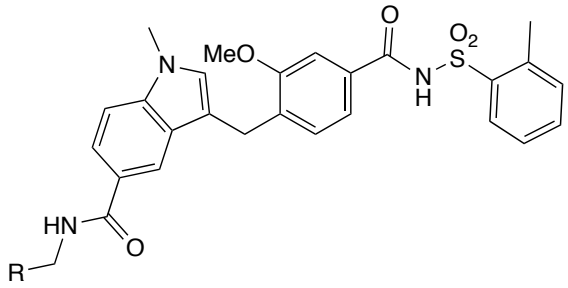
Lipophilicity is expressed as the partition coefficient (log *P*) between octanol and water. A drug must be lipophilic enough to pass through the lipid bilayer of cell but if its too lipophilic it will be trapped inside it. According to Lipinski's rule of 5, a log *P* value of less than 5 give good adsorption.[258] It is a common misapprehension that incorporation of a fluorine atom always increases lipophilicity. In the case of saturated alkyl chains, mono- or trifluoromethylation usually decreases lipophilicity due to their strong electron-withdrawing effect (Table 4.3).

Alkyl chain	log *P* (octanol/water)
CH_3CH_3	1.81
CH_3CHF_2	0.75
$CH_3(CH_2)_3CH_3$	3.11
$CH_3(CH_2)_3CH_2F$	2.33

Table 4.3. Effect of fluorine substitution of log *P*.

However, for aromatic compounds, per/polyfluorination and fluorination adjacent to atoms containing π-bonds is known to increase lipophilicity.[259] The reason for the increased lipophilicity is the excellent overlap of the 2s and 2p orbitals of fluorine with the corresponding orbitals in carbon making the C-F bond highly non-polarisable.

In the development of leukotriene receptor inhibitors, it was found that drug candidates containing amide substituents were more potent. Increasing the chain length of these substituents further improved lipophilicity but longer chains also reduced the ability of the compound to bind to the receptor. Installation of fluorine atoms solved this problem by successfully increasing the lipophilicity and on average increased the potency 10-fold compared to the non-fluorinated analogue (Table 4.4).[260]



Amide chain R =	log *P* (octanol/water)
$CH_3CH_2CH(CH_3)$	5.85
$CF_3CH_2CH(CH_3)$	6.18
$(CF_3CH_2)_2CHCH_2$	6.29
$CF_3CH_2CH(CH_3CH_2)CH_2$	6.45
$CF_3CH(CH_3)CH_2CH_2$	6.30
$CF_3CH(CH_3)CH_2$	5.89

Table 4.4. Influence of fluorine on the lipophilicity.[260]

4.2.1.4 Conformational changes and bioisosterism

Fluorine is also able to "mimic" a hydrogen atom due to their similarity in size (Van der Waals radius 1.47 Å vs. 1.2 Å), although the difference in electronegativity renders both the reactivity and polarity of the C-F bond orthogonal to the C-H bond. This ability of functional groups to be interchanged without causing biological behaviour (bioisoterism) is very important in drug development (Figure 4.5). The introduction of a trifluoromethyl group may impose a greater steric change. Its Van der Waals radius is compared to that of an ethyl group but has a shape closer to an isopropyl group.[261],[262] These steric changes combined with the high electronegativity of fluorine can lead to changes in the conformation of the compound.

Van der Waals radius	H	1.20 Å
	F	1.47 Å
	O	1.52 Å
Bond length	C-H	1.09 Å
	C-F	1.35 Å
		1.41 Å
	C-O	1.43 Å
Total extensions	C-F	2.82 Å
	C=O	2.72 Å
Van der Waal's volume	CF_3	39.8 Å^3
	CH_3	21.6 Å^3
	$(CH_3)_2CH$	56.2 Å^3
	CH_3CH_2	38.9 Å^3

C-H to C-F replacement
- conservative on steric grounds
- significant electronic changes

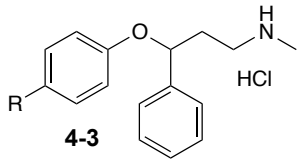
C-OH to C-F replacement
- no significant electronic changes
- relatively close size match
- loss of acidic hydrogen (H bonding donor ability)
- excellent tool in exploring roles of C-OH
- hydrogen bonding relative to inherent polarity
- " Polar Hydrophobic"

C=O to C-F or CF_2 replacement
- hydridisation change
- relatively close size match

CH_3 to CF_3 replacement
- electronic changes
- similar volume but different shape
- CF_3 ~ $CH(CH_3)_2$

Figure 4.5. Fluorine and Bioisoterism.

This was observed in the development fluoxentine (Prozac) **4-3**, a best-selling antidepressant acting as an inhibitor of the re-uptake of serotonin. This increases amount of serotonin available to bind to the serotonin receptor 5-TH. Increasing the steric bulk by the introduction of a trimethyl moiety in the *para*-position of the phenolic ring, increased the potency of inhibition 6-fold compared to the non-fluorinated analogue of fluoxetine (Figure 4.6).[263] The potency was even further increased when compared to the analogue containing a single fluorine atom in the same position. Studies showed that the steric bulk imposed by the introduction of the trifluoromethyl group significantly altered the conformation of the phenolic ring enabling fluoxetine to bind more effectively to the 5-HT receptor.[264]



4-3

	K_i (nM)
R = H	102
R = F	638
R = CF_3	17

Figure 4.6. Effect of the introduction of CF_3 on binding potency to 5-HT.[263]

4.2.2 PET in drug discovery and development.

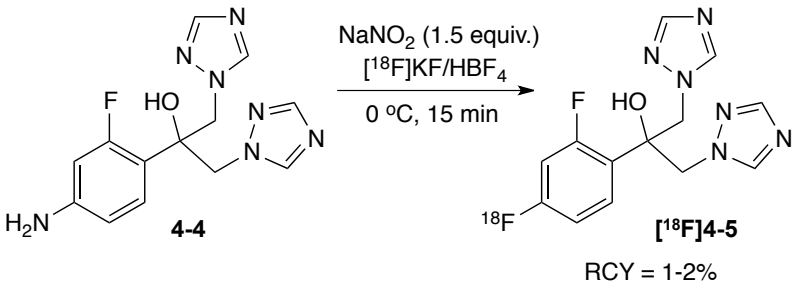
Traditionally, structure-activity relationships (SAR) were used to identify and chemically design ligands with optimum binding affinity for desired target receptors. However, a study carried out by seven UK pharmaceutical companies between 1964 and 1984 reported, that in reality, 40% of novel drug candidates were withdrawn due to serious deficits in their pharmacokinetic profile, such as unfavourable biodistribution, poor oral absorption and rapid metabolism by the liver.[265]

The immense potential and value of advanced molecular imaging modalities in drug discovery and development have only recently begun to be realised. Through the use of PET, it is possible to visualise a molecular target in a living animal while at the same time following a drug's distribution in the same subject and finally quantify the drug's effect on that target. As only a very small amount of compound is required (< 10 nmol), this strategy is non-invasive and images the biochemical or physiological process, without eliciting an actual pharmacological response (microdosing). This

refined approach, combining SAR with additional information regarding the drug's metabolitic, pharmacokinetic and pharmacodynamic profile and toxicological implications, allow detailed and improved evaluation of new drug candidates at an early stage of the development process. As a result the drug discovery and development process is substantially more focused and efficient.

There are two general strategies for the *in vivo* study of a potential drug. For imaging of biodistribution and pharmacokinetics, the drug is directly radiolabelled, while for imaging of target distribution and function, the radiolabelled tracer is administered in combination with a drug candidate selective for the same target.

The investigation of the biodistribution of fluconazole is an example of the first strategy. This drug was developed as a new class of antifungal agents and was found be exhibit low systemic toxicity[266] and a favourable pharmacokinetic profile.[267] However, the establishment of optimal dosing regimens was found challenging and information regarding the biodistribution of the drug in humans was lacking. To this end, 4-[^{18}F]fluconazole **[^{18}F]4-5** was prepared in a Balz-Schiemann reaction (Scheme 4.1).[268]



Scheme 4.1. Preparation of 4-[^{18}F]fluconazole [^{18}F]4-5.[268]

The biodistribution studies showed that the distribution of the compound in humans differed from the values obtained with rabbits, illustrating that extrapolation of pharmacokinetic properties from animal to human can be incorrect. Furthermore, it was found that the optimal dose of the drug differed depending on the site of infection.[268]

Imaging agents may also be used in combination with a drug in order to investigate drug occupancy at a target. This assists in the determination of the optimal dose of the drug and assesses selectivity and affinity for the target. [^{18}F]SPA-RQC, a NK_1 receptor-binding selective tracer, could be used to measure the level of NK_1 receptor occupancy obtained upon the administration of a therapeutic dose of aprepitant, used for the treatment of nausea and vomiting in patients undergoing chemotherapy (Figure 4.7). Aprepitant was administered to healthy subjects at a variety of dosing levels and after two weeks [^{18}F]SPA-RQC was injected and the volunteers were scanned. Comparison of the images to scans obtained before the drug-trial with no aprepitant present, allowed the calculation of the occupancy of the NK_1 receptors at each dose.[269]

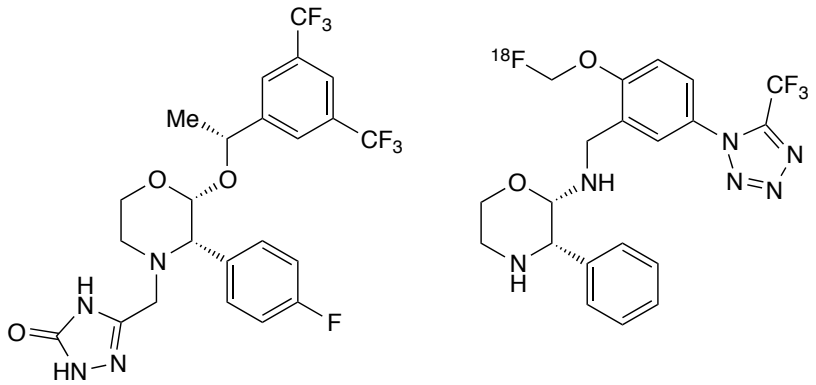


Figure 4.7. Use of [^{18}F]SPA-RQC in drug occupancy studies with aprepitant.[269]

Finally, it is important to note that drug candidates may act at novel targets and as a result there is no existing imaging agent selective for that molecular site. To be able to take full advantage of PET for the development of new therapeutic agents, it is important that the pharmaceutical industry increase collaboration with radiochemists to take advantage of the expertise at academic PET centres.

4.2.3 Trifluoromethylation

Due to their value, the formation of C-CF_3 bonds has received tremendous amount of attention and the field has been extensively reviewed.[270],[271],[272],[273] An introduction to the main strategies will be presented herein, with emphasis on transition metal-mediated strategies for the preparation of trifluoromethylated arenes.

Trifluoromethylation can be addressed in two ways: by installation of the CF_3 directly through the use of trifluoromethylation reagents (C-CF_3 bond formation) or by nucleophilic fluorination of a CF_2-LG species (C-F bond formation) (Figure 4.8).

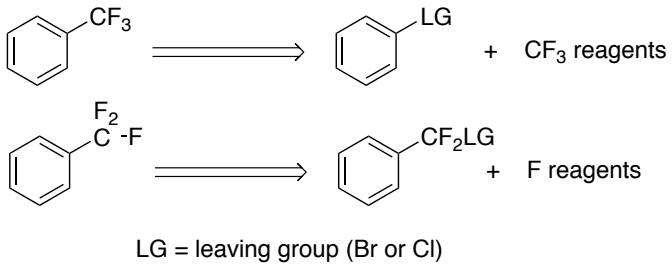
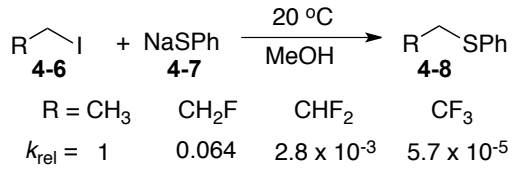


Figure 4.8. Retrosynthetic approaches for trifluoromethylation of arenes.

The latter strategy has been significantly less explored compared to the use of CF_3-reagents. The fluorinated carbon centres exhibit low reactivity as the rate of nucleophilic substitution is greatly reduced by the presence of fluorine substituents in the α-position. Even in the early studies conducted by McBee, in the reaction between phenylthiolate **4-6** and β-fluorinated ethyl iodide **4-7** it was found that the rate of nucleophilic substitution decreased as the number of fluorine atoms in the alkyliodide increased (Scheme 4.2).[274]

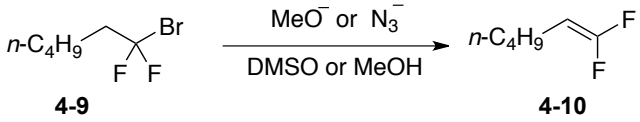


Scheme 4.2. Nucleophilic substitution on β-fluorinated ethyl iodides.[274]

Dolbier and co-workers recently carried out a comprehensive comparative study on the nucleophilic substitution of α,α-difluorinated alkyl and benzyl halides versus their non-fluorinated analogues.[107]

When the substitution of bromide in 1-bromo-1,1-difluorohexane **4-9** was attempted with either the azide ion or methoxide ion, the desired product was not observed in either case (Scheme 4.3). Calculations showed that the S_N2 reaction at CF_2Br was 13000 times slower than at CH_2Br. While the S_N2 reaction was strongly inhibited, the

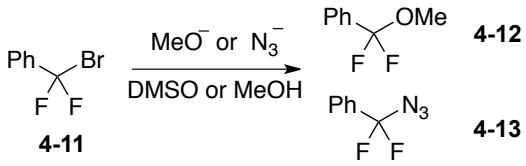
rate of the elimination increased. In the case of *n*-pentyl-CF_2Br, the rate of β-elimination in DMSO was 59 times faster compared to *n*-alkyl bromide.



4-9 **4-10**

Scheme 4.3. Nucleophilic substitution on α,α-difluorinated alkyl halides.[274]

By studying benzyl-CF_2 bromides it was possible to compare the rates of S_N2 reactions in the absence of competing elimination. Both methoxide and azide anions successfully underwent substitution with $PhCF_2Br$ **4-11**, but the rate was drastically decreased compared to the non-fluorinated benzyl bromide (Table 4.5).



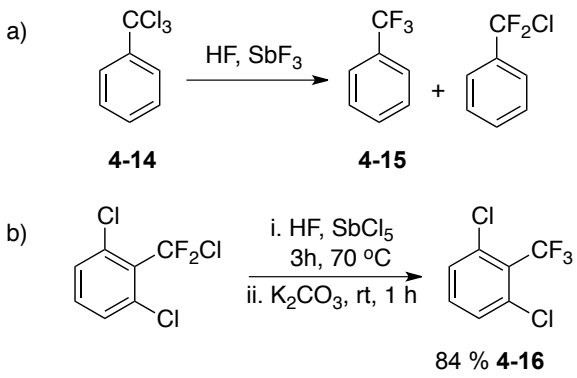
4-11

Nucleophile	Solvent	Temperature (°C)	k_{rel} (CH_2Br/CF_2Br)
OMe^-	MeOH	50	43800
OMe^-	DMSO	15	52000
N_3^-	MeOH	50	68200
N_3^-	DMSO	15	172000

Table 4.5. Nucleophilic substitution of $PhCF_2Br$ *vs.* $PhCH_2Br$.[274]

Experimentally, Dolbier found that magnitude of the energy barrier $\Delta G^{\ddagger}$ of the S_N2 reaction followed the trend: *n*-$C_7H_{15}Br$ < *n*-$C_4F_9CH_2CH_2Br$ < *n*-$C_8H_{17}CHFBr$ << *n*-C_3F_7 CH_2Br < *n*-$C_5H_{11}CF_2Br$. The calculations showed that the presence of fluorine near the active sites increases the energy barrier. The changes in $\Delta G^{\ddagger}$ may be explained in two ways. The positive partial charge developed at the carbon in the transition state of the S_N2 reaction may be destabilized by the negative inductive effect asserted by the fluorine atoms in the β- and γ-positions. However, in the case of α-fluorinated compounds there is a weak π-donation that may partially stabilise the positive charge. The low reactivity of these species towards substitution may be explained by the significant electrostatic interactions between the fluorine atoms and the incoming nucleophile. This effect should be the largest in *gem*-difluorinated substrates and has the larger effect on the energy barrier.

The few examples of this approach in the literature illustrate the low reactivity of the precursors, due to the need for very harsh reaction conditions to achieve nucleophilic substitution. Traditionally, simple benzotrifluorides **4-14** were prepared by the fluorination of benzotrichlorides **4-15** using hydrogen fluoride and antimony fluorides. However, this reaction reported by Swarts in 1892 didn't reach completion and also afforded $PhCF_2Cl$ (Scheme 4.4a).[275] The harsh reaction conditions required, only allowed for the preparation of structurally simple benzotrifluorides. A more recent example was reported by Cai and co-workers for the preparation of 2,6-dichlorobenzotrifluoride **4-16**, also using hydrogen fluoride in combination with an antimony Lewis acid (Scheme 4.4b).[276] This late stage introduction of a fluorine atom is attractive for radiochemistry, but it's value and limitations will be further discussed in section 4.4.



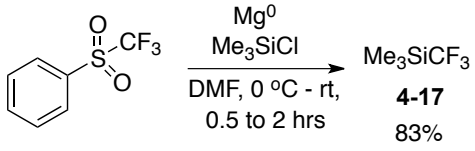
Scheme 4.4. Nucleophilic substitution for trifluoromethylation.[275],[276]

Alternatively, direct introduction of a trifluoromethyl moiety, by formation of the C-CF_3 bond, can be readily achieved through the use of nucleophilic, electrophilic or radical reagents, or transition metal catalysis.

4.2.3.1 Trimethylation using nucleophilic CF_3 reagents

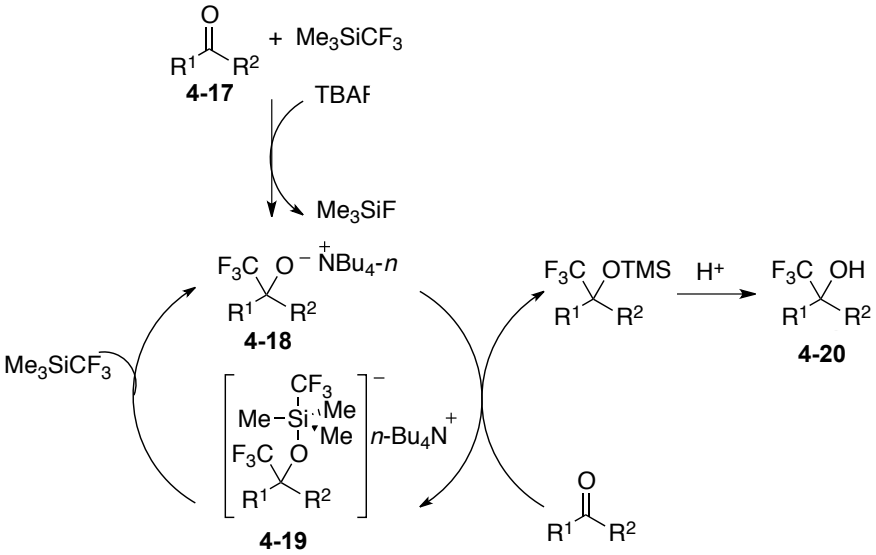
This is considered to be a very attractive approach for trifluoromethylation and with the development of range of nucleophilic CF_3 reagents, a range of electrophiles can now readily be trifluoromethylated. Fluoroform[277] and CF_3I/TDAE[278] have been used for this purpose, but is through the use of the Ruppert-Prakash reagent ($TMSCF_3$) **4-17** that this field has flourished.[279] The initial preparation of the reagent required

the use of the now banned trifluoromethyl bromide and a recently updated synthetic route was recently reported (Scheme 4.5).



Scheme 4.5. Preparation of Ruppert-Prakash reagent 4-17.

The reagent **4-17** is widely used for the trifluoromethylation of carbonyl compounds, but requires activation by a nucleophilic initiator in order to release the reactive trifluoromethide anion. Fluoride sources (TBAF, CsF) are the most commonly used initiators. When fluoride is added to a reaction mixture containing **4-17** and a carbonyl compound, the process starts activation of the C-Si bond of the reagent. This allows the formation of Me_3SiF and the *n*-Bu_4N cation stabilises the alkoxide adduct **4-18.** The pentavalent complex **4-19** is formed upon the reaction between **4-18** and Ruppert's reagent and finally the trifluoromethide anion was transferred to the carbonyl functionality of the starting material. Hydrolysis of the silyl enol ether affords the trifluoromethylated compound **4-20**. (Scheme 4.6).[280]



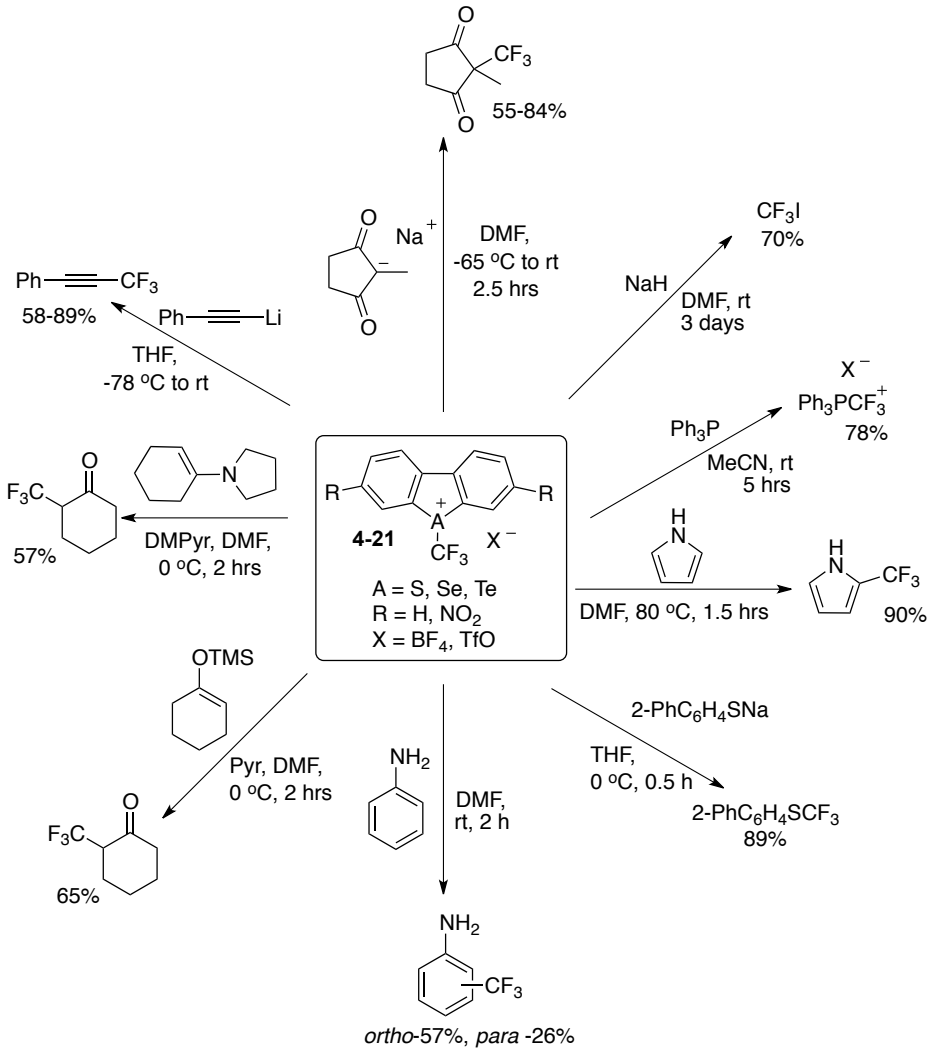
Scheme 4.6. Trifluoromethylation of carbonyls using 4-6 and fluoride.[280]

A wide range of aldehydes[281], ketones, esters and activated imines undergo trifluoromethylation under these reaction conditions.[282],[283]

4.2.3.2 Electrophilic trifluoromethylation

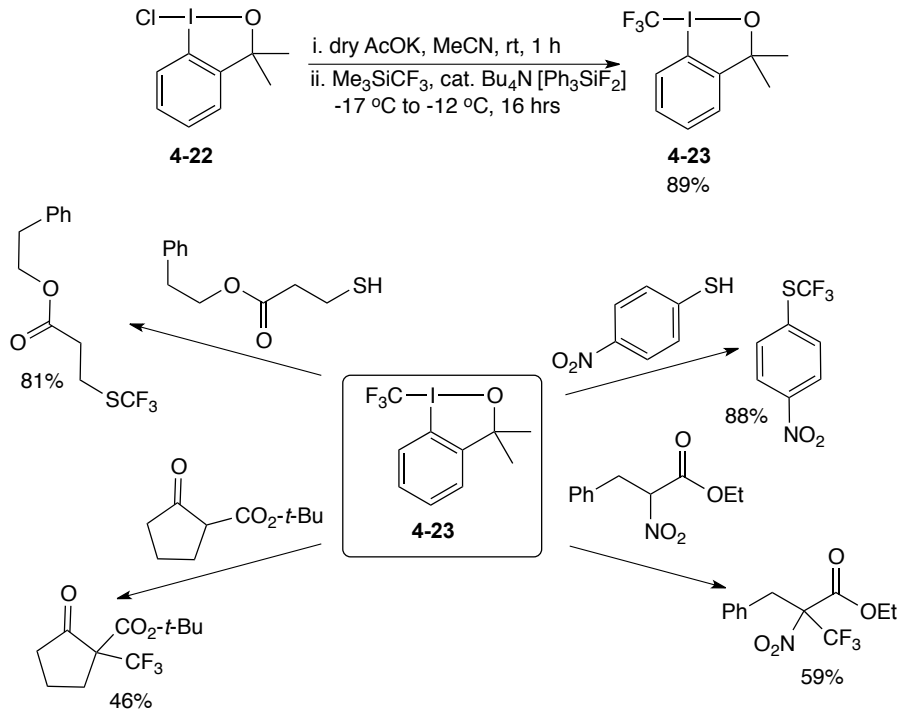
The formation of a free trifluoromethyl cation is challenging, as the positive charge is greatly destabilised due to the presence of the electronegative fluorine atoms. When attached to a nucleophile substituted with electronegative moieties, the trifluoromethyl group is polarised and can thereby act as an electrophile. This has lead to the development of two main classes of electrophilic trifluoromathylating reagents: Umemoto trifluoromethylchalcogen salts (sulfonium, selenium, telluronium and oxonium) and Togni's iodonium salts.

The electrophilic trifluoromethylchalcogen salts **4-21** developed by Umemoto and co-workers showed varying amount of power.[284] The reactivity of these reagents followed the trend Te < Se < S, due to the increasing nucleophilicity of the reagent core. Installing electron-withdrawing substituents on the arene also increased the reactivity of the reagents (NO_2 > H) (Scheme 4.7).[285]



Scheme 4.7. Reactivity of Umemoto's electrophilic CF_3 reagents.[285]

Recently, Togni and co-workers reported an alternative class of electrophilic CF_3 reagents: hypervalent iodine(III) reagents containing the CF_3 unit on the iodine atom.[286] These reagents are prepared using an overall Umpolung approach as the "CF_3^+" moiety is installed using the nucleophilic Ruppert-Prakash reagent **4-17**. A selection of the carbon and sulfur-centered nucleophiles which were successfully trifluoromethylated are shown in scheme 4.8.[287]



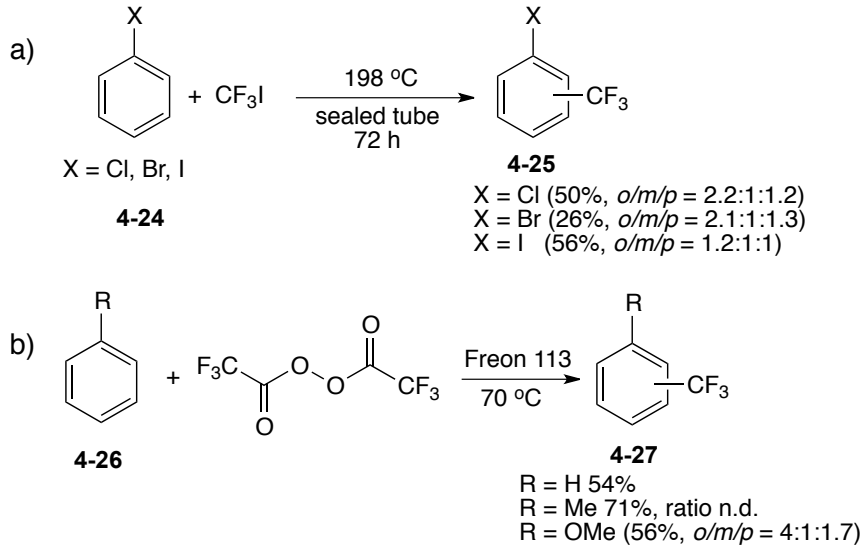
Scheme 4.8. Preparation of hypervalent iodine(III) trifluoromethylation reagent 4-23 and trifluoromethylation on C- and S-nucleophiles.[287]

4.2.3.3 Radical Trifluoromethylation.

In this trifluoromethylation reaction, the active species is the free trifluoromethyl radical.[272] The fluorine atoms are exerting a strong negative inductive effect on the carbon radical, while also behaving as weak π-donors due to the good overlap between fluorine atoms and the SOMO of the carbon. The net impact of the presence of the fluorine atoms will result form a combination of these effects. Compared to the planar CH_3 radical, the CF_3 radical is pyramidal (almost tetrahedral) and exhibit a large barrier for inversion (25 kcal/mol). Due to the loss of planarity, the required overlap between the SOMO and $\sigma^*_{C\text{-}F}$ orbital is less effective. This diminishes the effect of the π-donation from the fluorine atom. Hence, it was found that the stability of the CF_3 radical is strongly governed by stereoelectronic effects, i.e. mainly the strong inductive effect of the fluorine substituents. The stabilisation energy of the CF_3 radical is 2.4 kcal/mol, which makes it more electrophilic than the CH_3 radical, and therefore more reactive. The reaction with styrene was 440 times faster with the CF_3 radical than with the CH_3 radical.[288]

The electrophilic CF_3 radical possessing a low-lying SOMO may be generated under oxidative, reductive, photochemical, thermal and electrochemical conditions, from a variety of precursors.[287] Once formed, it is able to react with a variety of species such as electron-rich alkenes and arenes.

An early example of radical trifluoromethylation reported the use of CF_3I as the radical precursor. At elevated temperatures, halogenated arenes **4-24** were trifluoromethylated in moderate yields and with poor selectivity (Scheme 4.9a).[289] The CF_3 radical was also successfully generated from bis(trifluoroacetyl) peroxide **4-26** by thermal homolysis and decarboxylation, but upon the trifluoromethylation of electron-neutral and electron-rich arenes **4-25**, a mixture of regioisomers **4-27** was again obtained (Scheme 4.9b).[290] This low regioselectivity is a general problem in homolytic aromatic substitution. CF_3 radicals have also been employed in transition metal-mediated trifluoromethylation reactions and recent examples will be highlighted in the next section.



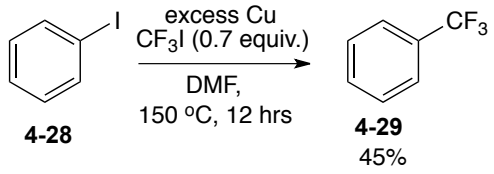
Scheme 4.9. Examples of radical trifluoromethylation of arenes.[289],[290]

4.2.4 Transition metal-mediated trifluoromethylation

The use of transition metals has enormous potential in trifluoromethylation reactions in analogous approaches to C-F bond formation. The difficulties associated with C-F reductive elimination from transition metals were previously explained in Chapter 3 and C-CF_3 bond formation is associated with the same obstacles. As discussed in the

introduction to Chapter 3, the high electronegativity (3.2) of the trifluoromethyl group increases the activation barrier of C-CF_3 reductive elimination, as the rate of this process decreases with more electron-withdrawing nucleophiles. In addition, the metal-CF_3 bond is considered to be relatively strong, partly due to the bonding interactions between the metal *d* orbitals and the $\sigma^*_{C\text{-}F}$, and this further reduces the viability of transition metal-catalysed C-CF_3 bond formation.[291] This strategy also relies on the availability of suitable electrophilic and nucleophilic CF_3-reagents.

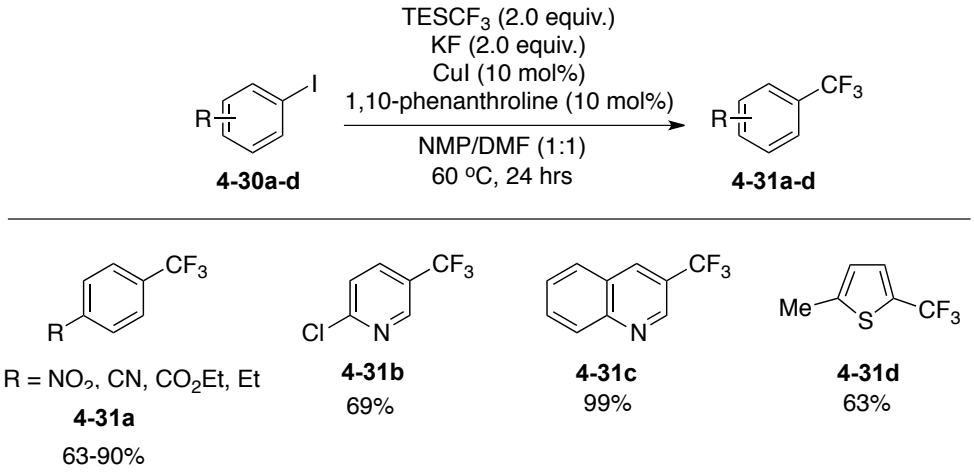
The pioneering transition metal-mediated polyfluoroalkylation of arenes was reported by McLoughlin and Thrower in the 1960's. Iodobenzene **4-28** was successfully trifluoromethylated in the presence of a stoichiometric amount of activated copper and CF_3I to yield benzotrifluoride in **4-29** in 45% yield (Scheme 4.10).[292]



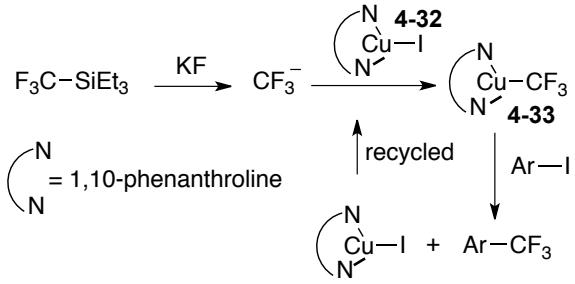
Scheme 4.10. First transition metal-mediated trifluoromethylation.[292]

Several modified and improved protocols have since been reported[293],[294], but the first copper-catalysed trifluoromethylated reaction was not reported until 2009.[295] In the presence of a catalytic amount of copper iodide and 1,10-phenanthroline, electron-poor iodides **4-30a-d** were successfully converted to a range of aryl and heteroaromatic trifluoromethylated compounds **4-31a-d** in good yields (Scheme 4.11). A variant of reagent Ruppert-Prakash reagent **4-17**, $TESCF_3$, was employed as the source of CF_3 and the trifluoromethide anion was released upon treatment with potassium fluoride. In the proposed mechanism, this species subsequently undergoes nucleophilic substitution with copper(I)-diamine complex **4-32** to yield Cu-CF_3 complex **4-33**. The presence of the bidentate amine ligand both stabilise complex **4-33** and also increase the reactivity of the CF_3 nucleophile. As a result, the final σ-bond metathesis between the aryl iodides and **4-33** was found to be fast and efficient (Scheme 4.12). The details of the final step are not known, but it is postulated to proceed *via* oxidative addition to form an arylcopper(III) intermediate.[296],[297] The

development of alternative copper-catalysed strategies have flourished in recent years.[298],[299]

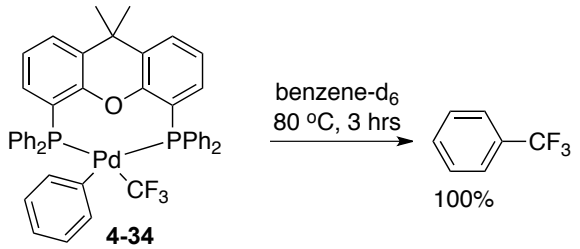


Scheme 4.11. Copper-catalysed trifluoromethylation.[295]



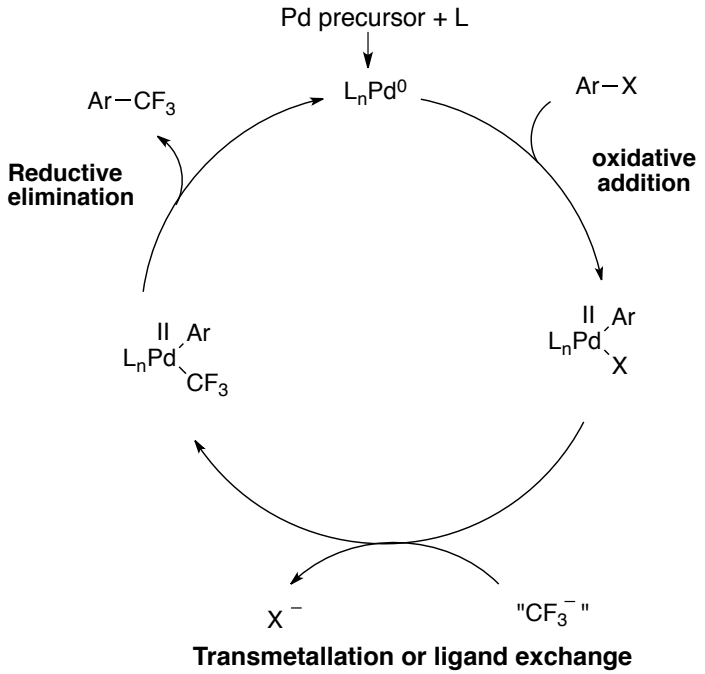
Scheme 4.12. Proposed mechanism for Cu-catalysed trifluoromethylation.[295]

The first palladium-mediated aryl-CF_3 bond formation was reported in 2006.[198] Reductive elimination was achieved from the palladium(II) complex **4-34** containing the large bidentate phosphine ligand, XanthPhos, on heating to 80 ^oC for 3 hrs (Scheme 4.13). The effect of employing XanthPhos, a ligand with a large bite angle (111^o), is to force the aryl group and the CF_3-moiety to exist spatially very close together, which promote reductive elimination.



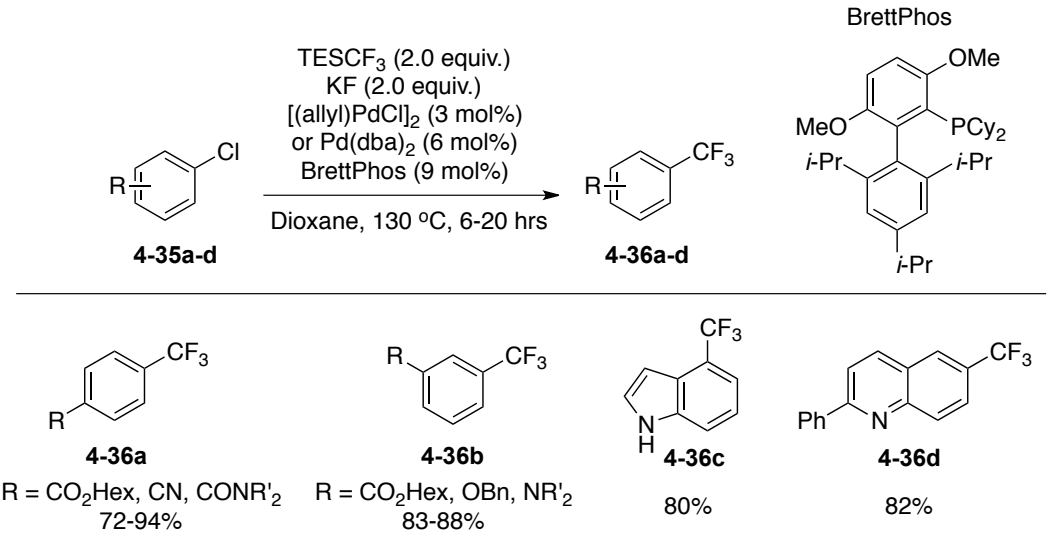
Scheme 4.13. Palladium-mediated aryl-CF_3 bond formation.[198]

In the same study by Grushin, it was established that all the required steps of the catalytic cycle for C-CF_3 bond formation were viable. However, the challenge is to design a system that would allow oxidative addition, transmetallation/ligand exchange and reductive elimination (the rate-determining step) to occur in a one-pot reaction (Scheme 4.14).



Scheme 4.14. General catalytic cycle for C-CF_3 bond formation.

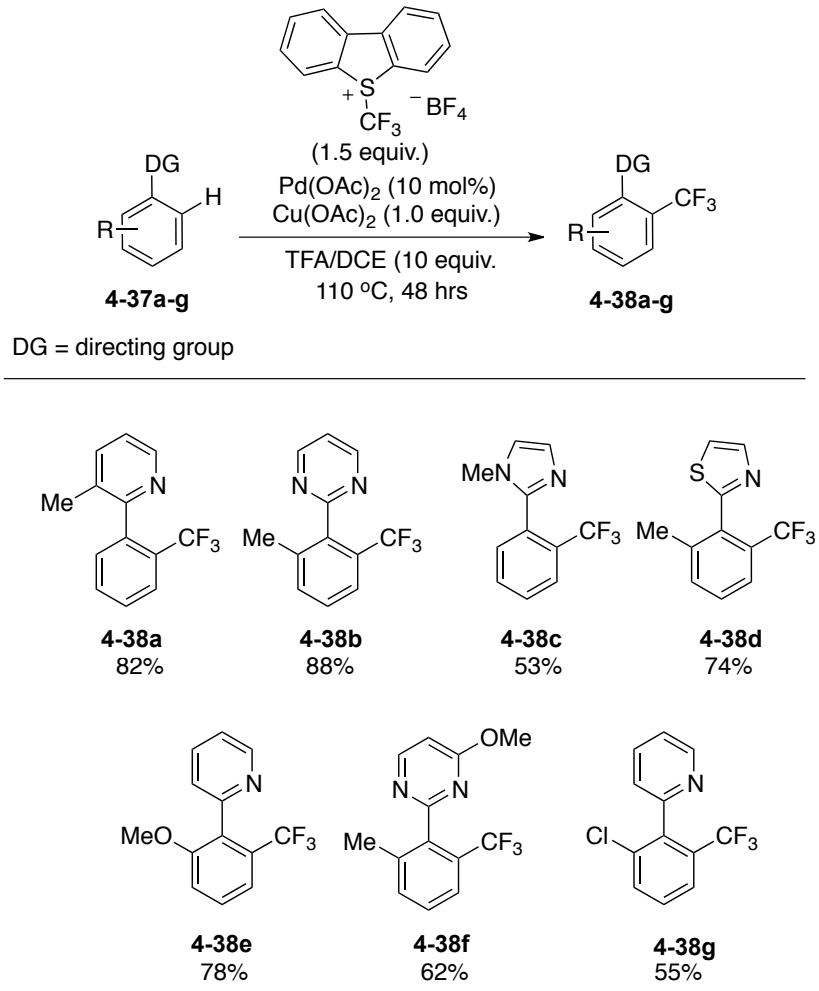
The pioneering trifluoromethylation reaction employing a catalytic amount of palladium was reported in 2010.[300a] A wide selection of aryl chlorides **4-35a-d** underwent trifluoromethylation in the presence of a palladium(II) catalyst, $TESCF_3$, KF and the sterically hindered phosphine ligand, BrettPhos (Scheme 4.15).



Scheme 4.15. Palladium-catalysed trifluoromethylation.[300a]

A wide range of functional groups was tolerated under the reaction conditions, but the reaction failed when substrates with protic functional groups were used. It was postulated that these substrates accelerated the decomposition of $TESCF_3$ or the aryl(trifluoromethyl)palladium(II) intermediate formed upon oxidative addition.

Aryl-CF_3 bond formation is also possible through direct activation of C-H bonds with the use of a directing group, $Pd(OAc)_2$ and an electrophilic trifluoromethylation reagent (Scheme 4.16).[300b]

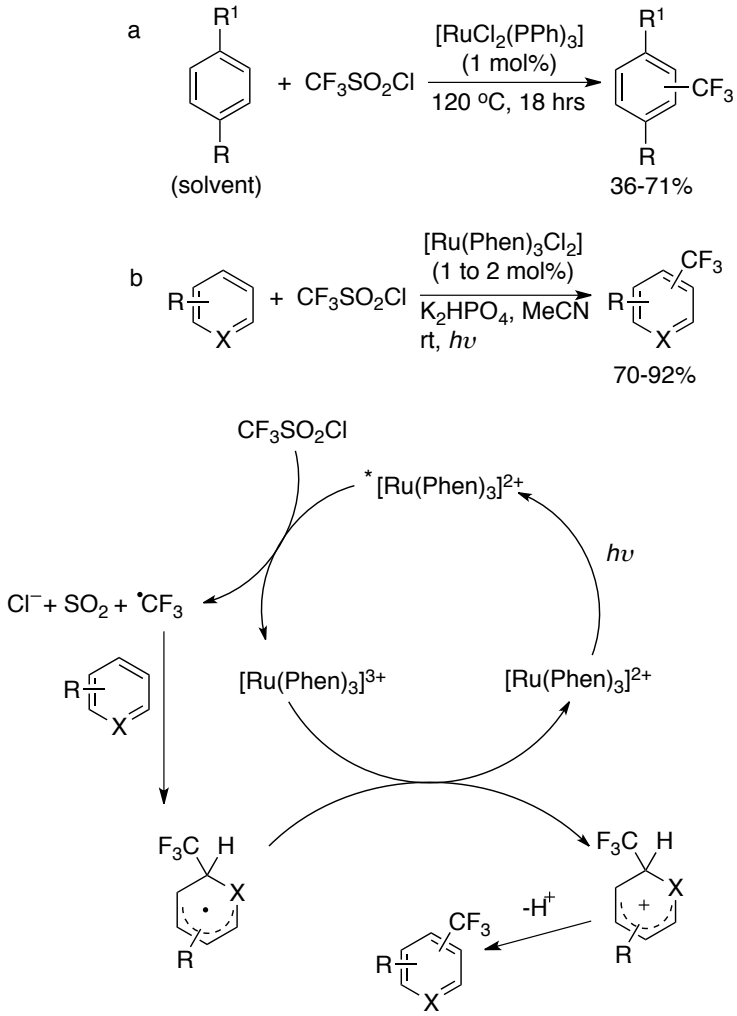


Scheme 4.16. Ar-CF_3 bond formation from C-H bonds. [300b]

A wide range of heterocycles, including pyridine, pyrimidine, imidazole, thiazoles could be used as directing groups and afforded simple trifluoromethylated arenes **4-38a-g** in good yields. The limitation of this protocol is the requirement for a directing group and the restrictive functional group scope: only methoxy, methyl and chloro groups were tolerated under the reaction conditions.

Several approaches employing CF_3 radicals have been reported for the trifluoromethylation of arenes and heteroarenes. In the presence of a catalytic amount of $[RuCl_2(PPh_3)_3]$ and trifluorosulfonyl chloride as the radical precursor, a selection of arenes (also used as the solvent) were successfully trifluoromethylated in yields ranging from 36-76% but with poor regioselectivity (Scheme 4.17a). Recently, an approach employing $[Ru(Phen)_3Cl_2]$ as a photoredox catalyst was developed for the trifluoromethylation of arenes and heteroarenes.[301] This approach benefited from

milder reaction conditions and the trifluoromethylated compounds were afforded in higher yields and selectivity (Scheme 4.17b). Irradiation of the $[Ru(Phen)_3]^{2+}$ catalyst generates the excited $*[Ru(Phen)_3]^{2+}$ complex, which reacts with the radical precursor by SET to afford the CF_3 radical, SO_2, chloride anion and $[Ru(Phen)_3]^{3+}$. Upon addition of the radical, the arene converted into the corresponding cyclohexadienyl radical. This species is oxidised by $[Ru(phen)_3]^{3+}$ to afford the corresponding cyclohexadienyl cation and $[Ru(Phen)_3]^{2+}$. Final deprotonation of the cation generates the trifluoromethylated products.

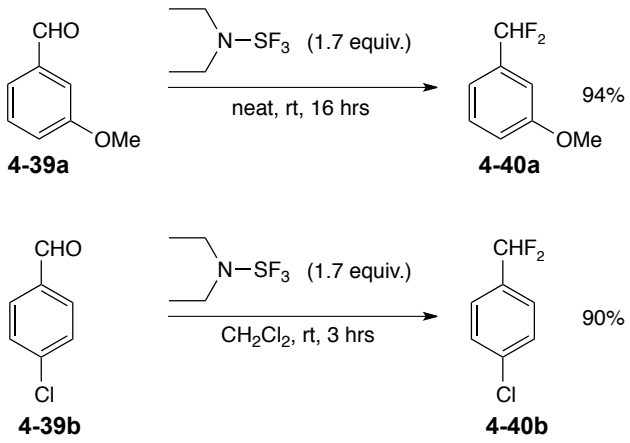


Scheme 4.17. Ru catalysed radical trifluoromethylation of arenes and heteroarenes.

4.2.5 Difluoromethylation

Although the preparation of mono-fluorinated and trifluoromethylated compounds has received most attention and the application of these moieties in a range of industries are widely recognised, the difluoromethyl (CF_2H) moiety is also an important functional group in medicinal chemistry. When present in bioactive compounds, it is capable of augmenting membrane permeability, binding affinity and bioavailability.[302] In terms of bioisosterism and polarity, the CF_2H group is comparable to the hydroxy functionality. Due to the presence of the weakly acidic hydrogen atom on the α,α-difluorinated carbon, this functionality is capable of acting as a participant in hydrogen bonding interactions.[303] Due to these favourable properties, the CF_2H moiety may be found in sugars[304] and agrochemicals[305].

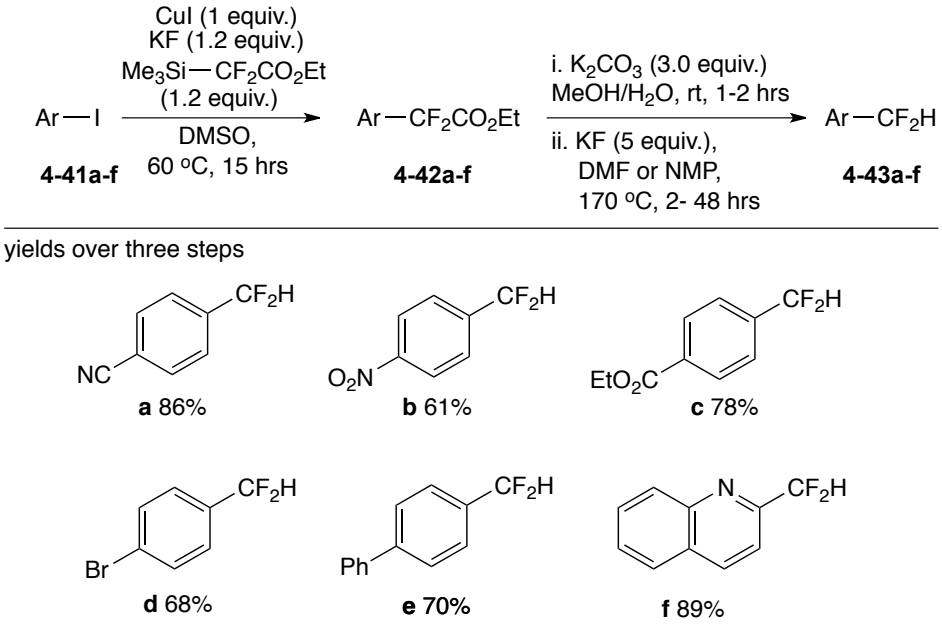
Early methods for the introduction of this moiety involved the deoxofluorination of aromatic aldehydes **4-39a-b**, using nucleophilic fluorinating reagents such as Deoxofluor and DAST (Scheme 4.18). [306]



Scheme 4.18. Difluorination of aldehydes using DAST.

Many regioselective copper-catalysed C-C coupling reactions have recently been developed for difluoromethylation of arenes. Amii and co-workers prepared aryldifluoroacetates by the reaction between aryl iodides **4-41a-f** and α-silyldifluoroacetates, catalysed by copper iodide. Upon hydrolysis in the presence of K_2CO_3 in methanol, the carboxylic acids underwent decarboxylation in the presence of potassium fluoride to yield the desired difluorinated arenes **4-43a-f** in three steps

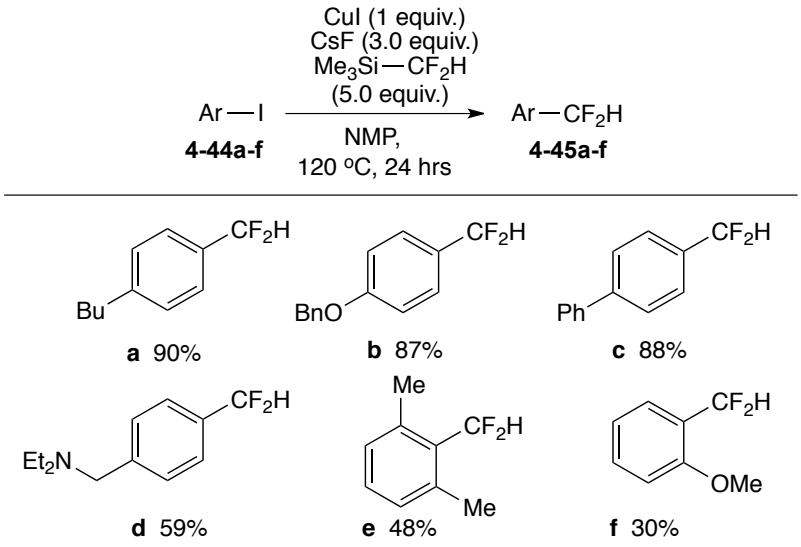
(Scheme 4.19).[307] This approach is limited to the use of electron-poor arenes, as electron-rich arenes were not compatible with the decarboxylation step.



Scheme 4.19. Cu-catalysed difluoromethylation of aryl iodides using α-silyldifluoroacetates.

Hartwig and co-workers modified the protocol reported by Amii and co-workers, and developed a one-step approach for the copper-catalysed difluoromethylation of aryl iodides using trimethylsilyl difluoromethane.[308] In the presence of 5 equivalents of trimethylsilyl difluoromethane and 3 equivalents of caesium fluoride, to activate the C-Si bond, electron-neutral, electron-rich and sterically hindered aryl iodides **4-44a-f** were converted to the corresponding difluoromethylated products **4-45a-f** (Scheme 4.20). It has been proposed that the reaction between aryl halides and Cu(I) catalysts may proceed *via* a radical pathway or through Cu(III) intermediates. The difluoromethylation reaction was carried out on 1-(allyloxy)-2-iodobenzene to probe whether the potential aryl radical undergoes a 5-exo-trig cyclisation. However, 3-methyl-2,3-dihydrobenzofuran was not observed, suggesting a radical mechanism is not occuring. An interesting feature of this protocol, is that the difluoromethylation of electron-poor arenes was not very efficient and instead afforded the corresponding arene as the major product. Hartwig and co-workers carried out preliminary studies into how the proton was introduced, but no conclusive assessments could be made for the formation of the arene. It was suggested that there are two separate pathways

operating for the formation of the desired difluoromethylated product arene, with the latter being faster for electron-poor aryl iodides.



4.20. Copper-catalysed difluoromethylation using trimethylsilyl difluoromethane.

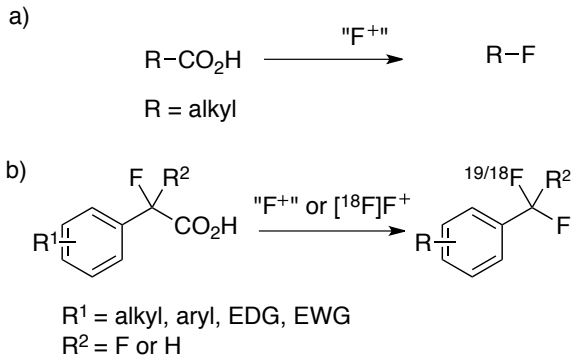
Similarly to transition metal-mediated trifluoromethylation protocols, these strategies require long reaction times and may not amenable to late-stage introduction of the fluorine-18 labelled prosthetic group. To the best of our knowledge the preparation of difluoromethylated compounds have not previously been investigated under radiochemical reaction conditions. It would therefore be of high value to investigate alternative approaches for the late-stage introduction of the [^{18}F]CF_2H moiety.

4.2.6 Fluorodecarboxylation as an Alternative Strategy

With a view to designing a new late stage approach for the preparation of [^{18}F]trifluormethylated compounds, it is clear that there are advantages and disadvantaged to both strategies presented in the previous section. Most efforts in the area of trifluoromethylation have focused on the installation of the trifluoromethyl group using trifluoromethylating reagents (C-CF_3 bond formation) as there is a multitude of ways of achieving this. However, from a radiochemical standpoint the label would be introduced at an early stage of the synthetic sequence and many of these protocols require long reaction times (up to 48 hrs). In comparison, the alternative strategy relying on a CF_2-F bond disconnection has been significantly less developed, due to the low reactivity of leaving groups in difluorinated precursors and

the resulting harsh reaction conditions. Despite these limitations, this strategy offers the huge advantage of late stage introduction of the fluorine-18 isotope.

A 'Hunsdiecker-like" radical fluorodecarboxylation reaction would be a very interesting alternative approach as a means of late-stage construction of aryl-CF_3 groups *via* C-F bond formation. Traditionally, this strategy has only been employed for the preparation of aliphatic fluorides. The outline of the reaction is: decarboxylation of the carboxylatic acid precursor in the presence of a reactive electrophilic fluorinating reagent to form the corresponding alkyl radical, which subsequently undergoes fluorination *via* a radical mechanism to install the C-F bond. (Scheme 4.21a). As a result it was decided to investigate an analogous reaction using α,α-difluoro arylacetic acids as substrates in the presence of an electrophilic fluorine source for the preparation of trifluoro- and difluoromethylated compounds (Scheme 4.21b).

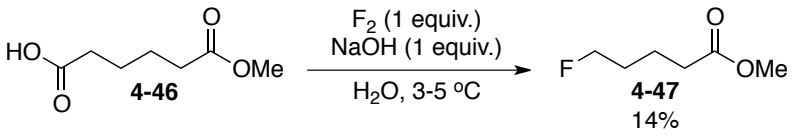


Scheme 4.21. Outline of fluorodecarboxylation strategies.

4.2.6.1 Fluorodecarboxylation for the preparation of aliphatic C-F bonds

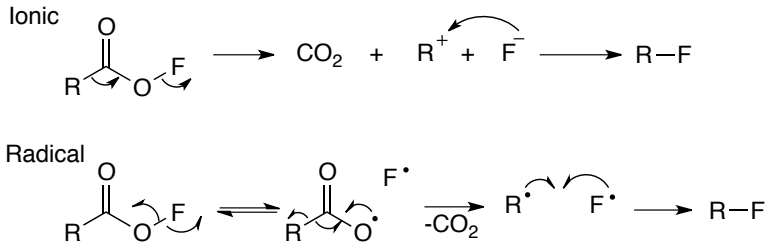
Fluorodecarboxylation strategies, for the fluorination of aliphatic carboxylic acid, have been extensively explored using a range of electrophilic fluorinating reagents. Reactions employing highly reactive reagents, such as F_2 and XeF_2, suffer from side-product formation and limited substrate scope.

A study was published in 1969 detailing the fluorination of alkaline carboxylic acid salts in aqueous solution using F_2 (Scheme 4.22).[309]



Scheme 4.22. Fluorodecarboxylation using F_2.

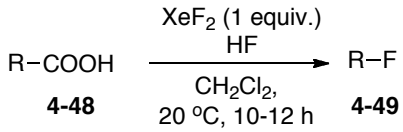
Aliphatic carboxylic acids of different lengths were investigated, but recovery of the starting material was observed in combination with various fluorinated side-products. The best result was obtained in the fluorodecarboxylation of 6-methoxy-6-oxohexanoic acid **4-46** in the presence of 1 equivalent of F_2 and sodium hydroxide in water allowed for the formation of the fluorinated product **4-47** in 14% yield. The reaction was postulated to proceed *via* an acyl fluoride intermediate. As the reaction was carried out in a polar solvent, the intermediate was suggested to undergo decarboxylation by an ionic pathway. However, a "Hunsdiecker-like" radical mechanism may also proceed (Scheme 4.23.).[310]



Scheme 4.23. Mechanism for 'Hunsdiecker-like" fluorodecarboxylation using F_2.

Conversely, 4-nitrobenzene carboxylic acid sufficiently electron-poor to inhibit direct unselective fluorination, but the desired fluorodecarboxylation product, 1-fluoro-4-nitrobenzene, was only observed in 4% yield.[309]

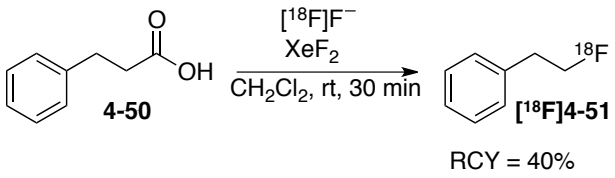
Xenon difluoride in the presence of hydrogen fluoride was found to be more selective for the carboxylic acid functionality and afforded a wide range of aliphatic fluorides in good yields (Scheme 4.24).[311],[312],[313] Both aliphatic and benzyl fluorides **4-49** could be selectively obtained in yields ranging from 54 to 84%.



R	Yield
$PhCH_2$	76
$PhCH_2CH_2$	76
$PhCH_2CH_2CH_2$	60
Ph_3C	65
$PhOCH_2$	64
$2,4\text{-}Cl_2PhOCH_2$	84
$CH_3(CH_2)_{14}$	62
$CH_3(CH_2)_8$	54

Scheme 4.24. Fluorodecarboxylation using XeF_2.

Pleasingly, the protocol could also be extended to radiochemistry (Scheme 4.25). 3-phenylpropanoic acid **4-50** was successfully radiolabelled in the presence XeF_2 and [^{18}F]fluoride within 30 minutes at room temperature. 1-[^{18}F]fluoro-3-phenylethane **[^{18}F]-4-51** was obtained in a RCY of 40%. It is possible that the presence of 'cold' XeF_2 reduced the specific activity of the product by undergoing isotopic exchange with [^{18}F]fluoride to generate ^{19}F-Xe-^{18}F. However, Patrick and co-workers carried out a test reaction by studying the reaction between XeF_2 and [^{18}F]fluoride in the absence of a substrate, and the XeF_2 obtained upon recovery did not contain any radioactivity. However, as previously described (Chapter 1, Scheme 1.25), a nucleophilic exchange reaction of this nature has been used for the preparation of [^{18}F]XeF_2 and hence the possibility of isotopic exchange can not be eliminated.



Scheme 4.25. [^{18}F]Fluorodecarboxylation using XeF_2.

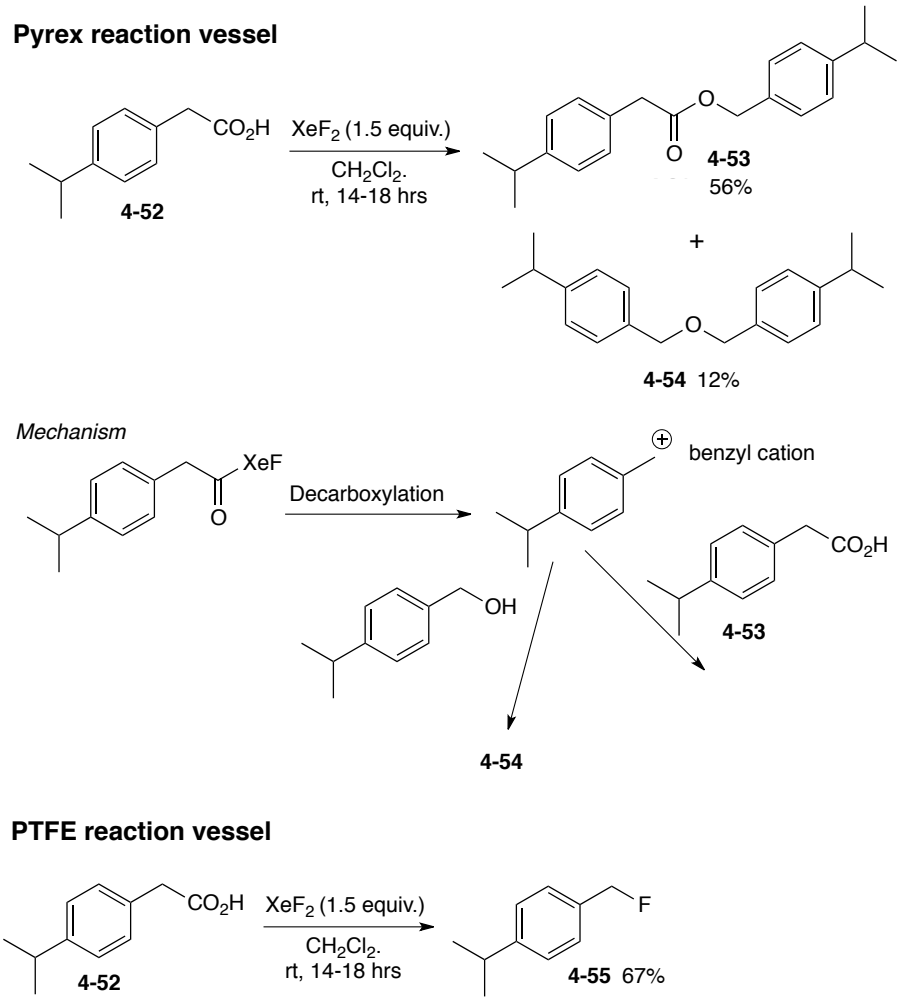
Recently, Ramsden and co-workers carried out a comprehensive study comparing the reaction between XeF_2 and carboxylic acids in either Pyrex or PTFE reaction vessels.[314] In the presence of XeF_2 in a Pyrex reaction vessel, 4-isopropylbenzoic acid **4-52** was converted to a mixture of ester **4-53** and ether **4-54**. 4-isopropylbenzyl

fluoride **4-55** was not observed. It was postulated that Pyrex, which may act as a Lewis acid, polarises XeF_2 and induces the reagent to react in an electrophilic manner. This suggests that the reaction between the carboxylic acid and XeF_2 yields the corresponding xenon ester. This species may then undergo decarboxylation to afford the intermediate benzylic cation, which reacts with either 4-isopropylbenzoic acid or alcohol to yield the observed products (Scheme 4.26).

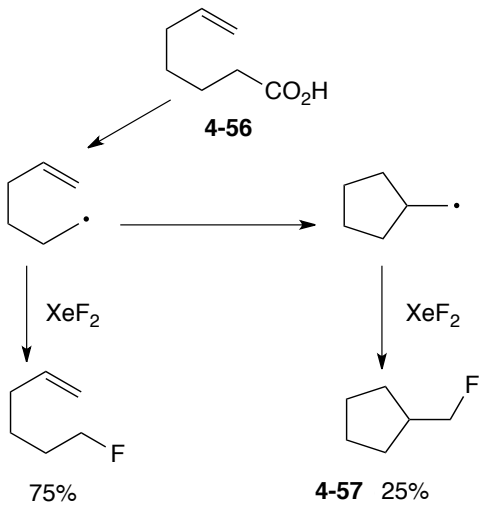
Conversely, in a PTFE reaction vessel, i.e. XeF_2 is not polarised, the same reaction afforded 4-isopropylbenzyl fluoride **4-55** in 67% yield, which does not suggest a cationic mechanism (Scheme 4.26). This would suggest a radical mechanism is under operation, which was also proposed by Patrick and co-workers.[312]

A control experiment was carried out by reacting XeF_2 with 6-heptenoic acid **4-56**, which would allow a radical intermediate to be trapped by intracyclisation.[315] The formation of fluoromethylcyclopentane **4-57** in 25% yield offers evidence for a radical mechanism (Scheme 4.27).

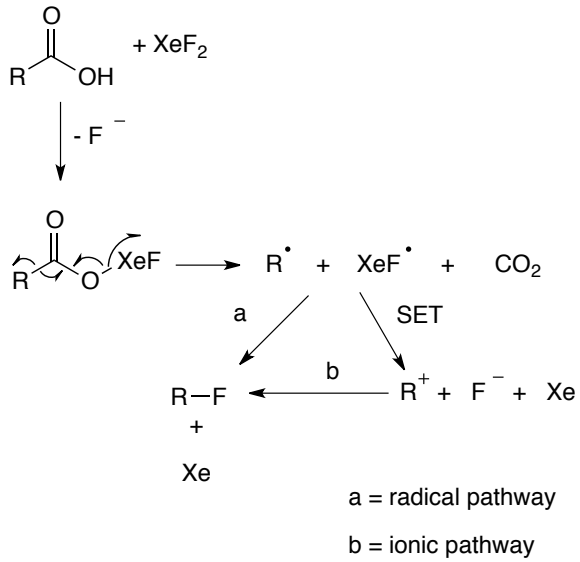
In the proposed mechanism, XeF_2 reacts with the carboxylic acid starting material to form the corresponding xenon ester. Following rapid decarboxylation, the alkyl radical may undergo direct reaction with the XeF radical to afford the alkyl fluoride (pathway a) or it may undergo a SET and form the product *via* an ionic pathway (pathway b) (Scheme 4.28).[314] Patrick and co-workers reacted XeF_2 with substrates able to form free radicals but not cations and found that only radical dimerisation occurred.[313] This indicates that pathway b) is favoured for the fluorodecarboxylation reaction.



Scheme 4.26. Difference in reaction outcome by using XeF_2 in Pyrex or PTFE.



Scheme 4.27. Evidence for a radical mechanism.



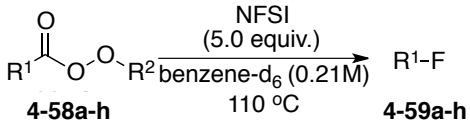
Scheme 4.28. Proposed mechanism for fluorodecarboxylation with XeF_2.

The toxicity and handing concerns associated with F_2 and XeF_2 prompted research into alternative reagents for fluorodecarboxylation reactions. Sammis and co-workers found that the more selective reagents NFSI and Selectfluor^{TM} were suitable alternatives for the radical fluorodecarboxylation of *tert*-butyl peresters.[316],[317]

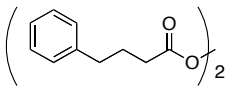
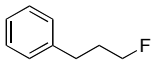
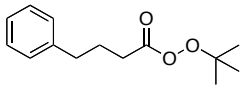
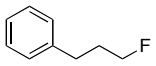
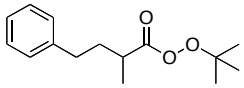
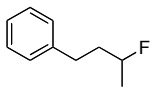
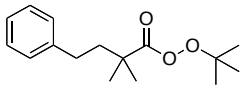
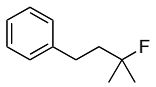
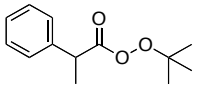
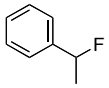
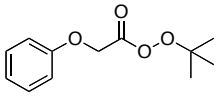
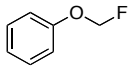
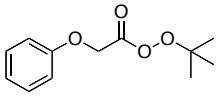
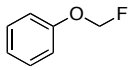
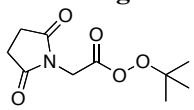
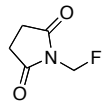
Sammis and co-workers showed that NFSI acts as a fluorine transfer reagent for the fluorination of alkyl radicals. At 110 ^{o}C, a wide range of *tert*-butyl peresters underwent thermolysis and subsequent decarboxylation, to afford the corresponding alkyl radical and fluorinated by NFSI present in excess (Table 4.6). In the case of primary alkyl radicals, **4-58a** and **4-58b**, long reaction times were required and the yield of the desired products **4-59a** and **4-59b** were only obtained in 24% yield, in each case. Stabilised secondary and tertiary radicals were more amenable to fluorodecarboxylation and **4-59c-e** could be afforded in good to excellent yields within 20 minutes. Pleasingly, the heteroaromatic *tert*-butyl perersters **4-58f-h** successfully underwent fluorodecarboxylation in the presence of NFSI within 10 minutes and the products **4-59f-h** were afforded in yields superior to 50%. The reaction times observed in this study, would make this process amenable to radiochemistry. However, the simultaneous formation of highly reactive *tert*-butoxy radicals is undesirable.[316]

Two potential mechanistic pathways are possible: 1) the fluorine may be transferred from NFSI to the radical in a concerted fashion or; 2) there is a transfer of one electron

from the radical to NFSI (SET), followed by fluorine transfer to the generated alkyl cation.



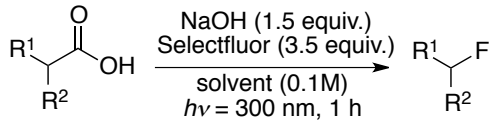
4-58a-h **4-59a-h**

Entry	Substrate	Product	Time	Yield (%)
1	 **4-58a**	 **4-59a**	16 hrs	24
2	 **4-58b**	 **4-59b**	12 hrs	24
3	 **4-58c**	 **4-59c**	19 min	98
4	 **4-58d**	 **4-59d**	15 min	98
5	 **4-58e**	 **4-59e**	6 min	45
6	 **4-58f**	 **4-59f**	4 min	44
7	 **4-58g**	 **4-59g**	6 min	57[a]
8	 **4-58h**	 **4-59h**	10 min	57

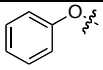
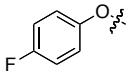
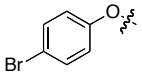
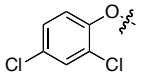
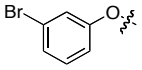
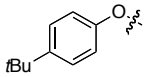
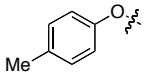
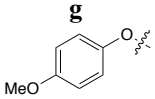
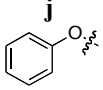
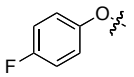
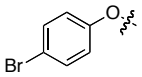
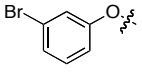
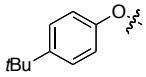
[a] Solvent: MeCN-d_3 (0.1 M).

Table 4.6. Fluorodecarboxylation using NFSI.

A complementary photochemical approach employing Selectfluor™ has also been developed for the fluorodecarboxylation of α-aryloxycarboxylic acids **4-60a-o**, avoiding the need for peresters (Table 4.7).[317]



4-60a-h **4-61a-h**

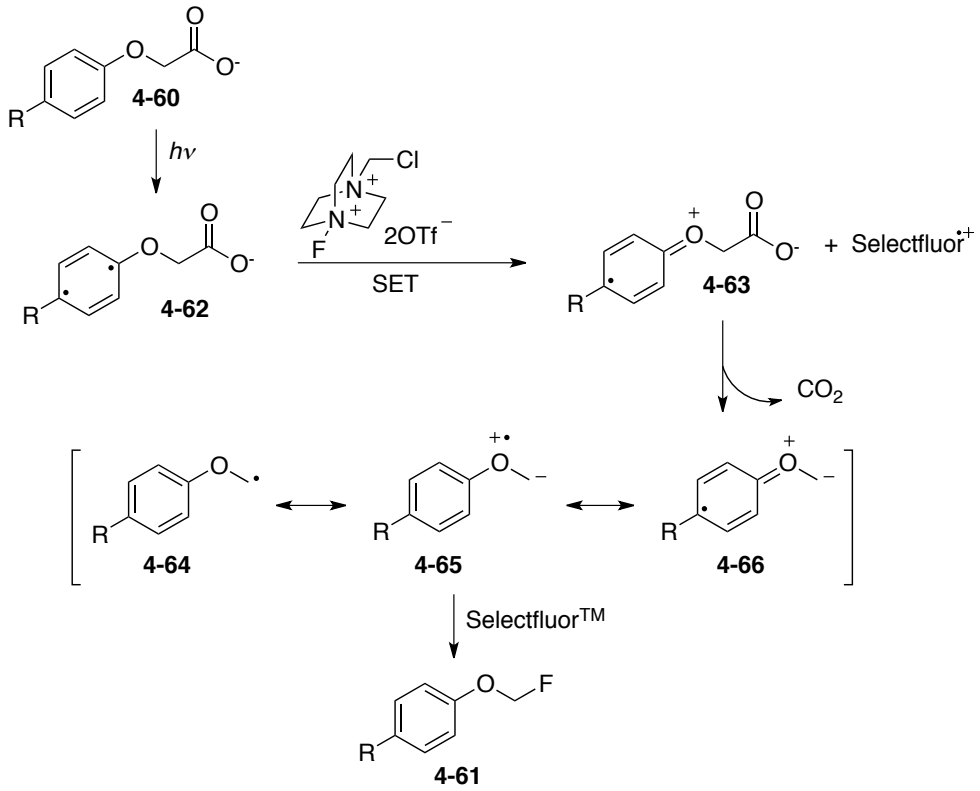
Entry	R^1	R^2	Solvent	Yield (%)
1	 **a**	H	H_2O	46
2	 **b**	H	H_2O	60
3	 **c**	H	H_2O	60
4	 **d**	H	MeCN/H_2O (1:2)	76
5	 **e**	H	H_2O	57
6	 **f**	H	MeCN/H_2O (1:2)	83
7	 **g**	H	H_2O	34[a]
8	 **h**	H	H_2O	78
9	 **i**	OAc	MeCN/H_2O (1:2)	68
10	 **j**	H	H_2O	72
11	 **k**	F	H_2O	25
12	 **l**	F	H_2O	44
13	 **m**	F	H_2O	64
14	 **n**	F	H_2O	44
15	 **o**	F	MeCN/H_2O (1:2)	77

[a] Yield determined by ^{1}H NMR.

Table 4.7. Synthesis of mono- and difluoromethyl ethers.

A range of electron-poor and electron-rich precursors **4-60a-j** underwent fluorodecarboxylation in the presence of Selectfluor, sodium hydroxide and a UV light within 1 hour to afford the corresponding fluorinated products **4-61a-j** in 34-83% yield (Table 4.7, Entries 1-10). Compounds that were insoluble in water were dissolved in a mixture of acetonitrile and H_2O. Difluoromethyl ethers **4-60k-o** could also be accessed under the same reaction conditions, and the tranformation was successful with both electron-poor and electron-rich arenes (Table 4.7, Entries 11-15). This transition-metal-free photo-fluorodecarboxylation reaction represents the first selective and direct formation of C-F bonds under photochemical conditions.

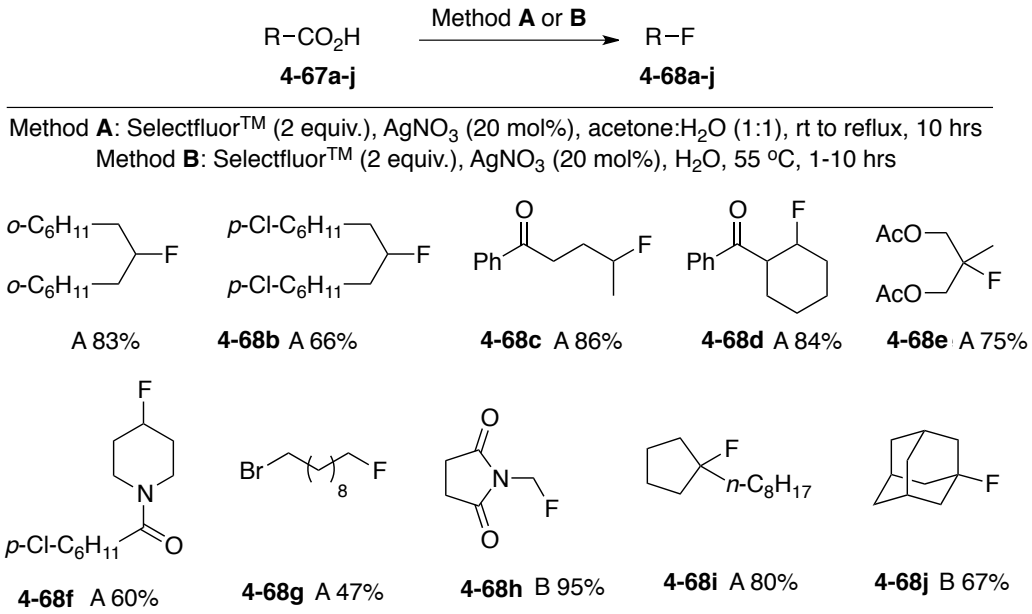
Upon irradiation the benzene nucleus in the starting material **4-60** was excited (π to π^*) generating the benzenoid nucleus **4-62** by homolytic cleavage of a double bond. This species is postulated to be a better electron-donor than **4-60**. The subsequent SET between Selecfluor and **4-60** affords oxidised radical cation species **4-63**, which is stabilised by the benzylic oxygen atom. Intermediate **4-63** rapidly undergoes decarboxylation and the resulting charged radical species can exist as three resonance forms **4-64, 4-65** and **4-66**. The fluorination of either of these species with Selectfluor^{TM}, independent of the major resonance contributor, may proceed *via* a radical pathway, relying on homolytic cleavage of the N-F bond and radical recombination to form the fluorinated product, or nucleophilic attack by the anion on Selectfluor^{TM} to generate the fluorinated product **4-61** (Scheme 4.29).[317], [101]



Scheme 4.29. Mechanism for formation of C-F bonds under photochemical conditions.

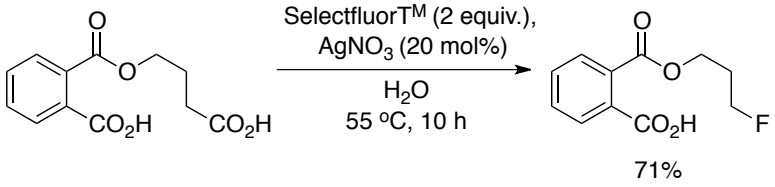
Li and co-workers have made further contributions to the field of selective fluorodecarboxylation reactions. In the presence of Selectfluor and $AgNO_3$ as a catalyst, a wide range of aliphatic secondary, secondary and tertiary carboxylic acids **4-67a-j** underwent fluorodecarboxylation in aqueous media to afford aliphatic fluorides **4-68a-j** in 47-95% yield (Scheme 4.30).[318]

During the optimisation studies Selectfluor was found to be a superior source of electrophilic fluorine compared to NFSI. The reactions were carried out in a 1:1 mixture of acetone:H_2O, but if the starting carboxylic acid was soluble, the reaction could also be carried out in H_2O alone. The wide substrate scope, mild reaction conditions and often short reaction time makes this fluorodecarboxylation reaction a potential protocol for the use in radiochemistry with [^{18}F]Selectfluor *bis*(triflate). For this fluorodecarboxylation reaction, a mechanism proceeding *via* Ag(III)-mediated SET followed by fluorine transfer was proposed (further discussed in Section 4.3.5).



Scheme 4.30. Preparation of aliphatic fluorides *via* fluorodecarboxylation.

It was also established by Li and co-workers, that the reactivity of the carboxylic acids follow the trend: tertiary > secondary > primary >> aromatic. This may be showcased by the rate constant for the decarboxylation of carboxyl radicals by β-cleavage. The rate constant for decarboxylation of an alkylradical was found to be extremely rapid ~10^9 s^{-1} compared to that of an arylcarboxylate radical (~10^5 s^{-1}).[319] It was also postulated that the decarboxylation, to afford the aryl radical, does not proceed under these reaction conditions. This allows for chemoselective fluorodecarboxylation in compounds containing both aryl and alkyl carboxylic acids (Scheme 4.31).[318]



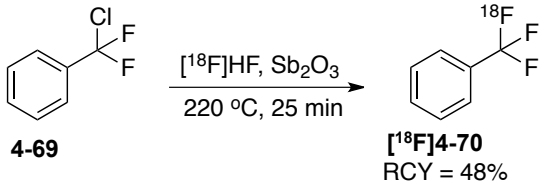
Scheme 4.31. Chemoselective fluorodecarboxylation.

4.2.7 Methods for the preparation of [^{18}F]CF_3-labelled compounds

Similarly to 'cold' trifluoromethylation approaches, two general strategies are available for [^{18}F]trifluoromethylation. Very few approaches for the preparation of [^{18}F]labelled trifluoromethyl moieties have been reported in the literature, due to the difficulties associated with nucleophilic substitution at α-fluorinated substrates

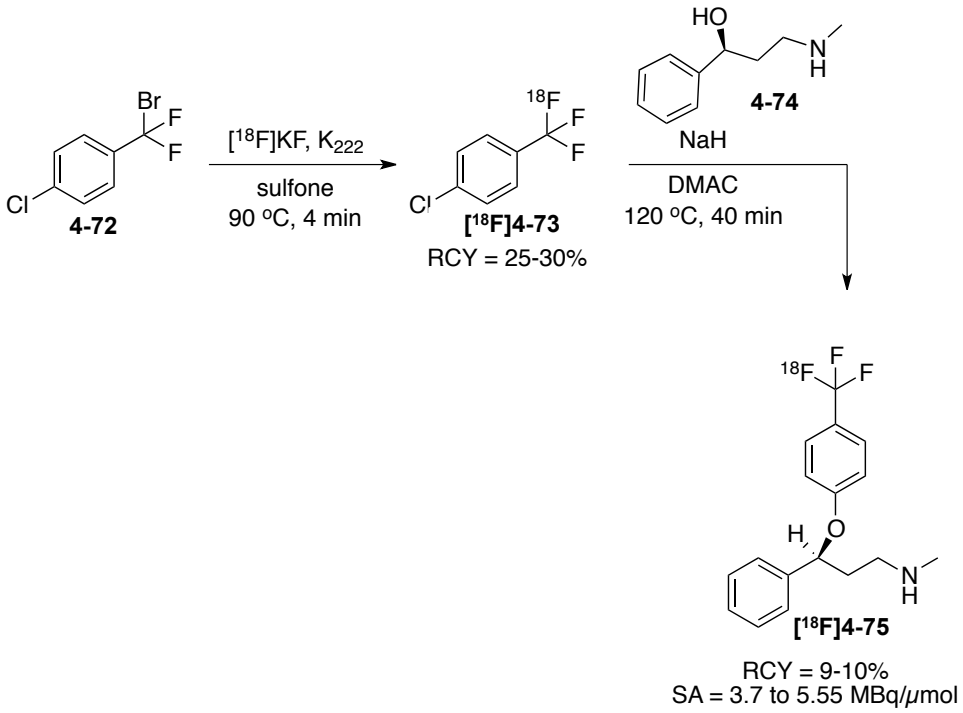
(Section 4.2.3). The level of specific activity obtainable in these transformations is also a concern. In the case of nucleophilic strategies, often requiring forcing reaction conditions, the SA may be compromised due to the potential for concomitant $^{19}F/^{18}F$ exchange reactions (isotopic exchange). When employing electrophilic fluorination, the SA will depend on the amount of carrier F_2 added in the preparation of $[^{18}F]F_2$.

An early example of exchange of chloride with [^{18}F]fluoride was reported in 1986. α-Chloro-α,α-difluorobenzene **4-69** underwent radiolabelling to afford α,α,α-tri[^{18}F]fluorotoluene **[^{18}F]4-70** in 48% yield in the presence of [^{18}F]HF and Sb_2O_3 upon heating at 220 ^{o}C for 25 minutes (Scheme 4.32).[320] No details were provided regarding the SA of this reaction. The reaction conditions required for the successful fluorination were extremely forcing and would limit the reaction scope significantly. Furthermore, it proved challenging to identify the exact nature of the active fluorine species present during the reaction.



Scheme 4.32. Trifluoromethylation with [^{18}F]HF and Sb_2O_3.

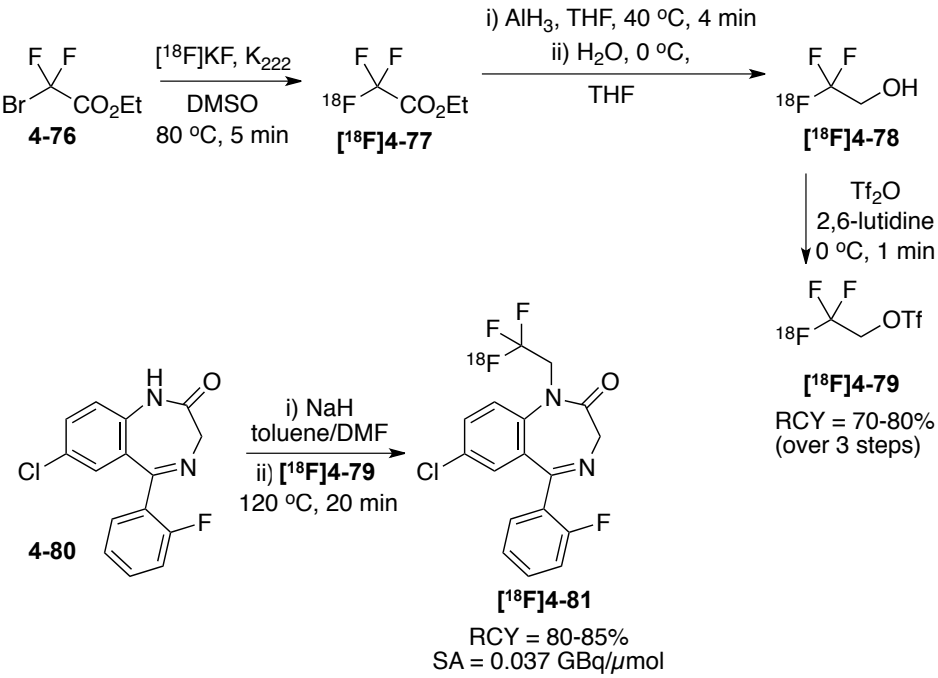
The [^{18}F]fluorination of CF_2Br-moieties have also been explored in the preparation of complex targets, under milder reaction conditions. [^{18}F]-(*S*)-Fluoxetine **[^{18}F]4-75** was prepared by nucleophilic aliphatic substitution in two steps (Scheme 4.33).[321]



Scheme 4.33. Preparation of [^{18}F]-(*S*)-fluoxetine.

α-Bromo-α,α-difluoro-4-toluene **4-72** underwent the desired substitution reaction in the presence of [^{18}F]fluoride to afford [^{18}F]-4-chlorobenzotrifluoride **[^{18}F]4-73**, which was subsequently coupled with **4-74** under basic conditions to afford [^{18}F]-(*S*)-fluoxetine, **[^{18}F]4-75** in 9-10% RCY over two steps. The specific activity obtained under these reaction conditions was very low at 3.7 to 5.55 MBq/μmol, suggesting that isotopic exchange did occur.

Johnström and co-workers developed 2,2,2-[^{18}F]trifluoroethyl triflate **[^{18}F]4-79** as a [^{18}F]trifluoroethyl prosthetic group that could be coupled with compounds of interest through alkylation (Scheme 4.34).[322]

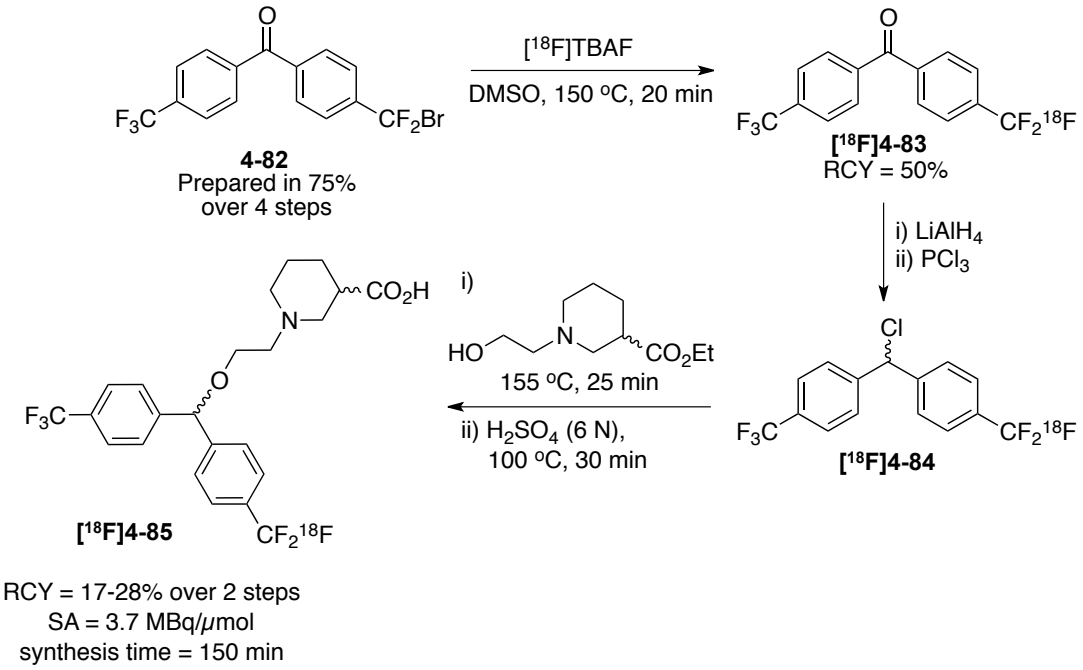


Scheme 4.34. Synthesis and reactivity of 2,2,2-[^{18}F]trifluoroethyl triflate.[322]

Compound **[^{18}F]4-79** was prepared in three steps. Ethyl 2-bromo-2,2-fluoroacetate **4-76** was radiolabelled by [^{18}F]fluoride in DMSO at 80 °C in 5 minutes and the resulting ester **[^{18}F]4-77** was reduced and hydrolysed by AlH_3 and H_2O, respectively. The final protection step afforded 2,2,2-[^{18}F]trifluoroethyl triflate **[^{18}F]4-79** in 70-80% RCY over three steps after protection of the alcohol with triflic anhydride under basic conditions.

The reactivity of **[^{18}F]4-79** was investigated in the *N*-alkylation of 2-oxo-quazepam **4-80** (Scheme 4.34). The precursor **4-80** was deprotonated by NaH and the labelled prosthetic group **[^{18}F]4-79** was added. Heating at 120 °C for 20 minutes afforded the desired labelled compound **[^{18}F]4-81** in 80-85% RCY. Similarly to other nucleophilic aliphatic substitutions, the SA obtained was very low (0.037 GBq/μmol) due to isotopic exchange.

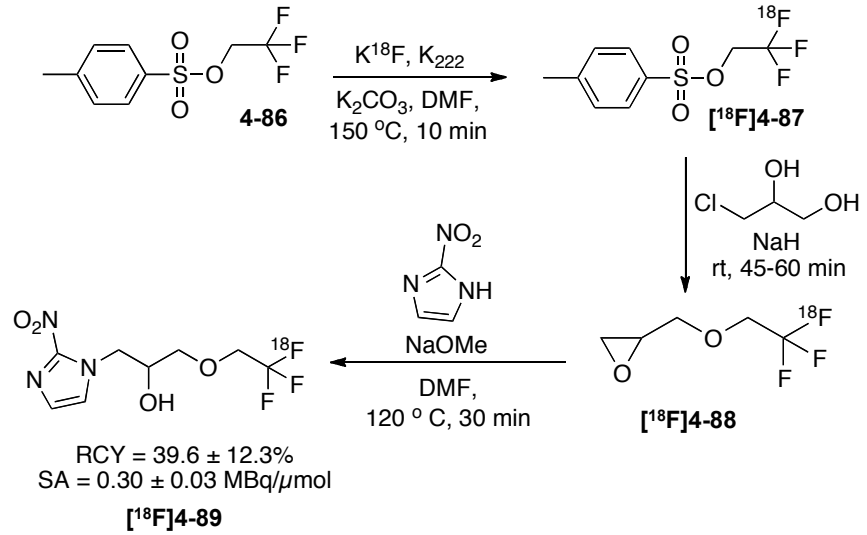
Kilbourn and co-workers investigated the preparation of a [^{18}F]labelled GABA reuptake inhibitor **[^{18}F]4-85** using [^{18}F]fluoride in a halogen exchange reaction (Scheme 4.35).[323]



Scheme 4.35. [^{18}F]Radiolabelling of a GABA reuptake inhibitor.[323]

The precursor **4-82** underwent halogen S_N2 substitution with [^{18}F]TBAF to afford the trifluoromethylated intermediate **[^{18}F]4-83**. Following reduction and chlorination, the resulting intermediate **[^{18}F]4-84** was coupled with *N*-(2-hydroxyethyl)-piperidine-3-carboxylate to obtain the final [^{18}F]radiolabelled imaging agent **[^{18}F]4-85** in RCYs ranging from 17-28% yield. The specific activity obtained was still low (3.7MBq/μmol).

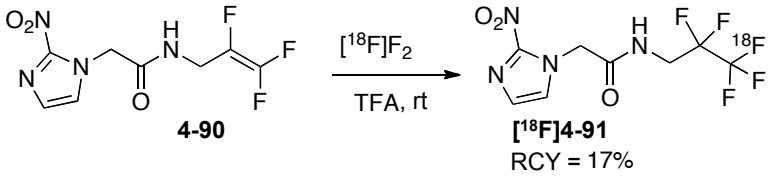
An alternative hypoxia marker, [^{18}F]TFMISO **[^{18}F]4-89** could be obtained *via* isotopic exchange (Scheme 4.36). The tosyl protected *O*-trifluoroethyl precursor **4-85** was radiolabelled by isotopic exchange and subsequently coupled with 3-chloro-1,2-propanediol to form intermediate **[^{18}F]4-87**. Final opening of the cyclopropyl group by 2-nitroimadazole in the presence of sodium methoxide afforded the desired radiotracer **[^{18}F]4-89** in 39.6 ± 12.3% RCY and a SA of 0.3 MBq/μmol.[324] This compound is a trifluoromethylated analogue of the well-documented [^{18}F]FMISO imaging agent.[325],[326]



Scheme 4.36. Preparation of [^{18}F]TMISO using isotopic exchange.[324]

The examples described herein showcase the difficulties associated with aliphatic nucleophilic substitution as a strategy for the introduction of ^{18}F. The label is installed at an early stage of multi-step synthetic sequences. The dilution of the radioactive material through isotopic exchange is also a significant side-reaction. Alternative approaches have been explored with the purpose of developing improved radiolabelling methodology and introducing the label at a later stage.

The electrophilic preparation of [^{18}F]EF5 **[^{18}F]4-91**, an imaging agent for hypoxia, could be prepared in one step by directly fluorinating a precursor containing a perfluorinated allyl group **4-90** with [^{18}F]fluorine gas (Scheme 4.37).[27]

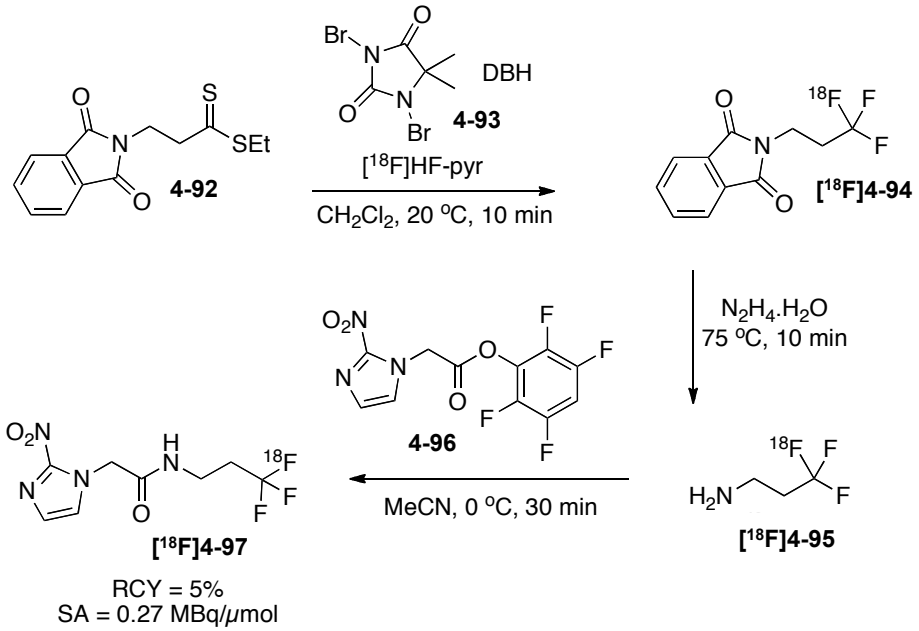


Scheme 4.37. Preparation of [^{18}F]EF5 using [^{18}F]F_2.

The radiolabelled imaging agent **[^{18}F]4-91** was obtained in a RCY of 17%, however the specific activity of the product was not calculated in the original publication.[27] As the [^{18}F]F_2 was prepared using standard ^{20}Ne(d,α)^{18}F nuclear reaction, the SA is expected to be within the range of 3-10 MBq/μmol.[55] [^{18}F]EF5 **[^{18}F]4-91** was recently

produced using high specific activity [^{18}F]F_2 in 2.8 ± 0.6% RCY with an SA of 6.6 ± 1.9 GBq.[51]

An analogous imaging agent, [^{18}F]EF3 **[^{18}F]4-94** could prepared from [^{18}F]fluoride (Scheme 4.38).[327] Marchand-Bryanert and co-workers adapted the 'oxidative desulfurisation-fluorination' protocol reported by Hiyama[328],[329], for the use in radiochemistry. The *ortho*-thioester precursor **4-69** underwent radiolabelling in the presence of [^{18}F]HF pyridine, prepared by the reaction between 'cold' HF pyridine and [^{18}F]KF, and the oxidant 1,3-dibromo-5,5-dimethylhydantoin (DBH) **4-70** at room temperature within 10 minutes. The resulting intermediate **[^{18}F]4-71** was obtained in 5.6% RCY. Subsequent hydrolysis of the phtalamide protecting group by hydrazine released the prosthetic group **[^{18}F]4-72**, which was coupled to the nitro-imidazole precursor **4-73** to afford [^{18}F]EF3 **[^{18}F]4-74** in an overall RCY of 5%.[327] The specific activity obtained for the final product was calculated as 0.27 MBq/µmol. Although this approach avoided the use of carrier-added [^{18}F]F_2, the SA was not improved.

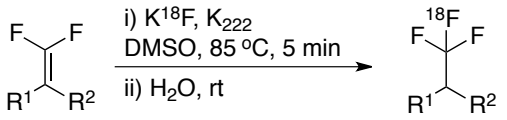


Scheme 4.38. Synthesis of [^{18}F]EF3.

Recent developments by Aigbirhio and co-workers showcased a nucleophilic route to aliphatic [^{18}F]trifluoromethyl groups by the radiolabelling of difluorovinyl-functionalised precursors **4-98a-j** (Scheme 4.39).[330],[331] The substrates **4-98a-j** were easily obtained by either elimination or Wittig-Horner reactions. All precursors were

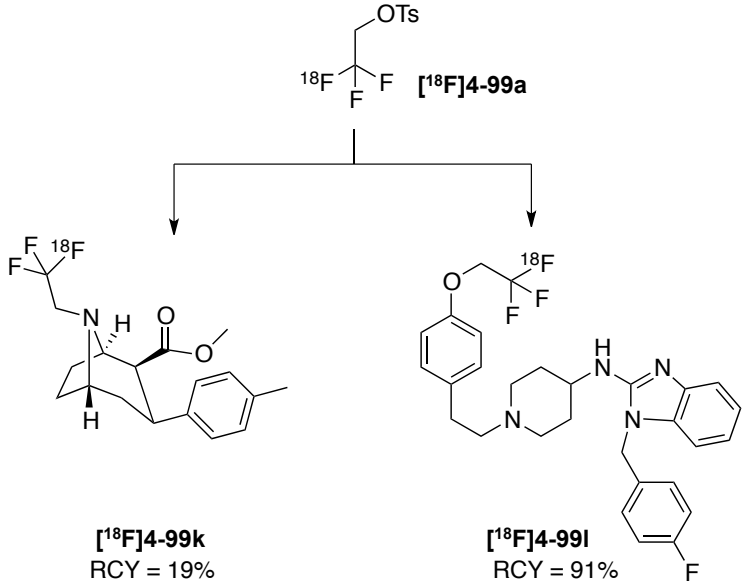
labelled in good RCYs apart from **4-98b**, which was found to be too sterically hindered. Control experiments were carried out to investigate the propensity of [^{18}F]CF_3 to undergo isotopic exchange under the reaction conditions and found to be very unfeasible. The calculated specific activity of 86 GBq/μmol, gave parallel evidence for low amounts of isotopic exchange. The radiolabelling protocol was also extended to the preparation of complex imaging agents. Compound [^{18}F]**4-99k** was afforded in 19% yield, while **[^{18}F]4-99l**, a potential compound for the imaging of Alzheimer's Disease, was obtained in an excellent 91% yield.

The postulated mechanism for this transformation is nucleophilic attack of the [^{18}F]fluoride on the *gem*-difluorinated electrophilic site of the alkene, illustrated by substrate **4-98a** in scheme 4.40. The anionic intermediate **[^{18}F]4-100a**, stabilised by both the [^{18}F]CF_3 moiety and the OTs, is rapidly trapped by traces of water present in the solvent. At low water concentrations (< 5 ppm), an addition-elimination process may occur from intermediate **[^{18}F]4-100a** to form the byproduct **[^{18}F]4-101a**, which may lead to isotopic dilution of the final radioactive product with ^{19}F. However, in the presence of 10 ppm of water, the formation of **[^{18}F]4-101a** could be suppressed.



4-98a-j **[18F]4-99a-j**

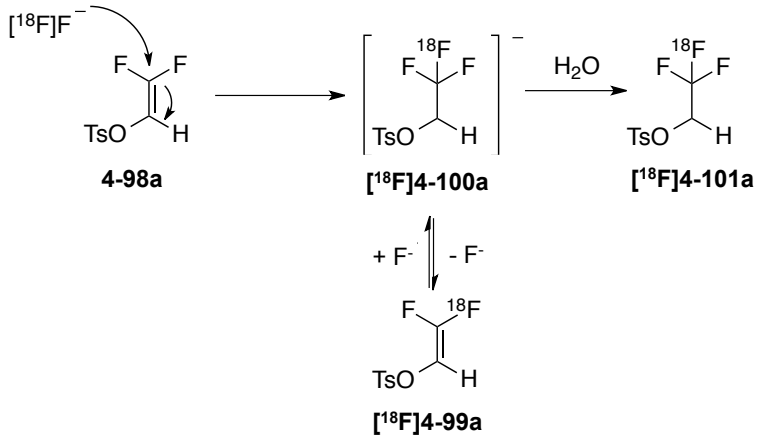
Product	R^1	R^2	RCY (%)
[18F]4-99a	OTs	H	93
[18F]4-99b	OTs	CH_3	52
[18F]4-99c	OBn	H	82
[18F]4-99d	NBn_2	H	79
[18F]4-99e	4-MeOPh	H	69
[18F]4-99f	4-Me_2NPh	H	67
[18F]4-99g	4-O_2NPh	H	89
[18F]4-99h	4-FPh	H	79
[18F]4-99i	$PhCH_2$	H	65
[18F]4-99j	6-$MeOC_{10}H_6$	CH_3	63



[18F]4-99k RCY = 19%

[18F]4-99l RCY = 91%

Scheme 4.39. [18F]trifluoromethylation by [18F]fluorination of 1,1-divinyl precursors.

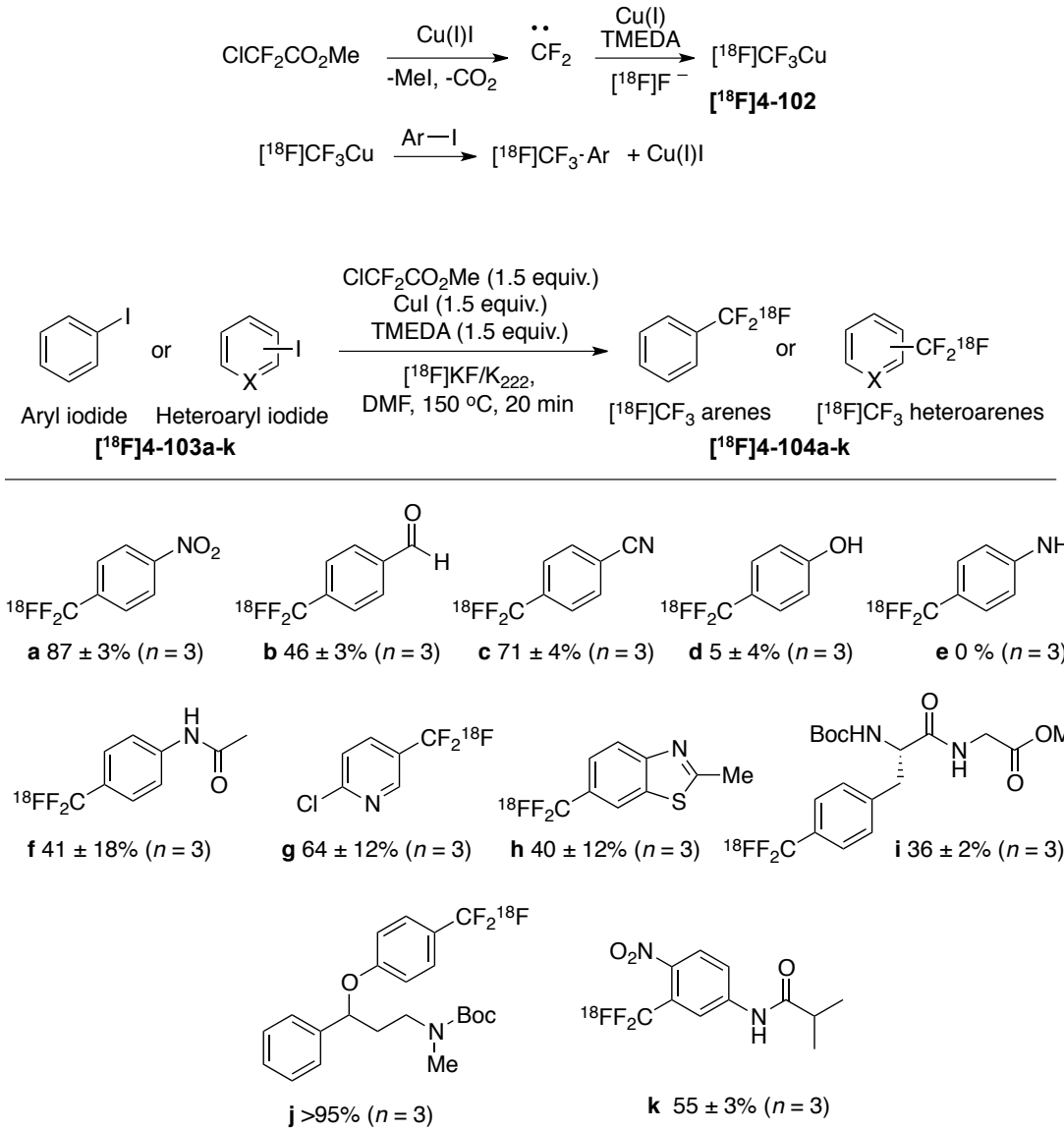


Scheme 4.40. Mechanism for nucleophilic [^{18}F]fluorination of *gem*-difluorinated alkenes.

Based on these strategies, it is evident that the field of [^{18}F]trifluoromethylation is in great need of the development of general approaches for the synthesis of this radiolabelled moiety. Gouverneur, Passchier and co-workers recently reported a strategy for the preparation of [^{18}F]trifluoromethylated arenes and heteroarenes using a [^{18}F]$CuCF_3$ **[^{18}F]4-102** reagent generated *in situ* (Scheme 4.41).[332]

The [^{18}F]$CuCF_3$ reagent was prepared using a multicomponent approach. The key intermediate difluorocarbene was generated by the halide-promoted decarboxylation of methyl chlorodifluoroacetate in the presence of CuI, TMEDA and [^{18}F]fluoride. The carbene reacts with [^{18}F]fluoride to generate the [^{18}F]trifluoromethide "CF_3^-" species which is trapped by the copper catalyst to generate **[^{18}F]4-102**. This reagent may then undergo copper-catalysed cross coupling reactions with aryl and heteraryl iodides.[333] A wide range of arenes and functional groups were tolerated by the reaction conditions, such as esters, amides, cyano and nitro groups.

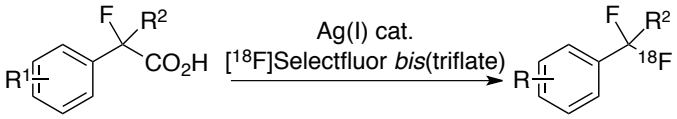
This strategy is a significant improvement towards the general and robust preparation of [^{18}F]trifluoromethylated compounds, but it is not without limitations. The specific activity obtained in this protocol (0.1 GBq/μmol) was relatively low for a nucleophilic [^{18}F]fluorination protocol and the high temperature required may compromise the stability of complex targets.



Scheme 4.41. [^{18}F]Trifluoromethylation of arenes using [^{18}F]CuCF$_3$ [^{18}F]4-102.

4.2.8 Outline of fluorodecarboxylation for the [^{18}F]tri- and [^{18}F]difluoromethylation of arenes

The recent development of a rapid and mild fluorodecarboxylation protocol for the synthesis of aliphatic fluorides using Selectfluor™ by Li and co-workers, could be amenable for transferral to radiochemistry as the preparation of [^{18}F]Selectfluor *bis*(triflate) is known and reliable. It was therefore decided to investigate a silver(I)-catalysed fluorodecarboxylation of α,α-difluoroaryl acetic acids for the preparation of trifluoromethylated arenes and further extend this approach to radiochemistry for the late-stage synthesis of [^{18}F]trifluoromethylated arenes using [^{18}F]Selectfluor *bis*(triflate) and a silver(I)-catalyst. An analogous approach, employing α-fluoroaryl acetic acids, will also be investigated for the preparation of the novel [^{18}F]difluoromethyl motif.



R^1 = alkyl, aryl, EDG, EWG
R^2 = F or H

Outline of the [^{18}F]fluorodecarboxylation strategy.

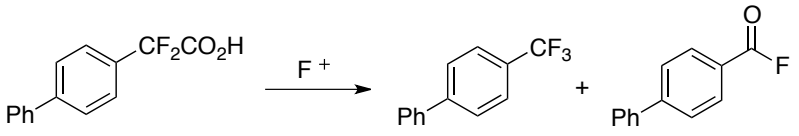
4.3 Results and Discussion

This project was carried out in collaboration with Dr. Satoshi Mizuta, Miriam O'Duill and Dr. Jamie Wolstenhulme.

Preliminary optimisation studies for the fluorodecarboxylation of α,α-difluoroaryl acetic acids were carried out, prior to the investigation of the substrate scope of the reaction and application to the analogous α-fluoroaryl acetic acids to access difluoromethylated arenes. In addition to N-F reagents, the application of F_2 as a source of fluorine will be assessed. With the optimised reaction conditions in hand, the reaction will be studied in a radiochemical setting. The reaction will be studied using both [^{18}F]Selectfluor *bis*(triflate) and [^{18}F]F_2. Finally, the stability of the radical intermediates will be discussed to allow a mechanism for this fluorodecarboxylation to be postulated.

4.3.1 Preliminary optimisation studies

Optimisation of the fluorodecarboxylation reaction conditions with different electrophilic fluorinating reagents and solvents were carried out by M. O'Duill using the electron-neutral biphenyl-4-yl(difluoro)acetic acid **4-105a** (Table 4.8). 1-Fluoro-3-nitrobenzene (-110 ppm) was added as an internal reference standard to determine the yield of 5-(trifluoromethyl)biphenyl **4-106a** by ^{19}F NMR.



4-105a **4-106a** **4-107a**

Entry	Fluorine source[a]	Reaction conditions	Yield 4-105a [%][b]	Yield 4-106a [%][b]
1	**I** (2 equiv)	20 mol% $AgNO_3$ Acetone:H_2O (1:1) 55 ^oC, 1h	> 95	-
2	**II** (2 equiv)	20 mol% $AgNO_3$ Acetone:H_2O (1:1) 55 ^oC, 1h	> 95	-
3	**I** (2 equiv)	Acetone:H_2O (1:1) 55 ^oC, 1h	-	-
4	**III** (2 equiv)	20 mol% $AgNO_3$ Acetone:H_2O (1:1) 60 ^oC, 1h	-	-
5	**III** (5 equiv)	20 mol% $AgNO_3$ MeCN, 100 ^oC, 1h	< 5	30
6	**IV** (1 equiv)	CH_2Cl_2, rt, 30 minutes	23	11

[a] **I** = Selectfluor; **II** Selectfluor *bis*(triflate); **III** *N*-fluorobenzene-sulfonimide (NFSI); **IV** XeF_2. [b] Determined by ^{19}F NMR with 1-fluoro-3-nitrobenzene as internal standard.

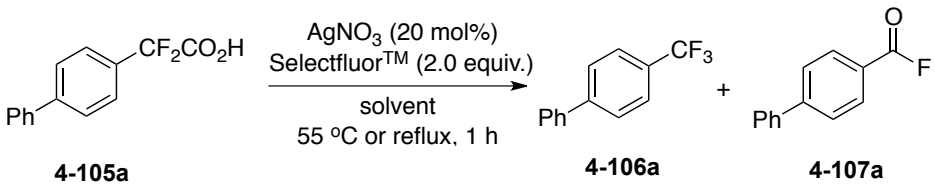
Table 4.8. Optimisation of fluorodecarboxylation of 4-105a.

Pleasingly, upon exposure to 20 mol% of $AgNO_3$ and 2 equivalents of Selectfluor^{TM} in a 1:1 (v/v) mixture of acetone and H_2O under reflux, substrate **4-105a** was trifluoromethylated in > 95% yield (Table 4.8, Entry 1). With the view of extending this methodology to radiochemistry, the alternative reagent Selectfluor *bis*(triflate) was employed and found to be equally successful (Table 4.8, Entry 2). $AgNO_3$ was essential for the reaction to proceed, as the reaction did not occur in its absence (Table 4.8, Entry 3). NFSI failed to provide any trifluoromethylated compound at 60 ^oC, and in the presence of 5 equivalents of NFSI in MeCN at 100 ^oC the undesired acyl fluoride **4-107a** was afforded in 30% yield in addition to a trace amount of **4-106a** (Table 4.8, Entries 4-5). When **4-105a** was treated with XeF_2 in CH_2Cl_2 at room temperature, **4-106a** and the acyl fluoride were provided in 23% and 11%, respectively (Table 4.8, Entry 6).

The formation of acyl fluoride **4-107a** may arise from the addition of water, elimination of hydrogen fluoride and decarboxylation of the carboxylic acid. Patrick and co-workers also observed the formation of the acyl fluoride side-product (at +17.1

ppm in $CDCl_3$) in the fluorodecarboxylation of benzoic acid in the presence of XeF_2, and suggested that its formation involved the decarboxylation of the $PhCO_2XeF$ intermediate. [313]

With the reagent system in hand, a short screening study of appropriate solvents was also carried out on precursor **4-105a** (Table 4.9).



4-105a **4-106a** **4-107a**

Entry	Solvent	Temperature (°C)	Conversion (%)	Yield (%)
1	MeCN	55	-	-
2	MeCN:H_2O (1:1)	55	13	-
3	CH_2Cl_2	reflux	8	-
4	THF	55	< 1	-
5	Acetone	reflux	-	-
6	Acetone:H_2O (1:1)	55	> 99	> 95

Table 4.9. Screening of solvents for the fluorodecarboxylation reaction.

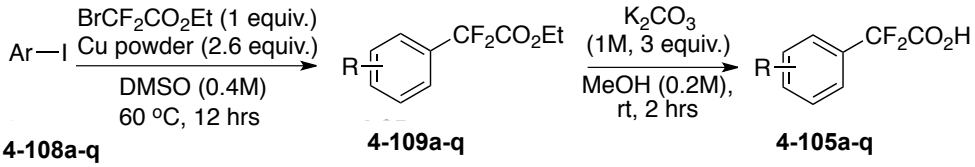
No reaction was observed with MeCN as the solvent (Table 4.9, Entry 1). When water was added, 13% conversion of the starting material to the acyl fluoride **4-107a** was observed but no trifluoromethylated product **4-106a** was formed (Table 4.9, Entry 2). Switching to CH_2Cl_2 or THF did not promote the fluorodecarboxylation reaction, only a small amount of conversion to afford **4-106a** was observed (Table 4.9, Entries 3 and 4). In the case of anhydrous acetone, no reaction occurred (Table 4.9, Entry 5). In contrast, using a 1:1 mixture of acetone and H_2O significantly encouraged the reaction. Over 99% conversion was observed, with the desired product being formed in > 95% yield (Table 4.9, Entry 6). These results corresponded well with Li's observations, as the fluorodecarboxylation of alkyl carboxylic failed in the absence of water. [318] It appears water is essential and likely promotes the reaction by increasing the solvation of $AgNO_3$ and Selectfluor™.

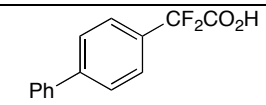
4.3.2 Preparation of α,α-difluoroaryl acetic acids and substrate scope of the reaction

With the optimised reaction conditions in hand, the preparation of a range of α,α-difluoroaryl acetic acids was initiated in order to allow the substrate scope of the fluorodecarboxylation to be assessed on this new class of substrates for trifluoromethylation.

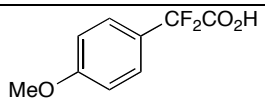
4.3.2.1 Preparation of α,α-difluoroaryl acetic acids

The α,α-difluoroaryl acetic acids **4-105a-q** were prepared upon modification of a literature procedure in two steps, from the corresponding aryl iodide **4-108a-q** and ethyl bromodifluoroacetate in a copper mediated Ullman coupling.[334] The hydrolysis of the ethyl esters **4-109a-q** to the corresponding acids **4-105a-q** was achieved in the presence of an excess amount of aqueous K_2CO_3 in methanol at room temperature. A wide range of arenes, with both electron-donating and electron-withdrawing substituents, was afforded in good to excellent yields (43-98%) (Table 4.10).

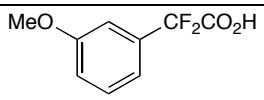




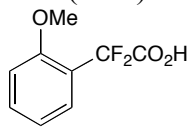
4-105a (79%)[a] 85%



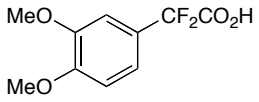
4-105b (37%)[a] 79%



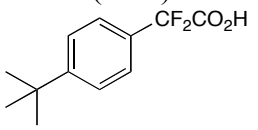
4-105c (78%)[a] 55%[b]



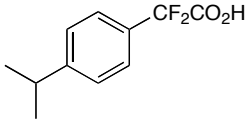
4-105d (66%)[a] 98%[b]



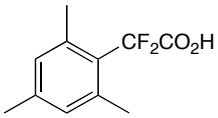
4-105e (63%)[a] 80%[b]



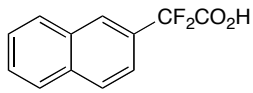
4-105f (47%)[a] 66%[b]



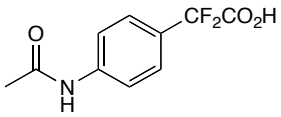
4-105g (44%)[a] 75%[b]



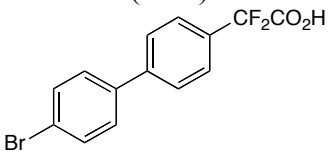
4-105h (65%)[a] 40%[b]



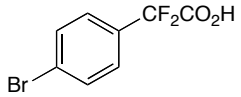
4-105i (34%)[a] 68%[b]



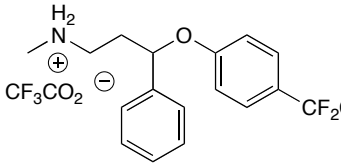
4-105j (86%)[a] 48%



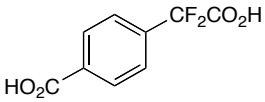
4-105k (54%)[a] 68%



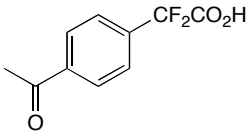
4-105l (31%)[a] 76%[b]



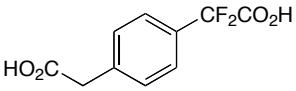
4-105m (77%)[a] 94%[c]



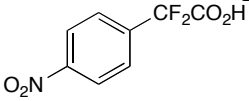
4-105n (59%)[a] 74%



4-105p (92%)[a] 53%



4-105o (37%)[a] 43%



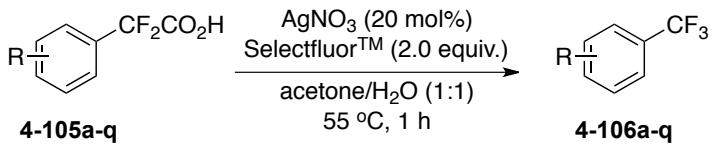
4-105q (66%)[a] 87%

[a] Yield of the ethyl esters in parenthesis. [b]Prepared by M. O'Duill. [c]Prepared by Dr. S. Mizuta.

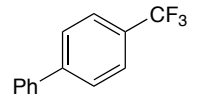
Table 4.10. Preparation of α,α-difluoroaryl acetic acids.

4.3.2.2 Optimisation and scope of the fluorodecarboxylation reaction using Selectfluor™

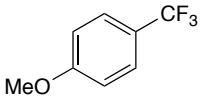
The scope of the fluorodecarboxylation reaction was subsequently investigated using 2 equivalents of Selectfluor™ and 20 mol% of silver(I) nitrate in a 1:1 mixture of acetone and water at 55 °C for 1 hour (Table 4.11). The fluorodecarboxylation of α,α-difluoroaryl acetic acids **4-105c-i** and **4-105l-n** was carried out by M. O'Duill.



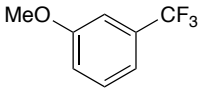
4-105a-q **4-106a-q**



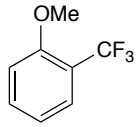
4-106a 85% (86%)[a]



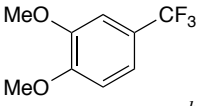
4-106b 82%



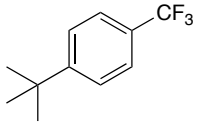
4-106c 86% (85%)[a]



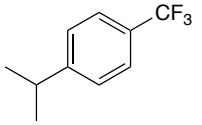
4-106d 88%



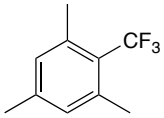
4-106e 0%[b]



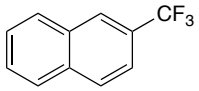
4-106f 77%



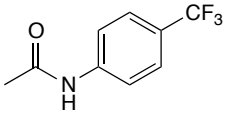
4-106g 66%



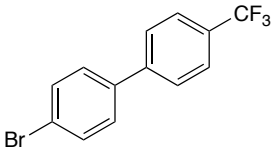
4-106h 56% (>90%)[c]



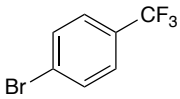
4-106i 51%



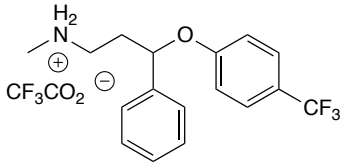
4-106j 86%



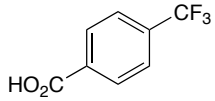
4-106k 83%



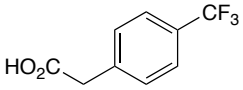
4-106l 33% (49%)[a]



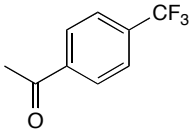
4-106m 59%



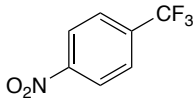
4-106n 49%[e,f]



4-106o 17%[e,g]



4-106p 21%



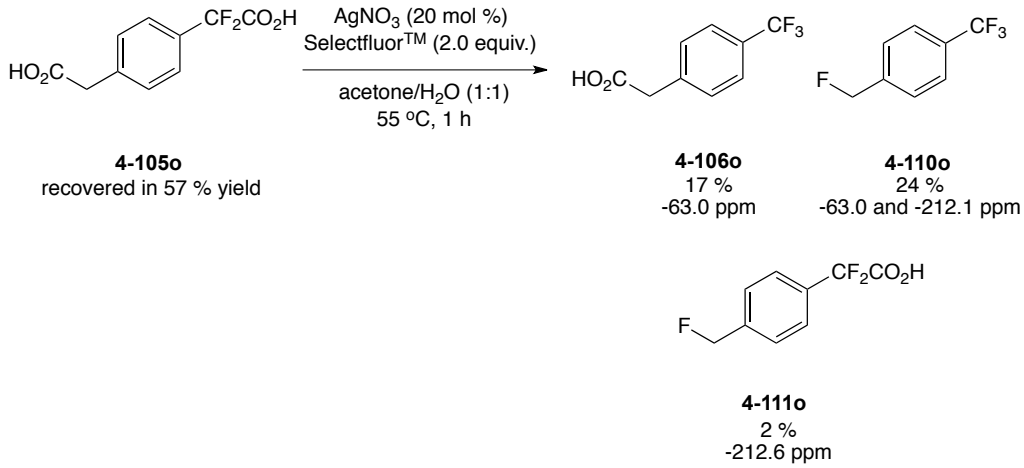
4-106q 0%

[a] Yield in parenthesis for the reaction performed on a 2.0 mmol scale. [b] Complex reaction mixture. [c] ^{19}F NMR yield using 1-fluoro-3-nitrobenzene as internal reference is given in parenthesis. [d] Yield in parenthesis for the reaction performed with 4.0 equiv of Selectfluor in acetone/H_2O 4:1. [e] ^{19}F NMR yield using 1-fluoro-3-nitrobenzene as internal reference. [f] No fluorination at the aryl carboxylic acid. [g] ^{19}F NMR of the crude product mixture revealed **4-105o** (57%), **4-106o** (17%), **4-110o** resulting from double fluorodecarboxylation (24%) and **4-111o** resulting from fluorination at the non fluorinated benzylic position (2%).

Table 4.11. Substrate scope of the fluorodecarboxylation reaction.

Fluorodecarboxylation of **4-105a** afforded the desired trifluoromethylated product **4-106a** in 85 % yield. The methoxysubstituted compounds **4-105b-d**, afforded the desired products **4-106b-d** in yields superior to 80 %. When the scale of the fluorodecarboxylation reaction of **4-105a** and **4-105c** were increased from 0.2 to 2.0 mmol, no erosion of the yields was observed. The veratrole substrate **4-105e** did not allow the reaction to proceed, conversely affording a complex reaction mixture. This suggested that highly electron-rich arenes are unsuitable due to competitive unselective

fluorination on the aromatic ring. A wide range of different functional groups were found to be tolerated under the reaction conditions, including ether **4-105b-e** alkyl **4-105f-h**, amide **4-105j**, halide **4-105k-l** and ketone **4-105p**, affording the corresponding trifluoromethylated products in varying yields. Increasing the steric bulk by double *ortho*-substitution with methyl groups still allowed the fluorodecarboxylation of **4-105h** in 56% yield. The yield of the *para*-bromo substituted arene could be improved from 33% to 49% upon the addition of 4 equivalents of Selectfluor in a 4:1 mixture of acetone and H_2O. Fluoxetine, a selective serotonin reuptake inhibitor, is one of the best selling antidepressants on the market, and following the reaction using the *N*-Boc protected precursor **4-105m**, the desired product was obtained in 59% yield as the TFA salt by final deprotection with trifluoroacetic acid. The selective trifluoromethylation of **4-105n** showcased that the aryl carboxylic acid was inert under the reaction conditions. The fluorodecarboxylation of **4-105o**, containing two benzylic carboxylic acid groups, led to a mixture of products. The starting material was recovered in 57% yield, while 17% of the desired product **4-106o** was obtained. The products **4-110o** and **4-111o** formed as a result of double decarboxylation and fluorodecarboxylation at the nonfluorinated benzylic position were formed in 24% and 2%, respectively (Scheme 4.42). Figure 4.9 shows the product distribution in the ^{19}F NMR spectrum. The product peaks from left to right are: trifluoromethylated product **4-106o** formed by fluorodecarboxylation at the *gem-difluorinated* benzylic position at -63.2 ppm, starting material **4-105o** at -105.0 ppm, 1-fluoro-3-nitrobenzene -110.2 ppm (internal reference standard, 1 equivalent), product formed by double fluorodecarboxylation **4-110o** -63.4 and -212.0 ppm and mono-fluorinated product **4-111o** by fluorodecarboxylation at the non-fluorinated benzylic position at -213.5 ppm.



4-105o
recovered in 57 % yield

4-106o
17 %
-63.0 ppm

4-110o
24 %
-63.0 and -212.1 ppm

4-111o
2 %
-212.6 ppm

Scheme 4.42. Fluorodecarboxylation of 4-105o.

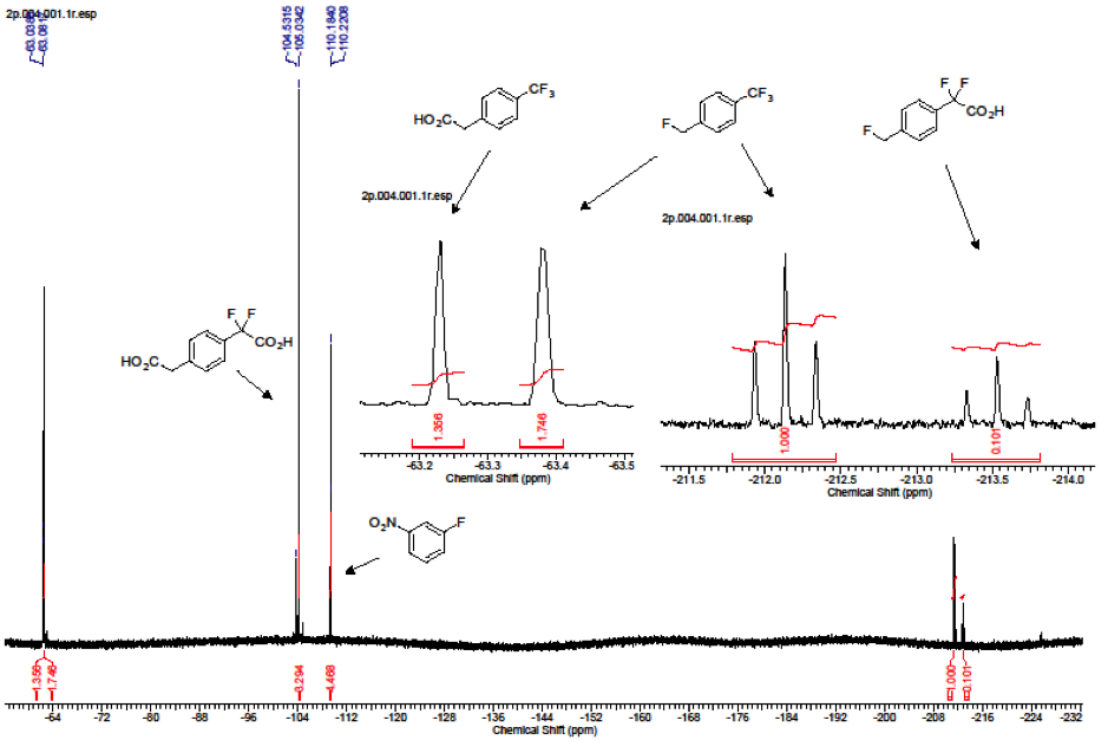


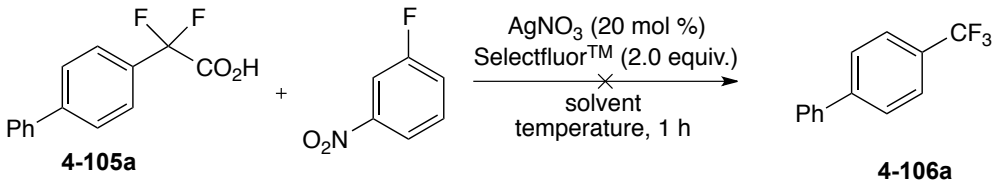
Figure 4.9. ^{19}F NMR spectrum of the fluorodecarboxylation of 4-105o.

The product distribution of **4-106o** and **4-111o** can be explained by the stability of the benzylic radicals formed upon decarboxylation of the corresponding benzylcarboxyl radicals. Pittman and co-workers have studied the *gem*-difluorinated benzyl radical by electron-spin resonance and the calculations showed that this radical adopts an all-planar confirmation, with a predicted out-of-plane rotation barrier of 18 kcal/mol.[335] This indicates that the phenyl group stabilise the benzylic radical similarly to the planar non-fluorinated analogue. Furthermore, the lone pairs on the fluorine atoms

donate π-electrons towards the *gem*-difluorinated benzyl radical, thereby increasing its reactivity in the fluorodecarboxylation reaction.

The success of the fluorodecarboxylation reaction was governed by the electronic properties of the arene and the presence of electron-withdrawing groups significantly reduced the yield of the fluorodecarboxylated products. Recovery of the starting carboxylic acids was observed. This suggests that the energy barrier for decarboxylation to generate the *gem*-difluorinated benzyl radical was too high to overcome under these reaction conditions. The presence of an acetyl group in the *para* position of the arene reduced the yield of **4-106p** to 21% and 4-nitrobenzotrifluoride **4-106q** could not be afforded under these reaction conditions. It is a possibility that the nitro group acted as a radical quencher.

A control reaction was carried out (by M. O'Duill) in the presence of the 1-fluoro-3-nitrobenzene to test whether the ^{19}F NMR internal reference standard could be added to the fluorodecarboxylation reaction mixture or whether the presence of the nitro group inhibited the desired reaction (Scheme 4.43).



Scheme 4.43. Fluorodecarboxylation in the presence of 1-fluoro-3-nitrobenzene.

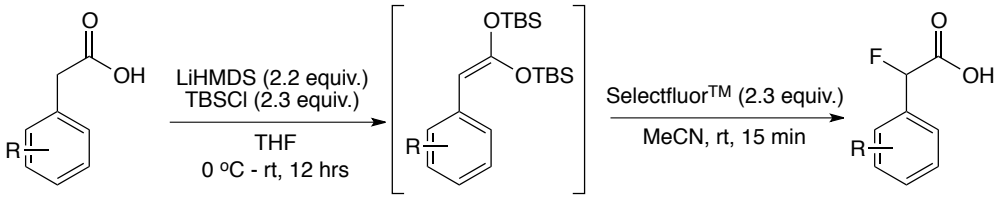
This control experiment confirmed that the decarboxylative fluorination of the model substrate **4-106a** did not proceed when the reaction was performed with the addition of 1 equivalent of 1-fluoro-3-nitro-benzene. This result confirms that the presence of a nitro-group is detrimental to the success of the reaction.

4.3.3 Preparation and fluorination of α-monofluoroaryl acetic acids for the synthesis of difluoromethylated arenes

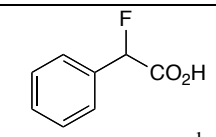
The success of the fluorodecarboxylation for the preparation of trifluoromethyl groups prompted us to investigate the formation of difluoromethylated arenes. Synthetic procedures amenable for the introduction of this motif at a late stage are limited as

explained in section 4.2.4. Therefore it would be highly valuable to access a general route for the preparation of this moiety.

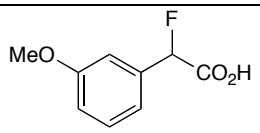
The α-monofluoroaryl acetic acids **4-113a-d** were readily accessed in two steps. The 2-phenylacetic acids **4-112a-d** were converted into the bis-silylketeneacetals in the presence of LiHMDS and TBSCl in THF before undergoing *in situ* fluorination using Selectfluor™ in MeCN at room temperature. All substrates were obtained in excellent yields (Table 4.12).[336]



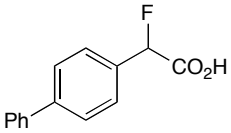
4-112a-d **4-113a-d**



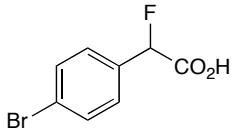
4-113a 84%[a,b]



4-113b 87%[a]



4-113c 80%

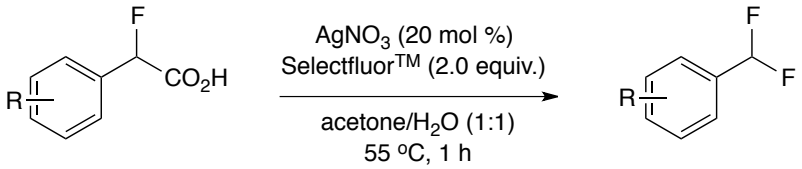


4-113d 82%[a]

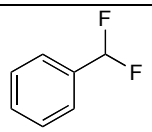
[a]**4-113a-d** prepared by Dr. J. Wolstenhulme.

Table 4.12. Preparation of α-monofluoroaryl acetic acids

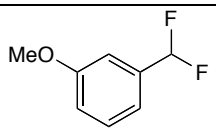
Subjecting the α-monofluoroaryl acetic acids **4-113a-d** to the optimised fluorodecarboxylation conditions afforded the fluoromethylated products **4-114a-d** in yields ranging from 72% to 91%. When comparing the reactivity patterns of **4-113a-d** to those observed for **4-105a,c** and **l**, they were found to correlate well in terms of the scope and limitations of the fluorodecarboxylation reaction (Table 4.13).



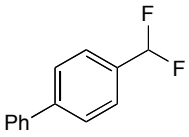
4-113a-d **4-114a-d**



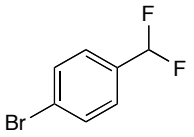
4-114a 72%[a,b]



4-114b 83 %[a]



4-114c 91%



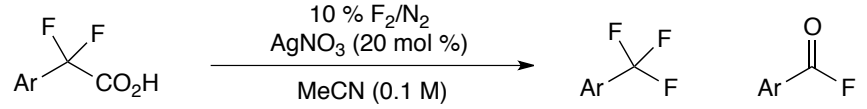
4-114d 82 %[a]

[a]**4-114a-d** prepared by Dr. J. Wolstenhulme. [b19]F NMR yield using 1-fluoro-3-nitrobenzene as internal reference.

Table 4.13. Preparation of difluoromethylated arenes.

4.3.4 Fluorodecarboxylation using fluorine gas

As described in the introduction, F_2 has been successfully employed in fluorodecarboxylation reactions for the synthesis of aliphatic fluorides (Section 4.2.6.1). Therefore, it was decided to investigate its potential in the fluorodecarboxylation of α,α-difluoroaryl acetic acids. It will also be interesting to compare Selectfluor™ and the more reactive F_2 in the fluorodecarboxylation of the same substrates. This study was carried out at Durham University under the supervision of Prof. G. Sandford using the equipment described in section 2.4.3. The results are summarised in table 4.14.



4-105a,b,j,k,q **4-106a,b,j,k,q** **4-107a,b,j,k,q**

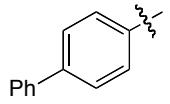
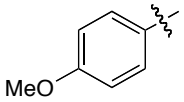
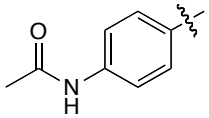
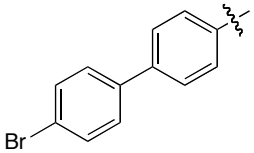
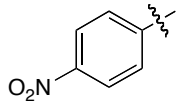
Entry	Substrate	F_2 (equiv.)	Temp (^oC)	Yield of 4-106 (%)[a]	Comments[b]
1	 **4-105a**	3	-35	17	**4-105a** (60 %), multiple peaks
2		3	-10	10	**4-105a** (54 %), multiple peaks
3		5	-35	36	**4-105a** (55 %), multiple peaks
4	 **4-105b**	2	-35	0	**4-105b** (36 %), -126 ppm (20 %), multiple peaks
5[c]		2	-35	0	**4-105b** (45 %), -126 ppm (24 %), multiple peaks
6		2	0	0	**4-105b** (57 %), -126 ppm (25 %), multiple peaks
7	 **4-105j**	2	-35	0	**4-105j** (45 %), -127 ppm (20 %), multiple peaks
8		2	0	0	**4-105j** (65 %), -127 ppm (24 %), multiple peaks
9		5	-35	0	multiple peaks
10	 **4-105k**	3	rt	13	**4-105k** (60 %), multiple peaks
11		6	rt	14	**4-105k** (5 %), multiple peaks
12		6	rt	18	multiple peaks
13	 **4-105q**	2	-35	13	**4-105q** (38 %), **4-107q** (25 %), multiple peaks
14		2	-35	10	**4-105q** (27 %), **4-107q** (23 %), multiple peaks
15		3	-35	10	**4-105q** (55 %), multiple peaks
16		5	-35	15	**4-105q** (14 %), **4-107q** (10 %), multiple peaks
17		3	-10	24	**4-105q** (23 %), multiple peaks
18		3	rt	1	**4-105q** (46 %), **4-107q** (6 %), multiple peaks

Table 4.14. Fluorodecarboxylation using fluorine gas.

The success of the reaction depended on the electronic profile of the substrates. When fluorine gas was bubbled through the reaction vessel containing the electron-neutral biphenyl substrate **4-106a** and 20 mol% of $AgNO_3$ in MeCN at -35 ^oC, 17% of the trifluoromethylated product **4-106a** was obtained. The starting material was recovered in 60% yield, alongside a multitude of different peaks (Table 4.14, Entry 1). Attempts

to increase the yield by carrying out the reaction at the elevated temperature of -10 ^{o}C did not improve the yield (Table 4.14, Entry 2). Increasing the amount of fluorine gas from 3 to 5 equivalents increased the yield to 36% (Table 4.14, Entry 3).

The electron-rich veratrole substrate **4-105b** proved unsuitable for fluorodecarboxylation in the presence of fluorine gas. At -35 ^{o}C and when using 2 equivalents of F_2, the desired trifluoromethylated product **4-106b** did not form. Conversely, fluorination of the aromatic ring was observed in 20% yield together with recovered starting material (36%) (Table 4.14, Entry 4). Diluting the reaction mixture to 0.05 M did not improve the yield (Table 4.14, Entry 5). Performing the reaction at 0 ^{o}C only afforded the product of ring fluorination (25%) and recovered starting material in 57% yield (Table 4.14, Entry 6). In the analogous reaction with Selectfluor^{TM}, unselective fluorination of the aromatic ring was the major reaction pathway, and it is therefore likely side-reaction proceeded in the presence of a more reactive fluorine source.

When the amide **4-105j** was reacted with 2 equivalents of fluorine gas at -35 ^{o}C, no trifluoromethylated product was obtained (Table 4.14, Entry 7). Similarly to the methoxy-substituted compound, **4-105j** was found to be too electron-rich to undergo the desired fluorodecarboxylation reaction in favour of fluorination of the aromatic moiety. Diluting the reaction mixture to 0.05 M or increasing the amount of F_2 to 5 equivalents did not improve the reaction. Only recovered starting material and aromatic fluorides were observed (Table 4.14, Entries 8 and 9).

Pleasingly, the deactivated *para*-bromobiphenyl compound **4-105k** afforded **4-106k** in 13% yield in the presence of 3 equivalents of F_2 at room temperature. No fluorination of the aromatic ring was observed, but the starting material was recovered in 60% yield (Table 4.14, Entry 10). When the amount of F_2 was increased to 6 equivalents, the yield of the reaction was not improved (14%), but analysis of the reaction mixture indicated that decomposition of the starting material occurred (Table 4.14, Entry 11). It was postulated that increasing the amount of $AgNO_3$ to 40 mol%, could promote the fluorodecarboxylation reaction. Unfortunately, mainly decomposition of **4-105k** was observed, together with 18% yield of the desired product (Table 4.14, Entry 12).

In the presence of Selectfluor™, the electron-poor substrate **4-105q** did not undergo fluorodecarboxylation. In contrast, highly reactive F_2 gas allowed the reaction to proceed in 13% yield at -35 °C. The starting material was recovered in 38% and the undesired acyl fluoride **4-107q** was formed in 25 % (Table 4.14, Entry 13). Diluting the reaction mixture had no positive effect on the distribution of products (Table 4.14, Entry 14). Increasing the amount of F_2 to 3 and 5 equivalents did not improve the conversion of the starting material or the yield of the desired product **4-106q** (Table 4.14, Entries 15-16). Pleasingly, increasing the temperature of the reaction to -10 °C increased the yield to 24%, while 23% of the starting material remained. No acyl fluoride **4-107q** was observed in this case (Table 4.14, Entry 17). Increasing the temperature of the reaction mixture to room temperature, reduced the yield of **4-106q** to 1% (Table 4.14, Entry 18).

Highly reactive F_2 is able to promote fluorodecarboxylation to afford trifluoromethylated electron-poor arenes, which are inaccessible or more challenging to afford in the presence of Selectfluor. However, several limitations are associated with the F_2 procedure. The choice of solvent is limited to MeCN as F_2, the best oxidant known, ignites spontaneously when in contact with acetone. The bond dissociation energy of F_2 is 156.9 kJ/mol, which is very low compared to that of C-F bond (536 kJ/mol). The large energy gain in any reaction between F_2 and acetone is therefore likely to be highly exothermic. The formation of gaseous species is also likely under these reactions conditions and would further increase the enthalpy of the reaction. In the optimisation studies, MeCN was found to be inferior to acetone, so this may partially be responsible for the significantly lower yields observed with F_2. Furthermore, in every reaction, mixtures of other fluorinated species were observed in the ^{19}F NMR spectra. It is known that fluorine gas is a highly reactive reagent and it is possible that several minor side-reactions are occurring during the fluorodecarboxylation reaction. Decomposition of the organic material is also a feasible process.

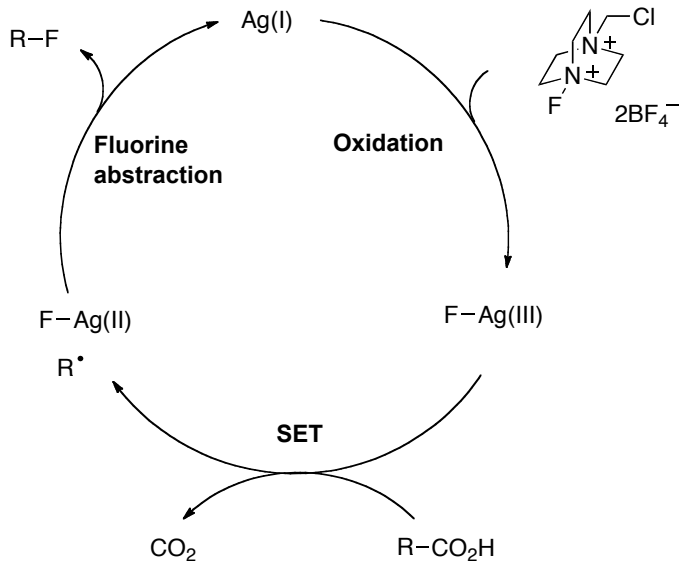
4.3.5 Mechanism of the fluorodecarboxylation reaction

As highlighted in section 4.2.6.1, the distinct radical mechanisms for the reported fluorodecarboxylation reactions with various electrophilic fluorinating reagents have been widely discussed. In the pioneering study carried out by Patrick and co-workers,

it was postulated that nature of the mechanism depended on the structure of the carboxylic acids used. Fluorodecarboxylation of stable tertiary carboxylic acids using XeF_2 were postulated to involve radical intermediates, while primary and secondary substrates relied on a nucleophilic pathway.[311]

Nearly a decade after this report, Patrick and co-workers carried out further studies that disagreed with the previously proposed mechanism. Experimental evidence was found which suggested that the reaction proceeds *via* a radical mechanism for primary, secondary and tertiary carboxylic acids in the presence of XeF_2 (Section 4.2.6.1, scheme 4.28).[313] A recent study by Ramsden and co-workers also proposed a similar radical mechanism based on the successful fluorodecarboxylation of benzyl, alkyl and allyl carboxylic acids with XeF_2.[314]

The mechanism of the Selecfluor-mediated and silver-catalysed fluorodecarboxylation reaction has not yet been fully elucidated, but Li and co-workers carried out several investigations on aliphatic carboxylic acids and suggested a putative radical mechanism involving Ag(II) or Ag(III) intermediates (Scheme 4.44).[318]



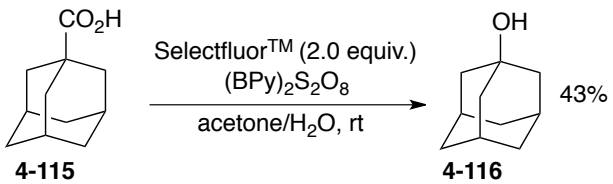
Scheme 4.44. Postulated Mechanism of the Ag-catalysed fluorodecarboxylation.

The first step is thought to involve the oxidation of the silver(I)-catalyst by Selectfluor™ and the formation of a silver(III)-fluoride intermediate. This process is believed to occur by oxidative insertion. This trivalent silver species subsequently

undergoes single electron transfer with a carboxylate anion to afford a divalent silver(II)-fluoride intermediate and a carboxyl radical. The decarboxylation of this radical is fast and affords the corresponding alkyl radical which readily abstracts the fluorine atom from the silver(II) complex to form the desired alkyl fluoride and regenerate the catalyst.[318] This reaction can be considered as an overall SET followed by fluorine atom transfer.

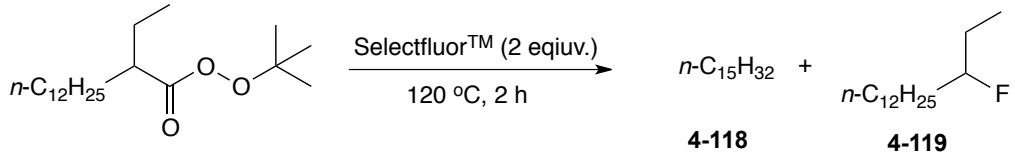
The intermediacy silver(II)- or silver(III) species in decarboxylation of carboxylic acids is well documented.[337],[338] The transfer of a fluorine atom from Ag(II)-F to an alkyl radical is unprecedented, but transition metal-assisted transfer of a chlorine or bromine atom, i.e. trapping of an alkyl radical by a halide complexed to a transition metal in a high transition state is known and affords the metal in a lower oxidation state.[339] An alternative to the fluorine transfer step would be the oxidation of the alkyl radical by the Ag(II)-intermediate to generate the alkyl cation which can be captured by a fluoride anion. Due to the large amount of water in the reaction mixture, solvated fluoride anion is expected to be much less nucleophilic than water, and no alkyl alcohols are observed.

Direct transfer of the fluorine atom from Selectfluor™ to the alkyl radical is another possibility. A set of experiments was carried out to test this hypothesis. Treatment of 1-adamantanecarboxylic acid **4-115** with 2 equivalents of Selectfluor™ and $(BPy)_2S_2O_8$ in a mixture of acetone and water at room temperature afforded the corresponding alcohol **4-116** as the major product (Scheme 4.45). This indicates that the oxidation of the adamantane radical is faster than fluorine transfer from Selectfluor™.



Scheme 4.45. Reaction of 1-adamantanecarboxylic acid with Selectfluor™ and $(BPy)_2S_2O_8$.

A second study, based on the methodology reported by Sammis[317] employing peresters was designed (Scheme 4.46). Upon the thermolysis of *tert*-butyl 2-ethyltetradecaneperoxoate **4-117** in the presence of Selectfluor in dry acetone, 30% of pentadecane **4-118** and 22% of the desired fluorinated product **4-119** was obtained. This suggested that the rate of F abstraction from Selectfluor and the abstraction of a hydrogen atom from the solvent was comparable. In a mixture of water and acetone, the product distribution changed. The pentadecane **4-118** and alkyl fluoride **4-119** was afforded in 26% and 4% yield, respectively. Furthermore, 7% of pentadecanol was observed. Both these experiments indicated that the direct transfer of a fluorine atom from Selectfluor was not very likely under the fluorodecarboxylation reaction conditions.



4-117

	4-118	**4-119**
in acetone:	30%	22%
in acetone/H_2O:	26%	4%

Scheme 4.46. Test reaction for the feasibility of fluorine transfer from Selectfluor.

The α,α-difluorobenzyl radical is a well characterised species stabilised by the presence of the aryl group and π-donation from the fluorine lone pairs and known to adopt a planar geometry, rather than the pyramidal structure often observed for non-fluorinated radicals.[335] The presence of the fluorine atoms suggests the following radical stability trend: *gem*-difluorinated benzyl > benzyl > tertiary alkyl > secondary alkyl > primary alkyl. As a result, it was thought that the proposed mechanism for Li's silver-catalysed fluorocarboxylation of aliphatic carboxylic acids could be extended to the trifluoromethylation reaction reported herein.

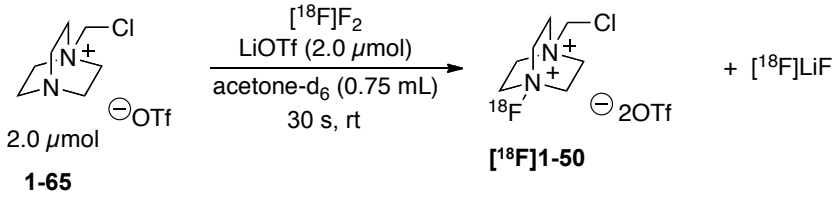
4.3.6 Radiochemistry

4.3.6.1 [^{18}F]Fluorodecarboxylation with [^{18}F]Selectfluor *bis*(triflate)

As a result of the success of these fluorodecarboxylation reactions, and since [^{18}F]Selectfluor *bis*(triflate) has been shown to be a valuble N-^{18}F reagent competent for the [^{18}F]fluorination of a variety of substrates,[70] extension of the methodology to

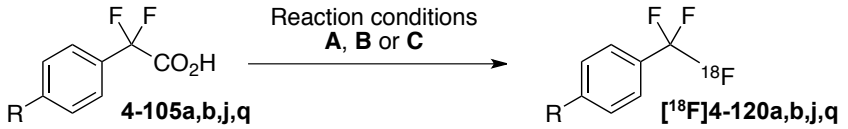
[^{18}F]radiolabelling was investigated. If successful, this strategy would offer an attractive strategy for the installation of fluorine-18 at a late stage in the synthetic protocol of [^{18}F]trifluoro- and [^{18}F]difluoromethylated arenes.

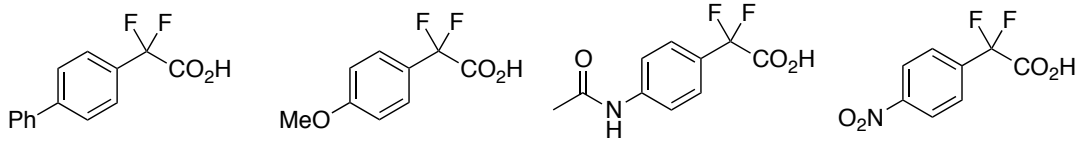
The experiments were carried out at the Turku PET Centre. The [^{18}F]fluoride was prepared using the ^{18}O(p,n)^{18}F nuclear reaction and azeotropically dried using MeCN and Kryptofix$_{222}$ according to the same procedure used in Chapter 2 (Section 2.4.5.1). [^{18}F]Selectfluor *bis*(triflate) was also prepared according to a modified version of the previously reported procedure (Section 2.4.6.1). In the original procedure the Selecfluor precursor **1-65** was labelled with [^{18}F]F_2 at -10 ^{o}C but in this study the reaction was carried out at room temperature (Scheme 4.47).



Scheme 4.47. Preparation of [^{18}F]Selectfluor *bis*(triflate).

The [^{18}F]fluorodecarbxoylation reaction was investigated using 4-biphenyl α,α-difluoroarylacetic acid **4-105a**, 4-methoxy α,α-difluoroarylacetic acid **4-105b**, 4-acetamide α,α-difluoroarylacetic acid **4-105j** and 4-nitro α,α-difluoroarylacetic acid **4-105q** (Table 4.15).





4-105a 4-105b 4-105j 4-105q

Description of reaction conditions	
A	Precursor (20 μmol), $AgNO_3$ (20 mol%), **[^{18}F]1-50** (100 μL), H_2O (100 μL), 55 ^{o}C, 30-60 min.
B	Stock solution of precursor (0.1 μmol) and $AgNO_3$ (20 mol%) in H_2O (0.01 M, 10 μL), **[^{18}F]1-50** (210 μL), 55 ^{o}C, 30 min.
C	Stock solution of precursor (0.1 μmol) and $AgNO_3$ (20 mol%) in H_2O (0.001 M, 100 μL), **[^{18}F]1-50** (210 μL), 55 ^{o}C, 30 min.

Entry	Substrate	Reaction condition	Yield (%)
1	**4-105a**	A	0
2	**4-105b**	A	0
3	**4-105b** [a]	A	0
4	**4-105b** [b]	A	0
5	**4-105b** [c]	A	0
6	**4-105j**	A	0
7	**4-105q**	A	0
8	**4-105a**	B	0
9	**4-105b**	B	0
10	**4-105j**	B	0
11	**4-105q**	B	0
12	**4-105a**	C	9.1 ± 2.4 (n = 3)
13	**4-105b**	C	0.4[d]
14	**4-105j**	C	18 ± 1.5 (n = 3)
15	**4-105q**	C	0
16	**4-105m**	C	0

[a] Solvent = 2.5% water in acetone-d_6. [b] Solvent = 15% water in acetone. [c] Solvent = MeCN. [d] 1.7% of a [^{18}F]radiolabelled side product was observed.

Table 4.15. Fluorodecarboxylation using [^{18}F]Selectfluor *bis*(triflate).

Under the reaction conditions **A**, an aliquot of [^{18}F]Selectfluor *bis*(triflate) (100 μL) was added to a reaction vial containing substrate **4-105a** and silver nitrate and stirred at

55 ^{o}C for 30 or 60 minutes, but the desired radiolabelled product **[^{18}F]4-120a** was not observed (Table 4.15, Entry 1). The electron-rich substrate **4-105b** also failed to undergo [^{18}F]fluorodecarboxylation under the same reaction conditions (Table 4.15, Entry 2). It was attempted to optimise the reaction conditions using **4-105b** (Table 4.15, Entries 3 to 5). Reducing the content of H_2O from 50 to 5 or 30 % did not encourage the reaction to proceed. Changing the solvent from acetone to acetonitrile failed to promote the desired reaction. [^{18}F]fluorodecarboxylation of the acetamide and electron-poor substrates **4-105j** and **4-105q** were also unsuccessful (Table 4.15, Entries 6-7).

In the 'cold' reaction conditions the concentration of the reaction mixture was 0.05 M compared to 5 x 10^{-4} M in the radiochemistry studies. Furthermore, the stoichiometry in reaction conditions **A** follow the standard protocol for radiochemistry with the substrate being present in a large excess compared to the amount of fluorine-18. In the 'cold' reaction 2.0 equivalents of Selectfluor was used. Both of these factors need to be addressed in order to design successful [^{18}F]fluorodecarboxylation reaction conditions.

The reaction conditions were drastically altered as described in **B** (Table 4.15, Entries 8-11). A stock solution was prepared containing the substrate (0.1 μmol) and $AgNO_3$ (0.02 μmol) in H_2O (0.01 M). [^{18}F]Selectfluor *bis*(triflate) (150 μL) in acetone-d_6 was added to 10 μL of the substrate stock in an Eppendorf vial and heated at 55 ^{o}C while the reaction mixture was concentrated under a stream of argon until ~15 μL remained. This increases the concentration of the reaction mixture by one magnitude (0.006 M). When preparing [^{18}F]F_2, a constant amount of F_2 (1 μmol) was added in the electric discharge step and considering that the reaction is normally 60-70% effective, the amount of [^{18}F]Selectfluor *bis*(triflate) was increased to an excess of 0.1 μmol.

Substrates **4-105a**, **4-105b**, **4-105j** and **4-105q** were all investigated using this set of reaction conditions (Table 4.15, Entries 8-11). Disappointingly, no [^{18}F]radiolabelled products were observed. Only [^{18}F]fluoride and peaks corresponding to the starting materials were observed by HPLC. We speculated that the solvent mixture (6% H_2O in acetone) did not contain enough water compared to the 'cold' conditions and since acetone is significantly more volatile than water, the organic phase of the reaction

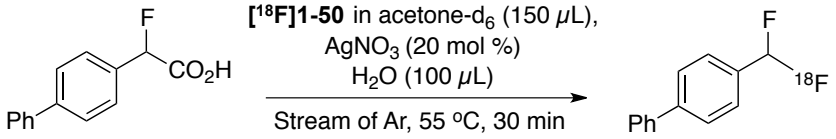
mixture might have evaporated too rapidly. To this end, we made the substrate and $AgNO_3$/wat stock more dilute so that a larger aliquot (100 μL) was added to the labelling reaction.

Pleasingly, under this optimised set of reaction conditions **C**, the [^{18}F]fluorodecarboxylation reaction was successful. The radiolabelled biphenyl product **[^{18}F]4-120a** was obtained in 9.1 ± 2.4% (Table 4.15, Entry 12). Although the reaction proceeded under 'cold' reaction conditions, the radiolabelling of **4-105b** only afforded **[^{18}F]4-120b** in 0.4% yield alongside a [^{18}F]radiolabelled side-product in 1.7% (Table 4.15, Entry 13). The radiolabelled amide-substituted arene **[^{18}F]4-120j** was pleasingly afforded in 18 ± 1.5% (Table 4.15, Entry 14). The radiochemical yield were determined by analytical radio-HPLC integration. The radio-HPLC chromatograms for **[^{18}F]4-120a** and **[^{18}F]4-120j** can be found in the experimental section (Chapter 5). Unsurprisingly, the nitro-substituted substrate **4-105q** failed to undergo [^{18}F]fluorodecarboxylation in accordance with the result observed in the 'cold' reaction (Table 4.15, Entry 15). Attempts to radiolabel the fluoxetine precursor **4-105m** only afforded the desired product **[^{18}F]4-120m** in 1.0% by radio-HPLC in addition to 6 other [^{18}F]radiolabelled side-products (Table 15, Entry 16). It is possible that [^{18}F]Selectfluor *bis*(triflate) **[^{18}F]1-50** unselectively fluorinates the aromatic moieties in the molecule. Further optimisation of the reaction conditions are required to enable the preparation of [^{18}]Fluoxetine **[^{18}F]4-120m**.

[^{18}F]4-120a and **[^{18}F]4-120j** were obtained with specific activities of 3.3 ± 0.20 and 0.3 ± 0.08 GBq/μmol, respectively. The value for **[^{18}F]4-120a** corresponds very well to the values afforded in the 6-[^{18}F]fluoro-L-DOPA study (Chapter 2), indicating that no isotopic exchange occurred during the reaction. In the case of **[^{18}F]4-120j** the value might seem low, but it was due to the inefficient [^{18}F]F_2 synthesis on the day the labelling reaction were performed. As the amount of F_2 added is constant, if the electric discharge reaction with [^{18}F]CH_3F does not work efficiently, the value of the SA will drastically decrease. The specific activities were calculated by collecting the HPLC peak corresponding to the [^{18}F]product and its mass was calculated by comparing the HPLC retention time and peak intensities of the UV peak to the [^{19}F]reference compound obtained using a calibration curve. The specific activities were decay corrected to the E.O.S of [^{18}F]Selectfluor *bis*(triflate).

The next objective of the radiochemical studies was the extension of the [^{18}F]fluorodecarboxylation methodology to the preparation of [^{18}F]difluoromethylated arenes. This functionality is capable of positively augmenting the pharmacokinetic profile of compounds of interest in the agrochemical- and pharmaceutical industry. In contrast to [^{18}F]fluorinated and [^{18}F]trifluoromethylated compounds, this compound has not yet been prepared under radiochemical conditions and if successful would offer a new [^{18}F]radiolabelled motif for the use in PET.

The electron-neutral compound **4-113c** was investigated using the optimised reaction conditions **C** (Scheme 4.48).



4-113c

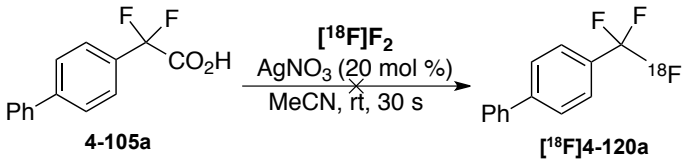
[^{18}F]4-121c
RCY = 8.6 ± 2.6 %
(*n* = 3)
SA = 2.5 ± 0.2 GBq/μmol

Scheme 4.48. [^{18}F]fluorodecarboxylation of 113c with [^{18}F]Selectfluor *bis*(triflate).

Under reaction conditions **C**, [^{18}F]**4-121c** was obtained in 8.6 ± 2.6% RCY and with a SA of 2.5 ± 0.2 Gbq/μmol. To the best of our knowledge, this transformation represents the first example of [^{18}F]radiolabelling of a difluoromethyl group, a novel moiety now available for PET imaging, especially as a tool for drug discovery and development.

4.3.6.2 [^{18}F]Fluorodecarboxylation with [^{18}F]F_2

In the 'cold' optimisation studies it was found that F_2 did allow the fluorodecarboxylation reaction to proceed, albeit in lower yields, due to its high reactivity. It was therefore decided to investigate the radiolabelling of electron-neutral biphenyl substrate **4-105a**. [^{18}F]F_2 was bubbled through a solution of **4-105a** in acetonitrile at room temperature for 30 seconds (Scheme 4.49).



Scheme 4.49. [^{18}F]Fluorodecarboxylation of 4-105a using [^{18}F]F_2.

The radiolabelled compound **[^{18}F]4-120a** was not observed under these reaction conditions. Instead a complex group of radioactive peaks were observed at the retention time corresponding to that of the starting material **4-105a**. This suggests rather than promoting the desired [^{18}F]fluorodecarboxylation reaction, the use of [^{18}F]F_2 lead to unselective [^{18}F]radiolabelling on the aromatic moiety of the starting material.

This transformation illustrates the disadvantage of the use of [^{18}F]F_2, as the high reactivity associated with this reagent can promote unselective reaction pathways over the selective introduction of the radiolabel. Through the use of selective N-^{18}F reagents, such as [^{18}F]Selectfluor *bis*(triflate), a wide variety of compounds may be efficiently accessed *via* electrophilic labelling routes.

4.4 Conclusion

Trifluoromethylated- and difluoromethylated arenes are compounds of high interest in medicinal chemistry and routes for their preparation have been widely explored. Many new potential drug candidates are substituted with these functional groups. The benefit of PET as a tool for drug discovery and development, for the discovery of valuable drugs at an early stage, has only recently begun to be realised. However, the development of general strategies for the late stage introduction of [^{18}F]trifluoromethylated- and [^{18}F]difluoromethylated groups into interesting targets for the use in PET are rare.

It was decided to explore new routes for the preparation of these functional groups under radiochemical conditions. Fluorodecarboxylation reactions for the introduction of a fluorine atom are known in the literature and have recently been explored with the N-F reagents NFSI and Selectfluor. To this end, the fluorodecarboxylation of α,α-tri- and trifluoroarylacetic acids, a novel of class of substrates for this transformation, were investigated in the presence of Selectfluor and silver nitrate.

This strategy afforded tri- and difluoromethylated arenes through late-stage fluorination. A wide range of functional groups was tolerated under the reaction conditions and Selectfluor^{TM} was found to be superior source of electrophilic fluorine compared to F_2. Finally, this strategy could be extended to the preparation of [^{18}F]labelled tri- and difluoromethylated species using [^{18}F]Selectfluor *bis*(triflate) in good radiochemical yields and specific activities. The analogous reaction, employing [^{18}F]F_2, was not successful and showcased the enormous benefit of developing a range of electrophilic [^{18}F]sources with tailored reactivity for the use in radiochemistry.

Chapter 5. Experimental Data

5.1 General Experimental Information

All reactions involving air or moisture-sensitive reagents were carried out under an atmosphere of nitrogen or argon in flame-dried glassware. All compounds used in thi thesis for which a synthetic route does not appear were commercially available. All compounds are racemic mixtures unless otherwise stated. Thin layer chromatograms (TLC, silica gel 60 F_{254} plates) were run and visualised using UV light (254 nm) and/or potassium permanganate stain. Flash column chromatography was performed on Merck silica gel C60 (40-60μm). Celite filtrations were performed using plastic cartridges. NMR spectra were recorded on Bruker DQX400, DPX200, DPX400, AVC500 and AVB500 spectrometers. Proton and carbon-13 NMR spectra are reported as chemical shifts (δ) in parts per million (ppm) relative to the solvent peak of the deuterated solvent using the Bruker internal reference procedure (edlock). Fluorine-19 NMR spectra are referenced relative to $CFCl_3$ in $CDCl_3$. Data were reported as follows: multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, sept =septet, m = multiplet, b = broad, app = apparent, m = multiplet), coupling constant (*J*) in hertz (Hz). Multiplicities are reported as observed in the spectra. Infrared (IR) spectra were recorded on a Bruker Tensor 27 FT-IR spectrometer as the neat compound. Selected characteristic peaks are reported in cm^{-1}. Low-resolution mass spectra were recorded on a Waters LCT Premier XE spectrometer whereas high resolution mass spectra (HRMS, m/z) measurements were run on a Bruker MicroTOF using positive/negative electrospray ionisation. Melting points of solids were measured on a Griffin apparatus and are uncorrected. Optical rotations were recorded on a Perkin Elmer 241 polarimeter in a 1 dm cell. $[\alpha]_D^{25}$ Values are given in $10^{-1}degcm^2g^{-1}$. Elemental analyses were recorded by the elemental analysis service of London Metropolitan University. For novel compounds the following characterisation data is provided: proton NMR spectra (^1H NMR), carbon-13 NMR spectra (^{13}C NMR), infrared spectra (IR) and high resolution mass spectra (HRMS). Fluorine-19 NMR spectra (^{19}F NMR) are also provided for compounds containing this heteroatom. For compounds where full NMR analysis was unsuccessful, elemental analysis was provided. For known compounds, a minimum of two pieces of characterisation data is provided.

5.2 General Experimental Information for F_2 studies

These studies were carried out at Durham University under the supervision of Prof. Graham Sandford.

Elemental fluorine is purchased as a 50% or 20% (v/v) mixture with nitrogen in high pressure cylinders (ca. 50 L). The fluorine is diluted further with nitrogen (10% F_2 in N_2) and transferred into smaller cylinders (3.7 L) with a maximum pressure of 5 bars. The fluorine rig is constructed of stainless steel pipes fitted with Monel® or Swagelok® valves. All tubing, fittings, valves and cylinders, which are used to handle elemental fluorine, are passivated prior to use in fluorination reactions. The flow of fluorine gas was controlled by a Brooks 5850S mass flow controller. PTFE reaction vessels were used in the fluorination reactions. A dewar with mixture of dry ice and acetone was used to perform the reactions at low temperatures. The reaction mixtures were analysed by NMR using either a Bruker Avance 400 MHz or a Varian 200 MHz NMR spectrometer.

5.3 General Experimental Information for Radiochemical Studies

$[^{18}F]F^-$ was obtained in the nuclear reaction $^{18}O(p,n)^{18}F$ by irradiating oxygen-18 enriched water (2.2 mL) with a 17 MeV proton beam of 35 μA produced with a CC-18/9 cyclotron (Efremov Institute of Electrophysical Apparatuses, St Petersburg, Russia). The target irradiation times for the different studies in these studies are summarised in Table 5.1.

Study	Target irradiation time (min)
Chapter 2: Arylstannane	30
Chapter 2: Arylboronic ester	15
Chapter 3	5
Chapter 4	5

Table 5.1. Target irradiation times for the different studies.

At the end of bombardment, the $[^{18}F]F^-$ was solubilised in a carbonate/acetonitrile aqueous solution and transferred into the reaction vessel in the hot cell in the device PET4134.

The subsequent synthesis of $[^{18}F]F_2$ is carried out this automated device designed for this task, which is controlled from a touch screen using RESET ALL, START, PAUSE, CONTINUE and SKIP buttons. Before starting the synthetic procedure automated system is reset from the RESET ALL button. The system allows remote override in the operations.

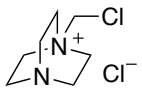
The synthetic procedure of $[^{18}F]F_2$ is started by pressing the START button. Initially the CH_3CN-water ($K_{2.2.2}$) (21-24 mg)/$[^{18}F]F^-$, potassium carbonate (6-7 mg) solution in reaction vessel V1 is evaporated to dryness under reduced pressure and a stream of He with heating unit in about 100 ^oC. After drying for about 4 min CH_3CN (1 mL) is added and the evaporation step repeated twice. The CH_3I-solution (1.0 ± 0.2 mL) is added to the dry cryptate. The resulting solution is then kept at about 100^oC in heating unit for 60-120 sec. The radioactive gases and flushing gas (Ne, 40 ml) are then transferred to a syringe, from which the gas mixture is injected to the GC column. The GC column is eluted with neon at room temperature and the $[^{18}F]$fluoromethane fraction is trapped in a steel loop lowered into liquid nitrogen.

After the trapping of $[^{18}F]$fluoromethane, the steel loop is allowed to warm up for 70 seconds, after which $[^{18}F]$fluoromethane is transferred in to an electrical discharge chamber using neon, containing a known amount of carrier fluorine (~ 1μmol), as a sweep gas. The electrical discharge is then initiated for 10 seconds, after which $[^{18}F]F_2$ is available for the labelling reaction.

5.4 Experimental Data for Chapter 2

5.4.1 Preparation of Selectfluor reagents

1-Chloromethyl-4-aza-1-azoniabicyclo[2.2.2]octane chloride (2-81)

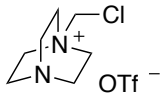


1,4-Diazobicyclo[2.2.2]octane (30.0 g, 267.0 mmol) was dissolved in CH_2Cl_2 (300 mL) and the mixture was stirred at room temperature, under an atmosphere of nitrogen for 48 hours. During this time, white crystals slowly formed. The crystals were filtered and washed with acetone to afford 1-chloromethyl-4-aza-1-

azoniabicylo[2.2.2]-octane chloride (45.9 g crude, 87%), which was used without further purification. The data corresponded to those reported in the literature.[92]

^{1}H NMR (400 MHz, D_2O) δ 5.06 (s, 2H), 3.42 (t, *J* = 7.5 Hz, 6H), 3.14 (t, *J* = 7.5 Hz, 6H); **^{13}C NMR** (101 MHz, D_2O) δ 70.7, 53.7, 46.4.

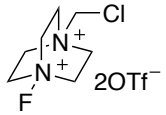
1-Chloromethyl-4-aza-1-azoniabicyclo[2.2.2]octane triflate (1-65)



Lithium trifluoromethanesulfonate (44.9 g, 182.0 mmol, 1.0 equiv.) was added to a solution of 1-chloromethyl-4-aza-1-azoniabicyclo[2.2.2]octane chloride **2-81** (35.9 g, 182.0 mmol) in anhydrous CH_3CN (550 mL) and the resulting solution was stirred at room temperature for 24 hours. The mixture was filtered and the precipitate washed with anhydrous CH_3CN. The combined filtrate and washings were concentrated *in vacuo* to yield the product (48.1 g, 85%) as a white solid. Counterion exchange was measured by addition of fluorobenzene (1.00 eq.) as the internal reference. The data corresponded to those reported in the literature.[92]

^{1}H NMR (400 MHz, CD_3CN) δ 5.02 (s, 2H), 3.39 (t, *J* = 7.5 Hz, 6H), 3.19 (t, *J* = 7.5 Hz, 6H); **^{13}C NMR** (101 MHz, CD_3CN) δ 68.0, 51.3, 45.2; **^{19}F NMR** (CD_3CN, 377 MHz) δ –79.3, -124.9 (from fluorobenzene); **Mp** 127-128 °C, lit. 130 °C.[340]

1-Chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane *bis*(triflate) (Selectfluor *bis*(triflate)) (2-79)

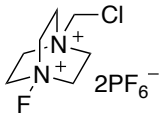


A solution of 1-chloromethyl-4-aza-1-azoniabicyclo[2.2.2]octane triflate **1-57** (2.0 g, 6.4 mmol), lithium triflluoromethanesulfonate (1.0 g, 6.4 mmol, 1.0 equiv.) and anhydrous CH_3CN (25 mL) was placed in a PTFE reactor. The reaction mixture was purged with N_2 and immersed in a cooling bath at –35 °C. Elemental F_2 (10% (v/v) in N_2) was bubbled through the reaction mixture for 100 minutes (1.2 equivalents of F_2). When reaction was complete, the reaction mixture was allowed to warm to room temperature and the system was purged with N_2 for 10 minutes. Lithium fluoride was removed by filtration and the solvent was concentrated under reduced pressure. Purification by recrystallisation (MeOH:Et_2O) afforded the desired product (1.57 g,

51%) as a white solid. Counterion exchange was measured by addition of fluorobenzene (1.0 eq.) as the internal reference. The data corresponded to those reported in the literature.[92]

^{1}H NMR (CD_3CN, 400 MHz), δ 5.38 (s, 2H), 4.82 (t, 6H, J = 7.4 Hz), 4.33 (t, 6H, J = 7.4 Hz); **^{13}C NMR** (CD_3CN, 101 MHz) δ 68.0, 51.3, 45.2; **^{19}F NMR** (377 MHz, CD_3CN, rt) δ –79.3 (3F, $CF_3SO_3^-$), 47.9 (1F, N-F); **LRMS** $(ESI)^+$ *m/z* 329 $[M\text{-}OTf]^+$; **Mp** 162-163 °C, lit. 165 °C.[104]

1-Chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane *bis*(hexafluorophosphate) (Selectfluor(PF_6)) (2-40)

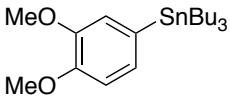


Ammonium hexafluorophosphate (8.79 g, 54 mmol, 6.0 equiv.) was added to a solution of 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane *bis*(tetrafluoroborate) (3.18 g, 9.00 mmol) in H_2O (27 mL). After stirring for 1 h, the suspension was filtered off and washed with H_2O (5 x 5 mL) and Et_2O (30 mL) to afford the desired compound as white solid (4.24 g, > 99%). The data corresponded to those reported in the literature.[108]

^{1}H NMR (400 MHz, CD_3CN) δ 5.27 (s, 2H), 4.70 (dt, J_{HF} = 8.0 Hz, 7.0 Hz, 6H), 4.24 (t, J = 7.0, 6H); **^{13}C NMR** (101 MHz, CD_3CN) δ 70.1, 58.2 (d, J_{CF} = 15.3 Hz), 54.7. **^{19}F NMR** (CD_3CN, 377 MHz) δ 47.6, –72.9 (d, J_{FP} = 710 Hz, 6F). **^{31}P NMR** (CD_3CN, 162 MHz) δ –143.5 (h, J_{FP} = 710 Hz); **Mp** 198-200 °C, lit. 199 °C (decomp.).[104]

5.4.2. Preparation of veratrole substrates

(3,4-Dimethoxyphenyl)tributylstannane (2-53)

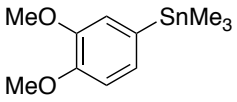


A solution of 4-bromoveratrole (0.48 g, 2.5 mmol) in dioxane (5.25 mL) was placed in a pressure tube and degassed with argon for 10 minutes. Hexabutylditin (1.51 mL, 3.0 mmol, 1.2 equiv.) and tetrakis(triphenylphosphino)palladium(0) (0.13 g, 0.12 mmol, 5 mol%) were added under an inert atmosphere and the tube was sealed under vacuum. The reaction mixture was heated to 105 °C and stirred for 16 hours, before being allowed to cool to room temperature. The reaction mixture was filtered and

concentrated under reduced pressure. Purification by flash column chromatography (5% EtOAc-hexane) afforded the desired product (0.47 g, 44%) as a yellow oil. The data corresponded to those reported in the literature.[341]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15 (td, *J* = 10.0 and 2.0 Hz, 1H), 6.93 (m, 2H), 3.97 (s, 3H), 3.95 (s, 3H), 1.63 (t, *J* = 7.0 Hz, 6H), 1.58 (quin, *J* = 7.1 Hz, 6H), 1.31 (sx, *J* = 7.1 Hz, 6H), 0.90 (t, *J* = 8.0 Hz, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 149.6, 149.5, 141.1, 134.3, 132.4, 122.5, 115.4, 56.1, 28.7, 27.2, 15.9, 13.8;

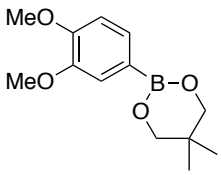
(3,4-Dimethoxyphenyl)trimethylstannane (1-69)



A solution of 4-bromoveratrole (0.95 g, 4.5 mmol) in dioxane (10.5 mL) was placed in a pressure tube and degassed with argon for 10 min. Hexamethylditin (2.0 g, 6.0 mmol, 1.3 equiv.) and tetrakis(triphenylphosphino)palladium(0) (0.25 g, 0.23 mmol, 5 mol%) were added under an inert atmosphere and the tube was sealed under vacuum. The reaction mixture was heated to 105 ^oC and stirred for 16 hours, before being allowed to cool to room temperature. The reaction mixture was filtered and concentrated under reduced pressure. Purification by flash column chromatography (1:19 EtOAc-hexane) afforded the desired product (1.00 g, 74%) as a yellow oil. The data corresponded to those reported in the literature.[70]

^{1}H NMR (400 MHz, CD_3CN) δ 7.05 (dd, *J* = 8.0 and 1.0 Hz, 1H), 7.01 (m, 1H), 6.91 (d, *J* = 8.0 Hz, 1H), 3.91 (s, 3H), 3.86 (s, 3H), 0.32 (s, with tin satellites $J^2_{Sn\text{-}H}$ = 54.0 Hz, 9H); **^{13}C NMR** (101 MHz, CD_3CN) δ 149.5, 148.9, 132.9, 128.7, 118.1, 111.4, 55.9, 55.7, -7.6, -9.3, -11.0 ($Sn(CH_3)_3$);

2-(3,4-dimethoxyphenyl)-5,5-dimethyl-1,3,2-dioxaborinane (2-59)

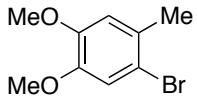


Neopentyl glycol (1.37 g, 13.2 mmol, 1.1 equiv.) and anhydrous $MgSO_4$ (1.44 g, 12 mmol, 1.0 equiv.) were added to 3,4-dimethoxyphenylboronic acid (2.18 g, 12.0 mmol) in anhydrous CH_2Cl_2 (15 ml) and stirred for 19 hours at room temperature. The reaction mixture was filtered and concentrated *in vacuo*. Flash column

chromatography (15% EtOAc-hexane) afforded the desired product as a white solid (2.90 g, 97%). The data corresponded to those reported in the literature.[169]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.23 (d, *J* = 1.5 Hz, 1H), 6.84 (d, *J* = 8.0 Hz, 1H), 3.85 (s, 3H), 3.83 (s, 3H), 3.69 (s, 4H), 0.95 (s, 6H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 151.2, 148.3, 127.4, 115.9, 110.4, 72.3, 55.8, 55.7, 31.9, 22.0; **IR** (neat) ν 2988, 1595, 1305; **HRMS** found 273.1264, calc. 273.1269 $[C_{13}H_{19}BO_4Na]^+$; **Mp** 91-92 °C.

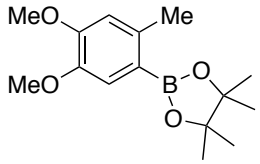
1-Bromo-4,5-dimethoxy-2-methylbenzene (2-62)



N-Bromosuccinimide (1.96 g, 11 mmol, 1.1 equiv.) was added to a solution of 3,4-dimethoxytoluene (1.44 mL, 10 mmol) in MeCN (50 mL) and the reaction mixture was stirred for 2 hours. The solvent was evaporated *in vacuo* and replaced with CCl_4 (40 mL). The precipitated succinimide was removed by filtration. The solvent was concentrated *in vacuo* and the crude product was recrystallised from hexane to afford 1-bromo-4,5-dimethoxy-2-methylbenzene as clear crystals (1.66 g, 72%). The data corresponded to those reported in the literature.[341]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.01 (s, 1H), 6.75 (s, 1H), 3.87 (s, 3H), 3.86 (s, 3H), 2.35 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 148.1, 147.6, 129.6, 115.3, 114.4, 113.5, 56.2, 56.0, 22.4;

2-(4,5-dimethoxy-2-methylphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2-63a)

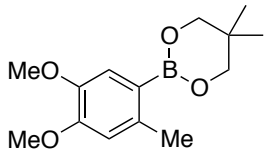


Bis(pinacolato)diboron (5.81 g, 22.9 mmol, 3.0 equiv.), $Pd(dppf)Cl_2.CH_2Cl_2$ (0.29 g, 0.4 mmol, 5 mol%), potassium acetate (3.07 g, 31.3 mmol) were placed in a dry flask under N_2. DMF (30 mL) was added and the mixture purged with nitrogen for 5 min. 1-Bromo-2-methylveratrole (1.80 g, 7.83 mmol) was added and the mixture was heated to 75 °C and stirred for 17 hours. The reaction mixture was cooled to room temperature and a saturated sodium chloride solution (aq., 20 mL) was added,

followed by extraction with EtOAc (3 x 25 mL). The combined organic extracts were washed with saturated sodium chloride solution (aq., 3 x 20 mL) and dried over $MgSO_4$. Flash column chromatography (15% EtOAc-hexane) afforded the desired product as a white solid (1.33 g, 82%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (s, 1H), 6.61 (s, 1H), 3.83 (s, 3H), 3.81 (s, 3H), 2.43 (s, 3H), 1.26 (s, 12H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 150.9, 146.1, 139.0, 118.1, 113.1, 83.3, 56.0, 55.7, 24.9, 21.7; **IR** (neat) ν 2982, 1599, 1349. **HRMS** found 279.1760, calc. 279.1762 $[C_{15}H_{24}BO_4]^+$; **Mp** 117-118 ^oC.

2-(4,5-dimethoxy-2-methylphenyl)-5,5-dimethyl-1,3,2-dioxaborinane (2-63b)



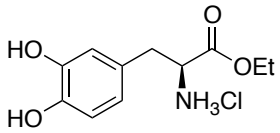
Bis(neopentylglycolato)diboron (4.27 g, 18.9 mmol, 3.0 equiv.), $Pd(dppf)Cl_2.CH_2Cl_2$ (0.23 g, 0.32 mmol, 5.0 mol%), potassium acetate (2.47 g, 25 mmol, 4.0 equiv.) were placed in a dry flask under N_2. DMSO (25 mL) was added and the mixture purged with nitrogen for 5 mins. 1-Bromo-2-methylveratrole (1.46 g, 6.3 mmol) was added and the mixture was heated to 75 °C and stirred for 17 hours. The reaction mixture was cooled to room temperature and a saturated sodium chloride solution (aq., 10 mL) was added, followed by extraction with EtOAc (3 x 15 mL). The combined organic extracts were washed with saturated sodium chloride solution (aq., 20 mL) and dried over $MgSO_4$. Flash column chromatography (15% EtOAc-hexane) afforded the desired product as a white solid (0.61 g, 37%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (s, 1H), 6.60 (s, 1H), 3.82 (s, 3H), 3.80 (s, 3H), 3.70 (s, 4H), 2.41 (s, 3H), 0.96 (s, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 150.2, 146.0, 138.0, 117.4, 113.4, 72.3, 55.9, 55.6, 31.7, 22.3, 21.9; **IR** (neat) ν 2982, 1599, 1349; **HRMS** found 265.1607, calc. 265.1606 $[C_{14}H_{22}BO_4]^+$; **Mp** 78-80 ^oC.

5.4.3 Preparation of arylstannane and arylboronic ester L-DOPA precursors

5.4.3.1 Arylstannane precursors

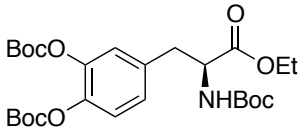
3,4-dihydroxy-L-phenylalanine ethyl ester hydrochloride salt (2-70a)



Thionyl chloride (18 mL, 253.6 mmol, 5.0 equiv.) was carefully added dropwise to a solution of L-DOPA (10.0 g, 50.7 mmol) in EtOH (60 mL) at 0 °C. The mixture was stirred at 0 °C for 2 hours and at room temperature for 12 hours. Evaporation of the reaction mixture *in vacuo* gave the desired product as a dense yellow oil (13.3 g, >99%), which was used without further purification. The data were consistent with those reported in the literature.[342]

^{1}H NMR (400 MHz, D_2O) δ 6.75 (d, *J* = 9.0 Hz, 1H), 6.63 (s, 1H), 6.56 (d, *J* = 8.0 Hz, 1H), 4.70 (bs, 1H), 4.24 (dd, *J* = 7.5, 5.5 Hz, 1H), 4.14 (q, *J* = 7.0 Hz, 2H), 3.07 – 2.95 (m, ABX system, 2H), 1.10 (t, *J* = 7.0 Hz, 3H); **^{13}C NMR** (101 MHz, D_2O) δ 174.2, 145.1, 144.2, 127.9, 120.8, 116.8, 115.9, 61.4, 55.0, 39.3, 14.1.

***N*-(*tert*-Butoxycarbonyl)-3,4-di(*tert*-butoxycarbonyloxy)-L-phenylalanine ethyl ester (2-71a)**

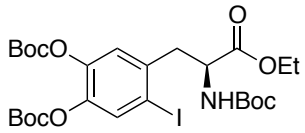


Triethylamine (23.4 mL, 167.6 mmol, 3.3 equiv.) was added to a solution of 3,4-dihydroxy-L-phenylalanine ethyl ester hydrochloride salt **2-70a** (13.3 g, 50.8 mmol) in DMF (33 mL) at 0 °C. To this solution, di-*tert*-butyl dicarbonate (47.9 mL, 208.5 mmol, 4.1 eqiuv.) in DMF (33 mL) was added dropwise and the mixture was stirred first at 0 °C for 2 hours and then for 48 hours at room temperature. After dilution with EtOAc (100 mL), the solution was washed with water (50 mL), brine (50 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude compound was purified by flash column chromatography (5% EtOAc-CH_2Cl_2) to give the desired product as a dense yellow oil (22.92 g, 86%). The data were consistent with those reported in the literature.[342]

^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.25 (d, *J* = 8.5 Hz, 1H), 7.10 (s, 1H), 7.06 (d, *J* = 1.5 Hz, 1H), 5.15 (bd, *J* = 8.0 Hz, 1H), 4.57 (bm, 1H), 4.21 (q, *J* = 7.0 Hz, 2H), 3.23 –

3.07 (ABX system, bm, 2H), 1.58 (s, 18H), 1.47 (s, 9H), 1.29 (t, *J* = 7.3, 3H); **^{13}C NMR** (101 MHz, CD_2Cl_2) δ 172.8, 156.3, 152.0, 143.8, 142.9, 136.6, 128.6, 125.3, 124.2, 85.0, 81.0, 62.8, 55.8, 38.8, 29.5, 28.7, 28.5, 15.3.

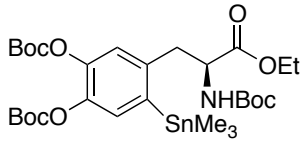
_N_-(_tert_-Butoxycarbonyl)-3,4-di(_tert_-butoxycarbonyloxy)-6-iodo-L-phenylalanine ethyl ester (2-72a).



Bis(trifluoroacetoxy)iodobenzene (0.84 g, 1.96 mmol) and iodine (0.41 g, 1.63 mmol) were added to a stirred solution of *N*-(*tert*-Butoxycarbonyl)-3,4-di(*tert*-butoxycarbonyloxy)-L-phenylalanine ethyl ester **2-71a** (0.86 g, 1.63 mmol) in dry CH_2Cl_2 at 0 ^{o}C and the resulting solution was stirred at this temperature for 15 minutes. The mixture was allowed to warm up to room temperature and stirred for a further 90 minutes. After dilution with CH_2Cl_2 (10 mL), the mixture was washed with 1 M $Na_2S_2O_3$ (15 mL x 2), water (15 mL) and brine (15 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography (10% EtOAc-hexane) yielded the desired product as a yellow oil (0.72 g, 79%). The data were consistent with those reported in the literature.[342]

^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.75 (s, 1H), 7.15 (s, 1H), 5.13 (bd, *J* = 8.0 Hz, 1H), 4.58 (bm, 1H), 4.20 (q, *J* = 7.0 Hz, 2H), 3.30 – 3.08 (ABX system, dd and bm, 2H), 1.57 (s, 18H), 1.42 (s, 9H), 1.27 (t, *J* = 7.0, 3H); **^{13}C NMR** (101 MHz, CD_2Cl_2) δ 172.8, 156.3, 151.6, 143.0, 142.9, 139.6, 134.6, 125.2, 96.5, 85.0, 81.0, 62.8, 55.8, 43.8, 29.5, 28.7, 28.5, 15.3.

_N_-(_tert_-Butoxycarbonyl)-3,4-di(_tert_-butoxycarbonyloxy)-6-trimethylstannyl-L-phenylalanine ethyl ester (2-67a).



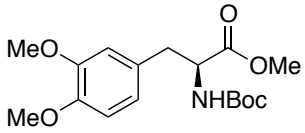
A solution of *N*-(*tert*-butoxycarbonyl)-3,4-di(*tert*-butoxycarbonyloxy)-6-iodo-L-phenylalanine ethyl ester **2-72a** (2.00 g, 3.1 mmol) in dioxane (40 mL) was placed in a pressure tube and degassed with argon for 10 minutes. Hexamethylditin (1.34 mL, 4.0 mmol, 1.3 equiv.) and tetrakis(triphenylphosphino)palladium(0) (0.20 g, 0.21 mmol,

6.7 mol%) were added under an inert atmosphere and the tube was sealed under vacuum. The reaction mixture was heated to 105 ^{o}C and stirred for 6 hours, before being allowed to cool to room temperature. The reaction mixture was filtered, diluted with EtOAc (70 mL), washed with water (50 mL) and brine (50 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography (10% EtOAc-hexane) afforded the desired product as a clear oil (1.63 g, 65% yield). The data were consistent with those reported in the literature. [342]

^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.30 (s, with tin satellites $J^{3}_{Sn\text{-}H}$ = 46.0 Hz, 1H), 7.09 (s, with tin satellites $J^{4}_{Sn\text{-}H}$ = 16.0 Hz, 1H), 5.01 (bd, J = 8.0 Hz, 1H), 4.48 (bm, 1H), 4.20 (q, J = 7.0 Hz, 2H), 3.17 – 2.99 (ABX system, dd and bm, 2H), 1.55 (s, 18H), 1.41 (s, 9H) 1.25 (t, J = 7.0, 3H), 0.40 (s, with tin satellites $J^{2}_{Sn\text{-}H}$ = 54.0 Hz, 9H); **^{13}C NMR** (101 MHz, CD_2Cl_2) δ 172.3, 156.3, 151.6, 143.0, 142.9, 142.1, 141.2, 131.2 (s, with tin satellites $J^{2}_{Sn\text{-}H}$ = 43.0), 124.5 (s, with tin satellites $J^{3}_{Sn\text{-}H}$ = 41.0), 85.0, 81.0, 62.8, 55.8, 41.8, 29.5, 28.7, 28.5, 15.3, –7.81 (s, ArC-Sn(CH_3)$_3$, with tin satellites $J^{1}_{Sn\text{-}C}$ = 339 Hz).

5.4.3.2 Arylboronic ester derivatives

_N_-(_tert_-Butoxycarbonyl)-3,4-(dimethoxy)-L-phenylalanine methyl ester (2-77)

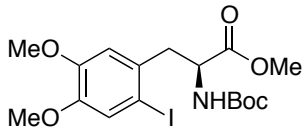


N-(*tert*-Butoxycarbonyl)-3,4-(dimethoxy)-L-phenylalanine methyl ester **2-77** was prepared in three steps from L-DOPA by the formation of the methyl ester, Boc-protection of the amine and methylation of the catechol functionality, using the procedure described by Lemaire *et al.*[343] Thionyl chloride (3.1 mL, 42 mmol, 1.7 equiv.) was added to a solution of L-DOPA (4.90 g, 25 mmol) in dry methanol (125 mL) at 0 °C under argon. The reaction mixture was refluxed for 20 hours, cooled and concentrated *in vacuo*. Toluene was added and the mixture concentrated *in vacuo*, giving crude 3,4-dihydroxy-L-phenylalanine methyl ester hydrochloride salt (6.50 g, >99%). Crude 3,4-dihydroxy-L-phenylalanine methyl ester hydrochloride salt (3.30 g, 12.6 mmol) was subsequently treated with triethylamine (1.8 mL, 12.9 mmol) and di-*tert*-butyl dicarbonate (2.90 g, 13.3 mmol, 1.03 equiv.) in ethanol (55 mL) at room temperature. The reaction mixture was stirred for 2 hours and the solvent was

evaporated *in vacuo*. The mixture was acidified with 1 M HCl (30 mL) at 0 °C and extracted with EtOAc (3 x 20 mL). The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo*. Flash column chromatography (15–50% EtOAc-hexane) gave *N*-(*tert*-butoxycarbonyl)-3,4-(dihydroxy)-L-phenylalanine methyl ester as a clear oil (3.67 g, 90%). Iodomethane (1.4 mL, 22.5 mmol, 4.5 equiv.) was added to *N*-(*tert*-butoxycarbonyl)-3,4-(dihydroxy)-L-phenylalanine methyl ester (1.63 g, 5 mmol) and potassium carbonate (6.22 g, 45 mmol, 9.0 equiv.) in DMF (11 mL). The reaction mixture was stirred for 24 hours at room temperature under argon. The reaction mixture was filtered and diluted with water (20 mL). The pH was adjusted to 1-2 using 1 M HCl and extracted with diethyl ether (2 x 20 mL). The combined organic phases were washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Flash column chromatography (5% EtOAc-CH_2Cl_2) gave *N*-(*tert*-butoxycarbonyl)-3,4-(dimethoxy)-L-phenylalanine methyl ester **2-77** as a white solid (1.38 g, 78% over three steps). The data corresponded with those reported in the literature.[343]

^{1}H NMR (400 MHz, acetone-d_6) δ 6.87-6.86 (m, 1H), 6.77-6.75 (m, 2H), 4.32-4.38 (m, 1H), 4.10-4.16 (m, 1H), 3.80 (s, 6H), 3.71 (s, 3H), 3.05-2.92 (m, ABX system, 2H), 1.36 (s, 9H); **^{13}C NMR** (101 MHz, acetone-d_6) δ = 172.9, 156.2, 150.3, 149.4, 130.7, 122.3, 114.2, 112.9, 79.4, 61.5, 56.3, 56.2, 52.2, 37.9, 28.3; **IR** (neat) ν 3555, 2970, 1739, 1229; **HRMS** found 376.1735 calc. 376.1736 $[C_{18}H_{27}NO_6 + Na]^+$; **Mp** 80-81 °C; **$[\alpha]_D$** = +4.4 (*c* = 1.0, MeOH, 20.0 °C).

_N_-(_tert_-Butoxycarbonyl)-3,4-(dimethoxy)-6-(iodo)-L-phenylalanine methyl ester (2-78)

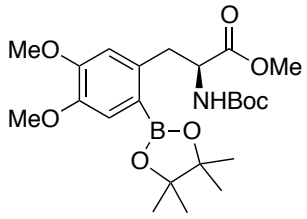


Bis(trifluoroacetoxy)iodobenzene (0.77 g, 1.8 mmol, 1.2 equiv.) and iodine (0.38 g, 1.5 mmol, 1.0 equiv.) were added to *N*-(*tert*-butoxycarbonyl)-3,4-(dimethoxy)-L-phenylalanine methyl ester **2-77** (0.53 g, 1.5 mmol) in CH_2Cl_2 (25 mL) at 0 °C. The reaction mixture was stirred for 15 min at 0°C before being warmed up to room temperature and stirred for a further 3 hours. The reaction mixture was transferred to a separatory funnel and washed with sodium thiosulfate (1 M aq., 15 mL), water (10 mL) and brine (10 mL). The organic phase was dried over $MgSO_4$, filtered and

concentrated. Flash column chromatography (10–20% EtOAc-hexane) afforded the product as a white solid (0.49 g, 68%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (s, 1H), 6.71 (s, 1H), 5.05 (bd, *J* = 8.0 Hz, 1H), 4.61 (q, *J* = 7.0 Hz, 1H), 3.85 (s, 6H), 3.75 (s, 3H), 3.22-3.05 (m, ABX system, 2H), 1.40 (s, 9H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 172.5, 155.1, 149.4, 148.6, 131.8, 121.8, 112.9, 89.0, 80.1, 61.7, 56.3, 54.0, 52.6, 42.8, 28.4; **IR** (neat) ν 3371, 2976, 1709, 1504, 1163; **HRMS** found 488.0542, calc. 488.0541 $[C_{17}H_{24}INO_6+Na]^+$. **$[\alpha]_D$** = –14.2 (*c* = 1.0, MeOH, 20.0 °C). **Mp** 56-57 °C.

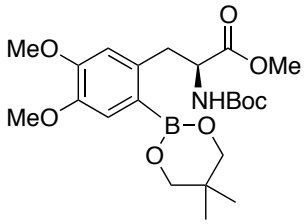
***N*-(*tert*-Butoxycarbonyl)-3,4-dimethoxy-6-(1,3,2-dioxaborinane-5,5-dimethyl)-L-phenylalanine methyl ester (2-68a).**



Bis(pinacolato)diboron (1.64 g, 6.42 mmol, 3.0 equiv.), Pd(dppf)Cl_2.CH_2Cl_2 (0.09 g, 0.11 mmol, 5 mol%) and potassium acetate (0.84 g, 8.56 mmol, 4.0 equiv.) were placed in a dry flask under N_2. DMF (13 mL) was added and the mixture purged with nitrogen for 5 min. *N*-(*tert*-butoxycarbonyl)-3,4-(dimethoxy)-6-(iodo)-L-phenylalanine methyl ester **2-78** (1.00 g, 2.14 mmol) was added and the mixture heated to 80 °C for 19 hours. The reaction mixture was cooled to room temperature and a 50% saturated sodium chloride solution (aq., 20 mL) was added, followed by extraction with EtOAc (3 x 15 mL). The combined organic extracts were washed with 50% saturated sodium chloride solution (aq., 20 mL), dried over $MgSO_4$, filtered and concentrated. Flash column chromatography (2-20% EtOAc-hexane) provided the desired product was a yellow solid (0.77 g, 77%).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.67 (s, 1H), 6.57 (s, 1H), 4.93 (d, *J* = 8.0 Hz, 1H), 4.48 (q, *J* = 8.0 Hz, 1H), 3.84 (s, 3H), 3.83 (s, 3H), 3.68 (s, 3H), 3.02-2.97 (m, ABX system, 2H), 1.35 (s, 9H), 1.30 (s, 6H), 1.27 (s, 6H); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 173.7, 155.6, 150.7, 147.1, 136.5, 117.3, 113.1, 79.3, 72.3, 56.2, 55.8, 55.7, 52.1, 36.9, 28.3, 21.9; **IR** (neat) ν 3412, 2978, 2456, 1706, 1167; **HRMS** found 488.2442, calc. 488.2432 $[C_{23}H_{36}BNO_8+Na]^+$; **$[\alpha]_D$** = +3.2 (*c* = 0.5, MeOH, 20.0 °C); **Mp** 67-68 °C.

_N_-(_tert_-Butoxycarbonyl)-3,4-dimethoxy-6-(1,3,2-dioxaborinane-5,5-dimethyl)-L-phenylalanine methyl ester (2-68b)



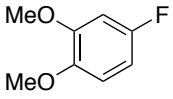
N-(*tert*-butoxycarbonyl)-3,4-(dimethoxy)-6-(iodo)-L-phenylalanine methyl ester **2-78** (1.80 g, 3.9 mmol) was dissolved in DMSO (25 mL) and purged with N_2 for 10 min. Potassium acetate (1.52 g, 15.6 mmol, 4.0 equiv.), *bis*(neopentyl glycolato)diboron (2.63 g, 11.7 mmol, 3.0 equiv.) and Pd(dppf)Cl_2.CH_2Cl_2 (0.17 g, 0.2 mmol, 5 mol%) were added and the mixture was purged with nitrogen for a further 3 min. The mixture was then heated to 80 °C, over 10 mins, and stirred at this temperature for 17 hours. The reaction mixture was cooled to room temperature and a 50% saturated sodium chloride solution (aq., 20 mL) was added, followed by extraction with EtOAc (2 x 40 mL). The combined organic extracts were washed with 50% saturated sodium chloride solution (aq., 3 x 40 mL), dried over $MgSO_4$, filtered and concentrated. Flash column chromatography (2–15% EtOAc-CH_2Cl_2) afforded the product as a white foam (600 mg, 33%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (s, 1H), 6.70 (s, 1H), 5.66 (bd, *J* = 8.0 Hz, 1H), 4.35-4.46 (m, 1H), 3.90 (s, 6H), 3.81 (s, 4H), 3.73 (s, 3H), 3.22-3.19 (bd, *J* = 7.5 Hz, ABX system, 2H), 1.36 (s, 9H), 1.06 (s, 6H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 173.7, 155.7, 150.8, 147.2, 136.6, 117.5, 113.2, 79.5, 72.5, 56.3, 56.0, 55.9, 52.2, 37.0, 31.8, 28.4, 22.0; **^{11}B NMR** (160 MHz, $CDCl_3$) δ = 27.05; **EA** Found: C, 58.04; H, 7.80; N, 2.99%, Calc. for $C_{22}H_{34}BNO_8$: C, 58.55; H, 7.59; N, 3.10%; **IR** (neat) ν 3375, 2970, 1742, 1718, 1161; **HRMS** found 474.2281, calc. 474.2270 $[C_{22}H_{34}BNO_8+Na]^+$; **$[\alpha]_D$** = –3.7 (*c* = 1.0, MeOH, 20.0 °C). The ester was stable for >6 months.

5.4.4 Fluorination Studies

5.4.4.1 Fluorination of arylstannane model substrates

General procedure for the fluorination of 4-trialkyltinveratrole (2-53 and 1-68)



Silver triflate (2.0 equiv.) and Selectfluor^{TM} (1.2 eq.) were added to a solution of aryl trialkyltin (0.3 mmol) in dry* acetone or MeCN (10 mL per mmol), at room temperature. The reaction mixture was stirred at room temperature for 30 mins, before being concentrated *in vacuo*. The ratio of the two products was determined at this stage by analysis of the ^{1}H NMR spectrum. Purification by flash column chromatography (5% EtOAc-hexane) afforded the mixture of 4-fuoroveratrole **2-54** and veratrole **2-55** products as a yellow oil and this mixture was used to calculate the yields of 4-fuoroveratrole **2-54** and veratrole **2-55**.

* Acetone was dried overnight over 3 Å MS and then distilled.

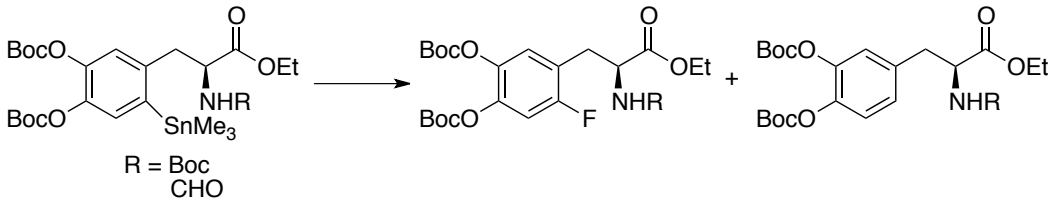
Sample reaction: fluorination of 4-trimethyltinveratrole **1-68** *(Table 2.3, Entry 3):*

4-Trimethyltinveratrole **1-68** (0.15 g, 0.30 mmol) was subjected to the general procedure above, using acetone as the solvent. The desired 4-fluoroveratrole **2-54** was isolated in a 1:1 mixture with the protodestannylated product **2-55**. From this reaction mixture, the yield of 4-fluoroveratrole was calculated to be 25 mg, 28%. The data were consistent with those reported in the literature.[70]

^{1}H NMR (400 MHz, $CDCl_3$), δ 6.78 (dd, *J* = 9.0, 5.5 Hz, 1H), 6.63 (dd, *J* = 10.0, 3.5 Hz, 1H), 6.59 (m, 1H), 3.89 (s, 3H), 3.86 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 157.5 (d, *J* = 240.0 Hz), 148.9 (d, *J* = 10.0 Hz), 143.9 (d, *J* = 3.0 Hz), 111.7 (d, *J* = 10.0 Hz), 106.1(d, *J* = 24.0 Hz), 101.4 (d, *J* = 28.0 Hz), 55.9, 55.7; **^{19}F NMR** (377 MHz, $CDCl_3$), δ –121.3 (ddd, *J* = 9.9, 8.2, 5.5 Hz).

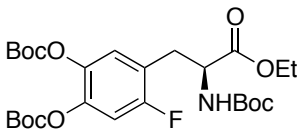
5.4.4.2 Fluorination of arylstannane and aryl boronic ester L-DOPA precursors

General procedure for the fluorination of arylstannane L-DOPA precursors 2-68a and 2-68b



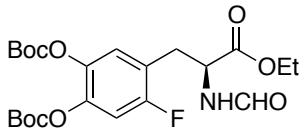
Silver triflate (2.0 equiv.) and Selectfluor^{TM} (1.2 equiv.) were added to a solution of precursor **2-68a** or **2-68b** in acetone (10 mL per mmol) at room temperature. The reaction mixture was stirred at room temperature for 30 min before being concentrated *in vacuo*. The ratio of the fluorodestannylated **2-82a-b** and protodestannylated **2-71a-b** products was calculated from the crude reaction mixture using ^{1}H NMR spectroscopy. The mixture of **2-82a-b** and 2**-71a-b** was isolated as a yellow oil after flash column chromatography (10 – 20% EtOAc-hexane) and the yield of **2-82a-b** and **2-71a-b** was calculated. The data for **2-82a** and **2-82b** corresponded to those reported in the literature.[343] Spectral data for the fluorinated products **2-82a** and **2-82b** are provided below:

***N*-(*tert*-Butoxycarbonyl)-3,4-di(*tert*-butoxycarbonyloxy)-6-fluoro-L-phenylalanine ethyl ester 2-82a**



^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.09 (d, $J^{4}_{F\text{-}H}$ = 7.0 Hz, 1H), 7.06 (d, $J^{3}_{F\text{-}H}$ = 10.0 Hz, 1H), 5.91 (bd, J = 8.0 Hz, 1H), 4.57 (bm, 1H), 4.17 (q, J = 7.0 Hz, 2H), 3.23 – 3.09 (ABX system, bm, 2H), 1.58 (s, 18H), 1.47 (s, 9H), 1.29 (t, J = 7.0 Hz, 3H); **^{13}C NMR** (101 MHz, CD_2Cl_2) δ 172.8, 156.8 (d, $J_{F\text{-}C}$ = 247 Hz), 152.3, 152.0, 143.8 (d, $J_{F\text{-}C}$ = 7 Hz), 142.9, 125.3 (d, $J_{F\text{-}C}$ =15 Hz), 121.5, 111.2 (d, $J_{F\text{-}C}$ = 30 Hz), 85.0, 81.0, 62.8, 52.8, 34.8, 28.7, 27.5, 14.9; **^{19}F NMR** (377 MHz, CD_2Cl_2), δ = –121.6;

***N*-(Formyl)-3,4-di(*tert*-butoxycarbonyloxy)-6-fluoro-L-phenylalanine ethyl ester 2-82b**

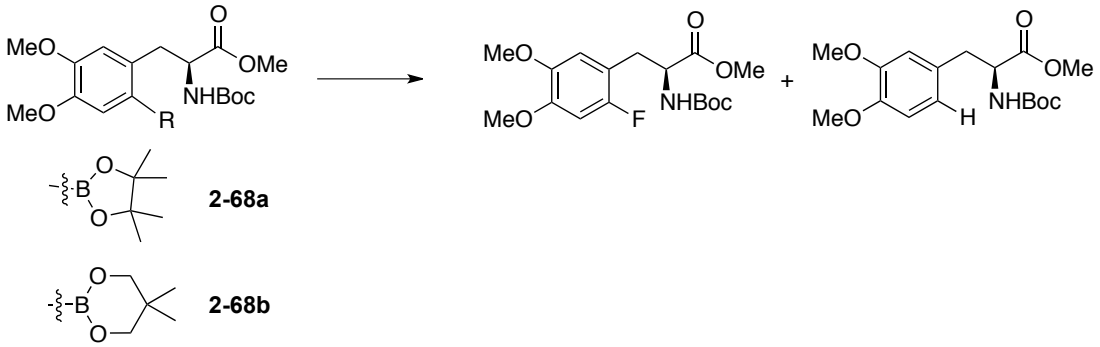


^{1}H NMR (400 MHz, CD_2Cl_2) δ 8.10 (s, 1H), 7.06 (d, $J^{4}_{F\text{-}H}$ = 7.0 Hz, 1H), 7.02 (d, $J^{3}_{F\text{-}H}$ = 10.0 Hz, 1H), 6.43 (bd, 1H), 4.67 (bm, 1H) 4.15 (q, J = 7.0 Hz, 2H), 3.21-3.09 (m, ABX system, 2H), 1.53 (s, 18H), 1.21 (t, J = 7.0 Hz, 3H); **^{13}C NMR** (101 MHz, CD_2Cl_2) δ 171.3, 160.7, 158.2 (d, $J_{F\text{-}C}$ = 246 Hz), 151.2, 143.7 (d, $J_{F\text{-}C}$ = 7 Hz), 140.4, 125.6 (d, $J_{F\text{-}C}$ =16 Hz), 121.3, 111.1 (d, $J_{F\text{-}C}$ =32 Hz), 84.4, 61.7, 53.2, 31.9, 28.1, 14.4; **^{19}F NMR** (377 MHz, CD_2Cl_2) δ –121.8;

Sample reaction: Fluorination of arylstannane L-DOPA precursor **2-68a** *(Table 2.7, Entry 1):*

N-(*tert*-Butoxycarbonyl)-3,4-di(*tert*-butoxycarbonyloxy)-6-trimethylstannyl-L-phenylalanine ethyl ester **2-68a** (0.33 g, 0.50 mmol) was subjected to the general procedure above. The mixture of **2-83a** and **2-71a** was isolated (0.17 g) in a ratio of 81:19 and yields of 50% and 12%, respectively.

General procedure for arylboronic ester L-DOPA precursors 2-68a and 2-68b



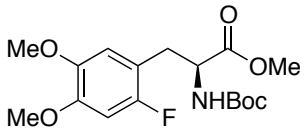
Boronated precursor **2-68a** or **2-68b** (0.125 mmol, 1 equiv.) was added to a solution of sodium hydroxide (1.2 equiv.) in dry methanol (5 mL per mmol boronic ester) and stirred at room temperature under nitrogen for 3 hours. The reaction mixture was cooled to 0 °C and silver triflate (3.0 equiv.) was added. The reaction mixture was stirred at 0 °C under nitrogen for 30 min followed by evaporation of methanol *in vacuo*, while keeping the flask at 0 °C. The solvent was further co-evaporated with acetone (2 x 5 mL) at 0 °C under the same conditions and then dried under high

vacuum for 20 min at 0 °C. The mixture was subsequently suspended in acetone (5 mL per mmol boronic ester), followed by addition of Selectfluor (1.05 equiv.) and powdered mol. sieves (100 mg per mmol). The reaction mixture was left stirring for 30 min at room temperature, concentrated *in vacuo,* suspended in CH_2Cl_2 and filtered through a plug of Celite. The ratio of the fluorodeboronated **2-83** and protodeboronated product **2-77** was calculated from the ^{1}H NMR spectrum of the crude reaction mixture and yield of **2-83** and **2-77** was calculated from the mixture of these two products isolated upon purification by flash column chromatography (10–20% EtOAc-hexane).

Sample reaction: Fluorination of arylboronic ester L-DOPA precursor **2-68b** *(Table 2.9, Entry 4)*

Arylboronic ester L-DOPA precursor **2-68b** was subjected to the general procedure above. The ratio of the two products, **2-83** and **2-77**, calculated from the ^{1}H NMR spectrum of the crude reaction mixture, was 81:19. Upon purification by flash column chromatography (10–20% EtOAc/hexane) the mixture of **2-83** and **2-77** was isolated (15.6 mg) and the yield of the two products calculated (30% and 7%, respectively). Spectral data for the fluorinated product **2-83** is provided below:

***N*-(*tert*-Butoxycarbonyl)-3,4-di(tert-butoxycarbonyloxy)-6-fluoro-L-phenylalanine methyl ester (2-83).**



^{1}H NMR (400 MHz, $CDCl_3$) δ 6.62-6.58 (m, 2H) 5.05 (bd, J = 8.2 Hz 1H), 4.53 (bq, J = 6.0 Hz, 1H), 3.84 (s, 3H), 3.83 (s, 3H), 3.73 (s, 3H), 3.13-2.99 (m, ABX system, 2H), 1.41 (s, 9H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 172.4, 156.5, 155.6 (d, J = 237 Hz), 149.0 (d, $J_{F\text{-}C}$ = 7.0 Hz), 145.2, 125.4 (d, $J_{F\text{-}C}$ =16.0 Hz), 113.6 (d, J = 18.0 Hz), 101.9 (d, J = 28.0 Hz), 80.1, 56.5, 56.2, 53.9, 52.5, 31.6, 28.5; **^{19}F NMR** (377 MHz, $CDCl_3$) δ –125.0; **IR** (neat) ν 1167, 1517, 1715, 2978, 3362; **HRMS** found 380.1467, calc. 380.1480 $[C_{17}H_{24}FNO_6 + Na]^+$.

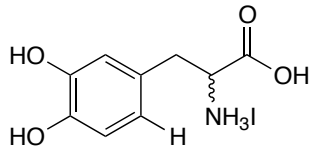
5.4.4.3 Investigation into the racemisation of arylboronic acid ester L-DOPA precursor 2-68b during the fluorination reaction

Details of HPLC systems

High performance liquid chromatography (HPLC) was performed on a Dionex UltiMate 3000 with a UliMate 3000 detector and a UltiMate 3000 Variable Wavelength Detector (λ=280 nm).

The semi-preparative HPLC studies were performed using a reverse phase analytical column (Phenomex Luna 5u C18 100A 150x10.00mm). Elution was performed using a gradient of acetonitrile:water (2:98 to 80:20% over 10 min) with a flow rate of 1 mL/min.)

Analysis of the enantiomeric purity of the protodeboronated product (L-DOPA) **2-77** was carried out on a Daicel Crownpak(+) (4mm x 150 mm) using 0.01M $HClO_4$ as the mobile phase and a flow rate of 1 mL/min.



2-85

N-(*tert*-Butoxycarbonyl)-3,4-di(*tert*-butoxycarbonyloxy)-L-phenylalanine methyl ester **2-77** was obtained by semi-preparative HPLC purification of the mixture of **2-77** and the fluorodestannylated analogue **2-83** after isolation by column chromatography. The DOPA compound **2-77** (3.6 mg, 10 μmol) was subsequently deprotected with 57% HI (0.3 mL) at 130 ^{o}C for 20 minutes and the reaction mixture was purified by semi-preparative HPLC. The fraction corresponding to DOPA **2-85** was collected and the solvent was evaporated to remove all traces of acetonitrile. The minor isomer D-dopa (4.18%) had a retention time of 4.44 min and the major isomer L-DOPA (95.82%) eluted at 5.98 min. The enantiomeric excess of L-DOPA obtained upon the fluorination of arylboronic acid ester L-DOPA precursor **2-68b** was found to be 91.6% (Figure 5.1). This indicates that racemisation of the amino acid functionality was not a predominant process under the fluorination reaction conditions.

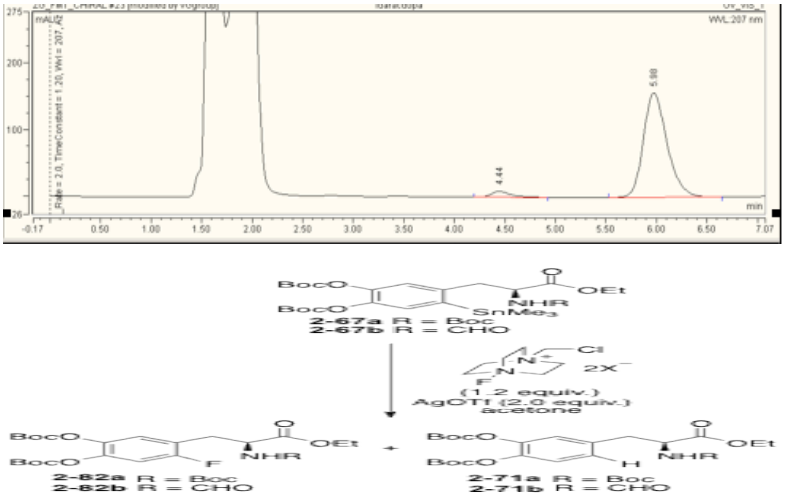
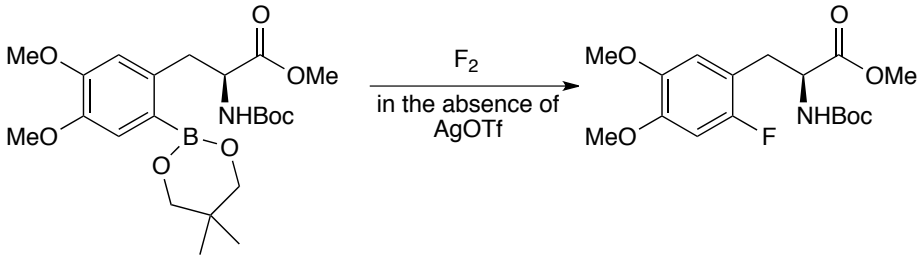


Figure 5.1. Determination of ee of L-DOPA obtained by fluorination of arylboronic acid ester L-DOPA precursor 2-68b.

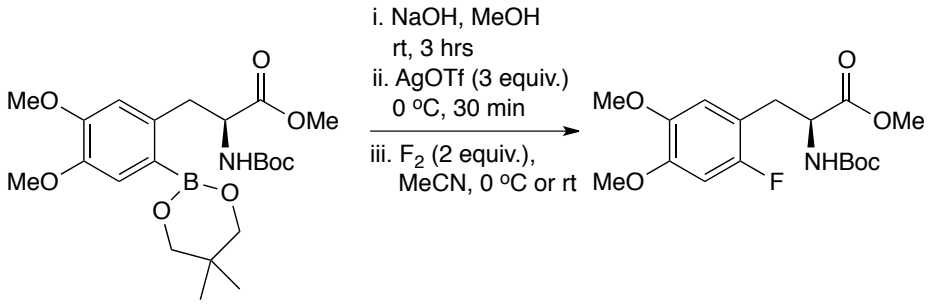
5.4.4.4 Fluorination of arylboronic acid ester L-DOPA precursor 2-68b using fluorine gas

Direct fluorination of arylboronic acid ester L-DOPA precursor 2-68b without AgOTf



Arylboronic acid ester L-DOPA precursor **2-68b** (0.27 g, 0.59 mmol) was dissolved in MeCN (5 mL) in a PTFE vial and the system was purged with nitrogen gas for 5 minutes. Fluorine gas (10% in N_2, 2 equiv., 18 minutes) was bubbled through the solution at a flow rate of 15 mL/min at either 0 ^{o}C or room temperature, before the reaction was purged with N_2 gas for 10 minutes. The solvent was evaporated *in vacuo* and replaced by MeCN-d_3 and 1 equivalent of 1-fluoro-3-nitrobenzene as an internal reference standard to allow analysis of the reaction mixture by ^{19}F NMR spectroscopy. Under these reaction conditions, no fluorinated product **2-83** was observed.

Silver-mediated fluorination of arylboronic acid ester L-DOPA precursor 2-68b



Arylboronic ester L-DOPA precursor **2-68b** (1.85 g, 2.6 mmol) was added to a solution of sodium hydroxide (0.13 g, 3.14 mmol, 1.2 equiv.) in dry methanol (11 mL) and stirred at room temperature under nitrogen for 3 hours. The reaction mixture was cooled to 0 °C and silver triflate (2.0 g, 7.89 mmol, 3.0 equiv.) was added. The reaction mixture was stirred at 0 °C under nitrogen for 30 min followed by evaporation of methanol *in vacuo*, while keeping the flask at 0 °C. The reaction mixture was divided into two equal batches and the solvent was further co-evaporated with acetone (2 x 5 mL) at 0 °C under the same conditions and then dried under high vacuum for 20 min at 0 °C. The reaction mixtures were dissolved in MeCN (5 mL) and transferred to PFTE vessels and purged with nitrogen gas for 5 minutes. Fluorine gas (10% in N_2, 4 equiv., 78 minutes) was bubbled through the solution at a flow rate of 15 mL/min at either 0 ^{o}C or room temperature, before the reaction was purged with N_2 gas for 10 minutes. The solvent was evaporated *in vacuo* and replaced by MeCN-d_3 and 1 equivalent of 1-fluoro-3-nitrobenzene as an internal reference standard to allow analysis of the reaction mixture by ^{19}F NMR spectroscopy. Under these reaction conditions, no fluorinated product **2-83** was observed.

5.4.5. Radiochemistry

5.4.5.1 Preparation of [^{18}F]Selectfluor *bis*(triflate) [^{18}F]1-51

The [^{18}F]F_2 gas was bubbled into a vial containing a mixture of 1-chloromethyl-4-aza-1- azoniabicyclo[2.2.2]octane triflate **1-57** (2 μmol (0.003 M) or 7.5 μmol (0.01 M)) and lithium triflate (1 equivalent) in acetone-d_6 (0.75 mL) at –10 ^{o}C for ~ 30 seconds. [^{18}F]Selectfluor *bis*(triflate) **[^{18}F]1-51** was formed instantaneously.[70] The activity of the crude stock solution in acetone-d_6 ranged from 5 to 10 GBq, depending on the cyclotron irradiation time. Aliquots (0.2 mL) of this crude stock solution were used directly in labelling reactions.

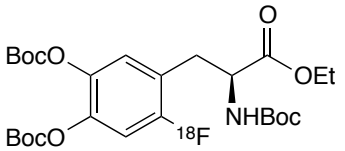
5.4.5.2 Radiolabelling of arylstannane L-DOPA precursor 2-67b

[^{18}F]1-51 in acetone-d_6 (2 μmol of prec. (0.003 M) or 7.5 μmol of prec. (0.01 M), 0.2 mL) was added to a reaction vial containing precursor **2-67b** (6.2 mg, 10 μmol) and silver triflate (5.1 mg, 20 μmol). The solution was stirred at room temperature for 20 minutes. Subsequently, acetone-d_6 was evaporated at room temperature under a stream of nitrogen. Hydrolysis of **[^{18}F]1-51** was carried out with 48% HBr (0.3 mL) at 130 ^{o}C for 5 minutes to afford 6-[^{18}F]fluoro-L-DOPA **[^{18}F]1-11**.

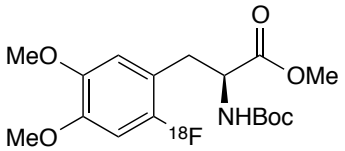
5.4.5.3 Radiolabelling of veratrole boronic ester precursor 2-59 and arylboronic ester L-DOPA precursor 2-68b

Compounds **2-59** and **2-68b** required activation prior to radiolabelling. This was achieved by reacting **2-59** or **2-68b** (10 μmol) with sodium hydroxide (1.2 equiv.) in methanol (50 μL) for 3 hours at room temperature. Subsequent treatment of the crude reaction mixture with silver triflate (3 equivalents) at 0 ^{o}C for 30 minutes led to the formation of transmetalated aryl silver complexes **2-88** or **2-89**. After removal of the solvent and co-evaporation with acetone (3 x 200 μL) at 0 ^{o}C, **[^{18}F]1-51** in acetone-d_6 (0.003 M, 0.2 mL) was added and the reaction mixture was stirred for 20 minutes at room temperature. Subsequently, acetone-d_6 was evaporated at room temperature under a stream of helium. Hydrolysis was carried out with 57% HI (0.3 mL) at 130 ^{o}C for 15 minutes to afford 6-[^{18}F]fluoro-L-DOPA **[^{18}F]1-11**.

5.4.5.4 Analysis of protected radiolabelled L-DOPA intermediates [^{18}F]2-87 (from trimethylstannane precursor 2-67b) and [^{18}F]2-90 (from boronic ester precursor 2-68b)



[^{18}F]2-87



[^{18}F]2-90

For both aryltrimethylstannane L-DOPA precursor **2-67b** and arylboronic ester precursor **2-68b**, a sample from the reaction mixture was taken after the [^{18}F]fluorination. Samples were analysed by HPLC (System A and B). The fraction corresponding to the protected intermediates **[^{18}F]2-87** or **[^{18}F]2-90**, was collected and analysed for the calculation of specific activity. The same procedure was repeated after

hydrolysis, when the fraction corresponding to 6-[^{18}F]fluoro-L-DOPA **[^{18}F]1-11** was collected after analysis by HPLC (System C).

5.4.5.5 HPLC systems and chromatograms

HPLC systems for [^{18}F]radiolabelling studies

High performance liquid chromatography (HPLC) was performed on a Spectra SYSTEM P2000 with a Spectra SYSTEM UV2000 detector and a Bioscan flow-count radioactivity detector in series, or a VWR-Hitachi L-2130 HPLC pump (VWR Hitachi, VWR International GmbH, Darmstadt, Germany) combined with a VWR- Hitachi L-2400 UV-absorption detector (λ=280 nm) and a 2 x 2 inch NaI-crystal for radioactivity detection.

SYSTEM A and B

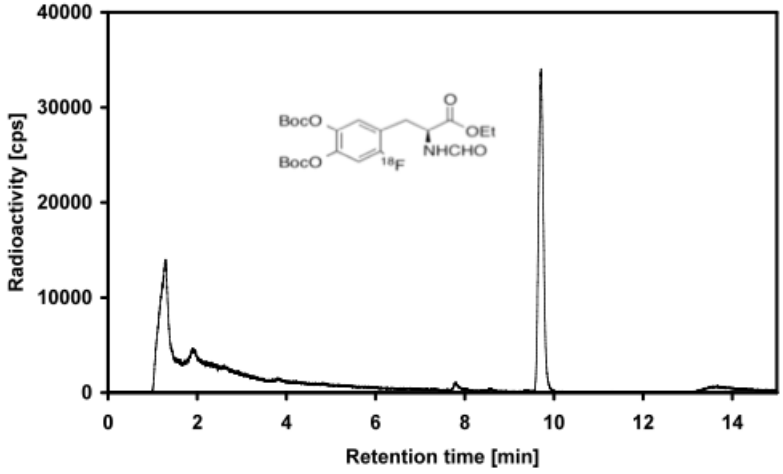
Semi-preparative (A) and analytical (B) HPLC studies of protected 6-[^{18}F]fluoro-L-dopa **[^{18}F]2-87** and **[^{18}F]2-90** were performed using a reverse phase analytical column (Waters Nova-Pak C-18 Column, 150mm x 3.9mm). Elution was performed at a gradient of acetonitrile:water (5:95 to 80:20 % over 10 min) with a flow rate of 1 mL/min.

SYSTEM C

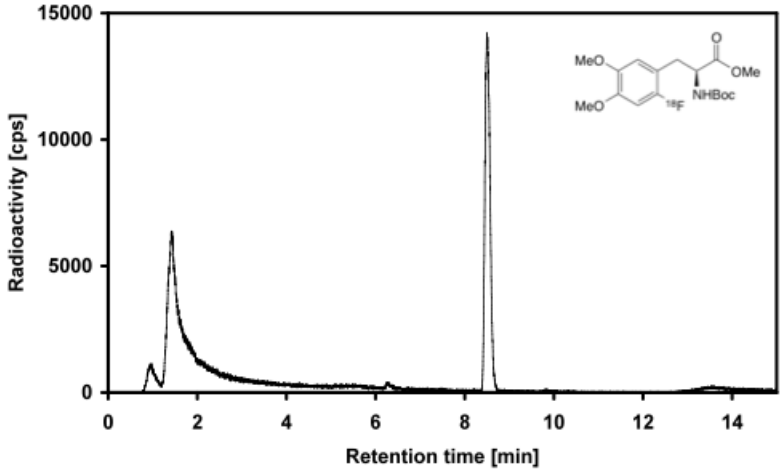
Specific radioactivity measurements of 6-[^{18}F]fluoro-L-dopa **[^{18}F]1-11** were performed using a reverse phase analytical column (Waters Atlantis dC18 Column 5µm, 150mm x 3,9mm). Elution was performed with 70mM KH_2PO_4, with a flow rate of 1 mL/min.

HPLC Chromatograms

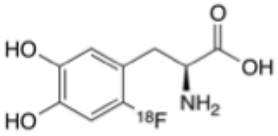
Radiolabelled L-DOPA intermediate [^{18}F]2-87



Radiolabelled intermediate [^{18}F]2-90



6-[^{18}F]Fluoro-L-dopa [^{18}F]1-11



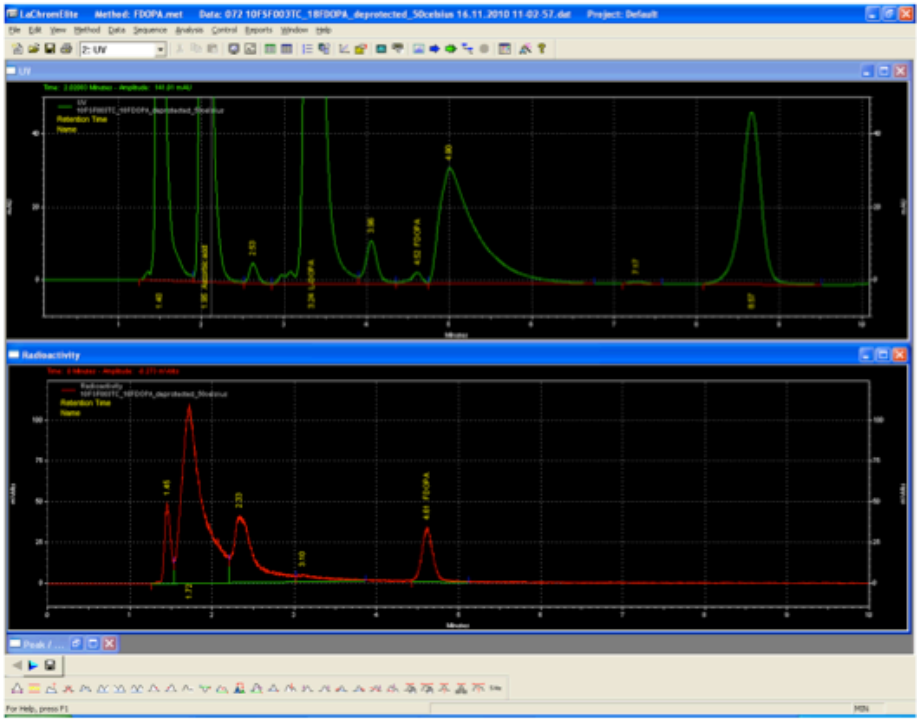


Figure 5.2. Crude reaction mixture of 6-[^{18}F]Fluoro-L-DOPA analysed by HPLC using System C. **Green:** UV absorption at 280 nm. Product retention time: 4.52 min. **Red:** Radioactivity. Product retention time: 4.61 min.

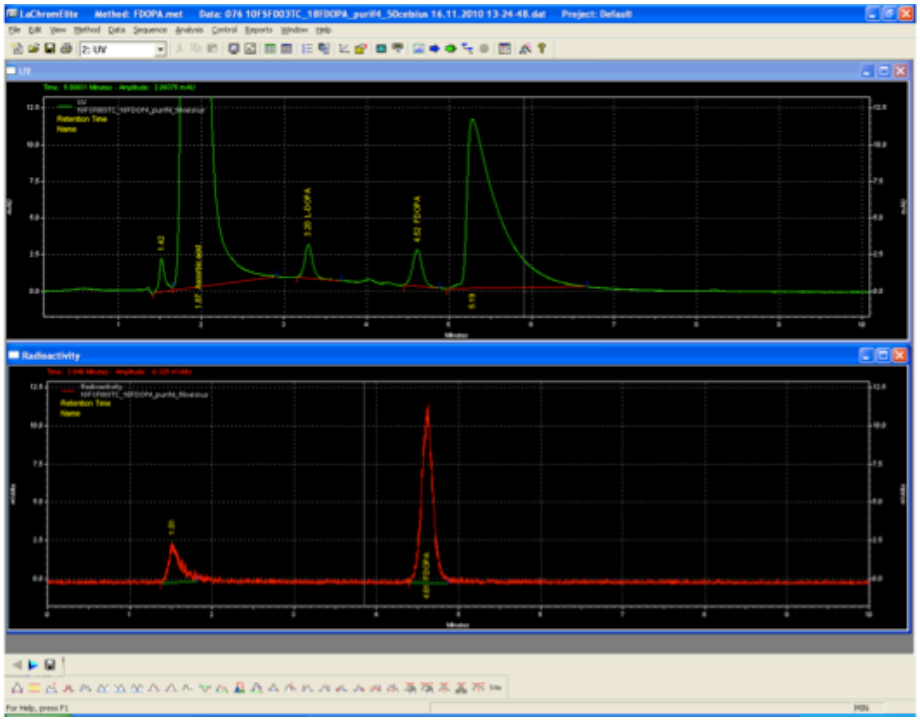


Figure 5.3. After preparative HPLC separation of 6-[^{18}F]-Fluoro-L-DOPA using System C. **Green:** UV absorption at 280 nm. Product retention time: 4.52 min. **Red:** Radioactivity. Product retention time: 4.61 min.

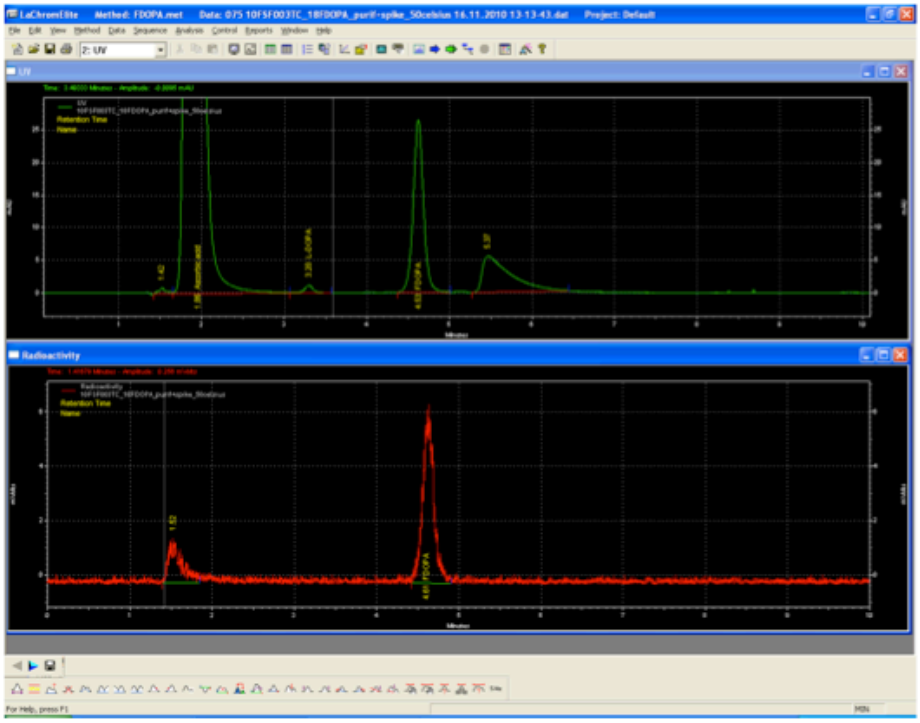
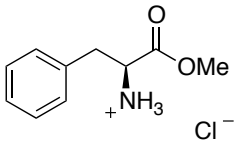


Figure 5.4. 6-[^{18}F]-Fluoro-L-DOPA after preparative HPLC separation co-injected with authentic 6-Fluoro-L-DOPA using System C. **Green:** UV absorption at 280 nm. Product retention time: 4.52 min. **Red:** Radioactivity. Product retention time: 4.61 min.

5.5 Experimental Data for Chapter 3

5.5.1 Palladium complexes, ligands and fluorinated reference compounds

L-Phenylalanine methyl ester hydrochloride salt (3-56)

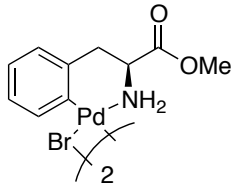


Thionyl chloride (13.2 mL, 181.6 mmol, 5.0 equiv.) was added dropwise to a solution of L-phenylalanine (6.00 g, 36.3 mmol) in MeOH (120 mL) at 0 °C. The solution was allowed to warm up to room temperature and stirred for a further 12 hours. The solvent was removed *in vacuo* and the resulting yellow foam used with out further purification (6.9 g, >99%). Data corresponded to those reported in the literature.[344]

^{1}H NMR (400 MHz, D_2O) δ 7.36-7.33 (m, 3H), 7.24-7.19 (m, 2H), 4.36 (m, 1H, ABX system), 3.76 (s, 3H), 3.26-3.17 (m, 2H, ABX system); **^{13}C NMR** (101 MHz, D_2O) δ 172.5, 136.6, 131.4, 131.2, 130.7, 54.7, 53.8, 36.2; **Mp** 159-160 °C (lit. 158-160 °C [345]).

Phenylalanine bromo-bridged palladium dimer (3-57)

(*S*,*S*)-[Pd2{2(C,N)-$C_6H_4CH_2CH(CO_2Me)NH_2$-2}2(μ-Br)$_2$]

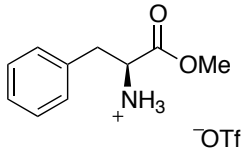


L-phenylalanine methyl ester hydrochloride (0.64 g, 2.96 mmol) was added to a solution of palladium(II) acetate (0.66 g, 2.96 mmol) in CH_2Cl_2 (40 mL) and stirred for 6 days and room temperature, before being filtered through $MgSO_4$ to remove the small amount of metallic palladium formed. The filtrate was concentrated *in vacuo* and the residue was dissolved in CH_2Cl_2 (3 mL). Et_2O (20 mL) was added to precipitate an orange/brown solid **A**, which was filtered and dried (320 mg). The precipitate is known to consist of a mixture of species so concise NMR analysis was unsuccessful.[222] As a result, the precipitate was carried on to the next step without further purification. Sodium bromide (0.50 g, 6.53 mmol) was added to a solution of the mixture **A** (320 mg) in acetone (17 mL) and stirred at room temperature for 12

hours. The solvent was evaporated and the resulting residue taken up in CH_2Cl_2 (10 mL) before being filtered through $MgSO_4$. The filtrate was concentrated *in vacuo* and Et_2O (10 mL) was added to obtain an orange solid, which was subsequently washed with Et_2O (2 x 2 mL) and recrystallised (CH_2Cl_2/Et_2O) to afford pure complex **3-57** (234 mg, 32%). Data corresponded to those reported in the literature.[222]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (d, *J* = 7.0 Hz, 1H), 6.83 (t, *J* = 7.0 Hz, 1H), 6.78-6.70 (m, 2H), 4.31 (br s, 1H), 4.25 (br s, 2H), 3.77 (br s, 1H) 3.58 (s, 3H), 3.23 (dd, *J* = 13.5, 5.0 Hz, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 172.2, 140.9, 136.9, 134.4, 127.5, 125.3, 124.8, 52.8, 49.8, 45.5. **Mp** 145-146 °C (lit. 147 °C [222]).

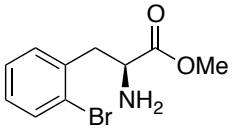
L-Phenylalanine methyl ester triflate salt (3-64)



A solution silver(I) triflate (2.50 g, 7.46 mmol, 1.0 equiv.) in water (1.2 mL) was added to L-phenylalanine methyl ester hydrochloride salt **3-56** (1.59 g, 7.46 mmol) in water (5.0 mL) at 0 °C and stirred for 20 minutes. The AgCl precipitate was removed by filtration and the filtrate was concentrated *in vacuo* to afford the product as a white solid (2.31 g, 94%). The data corresponded to those reported in the literature.[227]

^{1}H NMR (400 MHz, D_2O) δ 7.35-7.25 (m, 3H), 7.18 (dd, *J* = 7.5, 2.0 Hz, 2H), 4.32 (m, ABX system, 1H), 3.73 (s, 3H), 3.30-3.10 (m, ABX system, 2H); **^{13}C NMR** (101 MHz, D_2O) δ 170.4, 134.1, 129.7, 129.6, 128.4, 54.4, 53.9, 35.9; **Mp** 149-150 °C (lit. 151 °C[346]).

2-Bromo-L-phenylalanine ethyl ester (3-65)



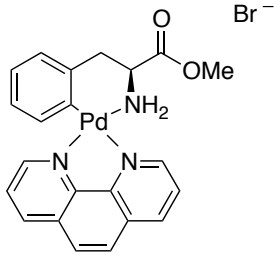
Bromine (0.05 mg, 2.3 µL, 0.28 mmol, 2.0 equiv.) was added carefully to a solution of complex **3-57** (0.1 g, 0.14 mmol) in CH_2Cl_2 (5 mL) and the resulting mixture was stirred at room temperature for 12 hours. The reaction mixture was filtered through a pad of Celite and the solvent was evaporated *in vacuo* until ~0.5 mL remained. Pentane (5 mL) was added to precipitate a yellow solid, which was obtained by filtration and redissolved in CH_2Cl_2 (5 mL). Phenanthroline hydrate (55 mg, 0.28

mmol) was added and the reaction mixture was stirred at room temperature for 3 hours. The resulting [$PdBr_2$(phen)] was removed by filtration and the filtrate was concentrated *in vacuo*. The crude product was subsequently purified by preparative TLC (Et_2O) to afford the product as a yellow oil (12 mg, 33%). Data corresponded to those reported in the literature.[222]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, *J* = 8.0 Hz, 1H), 7.33-7.23 (m, 2H), 7.12 (t, *J* = 7.5 Hz, 1H), 3.85 (br s, 1H), 3.65 (s, 3H), 3.50 (br s, 1H), 3.22 (br s, 1H), 1.61 (br s, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 171.4, 135.0, 133.1, 131.7, 129.1, 127.7, 125.0, 53.5, 52.5, 40.3.

Phenylalanine 1,10-phenanthroline palladium complex (3-67)

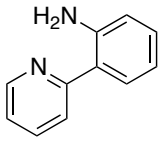
(*S,S*)-[Pd{(*C,N*)-$C_6H_4CH_2CH(CO_2Me)NH_2$}(phenanthroline)]Br



1,10-Phenanthroline (72 mg, 0.4 mmol, 2.0 equiv.) was added to a solution of phenylalanine bromo-bridged palladium dimer **3-57** (0.15 g, 0.2 mmol) in CH_2Cl_2 (0.3 mL) and stirred at room temperature for 20 minutes. Hexane (1 mL) was slowly added to precipitate the desired monomeric complex **3-67** as a pale beige yellow solid, which was dried under air for 20 minutes. Recrystallisation from CH_2Cl_2-pentane afforded the product as a pale brown solid (0.13 g, 59%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.79 (br s, 1H), 8.70 (d, *J* = 8.0 Hz, 1H), 8.58 (d, *J* = 8.0 Hz, 1H), 8.03 (br s, 3H), 7.81 (br s, 1H), 7.29 (s, 2H), 7.11 (br m, 2H), 6.99 (br s, 1H), 4.83-4.00 (br m, 2H), 3.66 (s, 3H), 3.35 (br d, *J* = 10.0 Hz, 1H), 1.91 (br s, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 172.6, 161.6, 152.5, 151.0, 147.0, 143.9, 139.2, 138.5, 137.1, 134.5, 129.9, 129.7, 127.9, 127.0, 126.6, 126.6, 126.1, 53.0, 50.8, 44.9; **IR** (neat) ν 3052, 2360, 1736, 1576, 1518, 1065; **EA** Found: C, 49.44; H, 3.84; N, 7.22%, Calc. for $C_{22}H_{20}$-BrN_3O_2Pd: C, 48.51; H, 3.70; N, 7.71%; **Mp** 230°C (decomp.).

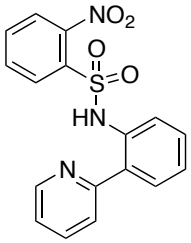
2-(2-Pyridinyl)aniline (3-70)



2-Bromopyridine (0.72 g, 4.56 mmol, 0.43 mL), $Pd(PPh_3)_4$ (0.27 g, 0.23 mmol, 5 mol%) and K_2CO_3 (0.95 g, 6.84 mmol, 1.5 equiv.) were added to 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (1.00 g, 5.46 mmol, 1.2 equiv.) in DME:H_2O (1:1, 16 mL) and heated to 100 ^oC for 3 hours. After cooling to room temperature, the two phases were separated and the aqueous layer extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (20 mL) and dried over $MgSO_4$. Filtration, concentration of the solvent *in vacuo* and flash column chromatography (20% EtOAc-petroleum ether (30 - 40 ^oC)) afforded the product as a brown oil (0.76 g, 97%). Data corresponded to those reported in the literature.[209]

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.66-8.57 (m, 1H), 7.81-7.61 (m, 2H), 7.53 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.29-7.08 (m, 2H), 6.88-6.68 (m, 2H), 5.49 (br s, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 159.4, 147.9, 146.5, 136.9, 129.9, 129.4, 122.2, 121.0, 117.7, 117.2;

2-(2-Pyridinyl)-2-nitrobenzenesulfonanilide (Ligand 3-71)

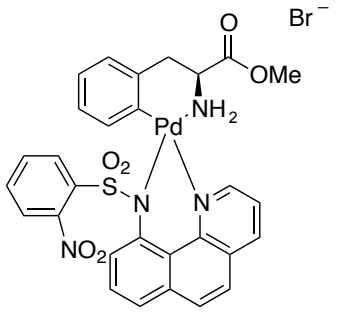


Pyridine (1.42 mL, 17.70 mmol, 4.0 equiv.) and 2-nitrobenzylsulfonyl chloride (1.95 g, 8.86 mmol, 2.0 equiv.) were added to 2-(2-pyridinyl)aniline **3-70** (0.76 g, 4.43 mmol) in CH_2Cl_2 (9 mL) at 0 ^oC. The reaction mixture was allowed to warm to room temperature and stirred for 2 hours, before water (5 mL) was added. The two resulting layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 5 mL), before the combined organic phases were dried over $MgSO_4$. Filtration, concentration of the solvent *in vacuo* and flash column chromatography (60% EtOAc-petroleum ether (30 - 40 ^oC) afforded the product as a yellow solid (0.75 g, 48%). Data corresponded to those reported in the literature.[209]

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.74 (d, *J* = 5.0, Hz, 1H), 7.93 (dd, *J* = 7.5, 2.0 Hz, 1H), 7.81-7.74 (m, 2H), 7.66-7.60 (m, 2H), 7.59-7.55 (m, 3H), 7.39 (td, *J* = 7.5, 1.5 Hz, 1H), 7.31-7.27 (m, 1H), 7.20 (td, *J* = 7.5, 1.0 Hz, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 156.6, 147.8, 137.8, 136.2, 133.4, 133.3, 132.1, 130.8, 130.2, 128.9, 127.0, 124.8, 124.6, 122.2, 121.8, 121.7; **Mp** 90-92 °C (lit. 91-94 °C[209]).

Phenylalanine phenanthroline palladium complex (3-72)

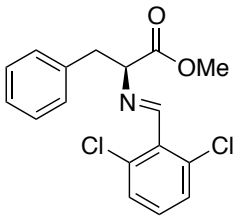
(*S*,*S*)-[Pd{(*C*,*N*)-$C_6H_4CH_2CH(CO_2Me)NH_2$}(ligand)]Br



Ligand **3-71** (0.14 mg, 0.4 mmol, 2.0 equiv.) was added to a solution of phenylalanine bromo-bridged palladium dimer **3-57** (0.15 g, 0.2 mmol) in CH_2Cl_2 (0.3 mL) and stirred at room temperature for 20 minutes. Hexane (1 mL) was slowly added to precipitate the desired monomeric complex **3-72** as a pale beige-yellow solid, which was dried under air for 20 minutes. Recrystallisation from CH_2Cl_2-pentane afforded the product as a pale brown solid (0.13 g, 59%). Owing to its insolubility in all common deuterated solvents, NMR analysis of this compound was unsuccessful.

IR (neat) ν 3089, 2361, 1738, 1541, 1171; **EA** Found: C, 45.79; H, 3.50; N, 7.69%, Calc. for $C_{28}H_{24}BrN_4O_6PdS$: C, 45.95; H, 3.44; N, 7.65 %; **Mp** 215 °C (decomp).

(*S*,*E*)-Ethyl 2-((2,6-dichlorobenzylidene)amino)-3-phenylpropanoate (3-78)

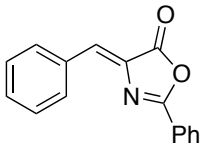


Triethylamine (0.28 mL, 2.0 mmol, 1.0 equiv.), 2,6-chlorobenzaldehyde (0.35 g, 2.0 mmol, 1.0 equiv.) and $MgSO_4$ (0.24 g, 2.0 mmol, 1.0 equiv.) were added to a solution of L-phenylalanine methyl ester hydrochloride (0.43 g, 2.0 mmol) in CH_2Cl_2 (30 mL) and stirred at room temperature for 20 hours. The solution was filtered and the solvent

was concentrated *in vacuo* to afford the desired product as a yellow oil (0.56 g, 84%) and used without further purification. Data corresponded to those reported in the literature.[231]

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (s, 1H), 7.22-7.08 (m, 8H), 4.26 (dd, *J* = 9.0, 5.0 Hz, 1H), 3.67 (s, 3H), 3.35 (dd, *J* = 14.0, 5.0 Hz, 1H), 3.12 (dd, *J* = 14.0, 8.5 Hz, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 171.3, 159.9, 136.9, 134.6, 132.4, 130.6, 129.5, 128.6, 128.5, 126.6, 75.5, 52.3, 39.3.

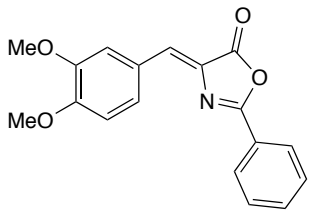
(*Z*)-4-Benzylidene-2-phenyloxazol-5(4*H*)-one (3-82a)



Sodium acetate (0.24 g, 1.4 mmol, 12 mol%), acetic anhydride (2.72 mL, 28.8 mmol, 2.4 equiv.) and hippuric acid (2.16 g, 12.0 mmol) were added to a solution of benzaldehyde (1.44 mL, 14.4 mmol, 1.2 equiv.) in THF (48 mL) at room temperature. The reaction mixture was refluxed for 12 hours before being cooled down, diluted with EtOAc (20 mL) and washed with $NaHCO_3$ (sat. aq., 20 mL). The organic layer was dried over $MgSO_4$ filtered and concentrated. Flash column chromatography (30% EtOAc-petroleum ether (30 - 40 ^{o}C) afforded the product as a pale yellow solid (1.71 g, 58%). Data corresponded to those reported in the literature.[347]

^{1}H NMR (400 MHz, $CO(CD_3)_2$) δ 8.35 (dd, *J* = 8.0, 2.0 Hz, 2H), 8.20 (dd, *J* = 8.0, 1.5 Hz, 2H), 7.73 (tt, *J* = 7.5, 2.0 Hz, 1H), 7.65 (t, *J* = 8.0 Hz, 2H), 7.58-7.49 (m, 3H), 7.29 (s, 1H); **^{13}C NMR** (101 MHz, $CO(CD_3)_2$) δ 167.3, 164.1, 134.2, 134.0, 133.8, 132.8, 131.5, 131.2, 129.6, 129.3, 128.5, 126.1; **Mp** 163-165 ^{o}C (lit. 165-166 ^{o}C[348]).

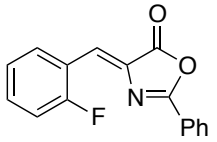
(*Z*)-4-(3,4-dimethoxybenzylidene)-2-phenyloxazol-5(4*H*)-one (3-82b)



Sodium acetate (0.24 g, 1.4 mmol), acetic anhydride (2.72 mL, 28.8 mmol) and hippuric acid (2.16 g, 12.0 mmol) were added to a solution of veratraldehyde (2.39 g, 14.4 mmol) in THF (48 mL) at room temperature. The reaction mixture was refluxed for 12 hours before being cooled down, diluted with EtOAc (20 mL) and washed with $NaHCO_3$ (sat. aq., 20 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated. Flash column chromatography (30% EtOAc-petroleum ether (30 - 40 ^oC) afforded the product as a bright yellow solid (3.57 g, 96%). Data corresponded to those reported in the literature.[349]

^{1}H NMR (400 MHz, $CO(CD_3)_2$) δ 8.28 (d, *J* = 2.0 Hz, 1H), 8.24-8.21 (m, 1H), 8.19 (d, *J* = 2.0 Hz, 1H), 7.81 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.76-7.59 (m, 3H), 7.27 (s, 1H), 7.14 (d, *J* = 8.0 Hz, 1H), 3.99 (s, 3H), 3.96 (s, 3H); **^{13}C NMR** (101 MHz, $CO(CD_3)_2$) δ 167.0, 162.4, 152.6, 149.5, 131.5, 131.0, 129.2, 127.8, 126.8, 126.0, 114.4, 111.9, 111.4, 55.3, 55.2; Mp 150-152 ^oC (lit. 152-153 ^oC[350])

(*Z*)-4-(2-Fluorobenzylidene)-2-phenyloxazol-5(4*H*)-one (3-84a)

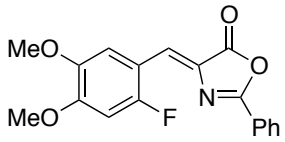


Sodium acetate (0.12 g, 0.8 mmol, 13 mol%), acetic anhydride (1.36 mL, 14.4 mmol, 2.4 equiv.) and hippuric acid (1.03 g, 6.0 mmol) were added to a solution of 2-fluorobenzaldehyde (0.89 g, 7.2 mmol, 1.2 equiv.) in THF (24 mL) at room temperature. The reaction mixture was refluxed for 12 hours before being cooled down, diluted with EtOAc (10 mL) and washed with $NaHCO_3$ (sat. aq., 10 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated. Purification by flash column chromatography (30% EtOAc-petroleum ether (30 - 40 ^oC) afforded the product as a pale yellow solid (1.24 g, 64%). Owing to its insolubility in all common

deuterated solvents, NMR analysis of this compound was unsuccessful. Data corresponded to those reported in the literature.[351]

^{1}H NMR (377 MHz, CD_3CN) δ 8.94 (td, *J* = 16.0, 2.0 Hz, 1H), 8.23 (dd, *J* = 8.5, 1.5 Hz, 2H), 7.74 (tt, *J* = 15.0, 2.5 Hz, 1H), 7.65 (t, *J* = 15.5 Hz, 2H), 7.57 (ddd, *J* = 15.5, 5.0, 2.0 Hz, 1H), 7.46 (s, 1H), 7.41 (t, *J* = 8.0 Hz, 1H), 7.27 (ddd, *J* = 11.3, 8.0, 1.0 Hz, 1H); **^{13}C NMR** (100 MHz, CD_3CN) δ **^{19}F NMR** (377 MHz, CD_3CN) δ –116.3; **Mp** 163-165 °C (lit. 166-167 °C[351])

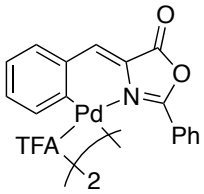
(*Z*)-4-(2-Fluoro-4,5-dimethoxybenzylidene)-2-phenyloxazol-5(4*H*)-one (3-84b)



Sodium acetate (0.05 g, 0.6 mmol, 30 mol%), acetic anhydride (1.0 mL, 9.8 mmol, 5 equiv.) and hippuric acid (0.36 g, 2.0 mmol) were added to a solution of 6-fluoroveratraldehyde (0.45 g, 2.5 mmol, 1.25 equiv.) in THF (7 mL) at room temperature. The reaction mixture was refluxed for 12 hours before being cooled down, diluted with EtOAc (5 mL) and washed with $NaHCO_3$ (sat. aq., 10 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated. Flash column chromatography (20% EtOAc-petroleum ether (30 - 40 °C) afforded the product as a bright yellow solid (0.43 g, 66%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (d, *J* = 7.0 Hz, 1H), 8.12 (d, *J* = 8.0 Hz, 2H), 7.63 (tt, *J* = 7.5, 2.0 Hz, 1H), 7.56 (t, *J* = 8.0 Hz, 3H), 6.68 (d, *J* = 11.5 Hz, 1H), 4.05 (s, 3H), 3.97 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 167.4, 162.8, 158.2 (d, *J* = 254.0 Hz), 153.3 (d, *J* = 10.0 Hz), 145.7, 133.3, 131.7, 129.0, 128.1, 127.7, 125.7, 123.0 (d, *J* = 6.5 Hz), 112.8, 99.4 (d, *J* = 28.0 Hz), 56.4, 56.3; **^{19}F NMR** (377 MHz, $CDCl_3$) δ –118.9; **IR** 3031, 1764, 1649, 1255, 1166; **HRMS** found 328.0998, calc. 328.0985 $[C_{18}H_{14}FNO_4 + H]^+$; **Mp** 179-180 °C.

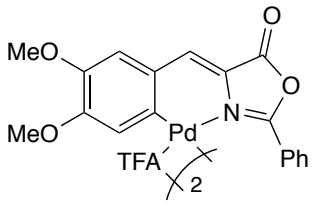
Orthopalladated (*Z*)-4-benzylidene-2-phenyloxazol-5(4*H*)-one TFA-bridged dimer (3-85a)



Palladium(II) acetate (0.18 g, 0.81 mmol) was added to (4*Z*)-benzylidene-2-phenyloxazol-5(4*H*)-one **3-82a** (0.2 g, 0.81 mmol, 1.0 equiv.) in trifluoroacetic acid (15 mL) and heated to 75 ^{o}C for 4 hours. The reaction mixture was cooled to room temperature and diluted with water (10 mL). The yellow solid formed was filtered, washed with water (3 x 5 mL) and dried under vaccum to provide the product (0.42 g, 56%). Data corresponded to those reported in the literature.[352]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, *J* = 7.5 Hz, 2H), 7.61 (tt, *J* = 7.5, 2.5 Hz, 1H), 7.56 (s, 1H), 7.47 (t, *J* = 8.0 Hz, 2H), 7.35 (d, *J* = 7.5 Hz, 1H), 7.30-7.24 (m, 1H), 7.19-7.15 (m, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 189.2, 168.2, 160.8, 138.8, 136.0, 134.9, 133.9, 133.5, 131.2, 130.7, 128.5, 126.4, 122.9, 122.2, 120.3; **^{19}F NMR** (377 MHz, $CDCl_3$) δ –75.2;

(*Z*)-4-(3,4-Dimethoxybenzylidene)-2-phenyloxazol-5(4*H*)-one TFA-bridged dimer (3-85b)

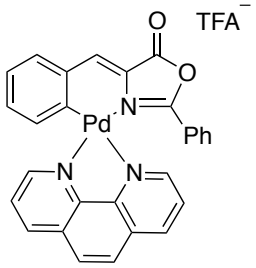


Palladium acetate (0.19 g, 0.85 mmol) was added to a solution of **3-82b** (0.26 g, 0.85 mmol) in TFA (10 mL) and stirred for 5 minutes at room temperature. Water (10 mL) was added and the precipitate formed was filtered and washed with water (3 x 5 mL) to remove any remaining acid. The solid was dried under high vacuum to provide the desired complex **3-85b** as an orange solid (0.45 g, 51%). Data corresponded to those reported in the literature.[237]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, *J* = 8.0 Hz, 2H), 7.51 (t, *J* = 8.0 Hz, 1H), 7.42 (s, 1H), 7.37 (t, *J* = 8.0 Hz, 2H), 6.79 (s, 1H), 6.57 (s, 1H), 3.95 (s, 3H), 3.71 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 186.5, 166.7, 161.2, 150.5, 147.6, 138.8, 134.5, 130.6,

129.9, 128.4, 122.5, 122.2, 120.9, 115.2, 114.3, 56.2, 55.8; **^{19}F NMR** (377 MHz, $CDCl_3$) δ = –74.8;

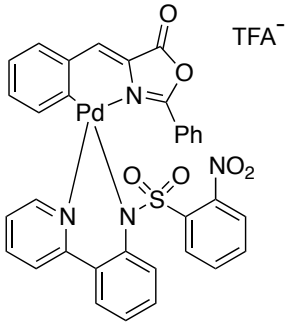
(*Z*)-4-Benzylidene-2-phenyloxazol-5(4*H*)-one 1,10-phenathroline monomer (3-88a)



1,10-Phenanthroline (72 mg, 0.4 mmol, 2.0 equiv.) was added to a solution of orthopalladated (*Z*)-2-phenyl-4-arylidene-5(4*H*)-oxazolone TFA-bridged dimer **3-85a** (0.15 g, 0.2 mmol) in CH_2Cl_2 (0.3 mL) and was stirred at room temperature until the reaction mixture formed a thick suspension (*ca.* 20 minutes). The suspension was filtered and the yellow solid was washed with CH_2Cl_2 (3 x 3 mL) and dried under vacuum for 20 minutes to give the product (0.17 g, 62%). Owing to its insolubility in all common deuterated solvents, NMR analysis of this compound was unsuccessful.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.05 (dd, *J* = 8.5, 1.5 Hz, 1H), 8.94 (dd, *J* = 5.5, 1.0 Hz, 1H), 8.88-8.79 (m, 2H), 8.77 (dd, *J* = 8.5, 1.5 Hz, 1H), 8.43 (dd, *J* = 5.5, 1.5 Hz, 1H), 8.32 (q, *J* = 9.0 Hz, 2H), 8.20 (dd, *J* = 8.0, 5.0 Hz, 1H), 7.97 (s, 1H), 7.81 (d, *J* = 8.0 Hz, 1H), 7.76 (tt, *J* = 7.5, 2.0 Hz, 1H), 7.70 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.62-7.52 (m, 4H), 7.43 (dt, *J* = 7.0, 1.0 Hz, 1H); **^{19}F NMR** (377 MHz, $CDCl_3$) δ –75.8; **IR** (neat) ν 2953, 1821, 1637, 1566, 1156; **EA** Found: C, 50.82; H, 2.63; N, 6.23%, Calc. for $C_{29}H_{18}F_3N_3O_5PdS$: C, 50.93; H, 2.65; N, 6.14%.

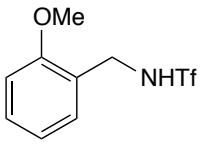
(*Z*)-4-Benzylidene-2-phenyloxazol-5(4*H*)-one 2-(2-Pyridinyl)-2-nitrobenzenesulfonanilide monomer (3-89a)



2-(2-Pyridinyl)-2-nitrobenzenesulfonanilide **3-71** (0.14 mg, 0.4 mmol, 2.0 equiv.) was added to a solution of orthopalladated (*Z*)-2-phenyl-4-arylidene-5(4*H*)-oxazolone TFA-bridged dimer **3-85a** (0.15 g, 0.2 mmol) in CH_2Cl_2 (0.2 mL) and was stirred at room temperature until the reaction mixture formed a thick suspension (*ca.* 10 minutes). The reaction mixture was diluted with CH_2Cl_2 (0.5 mL) and the yellow suspension was filtered. The yellow solid was washed with CH_2Cl_2 (3 x 3 mL) and dried under vacuum for 20 minutes to provide the product (0.21 g, 61%). Owing to its insolubility in all common deuterated solvents, NMR analysis of this compound was unsuccessful.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (d, *J* = 8.0 Hz, 2H), 7.65 (s, 1H), 7.63-7.58 (m, 2H), 7.44-7.38 (m, 3H), 7.35 (dd, *J* = 7.5, 2.0 Hz, 1H), 7.30 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.19-7.17 (m, 2H), 7.13 (d, *J* = 8.0 Hz, 1H), 7.07 (br d, *J* = 7.5 Hz, 2H), 7.01 (td, *J* = 7.5, 1.5 Hz, 1H), 6.96 (dd, *J* = 8.0, 1.5 Hz, 2H), 6.85 (dd, *J* = 8.0, 1.0 Hz, 1H), 6.78 (dd, *J* = 8.0, 1.5 Hz, 1H), 6.69-6.63 (m, 1H), 6.03 (dd, *J* = 8.0, 1.0 Hz, 1H); **^{19}F NMR** (377 MHz, $CDCl_3$) δ –75.6; **IR** (neat) ν 2980, 2543, 1829, 1618, 1541, 1151; **EA** Found: C, 47.91; H, 2.67; N, 6.52%, Calc. for $C_{34}H_{23}F_3N_4O_9PdS_2$: C, 47.53; H, 2.70, N, 6.52%.

2-Methoxybenzyltriflamide (3-93)



Triethylamine (2.5 mL, 18.19 mmol, 2.1 equiv.) was added dropwise to a solution of 2-methoxybenzylamine (1.13 mL, 8.66 mmol) in anhydrous CH_2Cl_2 (25 mL) at –78 ^oC. After stirring for 5 minutes, trifluoromethanesulfonic anhydride (1.5 mL, 9.09 mmol, 1.05 equiv.) was added dropwise and the resulting mixture was stirred at this temperature for 1 hour before being quenched by water (20 mL). The aqueous layer was extracted with CH_2Cl_2 (15 mL x 2) and the combined organic phases were washed with brine and dried over $MgSO_4$. Filtration, evaporation of the solvent *in vacuo* and purification by flash column chromatography (1:20 – 1:10, EtOAc-hexane) afforded the desired product as a yellow oil (1.59 g, 56%). Data corresponded to those reported in the literature.[207]

^{1}H NMR ($CDCl_3$, 400 MHz), δ 7.35 (dt, *J* = 7.5, 1.6 Hz, 1H), 7.25 (dd, *J* = 7.5, 1.6

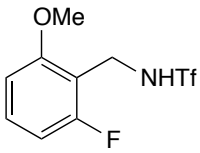
Hz, 1H), 6.96 (dt, *J* = 7.4, 1.0 Hz, 1H), 6.92 (d, *J* = 8.4 Hz, 1H), 5.71 (br, 1H), 4.42 (d, *J* = 5.2 Hz, 2H), 3.88 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 157.4, 130.6, 130.2, 124.2, 123.3, 121.3 (q, *J* = 321.6 Hz), 110.9, 55.8, 45.4; **^{19}F NMR** (377 MHz, $CDCl_3$) δ –77.8;

$[Pd(MeCN)_4](OTf)_2$ (3-94)

Trifluoromethanesulfonic acid (0.67 g, 4.42 mmol, 2.9 equiv.) was added dropwise to a stirred solution of $Pd(OAc)_2$ (0.34 g, 1.52 mmol) in MeCN (29 mL) and the colour of the solution changed from dark orange to pale yellow. The addition of Et_2O (40 mL) caused precipitation of a pale yellow powder and this suspension was left to stand for 2 hours at room temperature. This allowed the powder to settle and the liquid was carefully decanted. The solid was washed with Et_2O (2 x 10 mL) and dried under vacuum to afford xx as a pale yellow solid (0.48 g, 56%). The data corresponded to those reported in the literature.[246]

EA Found: C, 19.61; H, 2.02; N, 9.67%, Calc. for $C_{10}H_{12}F_6N_4O_6PdS_2$: C, 21.12; H, 2.13, N, 9.85%.

6-Fluoro-2-methoxybenzyltriflamide (3-95)



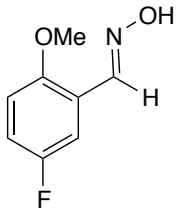
$[Pd(MeCN)_4](OTf)_2$ (28 mg, 0.05 mmol, 0.1 equiv.), *N*-fluoro-2,4,6-trimethylpyridinium triflate (0.22 g, 0.75 mmol, 1.5 equiv.) and NMP (24 µL, 0.25 mmol, 0.5 equiv.) were added to a solution of 2-methoxybenzyltriflamide **3-93** (0.13 g, 0.5 mmol) in DCE (1.3 mL) in a sealed tube under air. The reaction mixture was stirred at 120 ^{o}C for 1 hour before being cooled to room temperature. The solvent was evaporated *in vacuo* and, following purification by flash column chromatography (5-10% EtOAc- hexane), the product was afforded as a clear crystals (0.11 g, 76%). Data corresponded to those reported in the literature.[207]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33-7.27 (m, 1H), 6.75 (t, *J* = 8.6 Hz, 1H), 6.72 (d, *J* = 8.6 Hz, 1H), 5.54 (br, 1H), 4.53 (d, *J* = 6.2, 2H), 3.91 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 160.7 (d, $J_{C\text{-}F}$ = 247.5 Hz), 158.7 (d, $J_{C\text{-}F}$ = 6.9 Hz), 130.5 (d, $J_{C\text{-}F}$ = 10.7 Hz), 119.6 (q, $J_{C\text{-}F}$ = 320.6 Hz), 111.5 (d, $J_{C\text{-}F}$ = 18.0 Hz), 108.4 (d, $J_{C\text{-}F}$ = 23.0 Hz), 106.3

(d, $J_{C\text{-}F}$ = 3.1 Hz), 56.1, 36.9 (d, $J_{C\text{-}F}$ = 5.5 Hz); **^{19}F NMR** (377 MHz, $CDCl_3$) δ –77.8, –116.9; **Mp** 123-125 °C.

When the effect of different pyridine-based additives on the yield of **3-95** was investigated, the additives were added to the reaction mixture alongside the other reagents as described above.

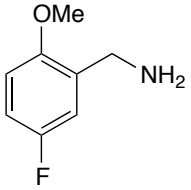
(*E*)-5-Fluoro-2-methoxybenzaldehyde oxime (3-99)



5-Fluoro-2-methoxybenzaldehyde **3-98** was added to a stirred solution of $NH_2OH{\cdot}HCl$ (7.14 g, 102.7 mmol, 1.2 equiv.) in H_2O (12 mL) and cooled to 5 °C. A solution of Na_2CO_3 (5.44 g, 51.4 mmol) in water (20 mL) was added dropwise while the reaction mixture was stirred at 0 °C. After stirring overnight at room temperature, the product was extracted with $CHCl_3$ (3 x 10 mL) and the combined organic extracts were dried over $MgSO_4$. Concentration of the solvent *in vacuo* afforded the oxime as a beige solid (11.2 g, 90%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46 (d, *J* = 1.7 Hz, 1H), 7.70 (br s, 1H), 7.44 (dd, *J* = 9.0, 3.0 Hz, 1H), 7.05 (ddd, *J* = 9.0, 8.0, 3.0 Hz, 1H), 6.85 (dd, *J* = 9.2, 4.0 Hz, 1H), 3.85 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 156.9 (d, $J_{C\text{-}F}$ = 241.7 Hz), 153.8, 145.8 (d, $J_{C\text{-}F}$ = 2.4 Hz), 121.6 (d, $J_{C\text{-}F}$ = 30.1 Hz), 117.4 (d, $J_{C\text{-}F}$ = 24.0 Hz), 112.9 (d, $J_{C\text{-}F}$ = 25.0 Hz), 112.3 (d, $J_{C\text{-}F}$ = 8.5 Hz), 56.2; **^{19}F NMR** (377 MHz, $CDCl_3$) δ –124.3; **HRMS** found 170.0623, calc. 170.0617 $[C_8H_9FNO_2 + H]^+$; **IR** (neat) ν 3223, 1499; **Mp** 123-125 °C.

5-Fluoro-2-methoxybenzylamine hydrochloride (3-100)

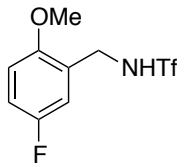


(*E*)-5-Fluoro-2-methoxybenzaldehyde oxime (0.49 g, 2.91 mmol) was added to $LiBH_4$ (2 M in THF, 16 mL) and the resulting mixture was stirred for 12 hours at 80 °C. The

reaction mixture was cooled to room temperature, before being diluted with EtOAc (50 mL). HCl (6 M, 50 mL) was added to acidify the reaction mixture (pH 1), the aqueous layer was extracted with EtOAc (3 x 50 mL) and the combined organic phases were discarded. The aqueous layer was basified with 3 M NaOH and extracted with EtOAc (3 x 50 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated to afford crude **3-100** as a pale yellow oil (0.17 g, 38%). The compound **3-100** was used without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.98 (dd, J = 9.0, 3.0 Hz, 1H), 6.90 (dt, J = 8.5, 3.0 Hz, 1H), 6.77 (dd, J = 9.0, 4.5 Hz, 1H), 3.82 (s, 3H), 3.80 (s, 2H), 1.71 (br s, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 156.9 (d, $J_{C\text{-}F}$ = 239.5 Hz), 153.4 (d, $J_{C\text{-}F}$ = 2.0 Hz), 131.7 (d, $J_{C\text{-}F}$ = 7.0 Hz), 115.2 (d, $J_{C\text{-}F}$ = 23.0 Hz), 113.4 (d, $J_{C\text{-}F}$ = 23.0 Hz), 110.9 (d, $J_{C\text{-}F}$ = 8.0 Hz), 55.7, 41.8; **^{19}F NMR** (377 MHz, $CDCl_3$) δ –124.2; **HRMS** found 156.0901, calc. 156.0825 $[C_8H_{11}FNO + H]^+$; **IR** (neat) ν 2861, 1600, 1492, 1204.

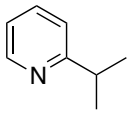
5-Fluoro-2-methoxybenzyltriflamide (3-96)



Triethylamine (0.36 mL, 2.58 mmol, 2.0 equiv.) and trifluoroacetic anhydride (0.19 mL, 1.35 mmol, 1.05 equiv.) was added to a solution of 5-fluoro-2-methoxybenzylamine **3-100** (0.2 g, 1.29 mmol) in CH_2Cl_2 (3 mL) at –78 ^{o}C and the resulting reaction mixture was stirred at this temperature for 1 hour. Water (2 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic extracts were dried over $MgSO_4$, filtered and the solvent evaporated *in vacuo*. Following purification by flash column chromatography (10% EtOAc-petroleum ether (30 - 40 ^{o}C), the product was obtained as a clear solid (0.23 g, 61%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11 (br s, 1H), 6.92-6.83 (m, 2H), 6.73 (dd, J = 8.0, 4.0 Hz, 1H), 4.37 (d, J = 6.0 Hz, 2H), 3.75 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 157.1 (q, $J_{C\text{-}F}$ = 36.5 Hz), 156.8 (d, $J_{C\text{-}F}$ = 241.0 Hz), 153.6 (d, $J_{C\text{-}F}$ = 2.0 Hz), 125.4 (d, $J_{C\text{-}F}$ = 7.5 Hz), 116.6 (d, $J_{C\text{-}F}$ = 24.0 Hz), 115.3 (d, $J_{C\text{-}F}$ = 23.0 Hz), 111.4 (d, $J_{C\text{-}F}$ = 8.0 Hz), 55.7, 41.8; **^{19}F NMR** (377 MHz, $CDCl_3$) δ –76.3, –123.5; **HRMS** found 310.0141, calc. 310.0137 $[C_9H_9F_4NO_3S + Na]^+$; **IR** (neat) ν 3102, 1739, 1391, 1199; **Mp** 64-65 ^{o}C.

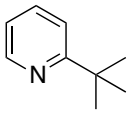
2-*iso*-Propylpyridine (3-112)



n-Butyllithium (9.5 mL, 21 mmol, 1.05 equiv.) was added dropwise, over 15 minutes, to a solution of 2-ethylpyridine (2.3 mL, 20 mmol) in THF (20 mL) at –30 ^{o}C, while keeping the temperature between –20 and –30 ^{o}C at all times. After stirring at –30 ^{o}C for 1 hour, the reaction mixture was cooled to –50 ^{o}C before iodomethane (1.4 mL, 22 mmol, 1.1 equiv.) in THF (5 mL) was added dropwise, keeping the temperature between –40 and –50 ^{o}C. After stirring for 30 min at –40 ^{o}C, water (10 mL) was added and the aqueous phase was made acidic (pH 1) by the addition of conc. HCl. The aqueous phase was extracted with Et_2O (20 mL) and this organic phase was discarded. The aqueous phase was basified by the addition of solid K_2CO_3 and was subsequently extracted with CH_2Cl_2 (3 x 15 mL). The combined organic extracts were dried over $MgSO_4$, filtered and the solvent was removed *in vacuo*. Following purification by flash column chromatography (5% EtOAc-hexane), the desired product was afforded as a clear oil (0.72 g, 30%). Data corresponded to those reported in the literature.[353]

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47-8.42 (m, 1H), 7.50 (td, *J* = 7.5, 2.0 Hz, 1H), 7.07 (d, *J* = 8.0 Hz, 1H), 7.01-6.96 (m, 1H), 2.98 (sept., *J* = 7.0 Hz, 1H), 1.23 (d, *J* = 7.0 Hz, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 167.2, 149.0, 136.3, 120.9, 120.5, 36.3, 22.5;

2-*tert*-Butylpyridine (3-110b)



Diisopropylamine (0.74 mL, 5.25 mmol, 1.5 equiv.) was added to a solution of potassium *tert*-butoxide (0.17 g, 5.25 mmol, 1.5 equiv.) in anhydrous THF (7 mL) at 0 ^{o}C. The resulting reaction mixture was cooled to –20 ^{o}C and *n*-butyllithium (2.4 mL, 5.25 mmol, 1.5 equiv.) was added dropwise. The resulting solution was stirred at this temperature for 10 minutes before the mixture was further cooled to –50 ^{o}C. 2-*iso*-Propylpyridine (0.43 g, 3.5 mmol) **3-112** was added and the reaction mixture was stirred for 30 minutes. The solution was then cooled to –78 ^{o}C and iodomethane (0.65 mL, 10.5 mmol, 3.0 equiv.) was added dropwise and the reaction mixture stirred at this temperature for a further 2 hours. Water (10 mL) was added and the aqueous phase was made acidic (pH 1) by the addition of conc. HCl. The aqueous phase was

extracted with Et_2O (20 mL) and this organic phase was discarded. The aqueous phase was basified by the addition of solid K_2CO_3 and was subsequently extracted with CH_2Cl_2 (3 x 15 mL). The combined organic extracts were dried over $MgSO_4$, filtered and the solvent was removed *in vacuo*. Following purification by flash column chromatography (5-10% EtOAc-hexane), the desired product was afforded as a clear oil (0.22 g, 47%). Data corresponded to those reported in the literature.[353]
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55-8.51 (m, 1H), 7.58-7.54 (m, 1H), 7.07 (br d, J = 8.0 Hz, 1H), 7.06-7.00 (m, 1H), 1.34 (s, J = 2.0 Hz, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 169.2, 148.5, 136.1, 120.9, 120.6, 119.0, 30.2.

5.5.2 Radiochemistry

5.5.2.1 Preparation of [^{18}F]NFSI

The NFSI precursor **1-55** (8.0 mg, 25 μmol) was dissolved in a mixture of water and acetonitrile (1:9, 1 mL) and the [^{18}F]F_2 gas (prepared as outlined in section 5.3) was bubbled through the solution for 30 seconds at room temperature (Scheme 3.57). Prior to the subsequent radiolabelling studies, water present in the stock solution was removed by azeotropic drying with MeCN. This was carried out by heating the [^{18}F]NFSI stock solution at 60 ^{o}C under a stream of helium until no solvent remained. Anhydrous MeCN (0.5 mL) was added and the drying step was repeated before another aliquot of MeCN (0.5 mL) was added. Aliquots of this [^{18}F]NFSI stock solution were used directly in the subsequent labelling studies without further purification.

The radiochemical yield (RCY) of [^{18}F]NFSI was calculated as the fraction of the injected activity that corresponded to [^{18}F]NFSI and given as a percentage. The mean RCY of [^{18}F]NFSI = 46 ± 8%. All RCYs were decay corrected to the end of the synthesis of [^{18}F]NFSI.

For the calculation of the SA, an authentic reference sample of 'cold' [^{19}F]NFSI (of known amount and volume) was injected onto the HPLC and the peak area of the NFSI peak was measured. This was repeated three times and the average peak area was calculated. Separately, the UV peak area of the radioactive product peak obtained upon the HPLC analysis of the reaction mixture was measured. This allowed for the determination of the amount of 'cold' NFSI in the radioactive sample and, as the

radioactivity of the product peak was known, for the calculation of the SA (radioactivity/amount of 'cold' compound).

Sample calculation of SA:

Average peak area of 'cold' NFSI sample (0.1 μmol/mL)= 787640 mAU

HPLC loop size = 20 μL

Decay-corrected activity of [^{18}F]NFSI product peak = 0.214 MBq

Peak area of [^{18}F]NFSI UV peak = 237217 mAU

Amount of 'cold' NFSI = (237217/787640) x 0.002 = 0.0006 μmol

SA = Radioactivity/micromoles of NFSI = (0.214/0.0006)/1000 = 0.5 GBq/μmol

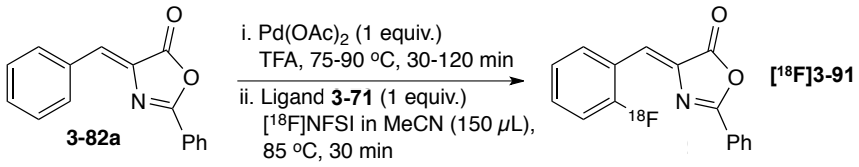
The SA for the preparation of [^{18}F]NFSI ranged from 0.5 to 1.2 GBq/μmol.

5.5.2.2 Strategy 1: One-pot [^{18}F]fluorination reaction

L-Phenylalanine oxazolone precursor **3-82a** (2.5 mg, 10 μmol) and palladium acetate (2.2 mg, 10 μmol, 1.0 equiv.) were dissolved in TFA (150 μL) and the reaction mixture was shaken in an Eppendorf mixer at 90 ^{o}C for 30 minutes. The solvent was evaporated under argon at room temperature, before 2-(2-pyridinyl)-2-nitrobenzenesulfonanilide **3-71** (3.6 mg, 10 μmol, 1.0 equiv.) and an aliquot of [^{18}F]NFSI in MeCN (150 μL) was added. After heating at 85 ^{o}C for 30 minutes, the reaction mixture was analysed by HPLC. The desired [^{18}F]radiolabelled compound **[^{18}F]3-91** was obtained in 6% RCY, in addition to several other radioactive side-products.

Attempts to optimise the selectivity of this radiolabelling reaction are summarised in Table 5.1. For the reaction in entry 4, a stock solution of **3-82a** (1.3 mg, 5 μmol) and palladium acetate (1.1 mg, 5 μmol, 1.0 equiv.) were dissolved in CH_2Cl_2 (100 μL). An aliquot (10 μL) was added to an Eppendorf vial and the solvent was removed under a flow of argon. TFA was added (10 μL) and the reaction mixture was shaken in an Eppendorf mixer at 80 ^{o}C for 90 minutes, before the TFA was evaporated under a flow of argon. An aliquot (10 μL) of a stock solution of 2-(2-pyridinyl)-2-nitrobenzenesulfonanilide **3-71** (1.3 mg, 5 μmol, 1.0 equiv.) in CH_2Cl_2 (100 μL) was

added to the reaction mixture and the solvent was removed under a flow of argon. An aliquot of [^{18}F]NFSI in MeCN (150 μL) was added and, after heating at 85 ^{o}C for 30 min, the reaction mixture was analysed by HPLC.

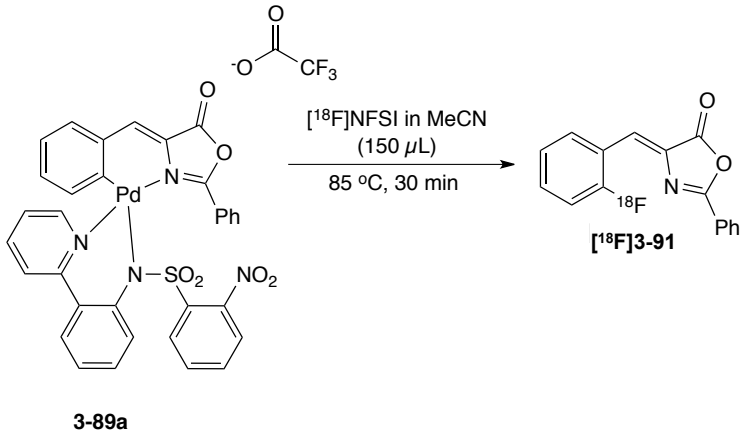


Entry	Precursor amounts (μmol)	Step i. Temp (^{o}C)/Time (min)	Step ii. Temp (^{o}C)/Time (min)	RCY (%)
1	10	90/30	85/30	6
2	10	75/60	70/30	< 1
3	5	80/90	85/30	8
4	0.5	80/90	85/30	2
5	10	80/120	80/30	5

Table 5.1. One-pot [^{18}F]fluorination

The specific activity of this transformation was not measured, as the 'cold' product **3-84a** was not visible in the HPLC-UV chromatogram. It was postulated that the 'cold' product **3-84a** peak overlapped with peaks corresponding to the starting materials.

5.5.2.3 Strategy 2: [^{18}F]Fluorination of pre-formed complex 3-89a



3-89a

An aliquot of [^{18}F]NFSI (150 μmol) in MeCN was added to an Eppendorf vial containing L-phenylalanine oxazolone pre-formed complex **3-89a** (2.5 μmol) and the reaction mixture was stirred at 85 ^{o}C for 30 minutes, before the reaction mixture was analysed by HPLC. The RCY of **[^{18}F]3-91** = 19.5 ± 10% (n = 3). The RCY was determined as the fraction of the activity injected onto the HPLC corresponding to

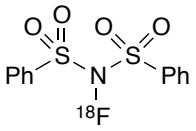
[^{18}F]3-91. The SA of **[^{18}F]3-91** was measured to be 0.29 ± 0.02 GBq/μmol and was calculated as described for [^{18}F]NFSI.

5.5.2.4 HPLC Chromatograms

High performance liquid chromatography (HPLC) was performed on a Spectra SYSTEM P2000 with a Spectra SYSTEM UV2000 detector and a Bioscan flow-count radioactivity detector in series, or a VWR-Hitachi L-2130 HPLC pump (VWR Hitachi, VWR International GmbH, Darmstadt, Germany) combined with a VWR- Hitachi L-2400 UV-absorption detector (λ=254 or 280 nm) and a 2 x 2 inch NaI-crystal for radioactivity detection.

HPLC studies on [^{18}F]NFSI were performed using a reverse phase analytical column (Waters Atlantis dC18 Column, 5μm, 150mm x 3.9mm). Elution was performed at a gradient of acetonitrile:water (5:95 to 80:20 over 15 min) with a flow rate of 1.0 mL/min.

HPLC studies in the radiolabelling reactions were performed using a reverse phase analytical column (Waters Nova-pak C18 Column, 150mm x 3.9mm). Elution was performed at a gradient of acetonitrile:water (5:95 to 80:20 over 15 min) with a flow rate of 1.0 mL/min.



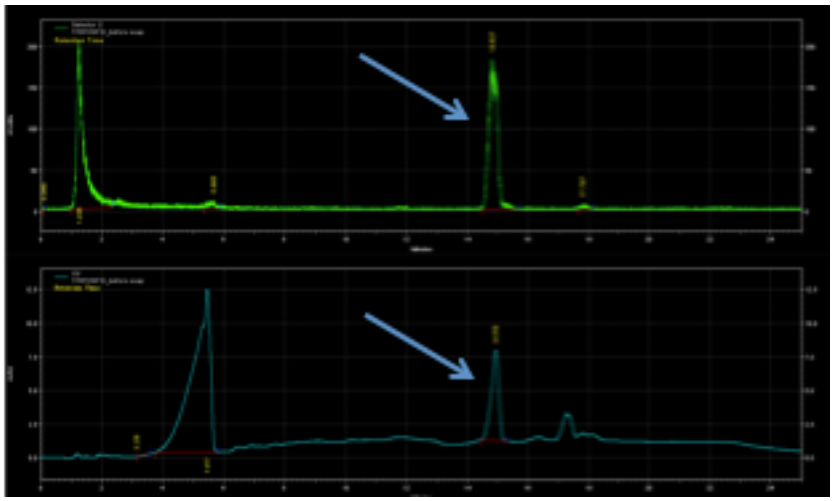
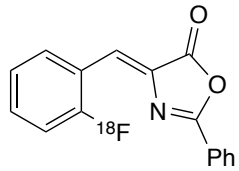


Figure 5.5. Identification of [^{18}F]NFSI (ret. time = 14.8 min). Top: radio-HPLC chromatogram. Bottom: UV-HPLC trace.



One-pot reaction

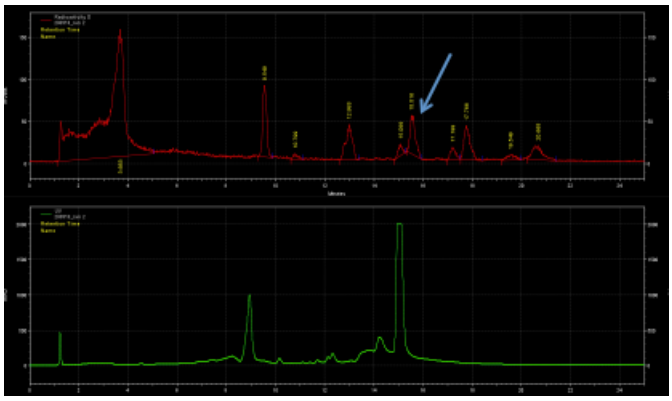
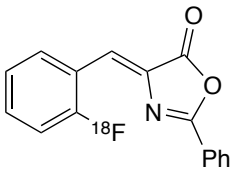


Figure 5.6. HPLC chromatogram of one-pot [^{18}F]fluorination. Top: Radio-HPLC chromatogram, Bottom: UV-HPLV chromatogram. Retention time of [^{18}F]3-91 = 15.5 min.



From pre-formed complex

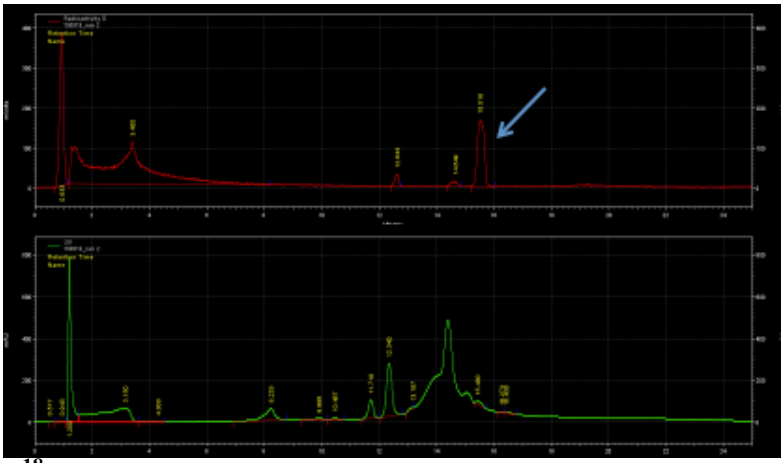


Figure 5.7 [^{18}F]fluorination of preformed oxazolone complex 3-89a (retention time of [^{18}F]3-91 = 15.5 min).

5.6 Experimental Data for Chapter 4

5.6.1 Synthesis of α,α-difluoroaryl acetic acids

General procedure for Cu-promoted cross-coupling of aryl iodide with ethyl bromodifluoroacetate (GP A)[334]**:**

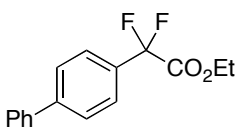
In a 50 mL round bottom flask under an atmosphere of N_2, the appropriate aryl iodide (10 mmol, 1.0 equiv) and ethyl bromodifluoroacetate (1.3 mL, 10 mmol, 1.0 equiv) were added to a suspension of activated Cu powder (1.7 g, 26 mmol, 2.6 equiv) in DMSO (26 mL, 0.4 M). The reaction mixture was stirred at 60 °C for 12 h, after which time it was poured into a mixture of ice and sat. aq. NH_4Cl, and the aqueous phase was extracted with Et_2O (3 × 50 mL). The combined organic phases were washed with sat. aq. NH_4Cl (2 × 50 mL) and brine (2 × 50 mL), then dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude mixture was purified by flash column chromatography.

Activation of Cu powder: Copper powder (< 424 μm, 26 mmol) was stirred vigorously in diluted aq. HCl (1 M, 10 mL) for 10 minutes at room temperature and filtered. This procedure was repeated with water (10 mL), MeOH (10 mL) and acetone (10 mL), respectively. Finally, the copper powder was dried under vacuum for 15 minutes before use.

***General procedure for hydrolysis of ethyl α,α-difluoroaryl acetate (GP B)*:**

In a 50 mL round bottom flask, ethyl α,α-difluoroaryl acetate (5 mmol, 1.0 equiv) obtained by **GP A** was added to a mixture of MeOH (15 mL, 0.3 M)and 1M K_2CO_3 aq. (15 mL) and stirred for 2 h at room temperature. The reaction mixture was then poured into 1 M HCl aq. to acidify to pH 1, and the aqueous phase was extracted with EtOAc (3 × 10 mL), washed with brine (10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Products were purified by washing with petroleum ether (30-40 ^oC).

Ethyl biphenyl-4-yl(difluoro)acetate[354] **(4-109a)**

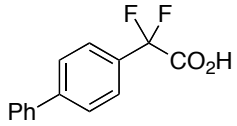


Synthesised following **GP A** (10 mmol scale). Purified by flash column chromatography (5% Et_2O-petroleum ether (30-40 ^oC)) to give 2.05 g (79% yield) of

the title compound as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58−7.52 (m, 4H), 7.44−7.47 (m, 2H), 7.30−7.33 (m, 2H), 7.22−7.26 (m, 1H), 4.18 (q, *J* = 7.0 Hz, 2H), 1.18 (t, *J* = 7.0 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 164.3 (t, *J* = 25.5 Hz), 144.0, 140.0, 131.7 (t, *J* = 26.0 Hz), 129.0, 128.1, 127.4, 127.3, 126.0 (t, *J* = 6.0 Hz), 113.6 (t, *J* = 251.5 Hz), 63.3, 13.9; **^{19}F NMR** (377 MHz, $CDCl_3$) δ −103.5 (s, 2F). Data corresponded to those reported in the literature.[354]

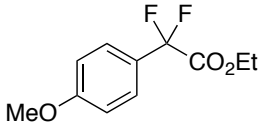
Biphenyl-4-yl(difluoro)acetic acid[355] (4-105a)



Synthesised following **GP B** (7.4 mmol scale), yielding 1.75 g (85 % yield) of **4-105a** as an off-white solid.

^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 7.84 (d, *J* = 8.5 Hz, 2H), 7.67−7.73 (m, 4H), 7.49−7.57 (m, 2H), 7.43 (m, 1H); **^{13}CNMR** (100 MHz, $(CD_3)_2SO$) δ 165.4 (t, *J* = 34.0 Hz), 143.4, 139.4, 132.1 (t, *J* = 24.5 Hz), 129.5, 128.7, 127.7, 127.4, 126.2 (t, *J* = 6.0 Hz), 114.1 (t, *J* = 248.5 Hz); **^{19}F NMR** (376.5 MHz, $(CD_3)_2SO$) δ −102.4 (s, 2F); Data corresponded to those reported in the literature.[355]

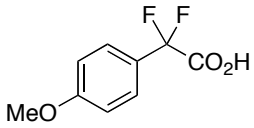
Ethyl difluoro-2-(4-methoxyphenyl)acetate[356] (4-109b)



Synthesised following **GP A** (10 mmol scale). Purified by flash column chromatography (5% EtOAc-petroleum ether (30-40 ^oC)) to give 846 mg (37% yield) of the title compound as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, *J* = 9.0 Hz, 2H), 6.97 (d, *J* = 9.0 Hz, 2H), 4.32 (q, *J* = 7.1 Hz, 2H), 3.86 (s, 3H), 1.33 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 164.5 (t, *J* = 36.0 Hz), 161.6, 127.1 (t, *J* = 6.1 Hz), 124.9 (t, *J* = 26.6 Hz), 114.0, 113.6 (t, *J* = 251.9 Hz), 63.0, 55.4, 13.9; **^{19}F NMR** (377 MHz, $CDCl_3$) δ −102.6 (s, 2F). Data corresponded to those reported in the literature.[356]

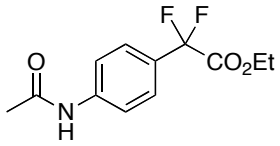
Difluoro(4-methoxyphenyl)acetic acid (4-105b)



Synthesised following **GP B** (3.7 mmol scale), yielding 588 mg (79% yield) of 4-**105b** as a yellow solid.

^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 7.51 (d, *J* = 8.8 Hz, 2H), 7.07 (d, *J* = 8.8 Hz, 2H), 3.80 (s, 3H); **^{13}C NMR** (100 MHz, $(CD_3)_2SO$) δ 165.7 (t, *J* = 34.7 Hz), 161.7, 127.3 (t, *J* = 6.0 Hz), 125.1 (t, *J* = 25.9 Hz), 114.7, 114.2 (t, *J* = 250.9 Hz), 55.8; **^{19}F NMR** (377 MHz, $(CD_3)_2SO$) δ −101.0 (s, 2F). **IR** (neat) ν 1739, 1610, 1514, 1439, 1252, 1177, 1141, 1098, 1030, 988, 890, 829, 744, 693, 638 cm^{-1}; **HRMS** (ESI) calc for $C_9H_7F_2O_3$ $[M-H]^-$ 201.0369, found 201.0361; **Mp** 72−74 °C.

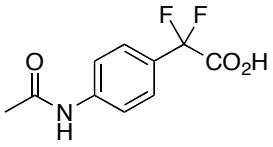
Ethyl [4-(acetylamino)phenyl](difluoro)acetate (4-109j)



Synthesised following **GP A** (5 mmol scale). Purified by flash column chromatography (30% EtOAc-petroleum ether (30-40 ^{o}C)) to give 1.10 g (86% yield) of the title compound as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (br. s, NH, 1H), 7.54 (d, *J* = 8.5 Hz, 2H), 7.45 (d, *J* = 8.5 Hz, 2H), 4.22 (q, *J* = 7.0 Hz, 2H), 2.11 (s, 3H), 1.22 (t, *J* = 7.0 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 169.0, 164.3 (t, *J* = 35.0 Hz), 140.5, 128.1 (t, *J* = 26.0 Hz), 126.4 (t, *J* = 6.0 Hz), 119.7, 113.3 (t, *J* = 252.0 Hz), 63.2, 24.5, 13.9; **^{19}F NMR** (377 MHz, $CDCl_3$) δ −103.2 (s, 2F); **IR** (neat) ν 1763, 1672, 1603, 1533, 1409, 1371, 1317, 1265, 1184, 1142, 1099, 1028, 1011, 992, 834, 761, 689 cm^{-1}; **HRMS** (ESI) calc for $C_{12}H_{13}F_2NNaO_3$ $[M+Na]^+$ 280.0756, found 280.0749.

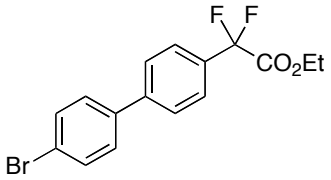
[4-(Acetylamino)phenyl](difluoro)acetic acid (4-105j)



Synthesised following **GP B** (4 mmol scale), yielding 576 mg (48% yield) of **4-105j** as a pale yellow solid.

^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 10.2 (s, NH, 1H), 7.73 (d, *J* = 8.8 Hz, 2H), 7.51 (d, *J* = 8.8 Hz, 2H), 2.07 (s, 3H); **^{13}C NMR** (100 MHz, $(CD_3)_2SO$) δ 169.2, 165.5 (t, *J* = 33.8 Hz), 142.2, 127.6 (t, *J* = 26.0 Hz), 126.4 (t, *J* = 6.0 Hz), 119.2, 114.1 (t, *J* = 251.5 Hz), 24.5; **^{19}F NMR** (377 MHz, $(CD_3)_2SO$) δ −101.5 (s, 2F); **IR** (neat) ν 3347, 1924, 1715, 1592, 1540, 1411, 1375, 1257, 1187, 1116, 1073, 996, 969, 838, 785, 755, 726, 688, 629, 609 cm^{-1}; **HRMS** (ESI) calc for $C_{10}H_8F_2NO_3$ $[M-H]^-$ 228.0478, found 228.0487; **Mp** 154−156 °C.

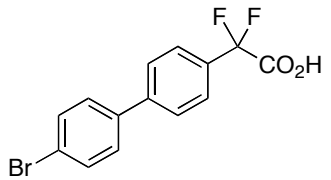
Ethyl (4'-bromobiphenyl-4-yl)(difluoro)acetate (4-109k)



Synthesised following **GP A** (10 mmol scale). Purified by flash column chromatography (2% EtOAc-petroleum ether (30-40 ^oC)) to give 1.91 g (54% yield) of the title compound as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.6 Hz, 2H), 7.66 (d, *J* = 8.6 Hz, 2H), 7.62 (d, *J* = 8.6 Hz, 2H), 7.48 (d, *J* = 8.6 Hz, 2H), 4.35 (q, *J* = 7.1 Hz, 2H), 1.36 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 164.1 (t, *J* = 35.4 Hz), 142.7, 138.9, 132.1, 132.1 (t, *J* = 25.6 Hz), 128.8, 127.2, 126.1 (t, *J* = 5.9 Hz), 122.5, 113.4 (t, *J* = 255.5 Hz), 63.2, 13.9; **^{19}F NMR** (377 MHz, $CDCl_3$) δ −103.7 (s, 2F); **IR** (neat) ν 1762, 1484, 1266, 1099, 1034, 1003, 856, 815, 772, 758, 679 cm^{-1}; **HRMS** (EI/FI) calc for $C_{16}H_{13}F_2{}^{79}BrO_2$ $[M]^+$ 354.0067, found 354.0063.

(4'-Bromobiphenyl-4-yl)(difluoro)acetic acid (4-105k)

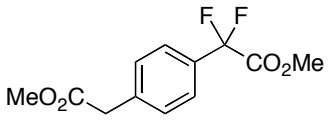


Synthesised following **GP B** (1.6 mmol scale), yielding 241 mg (68% yield) of **4-105k** as an off-white solid.

^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 7.65−7.72 (m, 6H), 7.83 (d, *J* = 8.3 Hz, 2H); **^{13}C NMR** (100 MHz, $(CD_3)_2SO$) δ 165.3 (t, *J* = 34.7 Hz), 142.1, 138.6, 132.4 (t, *J* = 25.4 Hz), 132.4, 129.5, 127.6, 126.3 (t, *J* = 5.9 Hz), 122.3, 114.0 (t, *J* = 252.2 Hz); **^{19}F**

NMR (377 MHz, $(CD_3)_2SO$) δ −102.5 (s, 2F); **IR** (neat) ν 1751, 1268, 1152, 1110, 1075, 991, 897, 852, 815, 747, 671 cm^{-1}; **HRMS** (ESI) calc for $C_{14}H_8F_2{}^{79}BrO_2$ $[M-H]^-$ 324.9681, found 324.9689; **Mp** 150−153 °C.

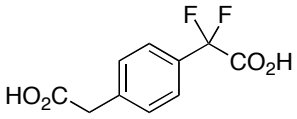
Methyl 2,2-difluoro-2[4-(2-methoxy-2-oxoethyl)phenyl]acetate (4-109o)



To a solution of the crude of 2-[4-(2-ethoxy-1,1-difluoro-2-oxoethyl)phenyl]acetic acid (synthesised following **GP A**, 10 mmol scale), in MeOH (25 mL) was added dropwise thionyl chloride (2.6 mL) at 0 °C. The mixture was allowed to warm to room temperature while stirring overnight, after which time it was concentrated *in vacuo* and the crude product was purified by flash column chromatography (10% EtOAc-*n*-hexane) to give 900 mg (37% yield over 2 steps) of the title compound as a pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, *J* = 8.3 Hz, 2H), 7.37 (d, *J* = 8.3 Hz, 2H), 3.83 (s, 3H), 3.69 (s, 3H), 3.67 (s, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 171.2, 164.5 (t, *J* = 35.5 Hz), 137.1, 131.5 (t, *J* = 26.1 Hz), 129.6, 125.7 (t, *J* = 6.3 Hz), 113.3 (t, *J* = 250.3 Hz), 53.5, 52.1, 40.7; **^{19}F NMR** (377 MHz, $CDCl_3$) δ −103.6 (s, 2F); **IR** (neat) ν 2360, 2170, 1735, 1487, 1435, 1253. 1158, 1009, 800 cm^{-1}; **HRMS** (ESI) calc for $C_{12}H_{12}F_2NaO_4$ $[M+Na]^+$ 281.0596, found 281.0604.

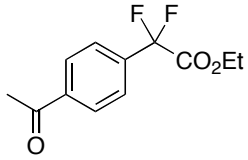
2-[4-(Carboxymethyl)phenyl]-2,2-difluoroacetic acid (4-105o)



In a 50 mL round bottom flask, Methyl 2,2-difluoro-2[4-(2- methoxy-2-oxoethyl)phenyl]acetate (900 mg, 7 mmol, 1.0 eq) was added to a mixture of MeOH (10 mL, 0.3 M) and 1M NaOH aq. (15 mL, 6 mmol, 6.0 eq) and stirred for 5 h at room temperature. The reaction mixture was then poured into 1M HCl to acidify to pH 1, extracted with EtOAc (3 × 5 mL), washed with brine, dried over Na_2SO_4 and concentrated *in vacuo* to give 700 mg (43% yield) of **4-105o** as a white solid. **^{1}H NMR** (400 MHz, $(CD_3)_2SO$) δ 7.52 (d, *J* = 8.3 Hz, 2H), 7.41 (d, *J* = 8.3 Hz, 2H), 3.61 (s, 2H); **^{13}C NMR** (100 MHz, $(CD_3)_2SO$) δ 172.3, 165.0 (t, *J* = 34.0 Hz), 131.1 (t, *J* =

25.3 Hz), 130.2, 130.0, 125.1 (t, *J* = 6.0 Hz), 113.6 (t, *J* = 248.7 Hz), 40.3; **^{19}F NMR** (377 MHz, $(CD_3)_2SO$) δ −102.2 (s, 2F); **IR** (neat) ν 2900, 2675, 1703, 1421, 1293, 1266, 1144, 1120, 994, 940, 829, 724, 670 cm^{-1}; **HRMS** calc for $C_{10}H_7F_2O_4$ $[M-H]^-$ 229.0318, found 229.0314; **Mp** 107−108 °C.

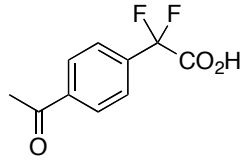
Ethyl difluoro(4-acetophenone)acetate (4-109p)



Synthesised following **GP A** (10 mmol scale). Purified by flash column chromatography (10% Et_2O-petroleum ether (30-40 ^oC)) to give 2.2 g (92% yield) of the title compound as a pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, *J* = 8.5 Hz, 2H), 7.69 (d, *J* = 8.5 Hz, 2H), 4.28 (q, *J* = 7.0 Hz, 2H), 2.60 (s, 3H), 1.27 (t, *J* = 7.0 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 197.2, 163.2 (t, *J* = 35.0 Hz), 139.0, 136.9 (t, *J* = 25.5 Hz), 128.5, 125.9 (t, *J* = 6.0 Hz), 112.9 (t, *J* = 252.0 Hz), 63.4, 26.7, 13.8; **^{19}F NMR** (377 MHz, $CDCl_3$) δ −104.5 (s, 2F); **IR** (neat) ν 2361, 1763, 1690, 1408, 1360, 1264, 1142, 1098, 1011, 993, 959, 833, 770, 752, 702, 628 cm^{-1}; **HRMS** (ESI) calc for $C_{12}H_{12}O_3F_2$ $[M+Na]^+$ 265.0755, found 265.0697.

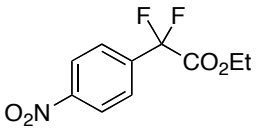
Difluoro(4-acetophenone)acetic acid (4-105p)



Synthesised following **GP B** (9.0 mmol scale), yielding 1.02 g (53% yield) of 1p as a pale red solid.

^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 8.10 (d, *J* = 8.0 Hz, 2H), 7.73 (d, *J* = 8.0 Hz, 2H), 2.63 (s, 3H); **^{13}C NMR** (100 MHz, $(CD_3)_2SO$) δ 197.9, 165.0 (t, *J* = 33.0 Hz), 139.3, 137.1 (t, *J* = 25.0 Hz), 129.2, 126.1 (t, *J* = 6.0 Hz), 113.7 (t, *J* = 251.0 Hz), 27.4; **^{19}F NMR** (377 MHz, $(CD_3)_2SO$) δ −103.8 (s, 2F); **IR** (neat) ν 2623, 1766, 1650, 1407, 1246, 1141, 1117, 1097, 994, 969, 845, 830, 778, 740, 689, 635 cm^{-1}; **HRMS** (ESI) calc for $C_{10}H_8O_3F_2$ $[M-H]^-$ 213.0369, found 213.0452. **Mp** 129−131°C

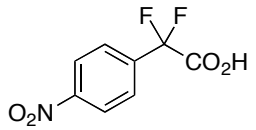
Ethyl difluoro-2-(4-nitrophenyl)acetate (4-109q)[354]



Synthesised following **GP A** (10 mmol scale). Purified by flash column chromatography (9% EtOAc-petroleum ether (30-40 °C)) to give 1.63 g (66% yield) of the title compound as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (d, *J* = 8.8 Hz, 2H), 7.84 (d, *J* = 8.8 Hz, 2H), 4.35 (q, *J* = 7.1 Hz, 2H), 1.34 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 163.1 (t, *J* = 33.9 Hz), 149.6, 138.8 (t, *J* = 26.3 Hz), 127.0 (t, *J* = 6.1 Hz), 123.9, 112.4 (t, *J* = 253.4 Hz), 63.8, 13.9; **^{19}F NMR** (377 MHz, $CDCl_3$) δ −104.5 (s, 2F). Data corresponded to those reported in the literature.[354]

Difluoro(4-nitrophenyl)acetic acid (4-105q)



Synthesised following **GP B** (6.6 mmol scale), yielding 1.24 g (87% yield) of **4-105q** as a pale yellow solid.

^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 8.38 (d, *J* = 8.8 Hz, 2H), 7.89 (d, *J* = 8.8 Hz, 2H),; **^{13}C NMR** (100 MHz, $(CD_3)_2SO$) δ 164.6 (t, *J* = 32.7 Hz), 149.7, 139.1 (t, *J* = 25.9 Hz), 127.5 (t, *J* = 6.1 Hz), 124.6, 113.2 (t, *J* = 252.3 Hz); **^{19}F NMR** (377 MHz, $(CD_3)_2SO$) δ −103.2 (s, 2F); IR (neat) ν 1755, 1525, 1348, 1291, 1262, 1153, 1122, 1106, 992, 865, 851, 706 cm^{-1}; **HRMS** (CI) calc for $C_8H_5NO_4F_2$ $[M]^+$ 217.0187, found 217.0181; **Mp** 162−164 °C.

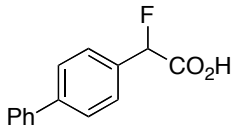
5.6.2 Synthesis of α-monofluoroaryl acetic acids

General procedure for the synthesis of α-monofluoroaryl acetic acids (GP C)[336]***:***

To a solution of arylacetic acid (5.0 mmol) and TBSCl (1.73 g, 11.5 mmol) in THF (10 mL) at 0 °C was added LiHMDS (1M in THF, 11.0 mL, 11.0 mmol) slowly. The reaction was stirred overnight, during which time it was allowed to warm to room temperature, before concentrating *in vacuo*. The crude *bis*-silylketeneacetal was dissolved in hexane (25 mL) and the LiCl was filtered off and washed with hexane (25 mL) before evaporating the combined solution under reduced pressure. The residue

was redissolved in acetonitrile (10 mL) and added to a solution of Selectfluor (2.30 g, 6.5 mmol) in acetonitrile (20 mL) at room temperature. After stirring for 15 minutes the reaction mixture was poured into a 1 M aq. HCl (50 mL) and extracted into ether (2 × 50 mL). The combined ether layers were extracted with 1 M NaOH (2 × 30 mL) and the combined basic phases were subsequently washed with ether (2 x 100 mL). The organic extracts were discarded and the aqueous phase was acidified with 6 M aq. HCl to pH 1. The acidic phase was then extracted with ether (2 × 100 mL) and the combined ether layers were dried over $MgSO_4$ and evaporated under reduced pressure to afford the corresponding α-monofluoroaryl acetic acids.

Biphenyl-4-yl(fluoro)acetic acid (4-113c)



Synthesised following **GP C**, yielding 926 mg (80% yield) of **4-113c** as a pale yellow solid.

^{1}H NMR (400 MHz, CD_3CN) δ 9.56 (br s, 1H, COOH), 7.53 (d, *J* = 8.0 Hz, 2H), 7.46−7.50 (m, 2H), 7.36 (dd, *J* = 1.5, 8.0 Hz, 2H), 7.26−7.32 (m, 2H), 7.21 (m, 1H), 5.74 (d, *J* = 47.5 Hz, 1H); **^{13}C NMR** (100 MHz, CD_3CN) δ 169.4 (d, *J* = 28.0 Hz), 142.9, 140.5, 134.3 (d, *J* = 20.0 Hz), 129.5, 128.5, 128.1 (d, *J* = 5.5 Hz), 128.0, 127.6, 89.3 (d, *J* = 182.0 Hz); **^{19}F NMR** (377 MHz, CD_3CN) δ −177.6 (d, *J* = 47.0 Hz, 1F); **IR** (neat) ν 3029, 1757, 1687, 1180, 1047, 1008, 831, 756, 732, 694 cm^{-1}; **HRMS** (EI/FI) calc for $C_{14}H_{11}FO_2$ $[M]^+$ 230.0743, found 230.0739; **Mp** 133−134 °C.

5.6.3 Fluorodecarboxylation of di- and monofluoroaryl carboxylic acids

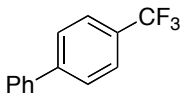
5.6.3.1 Selectfluor™

General Procedure for the fluorodecarboxylation of di- and monofluoroaryl carboxylic acids (GP D)[318]***:***

To a Schlenck tube containing a magnetic stirrer bar was added the carboxylic acid (49.6 mg, 0.2 mmol, 1.0 eq), Selectfluor (141.7 mg, 0.4 mmol, 2.0 eq) and silver nitrate (13.6 mg, 0.08 mmol, 20 mol%). The Schlenck tube was closed with a rubber septum and equipped with a nitrogen balloon, and the system was purged with nitrogen. Acetone (2 mL) and water (2 mL) were added and the reaction was stirred at 55 °C for 1 h, before diluting with water. The reaction mixture was extracted with

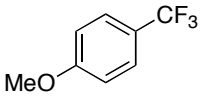
DCM (3 × 2 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Crude ^{19}F NMR yields were determined by comparing the integration of the product peak with the integration of 1.0 eq (0.2 mmol, 21 mL) 1-fluoro-3- nitrobenzene which was added to the reaction after workup as the internal standard. The crude mixture was purified by flash column chromatography using the indicated solvent system.

4-(Trifluoromethyl)biphenyl (4-106a)[356]



Synthesised following **GP D** (0.2 mmol scale). Purified by flash column chromatography (petroleum ether (30-40 ^oC)) to give 38 mg (85 % yield) of **4-106a** as a white solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.60 (s, 4H), 7.49−7.52 (m, 2H), 7.36−7.40 (m, 2H), 7.31 (dd, *J* = 7.5 Hz, 2.0 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 144.8, 139.8, 129.4 (q, *J* = 32.0 Hz), 129.0, 128.2, 127.4, 127.3, 125.7 (q, *J* = 4.0 Hz), 124.4 (q, *J* = 273.0 Hz); **^{19}F NMR** (377 MHz, $CDCl_3$) δ −62.4 (s, 3F). Data corresponded to those reported in the literature.[356]

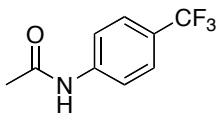
1-Methoxy-4-(trifluoromethyl)benzene (4-106b)[357]



Synthesised following **GP D** (0.2 mmol scale). Purified by flash column chromatography (petroleum ether (30-40 ^oC)) to give 29 mg (82% yield) of the product as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, *J* = 8.5 Hz, 2H), 6.88 (d, *J* = 8.5 Hz, 2H), 3.77 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 161.0, 125.8 (q, *J* = 4.0 Hz), 121.8 (q, *J* = 33.0 Hz), 123.4 (q, *J* = 270.0 Hz), 112.9, 54.4; **^{19}F NMR** (377 MHz, $CDCl_3$) δ −61.47 (s, 3F). Data corresponded to those reported in the literature. [357]

***N*-[4-(Trifluoromethyl)phenyl]acetamide (4-106j)**[358]

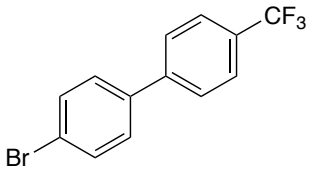


Synthesised following GP D (0.2 mmol scale). Purified by flash column chromatography (30% to 50% EtOAc-petroleum ether (30-40 ^oC)) to give 35 mg (86

%) of the product as an off-white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (br. s, NH, 1H), 7.57 (d, *J* = 8.5 Hz, 2H), 7.49 (d, *J* = 8.5 Hz, 2H), 2.14 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 168.7, 140.9, 126.3 (q, *J* = 4.0 Hz), 126.0 (q, *J* = 33.0 Hz), 124.1 (q, *J* = 271.5 Hz), 119.3, 24.7; **^{19}F NMR** (377 MHz, $CDCl_3$) δ −62.1 (s, 3F). Data corresponded to those reported in the literature.[358]

4-Bromo-4'-(trifluoromethyl)biphenyl (4-106k)



Synthesised following **GP D**. Purified by flash column chromatography (eluent:petroleum ether 30/40) yielding 50 mg (83% yield) of **4-106k** as a white solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.37 (dt, *J* = 8.5 Hz, 2.0 Hz, 2H), 7.51 (dt, *J* = 8.5 Hz, 2.0 Hz, 2H), 7.56 (d, *J* = 8.5 Hz, 2H), 7.61 (d, *J* = 8.5 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 122.6, 124.2 (q, *J* = 272.5 Hz), 125.9 (q, *J* = 4.0 Hz), 127.2, 128.8, 129.7 (q, *J* = 32.0 Hz), 132.2, 138.7, 143.5; **^{19}F NMR** (377 MHz, $CDCl_3$) δ −62.5 (s, 3F).
Data corresponded to those reported in the literature.[356]

5.6.3.2 Fluorodecarboxylation using fluorine gas

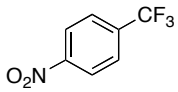
The experiments were carried out using the same equipment in the laboratory of Prof. Graham Sanford at Durham University, as described in Chapter 5, Section 5.2.

General procedure for elemental fluorine-promoted fluorodecarboxylation (GP E):

The substrate (0.5 mmol) and $AgNO_3$ (17 mg, 0.1 mmol) were dissolved in MeCN (5 mL) and placed in a PTFE reaction vessel fitted with a stirrer bar. The reaction vessel was connected to a gas inlet and outlet fitted to the elemental fluorine apparatus which allows for safe introduction of F_2. The reaction vessel was cooled to the appropriate temperature using an ice bath or an acetone/dry ice bath and the system was purged with nitrogen gas for 10 minutes before allowing 10 % fluorine gas in nitrogen (v/v) to flow through the system at a constant rate set by a mass flow control apparatus (15 mL/min). The reaction was rapidly stirred under these conditions for the time calculated to correspond to a known amount of F_2. Afterwards, the system was again purged with nitrogen gas for 10 minutes and warmed to room temperature. The

reaction mixture was concentrated under reduced pressure and the residue was redissolved in CD_3CN and 1-fluoro-3-nitrobenzene (0.5 mmol, 1 equiv.) was added as an internal reference to calculate ^{19}F NMR yields.

1-Nitro-4-(trifluoromethyl)benzene(4-106q) [359]



Synthesised following **GP E**. After purging the system with nitrogen gas for the required time, the reaction mixture was cooled to -10 °C and F_2 gas was introduced into the system for 22.4 min (corresponded to 3 equiv. F_2 gas under a constant flow rate of 15mL/min) followed by the normal work up procedure. Under these optimal conditions, **4-106q** was obtained in 23 % yield.

^{1}H NMR (400 MHz, CD_3CN) δ 8.42 (d, *J* = 8.5 Hz, 2H), 7.86 (d, *J* = 8.5 Hz, 2H); **^{13}C NMR** (400 MHz, CD_3CN) δ 150.0, 135.9 (q, *J* = 34.0 Hz), 126.7 (q, *J* = 4.0 Hz), 124.0, 123.0 (q, *J* = 274.0 Hz); **^{19}F NMR** (377 MHz, CD_3CN) δ -62.9.

Data corresponded to those reported in the literature.[359]

5.6.4 Radiochemistry

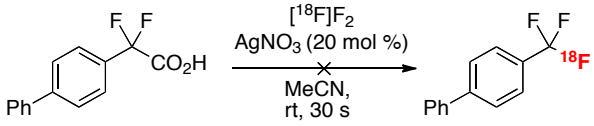
5.6.4.1 Synthesis of [^{18}F]Selectfluor *bis*(triflate):

[^{18}F]Fluoride and [^{18}F]F_2 was prepared according to the procedure outlined in Chapter 5, Section 5.3. The [^{18}F]F_2 gas was bubbled into a vial containing a mixture of 1-chloromethyl-4-aza-1-azoniabicyclo[2.2.2]octane triflate (2 μmol (0.003 M)) and lithium triflate (1 equiv.) in acetone-d_6 (0.75 mL) at room temperature for ~ 30 seconds. Aliquots (220 μL) of this crude stock solution were used directly in labelling reactions.

5.6.4.2 Reactions with [^{18}F]Selectfluor *bis*(triflate)

A stock solution of the precursor (10 μmol) and silver nitrate (2 μmol) in water (10 mL) was prepared. An aliquot (100 μL) was added to a Wheaton vial and [^{18}F]8 (220 μL) was added. At 55 °C the reaction volume was concentrated to ~ 15 μL under a flow of helium and the reaction stirred at this temperature for 30 minutes in total. The reaction mixture was analysed by radio-HPLC and radio-TLC.

5.6.4.3 Reaction with $[^{18}F]F_2$



$[^{18}F]F_2$ was bubbled into a Wheaton vial containing **4-105a** (0.5 μmol) and silver nitrate (0.1 μmol) in dry MeCN (500 μL) for 30 seconds at room temperature, before the reaction mixture was analysed by HPLC. In this reaction no desired product was observed at 17.4 minutes. A complex group of radioactive peaks (bottom chromatogram) were observed from 5.0 to 9.3 minutes corresponding to the expected retention time of the carboxylic acid starting material as seen in the top UV chromatogram. Hence, it is believed that the labelling reaction lead to unspecific $[^{18}F]$fluorination on the aromatic moiety of the starting material.

5.6.4.4 Measurement of Radiochemical Yield

Radiochemical yield and radiochemical purity were determined by radio-HPLC. High performance liquid chromatography (HPLC) was performed on a Spectra SYSTEM P2000 with a Spectra SYSTEM UV2000 detector and a Bioscan flow-count radioactivity detector in series, or a VWR-Hitachi L-2130 HPLC pump (VWR Hitachi, VWR International GmbH, Darmstadt, Germany) combined with a VWR- Hitachi L-2400 UV-absorption detector (λ=254 or 280 nm) and a 2 x 2 inch NaI-crystal for radioactivity detection. HPLC studies of all reactions were performed using a reverse phase analytical column (Waters Atlantis dC18 Column, 5 μm, 150 mm x 3.9 mm). Elution was performed at a gradient of MeCN/H_2O (gradient: 5:95 to 80:20% over 15 min) with a flow rate of 1 mL/min.

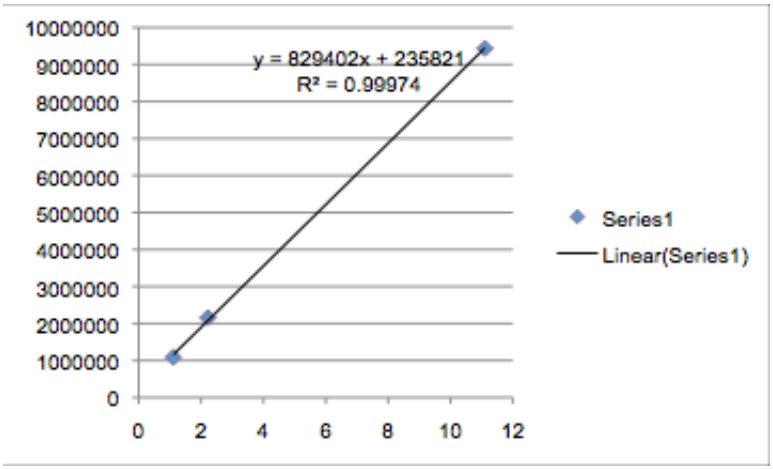
5.6.4.5 Calculation of specific activity in $[^{18}F]$Selectfluor *bis*(triflate) reactions

Determination of the specific activities for **$[^{18}F]$4-120a**, **$[^{18}F]$4-120j** and **$[^{18}F]$4-121c** was carried out by HPLC. The fraction corresponding to the $[^{18}F]$product was collected and its activity was measured. The mass of the $[^{18}F]$product in the collected fraction was calculated by comparing HPLC retention times and peak intensities to the $[^{19}F]$reference compound of known concentration. The specific activities were decay corrected to the E.O.S of $[^{18}F]$Selectfluor *bis*(triflate).

The mass of the $[^{18}F]$product was calculated by generating a calibration curve. Samples of the 'cold' reference compounds at different concentrations were injected onto the

HPLC, making sure to completely fill the injection loop (of a known volume). The injection was repeated for a minimum of three times at each concentration. The peak areas obtained at each injection were averaged for each sample concentration, before the average peak area was plotted against concentration of the sample in Excel to generate the calibration curve.

This was the plot generated for [^{18}F]CF3biphenyl **4-106a**:



The equation for the peak area = 829402 x [^{18}F]product concentration + 235821

In one reaction the UV peak area of the radioactive peak was 1227025

Concentration of stable material = (1227025+235821)/829402 = 1.76 mg/mL

Injected volume = 20 µL, so total stable material = 0.035 mg

MW of **4-106a** is 222.07 g/mol so 0.035 mg = 1.59 x 10^{-4} µmol

Decay corrected activity of [^{18}F]CF3biphenyl peak from sample = 0.363 MBq

SA = (0.363/1.59 x 10^{-4})/1000 = 2.29 GBq/µmol.

This calculation was carried out for every labelling reaction in this study and the SAs are summerised in Table 5.2.

Compound	SA of compound [GBq/µmol]
	2.01
[^{18}F]CF3biphenyl	2.06
[^{18}F]4-120a	2.29
	0.69
[^{18}F]amide	0.29
[^{18}F]4-120j	0.41
	4.90
[^{18}F]CF2biphenyl	4.93
[^{18}F]4-121c	4.64

Table 5.2 SA of [^{18}F]4-120a, [^{18}F]4-120j and [^{18}F]4-121c.

5.6.4.6 HPLC Chromatograms

High performance liquid chromatography (HPLC) was performed on a Spectra SYSTEM P2000 with a Spectra SYSTEM UV2000 detector and a Bioscan flow-count radioactivity detector in series, or a VWR-Hitachi L- 2130 HPLC pump (VWR Hitachi, VWR International GmbH, Darmstadt, Germany) combined with a VWR-Hitachi L-2400 UV-absorption detector (λ=254 or 280 nm) and a 2 x 2 inch NaI-crystal for radioactivity detection. HPLC studies of all reactions were performed using a reverse phase analytical column (Waters Atlantis dC18 Column, 5µm, 150mm x 9mm). Elution was performed at a gradient of acetonitrile:water (5:95 to 80:20 % over 15 min) with a flow rate of 1 mL/min.

4-[^{18}F](Trifluoromethyl)biphenyl – using [^{18}F]F_2

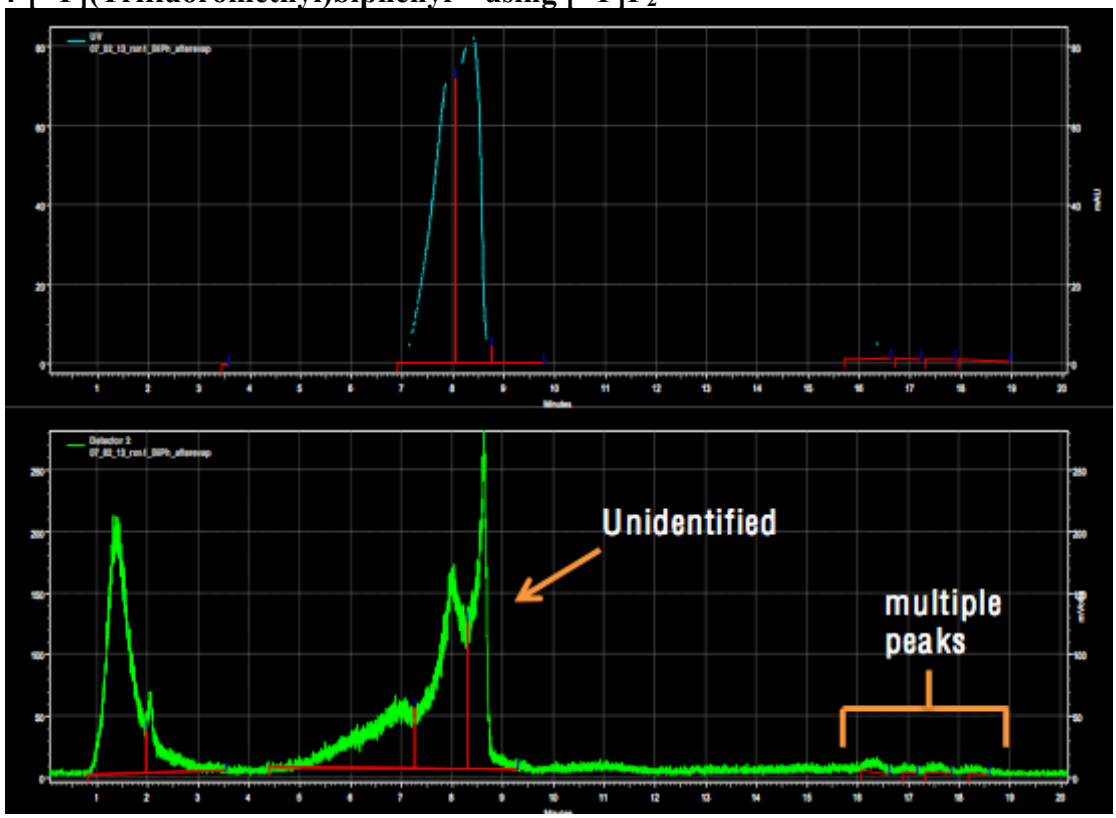


Figure 5.8 Top: UV HPLC chromatogram, side-product retention time = 8.0 to 9.2 min (starting material also included in this group of peaks). Bottom: Radio-HPLC chromatogram, side-product retention time = 5.0 to 9.3 min.

4-[^{18}F](Trifluoromethyl)biphenyl [^{18}F]4-120a

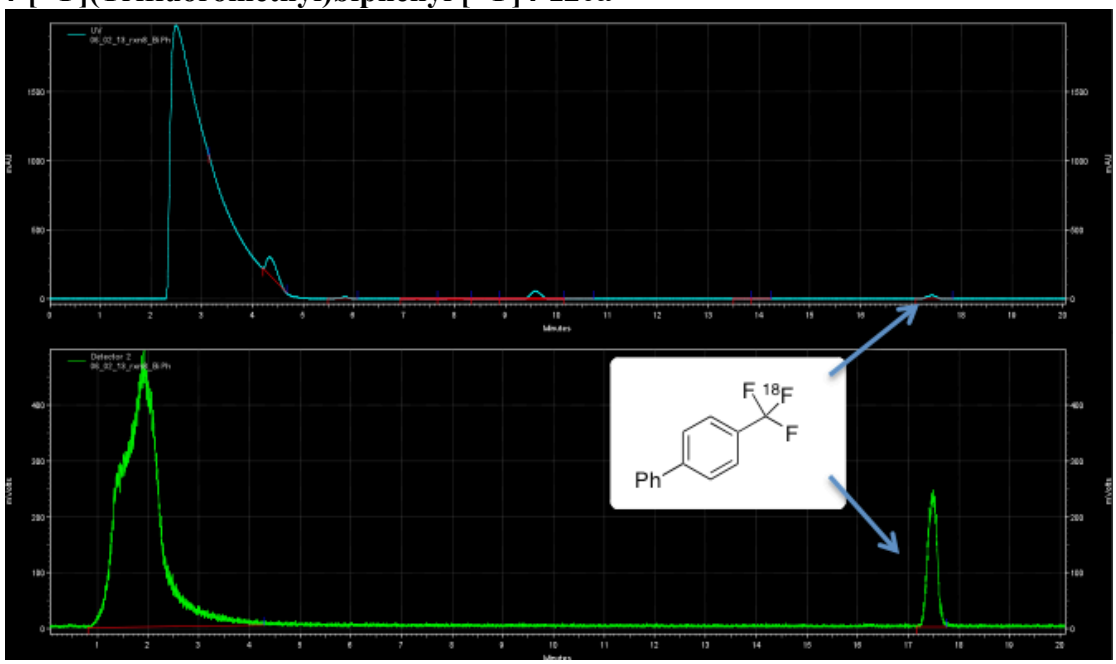
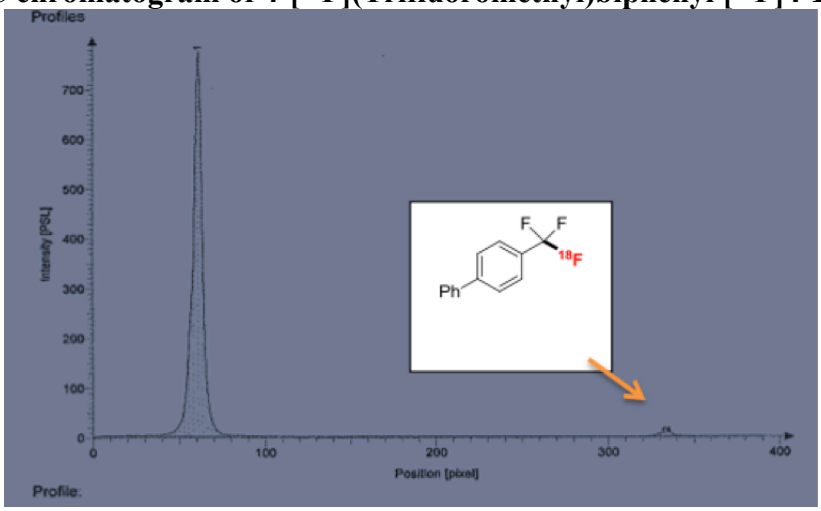


Figure 5.9 Top: UV HPLC chromatogram, product retention time = 17.42 min. Starting material retention time = 9.63 min. Bottom: Radio-HPLC chromatogram, product retention time = 17.49 min.

TLC chromatogram of 4-[^{18}F](Trifluoromethyl)biphenyl [^{18}F]4-120a



***N*-[^{18}F][4-(Trifluoromethyl)phenyl]acetamide [^{18}F]4-120j**

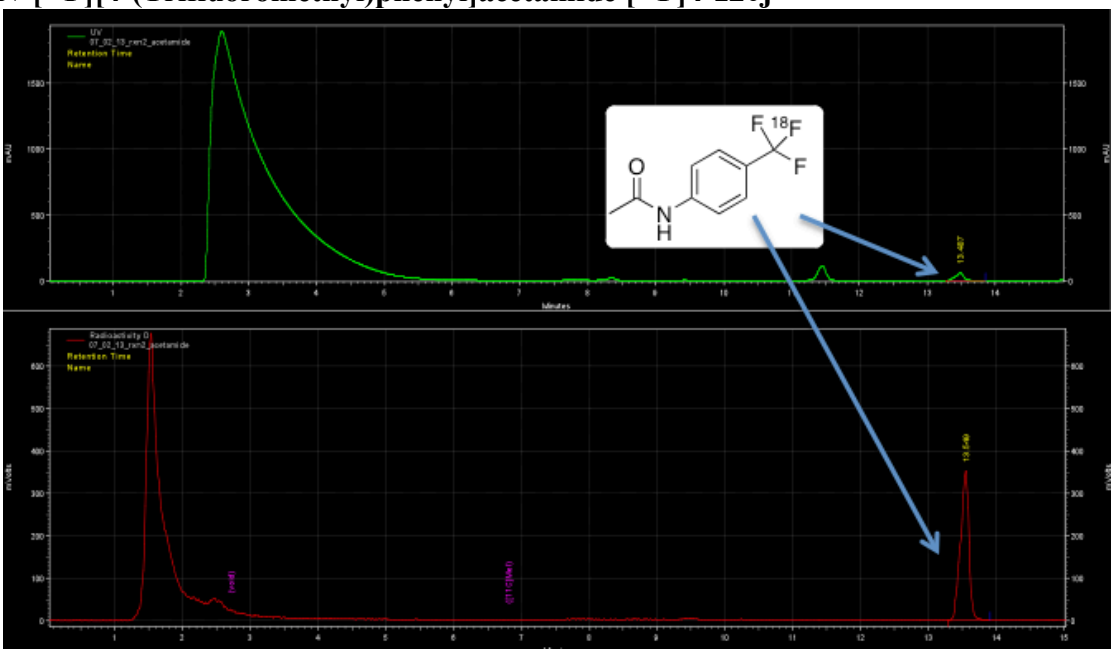
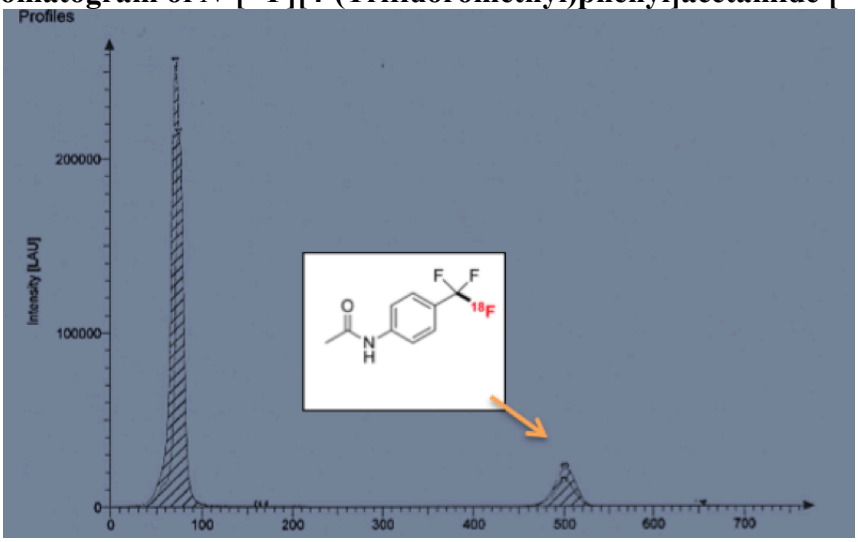


Figure 5.10 Top: UV HPLC chromatogram, product retention time = 13.49 min. Starting material retention time = 8.32 min. Bottom: Radio-HPLC chromatogram, product retention time = 13.55 min.

TLC chromatogram of *N*-[^{18}F][4-(Trifluoromethyl)phenyl]acetamide [^{18}F]4-120j



4-[^{18}F](Difluoromethyl)biphenyl [^{18}F]4-121c

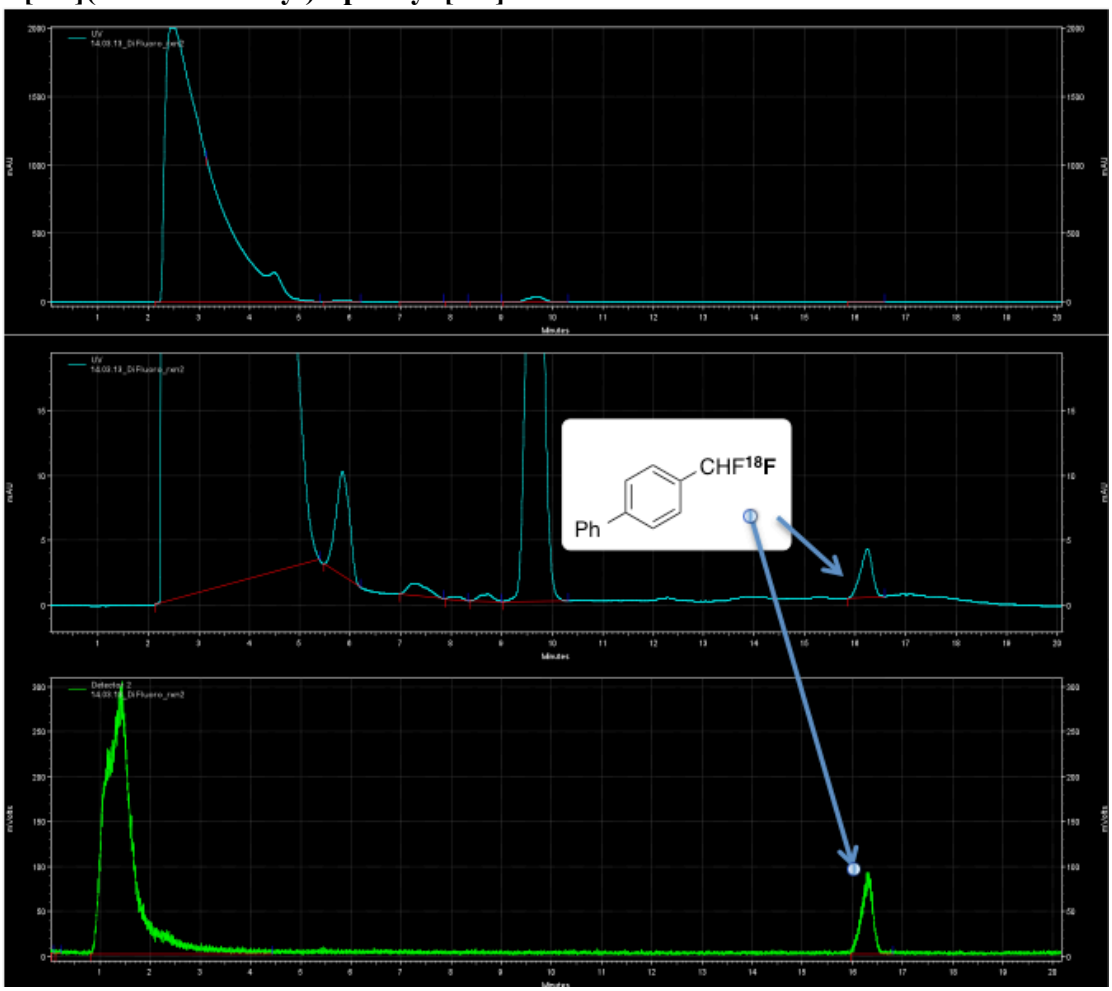
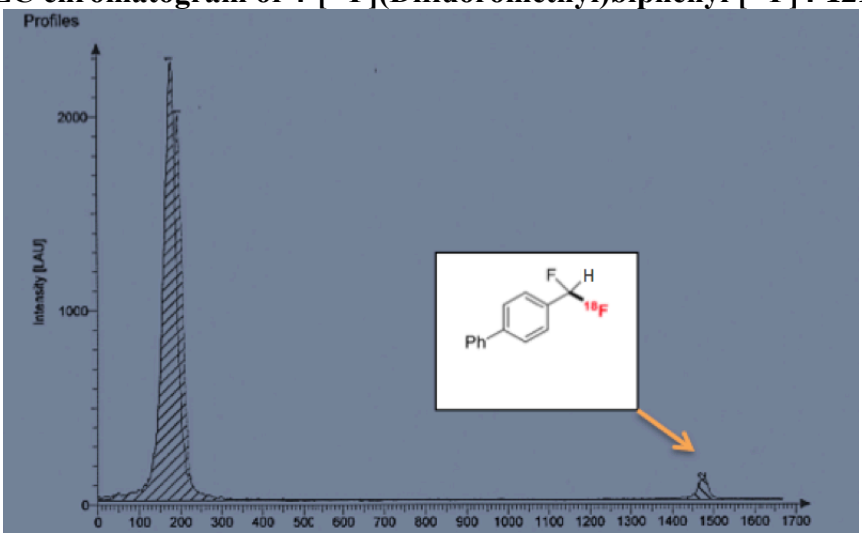


Figure 5.11 Top: UV HPLC chromatogram, product retention time = 16.30 min. Starting material retention time = 9.78 min. Middle: Close up of UV HPLC chromatogram, product retention time = 16.30 min. Starting material retention time = 9.78 min. Bottom: Radio-HPLC chromatogram, product retention time = 16.40 min

TLC chromatogram of 4-[^{18}F](Difluoromethyl)biphenyl [^{18}F]4-121c



Chapter 6: References

[1] S. M. Ametamey, M. Honer, P. A. Schubiger, *Chem. Rev.,* **2008**, *108*, 1501-1516.
[2] P. W. Miller, N. J. Long, R. Vilar, A. D. Gee, *Angew. Chem. Int. Ed.,* **2008**, *47*, 8998-9033.
[3] Y. F. Tai, P. Piccini, *J. Neurol. Neurosurg. Psych.* **2004**, *75*, 669-676.
[4] M. F. Di Carli, S. Dorbala, J. Meserve, G. El Fakhri, A. Sitek, S. C. Moore, *J. Nucl. Med.,* **2007**, *48*, 783-793.
[5] A. D. Gee, *Brit. Med. Bull.,* **2003**, *65*, 169-177.
[6] K. Strijckmans, *Comput. Med. Imag. Grap.,* **2001**, *25*, 69-78.
[7] S. Vallabhajosula, *Molecular Imaging: Radiopharmaceuticals for Pet and Spect* **2009**, 133-149.
[8] G. T. Bida, R. L. Ehrenkaufer, A. P. Wolf, J. S. Fowler, R. R. Macgregor, T. J. Ruth, *J. Nucl. Med.,* **1980**, *21*, 758-762.
[9] J. P. O'neil, H. F. VanBrocklin, *Nucl. Instrum. Meth. A,* **1999**, *438*, 166-172.
[10] A. Bishop, N. Satyamurthy, G. Bida, G. Hendry, M. Phelps, J. R. Barrio, *Nucl. Med, Biol.,* **1996**, *23*, 189-199.
[11] J. Bergman, O. Solin, *Nucl. Med, Biol.,* **1997**, *24*, 677-683.
[12] C. Lemaire, R. Cantineau, M. Guillaume, A. Plenevaux, L. Christiaens, *J. Nucl. Med.* **1991**, *32*, 2266-2272.
[13] E. K. J. Pauwels, M. J. Ribeiro, J. H. M. B. Stoot, V. R. McCready, M. Bourguignon, B. Maziere, *Nucl. Med, Biol.,* **1998**, *25*, 317-322.
[14] G. Lucignani, K. C. Schmidt, R. M. Moresco, G. Striano, F. Colombo, L. Sokoloff, F. Fazio, *J. Nucl. Med.,* **1993**, *34*, 360-369.
[15] M. M. Goodman, C. D. Kilts, R. Keil, B. Shi, L. Martarello, D. X. Xing, J. Votaw, T. D. Ely, P. Lambert, M. J. Owens, V. M. Camp, E. Malveaux, J. M. Hoffman, *Nucl. Med, Biol.,* **2000**, *27*, 1-12.
[16] A. F. Shields, J. R. Grierson, B. M. Dohmen, H. J. Machulla, J. C. Stayanoff, J. M. Lawhorn-Crews, J. E. Obradovich, O. Muzik, T. J. Mangner, *Nat. Med.,* **1998**, *4*, 1334-1336.
[17] M. Schou, C. Halldin, J. Sovago, V. W. Pike, H. Hall, B. Gulyas, P. D. Mozley, D. Dobson, R. B. Innis, E. Shchukin, L. Farde, *Neuroimage,* **2004**, *22*, T32-T32.
[18] T. G. Hamill, S. Krause, C. Ryan, C. Bonnefous, S. Govek, T. J. Seiders, N. D. P. Cosford, J. Roppe, T. Kamenecka, S. Patel, R. E. Gibson, S. Sanabria, K. Riffel, W. S. Eng, C. King, X. Q. Yang, M. D. Green, S. S. O'Malley, R. Hargreaves, H. D. Burns, *Synapse,* **2005**, *56*, 205-216.
[19] O. Solin, O. Eskola, T. G. Hamill, J. Bergman, P. Lehikoinen, T. Gronroos, S. Forsback, M. Haaparanta, T. Viljanen, C. Ryan, R. Gibson, G. Kieczykowski, J. Hietala, R. Hargreaves, H. D. Burns, *Mol. Imaging Biol.,* **2004**, *6*, 373-384.
[20] J. Mukherjee, Z. Y. Yang, M. K. Das, *Chemists' Views of Imaging Centers* **1995**, 265-275.
[21] L. X. Lang, E. Jagoda, B. Schmall, B. K. Vuong, H. R. Adams, D. L. Nelson, R. E. Carson, W. C. Eckelman, *J. Med. Chem.,* **1999**, *42*, 1576-1586.
[22] G. Firnau, S. Sood, E. R. Pantel, S. Garnett, *Mol Pharmacol.,* **1981**, *19*, 130-133.
[23] K. Hamacher, H. H. Coenen, *Appl. Radiat. Isotopes,* **2002**, *57*, 853-856.

[24] N. N. Ryzhikov, N. Seneca, R. N. Krasikova, N. A. Gomzina, E. Shchukin, O. S. Fedorova, D. A. Vassiliev, B. Gulyas, H. Hall, I. Savic, C. Halldin, *Nucl. Med, Biol.,* **2005**, *32*, 109-116.
[25] J. R. Grierson, J. M. Link, C. A. Mathis, J. S. Rasey, K. A. Krohn, *J. Nucl. Med.,* **1989**, *30*, 343-350.
[26] F. G. Simeon, A. K. Brown, S. S. Zoghbi, V. M. Patterson, R. B. Innis, V. W. Pike, *J. Med. Chem.,* **2007**, *50*, 3256-3266.
[27] W. R. Dolbier, A. R. Li, C. J. Koch, C. Y. Shiue, A. V. Kachur, *Appl. Radiat. Isotopes,* **2001**, *54*, 73-80.
[28] S. Vallabhajosula, *Molecular Imaging: Radiopharmaceuticals for PET and SPECT*, Springer, **2009**.
[29] S. M. Okarvi, *Eur. J. Nucl. Med.,* **2001**, *28*, 929-938.
[30] C. K. Younes, R. Boisgard, B. Tavitian, *Curr. Pharm. Des.,* **2002**, *8*, 1451-1466.
[31] M. Glaser, E. Arstad, *Bioconjugate Chem.,* **2007**, *18*, 989-993.
[32] M. C. Lasne, C. Perrio, J. Rouden, L. Barre, D. Roeda, F. Dolle, C. Crouzel, *Top. Curr. Chem.,* **2002**, *222*, 201-258.
[33] F. Dolle, *Curr Pharm Design* **2005**, *11*, 3221-3235.
[34] V. W. Pike, F. I. Aigbirhio, *J. Chem. Soc. Chem. Commun.* **1995**, 2215-2216.
[35] J. H. Chun, S. Y. Lu, Y. S. Lee, V. W. Pike, *J. Org. Chem.,* **2010**, *75*, 3332-3338.
[36] T. L. Ross, J. Ermert, C. Hocke, H. H. Coenen, *J. Am. Chem. Soc.,* **2007**, *129*, 8018-8025.
[37] Z. Miao, B. Shen, L. L. Qin, K. Neumann, S. DiMagno, F. T. Chin, *J. Cerebr. Blood F. Met.,* **2012**, *32*, S191-S191.
[38] O. T. DeJesus, C. J. Endres, S. E. Shelton, R. J. Nickles, J. E. Holden, *J. Nucl. Med.,* **1997**, *38*, 630-636.
[39] D. M. Wieland, K. C. Rosenspire, G. D. Hutchins, M. Vandort, J. M. Rothley, S. G. Mislankar, H. T. Lee, C. C. Massin, D. L. Gildersleeve, P. S. Sherman, M. Schwaiger, *J. Med. Chem.,* **1990**, *33*, 956-964.
[40] Z. H. Gao, Y. H. Lim, M. Tredwell, L. Li, S. Verhoog, M. Hopkinson, W. Kaluza, T. L. Collier, J. Passchier, M. Huiban, V. Gouverneur, *Angew. Chem. Int. Ed.,* **2012**, *51*, 6733-6737.
[41] C. Lemaire, P. Damhaut, A. Plenevaux, R. Cantineau, L. Christiaens, M. Guillaume, *Appl. Radiat. Isotopes,* **1992**, *43*, 485-494.
[42] O. Langer, F. Dolle, H. Valette, C. Halldin, F. Vaufrey, C. Fuseau, C. Coulon, M. Ottaviani, K. Nagren, M. Bottlaender, B. Maziere, C. Crouzel, *Bioorg. Med. Chem.,* **2001**, *9*, 677-694.
[43] C. Lemaire, M. Guillaume, L. Christiaens, A. J. Palmer, R. Cantineau, *Appl. Radiat. Isotopes,* **1987**, *38*, 1033-1038.
[44] P. Biginelli, *Berichte der deutschen chemischen Gesellschaft* **1891**, *24*, 1317-1319.
[45] E. W. Baader, *Angew. Chem.,* **1959**, *71*, 373-388.
[46] G. G. Aloisi, F. Elisei, L. Latterini, M. Passerini, G. Galiazzo, *J. Chem. Soc. Faraday Trans.,* **1996**, *92*, 3315-3320.
[47] K. Groebke, L. Weber, F. Mehlin, *Synlett* **1998**, 661-663.
[48] L. Li, M. N. Hopkinson, R. L. Yona, R. Bejot, A. D. Gee, V. Gouverneur, *Chem. Sci.,* **2011**, *2*, 123-131.
[49] T. G. M. Dhar, D. Nagarathnam, M. R. Marzabadi, B. Lagu, W. C. Wong, G. Chiu, S. Tyagarajan, S. W. Miao, F. Q. Zhang, W. Y. Sun, D. Tian, Q. R. Shen, J.

Zhang, J. M. Wetzel, C. Forray, R. S. L. Chang, T. P. Broten, T. W. Schorn, T. B. Chen, S. O'Malley, R. Ransom, K. Schneck, R. Bendesky, C. M. Harrell, K. P. Vyas, K. Y. Zhang, J. Gilbert, D. J. Pettibone, M. A. Patane, M. G. Bock, R. M. Freidinger, C. Gluchowski, *J. Med. Chem.,* **1999**, *42*, 4778-4793.
[50] S. Forsback, O. Eskola, M. Haaparanta, J. Bergman, O. Solin, *Radiochim. Acta,* **2008**, *96*, 845-848.
[51] O. Eskola, T. J. Gronroos, S. Forsback, J. Tuomela, G. Komar, J. Bergman, P. Harkonen, M. Haaparanta, H. Minn, O. Solin, *Mol Imaging Biol* **2012**, *14*, 205-212.
[52] J. K. Vahatalo, O. Eskola, J. Bergman, S. Forsback, P. Lehikoinen, J. Jaaskelainen, O. Solin, *J. Labelled Compd. Radiopharm.,* **2002**, *45*, 697-704.
[53] W. Fraenk, T. M. Klapotke, E. Banks, M. K. Besheesh, *J. Fluorine Chem.,* **2001**, *108*, 87-90.
[54] T. L. Cottrell, *The Strengths of Chemical Bonds*, Butterworths Scientific Publications, **1958**.
[55] M. Namavari, A. Bishop, N. Satyamurthy, G. Bida, J. R. Barrio, *Appl Radiat Isotopes* **1992**, *43*, 989-996.
[56] R. Bergmann, J. Pietzsch, F. Fuechtner, B. Pawelke, B. Beuthien-Baumann, B. Joharmsen, J. Kotzerke, *J. Nucl. Med.,* **2004**, *45*, 2116-2122.
[57] R. Haeckel, K. Weber, C. Germann, U. Haberkorn, S. Zeisler, J. Eisenbarth, M. Wiessler, F. Oberdorfer, *J. Labelled Compd. Radiopharm.,* **1996**, *38*, 1061-1070.
[58] E. Hess, S. Sichler, A. Kluge, H. H. Coenen, *Appl. Radiat. Isotopes,* **2002**, *57*, 185-191.
[59] O. Eskola, T. Gronroos, J. Bergman, M. Haaparanta, P. Marjamaki, P. Lehikoinen, S. Forsback, O. Langer, F. Hinnen, F. Dolle, C. Halldin, O. Solin, *Nucl. Med, Biol.,* **2004**, *31*, 103-110.
[60] C. Eaborn, *J. Organomet. Chem.,* **1975**, *100*, 43-57.
[61] A. G. Davies, *Organotin Chemistry*, Wiley, **2006**.
[62] E. F. J. de Vries, G. Luurtsema, M. Brussermann, P. H. Elsinga, W. Vaalburg, *Appl. Radiat. Isotopes,* **1999**, *51*, 389-394.
[63] R. D. Neirinckx, R. M. Lambrecht, A. P. Wolf, *Int. J. Appl. Radiat. Is.,* **1978**, *29*, 323-327.
[64] R. E. Ehrenkaufer, R. R. Macgregor, *Int. J. Appl. Radiat. Is.,* **1983**, *34*, 613-615.
[65] M. Constantinou, F. I. Aigbirhio, R. G. Smith, C. A. Ramsden, V. W. Pike, *J. Am. Chem. Soc.,* **2001**, *123*, 1780-1781.
[66] F. Oberdorfer, E. Hofmann, W. Maierborst, *J. Labelled Compd. Radiopharm.,* **1988**, *25*, 999-1005.
[67] F. Oberdorfer, E. Hofmann, W. Maierborst, *Appl. Radiat. Isotopes,* **1988**, *39*, 685-688.
[68] N. Satyamurthy, G. T. Bida, M. E. Phelps, J. R. Barrio, *Appl. Radiat. Isotopes,* **1990**, *41*, 733-738.
[69] H. Teare, E. G. Robins, E. Arstad, K. L. Sajinder, V. Gouverneur, *Chem. Commun.,* **2007**, 2330-2332.
[70] H. Teare, E. G. Robins, A. Kirjavainen, S. Forsback, G. Sandford, O. Solin, S. K. Luthra, V. Gouverneur, *Angew. Chem. Int. Ed.,* **2010**, *49*, 6821-6824.
[71] D. M. Jewett, J. F. Potocki, R. E. Ehrenkaufer, *J. Fluorine Chem.,* **1984**, *24*, 477-484.
[72] J. S. Fowler, C. Y. Shiue, A. P. Wolf, P. A. Salvadori, R. R. Macgregor, *J. Labelled Compd. Radiopharm.,* **1982**, *19*, 1634-1636.
[73] O. Lerman, Y. Tor, D. Hebel, S. Rozen, *J. Org. Chem.,* **1984**, *49*, 806-813.

[74] M. J. Adam, T. J. Ruth, S. Jivan, B. D. Pate, *J. Fluorine Chem.,* **1984**, *25*, 329-337.
[75] C. Y. Shiue, P. A. Salvadori, A. P. Wolf, J. S. Fowler, R. R. Macgregor, *J. Nucl. Med.,* **1982**, *23*, 899-903.
[76] P. Kirsch, in *Modern Fluoroorganic Chemistry*, Wiley-VCH Verlag GmbH & Co. KGaA, **2013**, pp. 25-106.
[77] A. Engelbrecht, H. Atzwanger, *J. Inorg. Nucl. Chem.,* **1956**, *2*, 348-357.
[78] A. Hiller, C. Fischer, A. Jordanova, J. T. Patt, J. Steinbach, *Appl. Radiat. Isotopes,* **2008**, *66*, 152-157.
[79] M. A. Tius, *Tetrahedron,* **1995**, *51*, 6605-6634.
[80] R. Filler, *Israel. J. Chem.,* **1978**, *17*, 71-79.
[81] T. B. Patrick, M. R. Kilbourn, M. J. Welch, *J. Nucl. Med.,* **1985**, *26*, 830-830.
[82] M. Eisenberg, D. D. Desmarteau, *Inorg. Nucl. Chem. Lett.,* **1970**, *6*, 29-33.
[83] M. Tamura, T. Takagi, H. Quan, A. Sekiya, *J. Fluorine Chem.,* **1999**, *98*, 163-166.
[84] S. Sood, G. Firnau, E. S. Garnett, *Int. J. Appl. Radiat. Is.,* **1983**, *34*, 743-745.
[85] G. Firnau, R. Chirakal, S. Sood, E. S. Garnett, *J. Labelled Compd. Radiopharm.,* **1981**, *18*, 7-8.
[86] S. Y. Lu, V. W. Pike, *J. Fluorine Chem.,* **2010**, *131*, 1032-1038.
[87] D. D. Desmarteau, M. Witz, *J. Fluorine Chem.,* **1991**, *52*, 7-12.
[88] W. E. Barnette, *J. Am. Chem. Soc.,* **1984**, *106*, 452-454.
[89] S. T. Purrington, W. A. Jones, *J. Org. Chem.,* **1983**, *48*, 761-762.
[90] T. Umemoto, K. Kawada, K. Tomita, *Tetrahedron Lett.,* **1986**, *27*, 4465-4468.
[91] E. Differding, H. Ofner, *Synlett,* **1991**, 187-189.
[92] R. E. Banks, *J. Fluorine Chem.,* **1998**, *87*, 1-17.
[93] S. Singh, D. D. Desmarteau, S. S. Zuberi, M. Witz, H. N. Huang, *J. Am. Chem. Soc.,* **1987**, *109*, 7194-7196.
[94] R. E. Banks, I. Sharif, R. G. Pritchard, *Acta Crystallogr. C,* **1993**, *49*, 492-495.
[95] A. G. Gilicinski, G. P. Pez, R. G. Syvret, G. S. Lal, *J. Fluorine Chem.,* **1992**, *59*, 157-162.
[96] T. D. Beeson, D. W. C. MacMillan, *J. Am. Chem. Soc.,* **2005**, *127*, 8826-8828.
[97] G. Verniest, E. Van Hende, R. Surmont, N. De Kimpe, *Org. Lett.,* **2006**, *8*, 4767-4770.
[98] Y. J. Ko, K. B. Park, S. B. Shim, J. H. Shin, *J. Fluorine Chem.,* **2006**, *127*, 755-759.
[99] B. Hill, L. Yong, S. D. Taylor, *Org. Lett.,* **2004**, *6*, 4285-4288.
[100] S. M. Kim, H. R. Kim, D. Y. Kim, *Org. Lett.,* **2005**, *7*, 2309-2311.
[101] P. T. Nyffeler, S. G. Duron, M. D. Burkart, S. P. Vincent, C. H. Wong, *Angew. Chem. Int. Ed.,* **2005**, *44*, 192-212.
[102] S. Thibaudeau, V. Gouverneur, *Org. Lett.,* **2003**, *5*, 4891-4893.
[103] M. D. Burkart, Z. Y. Zhang, S. C. Hung, C. H. Wong, *J. Am. Chem. Soc.,* **1997**, *119*, 11743-11746.
[104] R. E. Banks, M. K. Besheesh, S. N. MohialdinKhaffaf, I. Sharif, *J. Chem. Soc. Perkin Trans. 1,* **1996**, 2069-2076.
[105] G. S. Lal, *J. Org. Chem.,* **1993**, *58*, 2791-2796.
[106] M. R. Kilbourn, R. Subramanian, *J. Labelled Compd. Radiopharm.,* **1990**, *28*, 1355-1361.
[107] H. Martinez, A. Rebeyrol, T. B. Nelms, W. R. Dolbier, *J. Fluorine Chem.,* **2012**, *135*, 167-175.
[108] T. Furuya, A. E. Strom, T. Ritter, *J. Am. Chem. Soc.,* **2009**, *131*, 1662-1663.

[109] E. S. Garnett, G. Firnau, C. Nahmias, *Nature,* **1983**, *305*, 137-138.
[110] K. L. Leenders, A. J. Palmer, N. Quinn, J. C. Clark, G. Firnau, E. S. Garnett, C. Nahmias, T. Jones, C. D. Marsden, *J. Neurol. Neurosurg. Ps.,* **1986**, *49*, 853-860.
[111] A. Becherer, M. Szabo, G. Karanikas, P. Wunderbaldinger, P. Angelberger, M. Raderer, A. Kurtaran, R. Dudczak, K. Kletter, *J. Nucl. Med.,* **2004**, *45*, 1161-1167.
[112] R. R. Kapoor, C. Gilbert, K. Mohnike, O. Blankenstein, F. Fuechtner, K. Hussain, *Arch. Dis. Child Fetal,* **2008**, *93*, F166-F166.
[113] A. Carlsson, M. Lindqvist, T. Magnusson, B. Waldeck, *Science,* **1958**, *127*, 471-471.
[114] N. C. Andreasen, *Science*, **1988**, *239*, 1381-1388.
[115] J. R. Cooper, F. E. Bloom, R. H. Roth, *The biochemical basis of neuropharmacology*, Oxford University Press, **1996**.
[116] H. P. Rang, M. Dale, *Rang and Dale's Pharmacology*, Churchill Livingstone, **2007**.
[117] P. Hartvig, H. Agren, L. Reibring, J. Tedroff, P. Bjurling, T. Kihlberg, B. Langstrom, *J. Neural. Transm. Gen.,* **1991**, *86*, 25-41.
[118] P. Hartvig, K. J. Lindner, J. Tedroff, P. Bjurling, K. Hornfelt, B. Langstrom, *J. Neural Transm. Gen.,* **1992**, *87*, 15-22.
[119] O. T. DeJesus, *Drug. Develop. Res.,* **2003**, *59*, 249-260.
[120] J. L. Eberling, K. S. Bankiewicz, J. P. O'Neil, W. J. Jagust, *Frontiers in human neuroscience,* **2007**, *1*, 9.
[121] M. R. Kilbourn, J. N. DaSilva, K. A. Frey, R. A. Koeppe, D. E. Kuhl, *J. Neurochem.,* **1993**, *60*, 2315-2318.
[122] R. Goswami, D. E. Ponde, M. P. Kung, C. Hou, M. R. Kilbourn, H. F. Kung, *Nucl. Med. Biol.,* **2006**, *33*, 685-694.
[123] M. Freeby, R. Goland, M. Ichise, A. Maffei, R. Leibel, P. Harris, *Diabetes, Obes. Metab.,* **2008**, *10 Suppl 4*, 98-108.
[124] A. Laakso, J. Bergman, M. Haaparanta, H. Vilkman, O. Solin, E. Syvalahti, J. Hietala, *Schizophr. Res.,* **2001**, *52*, 115-120.
[125] P. H. Elsinga, K. Hatano, K. Ishiwata, *Curr. Med. Chem.,* **2006**, *13*, 2139-2153.
[126] S. M. Aquilonius, K. Bergstrom, S. A. Eckernas, P. Hartvig, K. L. Leenders, H. Lundquist, G. Antoni, A. Gee, A. Rimland, J. Uhlin, et al., *Acta Neurol. Scand.* **1987**, *76*, 283-287.
[127] M. Haaparanta, J. Bergman, A. Laakso, J. Hietala, O. Solin, *Synapse,* **1996**, *23*, 321-327.
[128] A. Luxen, M. Guillaume, W. P. Melega, V. W. Pike, O. Solin, R. Wagner, *Nucl. Med. Biol.,* **1992**, *19*, 149-158.
[129] G. Firnau, R. Chirakal, S. Sood, S. Garnett, *Can. J. Chem.,* **1980**, *58*, 1449-1450.
[130] R. Chirakal, G. Firnau, J. Couse, E. S. Garnett, *Int. J. Appl. Radiat. Is.,* **1984**, *35*, 651-653.
[131] G. Firnau, R. Chirakal, E. S. Garnett, *J. Nucl. Med.,* **1984**, *25*, 1228-1233.
[132] R. Chirakal, G. Firnau, E. S. Garnett, *J. Nucl. Med.,* **1986**, *27*, 417-421.
[133] M. Diksic, S. Farrokhzad, *J. Nucl. Med.,* **1985**, *26*, 1314-1318.
[134] A. Luxen, M. Perlmutter, G. T. Bida, G. Vanmoffaert, J. S. Cook, N. Satyamurthy, M. E. Phelps, J. R. Barrio, *Appl. Radiat. Isotopes,* **1990**, *41*, 275-281.
[135] F. Dolle, S. Demphel, F. Hinnen, D. Fournier, F. Vaufrey, C. Crouzel, *J. Labelled Compd. Radiopharm.,* **1998**, *41*, 105-114.
[136] K. Kawai, M. A. Channing, D. O. Kiesewetter, W. C. Eckelman, *Nucl. Med. Biol.,* **1995**, *22*, 37-43.

[137] L. P. Szajek, M. A. Channing, W. C. Eckelman, *Appl. Radiat. Isotopes,* **1998**, *49*, 795-804.
[138] Bibliography on tin poisoning and toxicity, *Vet. Hum. Toxicol.,* **1980**, *22*, 439-441.
[139] S. Forsback, O. Eskola, J. Bergman, M. Haaparanta, O. Solin, *J. Labelled Compd. Radiopharm.,* **2009**, *52*, 286-288.
[140] F. M. Wagner, J. Ermert, H. H. Coenen, *J. Nucl. Med.,* **2009**, *50*, 1724-1729.
[141] E. Lee, J. M. Hooker, T. Ritter, *J. Am. Chem. Soc.,* **2012**, *134*, 17456-17458.
[142] C. Lemaire, M. Guillaume, R. Cantineau, L. Christiaens, *J. Nucl. Med.,* **1990**, *31*, 1247-1251.
[143] G. N. Reddy, M. Haeberli, H. F. Beer, A. P. Schubiger, *Appl. Radiat. Isotopes,* **1993**, *44*, 645-649.
[144] C. Lemaire, M. Guillaume, R. Cantineau, A. Plenevaux, L. Christiaens, *Appl. Radiat. Isotopes,* **1991**, *42*, 629-635.
[145] A. Najafi, *Nucl. Med. Biol.,* **1995**, *22*, 395-397.
[146] C. Lemaire, A. Plenevaux, R. Cantineau, L. Christiaens, M. Guillaume, D. Comar, *Appl. Radiat. Isotopes,* **1993**, *44*, 737-744.
[147] C. Lemaire, P. Damhaut, A. Plenevaux, D. Comar, *J. Nucl. Med.,* **1994**, *35*, 1996-2002.
[148] C. Lemaire, S. Gillet, S. P. Guillouet, A. Plenevaux, J. L. Aerts, A. Luxen, *Eur. J. Org. Chem.,* **2004**, 2899-2904.
[149] B. Shen, W. Ehrlichmann, M. Uebele, H. J. Machulla, G. Reischl, *Appl. Radiat. Isotopes,* **2009**, *67*, 1650-1653.
[150] R. N. Krasikova, V. V. Zaitsev, S. M. Ametamey, O. F. Kuznetsova, O. S. Fedorova, I. K. Mosevich, Y. N. Belokon, S. Vyskocil, S. V. Shatik, M. Nader, P. A. Schubiger, *Nucl. Med. Biol.,* **2004**, *31*, 597-603.
[151] S. Kaneko, K. Ishiwata, K. Hatano, H. Omura, K. Ito, M. Senda, *Appl. Radiat. Isotopes,* **1999**, *50*, 1025-1032.
[152] L. C. Libert, X. Franci, A. R. Plenevaux, T. Ooi, K. Maruoka, A. J. Luxen, C. F. Lemaire, *J. Nucl. Med.,* **2013**, *54*, 1154-1161.
[153] H. K. Hofstee, J. Boersma, G. J. M. Vanderkerk, *J. Organomet. Chem.,* **1979**, *168*, 241-249.
[154] J. C. Cochran, H. G. Kuivila, *Organometallics,* **1982**, *1*, 97-103.
[155] J. C. Cochran, S. C. Bayer, J. T. Bilbo, M. S. Brown, L. B. Colen, F. J. Gaspirini, D. W. Goldsmith, M. D. Jamin, K. A. Nealy, C. T. Resnick, G. J. Schwartz, W. M. Short, K. R. Skarda, J. P. Spring, W. L. Strauss, *Organometallics,* **1982**, *1*, 586-590.
[156] M. Mehring, C. Nolde, M. Schurmann, *Inorg. Chim. Acta,* **2009**, *362*, 745-752.
[157] P. P. Tang, T. Furuya, T. Ritter, *J. Am. Chem. Soc.,* **2010**, *132*, 12150-12154.
[158] T. Furuya, T. Ritter, *Org. Lett.* **2009**, *11*, 2860-2863.
[159] D. P. Matthews, S. C. Miller, E. T. Jarvi, J. S. Sabol, J. R. Mccarthy, *Tetrahedron Lett.,* **1993**, *34*, 3057-3060.
[160] M. A. Tius, J. K. Kawakami, *Tetrahedron,* **1995**, *51*, 3997-4010.
[161] C. D. M. Beverwijk, G. J. M. van der Kerk, *J. Organomet. Chem.,* **1972**, *43*, C7-C10.
[162] E. M. Meyer, S. Gambarotta, C. Floriani, A. Chiesivilla, C. Guastini, *Organometallics,* **1989**, *8*, 1067-1079.
[163] N. G. Connelly, W. E. Geiger, *Chem. Rev.,* **1996**, *96*, 877-910.
[164] L. Song, W. C. Trogler, *Angew. Chem. Int. Ed.* **1992**, *31*, 770-772.

[165] A. N. Cammidge, V. H. M. Goddard, H. Gopee, N. L. Harrison, D. L. Hughes, C. J. Schubert, B. M. Sutton, G. L. Watts, A. J. Whitehead, *Org. Lett,.* **2006**, *8*, 4071-4074.
[166] D. G. Hall, in *Boronic Acids*, Wiley-VCH Verlag GmbH & Co. KGaA, **2006**, pp. 1-99.
[167] R. Haruta, M. Ishiguro, N. Ikeda, H. Yamamoto, *J. Am. Chem. Soc.,* **1982**, *104*, 7667-7669.
[168] W. R. Roush, A. E. Walts, L. K. Hoong, *J. Am. Chem. Soc.,* **1985**, *107*, 8186-8190.
[169] Y. Iwai, K. M. Gligorich, M. S. Sigman, *Angew. Chem. Int. Ed.,* **2008**, *47*, 3219-3222.
[170] K. W. Quasdorf, M. Riener, K. V. Petrova, N. K. Garg, *J. Am. Chem. Soc.,* **2009**, *131*, 17748-17749.
[171] F. Fuchtner, P. Angelberger, H. Kvaternik, F. Hammerschmidt, B. P. Simovc, J. Steinbach, *Nucl. Med. Biol.,* **2002**, *29*, 477-481.
[172] J. Jones, *Amino acids and peptide synthesis: CIP title*, Oxford University Press, Incorporated, **1992**.
[173] L. J. Diorazio, D. A. Widdowson, J. M. Clough, *Tetrahedron,* **1992**, *48*, 8073-8088.
[174] J. M. Clough, L. J. Diorazio, D. A. Widdowson, *Synlett,* **1990**, 761-762.
[175] C. Cazorla, E. Metay, B. Andrioletti, M. Lemaire, *Tetrahedron Lett.,* **2009**, *50*, 3936-3938.
[176] M. Guillaume, A. Luxen, B. Nebeling, M. Argentini, J. C. Clark, V. W. Pike, *Appl. Radiat. Isotopes,* **1991**, *42*, 749-762.
[177] A. Suzuki, *Pure Appl. Chem.,* **1991**, *63*, 419-422.
[178] K. L. Hull, W. Q. Anani, M. S. Sanford, *J. Am. Chem. Soc.,* **2006**, *128*, 7134-7135.
[179] S. Purser, P. R. Moore, S. Swallow, V. Gouverneur, *Chem. Soc. Rev.* **2008**, *37*, 320-330.
[180] N. D. Ball, M. S. Sanford, *J. Am. Chem. Soc.,* **2009**, *131*, 3796-3797.
[181] T. Furuya, H. M. Kaiser, T. Ritter, *Angew. Chem. Int. Ed.* **2008**, *47*, 5993-5996.
[182] E. Lee, A. S. Kamlet, D. C. Powers, C. N. Neumann, G. B. Boursalian, T. Furuya, D. C. Choi, J. M. Hooker, T. Ritter, *Science,* **2011**, *334*, 639-642.
[183] J. F. Hartwig, *Nature,* **2008**, *455*, 314-322.
[184] J. K. Stille, K. S. Y. Lau, *Acc. Chem. Res.,* **1977**, *10*, 434-442.
[185] K. R. Dixon, J. Mcfarland, *J. Chem. Soc. Chem. Commun.,* **1972**, 1274-&.
[186] S. L. Fraser, M. Y. Antipin, V. N. Khroustalyov, V. V. Grushin, *J. Am. Chem. Soc.,* **1997**, *119*, 4769-4770.
[187] V. V. Grushin, *Chem. Eur. J.,* **2002**, *8*, 1006-1014.
[188] M. A. Cairns, K. R. Dixon, J. J. Mcfarland, *J. Chem. Soc. Dalton Trans.,* **1975**, 1159-1164.
[189] W. J. Marshall, D. L. Thorn, V. V. Grushin, *Organometallics,* **1998**, *17*, 5427-5430.
[190] M. Yamashita, J. F. Hartwig, *J. Am. Chem. Soc.,* **2004**, *126*, 5344-5345.
[191] M. S. Driver, J. F. Hartwig, *J. Am. Chem. Soc.,* **1995**, *117*, 4708-4709.
[192] J. F. Hartwig, *Inorg. Chem.,* **2007**, *46*, 1936-1947.
[193] R. A. Widenhoefer, S. L. Buchwald, *J. Am. Chem. Soc.,* **1998**, *120*, 6504-6511.
[194] T. Furuya, J. E. M. N. Klein, T. Ritter, *Synthesis-Stuttgart,* **2010**, 1804-1821.
[195] M. B. Smith, J. March, *March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*, Wiley, **2007**.

[196] D. C. Roe, W. J. Marshall, F. Davidson, P. D. Soper, V. V. Grushin, *Organometallics,* **2000**, *19*, 4575-4582.
[197] V. V. Grushin, *Organometallics,* **2000**, *19*, 1888-1900.
[198] V. V. Grushin, W. J. Marshall, *J. Am. Chem. Soc.,* **2006**, *128*, 12644-12645.
[199] D. V. Yandulov, N. T. Tran, *J. Am. Chem. Soc.,* **2007**, *129*, 1342-1358.
[200] M. Beller, C. Bolm, *Transition Metals for Organic Synthesis: Building Blocks and Fine Chemicals*, Wiley, **2004**.
[201] J. F. Hartwig, *Synlett,* **2006**, 1283-1294.
[202] V. V. Grushin, W. J. Marshall, *Organometallics,* **2007**, *26*, 4997-5002.
[203] D. A. Watson, M. J. Su, G. Teverovskiy, Y. Zhang, J. Garcia-Fortanet, T. Kinzel, S. L. Buchwald, *Science,* **2009**, *325*, 1661-1664.
[204] R. H. Crabtree, *The Organometallic Chemistry of the Transition Metals*, Wiley, **2011**.
[205] J. Cardinale, J. Ermert, F. Kugler, A. Helfer, M. R. Brandt, H. H. Coenen, *J. Labelled Compd. Radiopharm.,* **2012**, *55*, 450-453.
[206] A. R. Dick, K. L. Hull, M. S. Sanford, *J. Am. Chem. Soc.,* **2004**, *126*, 2300-2301.
[207] X. S. Wang, T. S. Mei, J. Q. Yu, *J. Am. Chem. Soc.,***2009**, *131*, 7520-7521.
[208] K. S. L. Chan, M. Wasa, X. S. Wang, J. Q. Yu, *Angew. Chem. Int. Ed.,* **2011**, *50*, 9081-9084.
[209] T. Furuya, D. Benitez, E. Tkatchouk, A. E. Strom, P. P. Tang, W. A. Goddard, T. Ritter, *J. Am. Chem. Soc.,* **2010**, *132*, 14092-14103.
[210] A. Vigalok, *Chem-Eur J* **2008**, *14*, 5102-5108.
[211] a D. C. Powers, M. A. L. Geibel, J. E. M. N. Klein, T. Ritter, *J. Am. Chem. Soc.,* **2009**, *131*, 17050-17051; b D. C. Powers, T. Ritter, *Nature chemistry* **2009**, *1*, 302-309.
[212] A. S. Kamlet, C. N. Neumann, E. Lee, S. M. Carlin, C. K. Moseley, N. Stephenson, J. M. Hooker, T. Ritter, *PloS one* **2013**, *8*.
[213] a J. J. Topczewski, T. J. Tewson, H. M. Nguyen, *J. Am. Chem. Soc.,* **2011**, *133*, 19318-19321; b E. Benedetto, M. Tredwell, C. Hollingworth, T. Khotavivattana, J. M. Brown, V. Gouverneur, *Chem. Sci.,* **2013**, *4*, 89-96.
[214] C. Hollingworth, A. Hazari, M. N. Hopkinson, M. Tredwell, E. Benedetto, M. Huiban, A. D. Gee, J. M. Brown, V. Gouverneur, *Angew. Chem. Int. Ed.,* **2011**, *50*, 2613-2617.
[215] M. Mizutani, S. Tomosue, H. Kinoshita, K. Jitsukawa, H. Masuda, H. Einaga, *Bull. Chem. Soc. Jpn.,* **1999**, *72*, 981-988.
[216] A. C. Cope, R. W. Siekman, *J. Am. Chem. Soc.,* **1965**, *87*, 3272-3273.
[217] A. C. Cope, E. C. Friedrich, *J. Am. Chem. Soc.,* **1968**, *90*, 909-913.
[218] J. Vicente, I. SauraLlamas, M. G. Palin, P. G. Jones, M. C. R. deArellano, *Organometallics,* **1997**, *16*, 826-833.
[219] J. Vicente, I. Saura-Llamas, *Comment. Inorg. Chem.,* **2007**, *28*, 39-72.
[220] J. Vicente, I. Saura-Llamas, J. Cuadrado, M. C. R. de Arellano, *Organometallics,* **2003**, *22*, 5513-5517.
[221] A. D. Ryabov, I. K. Sakodinskaya, A. K. Yatsimirsky, *J. Chem. Soc. Dalton Trans.,* **1985**, 2629-2638.
[222] J. Vicente, I. Saura-Llamas, J. A. Garcia-Lopez, B. Calmuschi-Cula, D. Bautista, *Organometallics,* **2007**, *26*, 2768-2776.
[223] N. D. Ball, J. W. Kampf, M. S. Sanford, *Dalton Trans.,* **2010**, *39*, 632-640.
[224] R. Vanasselt, E. Rijnberg, C. J. Elsevier, *Organometallics,* **1994**, *13*, 706-720.

[225] N. D. Ball, J. W. Kampf, M. S. Sanford, *J. Am. Chem. Soc.,* **2010**, *132*, 2878-2879.
[226] N. D. Ball, J. B. Gary, Y. D. Ye, M. S. Sanford, *J. Am. Chem. Soc.,* **2011**, *133*, 7577-7584.
[227] M. J. Oliva-Madrid, J. A. Garcia-Lopez, I. Saura-Llamas, D. Bautista, J. Vicente, *Organometallics,* **2012**, *31*, 3647-3660.
[228] T. Furuya, T. Ritter, *J. Am. Chem. Soc.,* **2008**, *130*, 10060-10061.
[229] T. S. Mei, X. S. Wang, J. Q. Yu, *J. Am. Chem. Soc.,***2009**, *131*, 10806-10807.
[230] L. V. Desai, K. J. Stowers, M. S. Sanford, *J. Am. Chem. Soc.,* **2008**, *130*, 13285-13293.
[231] J. Albert, J. M. Cadena, A. Gonzalez, J. Granell, X. Solans, M. Font-Bardia, *J. Organomet, Chem.,* **2002**, *663*, 277-283.
[232] J. Albert, J. M. Cadena, A. Gonzalez, J. Granell, X. Solans, M. Font-Bardia, *Chem. Eur. J.,* **2006**, *12*, 887-894.
[233] M. Gomez, J. Granell, M. Martinez, *J. Chem. Soc. Dalton Trans.* **1998**, 37-43.
[234] R. Bosque, C. Lopez, J. Sales, *J. Org. Chem.,* **1995**, *498*, 147-154.
[235] E. E. Jun, *Justus Liebigs Annalen der Chemie,* **1893**, *275*, 1-8.
[236] K. Kumar, D. J. Phelps, P. R. Carey, *Can. J. Chem.,* **1978**, *56*, 232-239.
[237] G. D. Roiban, E. Serrano, T. Soler, G. Aullon, I. Grosu, C. Cativiela, M. Martinez, E. P. Urriolabeitia, *Inorg. Chem.,* **2011**, *50*, 8132-8143.
[238] G. D. Roiban, E. Serrano, T. Soler, M. Contel, I. Grosu, C. Cativiela, E. P. Urriolabeitia, *Organometallics,* **2010**, *29*, 1428-1435.
[239] B. Sen, G. Ozturk, S. Alp, M. Aygun, O. Buyukgungor, *Acta Crystallogr. C,* **2007**, *63*, O223-O224.
[240] T. Umemoto, K. Harasawa, G. Tomizawa, K. Kawada, K. Tomita, *J. Fluorine Chem.,* **1991**, *53*, 369-377.
[241] T. Umemoto, K. Harasawa, G. Tomizawa, K. Kawada, K. Tomita, *Bull. Chem. Soc. Jpn.,* **1991**, *64*, 1081-1092.
[242] R. D. Chambers, G. Sandford, *Chim. Oggi,* **2004**, *22*, 6-8.
[243] R. D. Chambers, D. Holling, R. C. H. Spink, G. Sandford, *Lab on a chip,* **2001**, *1*, 132-137.
[244] R. D. Chambers, J. Hutchinson, G. Sandford, *J. Fluorine Chem.,* **1999**, *100*, 63-73.
[245] S. Murata, Y. Ido, *Bull. Chem. Soc. Jpn.,* **1994**, *67*, 1746-1748.
[246] E. Drent, J. A. M. Vanbroekhoven, M. J. Doyle, *J. Organomet. Chem.,* **1991**, *417*, 235-251.
[247] P. A. Sibbald, F. E. Michael, *Org. Lett.* **2009**, *11*, 1147-1149.
[248] E. W. Oliver, D. H. Evans, *J. Electroanal. Chem.,* **1999**, *474*, 1-8.
[249] D. Grierson, in *Organic Reactions*, John Wiley & Sons, Inc., **2004**.
[250] P. Maienfisch, R. G. Hall, *Chimia,* **2004**, *58*, 93-99.
[251] D. O'Hagan, *J. Fluorine Chem.,* **2010**, *131*, 1071-1081.
[252] J.-P. Begue, D. Bonnet-Delpon, *Bioorganic and Medicinal Chemistry of Fluorine*, Wiley, **2008**.
[253] T. Yamazaki, T. Taguchi, I. Ojima, in *Fluorine in Medicinal Chemistry and Chemical Biology*, John Wiley & Sons, Ltd, **2009**, pp. 1-46.
[254] M. B. van Niel, I. Collins, M. S. Beer, H. B. Broughton, S. K. F. Cheng, S. C. Goodacre, A. Heald, K. L. Locker, A. M. MacLeod, D. Morrison, C. R. Moyes, D. O'Connor, A. Pike, M. Rowley, M. G. N. Russell, C. R. Moyes, D. O'Connor, A. Pike, M. Rowley, M. G. N. Russell, B. Sohal, J. A. Stanton, S. Thomas, H. Verrier, A. P. Watt, J. L. Castro, *J. Med. Chem.,* **1999**, *42*, 2087-2104.

[255] S. R. Rabel, S. Sun, M. B. Maurin, M. Patel, *Aaps Pharmsci.,* **2001**, *3*.
[256] J. C. Adkins, S. Noble, *Drugs,* **1998**, *56*, 1055-1064.
[257] J. Earl, P. Kirkpatrick, *Nat. Rev. Drug. Discov.,* **2003**, *2*, 97-98.
[258] C. A. Lipinski, F. Lombardo, B. W. Dominy, P. J. Feeney, *Adv. Drug. Delivery Rev.,* **1997**, *23*, 3-25.
[259] B. E. Smart, *J. Fluorine Chem.,* **2001**, *109*, 3-11.
[260] R. T. Jacobs, P. R. Bernstein, L. A. Cronk, E. P. Vacek, L. F. Newcomb, D. Aharony, C. K. Buckner, E. J. Kusner, *J. Med. Chem.,* **1994**, *37*, 1282-1297.
[261] K. Muller, C. Faeh, F. Diederich, *Science,* **2007**, *317*, 1881-1886.
[262] R. Betageri, Y. Zhang, R. M. Zindell, D. Kuzmich, T. M. Kirrane, J. Bentzien, M. Cardozo, A. J. Capolino, T. N. Fadra, R. M. Nelson, Z. Paw, D. T. Shih, C. K. Shih, L. Zuvela-Jelaska, G. Nabozny, D. S. Thomson, *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4761-4769.
[263] D. T. Wong, F. P. Bymaster, E. A. Engleman, *Life Sci.,* **1995**, *57*, 411-441.
[264] D. L. Roman, C. C. Walline, G. J. Rodriguez, E. L. Barker, *Eur. J. Pharmacol.* **2003**, *479*, 53-63.
[265] R. A. Prentis, Y. Lis, S. R. Walker, *Brit. J. Clin. Pharmacol.,* **1988**, *25*, 387-396.
[266] H. Vancauteren, A. Lampo, J. Vandenberghe, P. Vanparys, W. Coussement, R. Decoster, R. Marsboom, *Mycoses,* **1989**, *32*, 60-66.
[267] K. Richardson, *J. Chemotherapy,* **1990**, *2*, 51-54.
[268] E. Livni, A. J. Fischman, S. Ray, I. Sinclair, D. R. Elmaleh, N. M. Alpert, S. Weiss, J. A. Correia, D. Webb, R. Dahl, W. Robeson, D. Margouleff, R. Liss, H. W. Strauss, R. H. Rubin, *Nucl. Med. Biol.* **1992**, *19*, 191-199.
[269] M. Bergstrom, R. J. Hargreaves, H. D. Burns, M. R. Goldberg, D. Sciberras, S. A. Reines, K. J. Petty, M. Ogren, G. Antoni, B. Langstrom, O. Eskola, M. Scheinin, O. Solin, A. K. Majumdar, M. L. Constanzer, W. P. Battisti, T. E. Bradstreet, C. Gargano, J. Hietala, *Biol. Psychiat.,* **2004**, *55*, 1007-1012.
[270] T. Furuya, A. S. Kamlet, T. Ritter, *Nature,* **2011**, *473*, 470-477.
[271] O. A. Tomashenko, V. V. Grushin, *Chem. Rev.,* **2011**, *111*, 4475-4521.
[272] A. Studer, *Angew. Chem. Int. Ed.,* **2012**, *51*, 8950-8958.
[273] J. A. Ma, D. Cahard, *J. Fluorine Chem.,* **2007**, *128*, 975-996.
[274] E. T. Mcbee, H. P. Braendlin, R. D. Battershell, *J. Am. Chem. Soc.,* **1962**, *84*, 3157-3160.
[275] F. Swarts, *Acad. Roy. Belg.,* **1892**, *3*, 474.
[276] G. Cai, W. Li, Patent, **2012**, *CN102320919.*
[277] T. Shono, M. Ishifune, T. Okada, S. Kashimura, *J. Org. Chem.* **1991**, *56*, 2-4.
[278] S. Ait-Mohand, N. Takechi, M. Medebielle, W. R. Dolbier, *Org. Lett.,* **2001**, *3*, 4271-4273.
[279] I. Ruppert, K. Schlich, W. Volbach, *Tetrahedron Lett.,* **1984**, *25*, 2195-2198.
[280] G. K. S. Prakash, M. Mandal, *J. Fluorine Chem.,* **2001**, *112*, 123-131.
[281] R. P. Singh, D. Chakraborty, J. M. Shreeve, *J. Fluorine Chem.,* **2001**, *111*, 153-160.
[282] R. P. Singh, J. M. Shreeve, *Tetrahedron,* **2000**, *56*, 7613-7632.
[283] R. P. Singh, J. M. Leitch, B. Twamley, J. M. Shreeve, *J. Org. Chem.,* **2001**, *66*, 1436-1440.
[284] T. Umemoto, S. Ishihara, *Tetrahedron Lett.,* **1990**, *31*, 3579-3582.
[285] N. Shibata, A. Matsnev, D. Cahard, *Beilstein J. Org. Chem.,* **2010**, *6*.
[286] P. Eisenberger, S. Gischig, A. Togni, *Chem. Eur. J.,* **2006**, *12*, 2579-2586.

[287] I. Kieltsch, P. Eisenberger, A. Togni, *Angew. Chem. Int. Ed.,* **2007**, *46*, 754-757.
[288] W. R. Dolbier, *Chem. Rev.,* **1996**, *96*, 1557-1584.
[289] A. Studer, M. Bossart, *Tetrahedron,* **2001**, *57*, 9649-9667.
[290] H. Sawada, M. Nakayama, M. Yoshida, T. Yoshida, N. Kamigata, *J. Fluorine Chem.,* **1990**, *46*, 423-431.
[291] H. C. Clark, J. H. Tsai, *J. Organomet. Chem.,* **1967**, *7*, 515-517.
[292] V. C. Mcloughlin, J. Thrower, *Tetrahedron* **1969**, *25*, 5921-5940.
[293] Y. Kobayashi. I. Kumadaki, *Tetrahedron Lett* **1969**, 4095-4096.
[294] G. E. Carr, R. D. Chambers, T. F. Holmes, D. G. Parker, *J. Chem. Soc. Perkin Trans. 1,* **1988**, 921-926.
[295] M. Oishi, H. Kondo, H. Amii, *Chem. Commun.,* **2009**, 1909-1911.
[296] D. M. Wiemers, D. J. Burton, *J. Am. Chem. Soc.,* **1986**, *108*, 832-834.
[297] L. M. Huffman, S. S. Stahl, *J. Am. Chem. Soc.,* **2008**, *130*, 9196-9197.
[298] T. Knauber, F. Arikan, G. V. Roschenthaler, L. J. Goossen, *Chem. Eur. J.,* **2011**, *17*, 2689-2697.
[299] L. L. Chu, F. L. Qing, *Org. Lett.,* **2010**, *12*, 5060-5063.
[300] a. E. J. Cho, T. D. Senecal, T. Kinzel, Y. Zhang, D. A. Watson, S. L. Buchwald, *Science,* **2010**, *328*, 1679-1681. b. X. Wang, L. Truesdale, J.-Q. Yu, *J. Am. Chem. Soc.*, **2010**, *132*, 3648-3649.
[301] D. A. Nagib, D. W. C. MacMillan, *Nature,* **2011**, *480*, 224-228.
[302] G. K. S. Prakash, S. Chacko, *Curr. Opin. Drug. Disc.,* **2008**, *11*, 793-802.
[303] J. A. Erickson, J. I. Mcloughlin, *J. Org. Chem.,* **1995**, *60*, 1626-1631.
[304] J. S. Houlton, W. B. Motherwell, B. C. Ross, M. J. Tozer, D. J. Williams, A. M. Z. Slawin, *Tetrahedron,* **1993**, *49*, 8087-8106.
[305] W. F. Goure, K. L. Leschinsky, S. J. Wratten, J. P. Chupp, *J. Agr. Food Chem.,* **1991**, *39*, 981-986.
[306] R. P. Singh, J. M. Shreeve, *Synthesis-Stuttgart,* **2002**, 2561-2578.
[307] K. Fujikawa, Y. Fujioka, A. Kobayashi, H. Amii, *Org. Lett.,* **2011**, *13*, 5560-5563.
[308] P. S. Fier, J. F. Hartwig, *J. Am. Chem. Soc.,* **2012**, *134*, 10795-10798.
[309] V. Grakauskas, *J. Org. Chem.,* **1969**, *34*, 2446-2450.
[310] J. Li, in *Name Reactions*, Springer Berlin Heidelberg, **2009**, pp. 298-299.
[311] T. B. Patrick, K. K. Johri, D. H. White, *J. Org. Chem.,* **1983**, *48*, 4158-4159.
[312] T. B. Patrick, S. Khazaeli, S. Nadji, K. Heringsmith, D. Reif, *J. Org. Chem.,* **1993**, *58*, 705-708.
[313] T. B. Patrick, K. K. Johri, D. H. White, W. S. Bertrand, R. Mokhtar, M. R. Kilbourn, M. J. Welch, *Can. J. Chem.,* **1986**, *64*, 138-141.
[314] C. A. Ramsden, M. M. Shaw, *Tetrahedron Lett.,* **2009**, *50*, 3321-3324.
[315] D. Griller, K. U. Ingold, *Acc. Chem. Res.,* **1980**, *13*, 317-323.
[316] M. Rueda-Becerril, C. C. Sazepin, J. C. T. Leung, T. Okbinoglu, P. Kennepohl, J. F. Paquin, G. M. Sammis, *J. Am. Chem. Soc.,* **2012**, *134*, 4026-4029.
[317] J. C. T. Leung, C. Chatalova-Sazepin, J. G. West, M. Rueda-Becerril, J. F. Paquin, G. M. Sammis, *Angew. Chem. Int. Ed.,* **2012**, *51*, 10804-10807.
[318] F. Yin, Z. T. Wang, Z. D. Li, C. Z. Li, *J. Am. Chem. Soc.,* **2012**, *134*, 10401-10404.
[319] H. Togo, in *Advanced Free Radical Reactions for Organic Synthesis*, Elsevier Science, Amsterdam, **2004**, pp. 123-156.
[320] G. Angelini, M. Speranza, C. Y. Shiue, A. P. Wolf, *J. Chem. Soc. Chem. Commun.,* **1986**, 924-925.

[321] A. Hammadi, C. Crouzel, *J. Labelled Compd. Radiopharm.,* **1993**, *33*, 703-710.
[322] P. Johnstrom, S. Stoneelander, *J. Labelled Compd. Radiopharm.,* **1995**, *36*, 537-547.
[323] M. R. Kilbourn, M. R. Pavia, V. E. Gregor, *Appl. Radiat. Isotopes,* **1990**, *41*, 823-828.
[324] M. Suehiro, G. B. Yang, G. Torchon, E. Ackerstaff, J. Humm, J. Koutcher, O. Ouerfelli, *Bioorg. Med. Chem.,* **2011**, *19*, 2287-2297.
[325] P. A. Jerabek, T. B. Patrick, M. R. Kilbourn, D. D. Dischino, M. J. Welch, *Appl. Radiat. Isotopes,* **1986**, *37*, 599-605.
[326] G. H. Tang, M. F. Wang, X. L. Tang, M. Q. Gan, L. Luo, *Nucl. Med. Biol,.* **2005**, *32*, 553-558.
[327] O. Josse, D. Labar, B. Georges, V. Gregoire, J. Marchand-Brynaert, *Bioorg. Med. Chem.,* **2001**, *9*, 665-675.
[328] M. Kuroboshi, T. Hiyama, *Tetrahedron Lett.,* **1992**, *33*, 4177-4178.
[329] M. Kuroboshi, T. Hiyama, *Chem. Lett.,* **1992**, 827-830.
[330] P. J. Riss, F. I. Aigbirhio, *Chem. Commun.,* **2011**, *47*, 11873-11875.
[331] P. J. Riss, V. Ferrari, L. Brichard, P. Burke, R. Smith, F. I. Aigbirhio, *Org. Biomol. Chem.,* **2012**, *10*, 6980-6986.
[332] M. Huiban, Z. H. Wan, X. M. Zhang, S. Mizuta, M. Tredwell, V. Gouverneur, J. Passchier, *Nature Chem.* **2013**, *5,* 941-944.
[333] J. X. Duan, D. B. Su, Q. Y. Chen, *J. Fluorine Chem.,* **1993**, *61*, 279-284.
[334] K. Sato, M. Omote, A. Ando, I. Kumadaki, *J. Fluorine Chem.,* **2004**, *125*, 509-515.
[335] L. D. Kispert, H. Liu, C. U. Pittman, *J. Am. Chem. Soc.,* **1973**, *95*, 1657-1659.
[336] F. Zhang, J. Z. Song, *Tetrahedron Lett* **2006**, *47*, 7641-7644.
[337] J. M. Anderson, J. K. Kochi, *J. Am. Chem. Soc.,* **1970**, *92*, 1651-1659.
[338] J. M. Anderson, J. K. Kochi, *J. Am. Chem. Soc.,* **1970**, *35*, 986-989.
[339] A. J. Clark, *Chem. Soc. Rev.,* **2002**, *31*, 1-11.
[340] R. E. Banks, M. K. Besheesh, S. N. MohialdinKhaffaf, I. Sharif, *J. Fluorine Chem.,* **1996**, *78*, 43-50.
[341] B. J. Wang, L. L. Qin, K. D. Neumann, S. Uppaluri, R. L. Cerny, S. G. DiMagno, *Org. Lett.,* **2010**, *12*, 3352-3355.
[342] F. Dolle, S. Demphel, F. Hinnen, D. Fournier, F. Vaufrey, C. Crouzel, *J. Labelled Compd. Radiopharm.,* **1998**, *41*, 105-114.
[343] S. Aubry, S. Pellet-Rostaing, M. Lemaire, *Eur. J. Org. Chem.,* **2007**, 5212-5225.
[344] T. Hvidt, W. A. Szarek, D. B. Maclean, *Can. J. Chem.,* **1988**, *66*, 779-782.
[345] V. K. Tandon, D. B. Yadav, R. V. Singh, A. K. Chaturvedi, P. K. Shukla, *Bioorg. Med. Chem. Lett.,* **2005**, *15*, 5324-5328.
[346] J. Vicente, I. Saura-Llamas, M. J. Oliva-Madrid, J. A. Garcia-Lopez, *Organometallics,* **2011**, *30*, 4624-4631.
[347] S. W. King, J. M. Riordan, E. M. Holt, C. H. Stammer, *J. Org. Chem.,* **1982**, *47*, 3270-3273.
[348] G. Stefanovic, M. Stefanovic, *J. Org. Chem.,* **1956**, *21*, 161-168.
[349] H. N. C. Wong, Z. L. Xu, H. M. Chang, C. M. Lee, *Synthesis-Stuttgart,* **1992**, 793-797.
[350] J. A. R. Rodrigues, R. A. Abramovitch, J. D. F. de Sousa, G. C. Leiva, *J. Org. Chem.,* **2004**, *69*, 2920-2928.
[351] R. M. Mishra, A. Wahab, A. R. Mishra, *Indian J. Heterocylic Chem.,* **2003**, *13*, 29-32.

[352] D. Roiban, E. Serrano, T. Soler, I. Grosu, C. Cativiela, E. P. Urriolabeitia, *Chem. Commun.,* **2009**, 4681-4683.
[353] E. Pasquinet, P. Rocca, F. Marsais, A. Godard, G. Queguiner, *Tetrahedron,* **1998**, *54*, 8771-8782.
[354] K. Fujikawa, Y. Fujioka, A. Kobayashi, *Org. Lett.,* **2011**, *13*, 5560-5563.
[355] W. J. Middleton, E. M. Bingham, *J. Org. Chem.,* **1980**, *45*, 2883-2887.
[356] J. H. Lin, G. Q. Zong, R. B. Du, J. C. Xiao, S. B. Liu, *Chem. Commun.,* **2012**, *48*, 7738-7740.
[357] J. Y. Yu, R. Kuwano, *Angew. Chem. Int. Ed.,* **2009**, *48*, 7217-7220.
[358] P. Novak, A. Lishchynskyi, V. V. Grushin, *Angew Chem Int Edit* **2012**, *51*, 7767-7770.
[359] Y. D. Ye, M. S. Sanford, *J. Am. Chem. Soc.,* **2012**, *134*, 9034-9037.