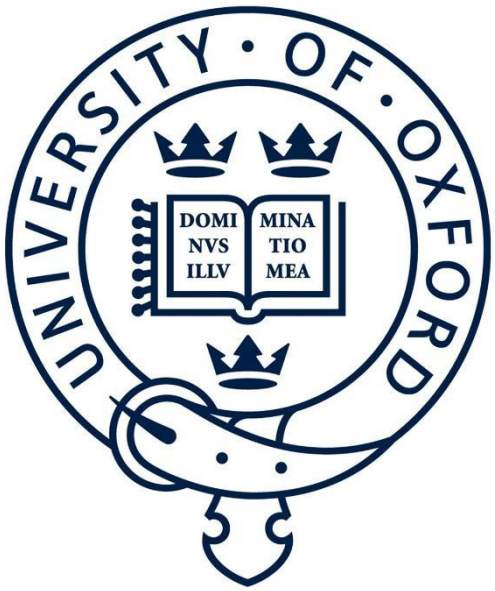
Copper-Mediated Nucleophilic ^{18}F-Radiolabelling of (Hetero)arenes for Applications in Positron Emission Tomography

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A thesis submitted to the board of the faculty of Physical Sciences in partial fulfilment of the requirements for the degree of Doctor of Philosophy at the University of Oxford



Magdalen College

Trinity Term 2017

Author's Declaration

The work presented in this thesis was conducted at the Chemistry Research Laboratory at the University of Oxford under the supervision of Professor Véronique Gouverneur, between Michaelmas Term 2013 and Trinity Term 2017. All the work is my own, except where otherwise stated, and has not been submitted for any other degree at this or any other university.

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October 2017

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Abstract

This thesis focuses on the development of a novel nucleophilic ^{18}F-fluorination of (hetero)arenes and of a rapid screening experiment to facilitate the application of this reaction to complex heterocyclic targets of medicinal importance.

Chapter 1 introduces the use of molecules labelled with fluorine-18 as tracers in positron emission tomography and reviews methods for the preparation of [^{18}F]fluoroarenes published prior to the start of the work in this thesis.

Chapter 2 describes the development of a novel method for the preparation of electronically-diverse [^{18}F]fluoroarenes from aryl boronic esters and [^{18}F]fluoride, mediated by a copper complex. Application of this ^{18}F-fluorodeboronation to electron-rich radiotracers is demonstrated. Methods for the preparation of [^{18}F]fluoroarenes published after the start of the work in this thesis are reviewed.

Chapter 3 outlines a rapid screening experiment for assessing the tolerance of the ^{18}F-fluorodeboronation towards heterocycles, and the use of this method to guide the retro-radiosynthesis of heterocycle-rich, medicinally relevant molecules.

Chapter 4 contains synthetic procedures and characterisation data for compounds in Chapters 2 and 3.

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people during my time in the group and made some good friends - thank you to Faye, Plum, Sean, Enrico, Greg, Tom, Michael, Thomas, Raul, Francesco, Osman, Jeroen, Anna and Gabriele for good times in F12, and for putting up with my taste in music. Thank you to Faye, Jamie, Miriam, Gregor, Wendy, Lukas, Emeline, Matt, Becky, Stefan, Kristina, Benoit, Sophie, Manu, Thomas, Tom, Raul, Michael, Sam, Steve, Paolo, Francesco, Yanlan, Kee, Anna, Jeroen and Gabriele for nights at the Uni Club and beyond.

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during the hand in, and to Faye and Stefan, for answering all my questions. Finally, Mum, Dad and Claire – thank you for all your love and support, for always being there, especially when times were tough, and for inspiring me to be the best that I can be.

Abbreviations and Acronyms

[^{18}F]	Enriched in fluorine-18
[^{18}F]FBnTP	4-[^{18}F]Fluorobenzyltriphenylphosphinium
[^{18}F]FDA	6-[^{18}F]Fluorodopamine
[^{18}F]FDG	2-[^{18}F]Fluoro-2-deoxy-D-glucose
[^{18}F]FDOPA	6-[^{18}F]Fluoro-3,4-dihydroxy-L-phenylalanine
[^{18}F]FMT	6-[^{18}F]Fluoro-3-hydroxy-L-phenylalanine
[^{18}F]FMTEB	3-[^{18}F]Fluoro-5-[(2-methyl-1,3-thiazol-4-yl)ethynyl]benzonitrile
[^{18}F]FPEB	3-[^{18}F]Fluoro-5-[(pyridinyl-3-yl)ethynyl]benzonitrile
[^{18}F]MFBG	(3-[^{18}F]Fluorobenzyl)guanidine
[^{18}F]MPPF	4-[^{18}F]Fluoro-*N*-(2-[4-(2-methoxyphenyl)piperazin-1-yl]ethyl)-*N*-(pyridine-2-yl)benzamide
[^{18}F]NFSI	*N*-[^{18}F]Fluorobenzenesulfonimide
[^{18}F]OMFD	6-[^{18}F]Fluoro-3-methoxy-4-hydroxy-L-phenylalanine
[^{18}F] Selectfluor	1-Chloromethyl-4-[^{18}F]fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(triflate)
[^{18}F]SFB	Succinimidyl 4-[^{18}F]fluorobenzoate
(−)-DTTA	(2*R*,3*R*)-di-*O*-*O*′-*p*-toluyl-D-tartaric acid
°C	Degrees Celsius
α	Alpha (particle)
β	Beta
β^+	Positron
γ	Gamma (ray)
δ	Chemical shift
μ	Micro
ν	Wavenumber
π	Pi (orbital)
σ	Sigma (orbital)
σ_p	Hammett para sigma constant
Å	Ångström
A	Ampere
Ac	Acetyl
AIBN	2,2′-Azobis(2-methylpropionitrile)
Anal.	Elemental analysis
aq.	Aqueous
Ar	Aryl
atm.	Atmosphere
B	Base
Bn	Benzyl
Boc	*tert*-Butyloxycarbonyl
Bpin	Pinacol boronate ester
Bq	Becquerel
br.	Broad

Bu	Butyl
Bz	Benzoyl
CA	Carbonic anhydrase
Ci	Curie
COD	1,5-Cyclooctadiene
COMT	Catecholamine *O*-methyltransferase
CT	Computed tomography
d	Deuteron
d	Doublet
d	Deuterated
d.c.	Decay-corrected
DAST	*N*,*N*-Diethylaminosulfur trifluoride
dba	Dibenzylideneacetone
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-Dichloroethane
DFT	Density functional theory
DIPEA	*N*,*N*-Di-*iso*-propylethylamine
DMA	*N*,*N*-Dimethylacetamide
DMAP	4-(Dimethylamino)pyridine
DMDO	3,3-Dimethyldioxirane
DMF	*N*,*N*-Dimethylformamide
DMI	1,3-Dimethyl-2-imidazolidinone
DMSO	Dimethylsulfoxide
dppf	1,1′-Bis(diphenylphosphino)ferrocene
dppp	1,3-Bis(diphenylphosphino)propane
dtbpy	4,4′-Di-*tert*-butyl-2,2′-bipyridyl
e.e.	Enantiomeric excess
EGFR	Epidermal growth factor receptor
EGFR-TK	Epidermal growth factor receptor tyrosine kinase
EP4	Prostaglandin E_2 receptor 4
EPR	Electron paramagnetic resonance
equiv.	Equivalent
ESI	Electrospray ionisation
Et	Ethyl
eV	Electron volt
EWG	Electron-withdrawing group
FDA	United States Food and Drug Administration
g	Gram(s)
G	Giga
GC	Gas chromatography
h	hour(s)
HATU	1-[Bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium-3-oxide hexafluorophosphate
(Het)Ar	(Hetero)aryl

HMBC	Heteronuclear multiple bond correlation
HPLC	High performance liquid chromatography
Hpz	Pyrazole
HRMS	High resolution mass spectrometry
Hz	Hertz
i	*Iso*
impy	imidazo[1,2,-*b*]pyridazine
IR	Infra red
J	Coupling constant
K_{222} or Kryptofix$_{222}$	4,7,13,16,21,24-Hexaoxa-1,10-diazabicyclo[8.8.8]hexacosane
k	Kilo
Koser's reagent	[Hydroxy(tosyloxy)iodo]benzene
L	Ligand
L	Litre
L-DOPA	3,4-Dihydroxy-L-phenylalanine
LG	Leaving group
m	milli
m	multiplet
m	*Meta*
M	Mega
M	Moles per cubic decimetre
M.P.	Melting point
M.S.	Molecular sieves
m/z	Mass-to-charge ratio
m-CPBA	3-Chloroperbenzoic acid
Me	Methyl
Me_3pyF	1-Fluoro-2,4,6-trimethylpyridinium
Meldrum's acid	2,2-Dimethyl-1,3-dioxane-4,6-dione
mGluR	Metabotropic glutamate receptor
MIDA	Methyliminodiacetic acid
min	Minute(s)
mol	Mole(s)
MRI	Magnetic resonance imaging
MS	Mass spectrometry
MTBD	1,5,7-Triazabicyclo[4.4.0]dec-5-ene
MW	Microwave
n	Nano
n	*Normal*
n	Number of data points
n.d.c	Non-decay-corrected
nAcR	Nicotinic acetylcholine receptor(s)

NBS	*N*-Bromosuccinimide
NMP	1-Methyl-2-pyrrolidinone
NMR	Nuclear magnetic resonance
o	*Ortho*
OAc	Acetate
OMs	Methansulfonate
OTf	Trifluoromethanesulfonate
OTs	4-Toluenesulfonate
p	Pico
p	*Para*
PBR	Peripheral benzodiazepine receptor
PET	Positron emission tomography
Ph	Phenyl
PIDA	(Diacetoxyiodo)benzene
PIFA	[Bis(trifluoroacetoxy)iodo]benzene
pin	Pinacol
Piv	Pivaloyl
pK_a	Acid dissociation constant
pK_{aH}	Dissociation constant of conjugate acid
ppb	Parts per billion
ppm	Parts per million
Prep	Preparative
Pr	Propyl
PTC	Phase transfer catalyst
py	Pyridine
q	Quartet
r.t.	Room temperature
RCC	Radiochemical conversion
RCP	Radiochemical purity
RCY	Radiochemical yield
R.D.S.	Rate-determining step
s	second(s)
s	singlet
S.A.	Specific activity
S_N2	Bimolecular nucleophilic substitution
S_NAr	Nucleophilic aromatic substitution
SOMIL	Siemens Oxford Molecular Imaging Laboratory
SPECT	Single photon emission computed tomography
SSRI	Selective serotonin reuptake inhibitor
t	triplet
t	*Tert*
TBAF	tetra-*n*-butylammonium fluoride
t-BuBrettPhos	2-(Di-*tert*-butyl phosphino)-2′,4′,6′-tri-*iso*-propyl-3,6-dimethoxy-1,1′-biphenyl

TEMPO	(2,2,6,6-Tetramethylpiperidin-1-yl)oxyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMEDA	*N*,*N*,*N*′,*N*′-Tetramethylethane-1,2-diamine
TMS	Trimethylsilyl
Tr	Triphenylmethyl
Trk	Tropomyosin receptor kinase
TSPO	Translocator protein
UHP	Urea-hydrogen peroxide complex
UV	Ultraviolet
W	Watt(s)
XPhosPdG2	Chloro(2-dicyclohexylphosphino-2′,4′,6′-tri-*iso*-propyl-1,1′-biphenyl)[2-(2′amino-1,1′-biphenyl)]palladium(II)

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Chapter 1

Introduction

Chapter 1: Introduction

1.1 Positron Emission Tomography

Structural imaging techniques, such as X-ray computed tomography (CT) and magnetic resonance imaging (MRI) play a crucial role in diagnostic medicine. Complementary to those methods are molecular imaging techniques, which allow the visualisation of in-vivo biological processes occurring in specific tissues via the use of imaging probes.[1] One such imaging technique is positron emission tomography (PET), which since the 1970s has become a vital tool in the diagnosis of cancers and neurological conditions.[1]–[3]

Positron emission tomography requires the injection of a biologically-active radioactive tracer molecule bearing a positron-emitting isotope. Within the body, this isotope undergoes nuclear decay, emitting a positron which travels only a short distance before interacting with an electron. The result of this interaction is annihilation, in which a pair of 511 keV γ-photons are produced. These photons travel at a 180° trajectory to each other and can be detected by scintillation detectors placed in a ring around the subject. The coincidence detection of two γ-photons allows the location of the annihilation event to be determined. Detection of many pairs of γ-photons allows the distribution of the tracer molecule to be determined computationally. This is particularly valuable when combined with anatomical images obtained via CT. Modern instruments are capable of recording both PET and CT images in the same session. The sensitivity of PET is very high; the amount of tracer injected is typically between 10 ng and 1 μg.[4] This is normally below the

amount required to have a pharmacological effect and causes minimal perturbation of the system under study. The amounts injected do not pose a significant risk to long-term health.[5]

Isotope	Main means of production	Half-life / min	Proportion of β^+ decay / %	Maximum β^+ energy / MeV	Decay product
^{11}C	$^{14}N(p,\alpha)^{11}C$	20.3	99	0.97	^{11}B
^{13}N	$^{16}O(p,\alpha)^{13}N$	10.0	100	1.20	^{13}C
^{15}O	$^{15}N(d,n)^{15}O$	2.04	100	1.74	^{15}N
^{18}F	$^{18}O(p,n)^{18}F$ $^{20}Ne(d,\alpha)^{18}F$	109.8	97	0.64	^{18}O
^{64}Cu	$^{64}Ni(p,n)^{64}Cu$	762	19	0.655	^{64}Ni
^{68}Ga	^{68}Ge generator	68.1	89	1.90	^{68}Zn

Table 1.1. Physical properties of positron-emitting isotopes. β^+ = Positron.

Positron emitting isotopes include carbon-11, nitrogen-13, oxygen-15, fluorine-18, copper-64 and gallium-68. These isotopes differ in their physical properties, including half-life, proportion of decay by positron emission and maximum positron energy (Table 1.1).[1], [6]–[8] Many factors are involved in the choice of positron-emitting isotope used for a PET scan. One crucial factor is the half-life; it is generally agreed that the time between synthesis of the isotope and injection into the subject should not exceed three half-lives. This means that rapid and efficient processes must be developed for incorporation of the isotope into the tracer, purification, formulation, and quality control. ^{13}N and ^{15}O have very short half-lives, making their introduction into tracer molecules very difficult; they are used in PET only rarely. The maximum positron energy is another important factor since this determines the average distance travelled by the emitted positron within the tissue before annihilation occurs with an electron. A lower positron energy is

desirable since this means that the site of annihilation is closer to the site of decay and thus the spatial resolution of the PET scan is better. Both the relatively low positron energy and relatively long half-life of fluorine-18 are advantageous characteristics compared to many other positron-emitting isotopes. Providing that incorporation of fluorine-18 into a tracer is efficient, the half-life is long enough to allow distribution of tracers from the site of production to more remote sites of use. In addition, the decay product is oxygen-18, from which no special issues arise.

Fluorine-18 and carbon-11 are the most widely-used isotopes for PET. Carbon is the basis of organic molecules, thus it is conceptually easy to design a tracer in which one carbon atom in the molecule of interest has been replaced by carbon-11; such a molecule would have the same chemical properties as an unlabelled molecule. Organofluorine compounds, on the other hand, are extremely rare in nature, so fluorine-18 is often used in place of a hydrogen atom or a hydroxyl group in a tracer molecule. For example, the tracer 6-[^{18}F]fluoro-L-DOPA ([^{18}F]FDOPA, **[^{18}F]1.1**), used for imaging of the presynaptic dopamine system, has a fluorine-18 substituent in place of a hydrogen atom in L-DOPA **1.2** (Figure 1.1).[9] 2-[^{18}F]Fluoro-2-deoxy-D-glucose ([^{18}F]FDG, **[^{18}F]1.3**), used in the detection and monitoring of cancers and currently the most important PET radiotracer, bears a fluorine-18 substituent in place of the hydroxy group in the 2-position of glucose **1.4**.[10] Crucially, whilst [^{18}F]FDG undergoes the same initial phosphorylation as glucose itself, the missing 2-hydroxy group prevents further progression through the Krebs cycle; [^{18}F]FDG-6-phosphate does not undergo further metabolism before it decays,

and so provides imaging of glucose metabolism, which is upregulated in cancerous cells.[6]

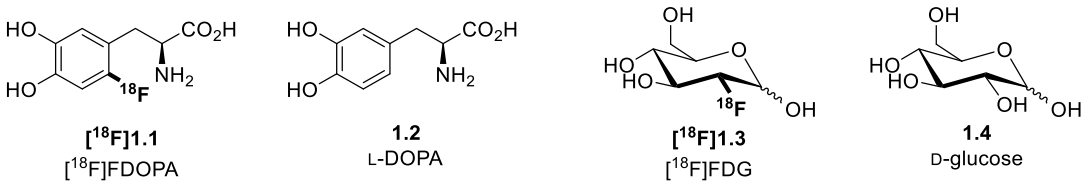


Figure 1.1. ^{18}F-Labelled derivatives of L-DOPA and D-glucose

Fluorine is the most electronegative of the elements; Pauling assigned it an electronegativity value of $\chi = 4.0$.[11] The atomic radius of fluorine (1.47 Å) is very small, intermediate between that of hydrogen (1.20 Å) and oxygen (1.52 Å).[12] These properties have resulted in extensive incorporation of fluorine substituents in medicinal chemistry to modulate lipophilicity and pK_a of drug molecules, as well as to control the metabolic properties.[13], [14] It has been estimated that 20% of small-molecule pharmaceuticals contain at least one fluorine atom; this figure rises to 36% for those approved between 2012 and 2015.[15], [16] The prevalence of fluorinated drug molecules allows the preparation of ^{18}F-labelled analogues in order to carry out PET studies. Direct labelling of a drug candidate can be used to determine the biodistribution, in order to ensure, for example, penetration of the blood/brain barrier or localisation in the tissue of interest.[5] Alternatively, a known radioligand for a receptor of interest can be injected and the displacement of this ligand by the drug candidate can be monitored. These experiments can facilitate the early stages of drug development and reduce the risk of an expensive late-stage failure of a candidate.

1.2 Production of Fluorine-18

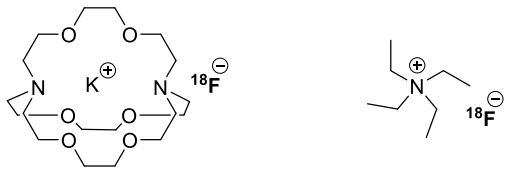
Fluorine-18 is an unnatural isotope, which is produced in a cyclotron. The process used determines whether the fluorine-18 is produced in the form of [^{18}F]fluoride, which is introduced into organic molecules via nucleophilic reactions, or [^{18}F]F_2, which is the primary source of electrophilic ^{18}F.

1.2.1 Production of [^{18}F]Fluoride

[^{18}F]Fluoride is produced by the ^{18}O(p,n)^{18}F nuclear reaction, in which an ^{18}O-enriched water target is bombarded with a beam of protons.[17] This affords a solution of [^{18}F]fluoride in [^{18}O]H_2O. The counterion is believed to depend on the metal from which the target chamber of the cyclotron is made.[18] The free energy of solvation of fluoride ion in aqueous solution has been calculated to be −104.3 kJ mol^{-1}.[19] This very high value results in cyclotron-produced aqueous [^{18}F]fluoride being highly solvated and poorly nucleophilic.[20] In order to use the [^{18}F]fluoride as a nucleophile, the [^{18}O]water must be removed and the [^{18}F]fluoride transformed into a more reactive form which is soluble in organic solvents.

There are two common ways in which a nucleophilic, organic-soluble source of [^{18}F]fluoride is formed. In both cases, the [^{18}F]fluoride is first trapped on an anion exchange cartridge, allowing the majority of the [^{18}O]H_2O to be removed. In the first case, the [^{18}F]fluoride is then eluted from the cartridge into a vial using a solution of a base such as an alkali metal carbonate (usually K_2CO_3) in an organic solvent such

as acetonitrile which contains 10-20% water. In this case, a crown ether or cryptand ligand such as Kryptofix$_{222}$ is also added in order to complex the potassium cation of [^{18}F]KF.[21], [22] The resulting [^{18}F]KF/K$_{222}$ complex **[^{18}F]1.5** (Figure 1.2) is more soluble than [^{18}F]KF in organic solvents, and the fluoride anion is more nucleophilic. The solvent is removed by heating under a stream of inert gas and anhydrous acetonitrile is added. The azeotropic drying process is repeated several times in order to remove a large proportion of the water. Finally, the [^{18}F]fluoride is dissolved in an anhydrous polar aprotic solvent, resulting in a solution of the [^{18}F]KF/K$_{222}$ complex and K$_2$CO$_3$ in the organic solvent.



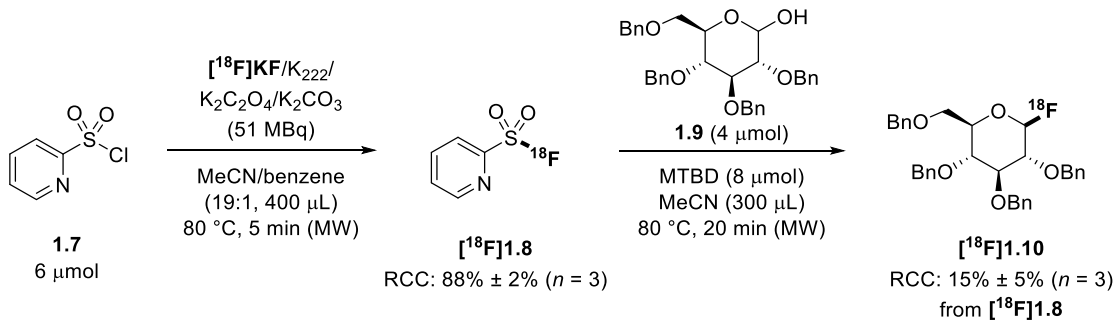
[^{18}F]1.5
[^{18}F]KF/K$_{222}$

[^{18}F]1.6
[^{18}F]Et$_4$NF

Figure 1.2. Common forms of nucleophilic [^{18}F]fluoride used in radiochemistry

It is not necessary to use an alkali metal as the counterion of the base. One alternative is the use of a tetraalkylammonium salt, most commonly tetraethylammonium bicarbonate.[23] In this case, the increased solubility of the [^{18}F]Et$_4$NF **[^{18}F]1.6** in organic solvents means that addition of a cryptand ligand is not required. Azeotropic drying and re-dissolving in an anhydrous polar aprotic solvent results in formation of a solution of [^{18}F]Et$_4$NF and Et$_4$NHCO$_3$ in the organic solvent. This may behave differently to [^{18}F]KF/K$_{222}$/K$_2$CO$_3$ in subsequent radiochemical reactions.

Whilst alkali metal [^{18}F]fluoride/cryptand complexes and tetraalkylammonium [^{18}F]fluorides are the most common sources of [^{18}F]fluoride for radiochemistry, some attempts have been made to investigate alternatives. For example, in 2014, Jiang and DeGrado reported the preparation of [^{18}F]acetyl fluoride and [^{18}F]propanoyl fluoride from [^{18}F]fluoride, and their subsequent use as latent sources of [^{18}F]fluoride by reaction with tetraethylammonium bicarbonate.[24] More recently, Doyle and co-workers described the synthesis of [^{18}F]2-pyridinesulfonyl fluoride ([^{18}F]PyFluor, **[^{18}F]1.8**) and its use in ^{18}F-deoxyfluorination of a protected sugar (Scheme 1.1).[25] [^{18}F]PyFluor was prepared from sulfonyl chloride **1.7** in 88% RCC via reaction with [^{18}F]KF/K_{222} complex. Deoxyfluorination of 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose **1.9** proceeded in 15% RCC from **[^{18}F]1.8** after microwave heating at 80 °C for 20 minutes. These reports provide a useful proof-of-concept that acyl and sulfonyl [^{18}F]fluorides can be used as sources of [^{18}F]fluoride, but they have not yet been widely used by the radiochemistry community.

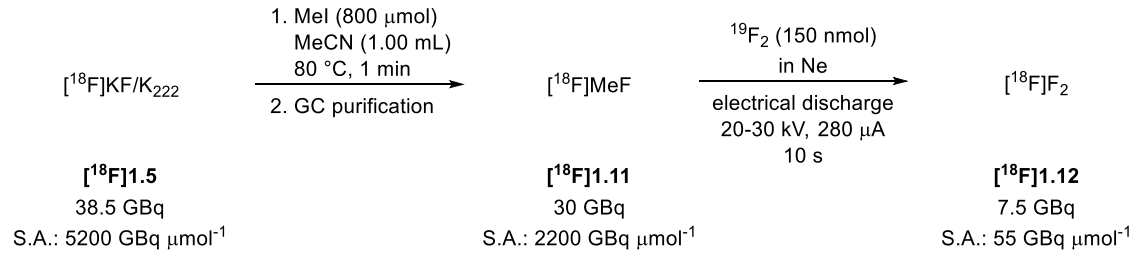


Scheme 1.1. Synthesis of [^{18}F]PyFluor and use in ^{18}F-deoxyfluorination.
MTBD = 7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene

1.2.2 Production of $[^{18}F]F_2$

If fluorine-18 must be introduced into the tracer molecule using electrophilic ^{18}F-fluorination, $[^{18}F]F_2$ must first be prepared. This was originally done via the $^{20}Ne(d,\alpha)^{18}F$ nuclear reaction; a nickel target containing 0.18% $^{19}F_2$ in ^{20}Ne was irradiated with a beam of deuterons.[26] The inclusion of a small amount of $^{19}F_2$ is necessary to recover the $[^{18}F]F_2$ from the target. An alternative approach is use of the $^{18}O(p,n)^{18}F$ nuclear reaction.[27] In this case, the nickel target chamber is first filled with $[^{18}O]O_2$ and bombarded with protons; this affords ^{18}F which adheres to the target walls. The $[^{18}O]O_2$ is then removed from the chamber and replaced with a 99:1 mixture of $Kr/^{19}F_2$ and the target is irradiated a second time. This causes an isotope exchange between the ^{18}F adsorbed to the target walls and the $^{19}F_2$, forming $[^{18}F]F_2$.

In 1997, Bergman and Solin disclosed a method for the preparation of $[^{18}F]F_2$ from [^{18}F]fluoride.[28] Initial formation of [^{18}F]fluoride via the $^{18}O(p,n)^{18}F$ nuclear reaction with an $[^{18}O]H_2O$ target was followed by purification and azeotropic drying as described in section 1.2.1, to form dry $[^{18}F]KF/K_{222}$ complex **[^{18}F]1.5**. Addition of a solution of iodomethane in acetonitrile resulted in the rapid formation of [^{18}F]fluoromethane **[^{18}F]1.11**, which was purified by gas chromatography (Scheme 1.2). The [^{18}F]fluoromethane was introduced into a discharge chamber containing neon with a very small amount of $^{19}F_2$ (ca. 150 nmol). An electrical discharge was then used to effect ^{18}F-^{19}F exchange. Starting from 37 GBq [^{18}F]fluoride, 7.5 GBq $[^{18}F]F_2$ was produced, with a specific activity up to 55 GBq μmol^{-1}.



Scheme 1.2. Synthesis of $[^{18}F]F_2$ from $[^{18}F]$fluoride

Developments in the preparation of $[^{18}F]F_2$ were driven not only by the preference for using proton-only cyclotrons, which are cheaper to construct and maintain than those also capable of accelerating other particles, but also by the desire to synthesise $[^{18}F]F_2$ in higher specific activity (S.A.). Specific activity is the amount of radioactivity of a species per unit mass.[1] However, the term "specific activity" is widely used by the radiochemistry community to refer to the molar activity, expressed in units of GBq μmol^{-1} or Ci μmol^{-1}; this convention will be followed in this thesis. Specific activity describes the ratio of labelled compound to unlabelled compound i.e. the ratio of ^{18}F:^{19}F in a sample. The specific activity of $[^{18}F]$fluoride, produced as described in section 1.2.1, as well as that of $[^{18}F]F_2$ produced by the three methods described in this section, is given in Table 1.2. In no case is the specific activity close to the theoretical maximum for ^{18}F, 63000 GBq μmol^{-1}, since some contamination with ^{19}F is unavoidable.[1]

Nuclear Reaction	Target	^{18}F-Labelled Product	Specific Activity / GBq μmol^{-1}
$^{18}O(p,n)^{18}F$	$[^{18}O]H_2O$	$[^{18}F]F^-$	5000
$^{20}Ne(d,\alpha)^{18}F$	$[^{20}Ne]Ne + F_2$	$[^{18}F]F_2$	0.10
$^{18}O(p,n)^{18}F$	$[^{18}O]O_2 + F_2$	$[^{18}F]F_2$	1.3
$^{18}O(p,n)^{18}F$	$[^{18}O]H_2O$	$[^{18}F]F_2$ from $[^{18}F]F^-$	55

Table 1.2. Specific activities of $[^{18}F]F^-$ and $[^{18}F]F_2$ by production method

Since a given activity of a tracer is required for a human PET scan (typically 300-400 MBq), the specific activity of a tracer determines the total mass that must be injected. The importance of this is dependent on both the tracer and the receptors/processes being studied. Imaging of low-density neuroreceptors requires the tracer to be prepared in high specific activity, otherwise the binding sites may be saturated with unlabelled compound. This reduces the image contrast and potentially causes undesired pharmacological effects.[1] The term "high specific activity" is generally applied to values above 50 GBq μmol^{-1}.

Whilst [^{18}F]F_2 has itself been used for ^{18}F-fluorination, its high reactivity has led to efforts to prepare more selective electrophilic ^{18}F-fluorination reagents. These include [^{18}F]xenon difluoride **[^{18}F]1.13**, [^{18}F]perchloryl fluoride **[^{18}F]1.14**, O–F reagents such as [^{18}F]acetyl hypofluorite **[^{18}F]1.15** and [^{18}F]trifluoromethyl hypofluorite **[^{18}F]1.16** and N–F reagents such as *N*-[^{18}F]fluoropyridinium triflate **[^{18}F]1.17**, *N*-[^{18}F]fluoro-2-pyridone **[^{18}F]1.18**, [^{18}F]NFSI **[^{18}F]1.19** and [^{18}F]Selectfluor **[^{18}F]1.20** (Figure 1.3).[4]

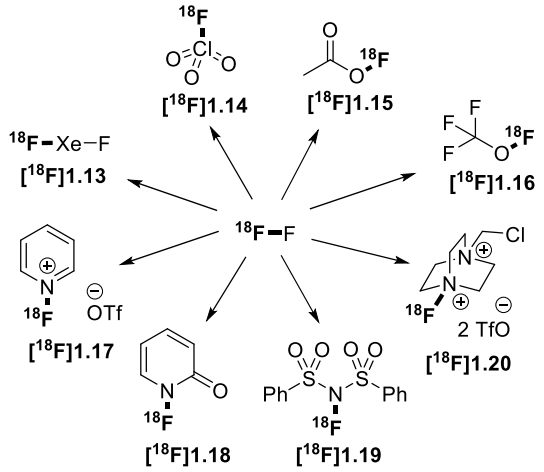


Figure 1.3. Electrophilic ^{18}F-fluorination reagents prepared from [^{18}F]F_2

1.3 Key Considerations for ^{18}F-Radiochemistry

There are several important differences between synthetic chemistry with fluorine-19 and ^{18}F-radiochemistry. Some of these are apparent based on the preceding discussion; for example, the half-life of fluorine-18 means that reactions and purification processes must be rapid and efficient. The nature of positron emission followed by annihilation demands that fluorine-18 be treated as a gamma emitter. In order to provide adequate protection for the radiochemist, syntheses using large amounts of activity must be carried out in "hot cells" with lead walls several centimetres thick. This makes manual manipulations challenging to impossible; routine productions of radiopharmaceuticals are conducted using automated synthesiser modules. Early-stage development of new methods for ^{18}F-fluorination may be conducted with much lower activities, enabling the use of lead-lined glove boxes. These allow physical manipulation, providing that this is carefully planned in order to minimise exposure of the researcher to radiation. However, since the ultimate aim of a new method is to be used in a clinical setting, it must be simple, reproducible and amenable to automation.

In addition to the need for rapid syntheses and the paucity of ^{18}F-fluorination reagents available in high specific activity, one of the key differences between ^{18}F-radiochemistry and synthetic chemistry with fluorine-19 is the relative stoichiometry between the substrate and fluorinating reagent. In standard synthetic chemistry, approximately equimolar amounts of substrates and reagents are generally employed. This is far from the case in ^{18}F-radiochemistry, in which the

concentration of the substrate is generally several orders of magnitude greater than that of the ^{18}F-fluorinating reagent. For example, a reaction starting with 50 GBq [^{18}F]fluoride in 1 mL solvent has an [^{18}F]fluoride concentration of approximately 800 nM. The concentration of substrate is generally 5-100 mM, corresponding to a 10^4 to 10^5-fold difference in concentration. During reaction development, concentrations of reagents are kept the same but in order to minimise risk to the researchers, screening reactions are routinely carried out with less than 50 MBq [^{18}F]fluoride, corresponding to a 10^7 to 10^8-fold difference in concentration. This concentration difference may be beneficial or detrimental to the desired reaction.

Since the ^{18}F-fluorinating reagent is limiting, yields of radiochemical reactions are reported with respect to fluorine-18. Unfortunately, there is inconsistency in the ^{18}F-radiochemistry literature regarding the reporting of yields. In this thesis, the term radiochemical yield (RCY) will be used to refer to the activity of an isolated radiolabelled product, as a percentage of the starting activity of ^{18}F-fluorinating reagent. This may or may not be corrected for physical decay of the isotope during the synthesis and purification. The term radiochemical conversion (RCC) will be used to refer to the activity of a radiolabelled product as a percentage of the total activity at the end of a reaction. This is commonly determined by radio-TLC or radio-HPLC and is, by definition, corrected for decay. Some reported yields do not clearly fit into either of these categories; herein, if the activity of an isolated product is not measured, the term radiochemical conversion will be used.

1.4 ^{18}F-Fluorination of Arenes and Heteroarenes

The position within a tracer molecule at which fluorine-18 is introduced should be carefully considered. If the tracer molecule is an ^{18}F-analogue of a fluorine-containing drug candidate, the best choice is generally direct replacement of fluorine-19 with fluorine-18. In this case, the tracer molecule should have the same chemical properties as the drug candidate itself. Amongst the 40 fluorine-containing drugs introduced to the market between 2001 and 2011, 48% contained an aryl fluoride.[29] If heteroaryl fluorides are included, the figure rises to 65%. Trifluoromethyl (hetero)arenes are represented in 23% of these drugs, with the remainder being made up of less common fluorinated groups such as alkyl fluorides, geminal difluorides, pentafluoroethyl groups, trifluoroethoxy groups, and difluoromethoxy groups. Thus, if one wishes to be able to prepare ^{18}F-analogues of fluorine-containing drugs, the primary concern ought to be ensuring that there are robust methods for the ^{18}F-labelling of aryl fluorides.

When designing a PET radioligand for the imaging of specific receptors, there is more flexibility in the position of the ^{18}F-fluorinated group. Nonetheless, ideally, this position should be that which confers the optimal tracer properties upon the molecule. One particularly important consideration is metabolic stability. Since the signal obtained in a PET scan results from decay of the radioisotope, this only correlates with the location of the tracer molecule providing that the radioisotope remains part of the tracer molecule for the duration of the scan. A metabolically-labile ^{18}F-fluorinated group is undesirable, since the signal will then result from both

the original tracer molecule and the labelled metabolite(s). This can make interpretation of the data very challenging. In terms of metabolic stability, aryl fluorides are generally more stable than alkyl fluorides, which can be vulnerable to defluorination via α-oxidation followed by elimination of HF to form an aldehyde or ketone.[30] Therefore, for metabolic reasons, it is more favourable to introduce fluorine-18 as an aryl fluoride rather than an alkyl fluoride when possible.

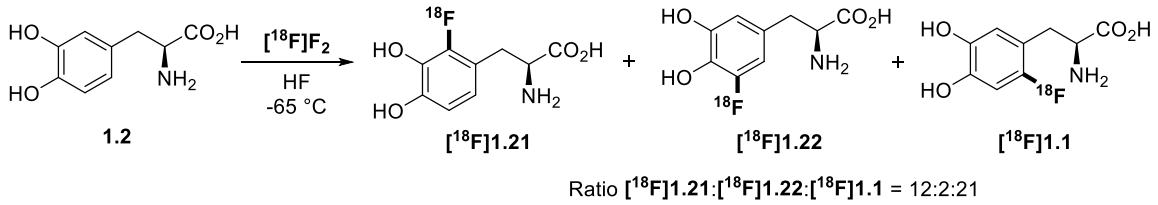
Literature in the field of ^{18}F-fluorination of arenes and heteroarenes has been reviewed recently.[4], [31] In the remainder of this chapter, the most important methods for the ^{18}F-fluorination of arenes and heteroarenes disclosed prior to the start of the research described in this thesis will be discussed. Methods disclosed after the work in this thesis began are discussed in Chapter 2, section 2.6.

1.4.1 Electrophilic Methods

1.4.1.1 Direct C–H ^{18}F-Fluorination

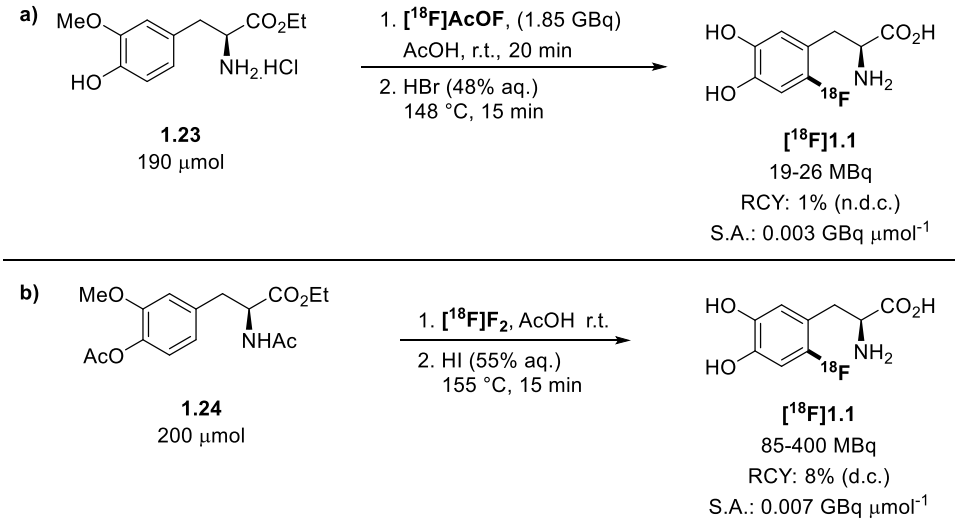
[^{18}F]Fluoroarenes can be synthesised via the direct reaction of arenes with cyclotron-produced [^{18}F]F_2. However, as with the analogous reactions with unlabelled F_2, selectivity is often very poor due to the high reactivity of F_2.[32] Direct C–H ^{18}F-fluorination with [^{18}F]F_2 was applied to the preparation of 6-[^{18}F]fluoro-L-DOPA ([^{18}F]FDOPA) in 1984 by Firnau et al. (Scheme 1.3).[33] [^{18}F]F_2 was first produced via the ^{20}Ne(d,α)^{18}F nuclear reaction and diluted to 0.5% in neon. This gas mixture was then bubbled through a solution of L-DOPA **1.2** in anhydrous liquid

HF at −65 °C. The 2-, 5- and 6- isomers of [^{18}F]fluoro-L-DOPA were formed in a 12:2:21 ratio; the desired 6-isomer could be isolated in an uncorrected radiochemical yield of 3% after four cycles of reverse-phase HPLC purification. The specific activity was very low, only 0.004 GBq μmol^{-1}. The authors subsequently demonstrated that addition of BF_3 to the ^{18}F-fluorination reaction mixture increased the radiochemical yield to 9%.[34]



Scheme 1.3. Synthesis of [^{18}F]FDOPA via direct C–H ^{18}F-fluorination with [^{18}F]F_2

Direct C–H ^{18}F-fluorination of arenes can also be carried out via initial formation of the slightly less reactive electrophilic ^{18}F-fluorinating reagent [^{18}F]acetyl hypofluorite ([^{18}F]AcOF).[35] This can be prepared by bubbling [^{18}F]F_2 through a solution of ammonium acetate in acetic acid. Firnau and co-workers used [^{18}F]AcOF prepared in this way in a reaction with the partially protected L-DOPA derivative **1.23** in acetic acid (Scheme 1.4a). After ^{18}F-fluorination was complete, deprotection was carried out using aqueous HBr. Again a mixture of the 2-, 5- and 6-[^{18}F]fluoro-L-DOPA isomers was formed, in a 4:3:13 ratio. Starting from 1.85 GBq [^{18}F]AcOF, 19-26 MBq **[^{18}F]1.1** was produced after purification, corresponding to an uncorrected radiochemical yield of 1%. The specific activity was 0.003 GBq μmol^{-1}. Adam et al. reported that starting from fully protected precursor **1.24** allowed isolation of **[^{18}F]X1.1** in higher RCY (8%, decay-corrected, Scheme 1.4b).



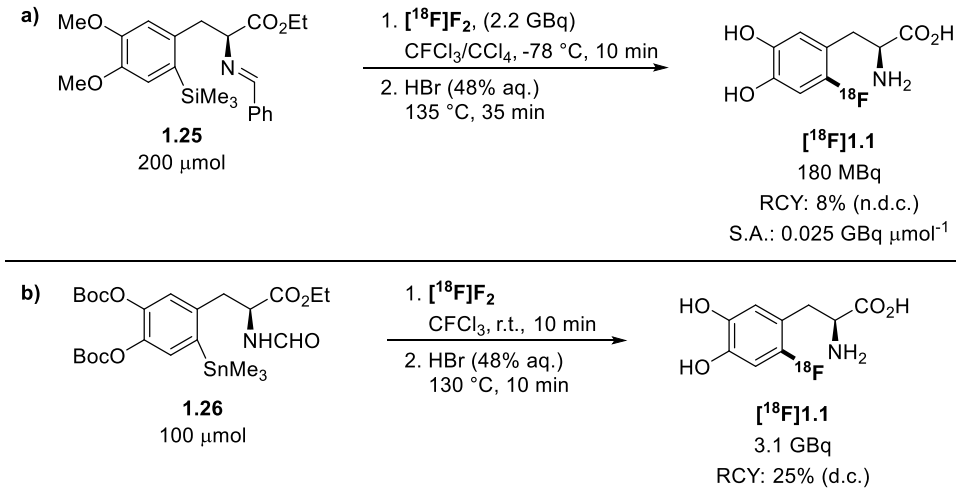
Scheme 1.4. Synthesis of [^{18}F]FDOPA direct C–H ^{18}F-fluorination with [^{18}F]AcOF. a) From partially protected precursor **1.23**. b) From fully protected precursor **1.24**.

1.4.1.2 Electrophilic ^{18}F-Fluorodemetallation

^{18}F-Fluorodemetallation, the replacement of a metal substituent on an arene with an ^{18}F-fluorine atom, offers a more regioselective approach to ^{18}F-fluorination than direct C–H ^{18}F-fluorination. During the 1980s, it was demonstrated that reaction of [^{18}F]F_2 with arylstannanes, arylsilanes, arylpentafluorosilicates and arylgermanes resulted in cleavage of the carbon-metal bond, with formation of a carbon-fluorine-18 bond at the ipso position.[36]–[41] Coenen and Moerlein compared the reactivity of arylstannanes, silanes and germanes and found that for a given aryl group, the radiochemical yield decreased in the order $ArSnMe_3$ > $ArGeMe_3$ > $ArSiMe_3$.[41] Electron-rich, electron-neutral and electron-deficient aryltrimethylmetal compounds underwent ^{18}F-fluorodemetallation, with electron rich substrates forming the corresponding [^{18}F]fluoroarenes in the highest radiochemical yields. However, reactions with electron-rich aryltrimethylmetal

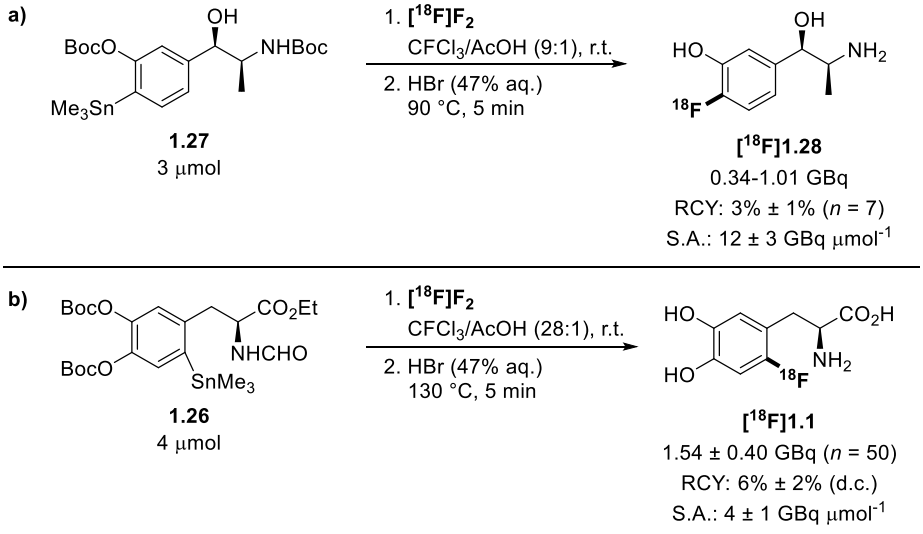
compounds were also less selective, giving rise to by-products arising from C–H ^{18}F-fluorination of the aromatic ring (in the case of a 4-anisyl substrate) or from C–H ^{18}F-fluorination of the methyl group (in the case of a 4-tolyl substrate).

^{18}F-Fluorodesilylation and ^{18}F-fluorodestannylation with [^{18}F]F_2 have been used in the preparation of [^{18}F]FDOPA. In 1985, Diksic and Farrokhzad described the synthesis of [^{18}F]FDOPA **[^{18}F]1.1** from silane **1.25**, in a two-step sequence consisting of ^{18}F-fluorodesilylation followed by deprotection under acidic conditions (Scheme 1.5a).[42] The uncorrected radiochemical yield was 8% and the specific activity was measured to be 0.025 GBq μmol^{-1}. In 1992, Satyamurthy and co-workers disclosed a synthesis of [^{18}F]FDOPA via ^{18}F-fluorodestannylation of arylstannane **1.26** with [^{18}F]F_2, followed by acidic hydrolysis (Scheme 1.5b).[43] Using this method, more than 3 GBq [^{18}F]FDOPA was produced. De Vries and co-workers later automated this synthesis, achieving decay-corrected radiochemical yields of 33% ± 4% and specific activities of 0.01 GBq μmol^{-1}.[44]



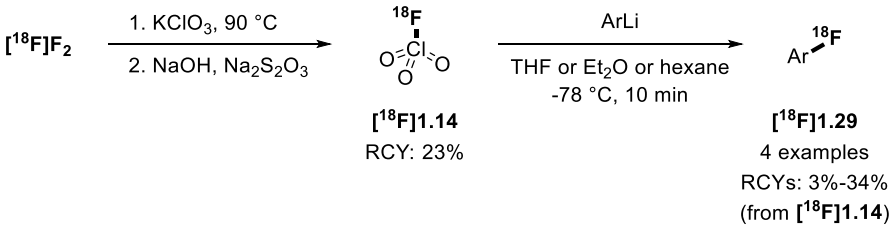
Scheme 1.5. Synthesis of [^{18}F]FDOPA via ^{18}F-fluorodemetallation with [^{18}F]F_2. **a)** From arylsilane precursor **1.25**. **b)** From arylstannane precursor **1.26**.

Following their development of post-target-produced [^{18}F]F_2, with specific activities up to 55 GBq μmol^{-1} (section 1.2.2), the Solin group applied this to the preparation of PET radiotracers in medium specific activity via ^{18}F-fluorodestannylation. Reaction of arylstannane **1.27** with [^{18}F]F_2, followed by hydrolysis with aqueous HBr, afforded 0.34 to 1.01 GBq (1*R*,2*S*)-4-[^{18}F]fluorometaraminol **[^{18}F]1.28**, corresponding to 3% RCY after purification and reformulation (Scheme 1.6a).[45] More importantly, the specific activity was 12 GBq μmol^{-1}, more than two orders of magnitude higher than previous syntheses of related molecules.[46] The method was also applied to the synthesis of [^{18}F]FDOPA.[47] In this case, ^{18}F-fluorodestannylation of **1.26**, followed by acidic hydrolysis, afforded 1.54 GBq [^{18}F]FDOPA **[^{18}F]1.1** in 6% RCY (d.c., from [^{18}F]fluoride). The specific activity was 3.7 GBq μmol^{-1}, two and a half orders of magnitude greater than that achieved using the method of de Vries.[44]



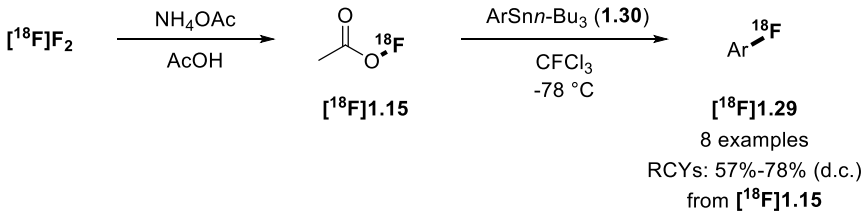
Scheme 1.6. Synthesis of PET radiotracers via ^{18}F-fluorodestannylation with post-target-produced [^{18}F]F_2. **a)** (1*R*,2*S*)-4-[^{18}F]Fluorometaraminol. **b)** [^{18}F]FDOPA.

Other electrophilic ^{18}F-fluorinating reagents have also been used for ^{18}F-fluorodemetallation reactions. [^{18}F]Perchloryl fluoride **[^{18}F]1.14** was prepared in 23% radiochemical yield by Ehrenkaufer and MacGregor via reaction of [^{18}F]F_2 with $KClO_3$ (Scheme 1.7).[48] **[^{18}F]1.14** reacted with electron-rich aryllithium reagents at -78 °C to afford the corresponding [^{18}F]fluoroarenes **[^{18}F]1.29** in 21%-34% RCY. However, an electron-deficient aryllithium reacted in only 3% RCY. The authors commented that reaction of [^{18}F]F_2 with aryllithiums under the same conditions resulted in very low radiochemical yields and complex mixtures of products.



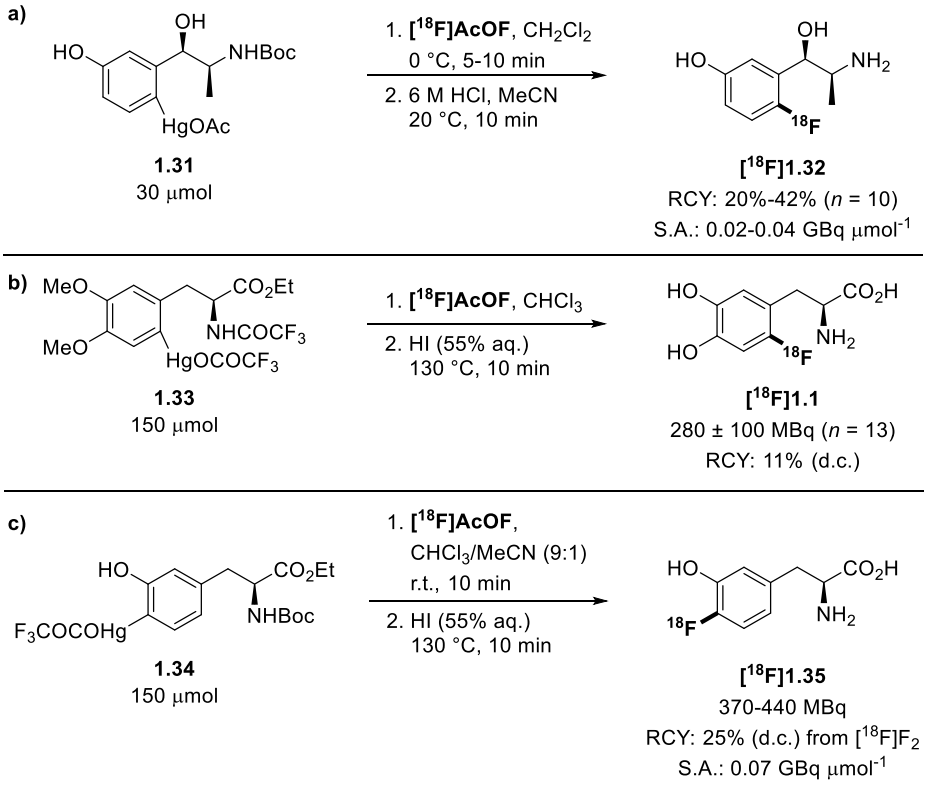
Scheme 1.7. Synthesis of [^{18}F]$FClO_3$ and use in ^{18}F-fluorodemetallation of aryllithium reagents

In 1984, Adam and co-workers described the use of [^{18}F]AcOF in the ^{18}F-fluorodestannylation of aryltributylstannanes.[38] [^{18}F]AcOF **[^{18}F]1.5** was first prepared by reaction of [^{18}F]F_2 with NH_4OAc in AcOH (Scheme 1.8). The **[^{18}F]1.15** was then transferred into a solution of the arylstannane in $CFCl_3$ at -78 °C. Simple electron-rich and electron-neutral arylstannanes **1.30** underwent ^{18}F-fluorodestannylation to afford [^{18}F]fluoroarenes **[^{18}F]1.29** in decay-corrected radiochemical yields of 57%-78%.



Scheme 1.8. Synthesis of [^{18}F]AcOF and use in ^{18}F-fluorodestannylation of arylstannanes

The same year, Visser and co-workers disclosed the ^{18}F-fluorodemercuration of electron-rich and electron-neutral arylmercuric chlorides and acetates using [^{18}F]AcOF.[49] Reactions were carried out in acetic acid at room temperature and were complete within 5 minutes, affording [^{18}F]fluoroarenes in 47%-65% decay-corrected radiochemical yields (based on [^{18}F]AcOF). This method was subsequently applied to the production of radiotracers bearing electron-rich [^{18}F]fluoroarenes. In 1988, Wieland and co-workers described the synthesis of (1*R*,2*S*)-6-[^{18}F]fluorometaraminol **[^{18}F]1.32** via ^{18}F-fluorodemercuration of arylmercuric acetate **1.31**, followed by acidic hydrolysis (Scheme 1.9a).[46] Radiochemical yields from [^{18}F]AcOF ranged from 20%-40%, and specific activity ranged from 0.02-0.04 GBq μmol^{-1}. **[^{18}F]1.32** was shown to have potential for the assessment of neuronal damage in heart diseases, but the authors were concerned that the low specific activity required the injection of quantities which could cause an increase in the blood pressure of the subjects.

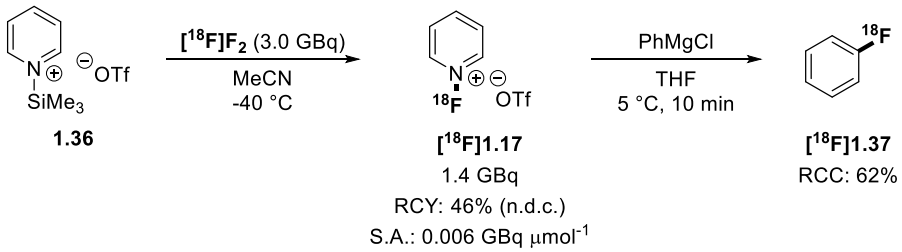


Scheme 1.9. Synthesis of PET radiotracers via ^{18}F-fluorodemercuration.
a) (1*R*,2*S*)-6-[^{18}F]Fluorometaraminol. **b)** [^{18}F]FDOPA **c)** 4-[^{18}F]fluoro-L-*m*-tyrosine

In 1990, two further examples were published of the application of ^{18}F-fluorodemercuration with [^{18}F]AcOF to the synthesis of PET radiotracers. Luxen and co-workers applied the method to the production of [^{18}F]FDOPA **[^{18}F]1.1** (Scheme 1.9b).[50] The decay-corrected radiochemical yield was 11% and residual mercury levels were measured to be below 20 ppb. The authors reported that using [^{18}F]F_2 directly, rather than [^{18}F]AcOF, resulted in a complex mixture of radiolabelled products. Barrio and co-workers prepared an analogue of [^{18}F]FDOPA, 4-[^{18}F]fluoro-L-*m*-tyrosine **[^{18}F]1.35**, achieving 25% RCY (d.c., from [^{18}F]F_2) and specific activity of 0.07 GBq μmol^{-1} (Scheme 1.9c).

Electrophilic fluorination reagents based on an N–F bond tend to be less reactive and less hazardous than those bearing an O–F bond. The first N–F

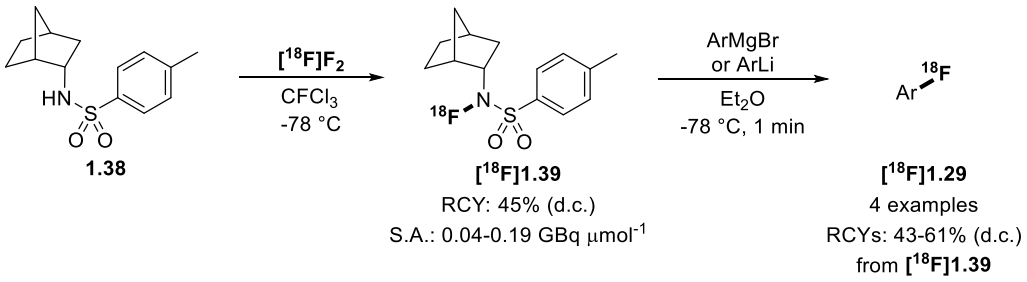
^{18}F-fluorination reagents, *N*-[^{18}F]fluoropyridinium triflate and *N*-[^{18}F]fluoro-2-pyridone, were prepared in 1988 by Oberdorfer and co-workers. *N*-[^{18}F]Fluoropyridinium triflate **[^{18}F]1.17** was prepared via reaction of [^{18}F]F_2, produced via the ^{20}Ne(d,α)^{18}F reaction, with *N*-trimethylsilylpyridinium triflate **1.36** (Scheme 1.10). The radiochemical yield was 46%, and the specific activity of **[^{18}F]1.17** was 0.006 GBq μmol^{-1}. **[^{18}F]1.17** reacted with phenylmagnesium chloride to afford [^{18}F]fluorobenzene in 62% RCC. The same group also reported the synthesis of *N*-[^{18}F]fluoro-2-pyridone in radiochemical yields up to 48% and specific activity of 0.004 GBq μmol^{-1} via reaction of 2-trimethylsilyloxypyridine with [^{18}F]F_2. No examples were given of aromatic ^{18}F-fluorination with this reagent.



Scheme 1.10. Synthesis of *N*-[^{18}F]fluoropyridinium triflate and subsequent use in synthesis of [^{18}F]fluorobenzene

In 1990, Satyamurthy and co-workers disclosed their studies on the preparation of *N*-[^{18}F]fluoro-*N*-alkylsulfonamides from [^{18}F]F_2 and their subsequent use as ^{18}F-fluorination reagents. [^{18}F]F_2 was bubbled through a solution of the sulfonamide precursor in $CFCl_3$ at -78 °C to afford the corresponding *N*-[^{18}F]fluoro-*N*-alkylsulfonamide in 13%-45% RCY (d.c.) and with a specific activity of 0.04-0.19 GBq μmol^{-1}. The best reagent, **[^{18}F]1.39**, was formed in 45% RCY (d.c.) from [^{18}F]F_2

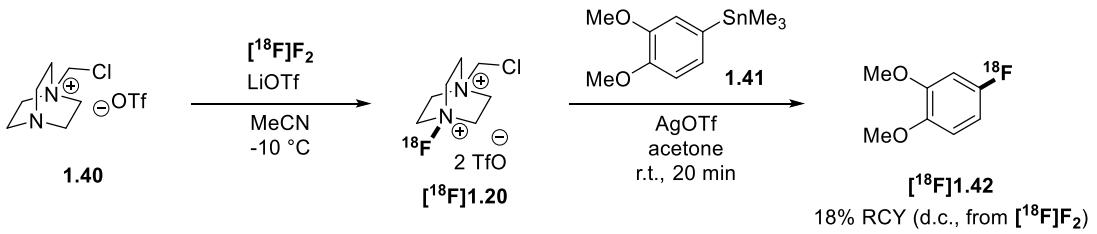
and reacted with simple aryl Grignard or aryllithium reagents to afford the corresponding [^{18}F]fluoroarenes **[^{18}F]1.29** in 43%-61% RCY (d.c., Scheme 1.11).



Scheme 1.11. Synthesis of *N*-[^{18}F]fluorosulfonamide reagent **[^{18}F]1.39** and subsequent use in synthesis of [^{18}F]fluoroarenes

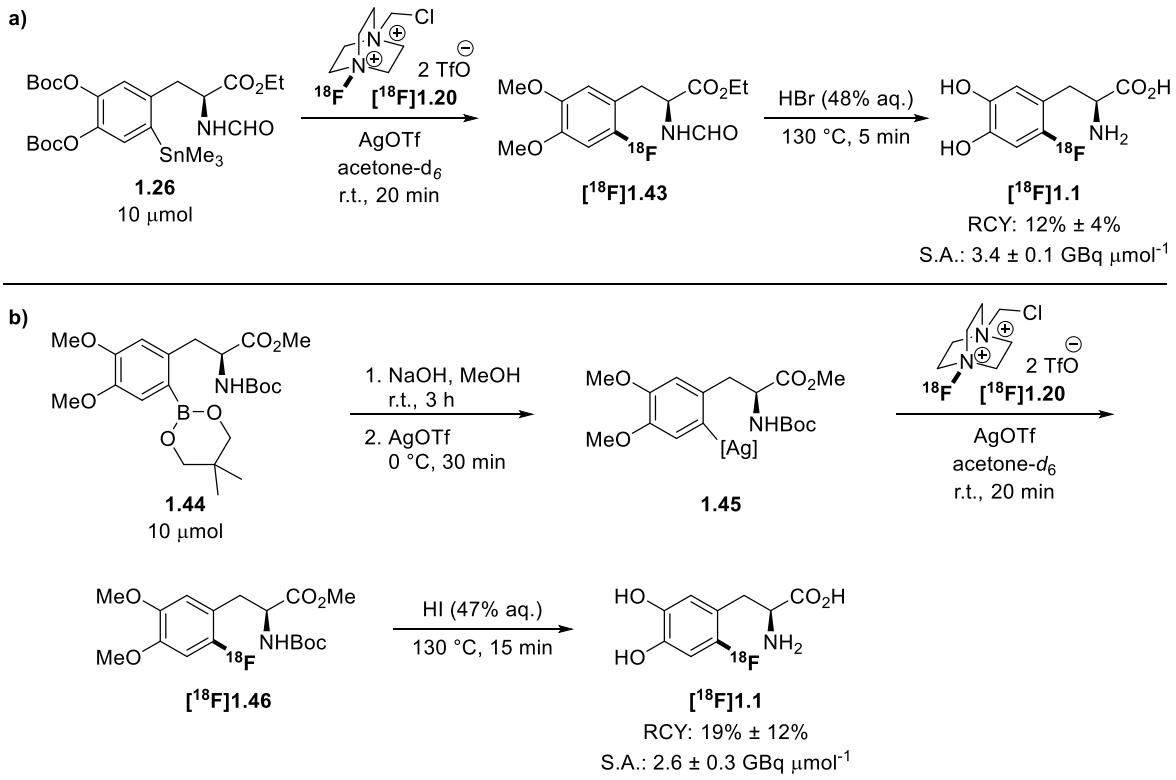
In an attempt to broaden the scope of reagents available for electrophilic ^{18}F-fluorination, in 2007, the Gouverneur group collaborated with GE Healthcare to prepare [^{18}F]NFSI from [^{18}F]F_2.[51] The [^{18}F]NFSI was not used for ^{18}F-fluorination of arenes, but was successfully used to ^{18}F-fluorinate silyl enol ethers and allylsilanes. The same authors later collaborated with the Solin group to synthesise the more reactive N–F reagent [^{18}F]Selectfluor from post-target-produced [^{18}F]F_2.[52] [^{18}F]F_2, produced by the method of Bergman and Solin (ca. 55 GBq μmol^{-1}), was bubbled through a solution of 1-chloromethyl-4-aza-1-azoniabicyclo[2.2.2]octane triflate **1.40** and lithium triflate in acetonitrile at -10 °C (Scheme 1.12). [^{18}F]Selectfluor bis(triflate) **[^{18}F]1.20** was formed instantly. This was used in the silver-mediated ^{18}F-fluorodestannylation of electron-rich arylstannanes including veratrole **1.41**, forming fluoroveratrole **[^{18}F]1.42** in 18% RCY (decay-corrected).[53] Specific activity was not measured for [^{18}F]fluoroarene products, but that of an α-[^{18}F]fluorotetralone

formed by ^{18}F-fluorination of the corresponding silyl enol ether was measured to be 16 GBq μmol^{-1}.



Scheme 1.12. Synthesis of [^{18}F]Selectfluor bis(triflate) **[^{18}F]1.20** from post-target-produced [^{18}F]F_2 and subsequent use in silver-mediated ^{18}F-fluorodestannylation.

The success of this method for the ^{18}F-fluorination of electron-rich arenes inspired the authors to investigate its use for the preparation of [^{18}F]FDOPA **[^{18}F]1.1** in higher specific activity than was offered by the ^{18}F-fluorodestannylation process used clinically. **[^{18}F]1.1** could be synthesised from arylstannane **1.26** in a decay-corrected radiochemical yield of 12%, with a specific activity of 3.4 GBq μmol^{-1} (Scheme 1.13a).[54] Alternatively, the silver-mediated fluorination of arylboronic esters developed by Ritter and co-workers could be adapted for ^{18}F-fluorination; starting from aryl neopentyl glycol boronate ester **1.44**, **[^{18}F]1.1** was prepared in 19% radiochemical yield, with a specific activity of 2.6 GBq μmol^{-1} (Scheme 1.13b).



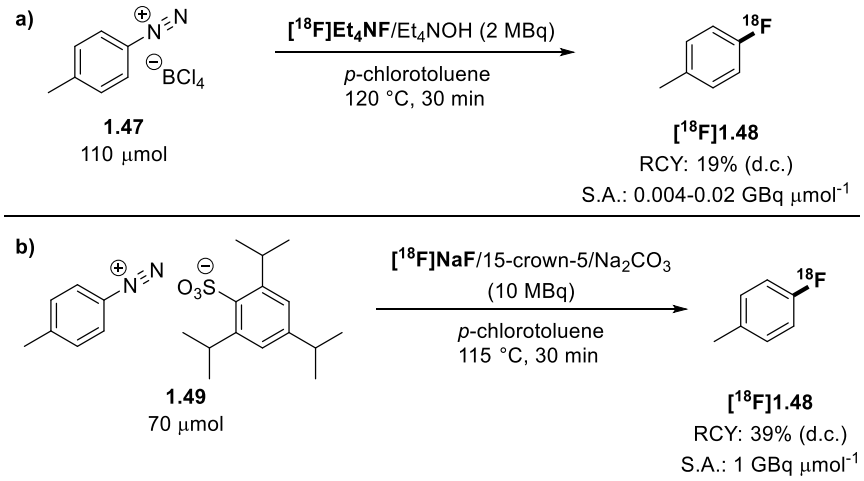
Scheme 1.13. Use of [^{18}F]Selectfluor bis(triflate) **[^{18}F]1.20** in the synthesis of [^{18}F]FDOPA **[^{18}F]1.1**. a) From arylstannane precursor **1.26**. b) From arylboronic ester precursor **1.44**.

1.4.2 Nucleophilic Methods

1.4.2.1 Balz-Schiemann and Wallach Reactions

Some of the earliest reactions used to introduce fluorine-18 substituents onto aromatic rings were Balz-Schiemann reactions. In 1967, Nozaki and Tanaka demonstrated that [^{18}F]fluoroarenes could be prepared by ^{18}F-fluorodediazonation of aryldiazonium [^{18}F]tetrafluoroborates.[55] These formed via exchange of [^{18}F]fluoride with the tetrafluoroborate anion, meaning that 75% of the activity was lost as [^{18}F]BF_3, and that the specific activity of the [^{18}F]fluoroarene products was very low. Knöchel and Zwernemann described improvements to this methodology, firstly by replacing the tetrafluoroborate anion with tetrachloroborate.[56] This

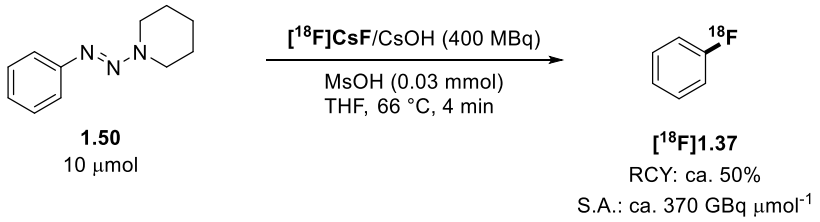
enabled synthesis of 4-[^{18}F]fluorotoluene **[^{18}F]1.48** in 19% RCY (d.c., Scheme 1.14a). The specific activity was only 0.004 to 0.02 GBq μmol^{-1}; the authors claimed that this was due to the very small amounts of activity employed (ca. 2 MBq). A large amount of activity was lost as gaseous [^{18}F]$BFCl_2$. In order to circumvent this problem, the same authors investigated alternative anions which would not incorporate [^{18}F]fluoride.[57] The best of these was 2,4,6-tri-*iso*-propylbenzenesulfonate (Scheme 1.14b), which allowed synthesis of 4-[^{18}F]fluorotoluene **[^{18}F]1.48** in 39% RCY (d.c.), with a specific activity of ca. 1 GBq μmol^{-1}.



Scheme 1.14. Synthesis of 4-[^{18}F]fluorotoluene by Balz-Schiemann reactions. **a)** BCl_4 anion. **b)** 2,4,6-tri-*iso*-propylbenzenesulfonate anion

Decomposition of diazonium tetrafluoroborate salts in the presence of [^{18}F]fluoride was used to synthesise ^{18}F-fluorinated derivatives of the amino acids phenylalanine,[58]–[61] tryptophan[62] and 3,4-dihydroxyphenylalanine (DOPA).[63], [64] Radiochemical yields were generally low and specific activities were very low.

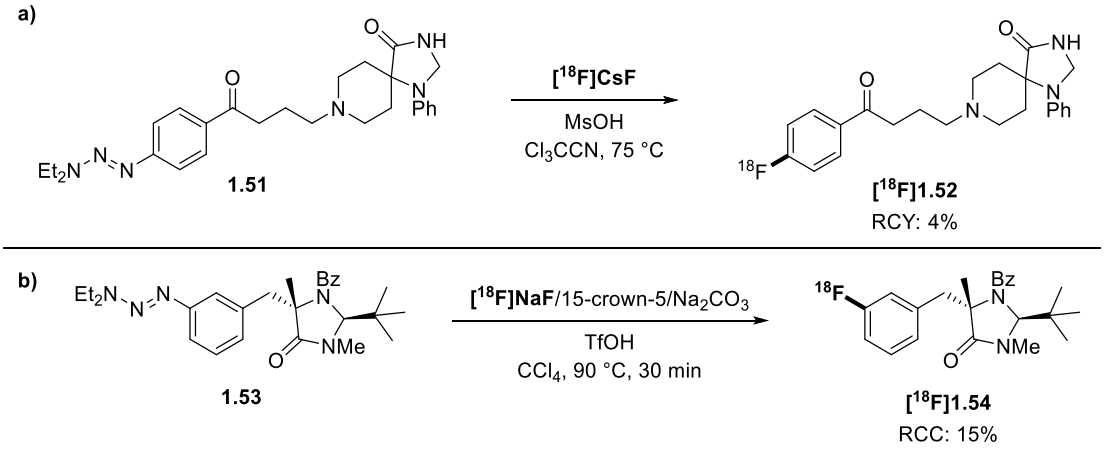
A related process is the Wallach reaction, the acid-mediated decomposition of a 3,3-dialkyl-1-aryl triazene to afford a diazonium species which subsequently undergoes fluorodediazonation.[65], [66] Triazenes are more stable than diazonium salts and are more readily purified. Tewson and Welch exemplified the application of the Wallach reaction to ^{18}F-radiochemistry via the synthesis of [^{18}F]fluorobenzene **[^{18}F]1.37** from piperidyl triazene **1.50** (Scheme 1.15).[67] The specific activity was considerably higher than related Balz-Schiemann processes.



Scheme 1.15. Wallach reaction of triazene **1.50** to afford [^{18}F]fluorobenzene **[^{18}F]1.37**

Welch and co-workers used the Wallach reaction to prepare the butyrophenone neuroleptic [^{18}F]haloperidol in high specific activity for a PET study in monkeys, but experimental details were not given.[68] The related compound [^{18}F]spiperone **[^{18}F]1.52** was synthesised in the same manner by Barrio and co-workers (Scheme 1.16a).[69] Use of trichloroacetonitrile as solvent was necessary in order to minimise protodediazonation; even under these conditions, **[^{18}F]1.52** could only be prepared in 4% RCY. A protected 3-[^{18}F]fluoro-α-methyl-L-phenylalanine **[^{18}F]1.54** was synthesised from triazene **1.53** in 15% RCC by Langlois and co-workers (Scheme 1.16b).[70] Whilst Riss et al. attempted to use solid-phase-supported (1-aryldiazenyl)piperazines for the synthesis of [^{18}F]fluoroarenes, the maximum RCC

obtained was 14% for a simple substrate.[71] Although some radiotracers were prepared using the Balz-Schiemann and Wallach reactions, these methods tended to afford [^{18}F]fluoroarenes in low radiochemical yields and have largely been superseded by more efficient methods.



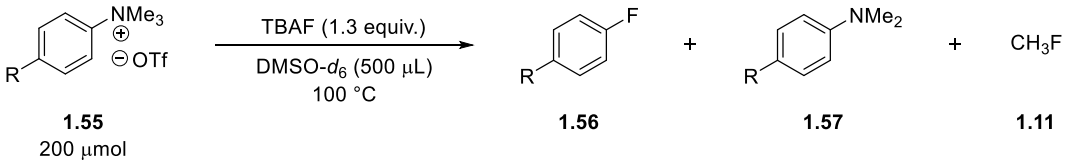
Scheme 1.16. Synthesis of ^{18}F-containing radiotracers by the Wallach reaction. **a)** [^{18}F]Spiperone. **b)** Protected 3-[^{18}F]fluoro-α-methyl-L-phenylalanine.

1.4.2.2 Nucleophilic Aromatic Substitution

Nucleophilic aromatic substitution (S_NAr) is one of the most commonly employed methods for the synthesis of [^{18}F]fluoro(hetero)arenes.[4], [31], [72] This normally involves heating the precursor with a source of [^{18}F]fluoride in a polar aprotic solvent at temperatures above 100 °C. In general, this reaction is suitable only when a strongly electron-withdrawing group is present in a site ortho or para to the site of ^{18}F-fluorination.[73] This restricts the applications of the method in late-stage ^{18}F-fluorination; alternatively, activating groups can be removed in post-^{18}F-fluorination steps or transformed into other functionality if this is required as

part of the structure of interest.[74] The effectiveness of these activating groups is generally in the order *p*-NO_2 > *p*-CN ~ *p*-CF_3 > *p*-CHO > *p*-COMe > *m*-NO_2.[75], [76]

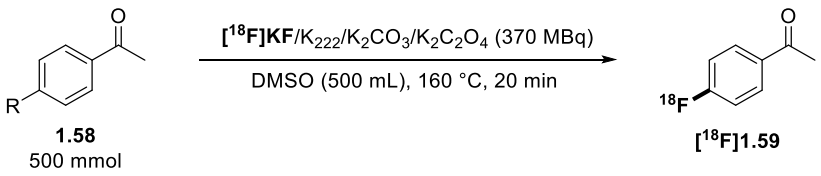
The most commonly employed leaving groups are the nitro and trimethylammonium groups. Studies by Wolf and co-workers, and Kilbourn and co-workers, established trimethylammonium salts as superior leaving groups to nitro groups in S_NAr reactions of electron-deficient arenes with [^{18}F]fluoride, due to slightly higher radiochemical yields but also more facile separation of the ^{18}F-labelled product from the starting material.[75], [76] When trimethylammonium groups are employed as leaving groups in S_NAr reactions with fluoride, two products are possible. Reaction of fluoride at the ipso carbon of trimethylanilinium triflates **1.55** (Table 1.3) results in formation of the desired fluoroarene **1.56**, whilst S_N2 at one of the methyl groups forms fluoromethane **1.11** and the corresponding dimethylaniline **1.57**. Banks and co-workers took advantage of this side reaction in a synthesis of [^{18}F]fluoromethane.[77] DiMagno and co-workers undertook a systematic study of the effects of para-substituents on the reaction of trimethylanilinium triflates **1.55** with unlabelled anhydrous TBAF. Whilst all reactions were complete within 30 minutes at 100 °C, those with more electron-withdrawing R groups proceeded faster. These substrates also gave the best selectivity for formation of fluoroarene **1.56** over fluoromethane **1.11**. This suggests that even for trimethylammonium salts, an appropriately-positioned strongly electron-withdrawing group is required for this reaction to be of use in ^{18}F-fluorination.



R	σ_p	Time / min	Ratio 1.56:1.57
NO_2	1.27	1	> 99:1
CHO	1.03	1	> 99:1
CN	1.00	1	99:1
COPh	0.84	1	99:1
CO_2Me	0.64	2	96:4
Br	0.25	10	2:98
H	0	10	< 1:99
Me	-0.17	10	< 1:99
OMe	-0.26	30	< 1:99

Table 1.3. Influence of activating group on product distribution in the reaction of trimethylanilinium triflates with fluoride

Halides have also been employed as leaving groups in S_NAr reactions with [^{18}F]fluoride. For example, whilst investigating the radiosynthesis of the antipsychotic [^{18}F]haloperidol, Hashizume and co-workers evaluated the ^{18}F-fluorination by S_NAr of a series of para-substituted acetophenones **1.58** (Table 1.4).[78] The nitro and trimethylammonium leaving groups provided **[^{18}F]1.59** in 34% RCC, with the chloride only slightly less efficient. Bromide and iodide were much less effective, affording **[^{18}F]1.59** in 6% and 2% RCC, respectively. Whilst fluoride itself was the best leaving group, this was not of interest, since separation of the starting material and product would be impossible, leading to formation of the product in low specific activity.



R	[18F]1.59 RCC / %
NO_2	34
NMe_3OTf	34
F	75
Cl	28
Br	6
I	2

Table 1.4. Influence of leaving group on efficiency of S_NAr of acetophenones. RCCs determined by radio-HPLC.

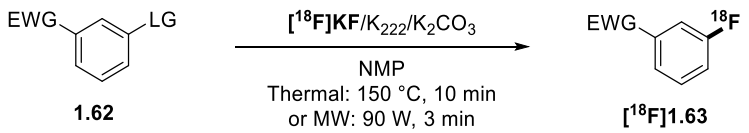
Despite the improved efficiency of nitro over chloride as a leaving group, in *p*-nitrochlorobenzenes, the chloride is selectively displaced since chloro is a poor activating group. This was exploited in the radiosynthesis of the translocator protein ligand [^{18}F]PK 14105 **[^{18}F]1.61** by Pike and co-workers (Scheme 1.17).



Scheme 1.17. Synthesis of [^{18}F]PK 14105 by S_NAr

Electron-deficient arenes bearing activating groups in the meta-position are challenging substrates for S_NAr with [^{18}F]fluoride. Pike and co-workers investigated the use of microwave heating in order to improve the RCY of S_NAr reactions on these substrates (Table 1.5). Microwave heating (90 W, 3 min) was superior to

thermal heating (150 °C, 10 min), with nitro groups being displaced more efficiently than trimethylammonium groups.



EWG	LG	RCY (d.c.) / %	
		Thermal	Microwave
NO_2	NO_2	21	47
CN	NO_2	20	46
CF_3	NO_2	8	13
Br	NMe_3I	3	17
CF_3	NMe_3I	1	12
NO_2	NMe_3I	4	8

Table 1.5. Use of microwave heating to increase RCY for the S_NAr of arenes with activating groups in the meta position with [^{18}F]fluoride.

Since the conditions employed for S_NAr reactions with [^{18}F]fluoride are rather harsh, sensitive substrates such as peptides and proteins tend to be ^{18}F-labelled by first ^{18}F-labelling a small "prosthetic group", which is then coupled to the molecule of interest. The preparation and use of ^{18}F-labelled prosthetic groups has been reviewed; Figure 1.4 shows some of the most common.[79], [80] These include 4-[^{18}F]fluorobenzoic acid **[^{18}F]1.64** and *N*-succinimidyl-4-[^{18}F]fluorobenzoate **[^{18}F]1.65**, which are coupled to the N-terminal amino group or to lysine amino groups, and *N*-[2-(4-[^{18}F]fluorobenzamido)ethyl]maleimide **[^{18}F]1.66** and *N*-[6-(4-[^{18}F]fluorobenzylidene)aminooxyhexyl]maleimide **[^{18}F]1.67**, which are coupled to cysteine residues. Synthesis of prosthetic groups usually requires functional group manipulation after introduction of fluorine-18, followed by conjugation to the molecule of interest, resulting in low RCCs of the ^{18}F-labelled peptide or protein.

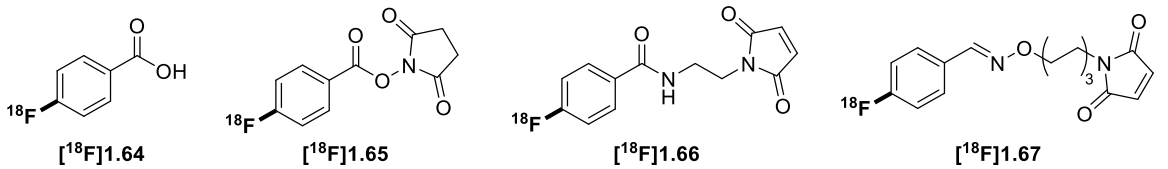
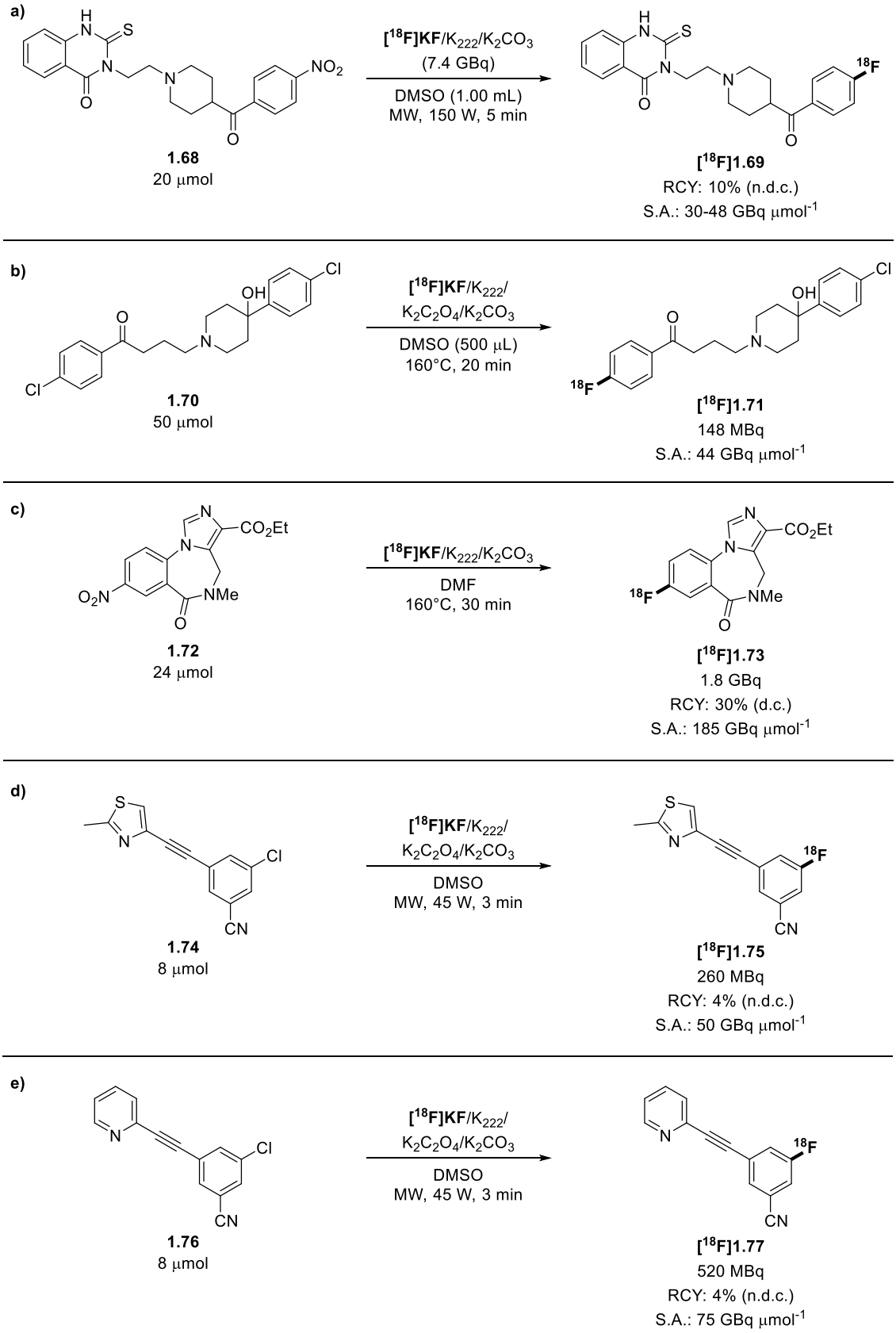


Figure 1.4. Common prosthetic groups bearing [18F]fluoroarenes

Several important PET radioligands have been prepared via SNAr of activated aromatic precursors. Scheme 1.18 shows a selection of those prepared in a single step. [18F]Altanserin **[18F]1.69** (Scheme 1.18a) was prepared as a serotonin S_2 PET radioligand by Lemaire et al.[81] Starting from 7.4 GBq [18F]KF/K_{222} complex, SNAr of nitroarene **1.68** afforded **[18F]1.69** in 10% RCY (n.d.c.), with a specific activity of 30-48 GBq μmol^{-1}. Hashizume and co-workers synthesised the butyrophenone neuroleptic [18F]haloperidol **[18F]1.71** via SNAr of aryl chloride precursor **1.70** (Scheme 1.18b).[78] [18F]Flumazenil **[18F]1.73** was prepared by Halldin and co-workers and demonstrated to be a suitable PET radioligand for assessment of the benzodiazepine receptors (Scheme 1.18c).[82] Substitution of the nitro group in **1.72** with [18F]fluoride allowed synthesis of 1.8 GBq **[18F]1.73** after HPLC purification, corresponding to a 30% RCY (d.c.). As expected, the specific activity was high (185 GBq μmol^{-1}). Hamill et al. reported the synthesis of the mGluR5 PET radiotracers [18F]FMTEB **[18F]1.75** (Scheme 1.18d) and [18F]FPEB **[18F]1.77** (Scheme 1.18e).[83] Although the RCYs were low (4% n.d.c. in both cases), enough was prepared to undertake PET studies with rhesus monkeys. Both [18F]FMTEB and [18F]FPEB were shown to be brain penetrant, to be highly selective for mGluR5 and to provide high quality PET images.

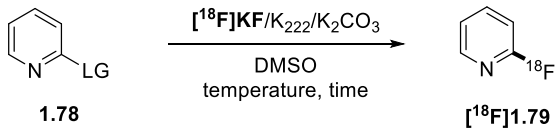


Scheme 1.18. One-step radiosynthesis of ^{18}F-containing PET tracers by S$_N$Ar. **a)** [^{18}F]Altanserin. **b)** [^{18}F]Haloperidol. **c)** [^{18}F]Flumazenil. **d)** [^{18}F]FMTEB. **e)** [^{18}F]FPEB

The radiosyntheses in Scheme 1.18 were generally not optimised, but provided enough of the ^{18}F-labelled tracer for evaluation in animal PET studies. In several cases, the authors commented that an aryl chloride was chosen over a nitro or trimethylammonium precursor due to synthetic accessibility. Whilst tracers bearing a fluorine-18 substituent on an electron-deficient arene can be amenable to single-step radiosynthesis by S_NAr, those in which the fluorine-18 is on an electron-neutral or electron-rich ring are not. The reliability of S_NAr with [^{18}F]fluoride on electron-deficient arenes has led to multistep syntheses of electron-rich [^{18}F]fluoroarenes via initial introduction of fluorine-18 by S_NAr on an electron-deficient arene, followed by functional group manipulations to construct the desired structure. Synthesis of [^{18}F]FDOPA in this manner is discussed in section 2.3.1.

Incorporation of [^{18}F]fluoride by nucleophilic aromatic substitution is not limited to arenes; electron-deficient heteroarenes are even more suitable substrates. Substitution of leaving groups at the 2- and 4-positions of pyridines is especially favourable due to mesomeric stabilisation of the intermediate Meisenheimer complex by the ring nitrogen atom. Dollé and co-workers studied the effects of the leaving group in the 2-position of pyridines **1.78** (Table 1.6).[84] At 120 °C, the trimethylammonium leaving group afforded 2-[^{18}F]fluoropyridine **[^{18}F]1.79** in excellent RCC within 5 minutes. The nitro leaving group required 10 minutes to achieve a high RCC, whilst the chloro, bromo and iodo substrates were completely unreactive. At 150 °C, the chloro and bromo substrates afforded **[^{18}F]1.79** in 23%-25% RCC after 20 minutes, whereas the iodide remained unreactive. Increasing the

temperature to 180 °C increased the RCCs for the chloro and bromo substrates; reaction of the iodide remained sluggish. Microwave heating was also investigated and afforded a very similar reactivity profile, but with lower reaction times required. For example, heating the bromo, nitro or trimethylammonium precursors at 100 W for 2 minutes afforded **[^{18}F]1.79** in > 70% RCC.



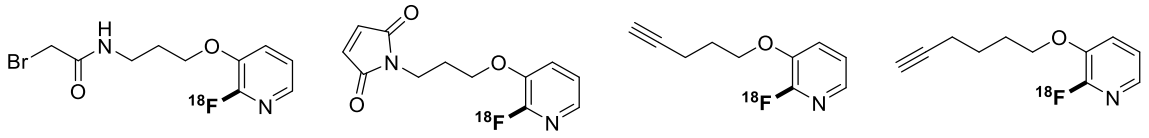
1.78 **[^{18}F]1.79**

Temperature / °C	LG	RCC (%) at Reaction Time (min)		
		5	**10**	**20**
120	Cl, Br or I	0	0	0
	NO_2	11	76	82
	NMe_3OTf	81	87	91
150	Cl	1	3	23
	Br	1	16	25
	I	0	0	1
	NO_2	52	85	92
	NMe_3OTf	89	89	90
180	Cl	11	28	57
	Br	56	60	87
	I	2	5	19
	NO_2	77	88	89
	NMe_3OTf	88	91	92

Table 1.6. Effects of leaving groups, temperature and time in substitution of 2-pyridines with [^{18}F]fluoride. RCCs were determined by radio-TLC.

In a second publication, the same group reported an investigation into the synthesis of 2-, 3- and 4-[^{18}F]fluoropyridines via S_NAr of the nitro precursors.[85] Heating 2- or 4-nitropyridine with [^{18}F]KF/K_{222} complex at 145 °C in DMSO for two minutes afforded the corresponding [^{18}F]fluoropyridine in good RCC. Use of 100 W microwave heating for two minutes resulted in higher RCCs. The 3-isomer was almost completely unreactive. Interestingly, the corresponding 3- and 4-

trimethylammonium triflates could not be compared with the nitropyridines due to difficulties in their preparation; methylation of the dimethylaminopyridines with methyl triflate occurred instead on the ring nitrogen. The facile synthesis of 2-[^{18}F]fluoropyridines via S_NAr led Dollé and co-workers, and Inkster and co-workers, to develop prosthetic groups **[^{18}F]1.80**-**[^{18}F]1.83** based on this motif (Figure 1.5).[86]–[89]

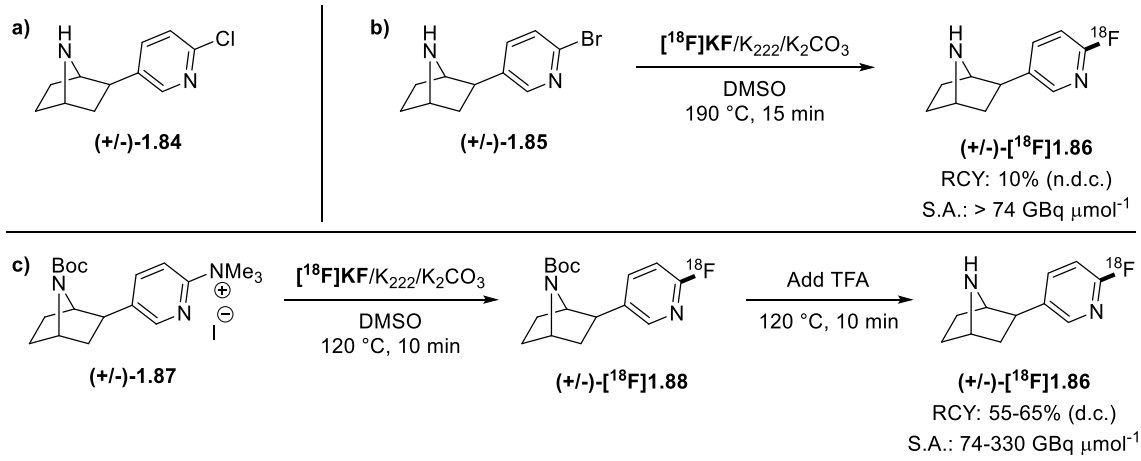


[^{18}F]1.80 **[^{18}F]1.81** **[^{18}F]1.82** **[^{18}F]1.83**

Figure 1.5. 2-[^{18}F]Fluoropyridine-based prosthetic groups

(+/−)-Epibatidine **(+/−)-1.84** (Scheme 1.19a), isolated from the skin of Anthony's poison arrow frog, exhibits a very high affinity and specificity for nicotinic acetylcholine receptors (nAcRs).[90] Dannals and co-workers synthesised an ^{18}F-labelled analogue **(+/−)-[^{18}F]1.86**, in which the chlorine is substituted by fluorine-18, for imaging of nAcRs (Scheme 1.19b).[91] **(+/−)-[^{18}F]1.86** was prepared via substitution of 2-bromopyridine **1.85** with [^{18}F]KF/K_{222} complex. A PET study in baboon showed that **(+/−)-[^{18}F]1.86** had potential for use in imaging nAcRs in humans.[92] Ding et al. subsequently disclosed an improved synthesis, starting from *N*-Boc protected trimethylammonium precursor **1.87** (Scheme 1.19c).[93] Substitution with [^{18}F]KF/K_{222} complex was followed by deprotection in the same pot to afford **(+/−)-[^{18}F]1.86** in 45%-55% RCY (d.c.) over two steps. Most importantly, excess precursor could be easily separated from the desired product. Later work by

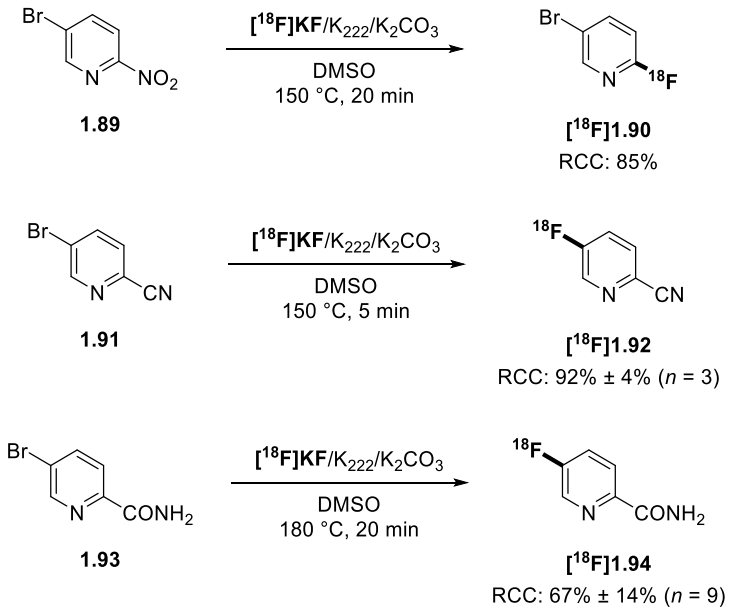
Dollé and co-workers used an N-Boc protected bromo precursor.[94] The acute toxicity of **(+/−)-[^{18}F]1.86** precluded its use in humans;[95] subsequent work by several groups focused on the design and synthesis of safer analogues.[96]–[100]



Scheme 1.19. a) Structure of (+/−)-epibatidine. **b)** Initial radiosynthesis of ^{18}F-fluorinated epibatidine analogue for imaging of nAcRs. **c)** Improved two-step, one-pot radiosynthesis.

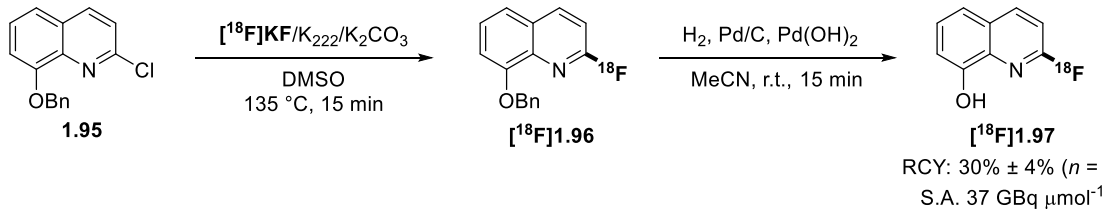
In order to achieve a nucleophilic substitution with [^{18}F]fluoride in the 3-position of a pyridine, an electron-withdrawing activating substituent is also required in the position para to the site of substitution.[101], [102] During studies towards the ^{18}F-labelling of a peptide deformylase inhibitor, Langer and co-workers heated 3-bromopyridines bearing nitro, cyano and carboxamide activating groups with [^{18}F]KF/K$_{222}$ complex in DMSO (Scheme 1.20). After heating at 150 °C for 20 minutes, the authors were surprised to observe that nitropyridine **1.89** exclusively afforded ^{18}F-fluorodenitration product **[^{18}F]1.90**. Cyanopyridine **1.91** afforded the desired halogen exchange product **[^{18}F]1.92** after only 5 minutes at 150 °C. Prolonging the reaction time caused formation of an unidentified hydrophilic by-product. Carboxamide was also shown to be a competent activating group; **1.93**

afforded halogen exchange product **[^{18}F]1.94**, but required heating at 180 °C for 20 minutes. Again, an unidentified hydrophilic by-product also formed; this was shown not to be the carboxylic acid nor 3-bromopyridine.



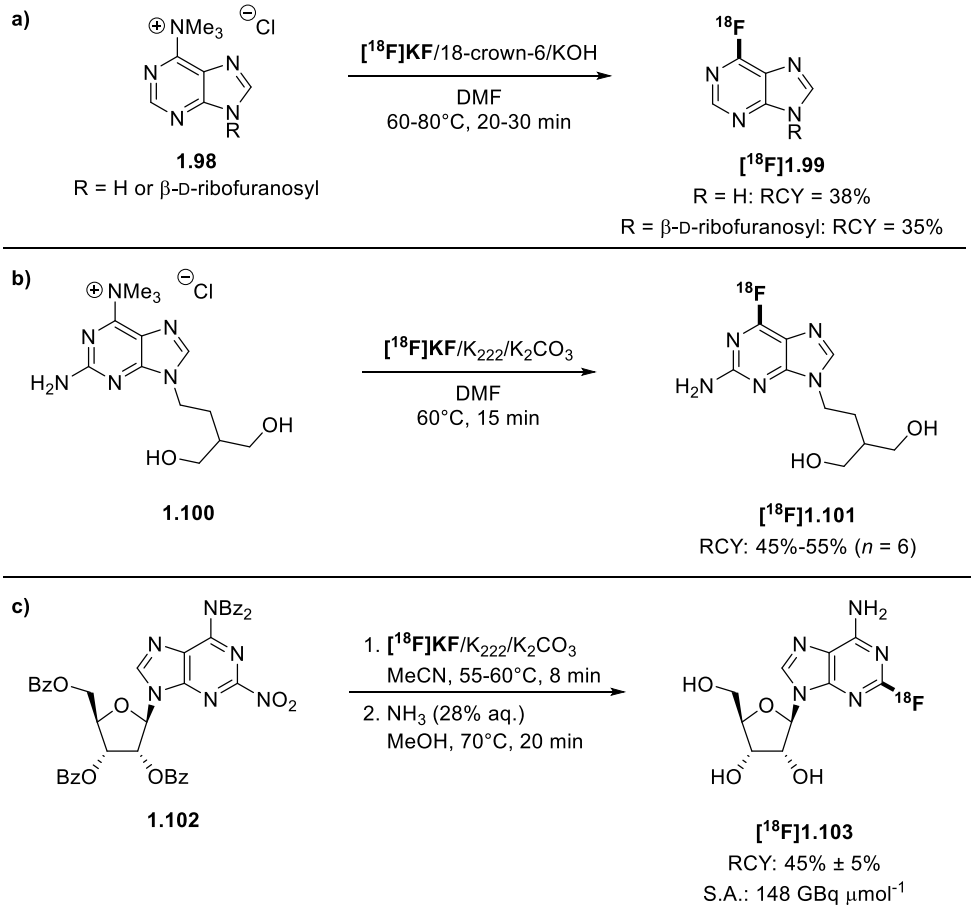
Scheme 1.20. Attempted halogen exchange on activated 3-bromopyridines with [^{18}F]fluoride

In 2012, Vasdev and co-workers disclosed use of an S$_N$Ar with [^{18}F]fluoride in the 2-position of chloroquinoline **1.95** for the preparation of fluoroquinolol **[^{18}F]1.97** for the imaging of Alzheimer's disease (Scheme 1.21).[103] An attempt to prepare the 4-isomer was unsuccessful due to instability of the product.



Scheme 1.21. Preparation of Alzheimer's radiotracer **[^{18}F]1.97** via S$_N$Ar on chloroquinoline **1.95** followed by hydrogenation

More complex heteroarenes have also been ^{18}F-labelled via SNAr. Some of the earliest studies were by Irie and co-workers, who showed that both 6-[^{18}F]fluoropurine and 6-[^{18}F]fluoro-9-β-D-ribofuranosylpurine **[^{18}F]1.99** could be accessed via displacement of a trimethylammonium group in precursors **1.98** with [^{18}F]KF/18-crown-6/KOH complex in RCYs of 38% and 35% respectively (Scheme 1.22a).[104], [105]

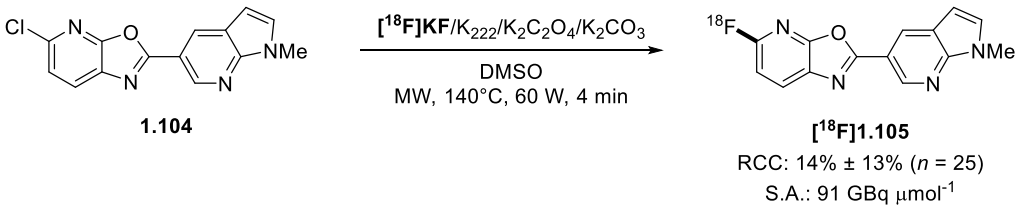


Scheme 1.22. a) Synthesis of 6-[^{18}F]fluoropurine and 6-[^{18}F]fluoro-9-β-D-ribofurosanylpurine via SNAr of trimethylammonium precursors. **b)** Synthesis of [^{18}F]penciclovir via SNAr of a trimethylammonium precursor. **c)** Synthesis of 2-[^{18}F]fluoroadenosine via SNAr of a nitro precursor followed by deprotection.

More than twenty years later, the same method was used by Yin and co-workers to prepare the HSV1-tk probe [^{18}F]penciclovir **[^{18}F]1.101** (Scheme

1.22b).[106] In 2010, Barré and co-workers reported the nucleophilic displacement of a nitro group in protected precursor **1.102** with [^{18}F]fluoride as a means to efficiently prepare 2-[^{18}F]fluoroadenosine **[^{18}F]1.103** (Scheme 1.22c).[107] Global benzoyl deprotection with aqueous ammonia in methanol afforded **[^{18}F]1.103** in 45% RCY, with a specific activity of 148 GBq μmol^{-1}.

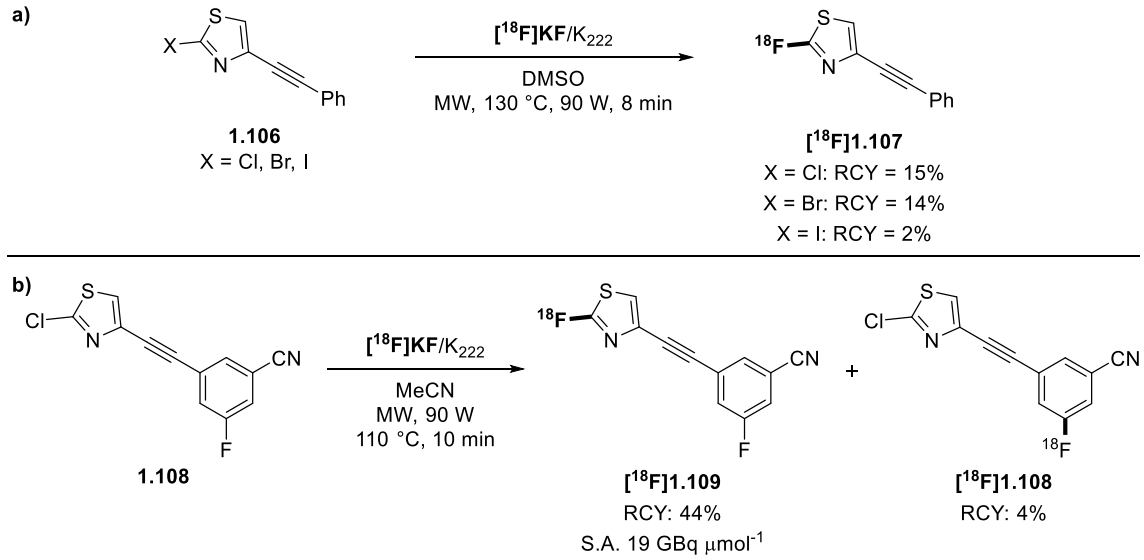
Whilst developing PET tracers for amyloid plaques, Hostetler and co-workers demonstrated that the chloro group of azabenzoxazole **1.104** could be displaced with [^{18}F]fluoride to form [^{18}F]fluoroazabenzoxazole **[^{18}F]1.105** (Scheme 1.23).[108] The RCC was relatively low, but sufficient activity was obtained to conduct PET studies in rhesus monkeys and to determine that **[^{18}F]1.105** was a promising PET tracer. Substitution of chloride with [^{18}F]fluoride in related chloroazabenzoxazoles proceeded in 35%-40% RCC.



Scheme 1.23. Synthesis of [^{18}F]fluoroazabenzoxazole **[^{18}F]1.105** via S$_N$Ar of chloro precursor **1.104**

Siméon and co-workers have shown that thiazoles are also amenable to ^{18}F-labelling via S$_N$Ar from halide precursors.[109], [110] With 2-bromothiazole itself, microwave heating was shown to be superior to thermal heating, affording 2-[^{18}F]fluorothiazole in 81% RCY (d.c.). Whilst investigating new mGluR5 radioligands, the authors carried out S$_N$Ar with [^{18}F]fluoride on 2-halothiazoles

1.106 (Scheme 1.24a). Chloride and bromide could be displaced in 15% and 14% RCY, respectively, whilst iodide was less reactive, affording **[^{18}F]1.107** in only 2% RCY. In a second publication, the same authors identified **[^{18}F]1.109** as a lead tracer candidate, although its synthesis from **1.108** was complicated by competing isotopic substitution on the benzonitrile ring to produce impurity **[^{18}F]1.108** (Scheme 1.24b). **[^{18}F]1.109** was isolated in > 99% radiochemical purity but with a specific activity of only 19 GBq μmol^{-1}, presumably due to the isotopic exchange side reaction.



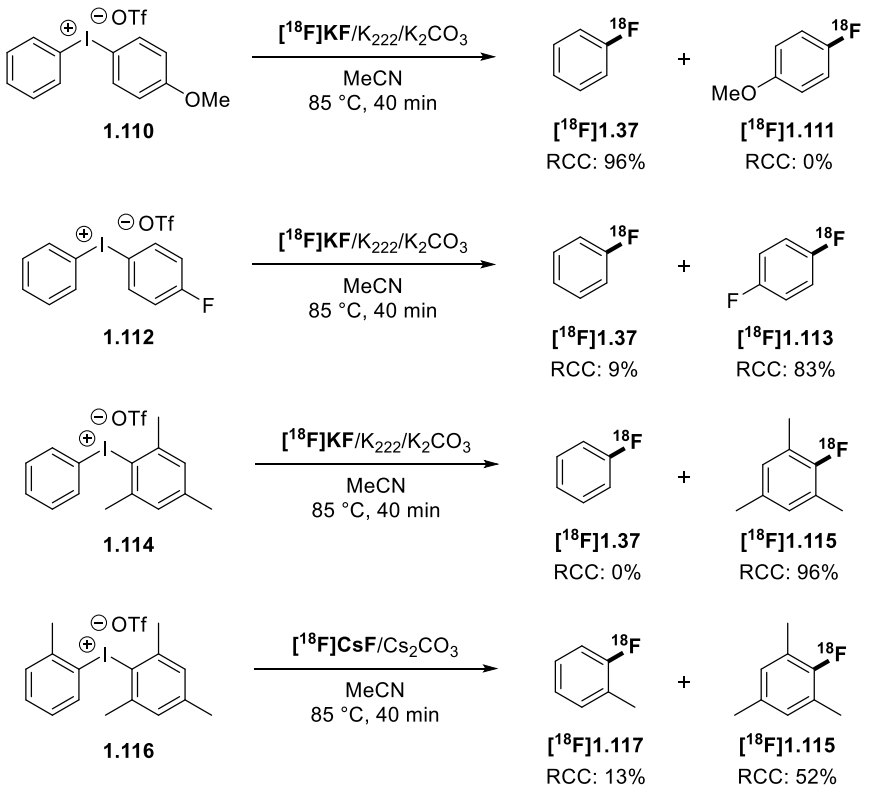
Scheme 1.24. a) Influence of halide in S$_N$Ar of 2-halothiazoles **1.105** with [^{18}F]fluoride. **b)** Synthesis of mGluR5 radioligand **[^{18}F]1.109** via S$_N$Ar of chlorothiazole **1.108**.

1.4.2.3 Diaryliodonium Salts

Nucleophilic aromatic substitution with [^{18}F]fluoride provides an excellent route for the ^{18}F-fluorination of arenes and heteroarenes bearing appropriately-positioned leaving and activating groups. However, many potential tracers do not fit into this category. In order to facilitate the ^{18}F-fluorination of such molecules, Pike

and Aigbirhio turned to the use of diaryliodonium salts.[111] These were first prepared in 1894 by Hartmann and Meyer and first used in fluorination of arenes by Grushin and co-workers in 1983.[112]–[115] In their initial 1995 publication, Pike and Aigbirhio showed that heating diphenyliodonium chloride with [^{18}F]KF/K$_{222}$ complex afforded [^{18}F]fluorobenzene in 55% RCC, a very promising result.

A more substantial study by the Pike group into the ^{18}F-fluorination of diaryliodonium triflates established the selectivity of the transformation.[116] When both aryl groups were unhindered, formation of the more electron-deficient [^{18}F]fluoroarene was favoured. For example, ^{18}F-fluorination of **1.110** afforded [^{18}F]fluorobenzene **[^{18}F]1.37** in 96% RCC; 4-[^{18}F]fluoroanisole **[^{18}F]1.111** was not observed (Scheme 1.25). Likewise, **1.112** afforded a 9:1 ratio of **[^{18}F]1.37** and **[^{18}F]1.113**. However, when one of the aryl groups bore a substituent ortho to iodine, the preference for ^{18}F-fluorination of the less electron-rich ring was overridden; ^{18}F-fluorination of **1.114** afforded exclusively the more sterically-hindered product **[^{18}F]1.115**. When both aryl groups bore ortho substituents, the more hindered product was again formed preferentially. In this case, [^{18}F]CsF was required to effect ^{18}F-fluorination; [^{18}F]KF/K$_{222}$ complex was not reactive.

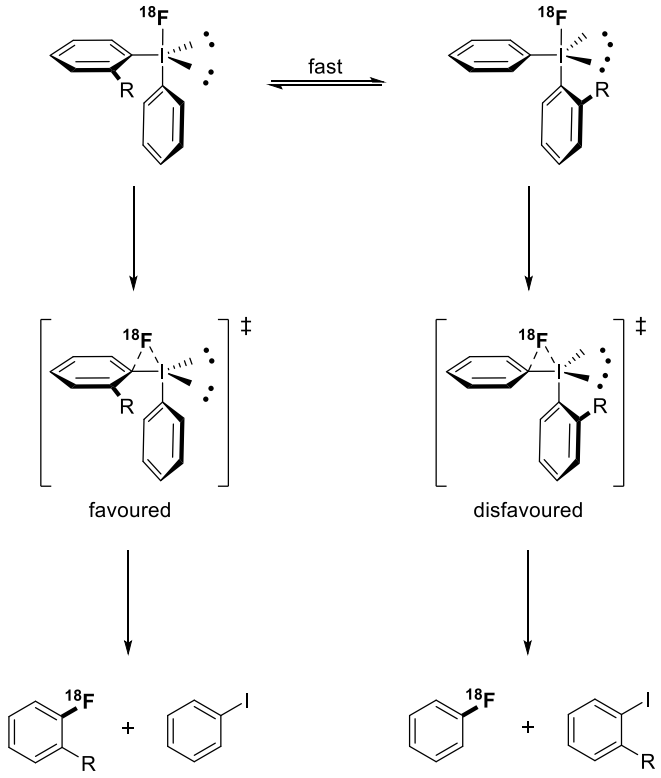


Scheme 1.25. ^{18}F-Fluorination of diaryliodonium triflates

Pike and co-workers later used a microreactor to undertake a systematic study of the ability of ortho substituents to direct attack by [^{18}F]fluoride to the same aromatic ring.[117] The order was shown to be 2,6-di-Me > 2,4,6-tri-Me > Br > Me > Et ~ *i*-Pr >> H > OMe.

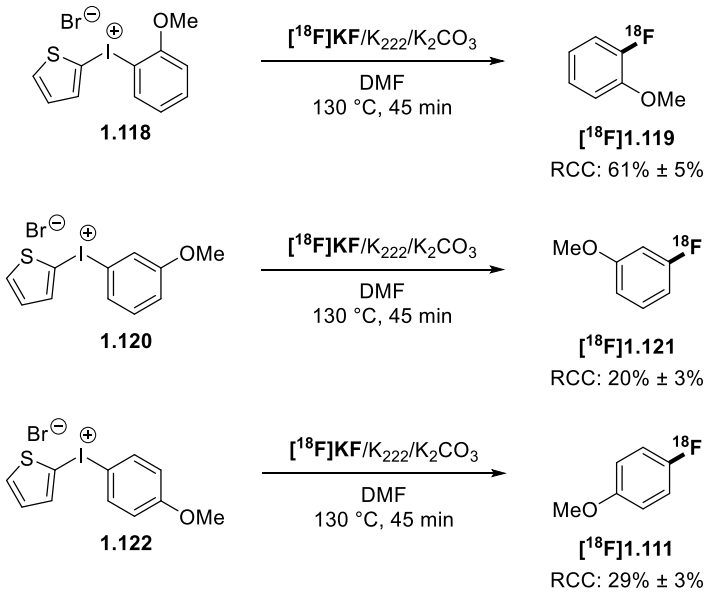
Whilst a nucleophilic substitution mechanism was initially proposed for the ^{18}F-fluorination of diaryliodonium salts, the mechanism is now believed to occur via initial binding of [^{18}F]fluoride to the iodine centre in an axial position, displacing the counterion.[4] Nucleophilic attack of [^{18}F]fluoride on the equatorial aromatic ring causes formation of the aryl [^{18}F]fluoride and aryl iodide products in a reductive-elimination-like process (Scheme 1.26). For unsymmetrical dialkynyliodinum fluorides, computational studies by Carroll et al. suggested that the lower energy

conformation is that in which the more electron-deficient ring occupies the axial site trans to the fluoride, with the more electron-rich ring in the equatorial site.[118] This would predict that the major product is that of ^{18}F-fluorination on the more electron-rich ring, which is not consistent with experimental results. However, the calculated transition state stabilities are in favour of reaction with the more electron-deficient ring, in accordance with experimental data. In addition, calculations suggested that the iodonium fluorides may form stable dimers, which provide a low-energy means for the axial and equatorial groups on iodine to interconvert.[119] Pike and co-workers suggested that the reaction may follow the Curtin-Hammett principle, in which the relative amounts of two products formed from two conformers is dependent on the ratio of the transition state energies for their formation and not on the relative populations of the two conformers, providing that the rate of interconversion between the conformers is much faster than that of the reaction.[117], [120]



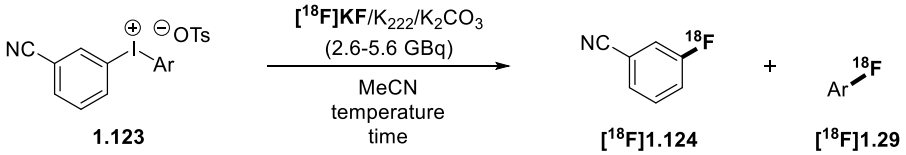
Scheme 1.26. Proposed mechanism for the ^{18}F-fluorination of diaryliodonium salts

Martín-Santamaría et al. prepared phenyl(heteroaryl)iodonium salts, where heteroaryl was 2-furyl, 2-*N*-methylpyrrole and 2-thienyl.[121] Fluorination with unlabelled CsF afforded exclusively fluorobenzene, as predicted by the authors' calculations. Coenen and co-workers further investigated the use of aryl(heteroaryl)iodonium salts in ^{18}F-radiochemistry.[122] The preference for ^{18}F-fluorination on the less electron-rich ring was exploited by using the ^{18}F-fluorination of (2-thienyl)(anisyl)iodonium salts in DMF at 130 °C to prepare all three isomers of [^{18}F]fluoroanisole (Scheme 1.27). The influence of the counterion on the RCC of 2-[^{18}F]fluoroanisole **[^{18}F]1.119** was also studied. Bromide afforded **[^{18}F]1.119** in the highest RCC, followed by triflate and iodide, with tosylate performing worst.



Scheme 1.27. Synthesis of [^{18}F]fluoroanisoles from (2-thienyl)(anisyl)iodonium bromides. RCC was determined by radio-HPLC.

Pike and co-workers used diaryliodonium salts to address the problem of synthesising meta-substituted [^{18}F]fluoroarenes.[123] Using microfluidic technology, the authors investigated the effects of the auxiliary arene on the radiochemical conversion and selectivity of the ^{18}F-fluorination (Table 1.7). Reactions were run in acetonitrile, although the authors commented that DMF may have been more suitable in some cases. It was noted that TEMPO was not required to achieve high RCCs, possibly since the reagents were protected from light inside the microreactor. For the preparation of 3-[^{18}F]fluorobenzonitrile **[^{18}F]1.124**, the iodonium precursor bearing a 4-methoxyphenyl auxiliary arene afforded **[^{18}F]1.124** in the highest RCC (82%), but this also afforded the largest amount of the undesired [^{18}F]fluoroarene **[^{18}F]1.29** (Table 1.7, entry 3). The selectivity of the precursor bearing the 5-methyl-2-thienyl auxiliary was much higher, affording **[^{18}F]1.124** in nearly as high RCC, but with only 1% of the undesired product **[^{18}F]1.29**.



Entry	Ar	Temperature / °C	Time / s	RCC / %	
				[18F]1.124	[18F]1.29
1	3-CN-C_6H_4	160	189	55	
2	Ph	130	146	25	< 1
3	4-MeO-C_6H_4	130	146	82	11
4	3-Me-C_6H_4	160	189	76	5
5	2-Thienyl	160	189	58	2
6	5-Me-2-thienyl	180	189	78	1

Table 1.7. Influence of auxiliary arene in microfluidic synthesis of 3-[18F]fluorobenzonitrile from diaryliodonium tosylate precursors. Time refers to residence time in the microreactor. RCCs were determined by radio-HPLC.

Other 3-substituted arenes were prepared in a similar manner. In general, the 4-methoxyphenyl or 2-thienyl auxiliary arenes gave the best results. The highest RCCs for each product are given in Table 1.8. Despite the reactions being carried out on a multi-GBq scale, no isolated yields were reported.

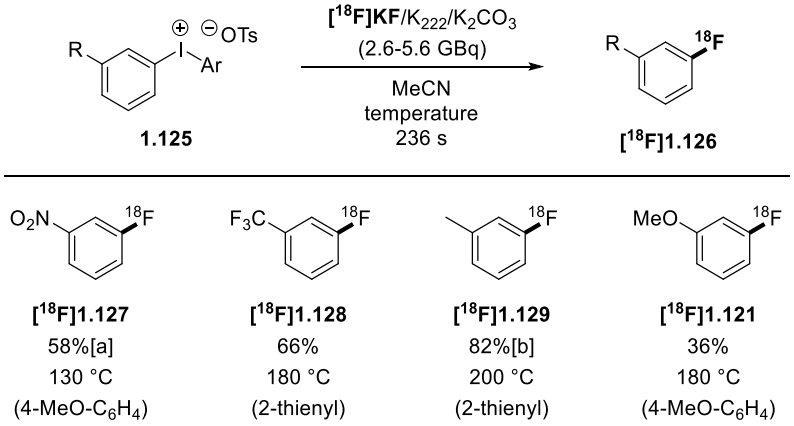


Table 1.8. Synthesis of 3-substituted [18F]fluoroarenes from diaryliodonium tosylate precursors. Time refers to residence time in the microreactor. Highest RCCs are given, with auxiliary arene in brackets. RCCs were determined by radio-HPLC. **[a]** Residence time: 191 s. **[b]** Reaction run in DMF.

Carroll and co-workers disclosed initial results towards the use of 3-pyridyl(aryl)iodonium salts for the synthesis of 3-[^{18}F]fluoropyridines, although details were sparse.[124] The authors reported that whilst synthesis of the (4-methoxyphenyl)(3-pyridyl)iodonium salt was challenging, ^{18}F-fluorination afforded exclusively 3-[^{18}F]fluoropyridine, in 55%-63% RCY. The corresponding 3-quinoline precursor afforded 3-[^{18}F]fluoroquinoline in 22%-25% RCY. Chun and Pike later published a study on the ^{18}F-fluorination of *p*-anisyl(pyridyl)iodonium tosylates **1.130** in a microreactor to prepare 2- and 3-[^{18}F]fluorohalopyridines **[^{18}F]1.131** (Table 1.9).[125] RCCs were moderate to high, and the authors were pleased to observe no competing nucleophilic substitution of the halogens. Selectivity for ^{18}F-fluorination of the pyridine over formation of 4-[^{18}F]fluoroanisole was high; in most cases 4-[^{18}F]fluoroanisole was not observed, whilst for **1.132**, **1.134** and **1.137** it was observed in ≤ 3% RCC. Products **1.134**-**1.137** would be very difficult to prepare by any other method.

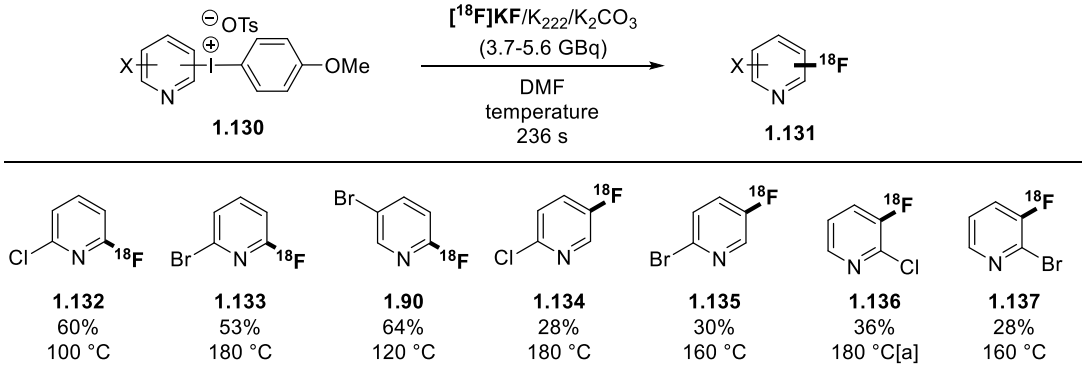
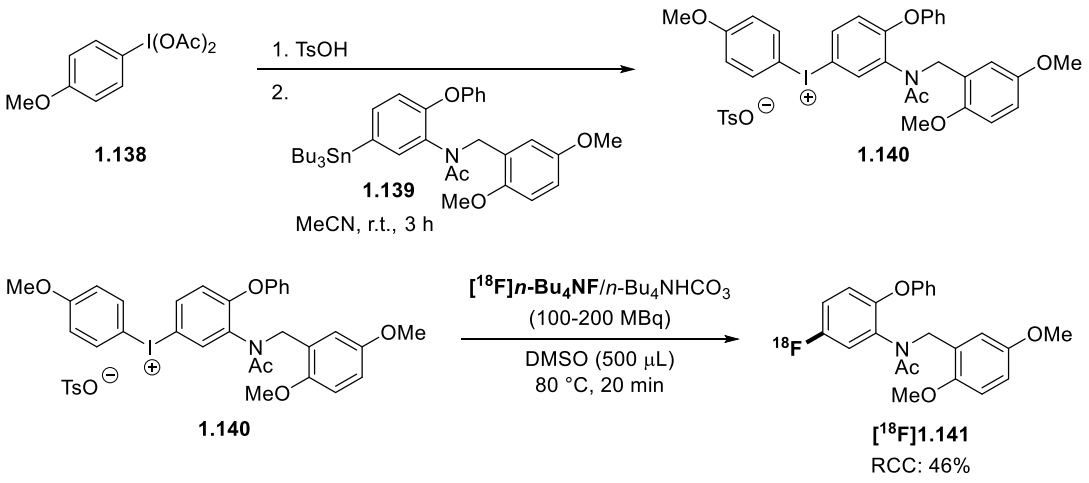


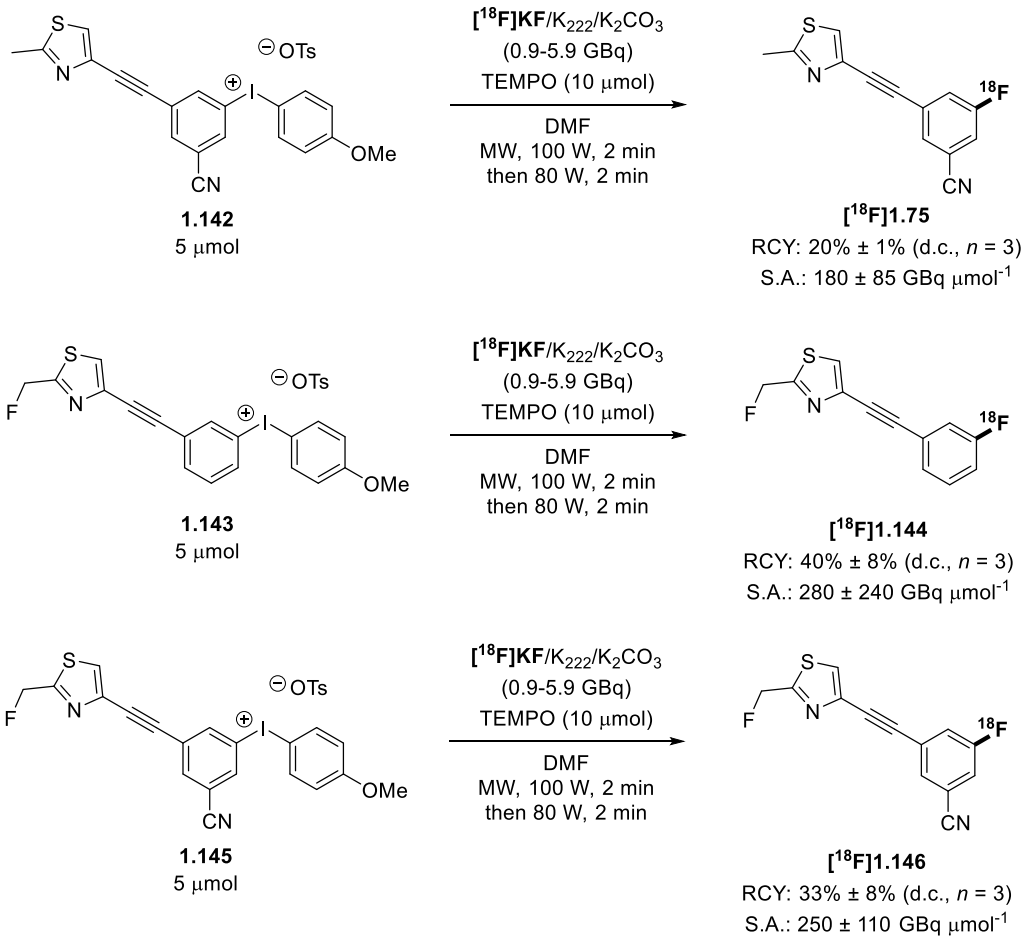
Table 1.9. Microfluidic synthesis of [^{18}F]fluorohalopyridines from *p*-anisyl(pyridyl)iodonium tosylates. RCCs were determined by radio-HPLC. [a] Reaction time = 188 s.

Initial attempts to use diaryliodonium salts as precursors for ^{18}F-fluorination of PET radioligands were challenging due to difficulties in preparing the precursors; the oxidising conditions required to prepare an iodonium salt from a complex aryl iodide may not be compatible with more sensitive functional groups.[126] The first successful synthesis of an ^{18}F-labelled radioligand from a diaryliodonium precursor was the preparation of the translocator protein ligand [^{18}F]DAA1106 in 2007 by Zhang and co-workers (Scheme 1.28). *p*-Methoxyphenyl(hydroxy)iodonium tosylate was formed from 4-methoxyphenyliodonium diacetate **1.138** and reacted with aryl stannane **1.139** to form diaryliodonium tosylate **1.140**, which was used directly in the ^{18}F-fluorination without purification. Small-scale ^{18}F-fluorination of **1.140** with [^{18}F]*n*-Bu$_4$NF/*n*-Bu$_4$NHCO$_3$ in DMSO at 80 °C for 20 minutes afforded **[^{18}F]1.141** in 46% RCC. 4-[^{18}F]Fluoroanisole was also formed in 19% RCC. This is unsurprising because the auxiliary aryl group of **[^{18}F]1.140** is also electron-rich. An initial attempt to use a phenyl group as the auxiliary arene resulted in formation of **[^{18}F]1.141** in only 2% RCC, whilst [^{18}F]fluorobenzene was formed in 72% RCC.



Scheme 1.28. Synthesis of diaryliodonium **1.140** and use in synthesis of [^{18}F]DAA1106 **[^{18}F]1.141**

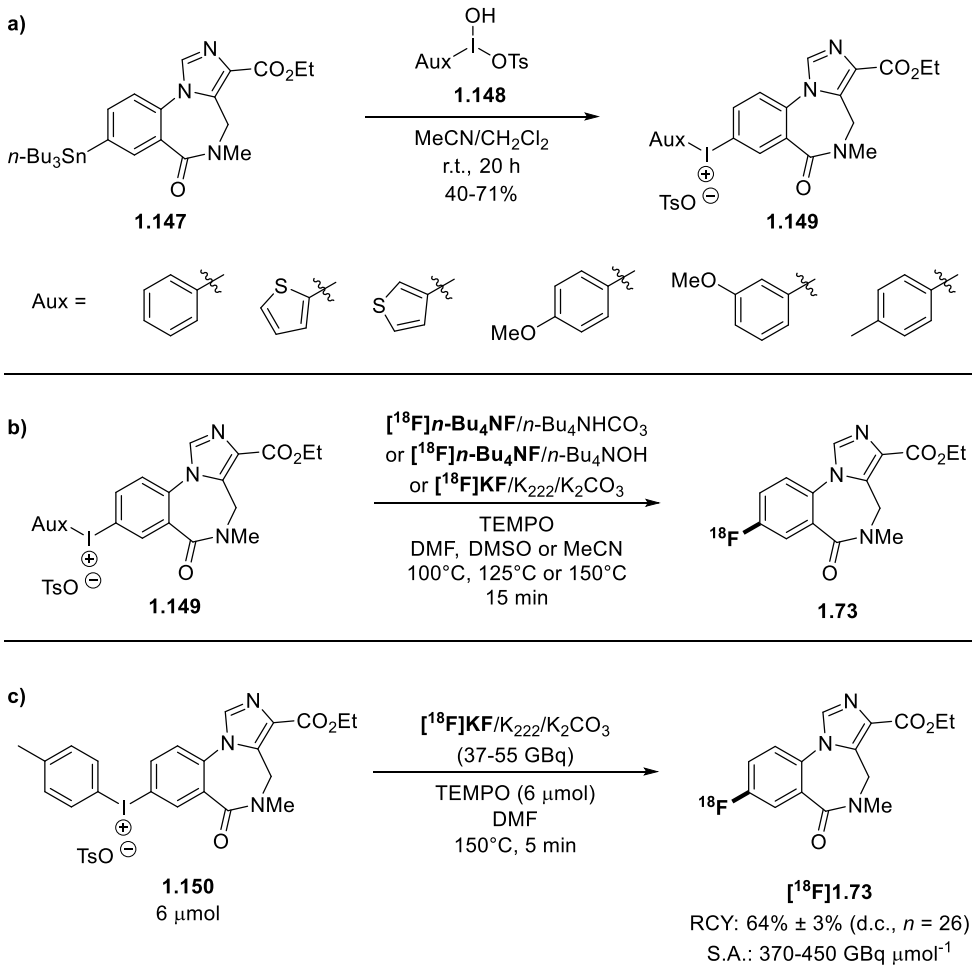
Pike and co-workers applied the ^{18}F-fluorination of diaryliodonium tosylates to the synthesis of mGluR5 radioligands (Scheme 1.29).[127] (*p*-Methoxyphenyl)(aryl)iodonium tosylates **1.142**, **1.143** and **1.145** were prepared and purified by recrystallisation; these were stable for > 12 months when stored in the dark at 4-5 °C under argon. Addition of the radical scavenger TEMPO resulted in significantly improved RCYs. Under the optimised conditions, using a modified Synthia apparatus, [^{18}F]FMTEB **[^{18}F]1.75** was prepared from iodonium **1.142** in 20% RCY (d.c.) and with a specific activity of 180 GBq μmol^{-1}. This represents a significant improvement upon the synthesis by nucleophilic substitution of the aryl bromide precursor. Likewise, the related mGluR5 radioligands **[^{18}F]1.144** and **[^{18}F]1.146** were prepared from the corresponding iodonium precursors **1.143** and **1.145**, in decay-corrected radiochemical yields of 33% and 40%, respectively. The authors were pleased to observe that the presence of an alkyl fluoride did not reduce the specific activity of the product in these cases.



Scheme 1.29. Synthesis of mGluR5 radioligands from diaryliodonium tosylate precursors

Diaryliodonium salts were used by Moon et al. to develop an improved synthesis of [^{18}F]flumazenil.[128] Six diaryliodonium tosylates **1.149** bearing different auxiliary arenes were synthesised via reaction of the corresponding aryl(hydroxy)iodonium tosylates **1.148** with arylstannane **1.147** (Scheme 1.30a). Each precursor **1.149** was used under three different [^{18}F]fluoride elution conditions; *n*-Bu$_4$NHCO$_3$, *n*-Bu$_4$NOH and K$_2$CO$_3$/K$_{222}$ (Scheme 1.30b). Iodonium precursor **1.150**, bearing a 4-tolyl auxiliary arene, afforded **[^{18}F]1.73** in the highest RCCs under all three elution conditions, followed by the precursor with the phenyl auxiliary. The authors showed that the diaryliodonium salts with more electron-rich auxiliary

arenes were more unstable under the reaction conditions. This highlights that precursor stability should be a key consideration when designing a radiosynthesis based on ^{18}F-fluorination of an iodonium salt.

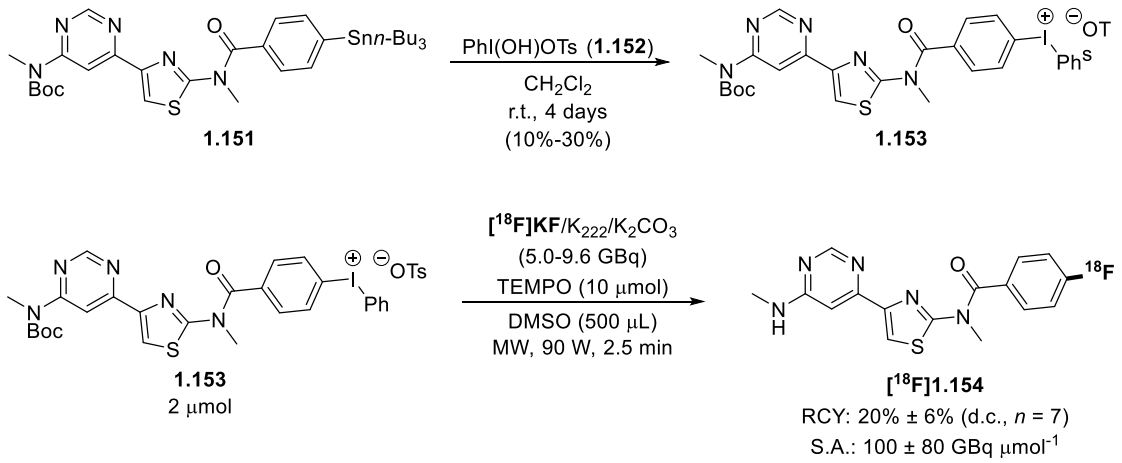


Scheme 1.30. a) Synthesis of diaryliodonium tosylate precursors for the ^{18}F-labelling of flumazenil. b) Optimisation of conditions for the ^{18}F-labelling of flumazenil.

The authors determined that using small amounts of K_2CO_3/K_{222} to elute the [^{18}F]fluoride was optimal; increasing the amount of K_2CO_3 beyond 0.8 equivalents with respect to starting material was detrimental to the RCC of **[^{18}F]1.73**. Addition of the radical scavenger TEMPO was shown to be required in order to obtain high RCCs. After determining the optimised conditions, the authors scaled up the

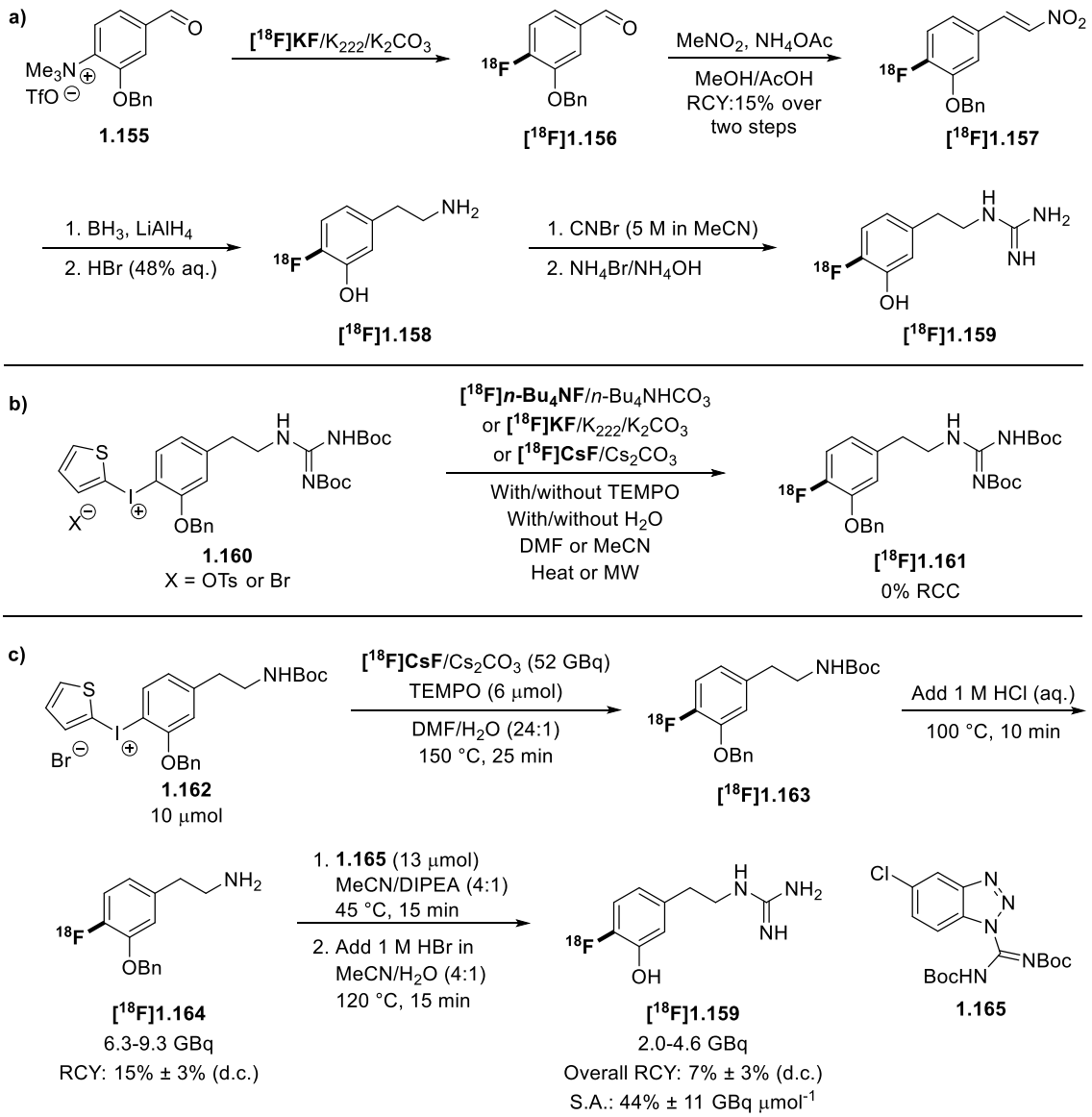
reaction on a GE TracerLab module. Starting from 37-55 GBq cyclotron-produced [^{18}F]fluoride, this automated synthesis afforded **[^{18}F]1.73** in a decay-corrected RCY of 64% ± 3% (n = 26), with a specific activity of 370-450 GBq μmol^{-1} (Scheme 1.30c).

During attempts to synthesise ^{18}F-labelled mGluR1 radioligands, Pike and co-workers again turned to diaryliodonium salts when conventional S$_N$Ar gave poor results.[129] The slightly electron-deficient aryl ring in nitro or bromo precursors to [^{18}F]FIMX **[^{18}F]1.154** was not sufficiently activated to undergo efficient nucleophilic substitution with [^{18}F]fluoride. Thus, iodonium tosylate **1.153** was prepared by reaction of arylstannane **1.151** with Koser's reagent **1.152** (Scheme 1.31). The stability of iodonium **1.153** was not discussed, but since neither arene is electron-rich, it would be expected to be stable if stored at 5 °C in the dark. ^{18}F-Fluorination of **1.153** with microwave heating occurred preferentially on the less electron-rich ring, as desired. The authors were pleased to observe that using DMSO as solvent for the ^{18}F-fluorination enabled in situ deprotection of the N-Boc group without the addition of acid. Starting from 5.0-9.6 GBq [^{18}F]fluoride, **[^{18}F]1.154** was produced in a decay-corrected radiochemical yield of 20%, with a specific activity of 100 GBq μmol^{-1}. PET studies were undertaken in rhesus monkey, showing that **[^{18}F]1.154** had high brain uptake, high specificity for mGluR1 and faster washout kinetics than related mGluR1 radiotracers.



Scheme 1.31. Synthesis of diaryliodonium **1.153** and subsequent synthesis of [^{18}F]FIMX **[^{18}F]1.154**

Raffel and co-workers used ^{18}F-fluorination of a diaryliodonium salt in their second synthesis of 4-[^{18}F]fluoro-*m*-hydroxyphenethylguanidine **[^{18}F]1.159** for the imaging of presynaptic sympathetic nerve terminals in the heart.[130] The initial synthesis, based on S_NAr of trimethylammonium salt **[^{18}F]1.155** followed by five post-labelling steps, afforded **[^{18}F]1.159** in 1%-2% decay-corrected radiochemical yield, with a specific activity of 11-19 GBq μmol^{-1} (Scheme 1.32a).[131] In a second publication, Raffel and co-workers disclosed an attempt to prepare **[^{18}F]1.159** via ^{18}F-fluorination of iodonium salts **1.160** (Scheme 1.32b). Despite screening a variety of [^{18}F]fluoride elution conditions, additives, solvents and heating methods, **[^{18}F]1.161** was not observed. The authors suggested that this may be due to instability of iodonium salts **1.160** at the elevated temperatures required for ^{18}F-fluorination. The simpler iodonium salt **1.162** was prepared and successfully ^{18}F-fluorinated when Cs_2CO_3 was used to elute the [^{18}F]fluoride (Scheme 1.32c). Both TEMPO and a small amount of water were required in order to achieve good RCYs.



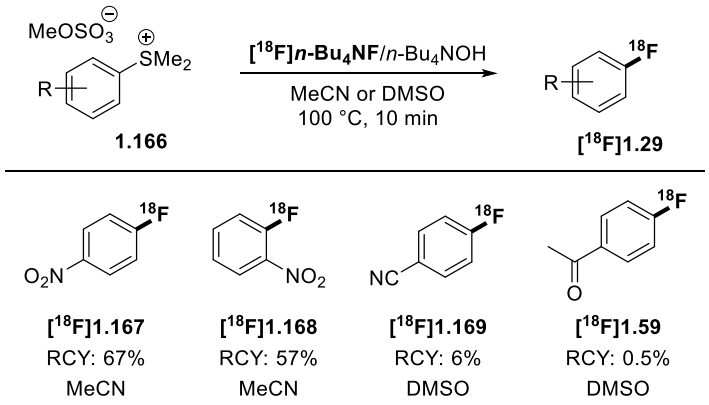
Scheme 1.32. a) Initial synthesis of **[^{18}F]1.159** based on SNAr. **b)** Attempted synthesis of **[^{18}F]1.159** via ^{18}F-fluorination of iodonium salt **1.160**. **c)** Improved synthesis of **[^{18}F]1.159** via initial ^{18}F-fluorination of diaryliodonium **1.162**

[^{18}F]1.159 was prepared in an automated procedure which required two GE TracerLab modules to be linked in series. In the first module, cyclotron-produced [^{18}F]fluoride was eluted from an anion exchange cartridge with Cs_2CO_3 and azeotropically dried. Heating the [^{18}F]CsF/Cs_2CO_3 with iodonium precursor **1.162**, TEMPO and water in DMF at 150 °C for 25 minutes afforded **[^{18}F]1.163**. The authors commented that radiochemical yields for this step were less than half of those

obtained manually. The *N*-Boc group was then hydrolysed to afford free amine **[^{18}F]1.164** in 15% RCY (d.c.) over two steps. After a C_{18} purification cartridge, **[^{18}F]1.164** was transferred to the second module. The guanidine group was introduced using transfer reagent **1.165**, after which the *O*-Bn and *N*-Boc groups were deprotected with HBr. Starting from 52 GBq [^{18}F]fluoride, 2.0 to 4.6 GBq **[^{18}F]1.159** was produced after HPLC purification, corresponding to a decay-corrected radiochemical yield of 7% over four steps. Specific activity was 44 GBq μmol^{-1}. The authors suggested that this was due to the relatively long synthesis time and that further optimisation was necessary.

1.4.2.4 ^{18}F-Fluorination of Sulfonium Salts and Sulfoxides

In 1987, Maeda and co-workers described the ^{18}F-fluorination of electron-deficient arenes via nucleophilic displacement of a dimethylsulfonium group with [^{18}F]*n*-Bu_4NF/*n*-Bu_4NOH complex (Scheme 1.33).[132] Whilst [^{18}F]fluoronitroarenes **[^{18}F]1.167** and **[^{18}F]1.168** could be prepared from the corresponding aryldimethylsulfonium methylsulfates **1.166** in high RCYs, less electron-deficient [^{18}F]fluoroarenes **[^{18}F]1.169** and **[^{18}F]1.59** were formed in only 6% and 0.5% RCY, respectively. In these cases, [^{18}F]fluoromethane was believed to be the main product. The authors commented that this method was inferior to the nucleophilic displacement of a nitro or trimethylammonium group, especially given the difficulty of installing the dimethylsulfonium group into a complex molecule.



Scheme 1.33. ^{18}F-Fluorination via nucleophilic displacement of dimethylsulfonium salts

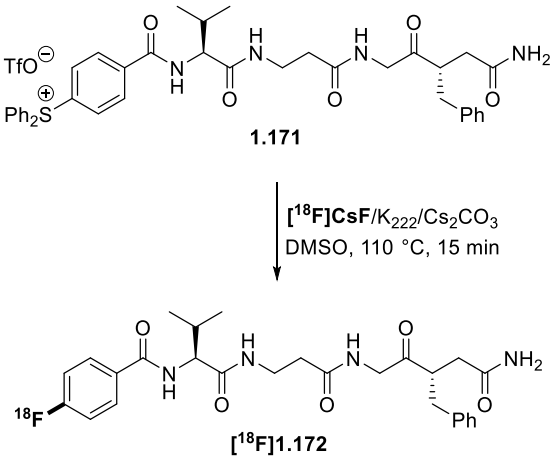
In 2012, Ametamay and co-workers disclosed their work on the use of triarylsulfonium salts as leaving groups in nucleophilic ^{18}F-fluorination of electron-neutral arenes.[133] Heating aryldiphenylsulfonium triflates **1.170** at 80-90 °C in MeCN, DMF or DMSO with either [^{18}F]KF/K_{222}/K_2CO_3 or [^{18}F]CsF/K_{222}/Cs_2CO_3 afforded [^{18}F]fluoroarenes **[^{18}F]1.56** (Table 1.10). The selectivity of the reaction was determined experimentally, with DFT calculations confirming that nucleophilic attack of fluoride should occur at the ipso carbon of the most electron-deficient aromatic ring. 4-[^{18}F]Fluoroiodobenzene was prepared in high RCC (entry 2), whilst that of 4-[^{18}F]fluorobromobenzene was lower (entry 3). 4-[^{18}F]Fluorotoluene and 4-[^{18}F]fluoroanisole could not be prepared in this way, since [^{18}F]fluorobenzene was formed in preference (entries 4 and 5). When the reaction was carried out on a 2.3 GBq scale, the specific activity of the 4-[^{18}F]fluoroiodobenzene produced was measured to be 5 GBq μmol^{-1}.



Entry	R	Solvent	RCC / % (n = 3)	
			[18F]1.56	[18F]1.37
1	H	DMF	70 ± 7	
2	I	MeCN	91 ± 1	7 ± 1
3	Br	MeCN	36 ± 1	6 ± 1
4	Me	DMF	2 ± 1	10 ± 3
5	MeO	DMF	0	71 ± 4

Table 1.10. ^{18}F-Fluorination via nucleophilic displacement of diphenylsulfonium salts

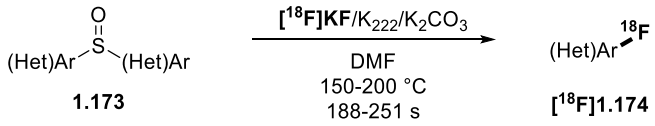
The authors were pleased to discover that the method was suitable for the ^{18}F-fluorination of more complex molecules, as exemplified by tetrapeptide **[^{18}F]1.172**, prepared from sulfonium triflate **1.171** (Scheme 1.34).



Scheme 1.34. Synthesis of tetrapeptide **[^{18}F]1.172** from sulfonium triflate **1.171**

Pike and co-workers demonstrated that aryl sulfoxides can also be used as leaving groups in nucleophilic ^{18}F-fluorination.[134] Initially, symmetrical di(hetero)arylsulfoxides **1.173** were heated in a microreactor with [^{18}F]KF/K_{222}/K_2CO_3 complex in DMF. The flow rate and temperature were varied to optimise the RCC for each substrate. Highly electron-deficient substrates bearing

para-nitro, cyano or trifluoromethyl groups afforded the corresponding [^{18}F]fluoroarenes in high RCCs (Table 1.11, entries 1-3), as did the 2- and 4-pyridyl substrates (entries 7 and 9). Less activated substrates afforded [^{18}F]fluoroarenes in lower RCCs (entries 4-6, 8) or did not afford the desired products at all (entries 10-12). The authors were surprised to observe no competing displacement of the nitro group, despite its well-known use as a leaving group in nucleophilic substitutions with [^{18}F]fluoride.

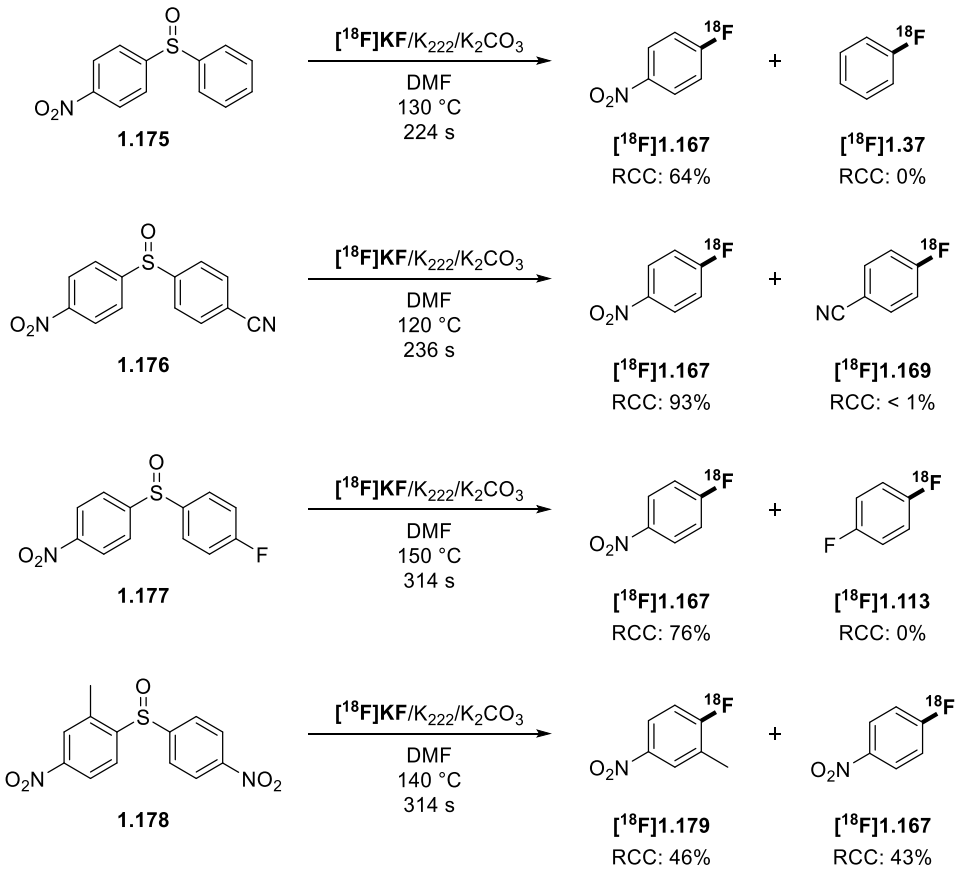


Entry	(Het)Ar	RCC / %
1	4-NO_2-C_6H_4	91
2	4-CN-C_6H_4	82
3	4-CF_3-C_6H_4	66
4	4-F-C_6H_4	21
5	4-Br-C_6H_4	7
6	3-NO_2-C_6H_4	2
7	4-pyridyl	94
8	3-pyridyl	4
9	2-pyridyl	68
10	Ph	0
11	4-Me-C_6H_4	0
12	4-MeO-C_6H_4	0

Table 1.11. ^{18}F-Fluorination of symmetrical di(hetero)arylsulfoxides

The authors then investigated unsymmetrical diarylsulfoxide substrates. When one aryl group bore a para-nitro group and the other did not, the para-[^{18}F]fluoronitrobenzene was always formed selectively (Scheme 1.35). For substrate **1.178** bearing an ortho-methyl group on one ring, the distribution of

[^{18}F]fluoronitrobenzene products **[^{18}F]1.167** and **[^{18}F]1.155** was approximately equal, showing that there is no "ortho effect", as is observed with diaryliodonium salts.

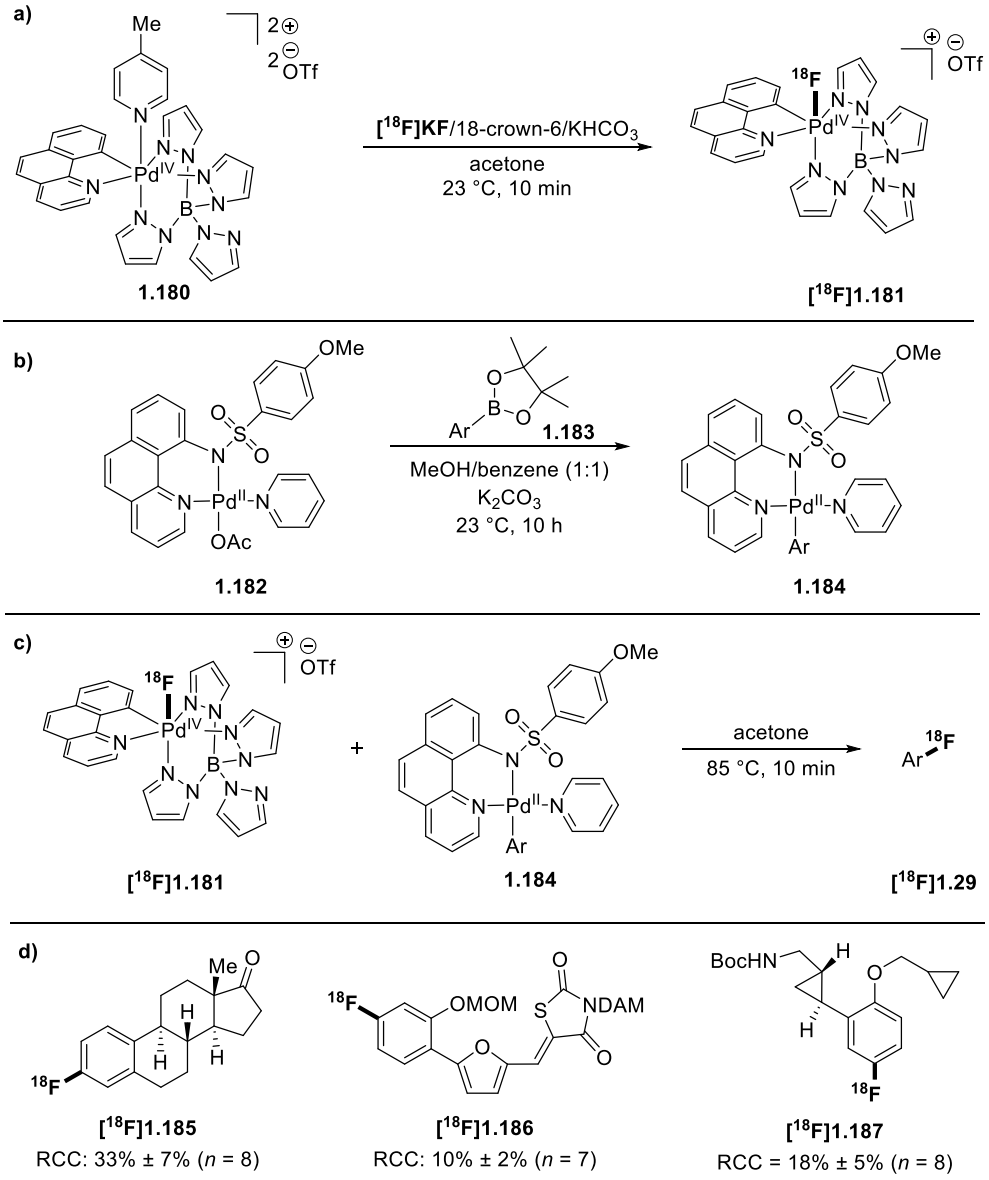


Scheme 1.35. ^{18}F-Fluorination of unsymmetrical diarylsulfoxides

The nucleophilic substitution of arylsulfonium salts or arylsulfoxides with [^{18}F]fluoride appears to have very similar characteristics to substitution of a nitro, halide or trimethylammonium leaving group. The method chosen for the ^{18}F-labelling of an aryl fluoride with an appropriately-positioned activating group is likely to be determined by the relative ease of synthesis of the potential precursors.

1.4.2.5 ^{18}F-Fluorination from Preformed Organometallic Complexes

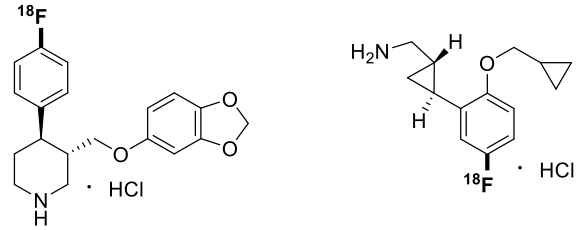
In 2011, Ritter, Hooker and co-workers disclosed an ingenious solution to the problem of low specific activity in electrophilic fluorination.[135] Whilst it is not feasible to directly oxidise [^{18}F]fluoride to [^{18}F]F_2, the authors designed an organometallic system which reacted with [^{18}F]fluoride to provide an electrophilic source of ^{18}F. Highly fluorophilic Pd(IV) complex **1.180** reacts with [^{18}F]fluoride to form Pd(IV) complex **[^{18}F]1.181** (Scheme 1.36a). This species is electrophilic, but the cleverly designed ligand system means that the only low-energy orbital that can be attacked by a nucleophile is the Pd–F σ* orbital. Nucleophilic attack occurs in an effective S_N2 reaction at fluorine, with loss of a Pd(II) complex as the leaving group. The nucleophiles required are arylpalladium(II) complexes **1.184**, prepared from arylboronic esters **1.183** (Scheme 1.36b). The authors report that these complexes can be purified by silica gel chromatography or recrystallisation, and are stable under air at ambient temperature. Reaction of crude complex **[^{18}F]1.181** with complexes **1.184** in acetone at 85 °C for 10 minutes affords the desired [^{18}F]fluoroarenes **[^{18}F]1.29** (Scheme 1.36c). In this reaction, complex **[^{18}F]1.181** is acting as an electrophilic [^{18}F]fluorine source and oxidises complex **1.184** to a Pd(IV) complex which reductively eliminates the [^{18}F]fluoroarene product. Molecules prepared in this way include electron-rich [^{18}F]fluoroarenes **[^{18}F]1.185**-**[^{18}F]1.187** (Scheme 1.36d). **[^{18}F]1.185** was prepared on a 37 GBq scale, and an aliquot was purified by preparative HPLC. The specific activity was measured to be 38 GBq μmol^{-1} and the level of residual palladium was only 5 ppb, well below the recommended guidelines.



Scheme 1.36. Fluoride umpolung strategy of Ritter and co-workers. **a)** Reaction of fluorophilic Pd(IV) complex **1.180** with [18F]fluoride to afford Pd(IV) complex **[18F]1.181**. **b)** Preparation of Pd(II) complex nucleophiles from aryl boronic esters **1.183**. **c)** Reaction of Pd(IV) complex **[18F]1.181** and Pd(II) complexes **1.184** to afford [18F]fluoroarenes **[18F]1.29**. **d)** 18F-Labelled molecules prepared by the reaction in c).

A follow-up paper concerned the scale-up of this methodology for the production of PET tracers.[136] The SSRI antidepressant paroxetine was successfully 18F-labelled starting from an appropriately-protected arylboronic ester-derived Pd(II) complex. Starting from approximately 37 GBq cyclotron-produced [18F]fluoride, > 370 MBq [18F]paroxetine **[18F]1.188** was produced after

^{18}F-incorporation, deprotection, purification and formulation, corresponding to an uncorrected radiochemical yield > 1% (Figure 1.6). The specific activity was as high as 480 GBq μmol^{-1}. Enough **[^{18}F]1.188** was produced to undertake a PET study in baboons. Brain penetration was modest, washout kinetics were slow and there was a high degree of nonspecific binding. Nevertheless, the authors suggested that further studies were warranted to evaluate the human brain pharmacokinetics and distribution.



[^{18}F]1.188
> 370 MBq
RCY: > 1% (n.d.c)
SA: Up to 480 GBq μmol^{-1}

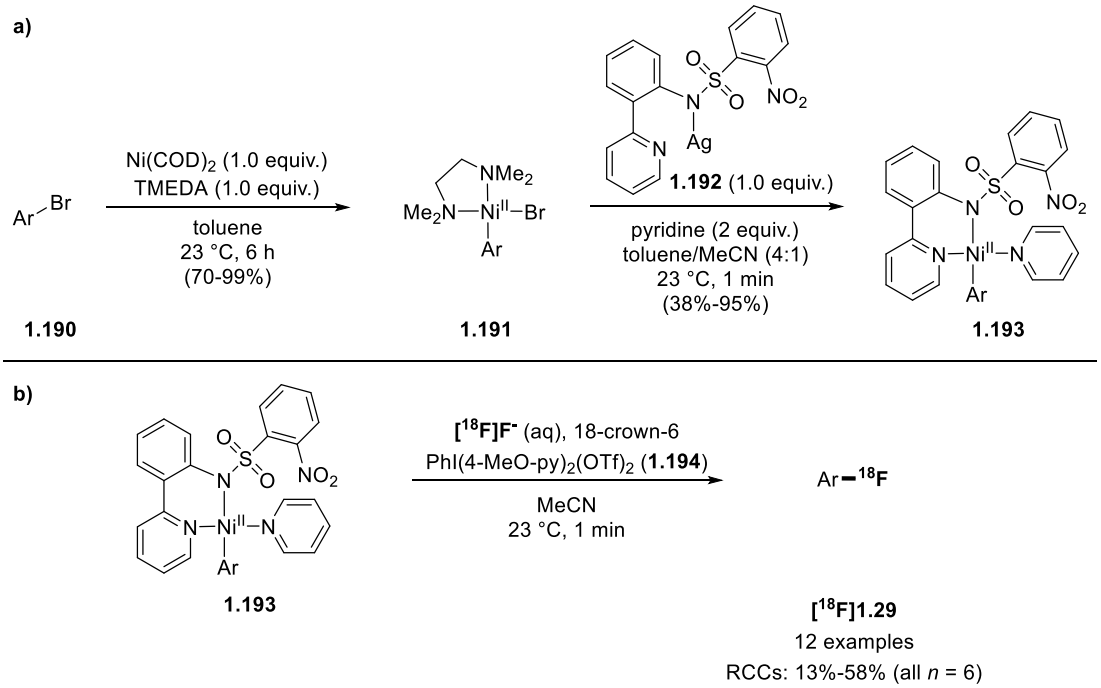
[^{18}F]1.189
> 370 MBq
RCY: > 1% (n.d.c)
SA: 37 GBq μmol^{-1}

Figure 1.6. ^{18}F-Labelled paroxetine **[^{18}F]1.188** and potential 5-HT$_{2c}$ radioligand **[^{18}F]1.189** prepared using the fluoride umpolung strategy

Using the same method, **[^{18}F]1.189** was also synthesised as a potential 5-HT$_{2c}$ radioligand. Starting from approximately 37 GBq cyclotron-produced [^{18}F]fluoride, > 370 MBq **[^{18}F]1.189** was produced (> 1% RCY), with a specific activity of 37 GBq μmol^{-1}. A PET study in baboons revealed that **[^{18}F]1.189** had excellent brain penetration and suitable metabolic stability, with modest specific binding to 5-HT$_{2c}$ receptors.

In 2012, Lee, Hooker and Ritter reported another ^{18}F-fluorination method starting from preformed organometallic complexes.[137] In this case, Ni(II)

complexes **1.193** were first prepared in generally high yields in a two-step sequence from aryl bromides **1.190** (Scheme 1.37a). $Ni(COD)_2$ is very air sensitive, thus access to a glovebox and skill in organometallic chemistry would be required for synthesis of the labelling precursors. However, these Ni(II) complexes **1.181** were purified by silica gel chromatography and were reported to be stable to air and moisture. In the presence of iodine(III) oxidant **1.194**, Ni(II) complexes **1.193** reacted rapidly with [^{18}F]fluoride to afford [^{18}F]fluoroarenes **[^{18}F]1.29** (Scheme 1.37b). Electron-rich, electron-neutral and electron-deficient arenes were all suitable substrates. RCCs ranged from 13% to 58%. Ethers, ketones, esters and carbamates were tolerated, as was a primary amide. The authors commented that tertiary amines were not tolerated, presumably due to a side reaction with oxidant **1.194**.



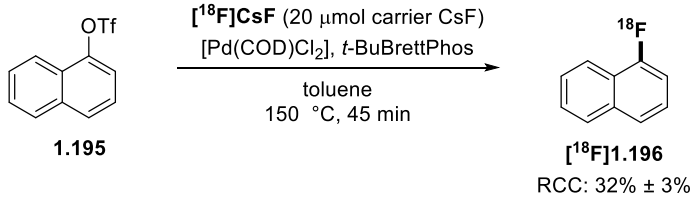
Scheme 1.37. ^{18}F-Fluorination of preformed arylnickel(II) complexes **1.193**. **a)** Preparation of labelling precursors from aryl bromides **1.190**. **b)** Rapid reaction of complexes **1.193** with cyclotron-produced [^{18}F]fluoride to afford [^{18}F]fluoroarenes **[^{18}F]1.29**.

The reaction tolerated small amounts of water; on a small scale, the ^{18}F-fluorination can be carried out in a 99:1 mixture of acetonitrile and target water, rendering azeotropic drying unnecessary. However, this would not be the case if the reaction was scaled up to higher activities for the production of radiotracers, unless [^{18}F]fluoride could be produced as an extremely concentrated aqueous solution.

1.4.2.6 Palladium-Catalysed ^{18}F-Fluorination of Aryl Triflates

Formation of C–F bonds via reductive elimination from phosphine-ligated arylpalladium(II) fluoride complexes is extremely challenging due to competing C–P and P–F bond forming processes.[138] In 2009, Buchwald and co-workers disclosed a solution to this problem via the use of a very bulky biaryl monophosphine ligand.[139] This system enabled the palladium-catalysed fluorination of aryl triflates. Most of the reactions were carried out for 12 hours using two equivalents of CsF. The authors showed that increasing the amount of CsF to six equivalents could reduce the reaction times to 30 minutes. In 2012, Cardinale et al. published their attempts to translate this method to ^{18}F-radiochemistry.[140] Using 20 μmol carrier Cs^{19}F, 1-[^{18}F]fluoronaphthalene **[^{18}F]1.184** could be formed in radiochemical conversions of up to 32% (Scheme 1.38). However, in the absence of carrier, none of the desired product was observed. Since the objective was to develop a no-carrier-added method for the synthesis of

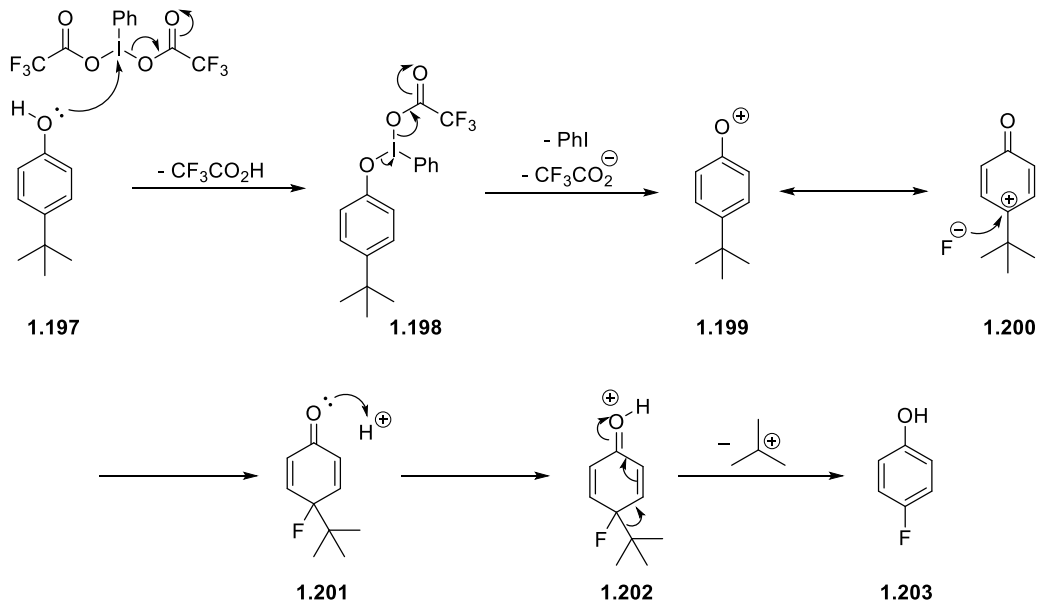
[^{18}F]fluoroarenes in high specific activity, further investigations were not carried out.



Scheme 1.38. Carrier-added palladium-mediated ^{18}F-fluorination of aryl triflate **1.195**

1.4.2.7 Metal-Free Oxidative ^{18}F-Fluorination of *tert*-Butyl Phenols

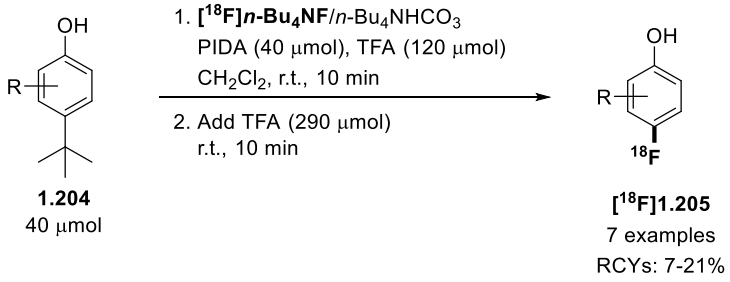
The strategy developed by Ritter and co-workers in section 1.4.2.5 involved the preparation of a source of electrophilic fluorine-18 from [^{18}F]fluoride i.e. "fluoride umpolung". In 2012, Gouverneur and co-workers disclosed a complementary strategy for the ^{18}F-fluorination of electron-rich arenes via "substrate umpolung".[141] This was based on earlier work by Langlois and co-workers, who had shown that the combination of $Et_3N.3HF$ and bis(trifluoroacetoxy)iodobenzene (PIFA) could be used to transform 4-*tert*-butylphenol **1.197** into 4-fluorophenol **1.203**.[142] This reaction was proposed to proceed via initial oxidation of phenol **1.197** by PIFA to phenoxenium ion **1.199**, which was attacked in the "para"-position by fluoride to form cyclohexadienone **1.201** (Scheme 1.39).[143] Protonation and loss of a *tert*-butyl cation under acidic conditions allowed re-aromatisation, affording 4-fluorophenol **1.203**.



Scheme 1.39. Proposed mechanism for oxidative fluorination of 4-*tert*-butylphenol **1.197**

Use of $Et_3N.3HF$ in ^{18}F-radiochemistry would lead to formation of [^{18}F]fluorophenol products in very low specific activity due to the presence of a large amount of ^{19}F carrier. Gouverneur and co-workers showed that high specific activity ^{18}F-fluorination could be achieved when $Et_3N.3HF$ was replaced with the [^{18}F]fluoride complexes [^{18}F]*n*-Bu_4NF/*n*-Bu_4NHCO_3 or [^{18}F]$KF/K_{222}/K_2CO_3$. A one-pot, two-step sequence was employed; initial reaction of 4-*tert*-butylphenols **1.204** with the [^{18}F]fluoride complex, trifluoroacetic acid and diacetoxyiodobenzene (PIDA) in CH_2Cl_2 at room temperature for 10 minutes was followed by addition of more trifluoroacetic acid to initiate re-aromatisation via loss of the *tert*-butyl cation to form 4-[^{18}F]fluorophenols **[^{18}F]1.205** (Scheme 1.40). [^{18}F]*n*-Bu_4NF/*n*-Bu_4NHCO_3 gave cleaner reactions than [^{18}F]$KF/K_{222}/K_2CO_3$, so this was used for an evaluation of substrate scope. Decay-corrected radiochemical yields of isolated [^{18}F]fluorophenols **[^{18}F]1.205** ranged from 7%-21%, and aryl bromide, ketone and vinylogous ester functionality was shown to be tolerated. The authors also showed

that 2-bromo-4-[^{18}F]fluorophenol synthesised in this way had a specific activity of 420 GBq μmol^{-1} and could undergo subsequent Suzuki-Miyaura cross coupling with phenylboronic acid in a methanol/water mixture. Whilst the method offers a means to prepare 4-[^{18}F]fluorophenols in high specific activity, the radiochemical yields are relatively low. More significantly, the tert-butyl group is relatively difficult to introduce into complex substrates and so is not an ideal precursor group for ^{18}F-fluorination.



Scheme 1.40. Oxidative ^{18}F-fluorination of 4-*tert*-butylphenols to afford 4-[^{18}F]fluorophenols

1.5 Conclusions and Thesis Outline

Over the past forty years, much work has been undertaken in developing methods for the ^{18}F-fluorination of arenes. However, the ease with which a fluoroarene can be ^{18}F-labelled is heavily dependent on the structure of the molecule, particularly on the electronic properties of the fluoroarene ring itself. Electron-deficient fluoroarenes bearing a strongly electron-withdrawing group in a position ortho or para to the site of ^{18}F-fluorination tend to be excellent substrates for nucleophilic aromatic substitution with [^{18}F]fluoride. This reaction is well-understood within the radiochemistry community and tends to deliver [^{18}F]fluoroarenes in moderate to high radiochemical yields and high specific activities. However, many fluoroarenes of interest for ^{18}F-labelling do not fit into this category. Reaction of appropriately-designed diaryliodonium salt precursors with [^{18}F]fluoride offers a potential solution for these molecules. Whilst a more electronically-diverse range of [^{18}F]fluoroarenes can be produced in this way, diaryliodonium salts are not without drawbacks. Preparation of the salts requires oxidising conditions which may not be compatible with functional groups in a complex molecule. In addition, for the labelling of an electron-rich fluoroarene, the auxiliary (hetero)aryl group of the iodonium precursor must be more electron-rich; such iodonium salts suffer from instability.

Electrophilic approaches form an important area of ^{18}F-radiochemistry methodology. Whilst unselective direct C–H ^{18}F-fluorination is no longer used, ^{18}F-fluorodestannylation remains the most important method for the clinical

production of [^{18}F]FDOPA. The synthesis of more selective electrophilic ^{18}F-fluorinating reagents such as [^{18}F]NFSI and [^{18}F]Selectfluor provides opportunities to translate fluorination methods developed more recently to ^{18}F-radiochemistry. However, all electrophilic ^{18}F-fluorination methods involve the use of $^{19}F_2$ as a carrier and therefore cannot provide [^{18}F]fluoroarenes in high specific activity. Whilst post-target production of [^{18}F]F_2 provides specific activities up to 55 GBq μmol^{-1}, radiotracers produced in this way exhibit only medium specific activities of 2-20 GBq μmol^{-1}. Even if high specific activity is not required, the high chemical reactivity of [^{18}F]F_2 necessitates the construction of highly specialised facilities, which are not available at many PET centres.

The fluoride umpolung and substrate umpolung approaches developed during the last ten years offer novel means to access electron-rich [^{18}F]fluoroarenes in high specific activity. There has not yet been a wide uptake of these methods within the ^{18}F-radiochemistry community; nonetheless, they illustrate a growing trend of organic and organometallic chemistry research groups joining more established radiochemistry groups in attempting to develop novel methods for ^{18}F-labelling. This is driven in no small part by increased interest from pharmaceutical companies in using PET to provide key information to facilitate aspects of drug discovery. The prevalence of fluoroarene moieties within drug candidates remains high; thus, the ability to prepare complex, electronically-diverse [^{18}F]fluoroarenes is of great importance.

This thesis aims to develop a new method for the synthesis of [^{18}F]fluoroarenes from precursors more stable and more easily-prepared than diaryliodonium salts. Whilst it would be desirable to have as broad a substrate scope as possible, facile access to electron-rich and electron-neutral [^{18}F]fluoroarenes not amenable to nucleophilic aromatic substitution with [^{18}F]fluoride is of the highest importance. Chapter 2 describes the development of a copper-mediated ^{18}F-fluorodeboronation reaction, enabling access to electron-rich, electron-neutral and electron-deficient arenes via reaction of arylboronic ester precursors with [^{18}F]fluoride and a commercially-available copper complex. Applicability of the method to radiotracer targets of clinical importance is demonstrated. Chapter 3 reports the design and use of an additive screening experiment for determination of the compatibility of heterocycles, and ultimately complex targets, with the ^{18}F-fluorodeboronation. This aims to guide the retro-radiosynthetic analysis of complex targets bearing multiple heterocyclic motifs and to provide a degree of confidence that ^{18}F-fluorodeboronation will be successful before resources are invested in precursor synthesis.

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Chapter 2

Copper-Mediated Nucleophilic ^{18}F-Fluorination of Arenes

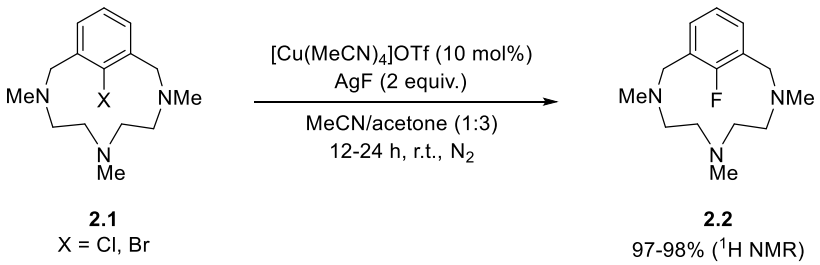
Chapter 2: Copper-Mediated Nucleophilic ^{18}F-Fluorination of Arenes

2.1 Copper-Mediated Fluorination of Arenes

As discussed in Chapter 1, prior to this work, reactions mediated by silver, palladium and nickel had been used in the synthesis of [^{18}F]fluoroarenes. However, despite several reports on the use of copper complexes to synthesise fluoroarenes, this approach had not been translated to ^{18}F-radiochemistry.

2.1.1 Fluorination of Macrocyclic Arenes

In 2011, Ribas and co-workers disclosed the first example of Cu(III)/Cu(I) reductive elimination to form an aryl C–F bond.[1] Via design of a chelating system, Ribas demonstrated a quantitative halide exchange reaction mediated by a Cu(I) catalyst (Scheme 2.1).



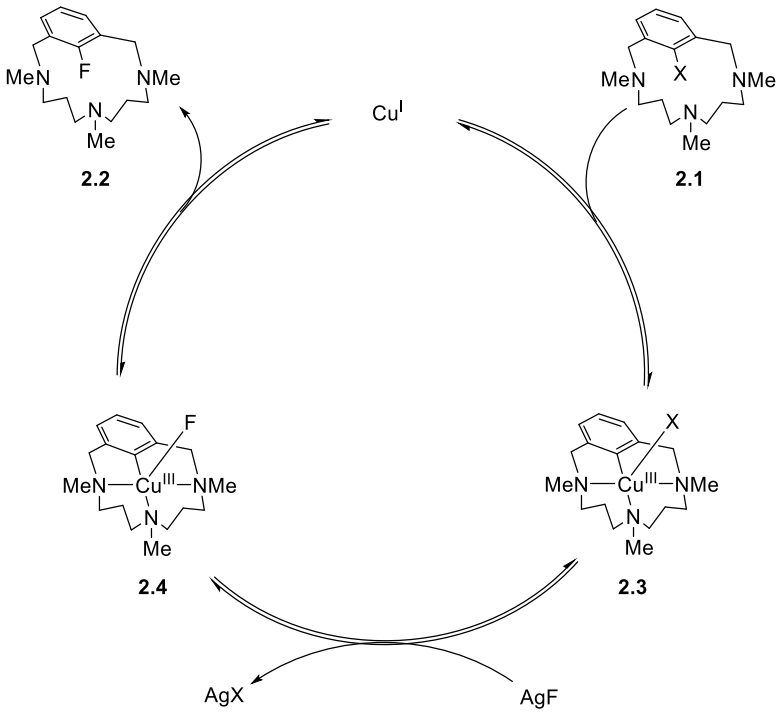
2.1
X = Cl, Br

2.2
97-98% (^{1}H NMR)

Scheme 2.1. First example of Cu(III)/Cu(I) reductive elimination to form an aryl C–F bond

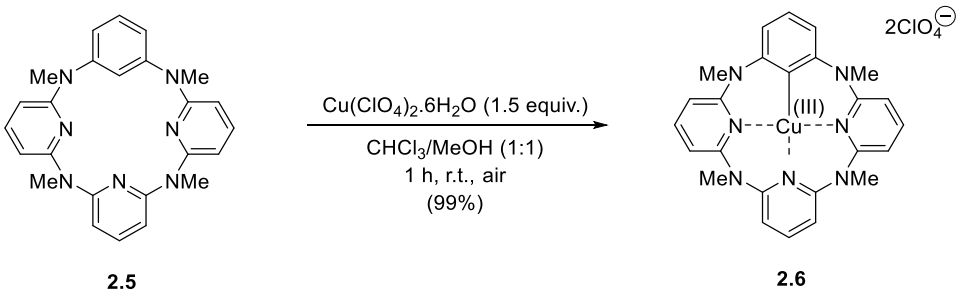
The proposed catalytic cycle consisted of oxidative addition of aryl halide **2.1** to Cu(I), followed by halide exchange to form key Cu(III)–F complex **2.4** and reductive elimination to regenerate the Cu(I) catalyst, with concomitant formation of the desired C–F bond (Scheme 2.2). DFT calculations showed that the desired

C–F reductive elimination is favoured, with only a small activation barrier, to form lower-energy products. This contrasts with the corresponding Cu(III)–Cl system, which was found to have a much higher barrier to reductive elimination and higher energy products.



Scheme 2.2. Proposed catalytic cycle for the Cu-mediated aryl halide exchange

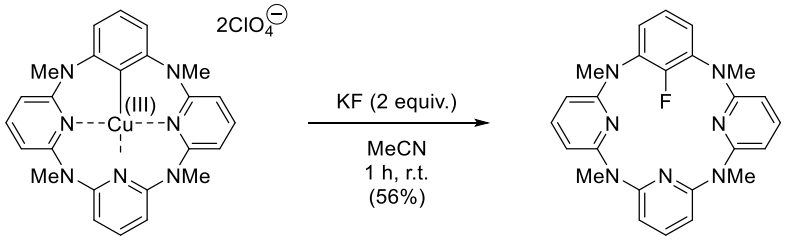
Subsequently, Wang and co-workers reported the first fluorination of an isolated organocopper(III) complex.[2] Previous studies in the group had focused on the formation of complex **2.6** from azacalixarene **2.5** and $Cu(ClO_4).6H_2O$ via a C–H activation process (Scheme 2.3), and the subsequent reaction of the isolated complex with nucleophiles including Cl^-, Br^-, I^-, CN^-, SCN^- and AcO^-.[3]



2.5 **2.6**

Scheme 2.3. Synthesis of isolable copper(III) complex **2.6**

In 2012, the Wang group described fluorination of complex **2.6** using two equivalents of KF in refluxing acetonitrile (Scheme 2.4). The work of the Ribas and Wang groups on these macrocyclic systems demonstrated the feasibility of reductive elimination from Cu(III)–F complexes to form aryl C–F bonds.



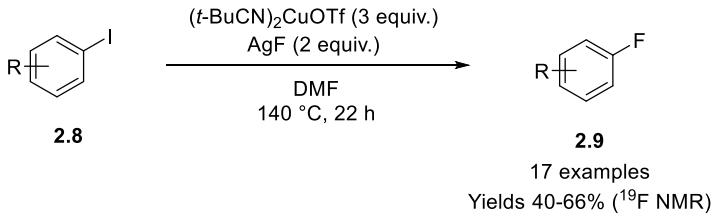
2.6 **2.7**

Scheme 2.4. Fluorination of copper(III) complex **2.6**

2.1.2 Fluorination of Simple Arenes

In 2012, Hartwig disclosed a Cu-mediated method for the formation of simple fluoroarenes **2.9** from iodoarenes **2.8** (Scheme 2.5).[4] Although excess Cu(I) was required, NMR yields were generally good and tolerance of ether, aldehyde, ketone, ester, amide and protected indole functionality was demonstrated. A hydro-dehalogenation by-product was observed; deuterium labelling experiments

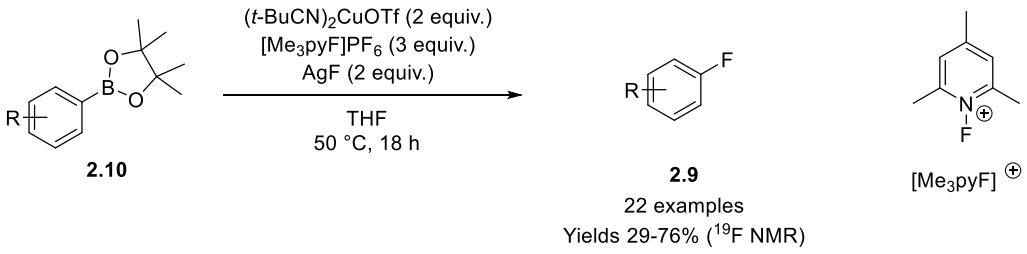
showed one source of this to be adventitious water. Whilst rigorous exclusion of water allowed formation of the hydro-dehalogenation product to be minimised, the authors emphasised the difficulty of separating this from the desired fluorinated product, a possible explanation for the reporting of only a single isolated yield. Mechanistic experiments suggested that radical and benzyne pathways were highly unlikely, supporting a mechanistic pathway mirroring that proposed by Ribas, in which reductive elimination from a Cu(III) fluoride complex was the key step.



Scheme 2.5. Cu-mediated halide exchange

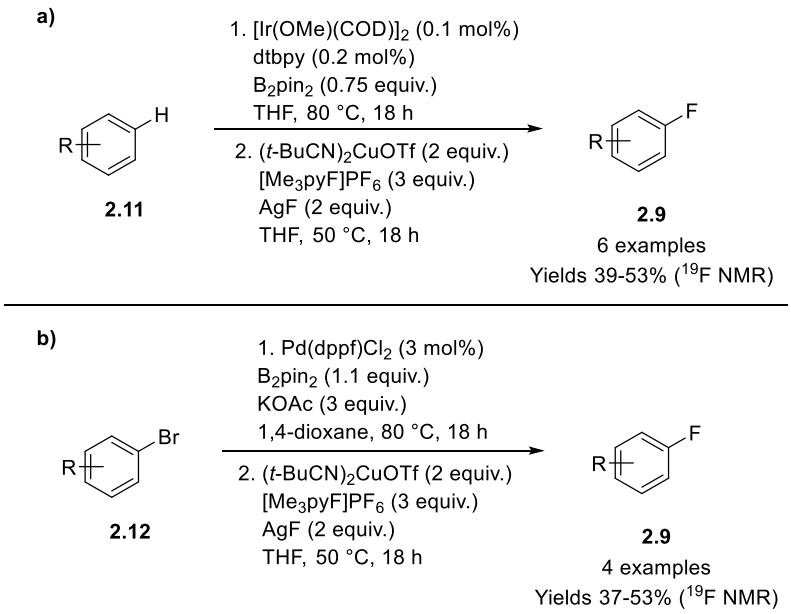
The following year, Hartwig demonstrated that aryl boronate esters could be used as substrates in a similar copper-mediated fluorodeboronation reaction, providing that an electrophilic source of fluorine was employed (Scheme 2.6).[5] Both $[Me_3pyF]PF_6$ and AgF were shown to be important for formation of the desired fluorinated product over a protodeboronation side product. The optimum conditions were considerably milder than those of the halide exchange, resulting in improved tolerance of functional groups, including aryl nitriles, chlorides, bromides and even iodides (Scheme 2.6). A screen of boronic acid derivatives showed that pinacol boronate esters **2.10** afforded the desired fluorinated products in the highest yield, as well as one of the best selectivities for fluorination over

protodeboronation. Boronic acids, trifluoroborates, MIDA boronates and neopentyl glycol boronates were also shown to react. Catechol boronates resulted only in protodeboronation.



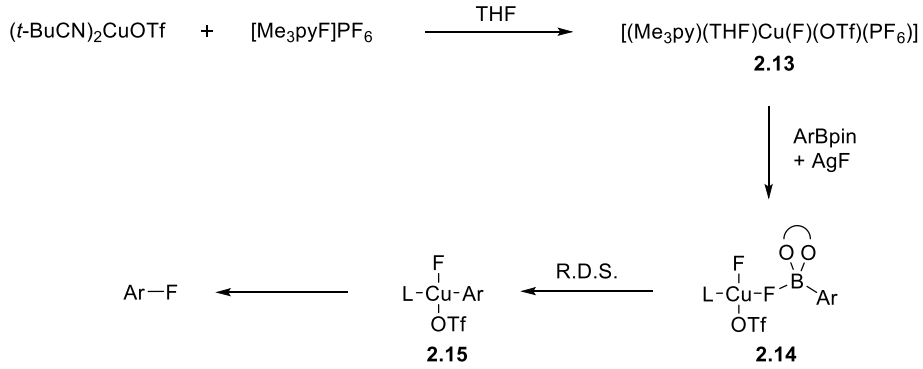
Scheme 2.6. Cu-mediated fluorodeboronation

In addition, Hartwig disclosed one-pot, two-step C–H and C–Br fluorinations via initial Ir- and Pd-catalysed borylation respectively (Scheme 2.7). This emphasises the value of boronic esters as substrates; their accessibility is a key advantage.



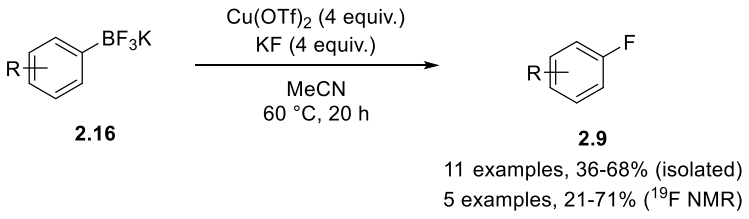
Scheme 2.7. **a)** One pot, two step C–H fluorination. **b)** One pot, two step C–Br fluorination

Mechanistic studies provided evidence against formation of either arylcopper(I) or arylsilver species. Copper(III) fluoride species could not be isolated, but species **2.13** and **2.14** were characterised in solution by NMR, IR and ESI-MS. Hartwig proposed a mechanism as detailed in Scheme 2.8, in which (*t*-BuCN)$_2$CuOTf and [Me$_3$pyF]PF$_6$ first reacted to form THF-coordinated Cu(III) fluoride complex **2.13**. This then reacted with the arylboronate substrate and AgF to form complex **2.14**, which underwent rate-limiting transmetalation of the aryl group from boron to copper to afford arylcopper(III) fluoride complex **2.15**. A rapid reductive elimination afforded the aryl fluoride product.



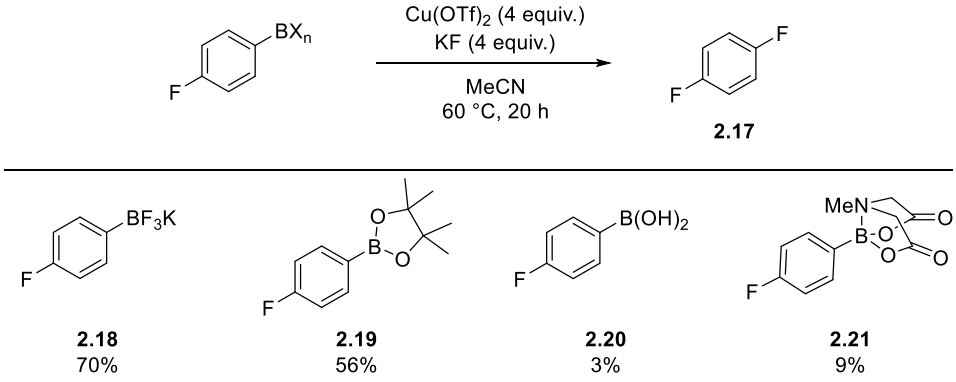
Scheme 2.8. Proposed mechanism for the fluorodeboronation

In 2013, Sanford and co-workers described the fluorodeboronation of aryltrifluoroborates **2.16** *via* reaction with excess Cu(OTf)$_2$ and KF (Scheme 2.9).[6]



Scheme 2.9. Nucleophilic fluorodeboronation with KF

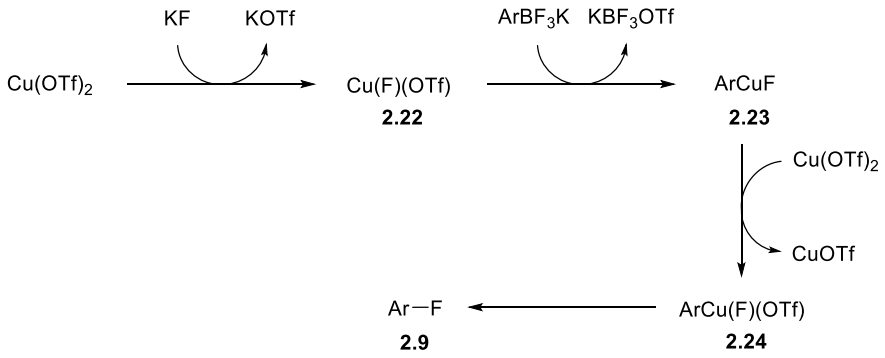
The use of KF, a cheap source of nucleophilic fluoride, represents a notable advance over previous methods. Sanford demonstrated that aryl trifluoroborate salt **2.18** afforded the highest yields of fluoroarene **2.17**, but importantly also showed that pinacol boronic ester **2.19** was nearly as reactive, with boronic acid **2.20** and MIDA boronate **2.21** affording **2.17** in low yields (Scheme 2.10). More isolated yields were given than for previous methods, although some of these were contaminated with approximately 3% of inseparable protodeboronated products. Interestingly, in addition to both electron-rich and electron-deficient aryl trifluoroborates, a pyridine was fluorinated in this way, albeit in low yield (21% by ^{19}F NMR).



Scheme 2.10. Nucleophilic fluorodeboronation with KF

Sanford proposed that superstoichiometric $Cu(OTf)_2$ was required due to a dual role of this species: as oxidant as well as mediator of C–F bond formation. Mechanistically, initial exchange of triflate for fluoride to form Cu(II) species **2.22** would be followed by transmetalation to afford arylcopper(II) fluoride **2.23** (Scheme 2.11). Disproportionation with another molecule of $Cu(OTf)_2$ would generate

CuOTf and the key arylcopper(III) fluoride **2.24**, which would be expected to undergo rapid reductive elimination to afford aryl fluoride **2.9**.



Scheme 2.11. Proposed mechanism for Cu-mediated fluorination of aryl trifluoroborates

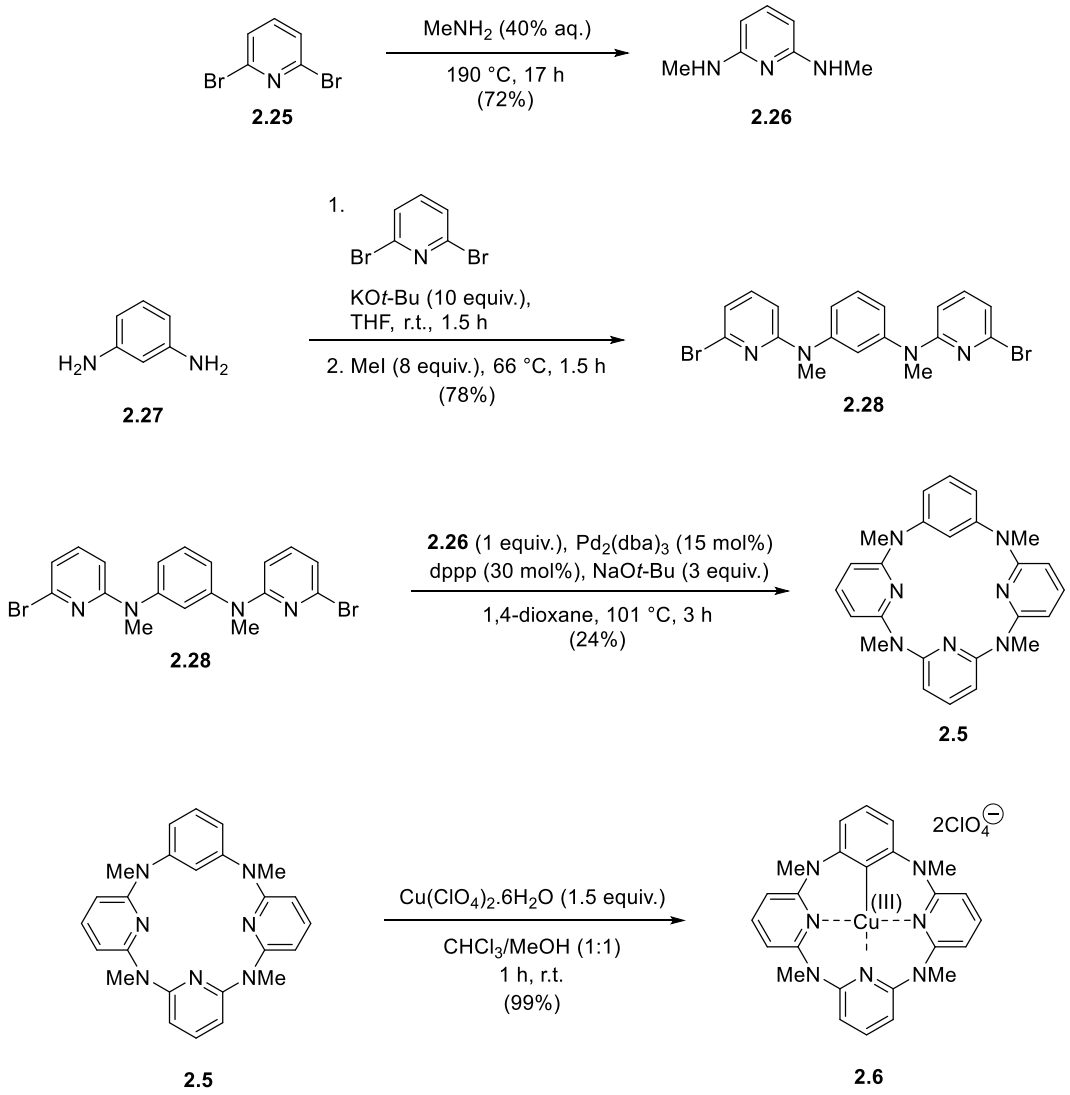
2.2 Development of a Copper-Mediated ^{18}F-Fluorination of Arenes

The literature precedents discussed in section 2.1 provided an excellent starting point for development of an ^{18}F-fluorination of arenes.

2.2.1 ^{18}F-Fluorination of Cu(III) Complex

Our first objective was to demonstrate the feasibility of an ^{18}F-fluorination of arenes based on reductive elimination from a Cu(III)–^{18}F species. In order to do this, Wang's Cu(III) complex **2.6** was synthesised by Dr. Enrico Emer following literature procedures.[3], [7], [8] Diamine **2.26** was first synthesised from 2,6-dibromopyridine **2.25** via treatment with aqueous $MeNH_2$ (Scheme 2.12). Triaryl fragment **2.28** was then synthesised via reaction of diamine **2.27** with 2,6-dibromopyridine **2.25** under basic conditions, followed by methylation. Union of fragments **2.26** and **2.28** by

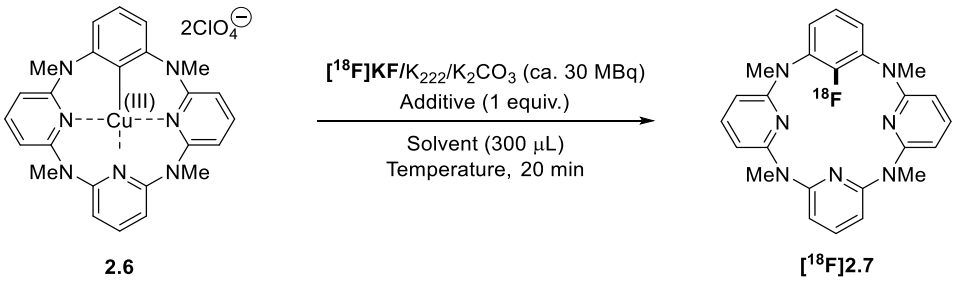
means of Buchwald-Hartwig aminations afforded azacalixarene **2.5**. Reaction with $Cu(ClO_4).6H_2O$ resulted in formation of the Cu(III) complex **2.6**.



Scheme 2.12. Synthesis of Cu(III) complex **2.6** by Dr. Enrico Emer

With complex **2.6** in hand, we began studies towards ^{18}F-fluorination. Reaction of complex **2.6** with [^{18}F]KF/K_{222} in MeCN at 80 °C did not afford any of the desired ^{18}F-fluorinated product **[^{18}F]2.7** after 20 minutes (Table 2.1). Increasing the temperature to 110 °C and changing solvent to DMF was also unsuccessful. At this point, we decided to increase the concentration of fluoride by adding unlabelled fluoride as a "carrier". Addition of one equivalent of fluoride, in the form of the

soluble complex TBAF.2pin, resulted in 16% radiochemical conversion (n = 2) to ^{18}F-fluorinated product **[^{18}F]2.7**. Although carrier-added conditions were required, this suggested that a Cu(III) species could be a viable intermediate in ^{18}F-fluorination of arenes.



2.6 **[^{18}F]2.7**

Entry	Solvent	Temperature	Additive	[^{18}F]2.7 RCC (n = 2)
1	MeCN	80	-	0%
2	DMF	110	-	0%
3	DMF	110	TBAF.2pin	16% ± 1%

Table 2.1. ^{18}F-Fluorination of Cu(III) complex **2.6**

Figure 2.1 shows the radio-HPLC trace of the crude reaction mixture, overlaid with the UV-HPLC trace of authentic **2.7**.

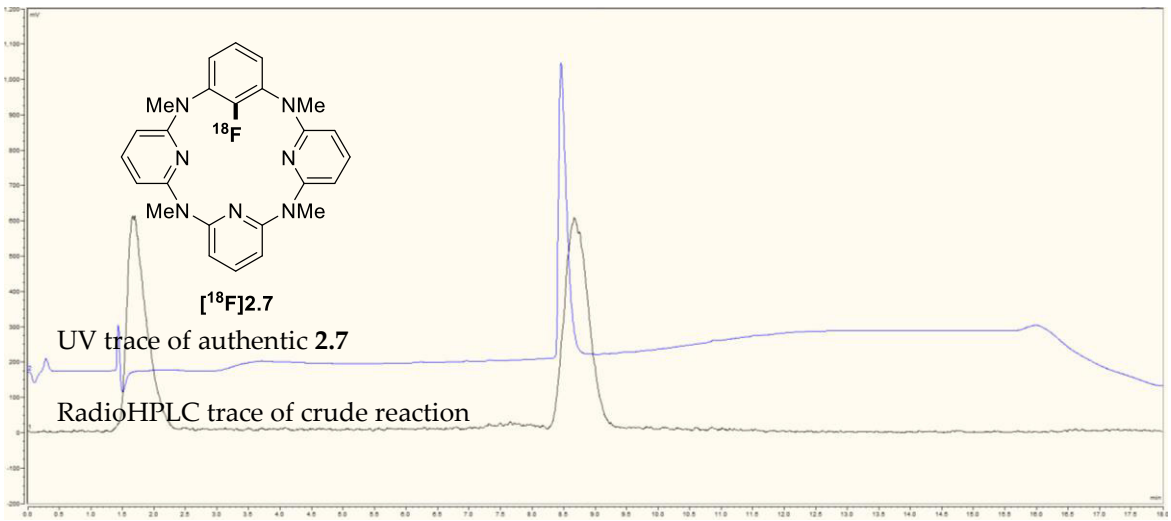
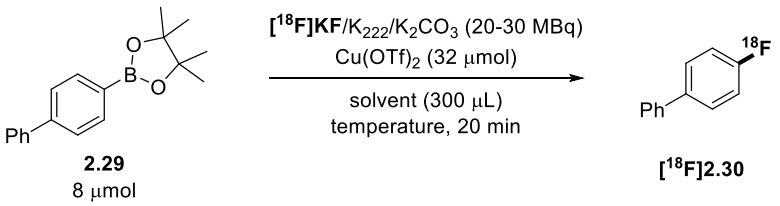


Figure 2.1. Radio-HPLC trace of the crude reaction mixture, overlaid with the UV-HPLC trace of authentic ^{19}F-reference **2.7** to confirm product identity

2.2.2 Initial Optimisation Studies

Optimisation of the reaction conditions was carried out on the model substrate 2-([1,1'-biphenyl]-4-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane **2.29**. In order to maximise the specific activity of the product, all reactions were carried out without the intentional addition of $^{19}F^-$, i.e. a no-carrier-added protocol. Conditions mimicking those used in Sanford's fluorodeboronation (ratio **2.29**:$Cu(OTf)_2$ = 1:4, in MeCN at 60 °C) did not result in formation of the desired product **[^{18}F]2.30** (Table 2.2, entry 1). Raising the temperature to 150 °C and switching solvent to *N*-methylpyrrolidinone (NMP) resulted in formation of **[^{18}F]2.30** in 6% RCC (entry 2). When this result was repeated with a new bottle of $Cu(OTf)_2$, the RCC increased to 22% (entry 3).



2.29
8 μmol

[^{18}F]2.30

Entry	$Cu(OTf)_2$ batch	Solvent	Temperature / °C	[^{18}F]2.30 RCC
1	Original	MeCN	60	0% (n = 2)
2	Original	NMP	150	6% ± 1% (n = 2)
3	New	NMP	150	22% ± 1% (n = 2)

Table 2.2. Initial investigations into the ^{18}F-fluorodeboronation of **2.29**

Figure 2.2 shows the radio-HPLC trace of the crude reaction mixture, overlaid with the UV-HPLC trace of authentic 4-fluorobiphenyl **2.30**. **[^{18}F]2.30** was the sole organic radiolabelled product; this high radiochemical purity boded well for the development of a synthetically-useful method.

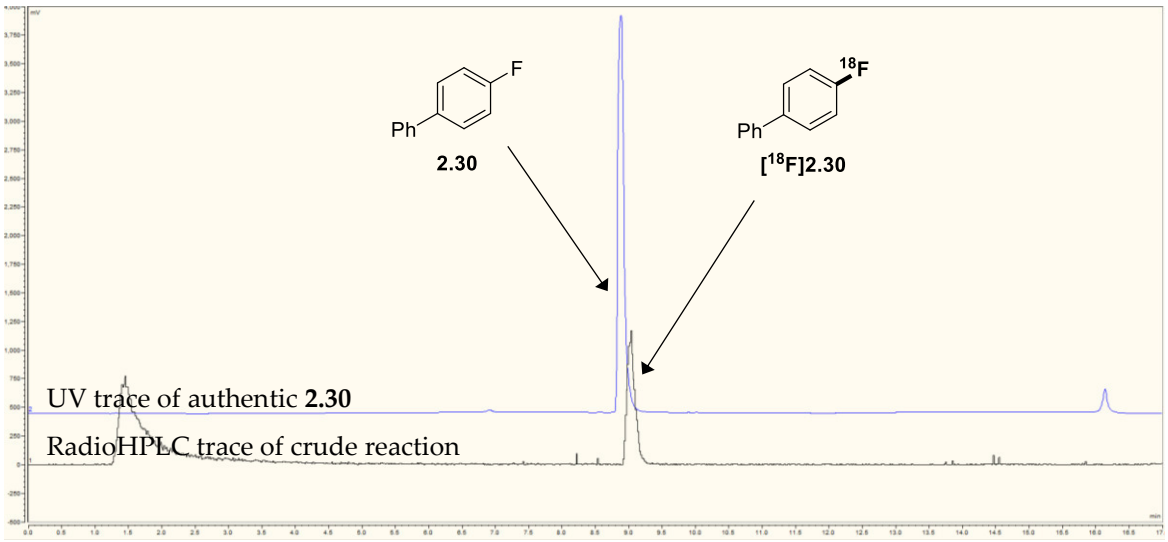


Figure 2.2. Radio-HPLC trace of the crude reaction mixture from Table 2.2, entry 3, overlaid with the UV-HPLC trace of authentic ^{19}F-reference **2.30** to confirm product identity

Changing solvent to *N*,*N*-dimethylformamide (DMF) resulted in formation of **[^{18}F]2.30** in a similar RCC (24% ± 1%, n = 2).

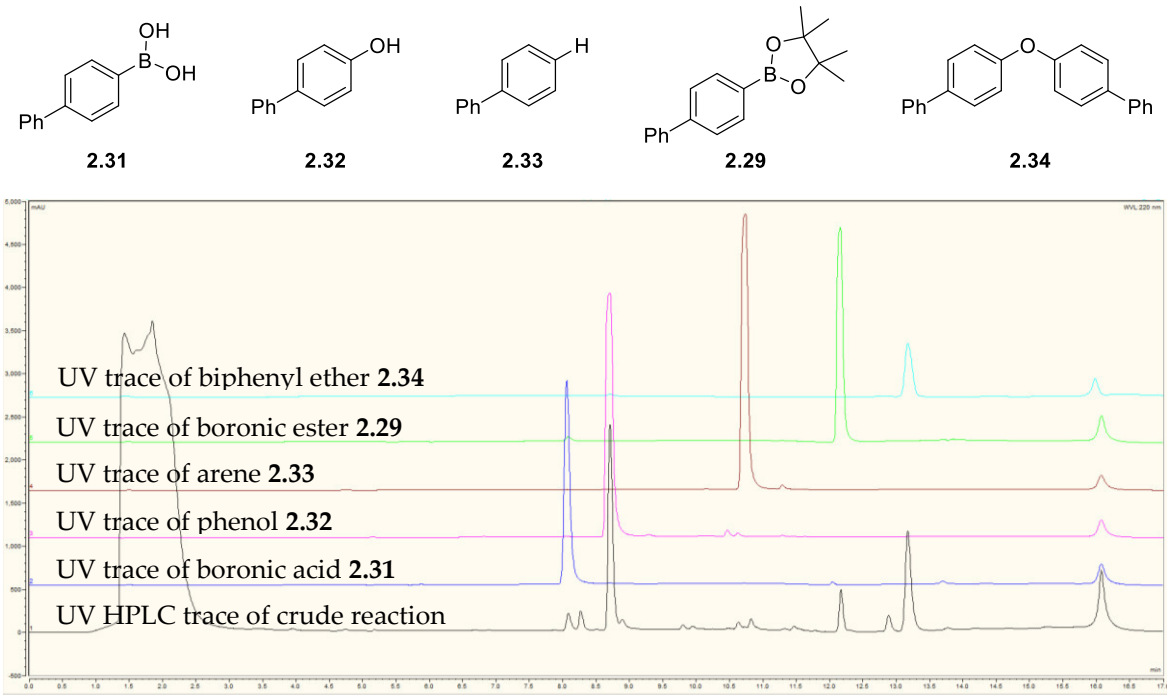
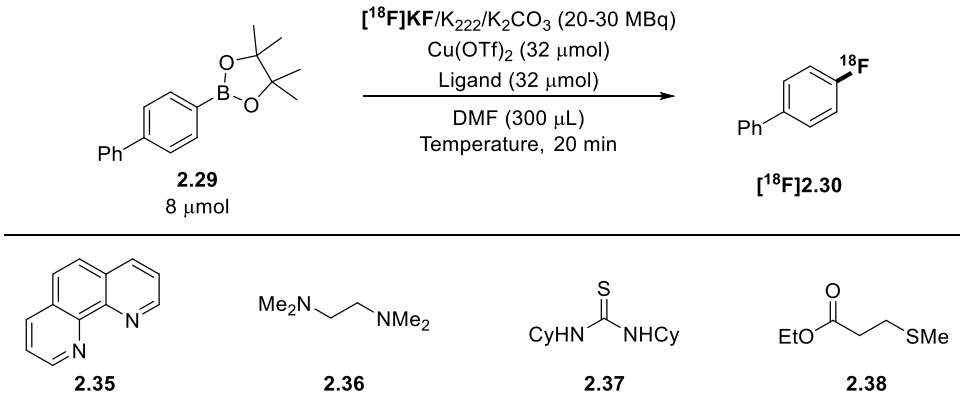


Figure 2.3. UV-HPLC trace of the crude reaction mixture in the ^{18}F-fluorodeboronation of **2.29** in DMF at 150 °C, overlaid with the UV-HPLC traces of authentic boronic acid **2.31**, phenol **2.32**, arene **2.33**, boronic ester **2.29** and biaryl ether **2.34**.

Figure 2.3 shows the UV-HPLC trace of the crude reaction mixture, overlaid with the UV-HPLC traces for several byproducts observed in the reaction. Significant peaks can be assigned to phenol **2.32**, starting material **2.29** and biphenyl ether **2.34**, which may arise from Chan-Lam coupling between phenol **2.32** and either boronic ester **2.29** or boronic acid **2.31**. Smaller peaks can be attributed to boronic acid **2.31** and arene **2.33**, which may result from protodeboronation.

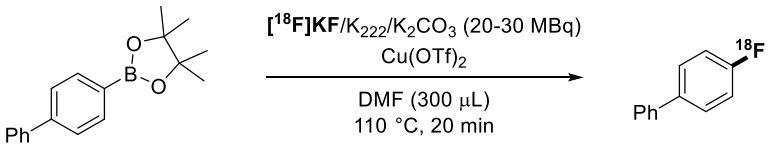
We wished to reduce the reaction temperature; experiments carried out on the same day showed that reducing the temperature to 90 °C resulted in a lower RCC (7%, Table 2.3, entry 1), whilst 110 °C afforded **[^{18}F]2.30** in only slightly reduced RCC (16%, entry 2). Disappointingly, addition of nitrogen or sulfur ligands **2.35**-**2.38** had only a detrimental effect (entries 3-6).



Entry	Temperature / °C	Ligand	[^{18}F]2.30 RCC (n = 2)
1	90	None	7% ± 4%
2	110	None	16% ± 0%
3	110	**2.35**	3% ± 0%
4	110	**2.36**	5% ± 6%
5	110	**2.37**	0%
6	110	**2.38**	0%

Table 2.3. Optimisation of stoichiometry and solvent in the ^{18}F-fluorodeboronation of **2.29**

At this point, we investigated the boronic ester:$Cu(OTf)_2$ stoichiometry. Reducing the amount of $Cu(OTf)_2$ whilst simultaneously increasing the amount of **2.29** resulted in an increase in the RCC of **[^{18}F]2.30**, to 31% (Table 2.4, entries 1 and 2). Keeping the amount of **2.29** constant, the amount of $Cu(OTf)_2$ could then be further reduced to an **2.29**:[Cu] ratio of 10:1 (entries 3-5). Further reduction in the amount of copper resulted in a slight decrease in the RCC (entry 6).

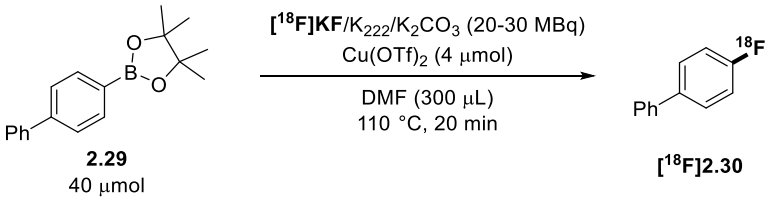


2.29 **[^{18}F]2.30**

Entry	Boronic ester / μmol	$Cu(OTf)_2$ / μmol	Ratio 2.29:[Cu]	[^{18}F]2.30 RCC
1	8	32	1:4	13% ± 7% (*n* = 4)
2	40	13	3:1	31% ± 7% (*n* = 2)
3	40	8	5:1	36% ± 8% (*n* = 2)
4	40	5.5	7:1	34% ± 4% (*n* = 2)
5	40	4	10:1	35% ± 8% (*n* = 4)
6	40	1	40:1	26% ± 0% (*n* = 2)

Table 2.4. Optimisation of stoichiometry and solvent in the ^{18}F-fluorodeboronation of **2.29**

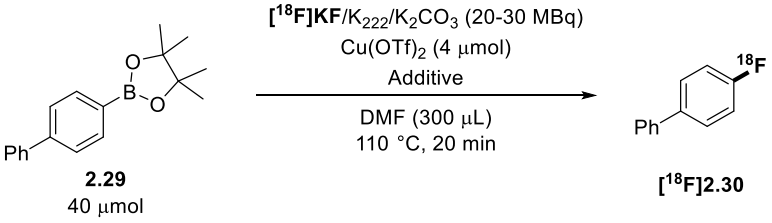
The atmosphere of the reaction was then investigated (Table 2.5). It was discovered that purging the reaction vial with nitrogen prior to adding the solvent sharply reduced the RCC of **[^{18}F]2.30** (entry 2 vs. entry 1); a large amount of protodeboronated product was formed in this reaction. Purging with oxygen was detrimental to the RCC, but less so than nitrogen. All further reactions were run under an atmosphere of air.



Entry	Purge prior to solvent addition?	Reaction atmosphere	[18F]2.30 RCC
1	No	Air	35% ± 8% (*n* = 4)
2	N_2	N_2	3% ± 1% (*n* = 2)
3	O_2	O_2	17% ± 3% (*n* = 2)

Table 2.5. Investigation of N_2 and O_2 atmospheres in the ^{18}F-fluorodeboronation of **2.29**

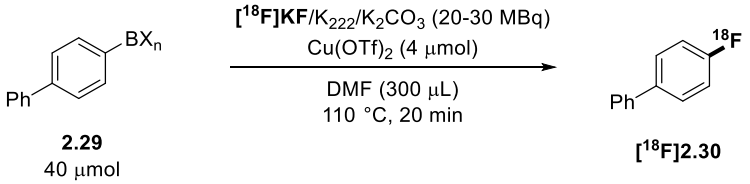
Addition of the inorganic base cesium carbonate reduced the RCC of **[^{18}F]2.30** to 11% (Table 2.6, entry 2 vs. entry 1). Tetraethylammonium bicarbonate had an even more detrimental effect on the RCC (entry 3), whilst potassium phosphate was only slightly detrimental (entry 4). Addition of di(pivaloyloxy)iodobenzene, an oxidant, completely shut down the reaction. Control reactions run in the absence of copper triflate (entry 6) confirmed that copper was required.



Entry	Additive	Additive μmol	[18F]2.30 RCC
1	None	N/A	35% ± 8% (*n* = 4)
2	Cs_2CO_3	8	11% ± 1% (*n* = 2)
3	Et_4NHCO_3	8	3% ± 4% (*n* = 2)
4	K_3PO_4	8	26% ± 0% (*n* = 2)
5	$PhI(OPiv)_2$	4	0% (*n* = 2)
6[a]	None	N/A	0% (*n* = 2)

Table 2.6. Investigation of inorganic bases and an oxidant in the ^{18}F-fluorodeboronation of **2.29**.
[a] Reactions were run in the absence of $Cu(OTf)_2$.

We then investigated common boronic acid derivatives, in order to determine which was the most suitable precursor for the reaction (Table 2.7). Neopentyl glycol ester **2.39** afforded **[^{18}F]2.30**, albeit in lower RCC than pinacol ester **2.29** (entries 1 and 2). Boronic acid **2.31** afforded **[^{18}F]2.30** in only 1% RCC (entry 3), whilst MIDA boronate **2.40** did not form **[^{18}F]2.30** (entry 4). With trifluoroborate **2.41**, **[^{18}F]2.30** was not observed, although **[^{18}F]2.41** was observed in 38% RCC, presumably due to isotopic exchange (entry 5).



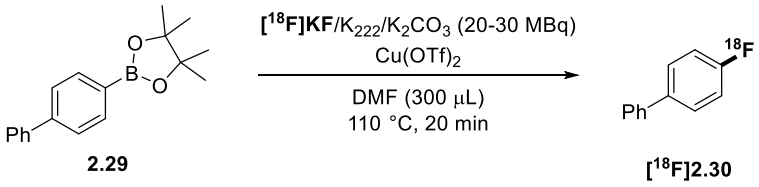
2.29
40 μmol

[^{18}F]2.30

Entry	Boronic acid derivative	BX_n	[^{18}F]2.30 RCC
1	**2.29**	Bpin	35% ± 8% (*n* = 4)
2	**2.39**	Bnpg	16% ± 2% (*n* = 2)
3	**2.31**	$B(OH)_2$	1% ± 0% (*n* = 2)
4	**2.40**	B(MIDA)	0% (*n* = 2)
5[a]	**2.41**	BF_3K	0% (*n* = 2)

Table 2.7. Investigation of boronic acid derivatives in the ^{18}F-fluorodeboronation of **2.29**.
[a] **[^{18}F]2.41** was observed in 38% RCC.

Comparing reactions run on the same day, increasing the amounts of boronic ester **2.29** and $Cu(OTf)_2$ increased the RCC from 21% to 32% (Table 2.8, entry 2 vs. entry 1). This was done only slightly, as we wished to maintain a homogeneous reaction mixture.



2.29 [18F]2.30

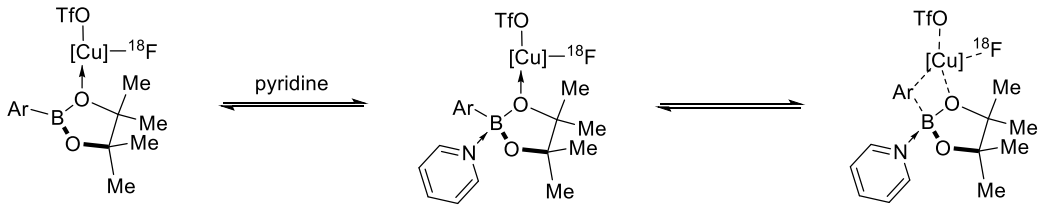
Entry	Boronic ester / μmol	$Cu(OTf)_2$ / μmol	[18F]2.30 RCC
1	40	4	21% ± 1% (*n* = 2)
2	60	5.5	32% ± 3% (*n* = 2)

Table 2.8. Investigation of concentration in the ^{18}F-fluorodeboronation of **2.29**.

Throughout these investigations, we had observed batch-to-batch variability of the $Cu(OTf)_2$. Over the course of a day, it was observed to turn from white to pale blue. We attempted to circumvent this problem by dividing a pot into smaller batches that were stored in a dessicator; a fresh batch was used each day. This was not a satisfactory solution and thus we considered alternative forms of $Cu(OTf)_2$. The tetrakis(pyridine) complex $[Cu(OTf)_2(py)_4]$ was commercially available. When $[Cu(OTf)_2(py)_4]$ was used in the ^{18}F-fluorodeboronation in place of $Cu(OTf)_2$, we were very pleased to observe a large increase in the RCC of **[18F]2.30**, from 32% ± 3% (*n* = 2) to 73% ± 11% (*n* = 4) for reactions otherwise run under the same conditions on the same day. In addition, the $[Cu(OTf)_2(py)_4]$ complex was air-stable and gave more reproducible results.

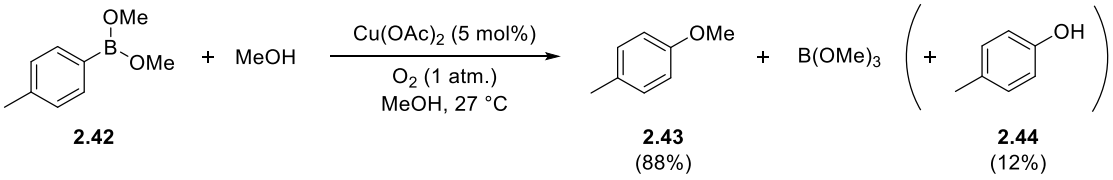
2.2.3 Role of Pyridine and Proposed Mechanism

The beneficial effect of pyridine on the ^{18}F-fluorodeboronation of **2.29** was significant. In addition to providing a more stable source of $Cu(OTf)_2$ for the reaction, the pyridine itself is likely to play a role in the mechanism. The lone pair on nitrogen could interact with vacant orbitals on copper, boron or both. Although the mechanism of the ^{18}F-fluorodeboronation is unknown, it is likely to involve transmetalation of the aryl group from boron to copper. In Suzuki-Miyaura couplings, transmetalation from boron to palladium requires formation of a four-coordinate "ate" species; neutral three-coordinate boron species are insufficiently nucleophilic to undergo this process.[9] Likewise, Watson and co-workers have recently shown that a 4-membered oxo-metal transmetalation pathway is most likely to be operational in the Chan-Lam coupling between aryl pinacol boronate esters and piperidine.[10] In their copper-mediated synthesis of aryl vinyl ethers from phenols and 2,4,6-trivinylcyclotriboroxane, McKinley and O'Shea proposed that coordination of pyridine to boron may facilitate transmetalation of the vinyl group from boron to copper.[11] Whilst in the ^{18}F-fluorodeboronation, the solvent DMF may fulfil the role of "fourth ligand for boron", it is also possible that pyridine could facilitate this process, as shown in Scheme 2.13.



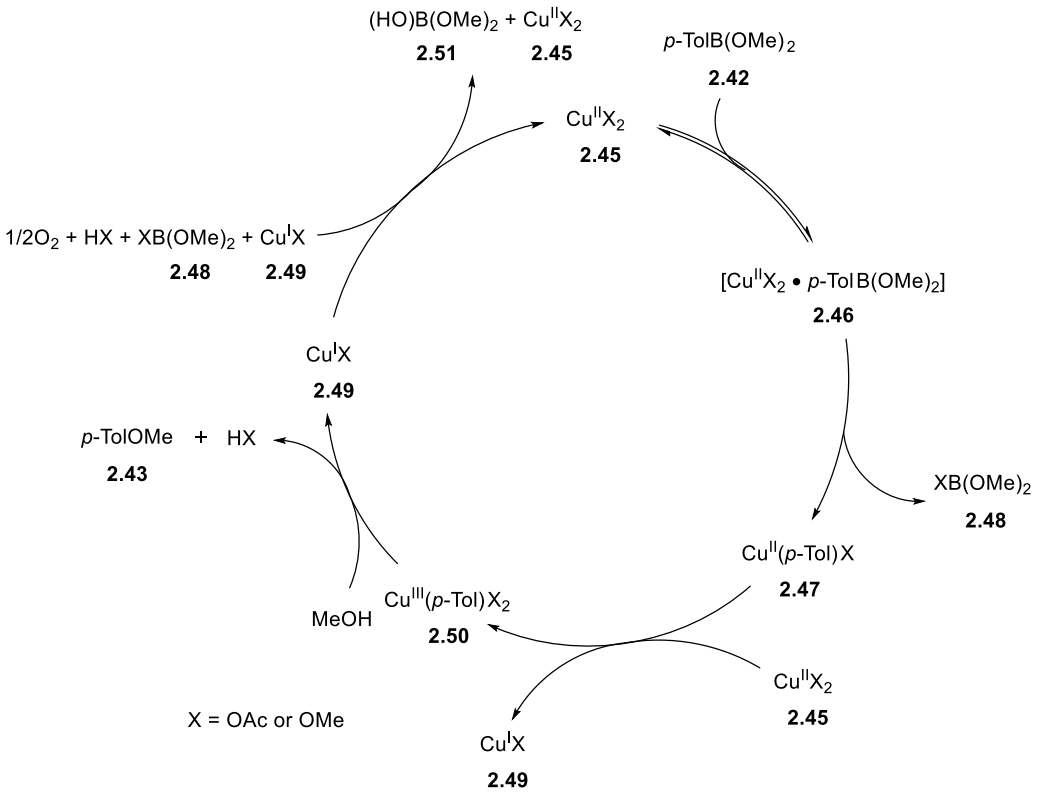
Scheme 2.13. Potential role of pyridine in facilitating transmetalation

One possible mechanism for the reaction could mirror that proposed by Stahl for the oxidative copper-catalysed coupling between the *p*-tolylboronic acid dimethyl ester **2.42** and methanol to form *p*-methylanisole **2.43**. (Scheme 2.14).[12] Stahl used gas-uptake experiments to demonstrate that Cu(II) acted as a one-electron oxidant; that two Cu(II) species were involved in the coupling and that both resulting Cu(I) species were re-oxidised to Cu(II) by reaction with O_2. Kinetic data indicated that transmetalation of the aryl group to the copper centre was the rate-limiting step. EPR spectroscopy indicated that the catalyst resting state consisted of a Cu(II) species with weak donor ligands, consistent with the aryl–Cu bond formation being rate limiting.



Scheme 2.14. Oxidative Cu-catalysed coupling of boronic ester **2.42** and methanol

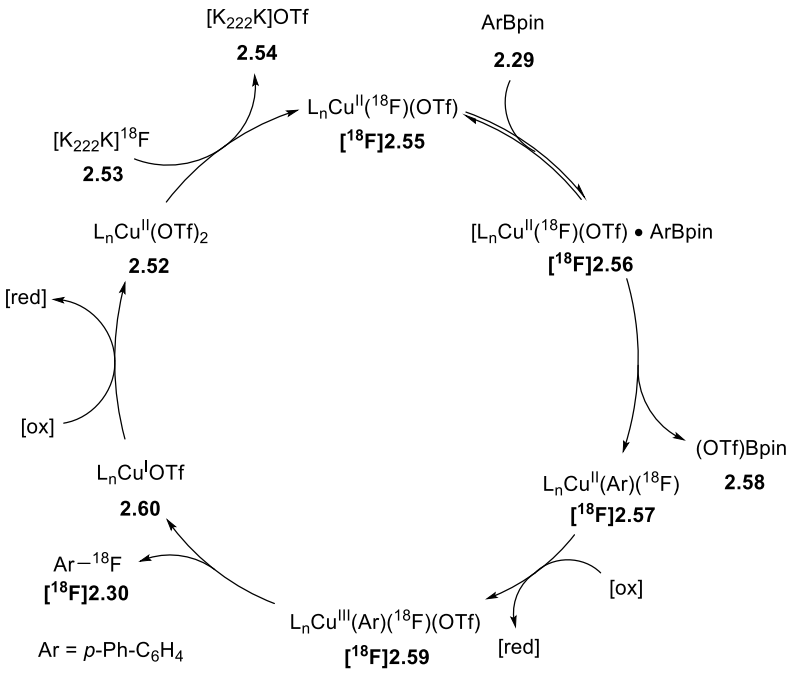
The mechanism proposed by Stahl is given in Scheme 2.15. Initial association between a copper(II) species **2.45** and boronic ester **2.42** formed complex **2.46**. Transmetalation of the aryl group from boron to copper was followed by oxidation of arylcopper(II) species **2.47** to arylcopper(III) species **2.50**. Reductive elimination of aryl ether **2.43** formed copper(I) species **2.49**. The copper(I) species were then re-oxidised to copper(II) by reaction with oxygen.



Scheme 2.15. Proposed catalytic cycle for the Cu-catalysed methoxylation of boronic ester **2.42**

With minor modifications, the same mechanistic pathway could apply in the ^{18}F-fluorodeboronation of **2.29** (Scheme 2.16). Initial ligand exchange of triflate in copper(II) species **2.52** with [^{18}F]fluoride from KF-Kryptofix complex **2.53** would form copper(II) fluoride **[^{18}F]2.55**. Association with boronic ester substrate **2.29** would form transmetalation complex **[^{18}F]2.56**. Transmetalation of the aryl group from boron to copper, potentially assisted by coordination of DMF or pyridine to boron, would form arylcopper(II) fluoride **[^{18}F]2.57**. This copper(II) species would then be oxidised, possibly by oxygen or via disproportionation with another copper(II) species, to form the key arylcopper(III) fluoride **[^{18}F]2.59**. Reductive elimination of the desired product, [^{18}F]fluoroarene **[^{18}F]2.30**, would form copper(I) triflate **2.60**, which could subsequently be oxidised to re-form the initial copper(II)

species **2.52**. Each of the copper complexes could be coordinated by pyridine or DMF (solvent) molecules; these may also play a role in facilitating the transmetalation step.



Scheme 2.16. Proposed mechanism for the Cu-mediated ^{18}F-fluorodeboronation of **2.29**. L = DMF or pyridine. [ox] = oxidant. [red] = reductant.

2.2.4 Substrate Scope of ^{18}F-Fluorodeboronation of Aryl Boronic Esters

Having developed conditions which afforded **[^{18}F]2.30** in good RCC, we investigated the scope of the reaction with respect to aryl boronic esters. Many boronic esters and corresponding ^{19}F-references were commercially available, although the boronic ester precursor for **[^{18}F]2.84** was prepared via Ir-catalysed C–H borylation and the precursor for **[^{18}F]2.87** was prepared *via* Miyaura borylation. The substrate scope of the ^{18}F-fluorodeboronation is given in Table 2.9.

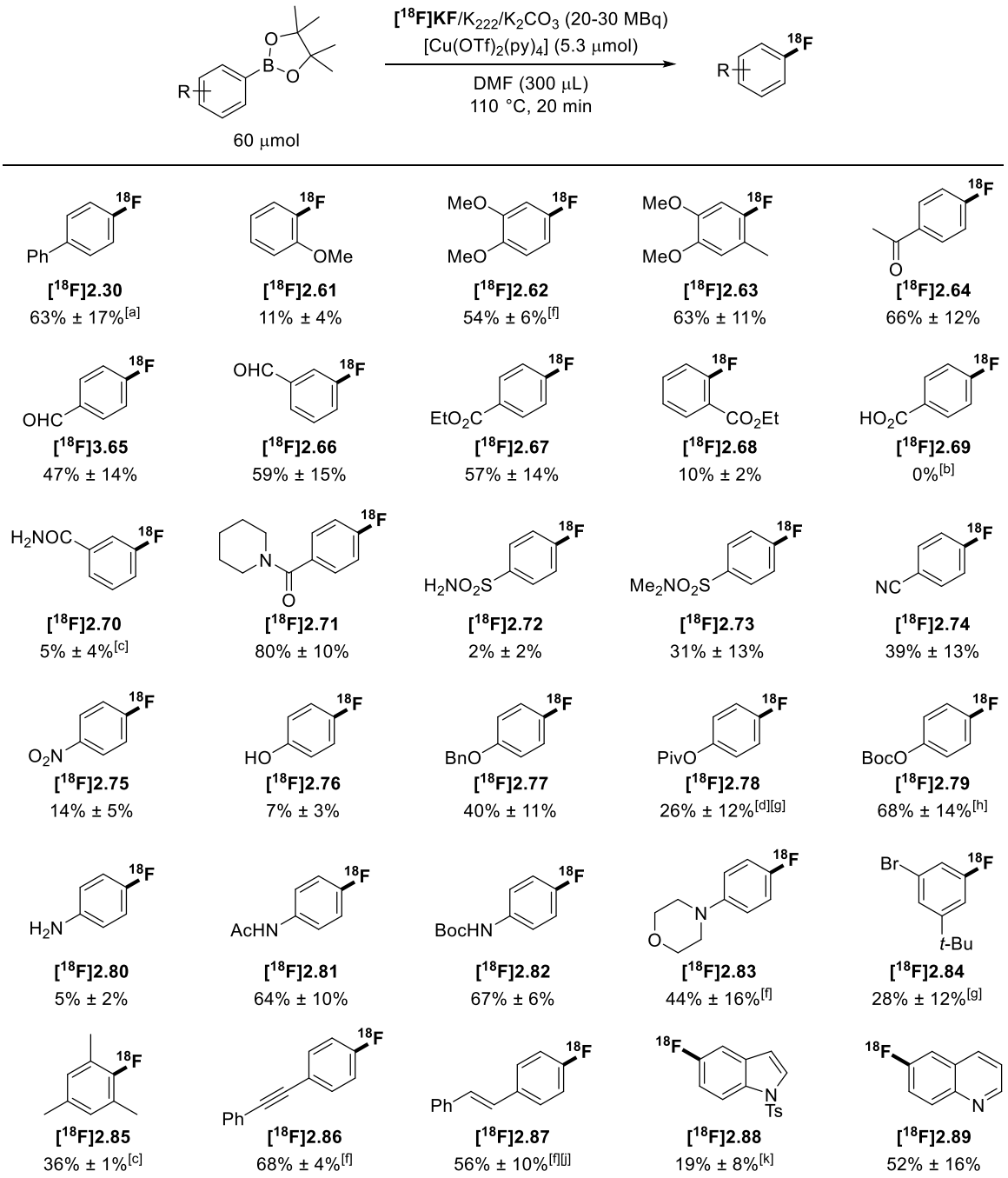


Table 2.9. Substrate scope of ^{18}F-Fluorodeboronation of aryl boronic esters. Reactions were performed four times (n = 4); radiochemical conversions were determined by radio-TLC and radio-HPLC and are given in the form mean ± standard deviation. [a] Reaction was performed 36 times (n = 36). [b] Reaction was performed twice (n = 2). [c] Reaction was performed three times (n = 3). [d] Partial deprotection occurred under the reaction conditions; **[^{18}F]2.76** was also formed in ca. 5% RCC. [e] Partial deprotection occurred under the reaction conditions; **[^{18}F]2.76** was also formed in ca. 7% RCC. [f] ^{19}F-Reference prepared by Dr. Matthew Tredwell. [g] Precursor and ^{19}F-reference prepared by Dr. Sean Preshlock. [h] ^{19}F-Reference prepared by Dr. Sean Preshlock. [j] Precursor prepared by Dr. Stefan Gruber. [k] Precursor and ^{19}F-reference prepared by Dr. Stefan Gruber.

Veratrole **[^{18}F]2.62** was formed in good RCC, as was **[^{18}F]2.63** which bore an additional methyl group in the ortho position. These results were particularly

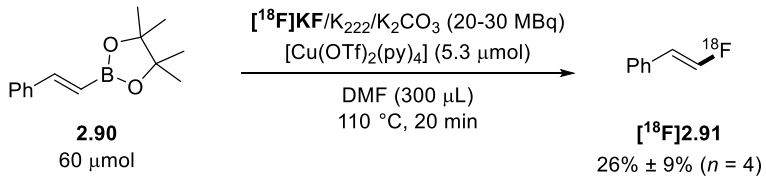
pleasing, since as discussed in Chapter 1, electron-rich [^{18}F]fluoroarenes are much more difficult to access via existing methods for ^{18}F-fluorination. In contrast, anisole **[^{18}F]2.61**, with the methoxy substituent ortho to the site of ^{18}F-fluorodeboronation, was formed in only 11% RCC. Substrates bearing carbonyl functionality were generally well-tolerated. Enolisable ketone **[^{18}F]2.64**, aldehydes **[^{18}F]2.65** and **[^{18}F]2.66** and ester **[^{18}F]2.67** were successfully ^{18}F-labelled in 47%–66% RCC. Again, **[^{18}F]2.68**, bearing a potentially-coordinating ester group in the ortho-position, was formed in relatively low RCC (10%). Carboxylic acid **[^{18}F]2.69** could not be directly synthesised in this manner. Whilst primary amide **[^{18}F]2.70** was formed in very low RCC, piperidine derivative **[^{18}F]2.71** was much better tolerated and was ^{18}F-labelled in 80% RCC. Sulfonamides **[^{18}F]2.72** and **[^{18}F]2.73** followed a very similar pattern; **[^{18}F]2.72** bearing two free N–H groups was formed in much lower RCC than dimethyl derivative **[^{18}F]2.73**. Whilst nitrile **[^{18}F]2.74** was formed in moderate RCC, more electron-deficient nitro-substituted **[^{18}F]2.75** was formed in only 14% RCC.

[^{18}F]2.76 and **[^{18}F]2.80**, bearing a free phenol and free aniline, were both ^{18}F-radiolabelled, although in only 7% and 5% RCC, respectively. Protected derivatives **[^{18}F]2.77**-**[^{18}F]2.79** and **[^{18}F]2.81**-**[^{18}F]2.82** were much better tolerated, with Boc-protected **[^{18}F]2.79** and **[^{18}F]2.82** being formed in highest RCCs. A small amount of hydrolysis was observed for Boc- and pivaloyl-protected phenols **[^{18}F]2.79** and **[^{18}F]2.78**, resulting in observation of small amounts of **[^{18}F]2.76** as a side product. Morpholine **[^{18}F]2.83** was successfully ^{18}F-labelled, as was **[^{18}F]2.84** containing an aryl bromide. **[^{18}F]2.85**, bearing substitution in both ortho-positions, was also

successfully labelled. **[^{18}F]2.86** and **[^{18}F]2.87**, featuring an internal alkyne and alkene, were both formed in > 50% RCC. Indole **[^{18}F]2.88** and quinoline **[^{18}F]2.89** were ^{18}F-labelled in 19% and 50% RCC, respectively.

Overall, the substrate scope of the ^{18}F-fluorodeboronation of aryl boronic esters was good, the high RCCs of electron-rich veratroles **[^{18}F]2.62** and **[^{18}F]2.63** being a particularly pleasing result. Whilst compounds bearing a free N–H or O–H were not well tolerated, this was not unexpected, as such species may be expected to undergo competing Chan-Lam coupling. Use of appropriate protecting groups solved this problem. More significant challenges included the low yields of electron-deficient **[^{18}F]2.75**, as well as **[^{18}F]2.61** and **[^{18}F]2.68** bearing potential coordinating groups in a position ortho to the reaction site.

In addition to aryl boronic esters, vinylboronic ester **2.90** was subjected to the ^{18}F-fluorodeboronation conditions (Scheme 2.17). This afforded vinyl fluoride **[^{18}F]2.91** in 26% RCC.



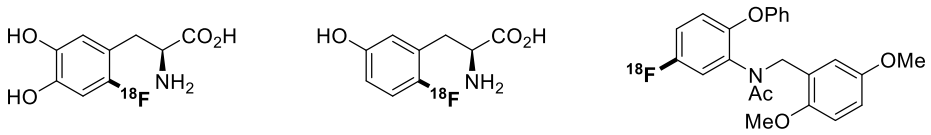
Scheme 2.17. ^{18}F-Fluorodeboronation of vinylboronic ester **2.90**

For translation of a radiolabelling process to clinical imaging, the residual levels of metal impurities must be considered. In order to assess the level of copper present in [^{18}F]fluoroarenes prepared via the ^{18}F-fluorodeboronation, four samples of **[^{18}F]2.30** were purified by preparative HPLC. A portion of each sample was analysed by ICP-MS to determine copper content. Residual levels of copper-63 were

measured to be 2.07 ppm, well below the guideline levels as identified by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use in the document ICH-Q3D.[13]

2.3 ^{18}F-Fluorodeboronation of Clinically-Relevant Radiotracers

Inspired by the success of the ^{18}F-fluorodeboronation with electron-rich arenes, we sought to use the method in the ^{18}F-labelling of electron-rich targets of clinical importance. The three targets chosen were 6-[^{18}F]fluoro-3,4-dihydroxyphenylalanine ([^{18}F]FDOPA, **[^{18}F]2.92**), 6-[^{18}F]fluoro-*meta*-tyrosine ([^{18}F]FMT, **[^{18}F]2.93**) and [^{18}F]DAA1106 **[^{18}F]2.94** (Figure 2.4). [^{18}F]FDOPA and [^{18}F]FMT are used in assessing the presynaptic dopaminergic pathway, and [^{18}F]DAA1106 is a radioligand for the translocator protein. All three are notoriously difficult to access from [^{18}F]fluoride.



[^{18}F]2.92
[^{18}F]FDOPA
imaging of dopamingergic system

[^{18}F]2.93
[^{18}F]FMT
imaging of dopamingergic system

[^{18}F]2.94
[^{18}F]DAA1106
TSPO ligand

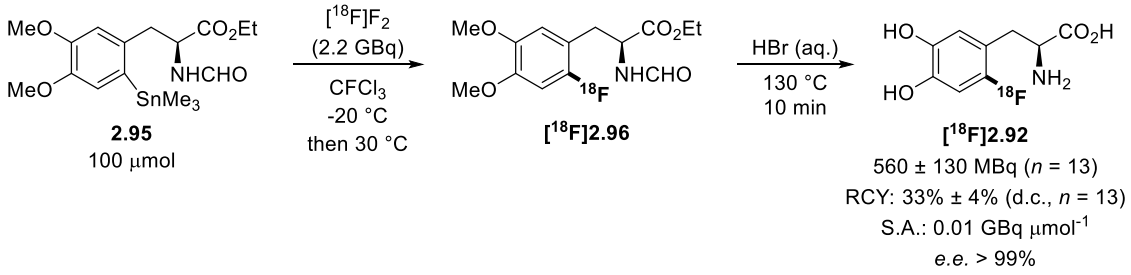
Figure 2.4. Clinically-relevant PET radiotracers chosen to exemplify the suitability of the copper-mediated ^{18}F-fluorodeboronation for the preparation of electron-rich targets.

2.3.1 Synthesis of [^{18}F]FDOPA via ^{18}F-Fluorodeboronation

The non-proteinogenic amino acid 3,4-dihydroxy-L-phenylalanine (DOPA) is biosynthesised from tyrosine by the enzyme tyrosine hydroxylase and is the main

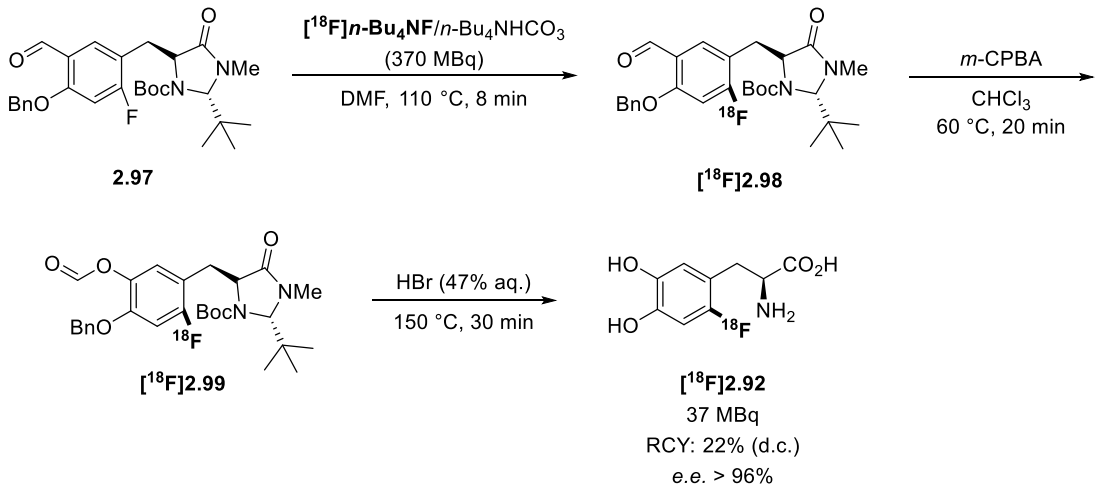
precursor for the neurotransmitter dopamine.[14], [15] The DOPA derivative bearing a fluorine-18 substituent in the 6-position ([^{18}F]DOPA) is an iconic radiotracer that has been used for over 30 years to image the presynaptic dopamine system in the human brain.[16] This has been used in the evaluation of schizophrenia and Parkinson's disease.[17]–[20] More recently, [^{18}F]FDOPA has been used to detect neuroendocrine tumours.[21]

Routes for the preparation of [^{18}F]FDOPA have been reviewed; only key examples will be discussed here.[16] The most common method employed for the clinical production of [^{18}F]FDOPA is the electrophilic fluorodestannylation of arylstannane **2.95**, initially disclosed by Satyamurthy and co-workers and automated by de Vries and co-workers (Scheme 2.18).[22], [23] This method has the advantage of producing [^{18}F]FDOPA in very high regio- and enantio-selectivity. Tin levels after purification are well below the required limits. However, as an electrophilic method, it suffers from the drawbacks discussed in Chapter 1, including low specific activity and the production of low amounts of activity (enough for the preparation of only one or two human doses per synthesis). Whilst low specific activity does not preclude the use of [^{18}F]FDOPA in imaging amino acid metabolism in brain malignancies, the doses employed (ca. 5 mg) can have undesired pharmacological effects.[16], [24] Most significantly, the specialised equipment required for the manipulation of [^{18}F]F_2 is available at only a minority of PET centres globally.



Scheme 2.18. Synthesis of [18F]FDOPA **[18F]2.92** via fluorodestannylation

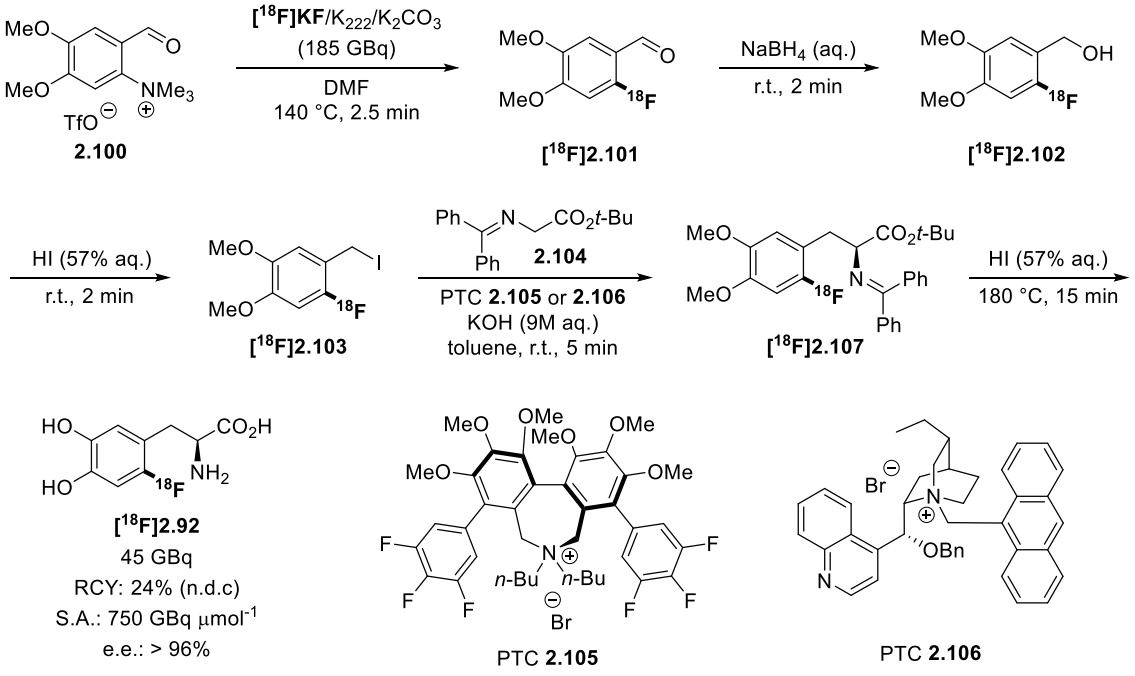
The limitations posed by the production of [18F]FDOPA via electrophilic fluorodestannylation have led to significant efforts within the radiochemistry community to develop syntheses from [18F]fluoride. These routes generally involve introduction of [18F]fluoride into an activated precursor via nucleophilic aromatic substitution, followed by multiple post-labelling steps. For example, Coenen and co-workers developed a three-step, one-pot synthesis from aldehyde **2.97** (Scheme 2.19).[25] Initial isotopic exchange was followed by Baeyer-Villiger oxidation of aldehyde **[18F]2.98** to formate ester **[18F]2.99**. Acidic hydrolysis afforded [18F]FDOPA **[18F]2.92** in 22% RCY (d.c.), with an enantiomeric excess above 96%.



Scheme 2.19. Three-step, one-pot synthesis of [18F]FDOPA **[18F]2.92** based on isotopic exchange

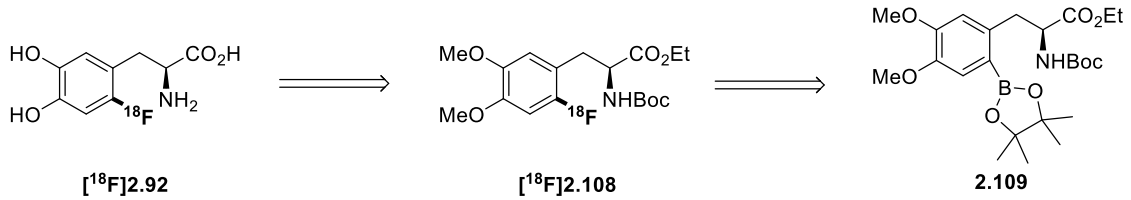
Syntheses based on 19F/18F isotopic exchange do not solve the problem of low specific activity. A much more promising approach is the enantioselective

alkylation route developed by Luxen and co-workers using a modified GE FASTlab module.[17], [26] Fluorine-18 was introduced via nucleophilic substitution of trimethylammonium precursor **2.100** (Scheme 2.20). Aldehyde **[^{18}F]2.101** was then reduced and transformed into alkyl iodide **[^{18}F]2.102** directly on the C18 purification cartridge. The key step was enantioselective alkylation of imine **2.104** with alkyl iodide **[^{18}F]2.103** using phase transfer catalyst **2.105** or **2.106**. Acidic hydrolysis furnished [^{18}F]DOPA **[^{18}F]2.92** in > 96% *e.e.*. Starting from 185 GBq [^{18}F]fluoride, 45 GBq **[^{18}F]2.92** was produced, corresponding to a RCY of 24% (n.d.c.). The specific activity was 750 GBq μmol^{-1}. This route has been optimised for more than a decade and provides a highly viable route for the production of multiple doses of high-specific-activity [^{18}F]FDOPA.



Scheme 2.20. Highly optimised automated synthesis of high-specific-activity [^{18}F]FDOPA **[^{18}F]2.92** based on enantioselective alkylation

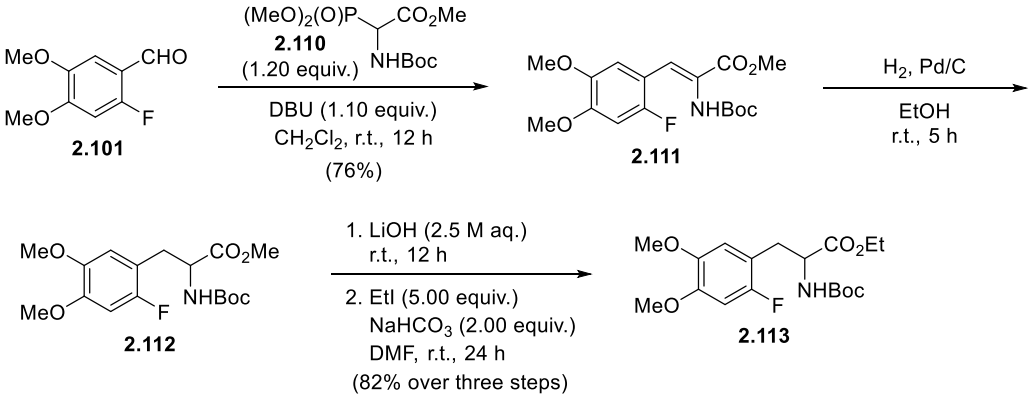
We sought to apply the copper-mediated nucleophilic ^{18}F-fluorodeboronation to the synthesis of [^{18}F]FDOPA. We envisaged that ^{18}F-fluorodeboronation of a protected precursor **2.109** could be followed by deprotection to afford high-specific-activity [^{18}F]DOPA **[^{18}F]2.92** in only two steps (Scheme 2.21). Acidic hydrolysis of protected compound **[^{18}F]2.108** to form [^{18}F]FDOPA **[^{18}F]2.92** was well established. Our first step was therefore to demonstrate that protected compound **[^{18}F]2.108** could be accessed via ^{18}F-fluorodeboronation of boronic ester **2.109**.



[^{18}F]2.92 **[^{18}F]2.108** **2.109**

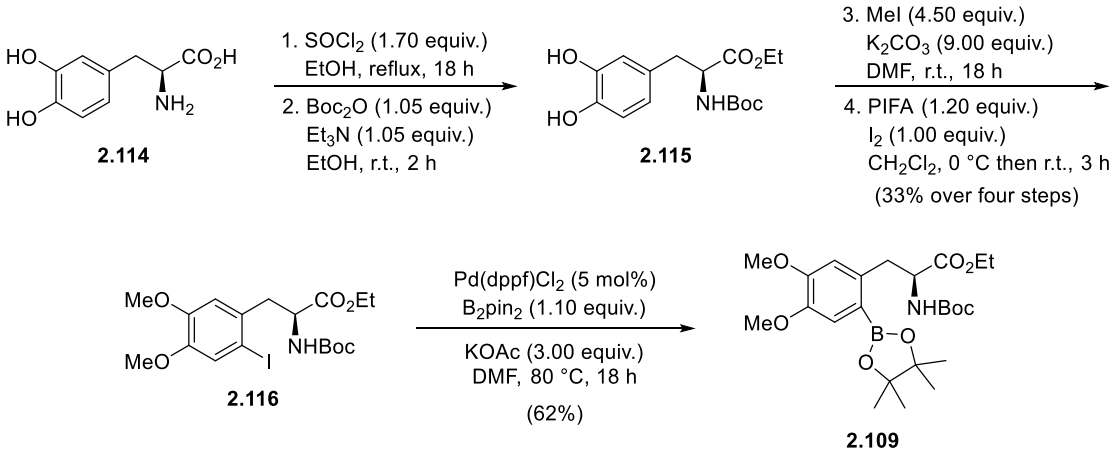
Scheme 2.21. Retrosynthetic approach to [^{18}F]FDOPA **[^{18}F]2.92** based on ^{18}F-fluorodeboronation

Synthesis of racemic ^{19}F-fluorinated reference **2.113** was carried out by Dr. Matthew Tredwell (Scheme 2.22). Horner-Wadsworth-Emmons reaction of aldehyde **2.101** with phosphonate **2.110** afforded alkene **2.111** in 76% yield. Palladium-catalysed hydrogenation of the alkene was followed by hydrolysis of the ester and alkylation of the resulting carboxylate to form ethyl ester **2.113** in 82% yield over three steps.



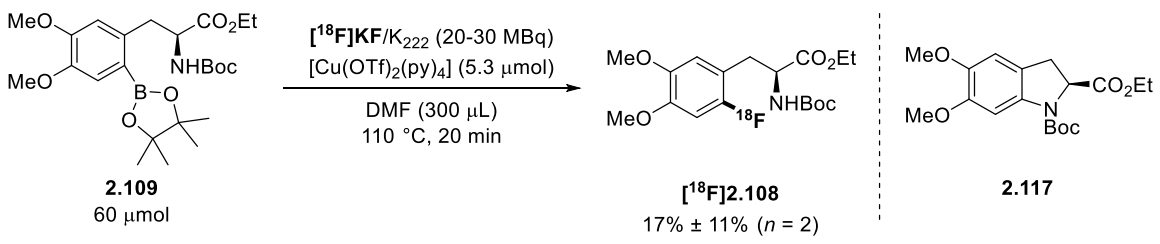
Scheme 2.22. Synthesis of reference **2.113**, carried out by Dr. Matthew Tredwell

I carried out the synthesis of boronic ester **2.109** following a literature procedure.[27] The acid group of 3,4-dihydroxyphenylalanine **2.114** was first protected as the ethyl ester (Scheme 2.23). Boc-protection of the amine was followed by methylation of both catechol oxygen atoms. Iodination with iodine and bis(trifluoroacetoxy)iodobenzene afforded iodide **2.116** in 33% yield over four steps. Palladium-catalysed Miyaura borylation afforded boronic ester **2.109** in 62% yield.



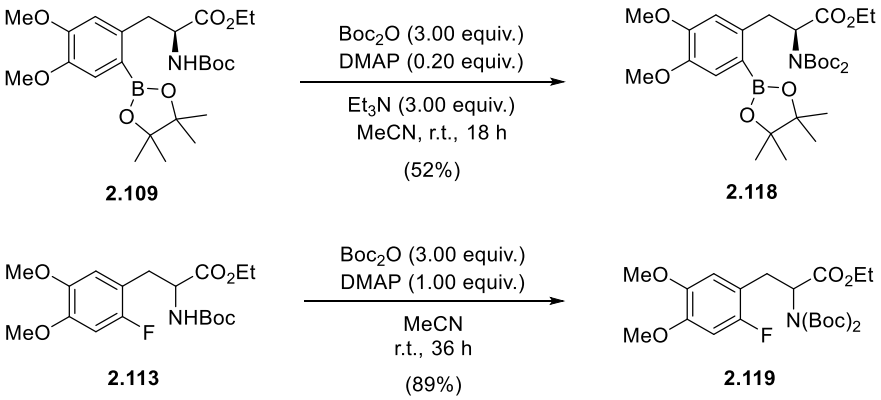
Scheme 2.23. Synthesis of boronic ester **2.109**

Disappointingly, subjecting boronic ester **2.109** to our standard ^{18}F-fluorodeboronation conditions afforded **[^{18}F]2.108** in only 17% RCC (Scheme 2.24). It was proposed that **2.109** may be undergoing a competing intramolecular Chan-Lam C–N bond formation under the reaction conditions, to form indoline **2.117**.



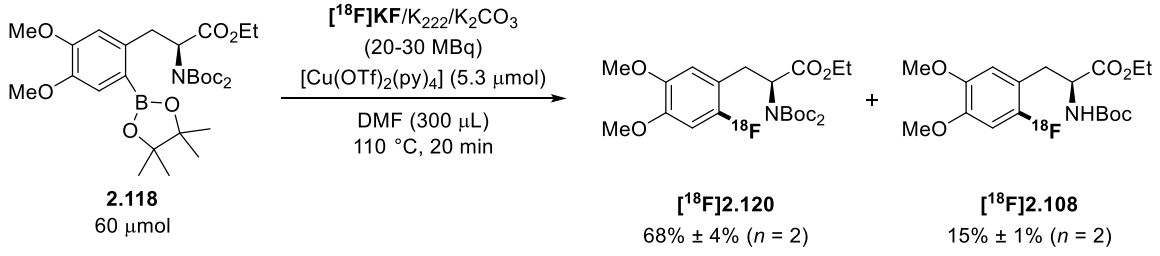
Scheme 2.24. Attempted ^{18}F-fluorodeboronation of **2.109** to afford **[^{18}F]2.108**

One possible solution to this problem would be bis-Boc protection of the boronic ester. Thus, boronic ester **2.118** was synthesised from **2.109**, and the racemic ^{19}F-reference **2.119** was synthesised from **2.113** (Scheme 2.25).



Scheme 2.25. Synthesis of bis-Boc-protected boronic ester **2.118** and reference **2.119**

Under the standard ^{18}F-fluorodeboronation conditions, bis-Boc-protected boronic ester **2.118** afforded **[^{18}F]2.120** in 68% RCC, in addition to partially-deprotected **[^{18}F]2.108** in 15% RCC (Scheme 2.26). Figure 2.5 shows the radio-HPLC trace of the crude reaction, overlaid with the UV-HPLC traces of references **2.119** and **2.113**. The combined RCC of 83% suggested that copper-mediated ^{18}F-fluorodeboronation may provide a viable alternative to Luxen's multistep route for the production of high-specific activity [^{18}F]FDOPA. Additional experiments towards this goal are described in section 2.3.4.



Scheme 2.26. ^{18}F-fluorodeboronation of **2.118** to afford **[^{18}F]2.120** and **[^{18}F]2.108**

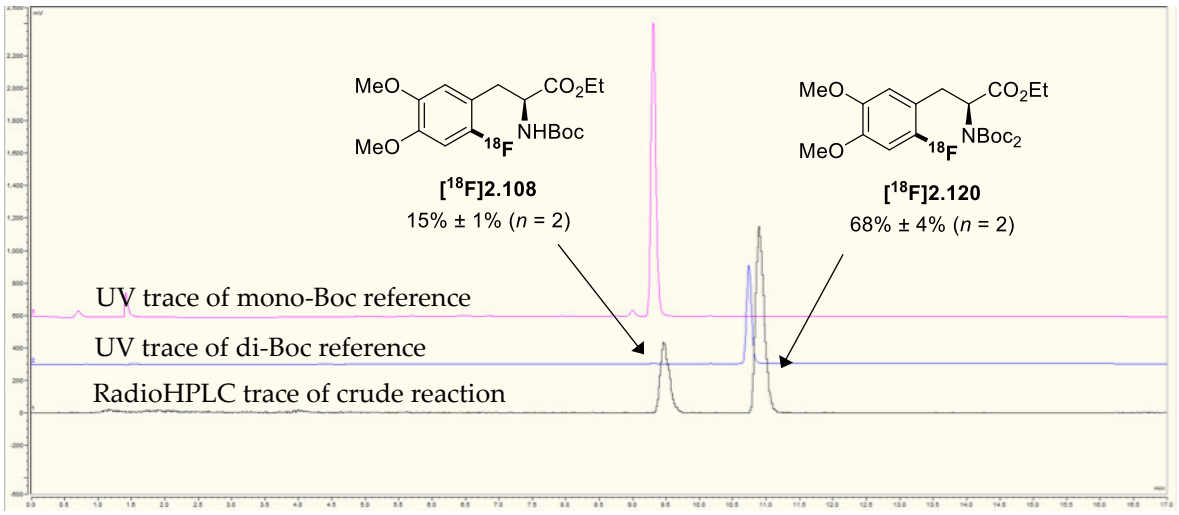
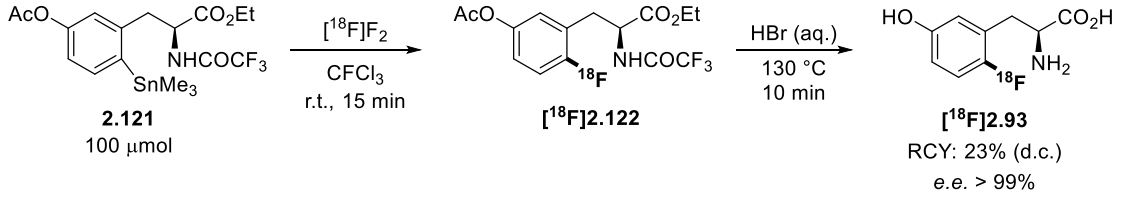


Figure 2.5. Radio-HPLC trace of the crude reaction mixture of the ^{18}F-fluorodeboronation of **2.118**, overlaid with the UV-HPLC traces of ^{19}F-references **2.113** and **2.119**

2.3.2 Synthesis of [^{18}F]FMT via ^{18}F-Fluorodeboronation

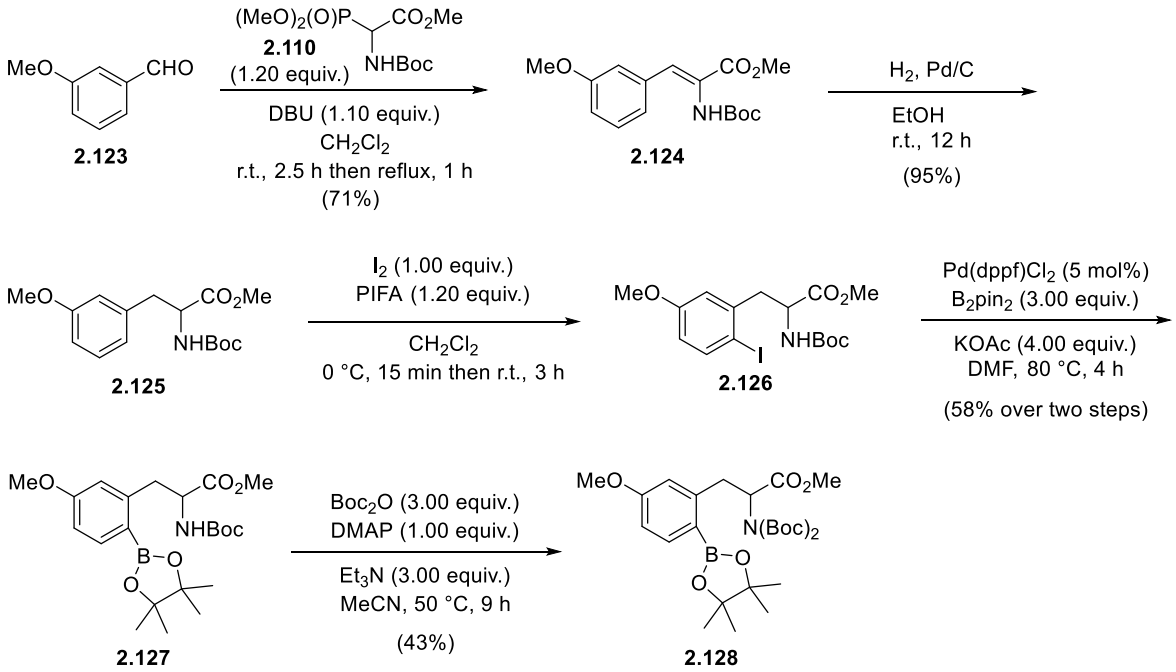
Whilst [^{18}F]FDOPA has been used widely for PET imaging, it is not without drawbacks. One important limitation is that [^{18}F]FDOPA is methylated in both the CNS and the periphery by the enzyme catecholamine *O*-methyltransferase (COMT), producing 6-[^{18}F]fluoro-3-*O*-methyl DOPA (OMFD).[28], [29] OMFD crosses the blood-brain barrier and distributes widely throughout the brain, reducing the contrast of the image. Complex modelling can take this metabolite into account,[30] or the patient can be pre-treated with a COMT inhibitor to suppress this metabolism.[31] An alternative approach, pioneered by Barrio and co-workers, is the use of *meta*-tyrosine derivatives labelled with fluorine-18.[32], [33] Both 4-[^{18}F]fluoro-L-*m*-tyrosine and 6-[^{18}F]fluoro-L-*m*-tyrosine have been prepared; neither is a substrate of COMT and thus both gave rise to better signal:noise ratios than [^{18}F]DOPA when used in imaging of the striatum. The 6-isomer was shown to be preferred over the 4-isomer due to slower metabolism.

6-[^{18}F]Fluoro-L-*m*-tyrosine ([^{18}F]FMT, **[^{18}F]2.93**, Scheme 2.27) was prepared via the electrophilic ^{18}F-fluorodestannylation of **2.121**, followed by acidic hydrolysis, which afforded **[^{18}F]2.93** in 23% RCY (d.c.).[34] Whilst alternative precursors for electrophilic ^{18}F-fluorodestannylation have been developed, at the time of this work, no route for the production of **[^{18}F]2.93** in high specific activity had been reported.[28]



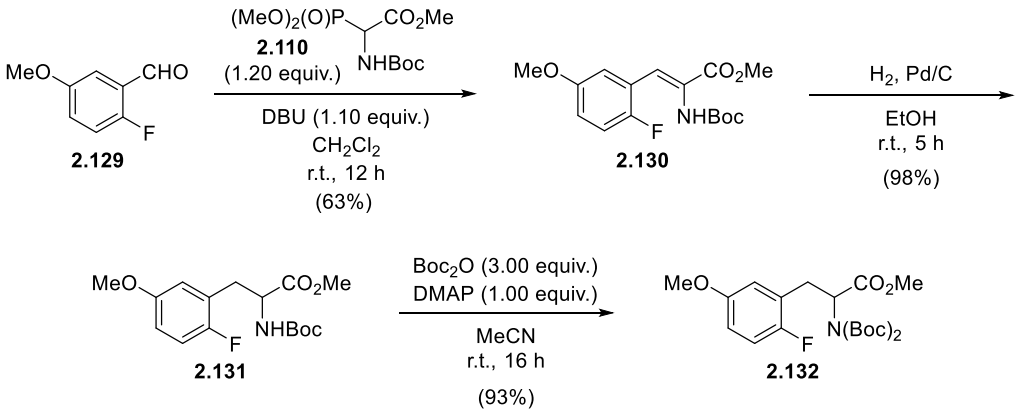
Scheme 2.27. Synthesis of [^{18}F]FMT **[^{18}F]2.93** via electrophilic ^{18}F-fluorodestannylation

As proof-of-concept that the ^{18}F-fluorodeboronation could also be applied to the synthesis of [^{18}F]FMT, we wished to prepare racemic [^{18}F]FMT in a protected form. Based on the results obtained for [^{18}F]FDOPA, it was decided to directly synthesise the bis-Boc-protected boronic ester **2.128** (Scheme 2.28). Horner-Wadsworth-Emmons reaction of aldehyde **2.123** and phosphonate **2.110** afforded alkene **2.124** in 71% yield. Palladium-catalysed hydrogenation of **2.124** afforded protected meta-tyrosine **2.125** in 95% yield. Iodination of **2.125** was followed by Miyaura borylation, affording boronic ester **2.127** in 58% yield over two steps. Unfortunately, use of a large excess of bis(pinacolato)diboron resulted in tedious chromatographic purification. Finally, Boc-protection of **2.127** afforded requisite boronic ester **2.128**.



Scheme 2.28. Synthesis of boronic ester **2.128**

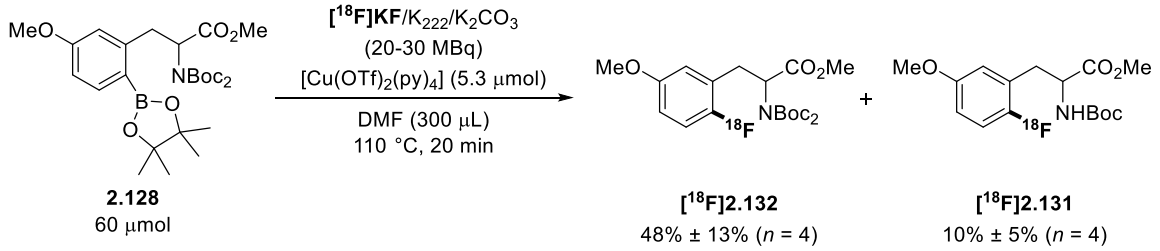
^{19}F-Reference **2.132** was prepared by Dr. Matthew Tredwell via a similar route (Scheme 2.29). Horner-Wadsworth-Emmons reaction of aldehyde **2.129** and phosphonate **2.110** afforded alkene **2.130**, which was hydrogenated under palladium catalysis. Boc-protection of **2.131** afforded reference **2.132**.



Scheme 2.29. Synthesis of ^{19}F-reference **2.132**, carried out by Dr. Matthew Tredwell

When boronic ester **2.128** was subjected to the standard ^{18}F-fluorodeboronation conditions, **[^{18}F]2.132** was formed in 48% RCC (Scheme 2.30). Partially-deprotected **[^{18}F]2.131** was also formed in 10% RCC. Figure 2.6 shows

the radio-HPLC trace of the crude reaction mixture, overlaid with the UV-HPLC traces of references **2.131** and **2.132**.



Scheme 2.30. ^{18}F-fluorodeboronation of **2.128** to afford **[^{18}F]2.132** and **[^{18}F]2.131**

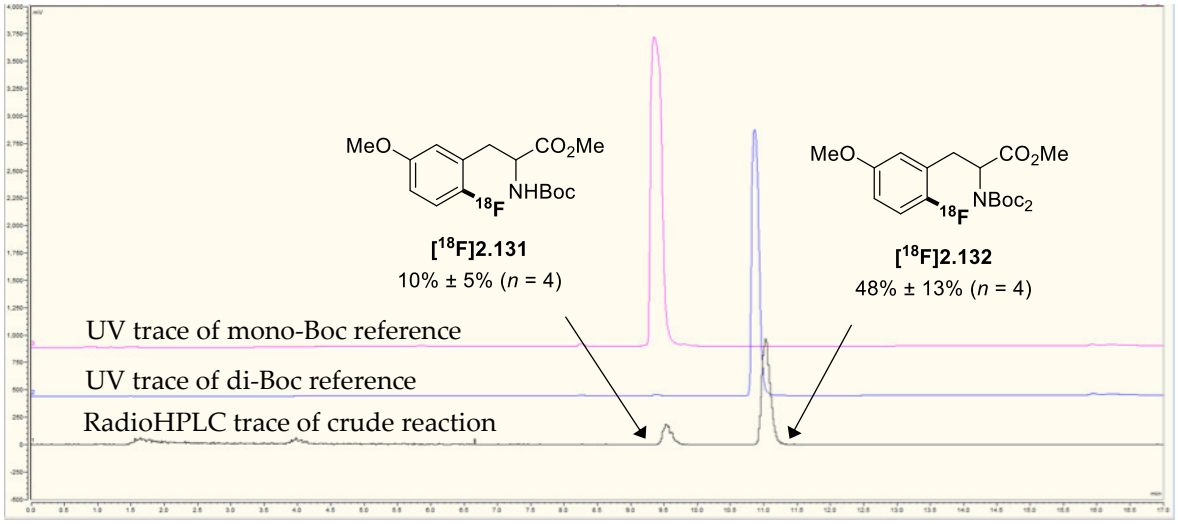


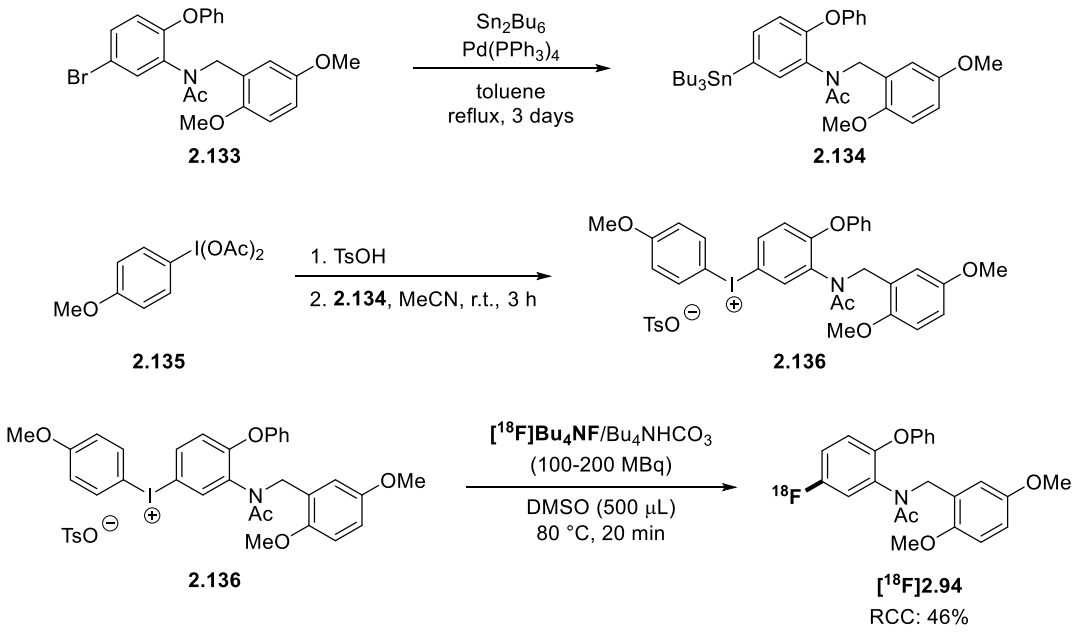
Figure 2.6. Radio-HPLC trace of the crude reaction mixture of the ^{18}F-fluorodeboronation of **2.128**, overlaid with the UV-HPLC traces of **2.131** and **2.132**

2.3.3 Synthesis of [^{18}F]DAA1106 via ^{18}F-Fluorodeboronation

The translocator protein (18 kDa) (TSPO), formerly known as the peripheral benzodiazepine receptor (PBR), is a transmembrane protein found widely throughout the human body.[35] It is believed to play an important role in the biosynthesis of steroids.[36] In the central nervous system, TSPO is located mainly in glial cells, which play a crucial role in neurodegeneration.[37], [38] Damage to brain tissue has been shown to be accompanied by an increase in the density of

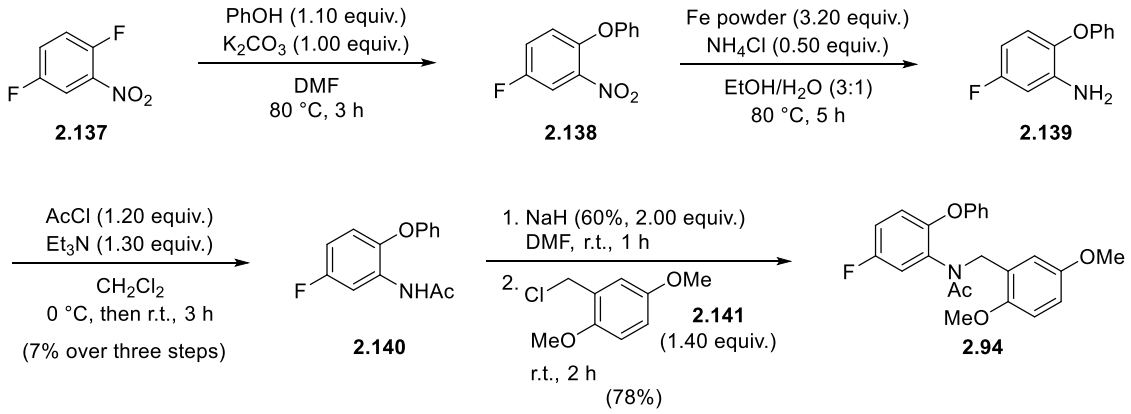
TSPO.[39], [40] PET and SPECT studies have shown this receptor to correlate with Alzheimer's disease and multiple schlerosis.[41], [42]

DAA1106 has been shown to have 0.28 nM affinity for TSPO and has previously been labelled with carbon-11, iodine-131 and fluorine-18.[43]–[46] A PET study of [^{11}C]DAA1106 in mice showed high specificity and selectivity for TSPO. The Zhang group were the first to label DAA1106 with fluorine-18, starting from diaryliodonium tosylate precursor **2.136** (Scheme 2.31).[46] This required initial synthesis of stannane **2.134** from bromide **2.133**, followed by reaction with an in situ generated iodine(III) species to form diaryliodonium tosylate **2.136**. The authors noted the instability of **2.136** as a challenge. Subjecting iodonium **2.136** to tetrabutylammonium [^{18}F]fluoride in DMSO at 80 °C resulted in formation of [^{18}F]DAA1106 **[^{18}F]2.94** in 46% RCC.



Scheme 2.31. Synthesis of iodonium **2.136** and subsequent synthesis of [^{18}F]DAA1106 **[^{18}F]2.94**

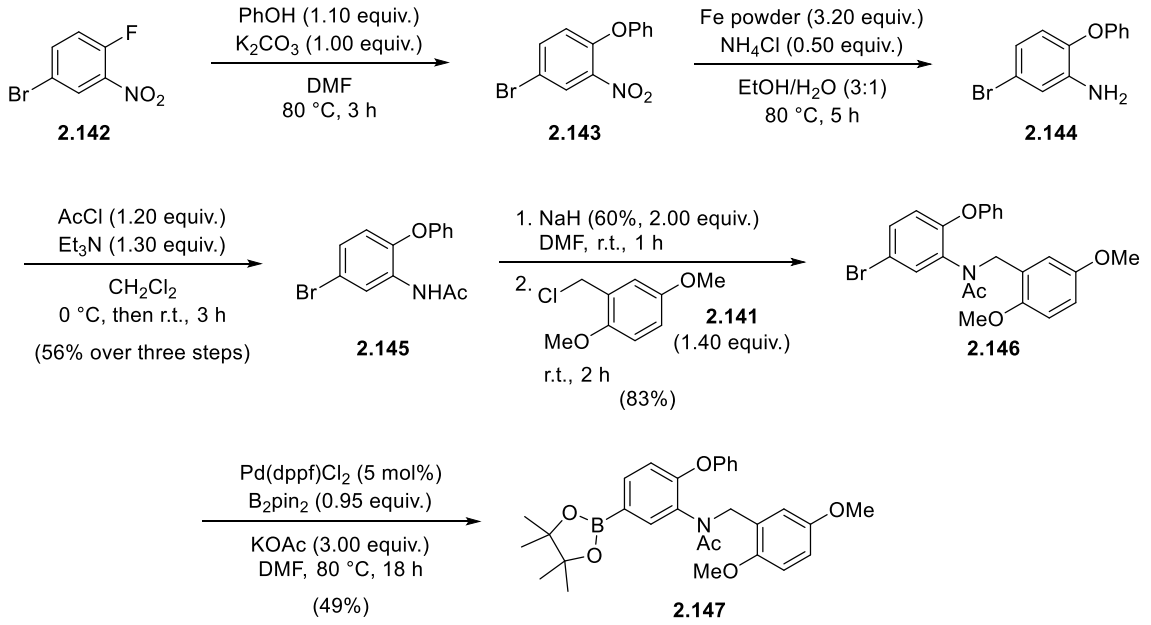
The electron-rich nature of the ^{18}F-labelling site in [^{18}F]DAA1106 led us to consider use of the copper-mediated ^{18}F-fluorodeboronation as an alternative route to this radioligand. Synthesis of the ^{19}F-reference compound was carried out by Dr. Matthew Tredwell following a reported procedure.[45] Nucleophilic substitution of aryl fluoride **2.137** with phenol resulted in formation of diaryl ether **2.138** (Scheme 2.32). Iron-mediated reduction of the nitro group to the aniline, followed by acetylation, formed acetanilide **2.140**. Finally, the amide was deprotonated with sodium hydride and alkylated with 2,5-dimethoxybenzyl chloride **2.141**.



Scheme 2.32. Synthesis of DAA1106, carried out by Dr. Matthew Tredwell

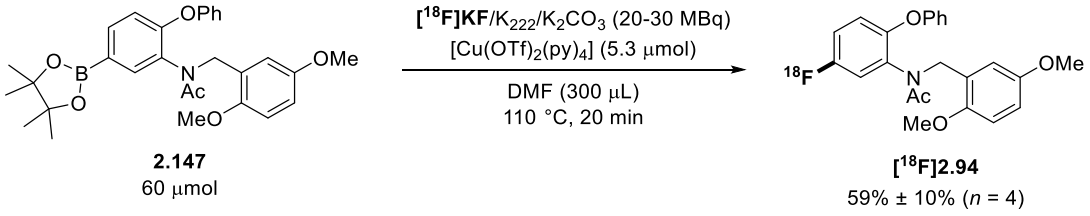
I carried out the synthesis of the boronic ester precursor for labelling. The synthesis of bromide **2.146** had been reported by Zhang; this route was followed (Scheme 2.33).[45] Nucleophilic substitution of aryl fluoride **2.142** with phenol was followed by iron-mediated reduction of the nitro group and acetylation of the resulting aniline to afford acetanilide **2.145** in 56% yield over three steps (Scheme 2.33). Deprotonation with sodium hydride and alkylation with 2,5-dimethoxybenzyl chloride **2.141** proceeded smoothly in 83% yield. The final step was Miyaura borylation, which afforded the requisite boronic ester **2.147** in 49%

yield. In this step, bis(pinacolato)diboron was used as the limiting reagent in order to facilitate purification.



Scheme 2.33. Synthesis of boronic ester **2.147**

Pleasingly, when boronic ester **2.147** was subjected to the standard ^{18}F-fluorodeboronation conditions, [^{18}F]DAA1106 **[^{18}F]2.94** was formed in 59% RCC (Scheme 2.34).



Scheme 2.34. ^{18}F-Fluorodeboronation of **2.147** to afford [^{18}F]DAA1106 **[^{18}F]2.94**

Figure 2.7 shows the radio-HPLC trace of the crude reaction mixture, overlaid with the UV-HPLC trace of ^{19}F-reference **2.94**.

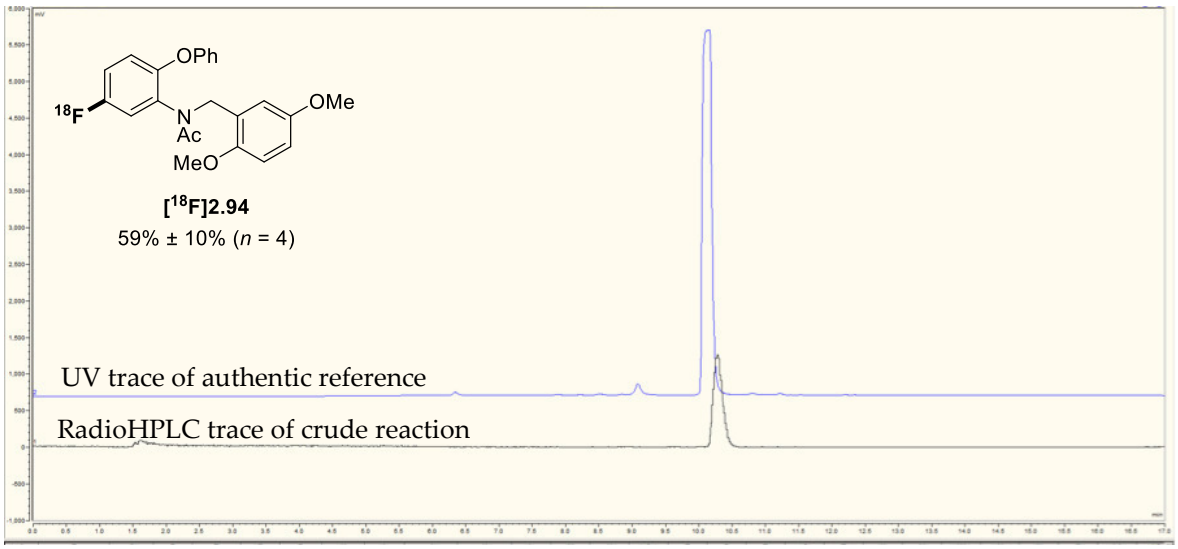


Figure 2.7. Radio-HPLC trace of the crude reaction mixture of the ^{18}F-fluorodeboronation of **2.147**, overlaid with the UV-HPLC trace of DAA1106 **2.94**

2.3.4 Scale-Up of ^{18}F-Fluorodeboronation Towards the Production of Clinically Relevant Doses

The ^{18}F-fluorodeboronation reactions described so far were carried out on a 20-30 MBq "research" scale. Analysis of the crude reaction mixtures by radio-TLC and radio-HPLC enabled determination of the radiochemical conversion, whilst the UV-HPLC profile offered insights into by-product formation. This reaction scale was chosen because it provided enough information for reaction development, whilst minimising the exposure of the researchers to radioactivity. However, this scale is insufficient for production of PET radiotracers for human imaging, for which approximately 300 MBq of the purified and reformulated tracer is injected.

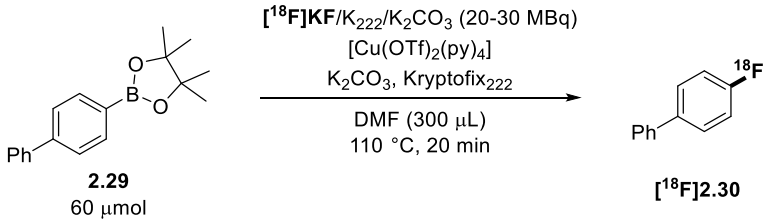
When carrying out reactions on the "research" scale, a solution of [^{18}F]KF/K_{222}/K_2CO_3 in acetonitrile was first prepared by re-dissolving the azeotropically-dried [^{18}F]KF/K_{222}/K_2CO_3 residue in 1 mL acetonitrile. For each reaction, an aliquot of the [^{18}F]KF/K_{222}/K_2CO_3 solution corresponding to 20-30 MBq

fluorine-18 was used. This aliquot corresponded to a volume of 10–50 μL, increasing over the course of the day as the fluorine-18 decayed. In addition to [^{18}F]fluoride, this aliquot also contains an average of 0.6 μmol potassium carbonate and an average of 1.1 μmol Kryptofix$_{222}$. These amounts are considerably lower than those of the substrate (60 μmol) and copper complex (5 μmol); the effect of potassium carbonate and Kryptofix on the "research" scale reactions is believed to be minimal.

When scaling up the reaction to provide enough of the final radiolabelled product for human imaging, the azeotropically-dried [^{18}F]KF/K$_{222}$/K$_2$CO$_3$ residue is instead dissolved in the reaction solvent, all of which is used in a single ^{18}F-fluorodeboronation. On this "isolation" scale, the amount of potassium carbonate in the reaction could be as high as 20 μmol; that of Kryptofix$_{222}$ could be as high as 36 μmol. These amounts are on the same order of magnitude as the amounts of substrate and copper complex employed, and have a more significant influence on the reaction.

We first investigated the effects of potassium carbonate and Kryptofix on the ^{18}F-fluorodeboronation by adding these to a reaction carried out under "research" conditions. As shown in Table 2.10, addition of a representative amount of potassium carbonate to the reaction reduced the RCC of **[^{18}F]2.30** by approximately half (entry 2 vs. entry 1). Addition of Kryptofix was more detrimental, reducing the RCC to only 7% (entry 3). The combination of both completely suppressed formation of **[^{18}F]2.30** (entry 4). However, we were pleased to discover that increasing the amount of copper complex to 20 μmol reduced the detrimental

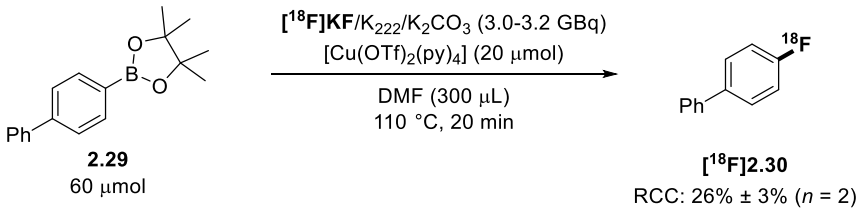
effects; **[^{18}F]2.30** was formed in 35% RCC (entry 5). Further increases in the loading of [Cu(OTf)$_2$(py)$_4$] did not have further beneficial effects.



Entry	[Cu(OTf)$_2$(py)$_4$] / μmol	K$_2$CO$_3$ / μmol	Kryptofix$_{222}$ / μmol	[^{18}F]2.30 RCC
1	5.3	-	-	63% ± 17% (*n* = 36)
2	5.3	14	-	35% ± 1% (*n* = 2)
3	5.3	-	23	7% ± 1% (*n* = 2)
4	5.3	14	23	0% (*n* = 2)
5	20	14	23	35% ± 14% (*n* = 2)
6	40	14	23	34% ± 11% (*n* = 2)
7	60	14	23	31% ± 1% (*n* = 2)

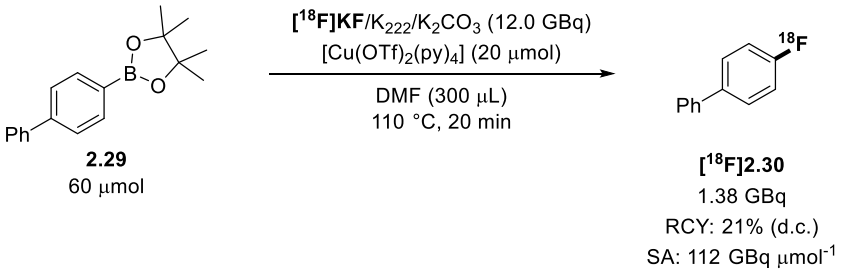
Table 2.10. Effect of added K$_2$CO$_3$ and Kryptofix$_{222}$ in the ^{18}F-fluorodeboronation of **2.29**

With improved conditions in hand, we applied these to the synthesis of **[^{18}F]2.30** on a larger scale. In these experiments, [^{18}F]fluoride was eluted from the anion exchange cartridge with potassium carbonate and Kryptofix and azeotropically dried with acetonitrile. A solution of the boronic ester and copper complex in DMF was added directly to the vial containing the dried [^{18}F]KF/K$_{222}$/K$_2$CO$_3$ complex. Starting from 3.0–3.2 GBq [^{18}F]KF/K$_{222}$/K$_2$CO$_3$ complex, ^{18}F-fluorodeboronation of boronic ester **2.29** afforded **[^{18}F]2.30** in 26% ± 3% RCC (*n* = 2, Scheme 2.35).



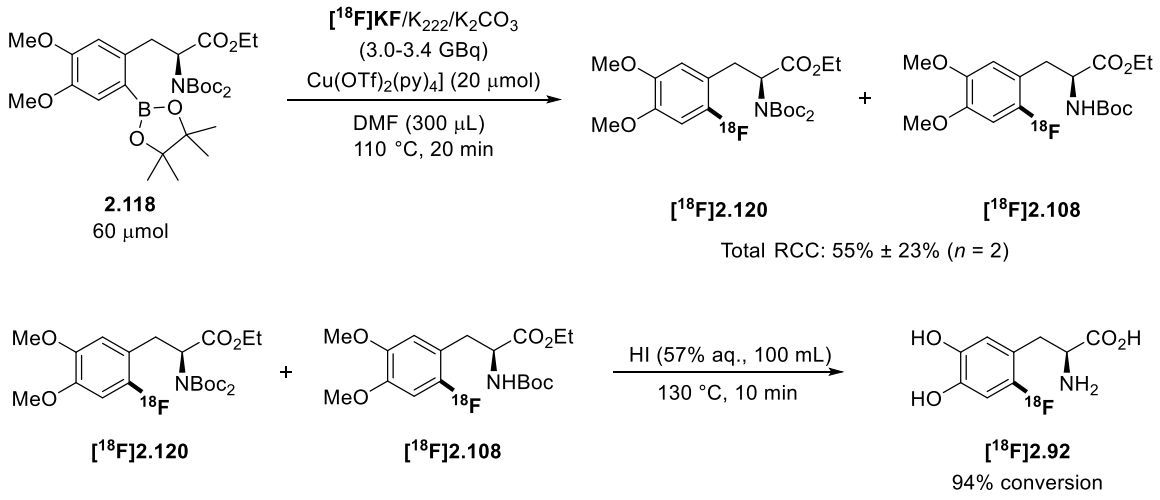
Scheme 2.35. Scale-up of ^{18}F-fluorodeboronation of **2.29** to 3 GBq

At the time of this work, SOMIL was limited to ordering a maximum of 4.0 GBq [^{18}F]fluoride. In order to investigate the behaviour of the reaction at higher activities, we collaborated with Imanova (London, UK). Starting from 12.0 GBq [^{18}F]fluoride, 1.38 GBq **[^{18}F]2.30** was isolated following preparative HPLC purification (Scheme 2.36). This corresponded to a decay-corrected radiochemical yield of 21%. The specific activity of **[^{18}F]2.30** was measured to be 112 GBq μmol^{-1}, which suggested that tracers produced using this method could be used for imaging of low-density neuroreceptors.



Scheme 2.36. Scale-up of ^{18}F-fluorodeboronation of **2.29** to 12.0 GBq, carried out by Imanova

We also sought to apply our scaled-up conditions to the ^{18}F-fluorination of [^{18}F]FDOPA **[^{18}F]2.92**. In these experiments, carried out in SOMIL, 3.0–3.4 GBq [^{18}F]KF/K_{222}/K_2CO_3 complex was used in the ^{18}F-fluorodeboronation of boronic ester **2.118**, affording a mixture of di-Boc **[^{18}F]2.120** and mono-Boc **[^{18}F]2.108** in 55% ± 23% total RCC (n = 2, Scheme 2.37). Deprotection of an aliquot using 57% aqueous HI at 130 °C for 10 minutes resulted in 94% conversion to [^{18}F]FDOPA **[^{18}F]2.92**.



Scheme 2.37. Synthesis of [^{18}F]FDOPA via ^{18}F-fluorodeboronation, scaled up to 3 GBq, followed by deprotection of an aliquot with aqueous HI

The enantiomeric purity of **[^{18}F]2.92** was determined by HPLC with a chiral stationary phase to be > 99%. Figure 2.8 shows the radio-HPLC trace after deprotection, overlaid with the UV-HPLC trace of the racemic ^{19}F-reference. These results suggest that ^{18}F-fluorodeboronation of an arylboronic ester precursor offers a viable route to the production of high-specific-activity [^{18}F]FDOPA for (pre)clinical imaging. The results discussed so far formed the basis of a publication in Angewandte Chemie.[47]

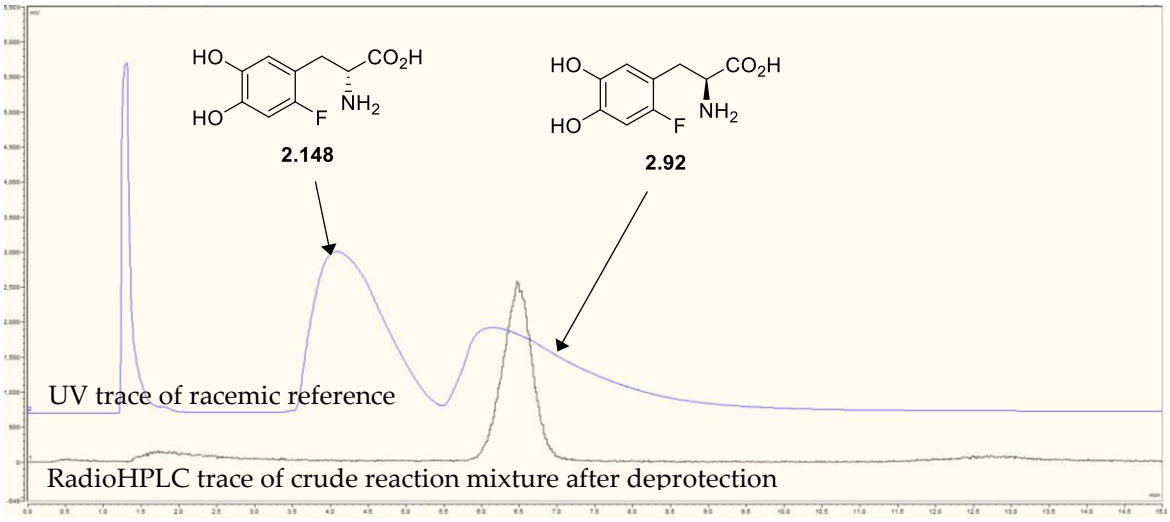
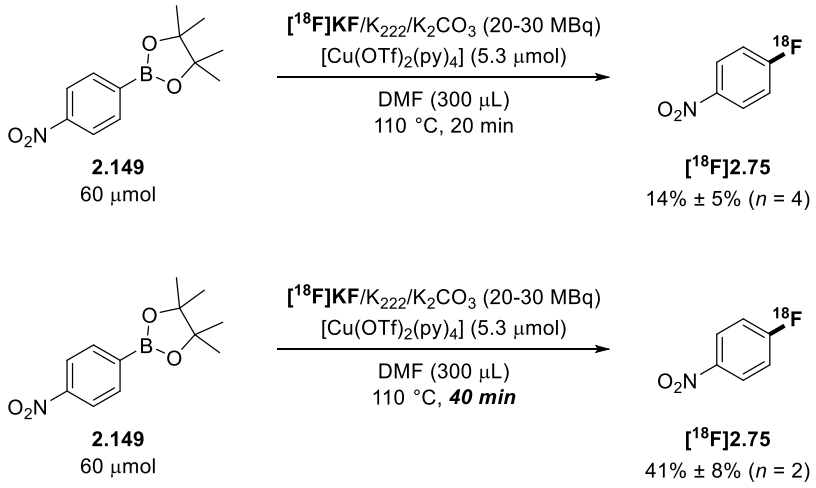


Figure 2.8. Radio-HPLC trace of crude reaction mixture after deprotection, overlaid with the UV-HPLC trace of racemic FDOPA. 6-[^{18}F]fluoro-D-DOPA **2.148** was not detected.

2.4 Re-Optimisation for Electron-Deficient Substrates

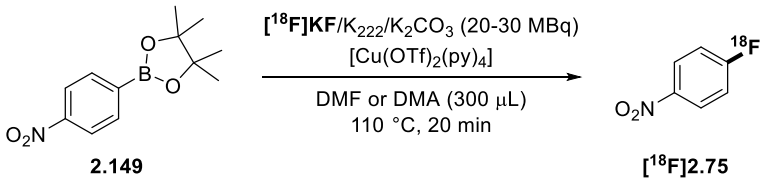
As discussed in section 2.2.4, electron-rich and electron-neutral aryl boronic esters performed much better in the ^{18}F-fluorodeboronation than electron-deficient arenes. Although the ability to label electron-rich arenes in good RCCs was highly significant, allowing access to electron-rich radiotracers from [^{18}F]fluoride, we sought to improve the RCCs for electron-deficient substrates, since this would further broaden the applicability of the method. Whilst *p*-nitrophenylboronic ester **2.149** afforded **[^{18}F]2.75** in only 14% RCC under the standard reaction conditions, we found that doubling the reaction time resulted in a significantly increased RCC, to 41% (Scheme 2.38). Whilst this was interesting, it was not a satisfactory solution to the problem of reactivity; as discussed in Chapter 1, section 1.3, a short reaction time is of great importance in ^{18}F-radiochemistry.



Scheme 2.38. ^{18}F-Fluorodeboronation of electron-deficient boronic ester **2.149** under standard conditions and with increased reaction time.

A better solution lay in changing the relative stoichiometry of boronic ester **2.149** and the copper complex (Table 2.11). It was discovered that using an excess of copper complex over boronic ester substrate significantly increased the RCC of

[^{18}F]2.75 (entry 3). Further increasing the amount of copper complex increased the RCC to 62% (entry 4). The highest RCC of **[^{18}F]2.75** using DMF as solvent was obtained when the amount of precursor was increased to 30 μmol. It was then found that changing the reaction solvent to *N*,*N*-dimethylacetamide (DMA) resulted in a further increase in RCC for a given amount of substrate and copper complex (entry 6 vs. entry 4, and entry 7 vs. entry 5). Using such a large amount of copper was not ideal, and we were pleased to observe that reducing the amount of **2.149** to 20 μmol and $[Cu(OTf)_2(py)_4]$ to 30 μmol did not significantly reduce the RCC (entry 8).



2.149 **[^{18}F]2.75**

Entry	Boronic ester / μmol	$[Cu(OTf)_2(py)_4]$ / μmol	Solvent	[^{18}F]2.75 RCC
1	60	5.3	DMF	14% ± 5% (*n* = 4)
2	15	5.3	DMF	10% ± 0% (*n* = 2)
3	15	20	DMF	49% ± 10% (*n* = 2)
4	15	40	DMF	62% ± 1% (*n* = 2)
5	30	40	DMF	70% ± 9% (*n* = 5)
6	15	40	DMA	81% ± 1% (*n* = 2)
7	30	40	DMA	85% ± 6% (*n* = 2)
8	20	30	DMA	81% ± 6% (*n* = 2)

Table 2.11. Optimisation of stoichiometry and solvent in the ^{18}F-fluorodeboronation of **2.149**

Having developed improved conditions for the ^{18}F-fluorodeboronation of boronic ester **2.149**, we investigated the effect of these conditions on the ^{18}F-fluordeboronation of other electron-deficient boronic esters. The RCCs for selected ^{18}F-fluoroarenes under the original conditions (A) and the re-optimised conditions (B) are compared in Table 2.12. In addition to **[^{18}F]2.75**, Conditions B were beneficial for **[^{18}F]2.150**, bearing the nitro substituent in the meta position, and

[^{18}F]2.74, bearing a para-cyano substituent. **[^{18}F]2.152** and **[^{18}F]2.153**, bearing ortho-fluoro substituents could be ^{18}F-labelled using conditions B, where conditions A failed to afford any radiolabelled product. The RCC of ortho-anisole **[^{18}F]2.61** was also increased on use of conditions B. Whilst these conditions were slightly superior to conditions A for ortho-nitro **[^{18}F]2.151**, this compound could not be ^{18}F-labelled in a satisfactory RCC.

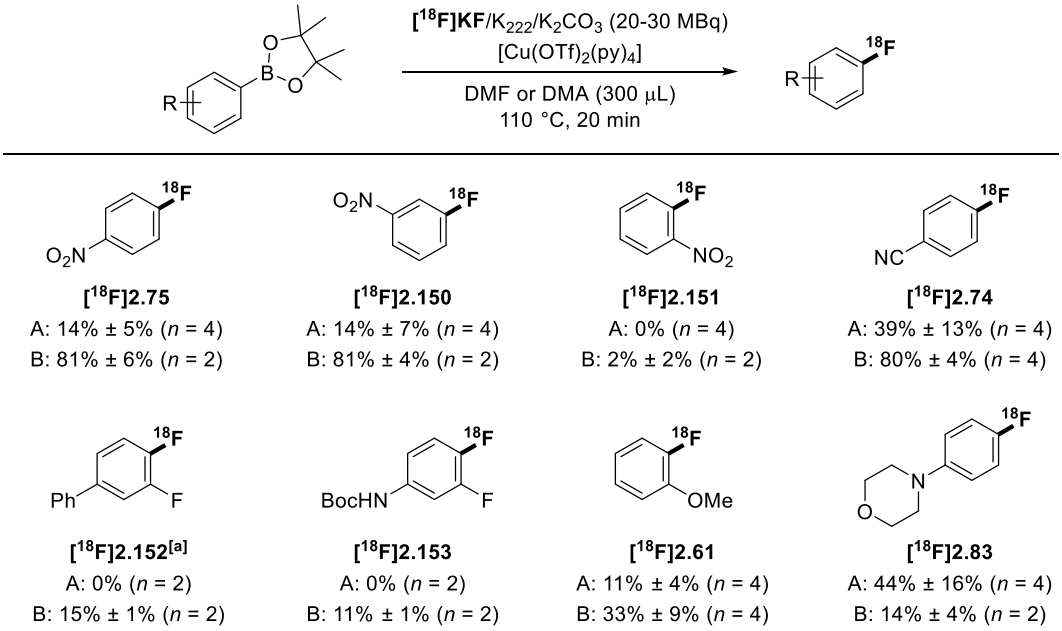


Table 2.12. Comparison between original and re-optimised conditions for selected substrates. Conditions A: Aryl boronic ester (60 μmol), $[Cu(OTf)_2(py)_4]$ (5.3 μmol), $[^{18}F]KF/K_{222}$ (20-30 MBq.), DMF (300 μL), air, 110 °C, 20 mins. Conditions B: Aryl boronic ester (20 μmol), $[Cu(OTf)_2(py)_4]$ (30 μmol), $[^{18}F]KF/K_{222}$ (20-30 MBq.), DMA (300 μL), air, 110 °C, 20 mins. [a] ^{19}F-Reference prepared by Dr. Stefan Gruber.

Whilst conditions B were superior for electron deficient substrates and those bearing ortho-substituents, the RCC of morpholine **[^{18}F]2.83** was considerably lower under these conditions than under conditions A. In addition, in this case, multiple unidentified radiolabelled byproducts were formed. This suggested that conditions B were not generally superior for all substrates.

2.5 Subsequent Developments within the Gouverneur Group

My involvement in the work in this section was limited to preparation of the boronic ester precursors to [^{18}F]FDOPA, [^{18}F]FMT and [^{18}F]DAA1106, as already discussed in section 2.3. This work is included here in order to provide a more complete description of the development of the ^{18}F-fluorodeboronation within the Gouverneur group.

Following the work described so far, and in parallel with the start of the work described in Chapter 3, further work was undertaken on the development of the reaction for the production of PET radiotracers on a clinically-relevant scale. The stoichiometry was re-optimised and DMA replaced DMF as the solvent of choice in many cases. Significantly, it was discovered that a large amount of the potassium carbonate used for fluoride elution could be replaced with the less basic potassium oxalate.[48], [49] These improvements allowed the synthesis of eight clinically-relevant radiotracers in isolated activities of 0.5 to 2.5 GBq starting from 4.0 to 10.0 GBq [^{18}F]fluoride; these activities would be more than enough for human PET imaging.

The radiotracers labelled with fluorine-18 via ^{18}F-fluorodeboronation from appropriately-protected aryl boronic ester precursors are given in Figure 2.9. The electron-rich tracers include [^{18}F]FDOPA **[^{18}F]2.92**, [^{18}F]FMT **[^{18}F]2.93** and [^{18}F]DAA1106 **[^{18}F]2.94**, which were discussed earlier, as well as [^{18}F]FDA **[^{18}F]2.154**, which has been used in the detection of pheochromocytomas and paragangliomas, and [^{18}F]MFBG **[^{18}F]2.155**, used to image norepinephrine transporter-expressing neuroblastomas.[50]–[52] The electron-deficient mGluR5 radioligands [^{18}F]FPEB

[^{18}F]2.156 and [^{18}F]FMTEB **[^{18}F]2.157** were also successfully radiolabelled via ^{18}F-fluorodeboronation, as was the central benzodiazepine receptor radioligand [^{18}F]flumazenil **[^{18}F]2.158**.[53]–[56] For [^{18}F]FDOPA, [^{18}F]FMT, [^{18}F]FDA and [^{18}F]MFBG, one-pot deprotection with aqueous HI was carried out following the ^{18}F-fluorodeboronation step. In all cases, the products were purified by semi-preparative HPLC; radiochemical yields refer to isolated products and are not decay-corrected.

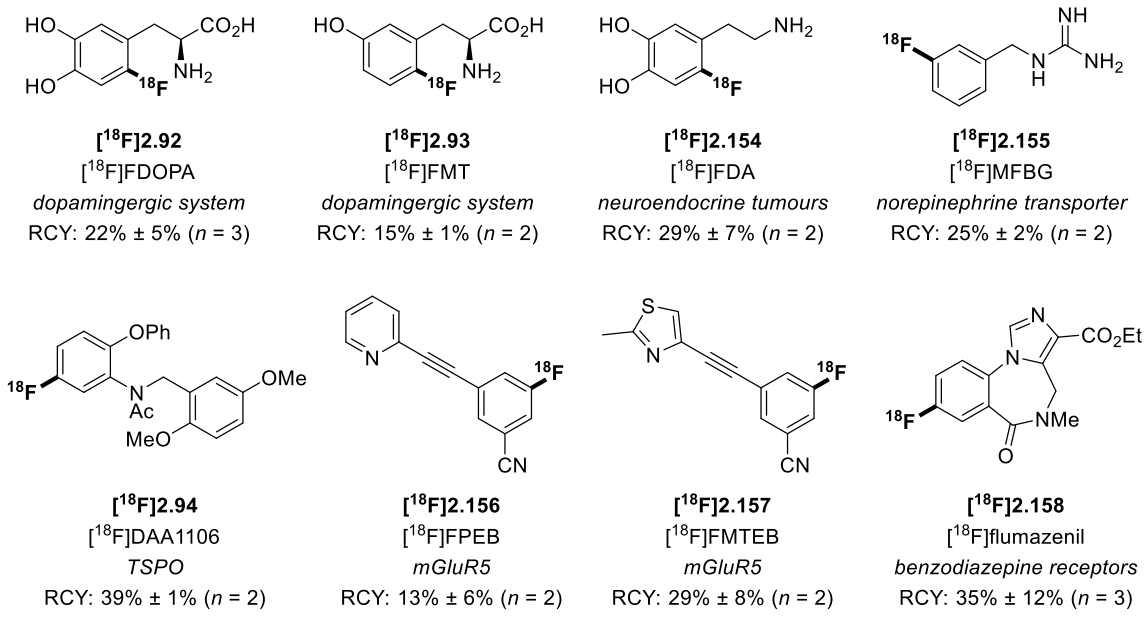
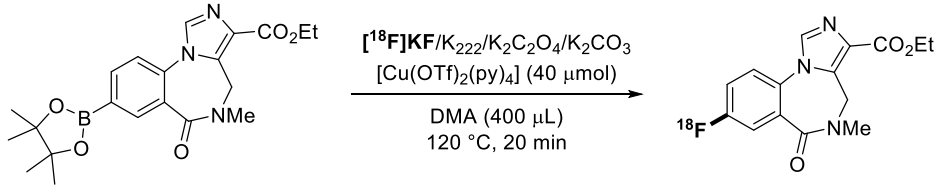


Figure 2.9. Clinically-relevant PET radiotracers synthesised from aryl boronic ester precursors via ^{18}F-fluorodeboronation. Radiochemical yields refer to isolated products after purification by semi-preparative HPLC and are non-decay-corrected.

The primary purpose of this study was to demonstrate that the Cu-mediated ^{18}F-fluorodeboronation of aryl boronic esters could be scaled up to provide adequate doses for human imaging studies. All eight radiotracers could be labelled using similar reaction conditions, with little optimisation for any one radiotracer. This demonstrates the flexibility and robustness of the ^{18}F-fluorodeboronation method.

In addition to work undertaken in Oxford, the group collaborated with the companies Imanova (London, UK) and ABX (Radeberg, Germany) in order to demonstrate reproducibility of the method in three different radiochemistry laboratories and on three different radiosynthetic platforms (NanoTek, Synthra and Neptis). [^{18}F]Flumazenil **[^{18}F]2.158** was synthesised on all three platforms by three different groups; the results are given in Table 2.13. The group at Imanova began with 26 GBq of [^{18}F]fluoride and isolated 5.1 GBq of **[^{18}F]2.158** (19% RCY), in > 99% radiochemical purity and with a specific activity of 124 GBq μmol^{-1}. Whilst the groups at Imanova and ABX obtained lower radiochemical yields than the group in Oxford, this demonstrated that the method could be applied in other radiochemistry laboratories. This work was published in Chemical Communications.[57] Further collaboration between our group and ABX resulted in the commercialisation of a boronic ester precursor for [^{18}F]FDOPA.[58]



2.159
30 μmol

[^{18}F]2.158

Entry	Laboratory	Synthesiser Platform	Starting Activity / GBq	[^{18}F]2.158 RCY / %, n.d.c.)
1	Oxford	NanoTek	4.0	35% ± 12% (*n* = 3)
2	Imanova	Synthra	26.0	19% (*n* = 1)
3[a]	ABX	Neptis	0.1-0.3	16% ± 4% (*n* = 10)

Table 2.13. ^{18}F-Fluorodeboronation of **2.159** in three different radiochemistry laboratories. **[a]** Conditions: **2.159** (36 μmol), $[Cu(OTf)_2(py)_4]$ (44 μmol), [^{18}F]KF/K_{222}/KH_2PO_4 (100-300 MBq), DMA (1.00 mL), air, 130 °C, 10 min.

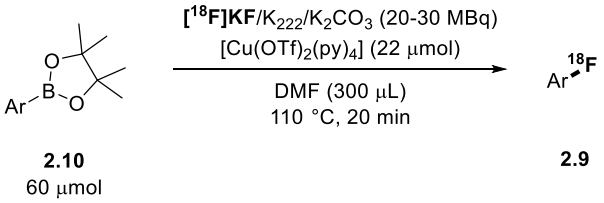
2.6 Subsequent Developments by Other Groups

An overview of the literature in ^{18}F-fluorination of arenes and heteroarenes up to 2013 was given in Chapter 1. However, since the start of this project, much work has been undertaken in the development of new methods for ^{18}F-fluorination of arenes, in particular by the groups of Sanford/Scott, Neumeier, Vasdev/Liang and Ritter/Hooker. Whilst the uptake of these methods by the wider radiochemistry community has been slow, they are likely to have a significant impact in the near future. Herein, developments in non-carrier-added methods for the ^{18}F-fluorination of arenes published since the beginning of the work described in this chapter will be discussed. Uses of previously-disclosed methods to label a specific target molecule with fluorine-18 will not be included.

2.6.1 ^{18}F-Fluorination from Arylboron Precursors

Following our initial disclosure, in 2015, Neumeier and co-workers evaluated the method and found the ^{18}F-fluorodeboronation of small aryl pinacol boronate esters to proceed well under small-scale aliquot conditions mimicking our own (Table 2.14).[59] When large amounts of potassium carbonate and Kryptofix were employed in the fluoride elution, in order to mimic the amount used in elution of a large batch of fluoride for synthesis of a clinical dose of a radiotracer, the RCCs were reduced to 5-7%. This mirrors our results given in section 2.3.4. Whilst our strategy was to replace some of the potassium carbonate with the less basic potassium oxalate, Neumeier and co-workers showed that significantly lower amounts of

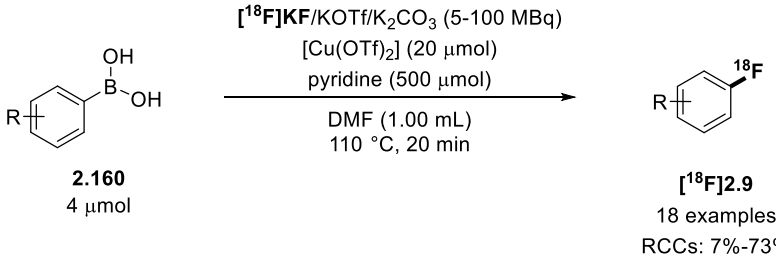
potassium carbonate and Kryptofix could be used in the elution, restoring RCCs to 41-64%.



Entry	Substrate	Aliquot RCC / % [a]	One-pot RCC / %	
			High base[b]	Low base[c]
1	C_6H_5	67	5	64
2	*p*-MeO-C_6H_4	66	7	42
3	*m*-CHO-C_6H_4	76	7	41

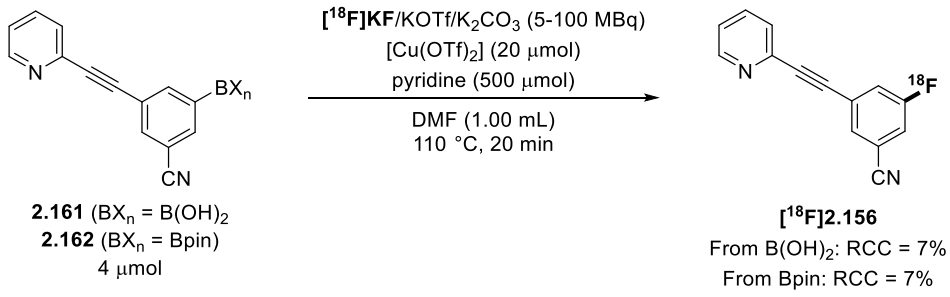
Table 2.14. ^{18}F-fluorodeboronation of arylboronic esters as reported by Neumeier and co-workers. Radiochemical conversions were determined by radio-HPLC. **[a]** Reactions were carried out using aliquots of [^{18}F]KF/K_{222}/K_2CO_3 following the procedure reported by our group. **[b]** Elution of fluoride was carried out using 13 mg K_{222} and 2.8 mg K_2CO_3. **[c]** Elution of fluoride was carried out using 270 μg K_{222} and 60 μg K_2CO_3.

In parallel with our work towards adapting the ^{18}F-fluorodeboronation of boronic esters towards the production of clinically-relevant doses described in section 2.5, the groups of Sanford and Scott developed a very similar copper-mediated ^{18}F-fluorodeboronation of boronic acid precursors.[60] Noting sensitivity of the reaction to large amounts of base, their optimised conditions involved elution of fluoride from a QMA cartridge using a 73:1 molar ratio of KOTf:K_2CO_3. After azeotropic drying, the reaction was carried out using a 1:5:125 ratio of boronic acid:$Cu(OTf)_2$:pyridine in DMF at 110 °C for 20 minutes (Scheme 2.39).



Scheme 2.39. Sanford and Scott's ^{18}F-fluorodeboronation of arylboronic acids

The substrate scope was similar to that of our ^{18}F-fluorodeboronation, albeit with slightly improved tolerance of an unprotected phenol. One advantage of the conditions developed by Sanford and Scott is the lower loading of precursor; this facilitates purification of the products and is of increased importance for more complex, expensive precursors. Interestingly, the supporting information contained a direct comparison of boronic acid and pinacol boronate ester precursors under their optimised conditions. In five of the seven cases, the boronic esters afforded the [^{18}F]fluoroarene products in improved RCCs. The authors described use of boronic acid substrates as advantageous due to the commercial availability of more boronic acids. However, the ultimate goal of this method development is to facilitate access to ^{18}F-labelled PET radiotracers. For complex targets, the pinacol boronate esters are generally easier to prepare than the corresponding boronic acids, due in part to the broad substrate scope of the palladium-catalysed Miyaura borylation. Indeed, Sanford and Scott prepared the boronic acid precursor **2.161** to [^{18}F]FPEB **[^{18}F]2.156** from the pinacol boronate **2.162**; both precursors performed equally well under their conditions (Scheme 2.40).



Scheme 2.40. Comparison of boronic acid and boronic ester precursors under Sanford/Scott conditions in the ^{18}F-fluorodeboronation to form [^{18}F]FPEB **[^{18}F]2.156**. RCCs determined by radio-TLC and radio-HPLC.

In 2017, following publication of our work described in section 2.5, Neumeier and co-workers disclosed further optimisation of the elution of fluoride in the ^{18}F-fluorodeboronation of arylboronic pinacol esters and arylboronic acids in order to obviate the need for azeotropic drying, which had been shown to result in loss of up to 50% of the fluoride due to adsorption onto the vessel walls.[61] It was shown that a solution of tetraethylammonium bicarbonate in alcohol solvents, ideally *n*-butanol, could be used to elute fluoride from the anion-exchange cartridge directly into a vial containing a solution of arylboron precursor and $[Cu(OTf)_2(py)_4]$ in DMA, which was then heated at 110 °C for 20 minutes under an atmosphere of air. This procedure was shown to afford [^{18}F]fluoroarenes with high RCCs; selected examples are given in Table 2.15.

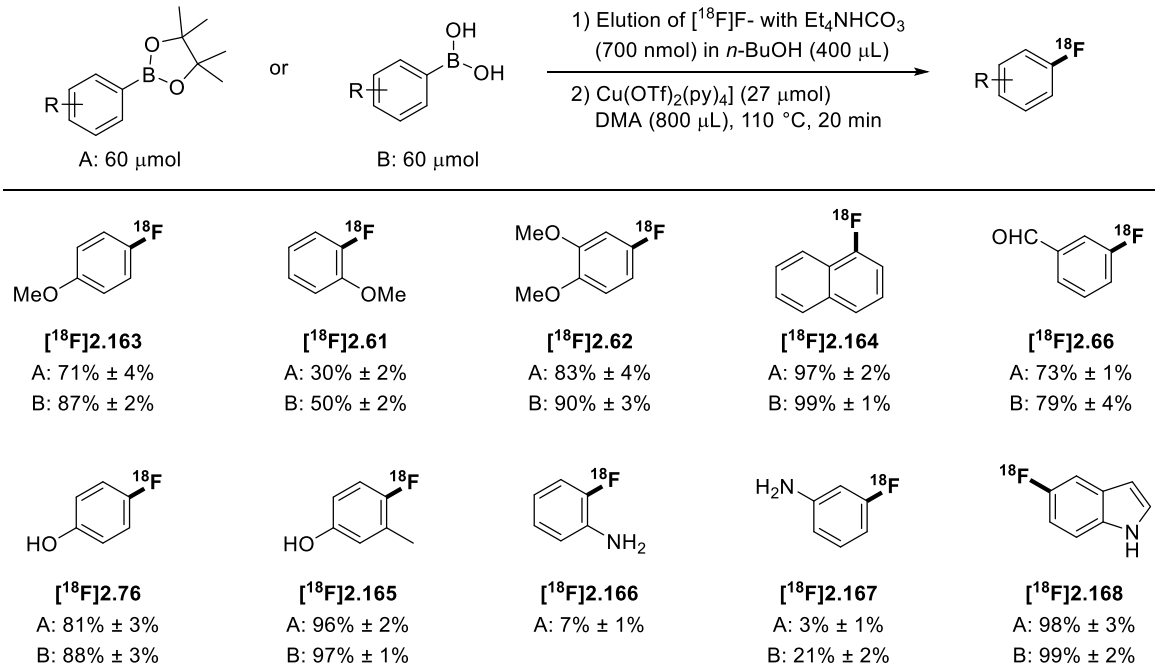
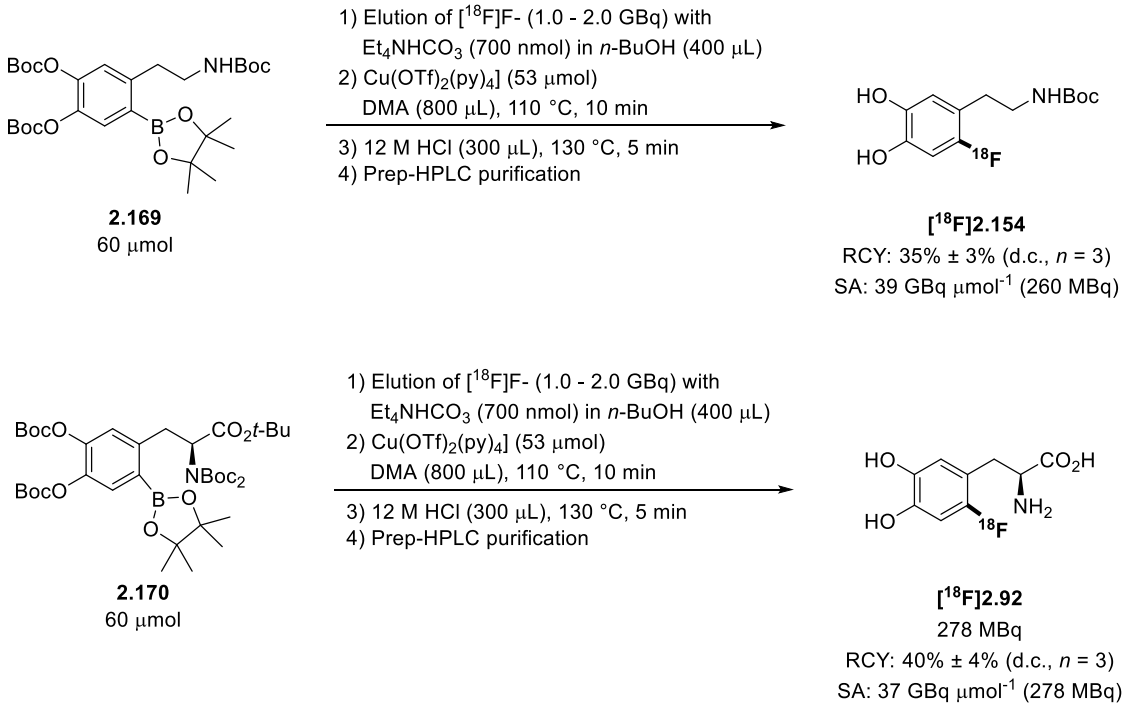


Table 2.15. Selected examples from substrate scope of Neumeier's alcohol-enhanced ^{18}F-fluorodeboronation of aryl boronic esters and aryl boronic acids. Reactions were performed three times (n = 3); radiochemical conversions were determined by radio-HPLC and are given in the form mean ± standard deviation. A: From aryl pinacol boronate ester substrate. B: From aryl boronic acid substrate.

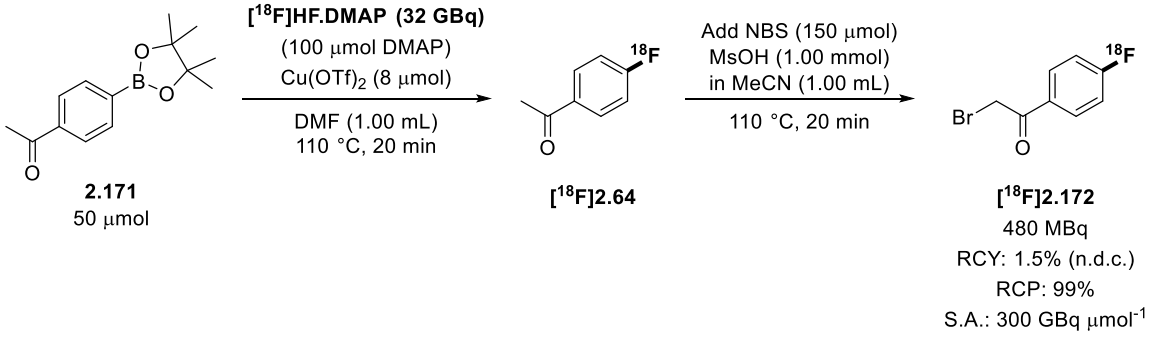
Most interestingly, in contrast to the original conditions published by ourselves and Sanford, phenols **2.76** and **2.165** could be ^{18}F-labelled from boronic ester or boronic acid precursors in high RCC without need for protection. However, this was not applied in the synthesis of [^{18}F]FDA **[^{18}F]2.154** or [^{18}F]FDOPA **[^{18}F]2.92**; in these cases, precursors **2.169** and **2.170**, bearing Boc-protected catechol groups, were employed (Scheme 2.40). The decay-corrected isolated yields of [^{18}F]FDA and [^{18}F]FDOPA (35% ± 3% and 40% ± 4%, respectively) were comparable to those obtained by our group following the optimisation described in section 2.5 (53% ± 9% and 40% ± 4%, respectively).



Scheme 2.40. Neumeier synthesis of [^{18}F]FDA **[^{18}F]2.154** and [^{18}F]FDOPA **[^{18}F]2.92** via alcohol-enhanced ^{18}F-fluorodeboronation of aryl boronic esters.

Later in 2017, Scott and Sanford disclosed their own studies towards optimisation of the elution of [^{18}F]fluoride from anion exchange cartridges.[62] These studies were primarily aimed towards an automated one-pot two-step

synthesis of 4-[^{18}F]fluorophenacyl bromide **[^{18}F]2.172** (Scheme 2.41) for evaluation as a radioligand for glycogen synthase kinase-3. The authors described elution of the [^{18}F]fluoride using aqueous solutions of organic bases. After azeotropic drying, the resulting [^{18}F]HF.base complexes were shown to be soluble in organic solvents; addition of a cryptand was not required. Automated synthesis of **[^{18}F]2.172** was achieved using an aqueous solution of DMAP to elute the [^{18}F]fluoride, followed by azeotropic drying with acetonitrile. ^{18}F-Fluorodeboronation of boronic ester **2.171**, followed by bromination of intermediate ketone **[^{18}F]2.64**, HPLC purification and reformulation, afforded 480 MBq **[^{18}F]2.172** in 1.5% RCY (n.d.c., Scheme 2.41). Radiochemical purity was 99%, and specific activity was 300 GBq μmol^{-1}.



Scheme 2.41. Automated synthesis of **[^{18}F]2.172** via ^{18}F-fluorodeboronation-bromination

In the same publication, Scott and Sanford described use of DMAP to elute [^{18}F]fluoride for the ^{18}F-fluorodeboronation of a small series of other boronic esters (Table 2.16). For **[^{18}F]2.74** and **[^{18}F]2.75**, a direct comparison can be drawn with our re-optimised conditions for electron-deficient substrates developed in section 2.5. In both cases, the RCC obtained under our re-optimised conditions was significantly higher (80% and 81% RCC, respectively).

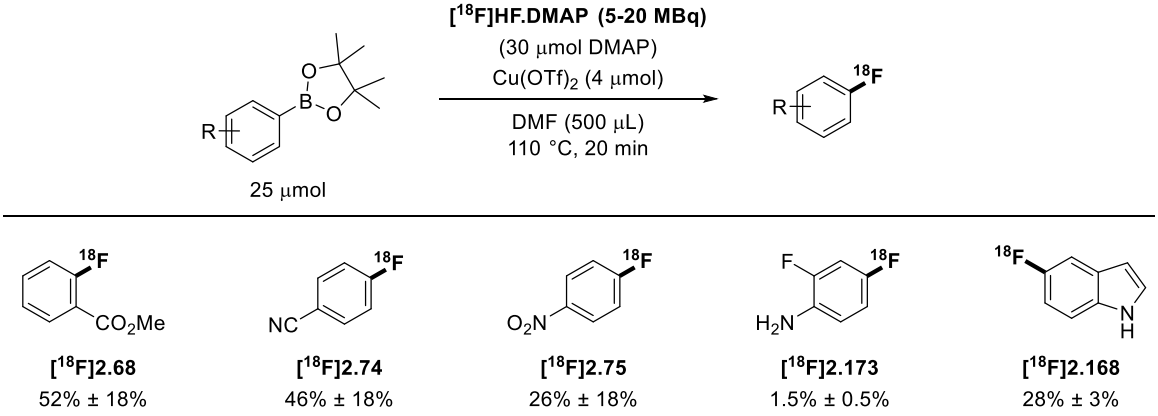
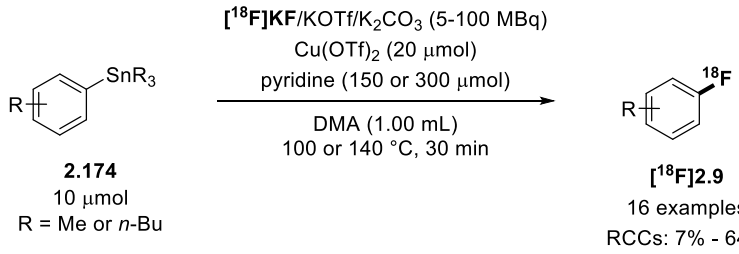


Table 2.16. ^{18}F-Fluorodeboronation of arylboronic esters using DMAP elution of [^{18}F]fluoride

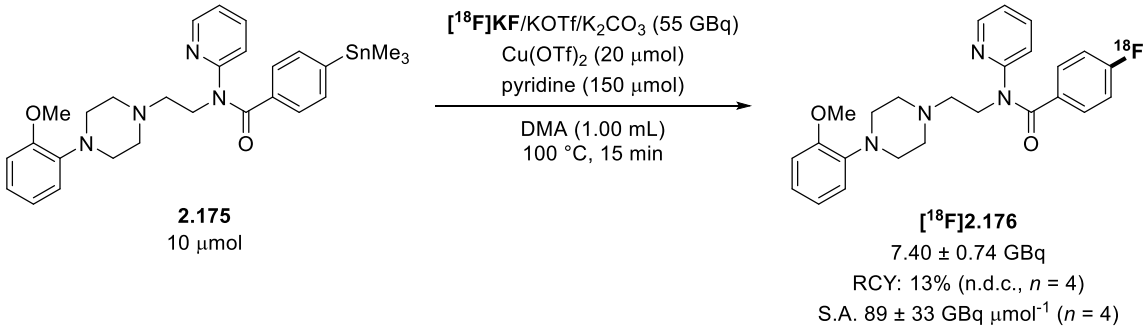
2.6.2 ^{18}F-Fluorination from Arylstannane Precursors

In 2016, Sanford and Scott disclosed a copper-mediated nucleophilic ^{18}F-fluorination of arylstannanes (Scheme 2.42).[63] The conditions employed were similar to those of the copper-mediated nucleophilic fluorodeboronation of arylboronic esters and acids. Most of the substrates were electron-neutral and electron-rich; no substrates contained unprotected O–H or N–H groups. In general, radiochemical conversions were comparable to those obtained using the ^{18}F-fluorodeboronation methods. Amongst the substrates were the radioligand [^{18}F]FPEB and a protected form of the radiotracer [^{18}F]FDOPA. The authors noted that the ^{18}F-fluorodestannylation was much more tolerant of an ortho-methoxy substituent than the corresponding ^{18}F-fluorodeboronation.



Scheme 2.42. Copper-mediated ^{18}F-fluorodestannylation developed by Sanford/Scott

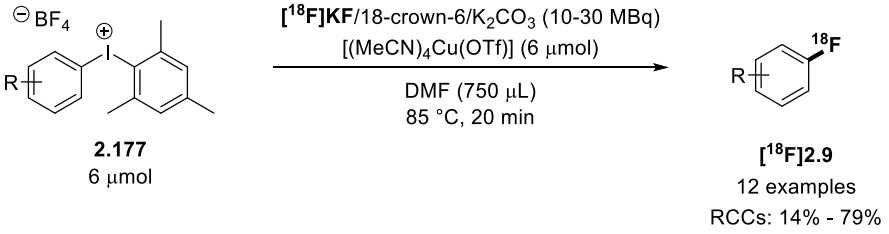
The method was automated for the production of the serotonin receptor ligand [^{18}F]MPPF **[^{18}F]2.176** (Scheme 2.43). Starting from 55 GBq cyclotron-produced [^{18}F]fluoride, 7.40 GBq **[^{18}F]2.176** was produced after HPLC purification and reformulation, corresponding to a non-decay-corrected radiochemical yield of 13%. The specific activity was measured to be 90 GBq μmol^{-1}. Importantly, the doses produced after purification and reformulation passed all cGMP quality control testing needed for clinical use, including residual levels of both copper and tin.



Scheme 2.43. Automated synthesis of [^{18}F]MPPF **[^{18}F]2.176** via ^{18}F-fluorodestannylation

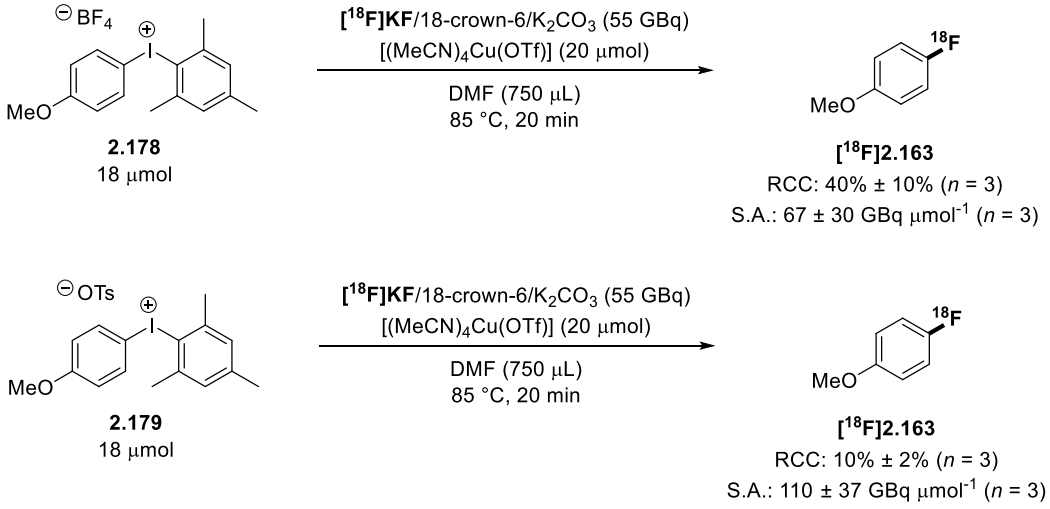
2.6.3 ^{18}F-Fluorination from (Mesityl)(Aryl)Iodonium Salts

In 2013, Sanford and co-workers reported the copper-catalysed fluorination of (mesityl)(aryl)iodonium salts with KF.[64] In previous syntheses of fluoroarenes via thermal decomposition of diaryliodonium salts in the presence of fluoride, selectivity was primarily driven by the relative electronic properties of the two aryl groups.[65] However, in this case, the selectivity was controlled by sterics; fluorination on the mesitylene ring was strongly disfavoured, and the alternative aryl fluoride product was formed in at least 19:1 selectivity in most cases.



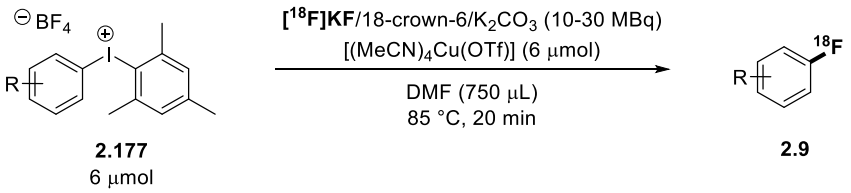
Scheme 2.44. Copper-mediated ^{18}F-fluorination from (mesityl)(aryl)iodonium salts

Later that year, Sanford and Scott reported the translation of the method for the ^{18}F-labelling of fluoroarenes (Scheme 2.44).[66] The reaction proceeded efficiently and tolerated ethers, aldehydes, ketones, esters, amides and aryl iodides, with RCCs ranging from 14% to 79%. The authors claimed that in contrast to (2-thienyl)(aryl)iodonium salts, which are often challenging to prepare and suffer from low stability and a short half-life, (mesityl)(aryl)iodonium salts are shelf-stable for months, provided that they are protected from intense light. Interestingly, the specific activity of 4-[^{18}F]fluoroanisole **[^{18}F]2.163** produced from (4-methoxyphenyl)(mesityl)iodonium tosylate **2.179** was compared with that produced from the corresponding tetrafluoroborate salt **2.178** (Scheme 2.45). The specific activity of **[^{18}F]2.163** produced from tetrafluoroborate **2.178** (67 GBq μmol^{-1}) was of the same order of magnitude as that produced from tosylate **2.179** (110 GBq μmol^{-1}), suggesting that isotopic dilution of ^{18}F with ^{19}F was not a significant problem under those reaction conditions.



Scheme 2.45. Copper-mediated ^{18}F-fluorination from (mesityl)(aryl)iodonium salts

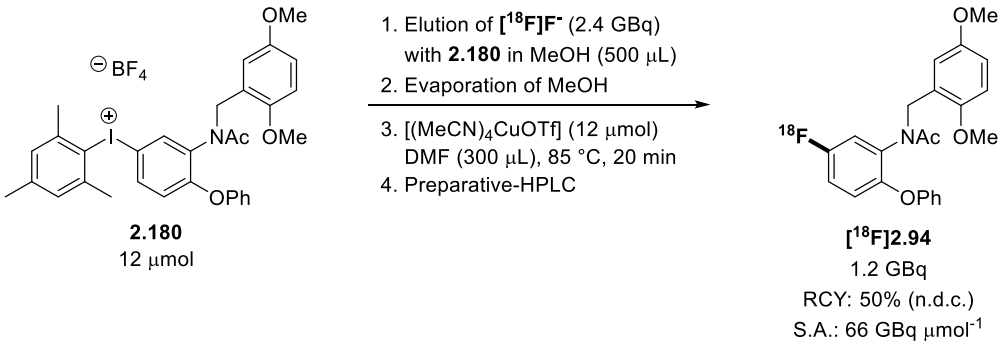
In 2015, Neumerier and co-workers disclosed their own studies on the copper-mediated ^{18}F-fluorination from (mesityl)(aryl)iodonium salts.[59] As with the copper-mediated ^{18}F-fluorodeboronation, they found that whilst Sanford and Scott's ^{18}F-labelling under small aliquot conditions was reproducible (Table 2.17), the azeotropic drying process led to high losses of [^{18}F]fluoride due to adsorption to the vessel walls. Subjecting the reaction to the full amount of 18-crown-6 and potassium carbonate used by Sanford and Scott in elution of the [^{18}F]fluoride resulted in low RCCs and a loss of selectivity. Reducing the amount of 18-crown-6 and potassium carbonate restored selectivity and increased RCCs.



Entry	Substrate	Aliquot RCC / % [a]		One-pot RCC / %	
		Sanford	Neumeier	High base[b]	Low base[c]
1	C_6H_5	-	56	1 (5)	28
2	*p*-MeO-C_6H_4	79	84	< 0.5 (3)	56
3	*m*-CHO-C_6H_4	35	36	5 (1)	26

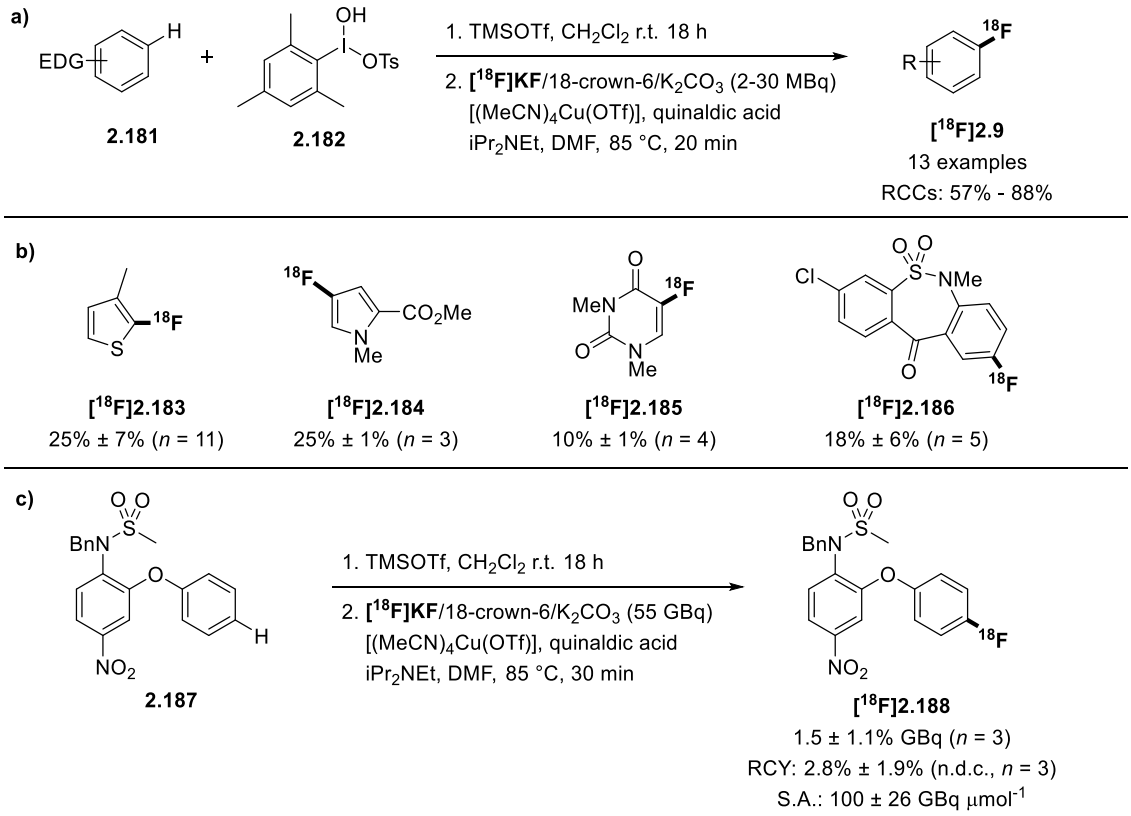
Table 2.17. ^{18}F-fluorodeboronation of (mesityl)(aryl)iodonium salts as reported by Neumeier and co-workers. Radiochemical conversions were determined by radio-HPLC. Figures in parentheses refer to [^{18}F]fluoromesitylene. **[a]** Reactions were carried out using aliquots of [^{18}F]KF/18-crown-6/K_2CO_3 following the procedure reported by Sanford and Scott. **[b]** Elution of fluoride was carried out using 15 mg 18-crown-6 and 3.0 mg K_2CO_3. **[c]** Elution of fluoride was carried out using 470 μg 18-crown-6 and 110 μg K_2CO_3.

The authors then demonstrated that a solution of the (mesityl)(aryl)iodonium salt in methanol could be used in place of potassium carbonate and 18-crown-6 for elution of the fluoride. In addition to simple (mesityl)(aryl)iodonium salts, this protocol was applied to radiotracers including the TSPO ligand [^{18}F]DAA1106 **[^{18}F]2.94** (Scheme 2.46). Starting from 2.4 GBq [^{18}F]fluoride, 1.2 GBq **[^{18}F]2.94** was isolated after preparative HPLC purification, corresponding to 50% RCY (n.d.c.). This result was superior to our group's 31% non-decay-corrected radiochemical yield from the boronic ester precursor described in section 2.5.



Scheme 2.46. Synthesis of [^{18}F]DAA1106 **[^{18}F]2.94** from iodonium **2.180**

Very recently, Sanford and Scott described a protocol for the in-situ synthesis of (mesityl)(aryl)iodonium salts from electron-rich (hetero)arenes and their subsequent ^{18}F-fluorination.[67] Electrophilic aromatic substitution of electron-rich arenes **2.181** with iodonium **2.182** was reported to be highly selective for formation of the para-isomer. The resulting (mesityl)(aryl)iodonium salts were not isolated; aliquots of the solution were used in the subsequent ^{18}F-fluorination step.



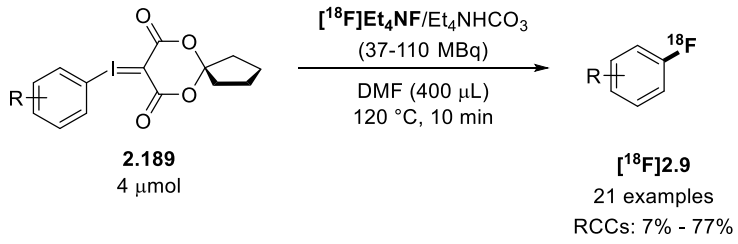
Scheme 2.47. a) In-situ formation of (mesityl)(aryl)iodonium salts from electron-rich arenes, followed by ^{18}F-fluorination. b) Heteroarenes successfully ^{18}F-fluorinated in this way. c) Scale up of this process applied to protected nimesulide derivative **2.187**.

For electron-rich arenes, the RCCs reported were generally excellent (Scheme 2.47a). Several examples of heteroaryl substrates were included; a pyrrole and a thiophene were ^{18}F-fluorinated directly on the heteroaryl ring (Scheme 2.47b). Although selectivity was poor in these cases, with formation of multiple

radiolabelled byproducts, preparation of these products via other methods would be extremely challenging.The authors also reported use of the method on a benzyl-protected derivative **2.187** of the non-steroidal anti-inflammatory drug nimesulide (Scheme 2.47c). Starting from 55 GBq [^{18}F]fluoride, 1.5 GBq **[^{18}F]2.188** was produced, corresponding to a 2.8% RCY (n.d.c.). The RCC of the same reaction on an aliquot scale was reported to be 81% ± 5% (n = 7). This huge discrepancy between RCCs and isolated yields suggests that further work is required before this method is used in the preparation of radiotracers for PET imaging.

2.6.3 ^{18}F-Fluorination from Spirocyclic Aryliodonium Ylides

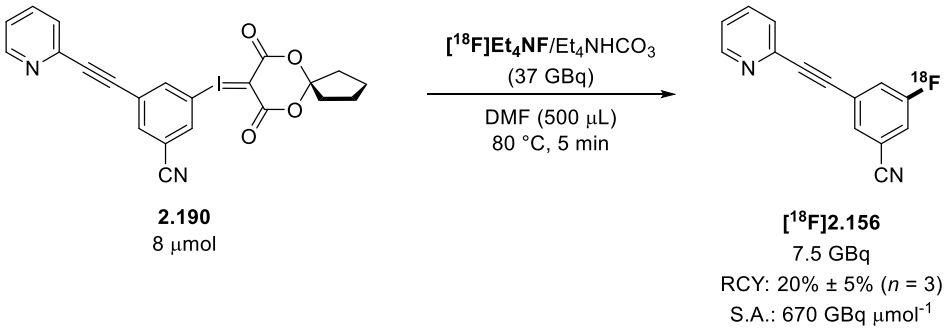
In 2014, Vasdev and Liang described the use of aryliodonium ylides based on a spirocyclic variant of the Meldrum's acid scaffold as alternative precursors for ^{18}F-fluorination of arenes (Scheme 2.48).[68] Heating spirocyclic iodonium ylides **2.189** with tetraethylammonium [^{18}F]fluoride complex in DMF at 120 °C for 10 minutes afforded [^{18}F]fluoroarenes **[^{18}F]2.9** in RCCs ranging from 7% to 77%. In general, electron-deficient arenes could be ^{18}F-fluorinated in higher RCCs than electron-rich arenes. Ketone, ester, amide, nitro and aryl bromide functionality was shown to be tolerated. Arenes bearing alkyl groups in both ortho positions could be ^{18}F-fluorinated efficiently in this way, although those with coordinating groups in the ortho position were much more variable in terms of RCC. Most significantly, pyridine could be ^{18}F-fluorinated in the 3-position in 65% RCC, potentially making this the method of choice for the preparation of 3-[^{18}F]fluoropyridines.



Scheme 2.48. ^{18}F-Fluorination of arenes from spirocyclic iodonium ylide precursors

The authors described these spirocyclic iodonium ylides as stable crystalline solids, addressing some of the instability problems associated with earlier precursors for ^{18}F-fluorination based on iodine(III) reagents. However, the ylides required preparation from the corresponding aryl iodides under oxidising conditions; reagents used include $NaBO_3$, *m*-CPBA, Selectfluor, UHP, Oxone and DMDO. Yields of the ylides from the aryl iodides ranged from 9% to 61%, with many around 30%. Functional groups sensitive to these oxidising conditions would not be tolerated; no examples were shown of aldehydes or unprotected alcohols or amines.

In 2015, the same group described validation of the method for human use in the preparation of [^{18}F]FPEB **[^{18}F]2.156** (Scheme 2.49).[69] A reduction in both temperature and base concentration was required in order to suppress a hydrolysis side-reaction. Automated synthesis using a GE TRACERlab module afforded 7.5 GBq **[^{18}F]2.156**, corresponding to a non-decay-corrected RCY of 20%, with a specific activity of 670 GBq μmol^{-1}.



Scheme 2.49. Synthesis of [^{18}F]FPEB **[^{18}F]2.156** via ^{18}F-fluorination of iodonium ylide **2.190**

A third publication from Vasdev and Liang disclosed mechanistic studies via DFT calculations, in addition to the use of iodonium ylides derived from adamantanone, which exhibited increased stability and improved RCCs for electron-rich substrates.[70] This enabled the synthesis of [^{18}F]FMT in 12% RCY (n.d.c.), compared to only 1-2% from the cyclopentanone-derived iodonium ylide. Several [^{18}F]fluoroheteroarenes and [^{18}F]fluoroarenes bearing medicinally-relevant heterocyclic motifs were also prepared; selected examples are given in Table 2.18.

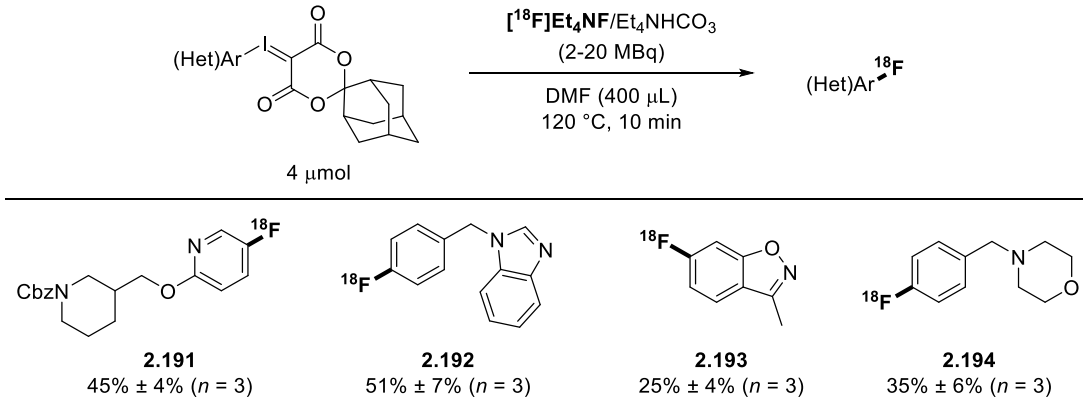


Table 2.18. ^{18}F-Fluorination of arenes bearing medicinally-relevant heterocyclic motifs from spirocyclic iodonium ylide precursors

2.6.4 ^{18}F-Fluorination from Phenols

In 2011, the Ritter group described use of an imidazoline-type reagent for the deoxyfluorination of phenols. A follow-up study in 2016 by Ritter and Hooker disclosed computational and kinetic mechanistic studies, as well as the translation of this method to the preparation of [^{18}F]fluoro(hetero)arenes.[71] The first step was the reaction of chloroimidazolium chloride **2.196** with the phenol **2.195** to form aryloxyimidazolium chlorides **2.197**, which were isolated by filtration (Table 2.19). A solution of aryloxyimidazolium chloride **2.197** and either potassium bicarbonate or tri-*n*-butylamine in a 10:1 mixture of butanone and ethanol was used to elute [^{18}F]fluoride from an anion-exchange cartridge; azeotropic drying was not required. Stirring at 130 °C for 20 minutes afforded [^{18}F]fluoro(hetero)arenes **[^{18}F]2.198** in 13%-99% RCC. Selected examples are given in Table 2.19. A range of unprotected O–H and N–H groups were tolerated. The method was restricted to electron-deficient phenols as a consequence of the mechanism: a concerted nucleophilic aromatic substitution.

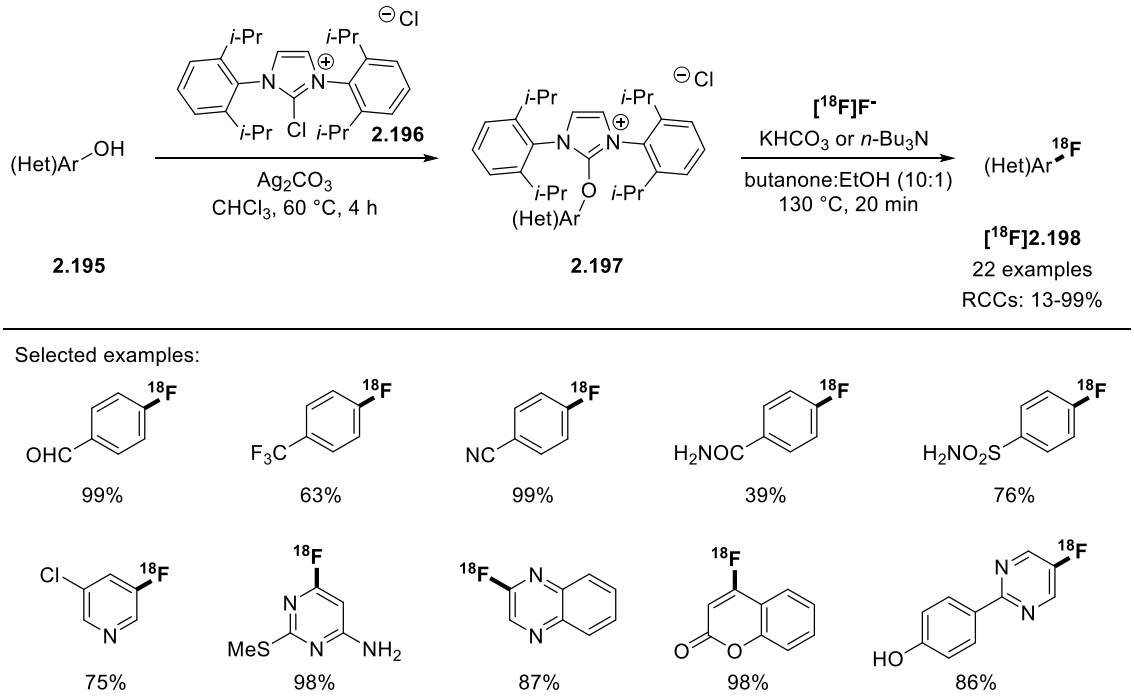


Table 2.19. ^{18}F-Deoxyfluorination for the synthesis of [^{18}F]fluoro(hetero)arenes. RCCs were determined by radio-HPLC.

Recently, Ritter and Hooker revealed the use of ruthenium π-complexes to broaden the substrate scope of the transformation via reduction of the electron density on the arene (Table 2.20). Under these conditions, more electron-rich substrates such as anisole **[^{18}F]2.163**, piperazine **[^{18}F]2.199** and indole **[^{18}F]2.200** could be formed from the corresponding phenols. The authors identified the rate-limiting step of the transformation to be decomplexation of the [^{18}F]fluoroarene product from ruthenium. This, the relatively low elution efficiency (generally between 60-70%) and the requirement for 30-40 mg reagents, were described as limitations of the method. It should also be noted that although the ruthenium complex employed is air- and moisture-stable, it is not commercially available and must be prepared in a glovebox using a highly toxic organothallium reagent.

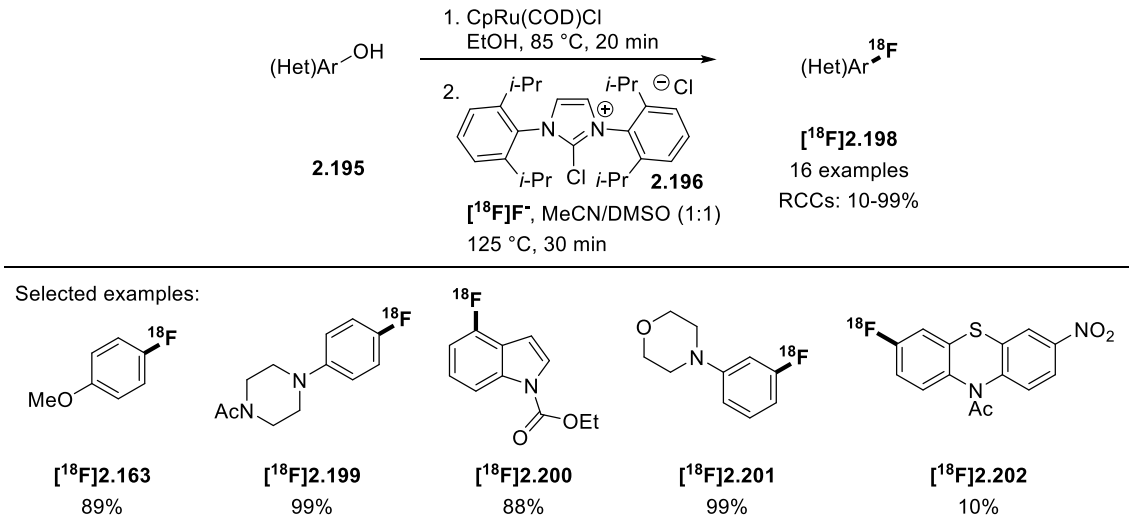
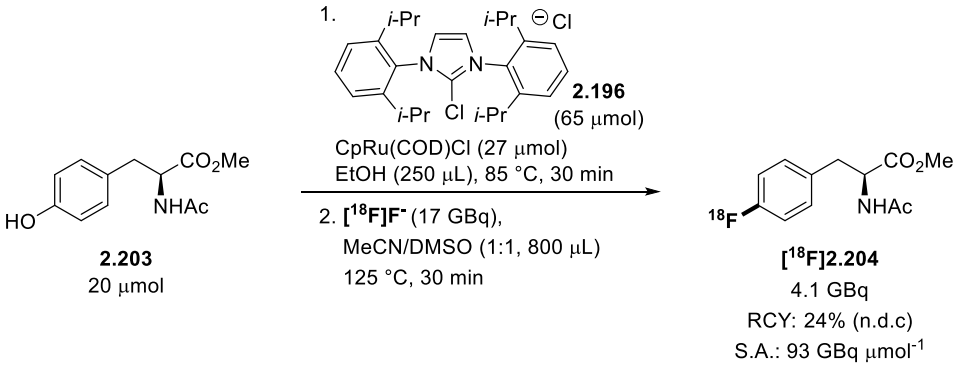


Table 2.20. ^{18}F-Deoxyfluorination assisted by π-complexation to ruthenium for the synthesis of [^{18}F]fluoro(hetero)arenes. RCCs were determined by radio-HPLC.

The scalability of the method was demonstrated by the synthesis of protected 4-[^{18}F]fluorophenylalanine **[^{18}F]2.204** (Scheme 2.50). Starting from 17 GBq [^{18}F]fluoride, 4.1 GBq **[^{18}F]2.204** was isolated after preparative HPLC purification, corresponding to a RCY of 24% (n.d.c). Specific activity was 93 GBq μmol^{-1} and levels of ruthenium were measured to be 101 ppb, significantly lower than the specified limit of 1 ppm.



Scheme 2.50. Automated synthesis of **[^{18}F]2.204** via deoxyfluorination of **2.203** assisted by π-complexation to ruthenium

2.7 References

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Chapter 3

Derisking the Copper-Mediated ^{18}F-Fluorination of Complex Targets

Chapter 3: Derisking the Copper-Mediated ^{18}F-Fluorination of Complex Targets

3.1 Challenges Associated with ^{18}F-Fluorination of Complex Targets

The method developed in Chapter 2 was shown to be suitable for the ^{18}F-fluorination of both electron-rich and electron-deficient arenes. Applicability to the synthesis of clinically-relevant radiotracers was then demonstrated, as was the reproducibility of the method on three different radiosynthetic platforms. The next aim was to demonstrate suitability of the method in a medicinal chemistry context. As discussed in Chapter 1, ^{18}F-radiolabelling of drug candidates could allow for PET studies at an early stage in the drug discovery pipeline, providing evidence for target occupancy, target engagement and biodistribution. However, many FDA approved drugs are more complex and heterocycle-rich than the radiotracers ^{18}F-labelled in section 2.3; an analysis by Njardarson and co-workers revealed that 59% of the small-molecule drugs approved by the FDA up to 2012 contain at least one nitrogen heterocycle.[1] This is unsurprising; due to their unique electronic distribution, shape and scaffold rigidity, these motifs have been used to tailor potency, physicochemical and pharmacokinetic properties of drug candidates.[2] When looking to apply the Cu-mediated ^{18}F-fluorodeboronation to the ^{18}F-labelling of drugs bearing multiple heterocycles, such as those in Figure 3.1, it was unclear as to whether these complex molecules would be tolerated by the reaction. Specifically, coordination of a heterocycle to the copper might be expected to reduce the efficiency of the ^{18}F-fluorodeboronation, or even stop the reaction completely.

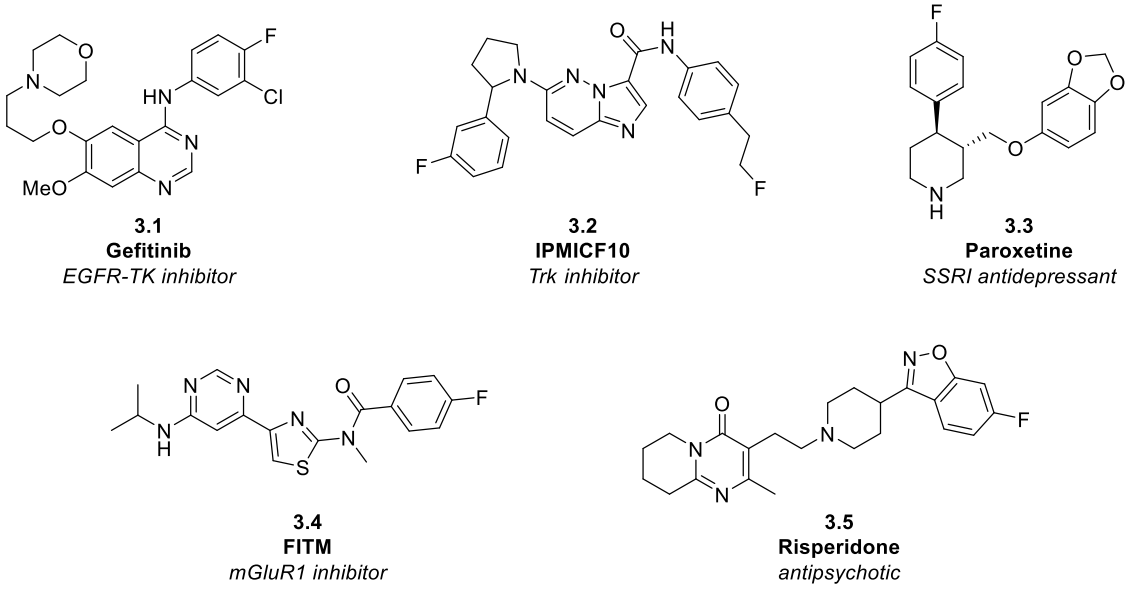


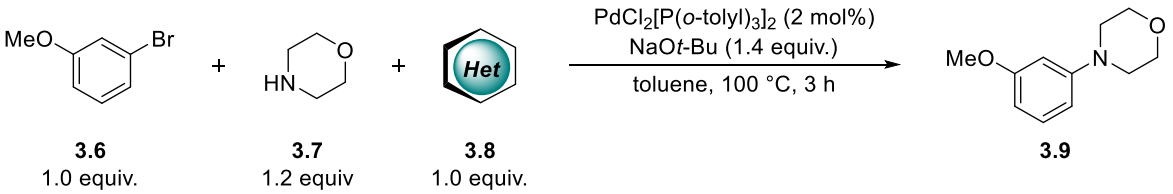
Figure 3.1. Heterocycle-containing fluorinated drugs of interest for ^{18}F-labelling

Synthesis of complex radiolabelling precursors can be expensive in terms of both time and resources. Whilst in most cases, the synthetic route used for the fluorinated drug of interest is known, an analogous synthetic route may not be suitable for synthesis of the boronic ester precursor required for ^{18}F-fluorination. In order to justify the expense of precursor synthesis, it would be highly desirable to be reasonably confident that the target precursor would be compatible with the desired ^{18}F-fluorination before embarking on the necessary route development.

3.2 The Paucity of Information on Compatibility with Heterocycles

Whilst our earlier studies provided information on the compatibility of the ^{18}F-fluorodeboronation with key functional groups (section 2.2.4), the compatibility with the heterocyclic rings commonly found in drug molecules was unknown. This situation was far from unique; an analysis by Nelson and Marsden of the substrate

scope of synthetic methodology papers with (hetero)aryl substrates showed that heteroaryl groups accounted for only 11% of the substrate scope.[3] In order to provide a degree of confidence that a boronic ester precursor of interest would be compatible with the ^{18}F-fluorodeboronation, we sought to develop a simple method for the evaluation of the compatibility of the method with specific heterocycles. We were inspired by the work of Collins and Glorius, who developed a robustness screen for the rapid evaluation of the compatibility of a reaction with a given heterocycle.[4]



3.6 1.0 equiv. + **3.7** 1.2 equiv + **3.8** 1.0 equiv. → **3.9**

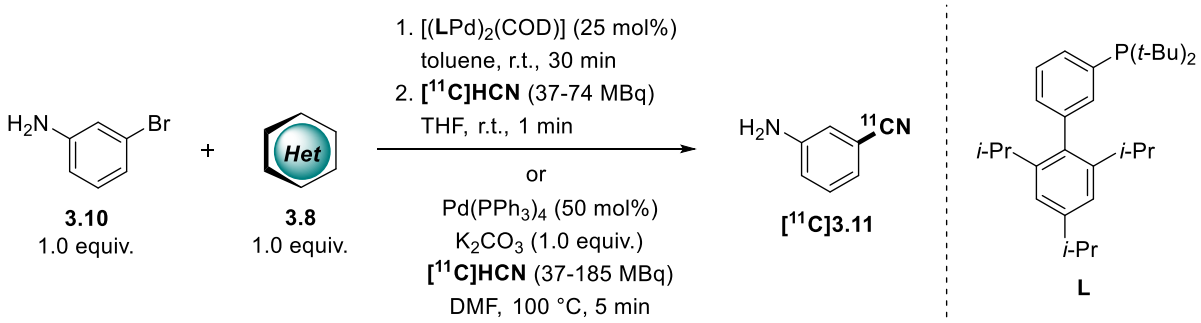
Entry	Heterocyclic Additive	Yield of 3.9 (%)	Additive remaining (%)	Starting material remaining (%)
1	None	89	-	0
2		82 ✓	100 ✓	0
3		0 ✗	0 ✗	96
4		11 ✗	100 ✓	75

Table 3.1. Excerpt from robustness screen for a Buchwald-Hartwig amination

Their method began with a model Buchwald-Hartwig amination between 3-bromoanisole **3.8** and morpholine **3.9**, for which the yield was known (Table 3.1, entry 1). This reaction was then repeated in the presence of one molar equivalent of a given heterocyclic additive, and the yield was measured by gas chromatography, as was the amount of additive and starting material remaining. This mimicked the

presence of the additive within a more complex target, without requiring the synthesis of such a target. In this way, the compatibility of 16 heterocycles with the amination was rapidly evaluated. Categorisation of the results using a red-yellow-green system provided a simple and clear means of visualisation.

Other groups have since adopted similar approaches,[5] however, no significant investigations of this kind have been carried out in ^{18}F-radiochemistry. To the best of our knowledge, the sole example of such a screening approach in radiochemistry was that of Buchwald and Hooker in their ^{11}C-cyanation of (hetero)aryl halides using biaryl phosphine Pd(0) complexes.[6] Their screening experiments were limited in scope, consisting of only six additives, of which three were heterocycles (Table 3.2, entries 5-7).



Entry	Additive	RCC of [^{11}C]3.11 with [(LPd)$_2$(COD)] (%)	RCC of [^{11}C]3.11 with Pd(PPh$_3$)$_4$ (%)
1	None	81	30
2	Water	80	n.d.
3	Phenol	94	25
4	4-Methoxybenzamide	88	9
5	Pyridine	90	14
6	Imidazole	92	0
7	5-Fluoroindole	80	n.d.

Table 3.2. Robustness screen for the ^{11}C-cyanation

3.3 Heterocycle Screening Experiment

3.3.1 Hypothetical Approach

Consider the hypothetical ^{18}F-fluorodeboronation of precursor **3.12**, a complex aryl boronic ester bearing multiple potentially problematic heterocycles A, B, C and D (Figure 3.2a). Synthesis of precursor **3.12** followed by subjecting it to ^{18}F-fluorodeboronation conditions is a high-risk approach; if any of A, B, C or D is incompatible with the ^{18}F-fluorodeboronation conditions, the reaction to form **[^{18}F]3.13** is likely to fail. A lower-risk approach is to first determine the compatibility of heterocycles A, B, C and D with the ^{18}F-fluorodeboronation. Our approach, inspired by the work of Glorius, begins with a simple model boronic ester substrate **3.14**, for which the radiochemical conversion is known (Figure 3.2b). Repeating the known ^{18}F-fluorodeboronation of **3.14**, with the addition of one equivalent of heterocycle A, allows the effect of A on the radiochemical conversion to be determined. By repeating this for each heterocycle within a target molecule of interest, it becomes possible to determine whether ^{18}F-fluorodeboronation of the target molecule is likely to succeed.

In this example, suppose that screening experiments with model compound **3.14** show that heterocycles B, C and D have negligible effect on the radiochemical conversion to **[^{18}F]3.15**; they are considered to be tolerated. However, heterocycle A is not tolerated. This suggests that attempting ^{18}F-fluorodeboronation of **3.12** is unwise; the reaction is likely to fail. An alternative approach is therefore needed, in which heterocycle A is introduced after the ^{18}F-fluorodeboronation step. For

example, this could be ^{18}F-fluorodeboronation of fragment **3.16**, followed by coupling of ^{18}F-labelled product **[^{18}F]3.17** with heterocycle A (Figure 3.2c). Alternatively, fragment CD **3.18** could be ^{18}F-fluorodeboronated, followed by coupling of product **[^{18}F]3.19** with fragment AB. The approach chosen is likely to be determined by the ease of the chemistry required in the post-labelling step.

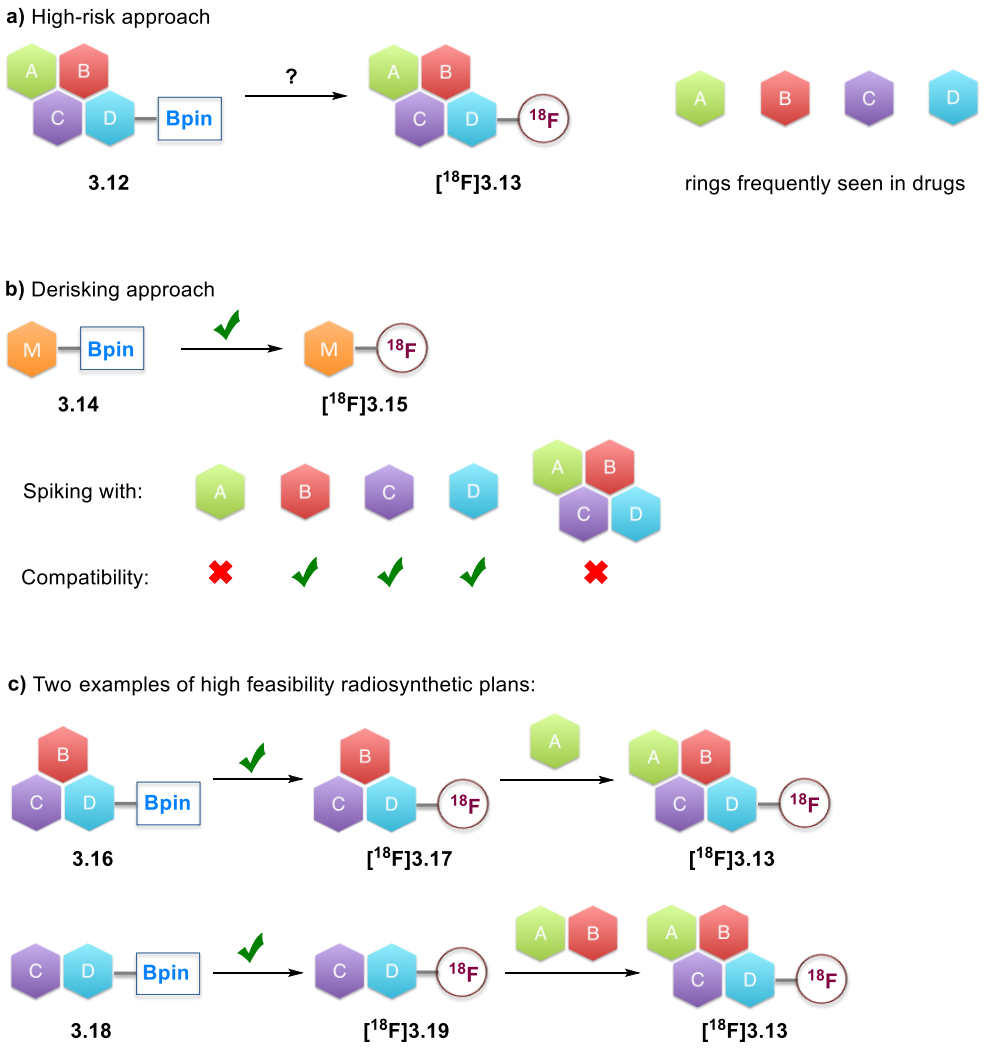


Figure 3.2. **a)** Late stage fluorination of a complex target bearing multiple heterocycles (A, B, C, D) is a high-risk approach. **b)** A rapid screen on the compatibility of the reaction of a readily available model substrate (M) in the presence of each heterocycle and/or the target molecule provides information on feasibility of a final-step ^{18}F-fluorodeboronation. **c)** As a result, new high-feasibility retrosynthetic schemes can be designed featuring a post-fluorination step to introduce any incompatible heterocycle (here A).

Using information on the tolerance of each individual heterocycle to determine the likelihood of successfully ^{18}F-fluorodeboronating a molecule bearing multiple heterocycles makes a simplifying assumption that the inhibitory effect of a heterocycle is the same whether it is alone or in proximity to other heterocycles. This may not be true, for example due to potential chelating effects. In order to determine whether the specific arrangement of heterocycles in the target molecule is likely to be problematic, one could screen a molecule ABCD consisting of the heterocycles in the target molecule in the correct arrangement (Figure 3.2b). A more realistic alternative is to screen the unlabelled compound ABCD-F **3.13**. This also has the advantage that this molecule would be expected to be in hand, since it is the drug candidate itself. However, in the case of a negative result, screening the drug candidate alone gives no information on how to proceed. Without information on the tolerance of each individual heterocycle, alternative synthetic routes to avoid a problematic heterocycle cannot be devised.

Based on these considerations, the objectives of this project were as follows:

1) Screen a large number of medicinally-relevant heterocycles, in order to build up data to aid others in attempting to use the ^{18}F-fluorodeboronation for the ^{18}F-labelling of their own molecules.
2) Provide evidence that this screening approach can correctly predict the labelling of small molecules bearing the corresponding heterocycles.
3) Demonstrate that the screening approach aids in the ^{18}F-labelling of a selection of fluorinated drugs.

3.3.2 Choice of Heterocycles

In order to aid use of the ^{18}F-fluorodeboronation in ^{18}F-labelling of drug candidates, it was essential to include those heterocycles most commonly found in drug molecules. Two studies published in the Journal of Medicinal Chemistry provided an excellent starting point. In 2014, Taylor and co-workers disclosed an analysis of the ring systems of all of the small molecule drugs listed in the FDA Orange Book.[7] The most prominent ring systems include both carbocyclic and heterocyclic rings; those found within at least eight FDA-approved drugs are shown in Figure 3.3.

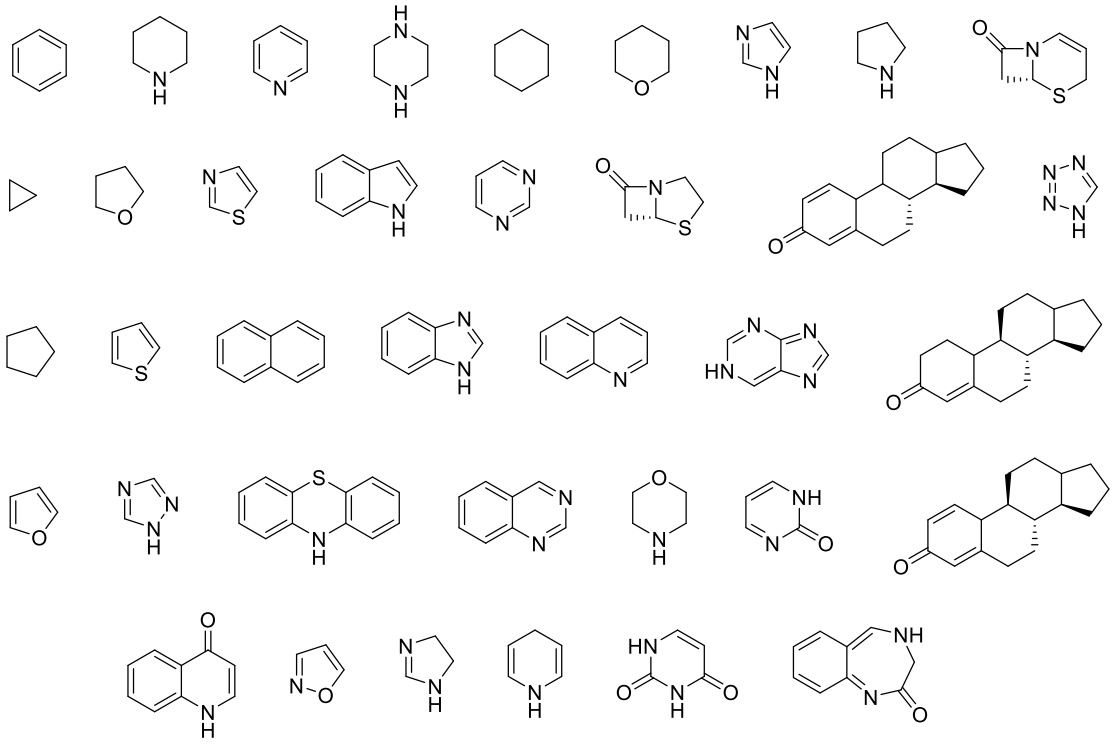


Figure 3.3. Ring systems found within at least eight FDA-approved drugs, in descending order of frequency.

Later that year, the Njardarson group described a similar analysis which focused only on nitrogen heterocycles.[1] The results were very similar, with slight differences arising from differences in the data included and in the categorisation

of ring systems. In addition to an overall analysis of frequency (Figure 3.4), Njardarson described, in some detail, the most common substitution patterns of the most frequently occurring heterocycles.

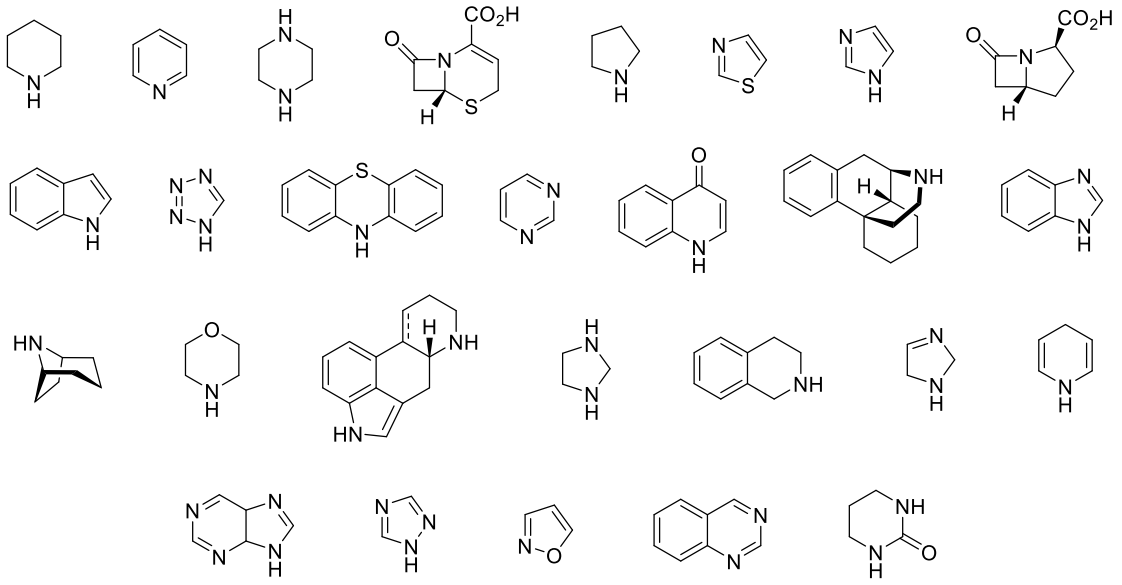
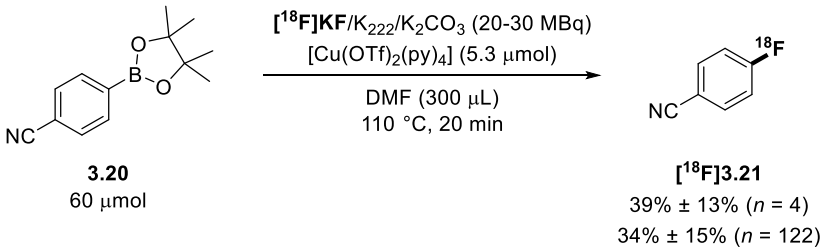


Figure 3.4. Top 25 most frequently-occurring nitrogen heterocycles within FDA-approved drugs, in descending order of frequency.

The majority of the heterocycles in Figure 3.4 were to be included in the screening study. Notable exceptions included the penam and cephem scaffolds, which are found almost exclusively within β-lactam antibiotics,[1] as well as the morphinan, tropane and ergoline natural product-derived scaffolds, for which we believed the parent heterocycles pyrimidine, pyrrolidine and indole provided sufficient information.

3.3.3 Model Substrate

The model substrate chosen for the screening experiments was 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzonitrile **3.20** (Scheme 3.1). As discussed in Chapter 2, section 2.2.4, this substrate afforded 4-[^{18}F]fluorobenzonitrile **[^{18}F]3.21** in moderate radiochemical conversion under the standard conditions A (RCC = 39% ± 13%, *n* = 4). Use of a model reaction with moderate RCC allowed observation of the detrimental effects of heterocyclic additives, which was essential for understanding the tolerance of the ^{18}F-fluorodeboronation, as well as beneficial effects, which might offer insight into potential means of increasing the efficiency of the reaction.



Scheme 3.1. Model reaction for the heterocyclic additive screening experiment

Over the course of the screening experiment, this standard reaction without a heterocyclic additive was repeated at the start of each day of screening. In total, the reaction was carried out 122 times, giving an overall RCC of 34% ± 15% (*n* = 122). A histogram showing the distribution of the RCCs is shown in Figure 3.5; individual RCCs are given in Chapter 4, section 4.4.23. The data shows considerable variation; the minimum RCC observed was 3% whilst the maximum was 73%. Although the standard deviation was relatively large, the large data set caused the standard error

of the mean to be less than 2%. Thus, we could be confident that the mean value of 34% for the RCC of the reaction was close to the true population mean.

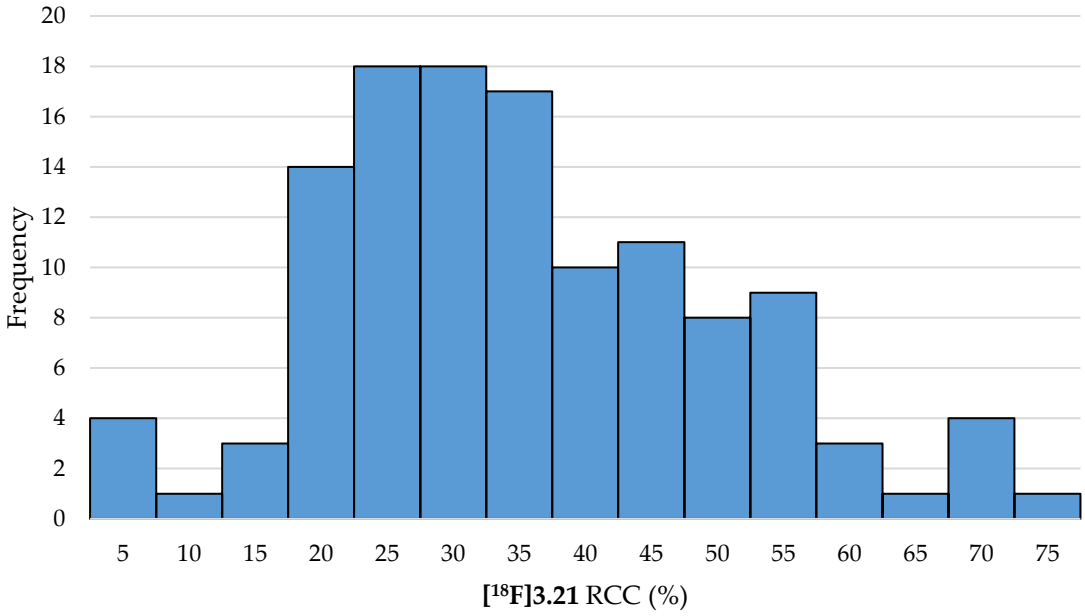


Figure 3.5. Histogram showing the distribution of the RCCs for the model reaction

3.3.4 Categorisation of Screening Results

Since a large number of heterocyclic additives were to be screened, it was decided to screen the majority of them only twice. Whilst the screening reactions for particularly important heterocyclic additives could be repeated more times, it was not considered feasible to do this for all heterocyclic additives. We recognised that the RCCs obtained may not accurately reflect the true population RCC, but should be fairly close. In addition, for such a small sample size, the standard deviations obtained would not be meaningful. For these reasons, rather than focusing on the exact RCCs obtained, it was decided to categorise the screening results using a traffic-light system similar to that used by Glorius.[4] Additives reducing the RCC

of the ^{18}F-fluorodeboronation of **3.20** to form **[^{18}F]3.21** to below 5% were considered severely detrimental and colour-coded red. Those reducing the RCC to between 5% and 19% were considered detrimental and colour-coded orange. Additives for which product **[^{18}F]3.21** was formed in 20% RCC or higher were considered not to have a significant effect and were colour-coded green.

3.3.5 Screening of Six-Membered Aromatic Heterocycles

Initial heterocyclic additive screening experiments began with six-membered aromatic heterocycles. The results are shown in Table 3.3; for each heterocycle, the RCC of **[^{18}F]3.21** obtained in each of the two screening experiments is given, as is the mean of the two RCCs. The structure number of the heterocycle is colour coded as described in section 3.3.4, providing a simple visual means of interpreting the results. Pyridine **3.22** is one of the most common heterocycles in medicinal chemistry; it is found in 62 FDA-approved drugs.[1] We were pleased to observe that this heterocycle was in fact beneficial for the ^{18}F-fluorodeboronation of **3.20**, affording **[^{18}F]3.21** in a mean RCC of 63% (n = 2). The two benzo-fused congeners, quinoline **3.23** and isoquinoline **3.24** were well-tolerated by the reaction, affording **[^{18}F]3.21** in 25% and 71% RCC respectively. As discussed in Chapter 2, section 2.2.3, the beneficial effects of pyridine and isoquinoline may arise from modulating the electronic environment of a copper centre or from facilitating transmetalation of the aryl group from boron to copper.

Of the three diazines, pyrimidine **3.26** is the most common, occurring in 16 FDA-approved drugs.[1] Pyrimidine **3.26**, pyrazine **3.28** and pyridazine **3.25** were all tolerated by the model reaction, affording **[^{18}F]3.21** in 35%, 30% and 25% RCC, respectively. Likewise, quinazoline **3.27** and quinoxaline **3.29** were also tolerated. However, none of the diazines showed a beneficial effect on the RCC.

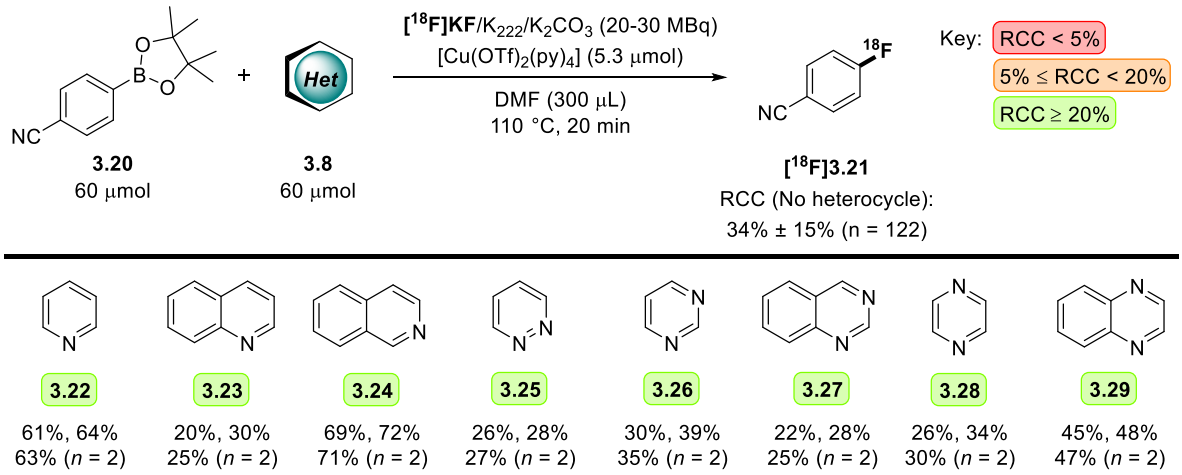


Table 3.3. Screening of six-membered aromatic heterocycles

3.3.6 Screening of Five-Membered Aromatic Heterocycles

Whilst none of the five-membered aromatic heterocycles are as prevalent in FDA-approved drugs as pyridine, four of these (thiazole, imidazole, tetrazole and indole) feature within the top 10 most prevalent nitrogen heterocycles.[1] For the purposes of the screening experiment, this category of heterocycles was sub-divided into those bearing a pyrrole-like nitrogen and those not.

Amongst those bearing a pyrrole-like nitrogen atom, only pyrrole **3.30** and indole **3.31** were tolerated when unprotected (Table 3.4). Pyrazole **3.32**, indazole **3.34**, 1,2,3-triazole **3.36**, benzotriazole **3.38**, 1,2,4-triazole **3.40** and 5-methyltetrazole

3.42 were all highly detrimental, reducing the RCC of the model reaction to zero. Reactivity was restored by alkylation of these heterocycles; 1-Methylpyrazole **3.33** exhibited a beneficial effect on the RCC of **3.20** into **[^{18}F]3.21**, as did 1-benzyl-1,2,3-1*H*-triazole **3.37** and 1-benzyl-1,2,4-1*H*-triazole **3.41**. 1-Methyl-1*H*-indazole **3.35**, 1-methyl-1,2,3-1*H*-benzotriazole **3.39** and 1-benzyl-5-methyl-1*H*-tetrazole **3.43** had no significant effect.

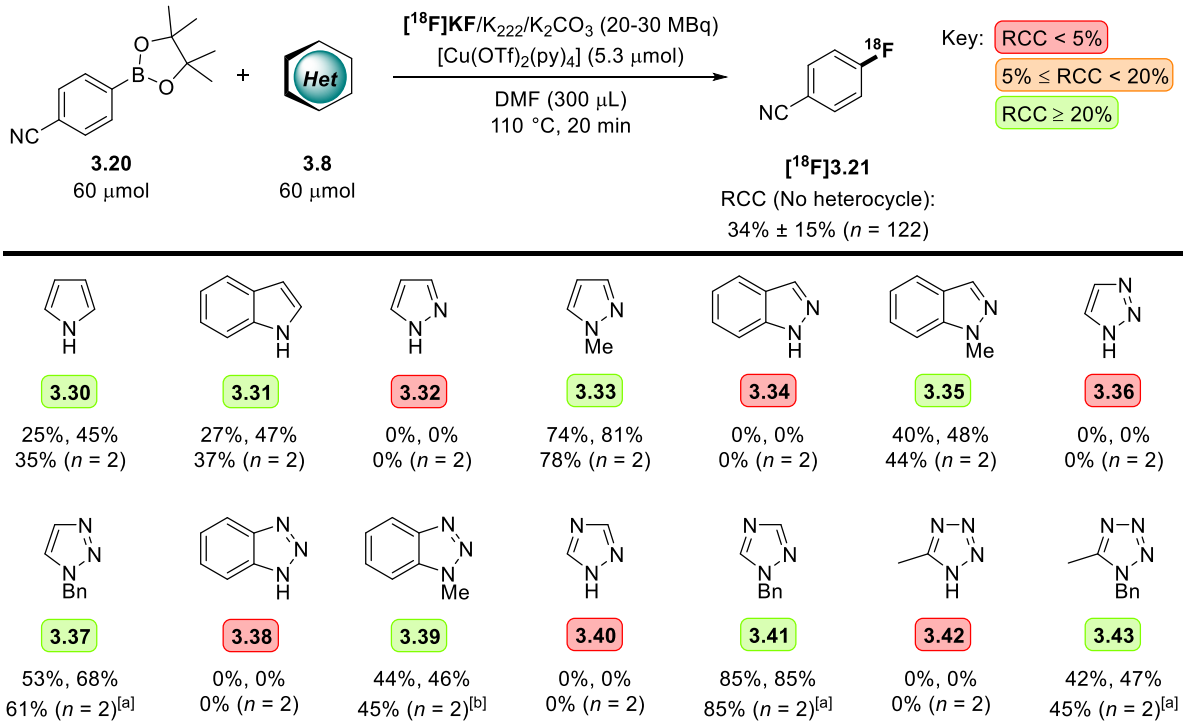


Table 3.4. Screening of pyrroles, pyrazoles, triazoles and tetrazoles. [a] Prepared by Dr. Michael Schedler. [b] Prepared by Dr. Enrico Emer.

There are several possible explanations for the highly detrimental effects of these azoles bearing a free N–H. Firstly, the acidity of the heterocycles should be considered. The pK_a values of pyrazole (19.8), 1,2,3-triazole (13.9), 1,2,4-triazole (14.8) and tetrazole (8.2) are lower than those of pyrrole (23.0) and indole (21.0).[8] It may be that species with a pK_a lower than a certain threshold value are not tolerated by the reaction. This is discussed further in section 3.3.11.

Alternatively, these species with unprotected N–H could act as Chan-Lam coupling partners with the boronic ester substrate. If an undesired C–N coupling process occurred at a faster rate than the desired C–^{18}F coupling process, the substrate could be consumed before reacting with the [^{18}F]fluoride. Table 3.5 shows the yield of C–N coupling products in the Cu-mediated coupling between *p*-tolylboronic acid **3.45** and various heterocycles **3.44**, as reported by Chan and Lam.[9] The most challenging substrates for the C–N coupling were pyrrole **3.30** and indole **3.31**; it is notable that these heterocycles did not affect the ^{18}F-fluorodeboronation of model substrate **3.20**. However, triazoles **3.32** and **3.36**, which completely inhibited the ^{18}F-fluorodeboronation of **3.20**, did not afford high yields of C–N coupling products. The authors reported formation of large amounts of *p*-cresol and *p*-tolyl ether in these cases.

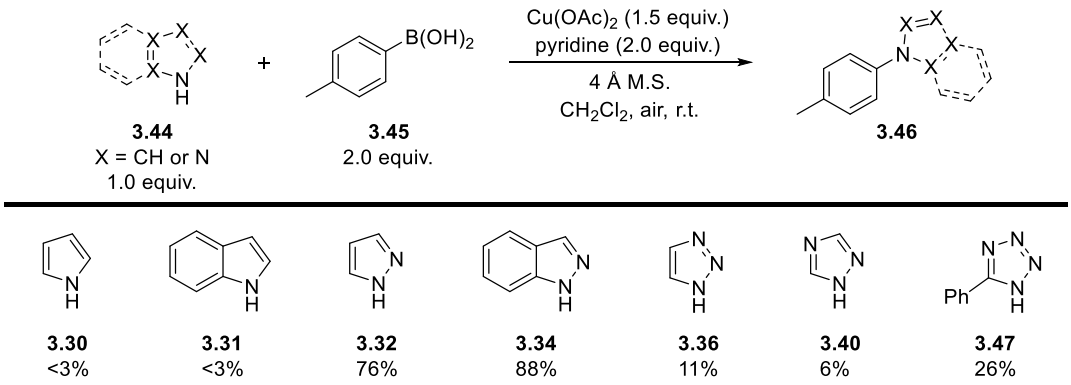
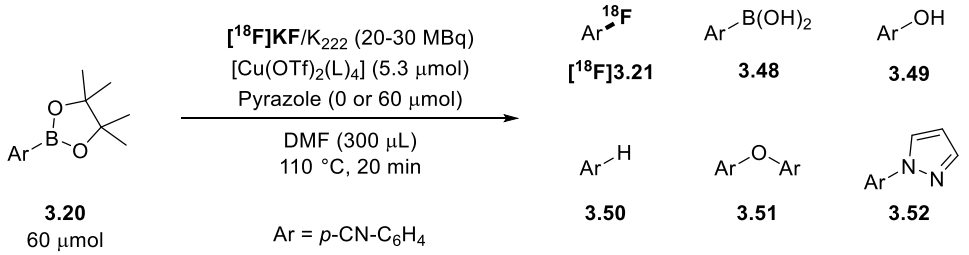


Table 3.5. Chan-Lam coupling of N–H containing heteroarenes with p-tolylboronic acid

In order to investigate whether the boronic ester substrate **3.20** was being consumed by C–N bond formation during the attempted ^{18}F-fluorodeboronation in the presence of pyrazole, the reaction was repeated in the absence and presence of pyrazole and the UV spectra of the reaction mixtures were compared. Use of

calibration curves allowed quantification of some of the species present. The results, shown in Table 3.6, are based on only one reaction for each entry, so care should be taken in their interpretation. There are several additional challenges in interpretation of these results. Firstly, at the concentrations required to observe the other species, the peak corresponding to boronic acid **3.48** was very large and saturated the response of the detector. Secondly, boronic ester **3.20** may partially hydrolyse to boronic acid **3.48** during the aqueous quench of the reaction. This quench was necessary in order to obtain a meaningful RCC by radio-TLC. These problems meant that the amounts of **3.20** and **3.48** could not be accurately quantified. In addition, there was a slight overlap between the shoulder of the peak of boronic acid **3.48** and the peak of phenol **3.49**. This means that the values obtained for phenol **3.49** may be over-estimates.



Entry	L	Pyrazole / mmol	[18F]3.21 / RCC %	3.49 / %	3.50 / %	3.51 / %	3.52 / %
1	Pyridine	0	25	43	6.3	8.2	N/A
2	Pyridine	0.06	0	0.1	0	0	1.4
3	Pyrazole	0	0	0.5	0.1	0	1.7

Table 3.6. Product distribution of the ^{18}F-fluorodeboronation of **3.20** determined by UV spectra

Despite these limitations, analysis of the UV profile did reveal useful information about the reaction. In the absence of pyrazole (Table 3.6, entry 1), the major product of the reaction was phenol **3.49**. Protodeboronation product **3.50** was

also formed, as was diaryl ether **3.51**. In the presence of one equivalent of pyrazole (entry 2), the reaction profile was very different. No radiolabelled product **[^{18}F]3.21** was formed and only a trace of phenol **3.49** was observed. Protodeboronation product **3.50** and ether **3.51** were not observed. Interestingly, less than 2% of C–N coupling product **3.52** was observed. This suggests that competing Chan-Lam C–N coupling is not a significant explanation for the absence of **[^{18}F]3.21** in the presence of pyrazole. Instead, it appears that in the presence of pyrazole, the rates of all the copper-mediated processes are sharply reduced.

In order to confirm this, the complex $[Cu(OTf)_2(Hpz)_4]$ (Hpz = pyrazole) was prepared by Dr. Enrico Emer and used in the ^{18}F-fluorodeboronation in place of $[Cu(OTf)_2(py)_4]$ (Table 3.6, entry 3).[10] The results were very similar to those obtained when pyrazole was used as an additive. This suggests that pyrazole may displace pyridine as a ligand for copper, forming an inactive copper species. The crystal structures of both $[Cu(OTf)_2(py)_4]$ and $[Cu(OTf)_2(Hpz)_4]$ are known; the Cu–N distance is shorter in $[Cu(OTf)_2(Hpz)_4]$ (2.009 Å) than in $[Cu(OTf)_2(py)_4]$ (2.035 Å), indicating that pyrazole is more strongly coordinated to copper.[10], [11]

For imidazoles and benzimidazoles, the situation was more complicated. As expected, given the results with pyrazole **3.32**, imidazole **3.53** bearing a free N–H was not tolerated by the model reaction (Table 3.7). However, *N*-methylated imidazole **3.54** was also detrimental; **[^{18}F]3.21** was formed in only 7% RCC. In order to restore reactivity, substitution at both *N*1 and *C*2 was necessary; screening of **3.56** afforded **[^{18}F]3.21** in 30% RCC. The same pattern was observed for benzimidazoles

3.59 to **3.62**. Screening of *N*-Boc-protected benzimidazole **3.63** afforded **[^{18}F]3.21** in 8% RCC. It is not known whether **3.63** is a partial inhibitor of the ^{18}F-fluorodeboronation of **3.20** or whether **3.63** decomposes to **3.59** over the course of the reaction. The hydrolysis of **3.63** to **3.59** in boiling water has been reported to be complete within 10 minutes.[12]

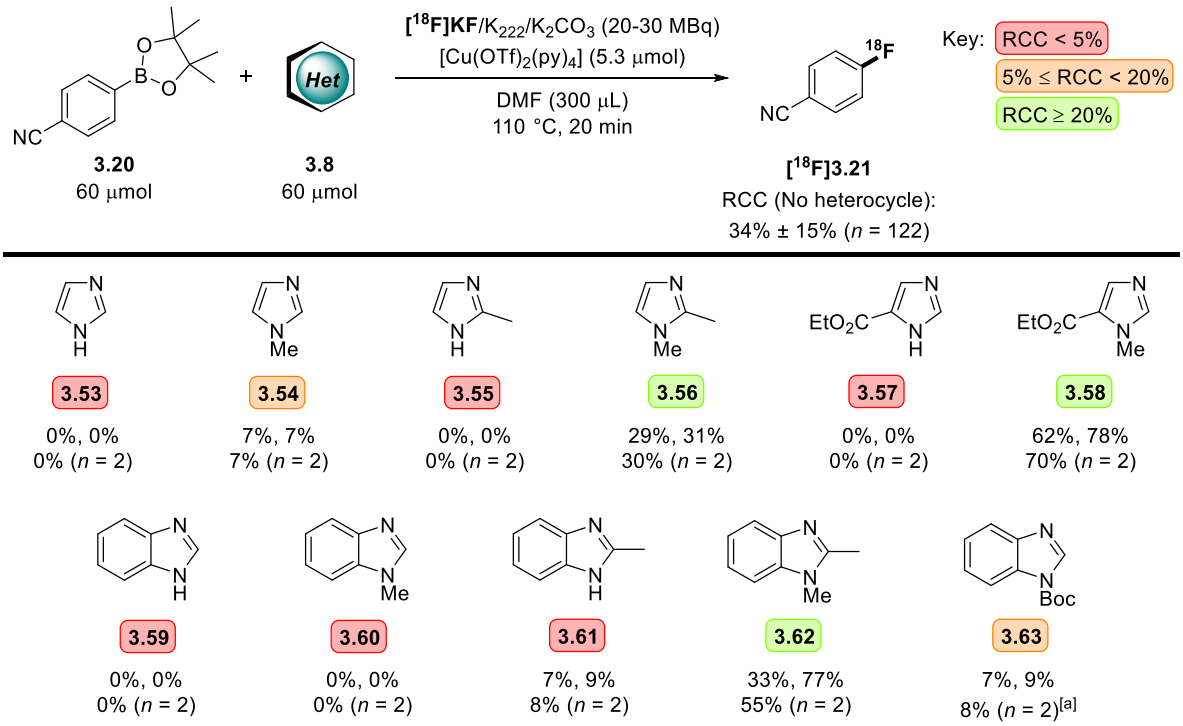
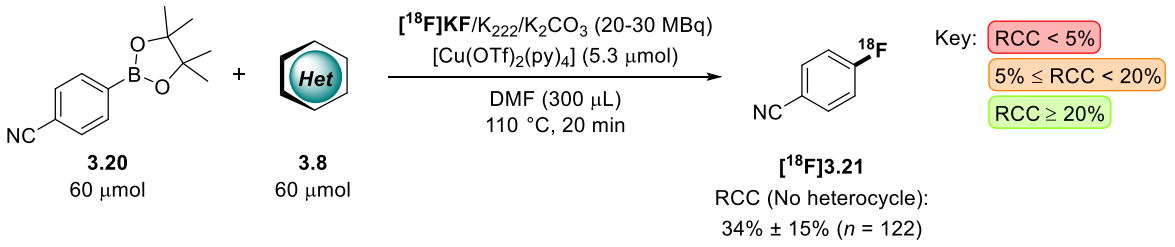


Table 3.7. Screening of imidazoles. [a] Prepared by Dr. Michael Schedler.

The presence of a substituent on a particular heteroarene will influence its electronic and steric properties, which may affect its compatibility with the ^{18}F-fluorodeboronation. For example, electron-deficient imidazole **3.58** was well tolerated without the need for substitution at *C*2, in contrast to imidazoles **3.54** and **3.56**, for which the presence of a methyl group at that position was essential to obtain **[^{18}F]3.21** in good RCCs. In order to control the scope of the project, only the parent heterocycles were screened in most cases, but when applying the results to

aid in planning the radiosynthesis of a target molecule, the effects of substituents should be considered.

Five-membered heterocycles not containing a pyrrole-like nitrogen atom were well-tolerated by the ^{18}F-fluorodeboronation in almost all cases (Table 3.8). Screening of 2-*n*-butylfuran **3.64**, used as a higher-boiling surrogate for furan, resulted in formation of **[^{18}F]3.21** in 50% RCC. Benzofuran **3.65**, thiophene **3.66**, benzothiophene **3.67**, thiazole **3.68**, benzothiazole **3.69** and oxazole **3.70** were also well tolerated. Benzoxazole **3.71** was slightly less well tolerated, the RCC of 21% verges on a classification of "detrimental". In order to investigate whether this was due to activation at the *C*2 position, this position was blocked with a phenyl group; screening of 2-phenylbenzoxazole **3.72** afforded **[^{18}F]3.21** 28% RCC.



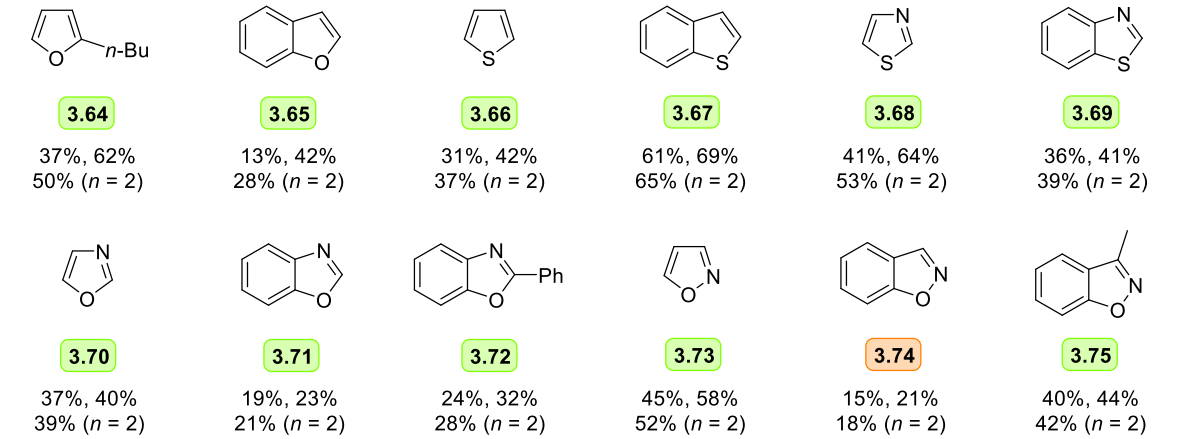
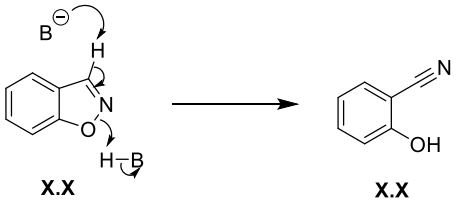


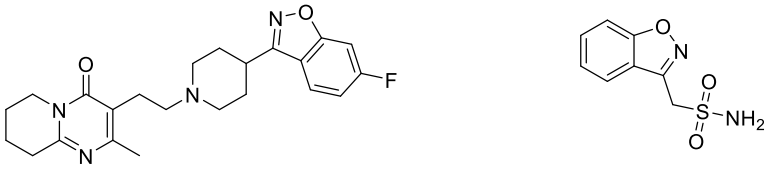
Table 3.8. Screening of furans, thiophenes and *O*- and *S*-containing azoles

Whilst isoxazole **3.73** was well-tolerated, 1,2-benzisoxazole **3.74** was somewhat detrimental towards the model reaction. This was not unexpected; **3.74** is known to undergo Kemp elimination under basic conditions.[13] Deprotonation of **3.74** at the 3-position results in ring opening and formation of 2-cyanophenol **3.76** (Scheme 3.2). As described in Chapter 2, section 2.2.4, attempted synthesis of **[^{18}F]2.76** bearing a free phenol via ^{18}F-fluorodeboronation proceeded with only low RCC. Formation of an unprotected phenol would therefore be expected to be detrimental to the model reaction. The role of the base required for formation of **3.76** could be fulfilled by potassium carbonate; this is present within the reaction mixture due to its use in eluting the [^{18}F]fluoride from the ion exchange cartridge during the drying process.



Scheme 3.2. Kemp elimination of benzisoxazole to afford 2-cyanophenol

Methylation at *C*3 prevents this decomposition pathway from occurring; pleasingly, 3-methylbenzisoxazole **3.75** was not detrimental to the model reaction (Table 3.8). All of the benzisoxazole-containing drug molecules approved by the FDA are alkylated at *C*3. Examples include the antipsychotic risperidone **3.5** and the anticonvulsant zonisamide **3.77** (Figure 3.6).



3.5
Risperidone
antipsychotic

3.77
Zonisamide
anticonvulsant

Figure 3.6. Benzisoxazole-containing FDA-approved drugs

3.3.7 Screening of Cyclic Amines and Ethers

Cyclic amines constitute a very important class of compounds in medicinal chemistry. Piperidine, piperazine and pyrrolidine are all within the top five most prevalent nitrogen heterocycles in FDA approved drugs.[1] Incorporation of cyclic amines is a tactic commonly used by medicinal chemists to improve the pharmacokinetic profiles of lead compounds.[14]

Screening of unsubstituted pyrrolidine **3.78**, *N*-methylpyrrolidine **3.79** and *N*-benzylpyrrolidine **3.80** showed that these molecules were severely detrimental to the model reaction, reducing the RCC to zero (Table 3.9). In contrast, *N*-Boc-pyrrolidine **3.81** was tolerated. Very similar results were observed for the piperidines; piperidine **3.82** and alkylated piperidines **3.83** and **3.84** were highly detrimental to the model reaction, whereas *N*-Boc-piperidine **3.85** was tolerated.

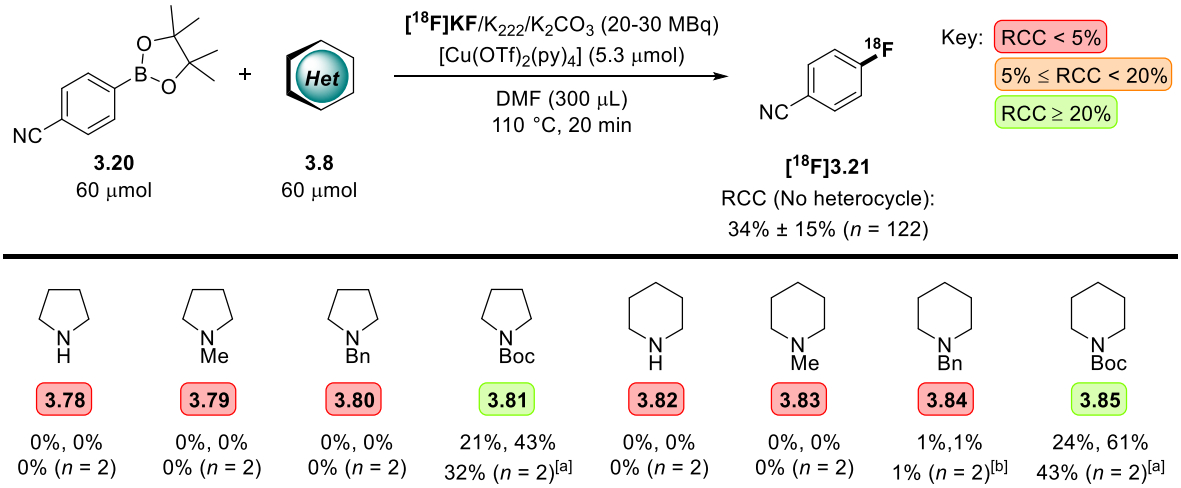


Table 3.9. Screening of pyrrolidines and piperidines. [a] Prepared by Dr. Michael Schedler. [b] Prepared by Dr. Enrico Emer.

The *N*-alkylated piperidine moiety is found in many FDA-approved drugs; examples also containing an aryl fluoride are shown in Figure 3.7. The detrimental effects of alkylated piperidines on the model ^{18}F-fluorodeboronation suggest that this method is unlikely to be successful for final-stage ^{18}F-labelling of these molecules; an alternative strategy must be found.

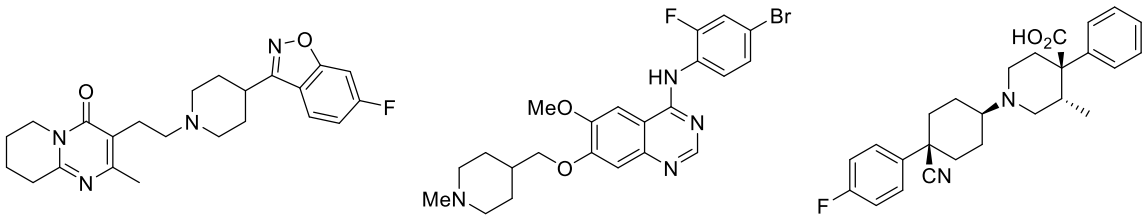


Figure 3.7. FDA-approved drugs containing both an alkylated piperidine and an aryl fluoride

For piperazines and morpholines, the screening results were more promising. Although piperazine **3.88** and morpholine **3.7** were not tolerated, the *N*-benzyl derivatives **3.90** and **3.93** were not detrimental towards the model reaction (Table

3.10). Tolerance of **3.90**, bearing a free N–H, was particularly noteworthy, although screening of the Boc-protected derivative **3.91** afforded **[^{18}F]3.21** in higher RCC.

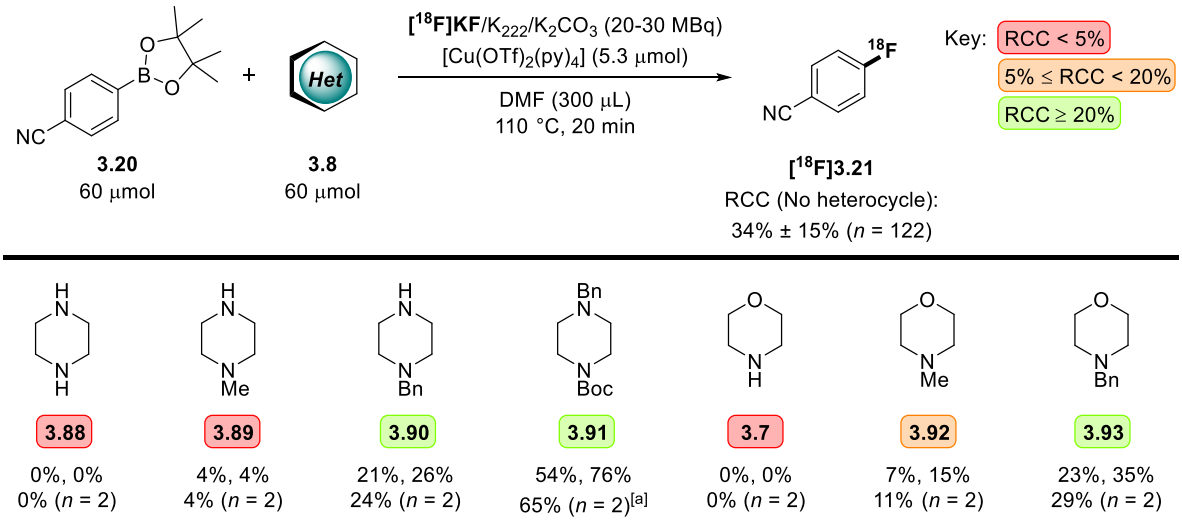


Table 3.10. Screening of piperazines and morpholines. [a] Prepared by Dr. Michael Schedler.

Although less common in drugs, tetrahydroisoquinolines, phenothiazines and cyclic ethers were also screened. Tetrahydroisoquinolines **3.94** and **3.95** (Table 3.11) behaved very similarly to morpholines **3.7** and **3.93**; *N*-benzylation allowed this cyclic amine to be tolerated. All FDA-approved phenothiazine drugs are antipsychotics and are alkylated at nitrogen. *N*-Methylphenothiazine **3.97** was slightly detrimental towards the model reaction. Phthalan **3.98** and isochroman **3.99**, chosen due to their higher boiling point than tetrahydrofuran and tetrahydropyran, were well tolerated, as predicted based on the success of ether-containing substrates (section 2.2.4).

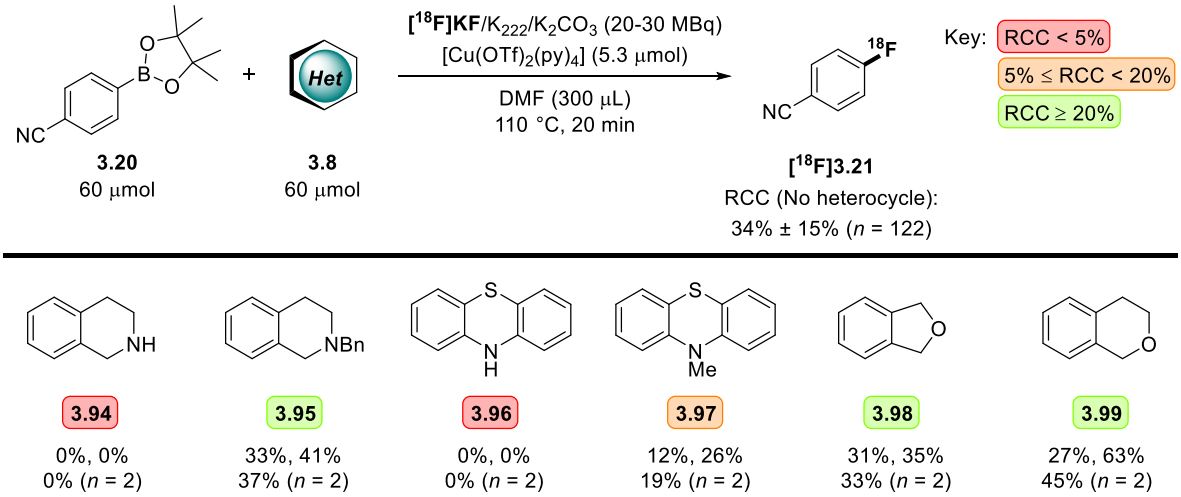


Table 3.11. Screening of tetrahydroisoquinolines, phenothiazines and cyclic ethers

Two factors appear to be important in rationalising the results observed for the screening of cyclic amines. Firstly, with the exception of *mono*-alkylated piperazines **3.89** and **3.90**, all of the secondary amine additives were highly detrimental to the model reaction. This could be due to competing Chan-Lam coupling or formation of an unreactive copper species, potentially stabilised by hydrogen bonding. In addition, basicity appears to play a role; the more basic *N*-methylpyrrolidine (pK_{aH} = 10.5) and *N*-methylpiperidine (pK_{aH} 10.1) were not tolerated, whilst the less basic *N*-methylmorpholine (pK_{aH} 7.4) was less detrimental.[15] The influence of heterocyclic additive pK_{aH} on the model reaction is discussed further in section 3.3.12.

3.3.8 Screening of Cyclic Amides and Ureas

The final major class of heterocyclic additives screened was cyclic amides and ureas. 2-Pyrrolidinone **3.100** was highly detrimental in the model

^{18}F-fluorodeboronation of **3.20**, whilst *N*-methylpyrrolidinone **3.101** was well tolerated (Table 3.12). For the benzannelated congener, oxindole, the results were more complex. As expected based on the results for pyrrolidinone, unsubstituted oxindole **3.102** was highly detrimental to the model reaction. However, in contrast to *N*-methylpyrrolidone **3.101**, *N*-methyloxindole **3.103** was also somewhat detrimental; **[^{18}F]3.21** was formed in 19% RCC. Additive **3.104**, in which the 3-position was blocked by the introduction of two methyl groups, allowed the model reaction to proceed unimpeded. Quinolone **3.105**, a vinylogous amide bearing a free N–H, was detrimental, whilst *N*-methylated **3.106** was well tolerated. Screening of unprotected imidazolidinone **3.107** resulted in only trace formation of **[^{18}F]3.21**, whilst for monomethylated **3.108**, the RCC was 4%. Dimethylated **3.109** had no effect on the model reaction. Six-membered ureas **3.110**-**3.112** followed the same pattern of increasing RCC of **[^{18}F]3.21** from screening unsubstituted **3.110** (6%) to monomethylated **3.111** (11%) to dimethylated **3.112** (31%). In general, the six-membered ureas were better tolerated than the five-membered ureas.

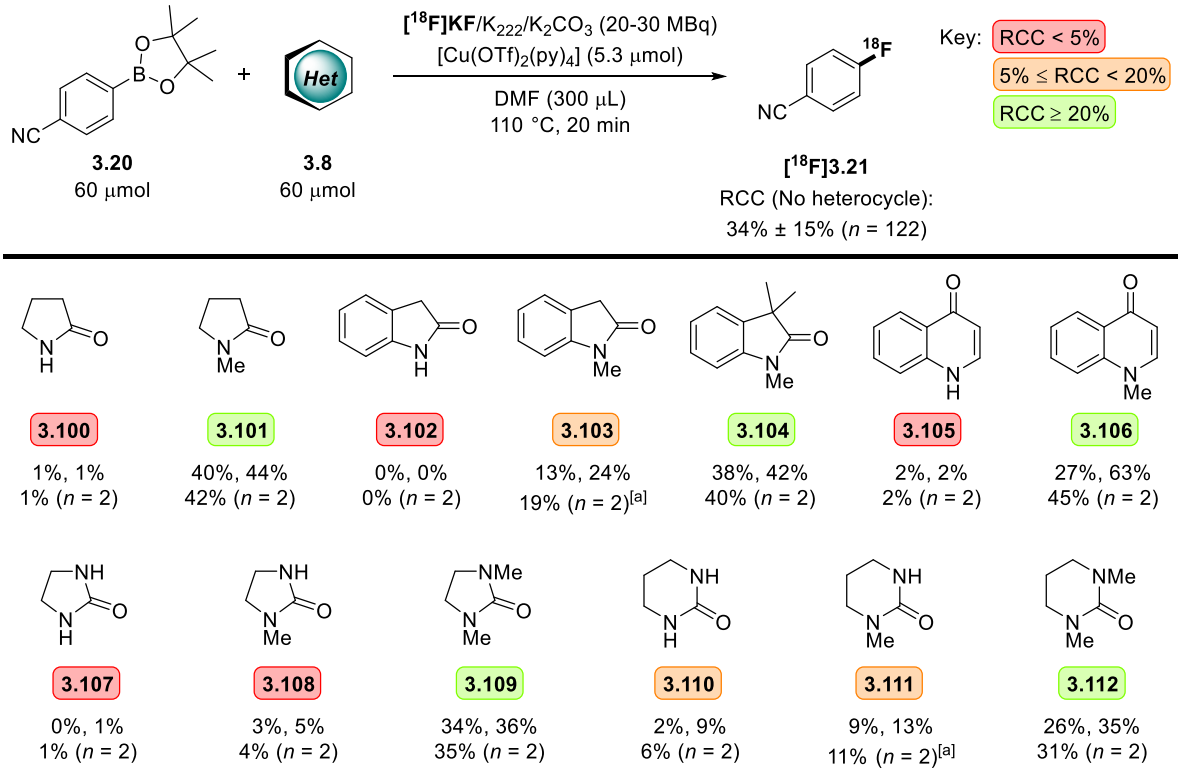


Table 3.12. Screening of cyclic amides and ureas. [a] Prepared by Dr. Michael Schedler.

3.3.9 Screening of Fused Systems

A huge variety of fused systems containing two or more heteroarenes exist. Due to time limitations, only a small selection was screened. 4-Azaindole **3.113** was somewhat detrimental towards the model reaction; **[^{18}F]3.21** was formed in 18% RCC (Table 3.13). In contrast, 7-azaindole **3.114** was highly detrimental, allowing formation of only a trace of **[^{18}F]3.21**. *N*-Methylated **3.115** was tolerated. Caffeine **3.116**, with no free N–H groups but containing a *C*2-unsubstituted imidazole moiety, was well tolerated. This is consistent with the results observed for electron-deficient imidazole **3.58** (section 3.3.6). When imidazo[1,2-*b*]pyridazine **3.117** was screened, **[^{18}F]3.21** was formed in very high RCC (81%). The beneficial effect of this

heterocycle was greater than that of pyridine; this result is discussed further in section 3.5.8.

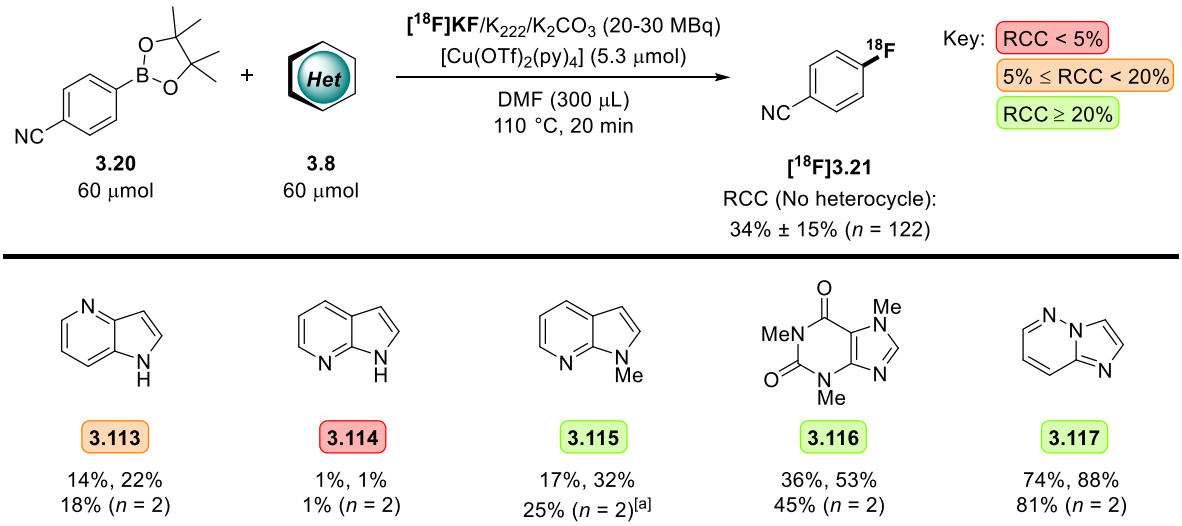
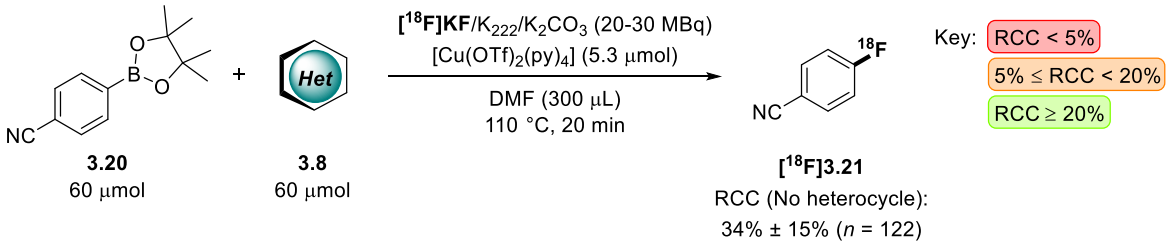


Table 3.13. Screening of fused systems. [a] Prepared by Dr. Enrico Emer.

3.3.10 Reproducibility of Screening Results

At this stage, more than eighty different heterocyclic additives had been screened in the model reaction. Due to time and cost limitations, the screening reactions were carried out only twice (n = 2). In order to provide a measure of confidence that these results were sufficiently representative of a larger number of experiments, a small selection of experiments were repeated up to n = 8. For each of these heterocyclic additives, pairs of reactions were carried out on four different days. The heterocycles chosen included examples of severely detrimental, detrimental, tolerated and beneficial heterocycles.



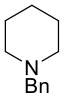
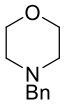
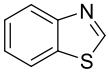
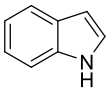
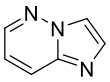
					
3.80	**3.81**	**3.83**	**3.93**	**3.111**	**3.66**
0%, 0% 0% (*n* = 2)	21%, 43% 32% (*n* = 2)	1%, 1% 1% (*n* = 2)	23%, 35% 29% (*n* = 2)	9%, 13% 11% (*n* = 2)	31%, 42% 37% (*n* = 2)
0%, 1%, 2% 4%, 2%, 4% **2% ± 2% (*n* = 8)**	10%, 39%, 49% 64%, 45%, 47% **40% ± 17% (*n* = 8)**	1%, 3%, 4% 6%, 5%, 7% **4% ± 2% (*n* = 8)**	36%, 22%, 35% 51%, 56%, 51% **39% ± 13% (*n* = 8)**	5%, 10%, 8% 23%, 19%, 12% **12% ± 6% (*n* = 8)**	41%, 60%, 41% 39%, 44%, 38% **42% ± 8% (*n* = 8)**
					
3.68	**3.69**	**3.31**	**3.41**	**3.22**	**3.117**
41%, 64% 53% (*n* = 2)	36%, 41% 39% (*n* = 2)	27%, 47% 37% (*n* = 2)	85%, 85% 85% (*n* = 2)	61%, 64% 63% (*n* = 2)	74%, 88% 81% (*n* = 2)
50%, 63%, 63% 71%, 36%, 36% **53% ± 14% (*n* = 8)**	37%, 60%, 28% 52%, 51%, 27% **42% ± 12% (*n* = 8)**	28%, 34%, 27% 45%, 46%, 39% **37% ± 9% (*n* = 8)**	53%, 60%, 61% 65%, 82%, 84% **72% ± 13% (*n* = 8)**	71%, 77%, 65% 76%, 73%, 62% **69% ± 6% (*n* = 8)**	73%, 76%, 75% 71%, 88%, 92% **80% ± 8% (*n* = 8)**

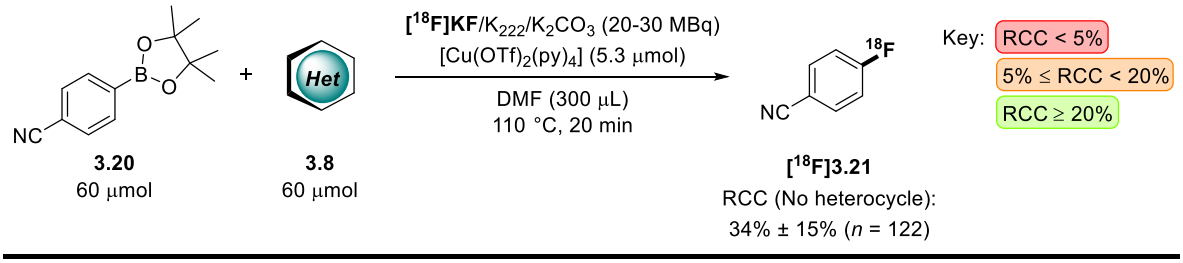
Table 3.14. Comparison of screening results based on $n = 2$ and $n = 8$

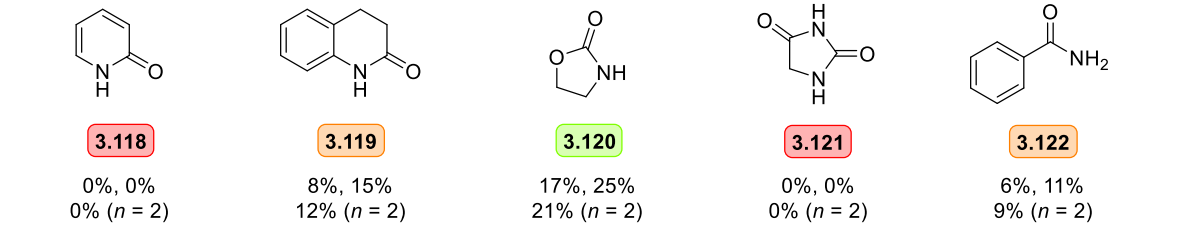
For each heterocyclic additive in the sub-set, Table 3.14 shows the RCCs of **[^{18}F]3.21** obtained in each of the eight screening experiments, with the original results at the top. A new mean and standard deviation of the RCC, based on $n = 8$, is also given. For six of the twelve heterocycles, the mean RCC for $n = 8$ is within a 10% error of that for $n = 2$. The $n = 8$ mean RCCs for **3.66** and **3.41** are within a 20% error of the $n = 2$ mean; for **3.81** and **3.93**, the corresponding results are within a 30% error. The most significant differences occurred for detrimental heterocycles **3.80** and **3.83**, for which there was an increase in mean RCC for $n = 8$. However, in both cases, the mean RCC remained below 5%. Importantly, in no case did the additional experiments change the mean RCC enough to result in a change of classification, for

example from detrimental to severely detrimental. This provided a degree of confidence that the mean RCC data obtained in the screening experiment was sufficiently representative of the population mean.

3.3.11 Correlation of Screening Results with pK$_a$ of N–H Heterocycles

It was suggested in section 3.3.6 that acidity could be a contributing factor towards the detrimental effects of azoles bearing a free N–H. In order to investigate this hypothesis, additional N–H containing molecules of known pK$_a$ were also screened in the model reaction (Table 3.15). 2-Pyridone **3.118** and hydantoin **3.121** both completely inhibited the model reaction, whilst amides **3.119** and **3.122** were only somewhat detrimental. Oxazolidinone **3.120** was tolerated.





3.118	3.119	3.120	3.121	3.122
0%, 0% 0% (*n* = 2)	8%, 15% 12% (*n* = 2)	17%, 25% 21% (*n* = 2)	0%, 0% 0% (*n* = 2)	6%, 11% 9% (*n* = 2)

Table 3.15. Screening of N–H containing molecules

Figure 3.8 shows a plot of N–H containing molecules against their pK$_a$ in DMSO, as reported by Bordwell.[8] The colour indicates the screening result obtained for the heterocycle, using the same definition as in the screening experiments. There does not appear to be a clear correlation between pK$_a$ of N–H

and whether the heterocycle is tolerated in the model ^{18}F-fluorodeboronation; pyrrole **3.30**, with $pK_a = 23.0$, is tolerated, whilst pyrrolidinone **3.100**, with $pK_a = 24.2$, is not. However, there may be significance in the observation that no heterocycle with $pK_a < 20$ is tolerated in the model reaction.

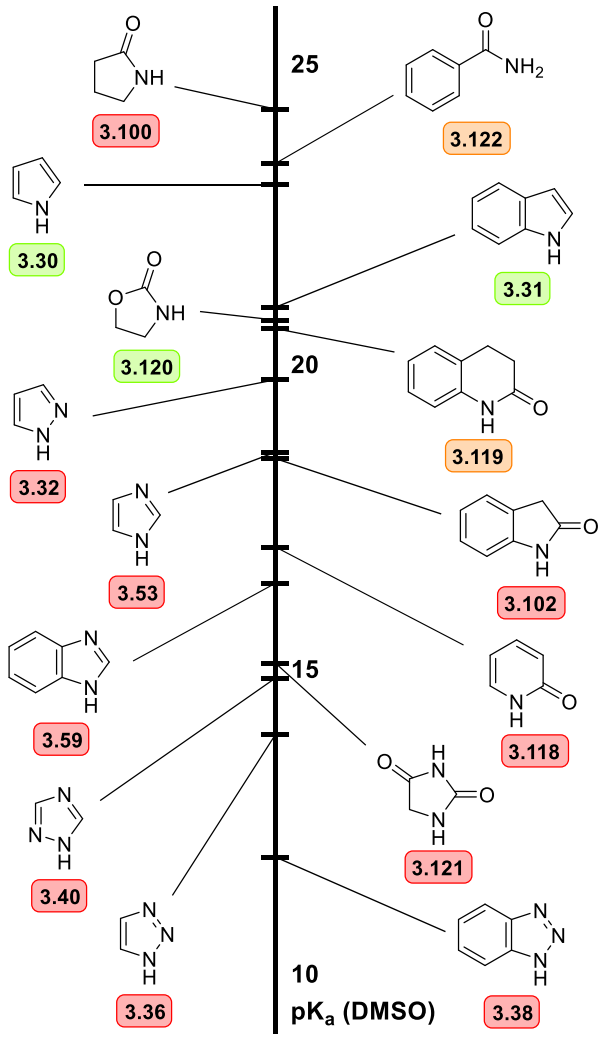
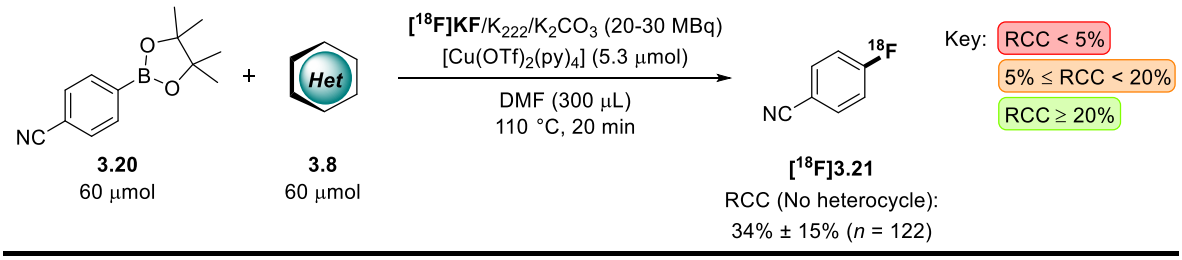


Figure 3.8. A plot of N–H containing molecules against pK_a (DMSO). Colours reflect RCC when screened in the model reaction; red: RCC < 5%; orange: 5% ≤ RCC < 20%; green: RCC ≥ 20%.

3.3.12 Correlation of Screening Results with pK_{aH} of Nitrogen Heterocycles

In section 3.3.6, it was suggested that there may be a correlation between the basicity of a nitrogen heterocycle and how well it is tolerated in the

^{18}F-fluorodeboronation. In order to investigate this, additional heterocycles of known pK_{aH} were screened in the model reaction. *N*,*N*-Dimethylaminopyridine (DMAP) **3.123** completely inhibited the ^{18}F-fluorodeboronation of **3.20** (Table 3.16). This contrasts sharply with the beneficial effect observed when pyridine itself was screened the model reaction (in that case, the RCC of **[^{18}F]3.21** was 69%). DMAP is more basic than pyridine (pK_{aH} = 9.7 and 5.3 respectively); as with imidazoles **3.54**, **3.56** and **3.58**, this difference shows that the electronic effects of substituents on a particular heterocycle can have a significant influence on whether the heterocycle is tolerated.[16], [17] 1,8-Bis(dimethylamino)naphthalene **3.124**, known as "proton sponge" and even more basic than DMAP, also was not tolerated. *N*,*N*-Dimethylbenzylamine **3.125** was rather detrimental to the model reaction (RCC = 4%), but the less basic and more sterically-hindered tribenzylamine **3.126** was tolerated.



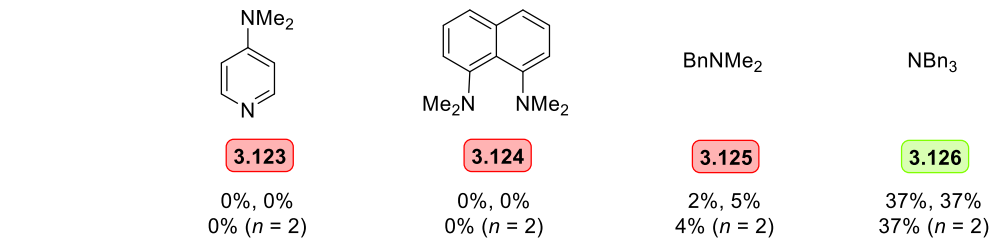


Table 3.16. Screening of additional nitrogen heterocycles for basicity correlation

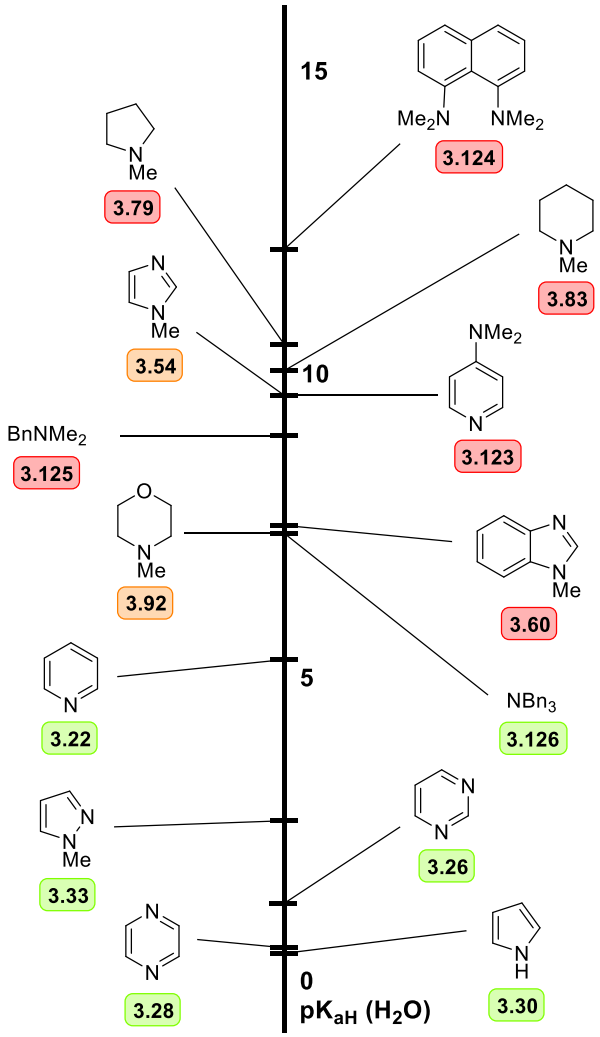


Figure 3.9. A plot of nitrogen heterocycles against pK_{aH} (H_2O). Colours reflect RCC when screened in the model reaction; red: RCC < 5%; orange: 5% ≤ RCC < 20%; green: RCC ≥ 20%.

Figure 3.9 shows a plot of nitrogen heterocycles against their pK_{aH} in water.[16]–[22] Again, the colour indicates the screening result obtained for the heterocycle, using the same definition as in the screening experiments. All of the heterocycles with $pK_{aH} < 6$ were tolerated; all of those with $pK_{aH} > 10$ were not tolerated. However, the basicity explanation does not seem satisfactory since *N*-methylbenzimidazole **3.60** ($pK_{aH} = 7.6$), *N*-methylmorpholine **3.92** ($pK_{aH} = 7.4$) and tribenzylamine **3.126** ($pK_{aH} = 7.4$) have pK_{aH} values within 0.2 units and yet **3.60** is detrimental, **3.92** is somewhat detrimental and **3.126** is tolerated. Whilst the pK_{aH}

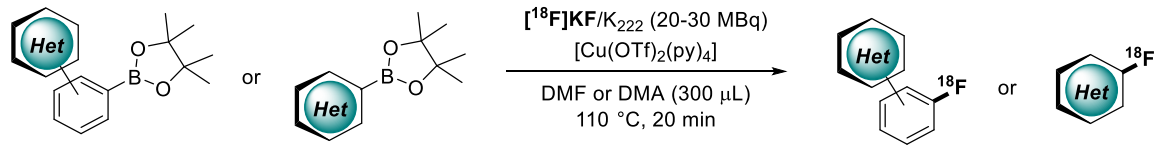
values come from different sources, one would expect to be able to compare them in this way; this should not account for the discrepancy. It seems much more likely that basicity of the nitrogen atom is not a sufficient explanation for whether a heterocycle is tolerated in the model ^{18}F-fluorodeboronation.

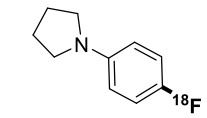
An alternative explanation concerns the ability of the heterocycle to act as a ligand for copper; weakly binding heterocycles would be expected to form labile complexes, whilst strongly binding heterocycles may form stable, unreactive complexes. The strength of binding would be expected to depend on the oxidation state of copper. The mechanism of the reaction is unknown; Cu(I), Cu(II) and Cu(III) species may be involved, so it is difficult to speculate on the importance of the binding strength of a heterocycle to copper in a particular oxidation state. However, a study by Ogle and co-workers reported that in a series of Cu(III) intermediates [EtMe$_2$Cu(Het)], [EtMe$_2$Cu(DMAP)] and [EtMe$_2$Cu(1-methylimidazole)] were much more stable than [EtMe$_2$Cu(pyridine)] and underwent reductive elimination to propane more slowly.[23] By analogy, it is plausible that the more strongly electron-donating DMAP and 1-methylimidazole may be detrimental to the ^{18}F-fluorodeboronation if they stabilise a copper(III) intermediate and reduce the rate of reductive elimination.

3.4 ^{18}F-Fluorodeboronation of Aryl Boronic Esters Bearing Heterocycles

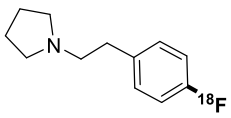
Having screened a large number of heterocyclic additives in the model reaction, the next phase of the project involved verification of the value of the screening experiment in predicting the ^{18}F-fluorodeboronation of aryl boronic ester substrates. Most of the substrates consisted of aryl boronic esters bearing a heterocyclic substituent; selected substrates featured the boronic ester group on the heterocycle itself. In contrast to the substrates in Chapter 2, section 2.2.4, the majority of the desired substrates were not commercially-available and required synthesis. Preparation of the corresponding aryl bromides was followed by Miyaura borylation to afford the requisite boronic esters.[24] This process was generally satisfactory, although some heteroaryl boronic esters proved difficult to prepare and/or purify.

More than fifty aryl boronic esters were subjected to ^{18}F-fluorodeboronation conditions A. These conditions, consisting of an 11:1 ratio of substrate to $[Cu(OTf)_2(py)_4]$ in DMF at 110 °C, were the same conditions employed in the initial investigation into substrate scope (section 2.2.4) and in the screening experiment. Substrates which performed poorly under conditions A (RCC < 10%) were also evaluated under conditions B, the conditions developed in section 2.4 for electron-deficient aryl boronic esters. These consisted of a 1:1.5 ratio of substrate to $[Cu(OTf)_2(py)_4]$ in DMA at 110 °C. Conditions B were generally required for electron-deficient heteroaromatics, substrates bearing an unprotected N–H and certain tertiary amines.

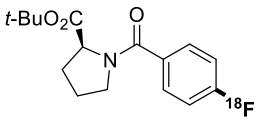




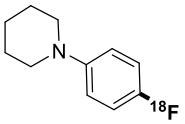
[18F]3.127: **A**: 17% ± 14%[b]



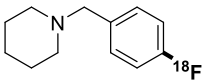
[18F]3.128: **A**: 0%
B: 7% ± 7%[c]



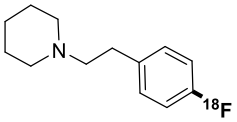
[18F]3.129: **A**: 42% ± 21%



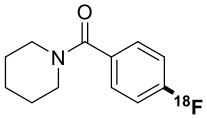
[18F]3.130: **A**: 67% ± 5%[b]



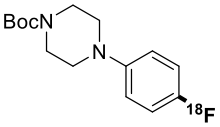
[18F]3.131: **A**: 8% ± 5%
B: 47% ± 7%[d]



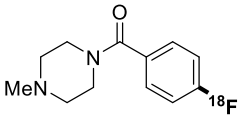
[18F]3.132: **A**: 20% ± 3%[c]



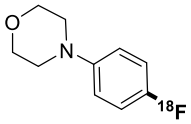
[18F]3.133: **A**: 80% ± 10%



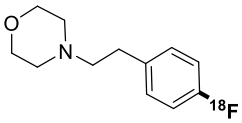
[18F]3.134: **A**: 0%
B: 16% ± 9%[b]



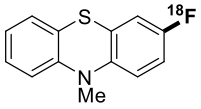
[18F]3.135: **A**: 25% ± 3%[c]



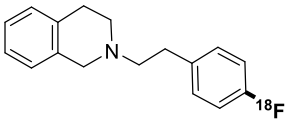
[18F]3.136: **A**: 44% ± 16%[e]



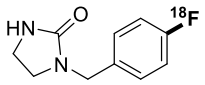
[18F]3.137: **A**: 39% ± 15%



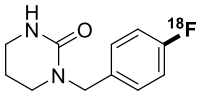
[18F]3.138: **A**: 11% ± 6%[b]



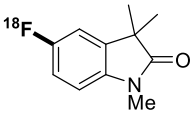
[18F]3.139: **A**: 41% ± 15%



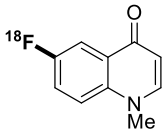
[18F]3.140: **A**: 3% ± 1%
B: 32% ± 2%[c]



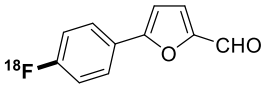
[18F]3.141: **A**: 9% ± 9%[a]
B: 28% ± 16%[c]



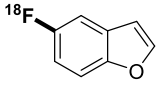
[18F]3.142: **A**: 53% ± 20%



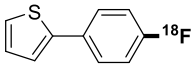
[18F]3.143: **A**: 22% ± 5%[c]



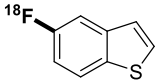
[18F]3.144: **A**: 20% ± 11%[c]



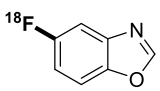
[18F]3.145: **A**: 20% ± 15%



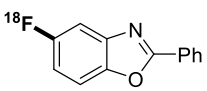
[18F]3.146: **A**: 68% ± 2%[c]



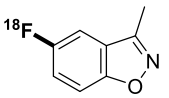
[18F]3.147: **A**: 50% ± 16%



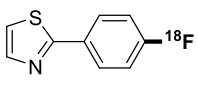
[18F]3.148: **A**: 8% ± 2%
B: 11% ± 2%



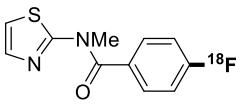
[18F]3.149: **A**: 24% ± 5%[d]



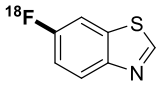
[18F]3.150: **A**: 27% ± 10%[c]



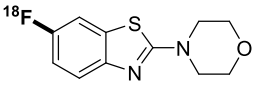
[18F]3.151: **A**: 6% ± 2%[a]
B: 51% ± 15%[d]



[18F]3.152: **A**: 27% ± 3%[c]



[18F]3.153: **A**: 33% ± 11%[d]

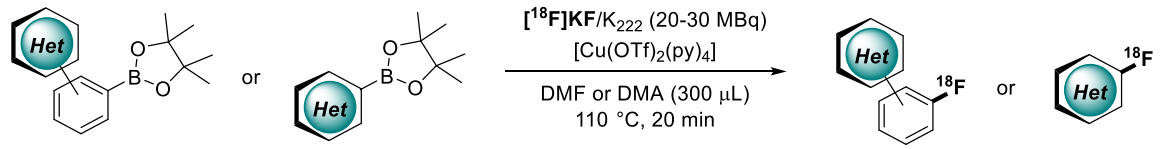


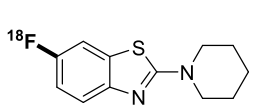
[18F]3.154: **A**: 21% ± 4%[d]

Table 3.17. ^{18}F-Fluorodeboronation of aryl boronic esters bearing heterocycles. Conditions A: (Hetero)aryl boronic ester (60 µmol), $[Cu(OTf)_2(py)_4]$ (5.3 µmol), $[^{18}F]KF/K_{222}$ (20-30 MBq.), DMF (300 µL), air, 110 °C, 20 mins; Conditions B: (Hetero)aryl boronic ester (20 µmol), $[Cu(OTf)_2(py)_4]$ (30 µmol), $[^{18}F]KF/K_{222}$ (20-30 MBq.), DMA (300 µL), air, 110 °C, 20 mins. Reactions were performed four times (n = 4); radiochemical conversions were determined by radio-TLC and radio-HPLC and are given in the form mean ± standard deviation. [a] Reactions were performed twice (n = 2). [b] ^{19}F-Reference prepared by Dr. Michael Schedler. [c] Precursor and ^{19}F-reference prepared by Dr. Michael Schedler. [d] Precursor and ^{19}F-reference prepared by Dr. Enrico Emer. [e] ^{19}F-Reference prepared by Dr. Matthew Tredwell.

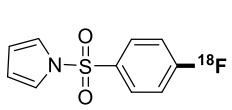
[^{18}F]3.127-**[^{18}F]3.139**, containing tertiary amines, were labelled in radiochemical conversions ranging from 7% to 80% (Table 3.17). Whilst pyrrolidines **[^{18}F]3.127** and **[^{18}F]3.129** could be ^{18}F-labelled satisfactorily under conditions A, *N*-alkylpyrrolidine **[^{18}F]3.128** was not observed under conditions A and could only be formed in 7% RCC under conditions B. This is consistent with the results observed for pyrrolidines **3.79**-**3.81** in the screening experiment. Although benzylpiperidine **[^{18}F]3.131** required use of conditions B in order to achieve acceptable RCCs, phenethylpiperidine **[^{18}F]3.132** did not. This would not have been predicted based on the screening results, showing that alkylated piperidines are one area in which more detailed screening data would be useful for predicting the likelihood of successful ^{18}F-fluorodeboronation of target molecules bearing this motif. Piperazines **[^{18}F]3.134** and **[^{18}F]3.135**, morpholines **[^{18}F]3.136** and **[^{18}F]3.137**, phenothiazine **[^{18}F]3.138** and tetrahydroisoquinoline **[^{18}F]3.139** were all successfully ^{18}F-labelled from the corresponding aryl boronic ester precursors.

The screening experiment showed that mono-alkylated ureas **3.108** and **3.111** were detrimental to the model reaction, but did not completely inhibit formation of **[^{18}F]3.21** (section 3.3.8). ^{18}F-Labelling of **[^{18}F]3.140** and **[^{18}F]3.141** was consistent with this, **[^{18}F]3.140** and **[^{18}F]3.141** were formed in 3% and 9% RCC respectively under conditions A. Use of conditions B resulted in much higher RCCs; 32% and 28% respectively. Trimethylated oxindole **[^{18}F]3.142** and methylated quinolone **[^{18}F]3.143** were successfully ^{18}F-labelled under conditions A, which is consistent with the observation that **3.104** and **3.106** were well-tolerated in the screening experiment.

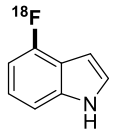




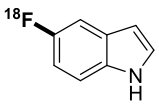
[18F]:3.155 **A**: 36% ± 10%[c]



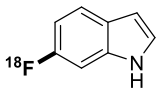
[18F]3.156: **A**: 18% ± 14%



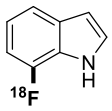
[18F]3.157: **A**: 38% ± 15%



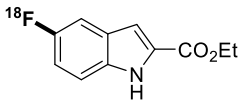
[18F]3.158: **A**: 52% ± 8%



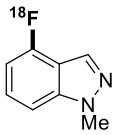
[18F]3.159: **A**: 30% ± 9%



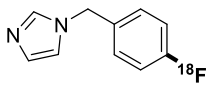
[18F]3.160: **A**: 27% ± 3%



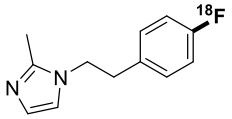
[18F]3.161: **A**: 32% ± 12%



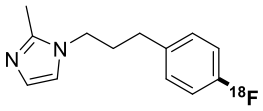
[18F]3.162: **A**: 44% ± 12%[d]



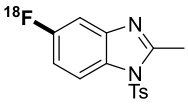
[18F]3.163: **A**: 0%[a][d]
B: 0%[a]



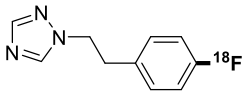
[18F]3.164: **A**: 0%[a][e]
B: 0%[a]



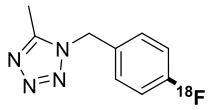
[18F]3.165: **A**: 19% ± 4%
B: 78% ± 6%



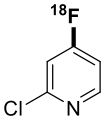
[18F]3.166: **A**: 6% ± 5%
B: 12% ± 7%[c]



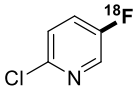
[18F]3.167: **A**: 54% ± 8%[e]



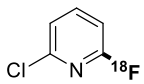
[18F]3.168: **A**: 9% ± 5%
B: 34% ± 9%[e]



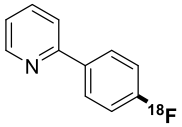
[18F]3.169: **A**: 2% ± 1%
B: 53% ± 8%



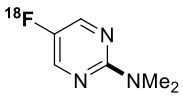
[18F]3.170: **A**: 1% ± 1%
B: 7% ± 4%



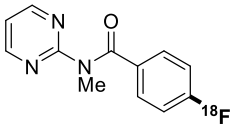
[18F]3.171: **A**: 0%
B: 6% ± 2%



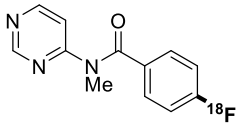
[18F]3.172: **A**: 29% ± 12%



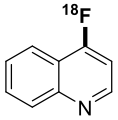
[18F]3.173: **A**: 0%
B: 1% ± 1%[f]



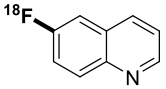
[18F]3.174: **A**: 5% ± 2%
B: 28% ± 5%[e]



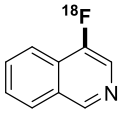
[18F]3.175: **A**: 31% ± 4%[e]



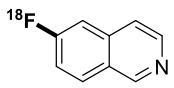
[18F]3.176: **A**: 5% ± 4%
B: 76% ± 4%[g]



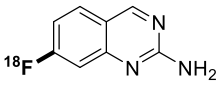
[18F]3.177: **A**: 52% ± 16%



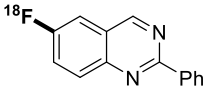
[18F]3.178: **A**: 5% ± 2%
B: 25% ± 8%[g]



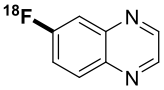
[18F]3.179: **A**: 59% ± 9%



[18F]3.180: **A**: 0%
B: 47% ± 7%[b][e]



[18F]3.181: **A**: 3% ± 1%
B: 63% ± 11%[e]



[18F]3.182: **A**: 21% ± 5%

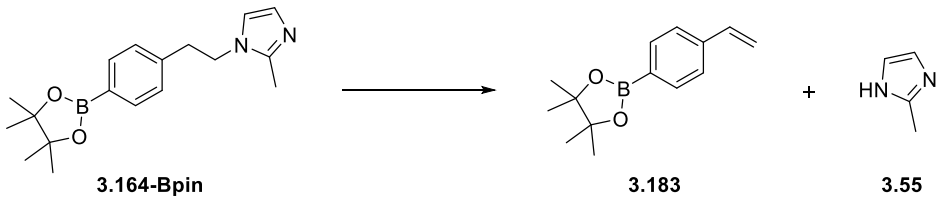
Table 3.18. ^{18}F-Fluorodeboronation of aryl boronic esters bearing heterocycles. Conditions A: (Hetero)aryl boronic ester (60 μmol), $[Cu(OTf)_2(py)_4]$ (5.3 μmol), [^{18}F]KF/K_{222} (20-30 MBq.), DMF (300 μL), air, 110 °C, 20 mins; Conditions B: (Hetero)aryl boronic ester (20 μmol), $[Cu(OTf)_2(py)_4]$ (30 μmol), [^{18}F]KF/K_{222} (20-30 MBq.), DMA (300 μL), air, 110 °C, 20 mins. Reactions were performed four times (n = 4); radiochemical conversions were determined by radio-TLC and radio-HPLC and are given in the form mean ± standard deviation. [a] Reactions were performed twice (n = 2). [b] Starting from *N,N*-di-Boc protected starting material; deprotection occurred under reaction conditions. [c] Precursor and ^{19}F-reference prepared by Dr. Enrico Emer. [d] ^{19}F-Reference prepared by Dr. Enrico Emer. [e] Precursor and ^{19}F-reference prepared by Dr. Michael Schedler. [f] ^{19}F-Reference prepared by Dr. Sean Preshlock. [g] ^{19}F-Reference prepared by Dr. Michael Schedler.

Furans and thiophenes **[^{18}F]3.144**-**[^{18}F]3.147** could be ^{18}F-labelled in 20%-68% RCC. Use of conditions A afforded benzoxazole **[^{18}F]3.148** in only 8% RCC; changing to conditions B did not significantly improve the RCC. 2-Phenylbenzoxazole **[^{18}F]3.149**, was ^{18}F-labelled in more than 20% RCC, as was 3-methylbenzisoxazole **[^{18}F]3.150**. Aminothiazole **[^{18}F]3.152** responded well under conditions A, whereas thiazole **[^{18}F]3.151** required use of conditions B. Benzothiazole **[^{18}F]3.153** was labelled in satisfactory RCC under conditions A, as were aminobenzothiazoles **[^{18}F]3.154** and **[^{18}F]3.155** (Table 3.18).

The ability to install the fluorine-18 substituent at the optimum site for biological activity of a target molecule, rather than the site dictated by feasibility of the available radiochemistry, is a long-term goal in radiochemistry. Thus, we were pleased to demonstrate that unprotected indoles **[^{18}F]3.157**-**[^{18}F]3.160**, differing in placement of the fluorine-18 substituent, were ^{18}F-labelled in RCCs from 27% to 52% (Table 3.18), indicating that the ^{18}F-fluorodeboronation method offers some progress towards this goal. Electron-deficient indole **[^{18}F]3.161** was also ^{18}F-labelled without need for *N*-protection, although this was required for indazole **[^{18}F]3.162**.

Both benzylimidazole **[^{18}F]3.163** and dialkylimidazole **[^{18}F]3.164** could not be ^{18}F-labelled under conditions A or B. Whilst the failure of **[^{18}F]3.163** was fairly consistent with the detrimental effects observed for 1-methylimidazole **3.54** in the screening experiment, that of **[^{18}F]3.164** was not consistent with the tolerance of dimethylimidazole **3.56**. One possible explanation is that the precursor to **[^{18}F]3.164**, boronic ester **3.164-Bpin**, may undergo elimination under the reaction conditions,

forming styrene **3.183** and 2-methylimidazole **3.55**, which was shown in the screening experiment to be highly detrimental (Scheme 3.3).

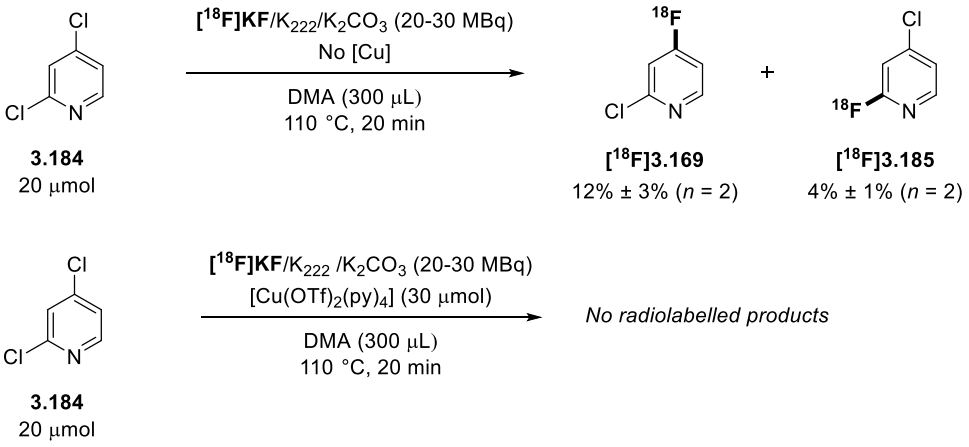


Scheme 3.3. Potential elimination of **3.164-Bpin** to form styrene **3.183** and imidazole **3.55**

In order to probe this, the linking alkyl chain was extended; **[^{18}F]3.165**, which would not undergo such a favourable elimination was successfully ^{18}F-labelled under both conditions, although the RCC was much higher under conditions B (Table 3.18). Tosylated benzimidazole **[^{18}F]3.166** could be ^{18}F-labelled in only 12% RCC, even under conditions B. Benzylated tetrazole **[^{18}F]3.168** also required use of conditions B, whilst conditions A were sufficient for triazole **[^{18}F]3.167**.

Chloropyridines **[^{18}F]3.169**-**[^{18}F]3.171**, chosen for their higher boiling points than the corresponding *des*-chloro pyridines, as well as commercial availability of both boronic ester precursors and ^{19}F-fluorinated references, were formed in 0%-2% RCCs under conditions A. Use of conditions B resulted in improved RCCs in all cases, although only the 4-isomer could be ^{18}F-labelled with RCC exceeding 10%, indicating that the position of ^{18}F-fluorodeboronation can have a significant influence on reactivity. Control experiments were carried out in order to demonstrate that competing displacement of chloride by [^{18}F]fluoride did not occur under the reaction conditions (Scheme 3.4). Whilst heating 2,4-dichloropyridine **3.184** with [^{18}F]KF/K_{222} complex in DMA afforded a mixture of substitution products

[^{18}F]3.169 and **[^{18}F]3.185**, repeating the reaction in the presence of 30 μmol [Cu(OTf)$_2$(py)$_4$] did not result in the formation of radiolabelled products. This may be of utility for target molecules which could otherwise undergo competing substitution reactions.



Scheme 3.4. SNAr control experiments

A distinction must be made between the ability of the screening experiment to predict the success of ^{18}F-fluorodeboronation of an aryl boronic ester with a heterocyclic substituent, as in **[^{18}F]3.172**, and the ability to predict the efficiency of ^{18}F-fluorodeboronation on the heterocycle itself, as in **[^{18}F]3.169**-**[^{18}F]3.171**. The experiments with pyridines **[^{18}F]3.169**-**[^{18}F]3.172** suggest that the screening experiments offer good predictive ability in the former case; phenylpyridine **[^{18}F]3.172** was ^{18}F-labelled in 29% RCC. However, the screening experiments should not be used to predict the efficiency of ^{18}F-fluorodeboronation directly on a heteroaromatic ring.

Similar situations were observed for pyrimidines **[^{18}F]3.173**-**[^{18}F]3.175**. Whilst only a trace of **[^{18}F]3.173** could be obtained, even under conditions B, **[^{18}F]3.174** and **[^{18}F]3.175** bearing aminopyrimidine substituents could be ^{18}F-labelled in good RCC.

In the case of quinoline **[^{18}F]3.177** and isoquinoline **[^{18}F]3.179**, ^{18}F-labelling on the benzenoid ring was facile under conditions A, affording **[^{18}F]3.177** and **[^{18}F]3.179** in greater than 50% RCC. In constrast, quinoline **[^{18}F]3.176** and isoquinoline **[^{18}F]3.178**, in which [^{18}F]fluorodeboronation takes place on the heterocyclic ring, required use of conditions B; **[^{18}F]3.176** and **[^{18}F]3.178** were ^{18}F-labelled in 76% and 25% RCC, respectively.

Aminoquinazoline **[^{18}F]3.180** was ^{18}F-labelled in 47% RCC under conditions B, starting from the *N,N-di*-Boc boronic ester precursor; deprotection of both Boc groups occurred under the reaction conditions. Conditions B were also required for phenylquinazoline **[^{18}F]3.181**, which was unsurprising due to the electron-deficient nature of this heterocycle. For quinoxaline **[^{18}F]3.182**, conditions A were sufficient; **[^{18}F]3.182** was ^{18}F-labelled in 21% RCC.

3.4.1 Comparison between Screening and Substrate Labelling

In general, there is reasonable agreement between the screening results in section 3.3 and the substrate labelling results obtained in section 3.4. In order to highlight key trends, Figure 3.10 compares a selection of labelling results with the corresponding screening results. Pairs with the same colour code indicate agreement between the screening and ^{18}F-labelling experiments. The screening experiment correctly predicted that *N*-alkylated pyrrolidines and piperidines were highly challenging motifs (0% and 8% RCC for **[^{18}F]3.128** and **[^{18}F]3.131** respectively) and that reduced basicity restored reactivity, as illustrated with the successful ^{18}F-labelling of **[^{18}F]3.129** and **[^{18}F]3.137**. Good agreement between screening and ^{18}F-labelling results was also obtained for ureas **3.111** and **[^{18}F]3.141**, thiophenes **3.66** and **[^{18}F]3.146**, benzothiazoles **3.69** and **[^{18}F]3.153**, indoles **3.31** and **[^{18}F]3.158** and triazoles **3.41** and **[^{18}F]3.167**. As discussed in section 3.4, the screening experiment correctly predicted compatibility in the case of **[^{18}F]3.172** bearing a pyridine substituent, but agreement between the screening and ^{18}F-labelling results was very poor for pyridines **[^{18}F]3.169** and **[^{18}F]3.170** in which the ^{18}F-fluorodeboronation takes place on the heterocycle itself.

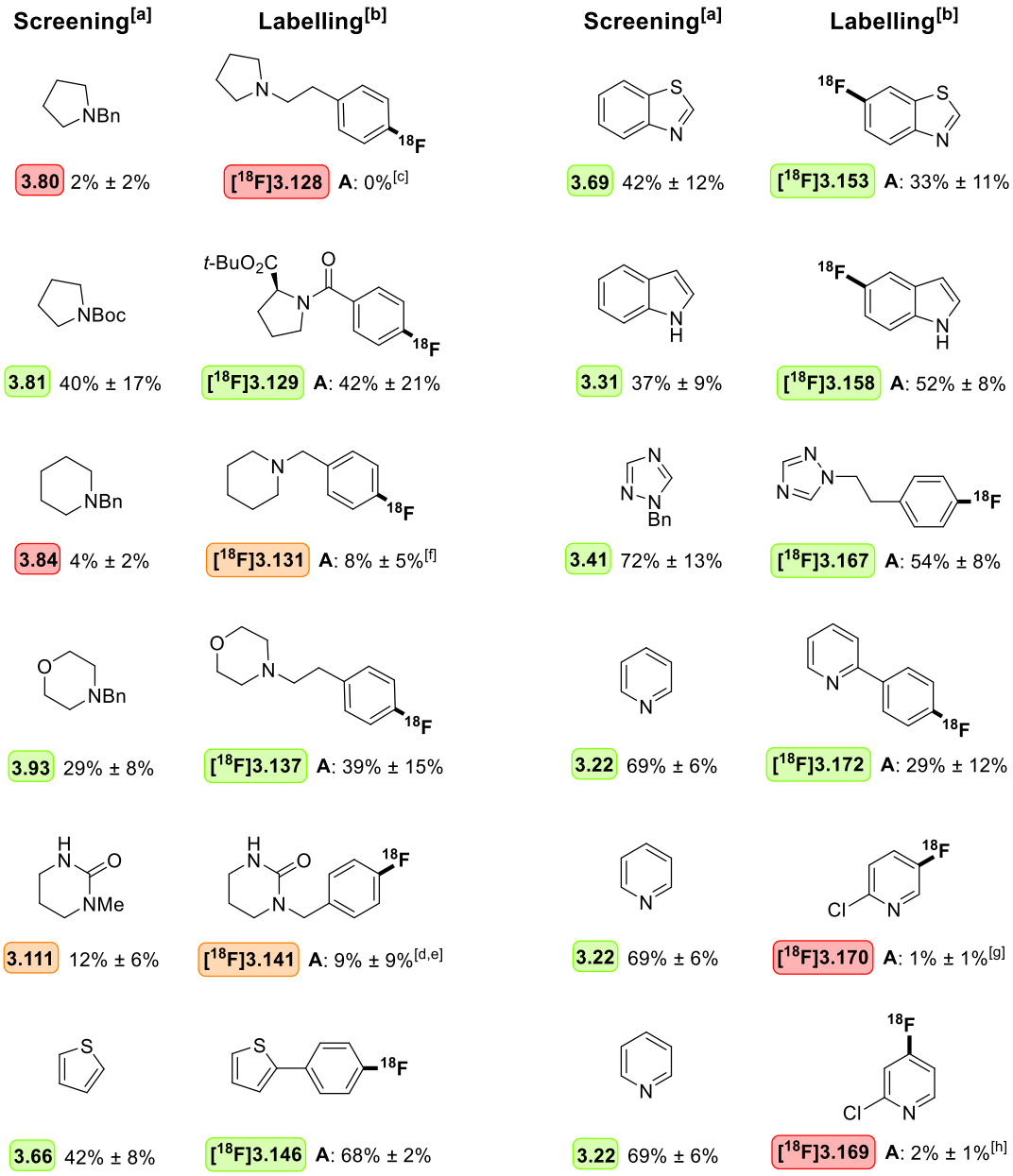


Figure 3.10. A comparison of the heterocyclic additive screening and corresponding labeling results for selected substrates. Red highlight: RCC < 5%. Orange highlight: 5% ≤ RCC < 20%. Green highlight: RCC ≥ 20%. Screening conditions: **3.20** (60 µmol), heterocycle (60 µmol), $[Cu(OTf)_2(py)_4]$ (5.3 µmol), $[^{18}F]KF/K_{222}$ (20-30 MBq.), DMF (300 µL), air, 110 °C, 20 mins. Labelling conditions (A): (Hetero)aryl boronic ester (60 µmol), $[Cu(OTf)_2(py)_4]$ (5.3 µmol), $[^{18}F]KF/K_{222}$ (20-30 MBq.), DMF (300 µL), air, 110 °C, 20 mins. Radiochemical conversions were determined by radio-TLC and radio-HPLC and are given in the form mean ± standard deviation. [a] Reactions were performed eight times (n = 8). [b] Reactions were performed four times (n = 4). [c] Under conditions B, RCC = 7% ± 7% (n = 4). [d] Reactions were performed twice (n = 2). [e] Under conditions B, RCC = 32% ± 2% (n = 4). [f] Under conditions B, RCC = 47% ± 7% (n = 4). [g] Under conditions B, RCC = 7% ± 4% (n = 4). [h] Under conditions B, RCC = 53% ± 8% (n = 4).

Several key conclusions should be drawn from the screening and labelling experiments. Firstly, whilst the screening results are generally in good agreement with ^{18}F-labelling results for an aryl boronic ester featuring a heterocycle as a substituent, caution should be taken if one requires that the heterocycle itself is ^{18}F-labelled. Secondly, as with many reactions, the ^{18}F-fluorodeboronation is sensitive to steric and electronic effects; these should be taken into account in addition to compatibility with a particular heterocycle. Finally, the radiochemical yield is dependent on the reaction conditions employed. Since optimisation for ^{18}F-labelling a specific molecule was not the aim of this investigation, only two sets of conditions were employed; conditions B generally gave improved RCCs for the most challenging substrates. There is scope for optimisation of reaction conditions for the ^{18}F-labelling of a specific target molecule.

3.5 ^{18}F-Fluorodeboronation of Drug Molecules

Having achieved the first two objectives of the project, the final objective was to demonstrate that data obtained via the screening method aids in the ^{18}F-labelling of a selection of fluorinated drugs. Several criteria should be considered when planning to use the copper mediated ^{18}F-fluorodeboronation to ^{18}F-label a complex target bearing multiple heterocyclic sub-motifs. Firstly, due to the short half-life of fluorine-18, ^{18}F-incorporation should take place at a late stage, ideally as the final step. Secondly, the ^{18}F-fluorodeboronation should be compatible with the functional groups in the target molecule, including any heterocyclic motifs. Furthermore, if

^{18}F-fluorodeboronation is not the final step of the radiosynthesis, any subsequent steps should be rapid and facile. Finally, the aryl boronic ester precursor should be accessible and stable.

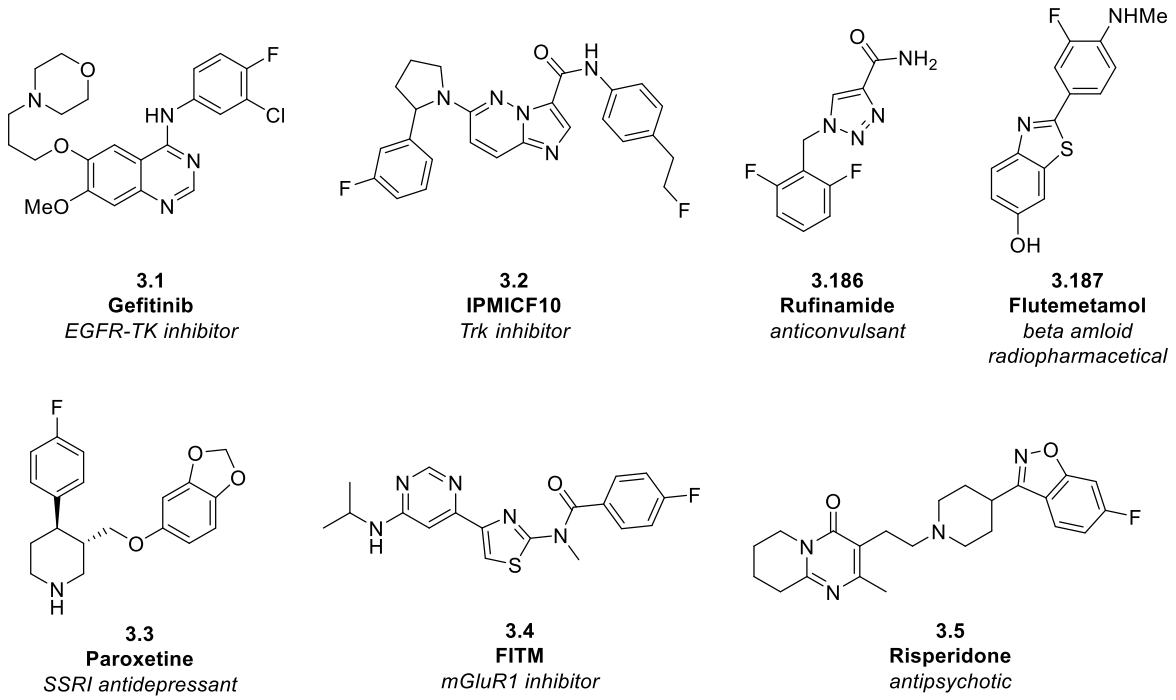
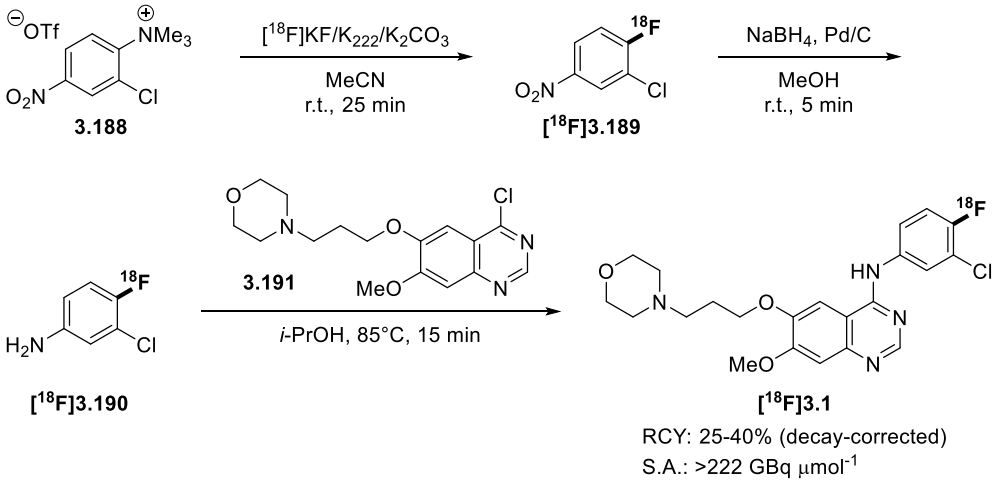


Figure 3.11. Heterocycle-containing fluorinated drugs of interest for ^{18}F-labelling

The target molecules chosen for this study, shown in Figure 3.11, contain a variety of different heterocycles and represent a range of disease areas. Most of these targets have already been labelled with fluorine-18, although prior to this work, rufinamide **3.186** and risperidone **3.5** had not. The primary objective of this study was to present examples to guide future users of the copper-mediated ^{18}F-fluorodeboronation in using the information gained by the screening study to plan their own radiosyntheses. In doing so, we also demonstrated that the copper mediated ^{18}F-fluorodeboronation often provides a route comparable or superior to the established radiosyntheses.

3.5.1 ^{18}F-Labelling of Gefitinib

Epidermal growth factor receptor (EGFR) is a member of the *erb*B family of cell surface receptors.[25] EGFR can be bound by a variety of ligands, including epidermal growth factor, transforming growth factor-α and heparin-binding epidermal growth factor.[26] This causes activation of the EGFR tyrosine kinase (EGFR-TK), which is a key initiator of cell proliferation.[27] EGFR is over-expressed in many human tumours, including non-small-cell lung, prostate and breast, and especially in advanced cases, for which the prognosis is poor.[28] Gefitinib, ZD1839, is an orally-active, selective inhibitor of EGFR-TK function which was approved by the FDA in 2003 for treatment of advanced non-small-cell lung cancers after failure of both platinum-based therapies and docetaxel.[29], [30]



Scheme 3.5. Synthesis of [^{18}F]gefitinib **[^{18}F]3.1** from trimethylammonium precursor **3.188**

The synthesis of [^{18}F]gefitinib **[^{18}F]3.1** was reported by Seimbille and co-workers in 2005 (Scheme 3.5).[31] Trimethylammonium triflate **3.188** initially reacted with [^{18}F]KF/K$_{222}$ complex to form ^{18}F-labelled nitroarene **[^{18}F]3.189**. This was reduced to aniline **[^{18}F]3.190** with $NaBH_4$ and Pd/C. Substitution of

chloroquinazoline **3.191** with **[^{18}F]3.190** afforded [^{18}F]gefitinib **[^{18}F]3.1**. The authors reported that 400-600 MBq of **[^{18}F]3.1** could be produced from an initial batch of 3.4 to 6.1 GBq cyclotron-produced [^{18}F]fluoride in a two hour synthesis, giving decay-corrected radiochemical yields of 25-40%.

In 2008, the same group reported PET/CT studies with [^{18}F]gefitinib in mice and vervet monkeys.[32] Since [^{18}F]gefitinib did not accumulate specifically in EGFR-expressing tumour xenografts, it is unlikely that PET with [^{18}F]gefitinib could be used to image levels of EGFR expression in patients. Radiometabolites were not observed, suggesting that this was due to non-specific binding rather than metabolic instability. However, [^{18}F]gefitinib could be used as a tracer to study the tissue pharmacokinetics of gefitinib and to determine intratumoural drug concentrations, which may provide insights into the mechanisms of gefitinib resistance. In order to facilitate further PET studies with [^{18}F]gefitinib, Läppchen and co-workers subsequently developed an automated radiosynthesis on an Eckert and Ziegler modular system.[33]

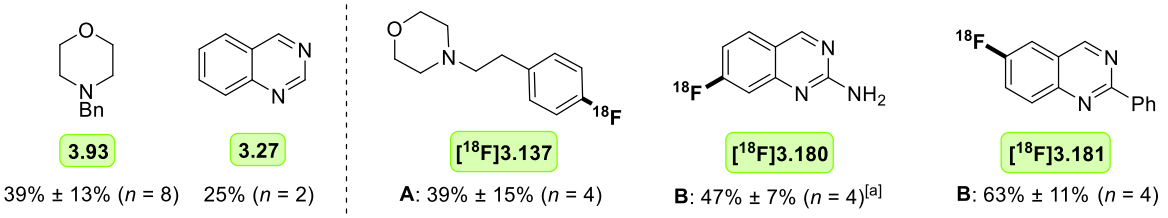
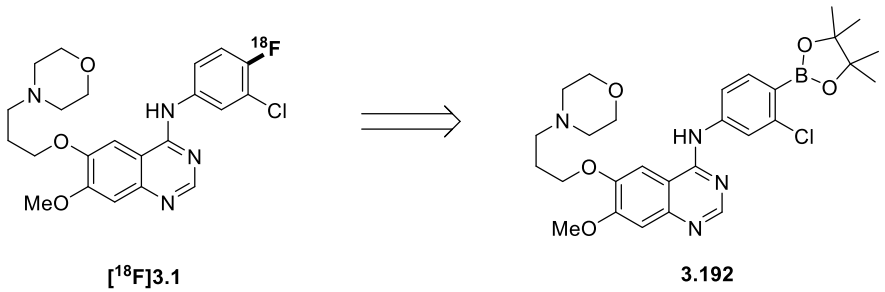


Figure 3.12. Key screening and ^{18}F-labelling results relevant to the ^{18}F-labelling of gefitinib.
[a] Starting from *N*,*N*-di-Boc protected starting material; deprotection occurred during reaction.

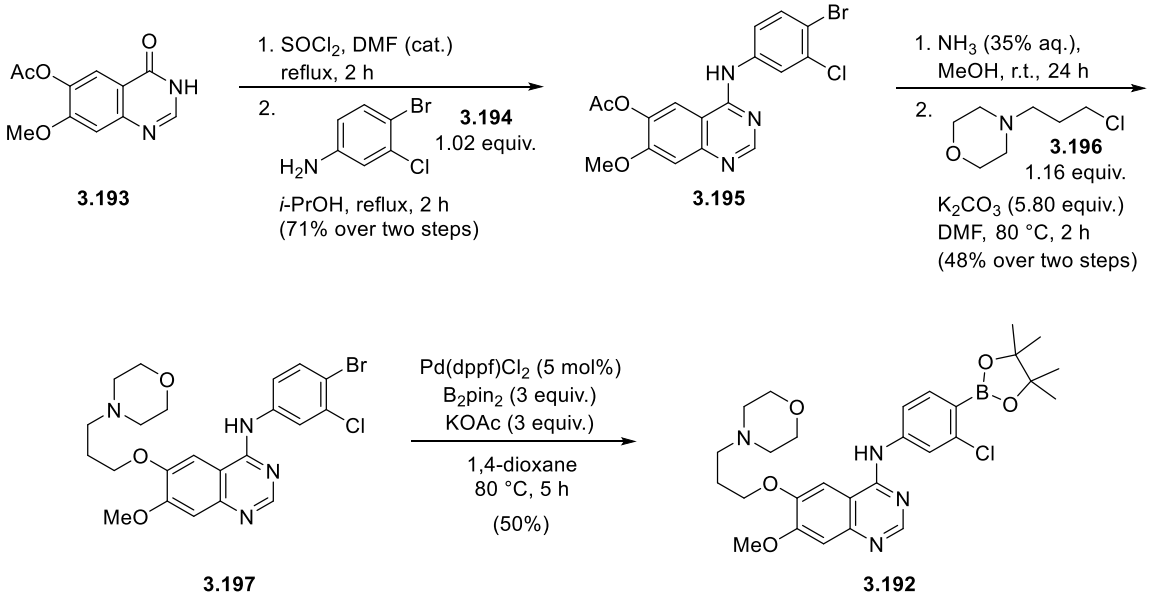
Key screening and fragment ^{18}F-labelling results for application of ^{18}F-fluorodeboronation to the ^{18}F-labelling of gefitinib are given in Figure 3.12. The screening experiment showed that *N*-benzylmorpholine **3.93** was well-tolerated;

this, together with the positive result for the ^{18}F-labelling of phenethylmorpholine **3.137** provided evidence that the *N*-alkylmorpholine group was unlikely to cause any difficulties. Quinazoline **3.27** was well-tolerated in the screening study and quinazoline-containing small molecules **3.180** and **3.181** were successfully ^{18}F-labelled under conditions B. We therefore envisaged that a final-stage ^{18}F-fluorodeboronation of boronic ester **3.192** under conditions B would afford the desired **[^{18}F]3.1** (Scheme 3.6).



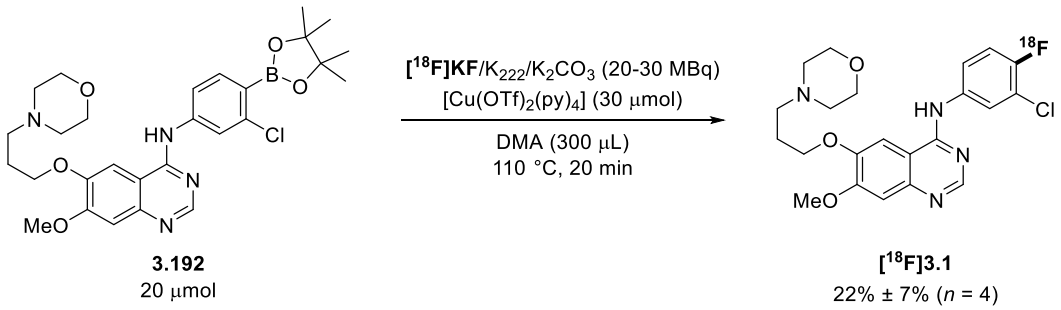
Scheme 3.6. Retro-radiosynthesis of [^{18}F]gefitinib **[^{18}F]3.1**

Boronic ester **3.192** was synthesised by Dr. Enrico Emer based on literature procedures for gefitinib analogues.[34] The synthesis began with the chlorination of commercially-available quinazolone **3.193**, followed by nucleophilic aromatic substitution with aniline **3.194**, affording aminoquinazoline **3.195** in 71% yield over two steps (Scheme 3.7). Deprotection of the acetate protecting group with aqueous ammonia in methanol, followed by alkylation with morpholine-containing fragment **3.196** furnished bromide **3.197** in 48% yield over two steps. Miyaura borylation afforded requisite boronic ester **3.192** in 50% yield after purification by column chromatography.



Scheme 3.7. Synthesis of boronic ester **3.192** (carried out by Dr. Enrico Emer)

Pleasingly, when boronic ester **3.192** was subjected to ^{18}F-fluorodeboronation conditions B, [^{18}F]gefitinib **[^{18}F]3.1** was formed in 22% RCC (Scheme 3.8).



Scheme 3.8. ^{18}F-Fluorodeboronation of **3.192** to afford [^{18}F]gefitinib **[^{18}F]3.1**

Figure 3.13 shows the radio-HPLC trace of the crude reaction mixture, overlaid with the UV-HPLC trace of authentic gefitinib **3.1**.

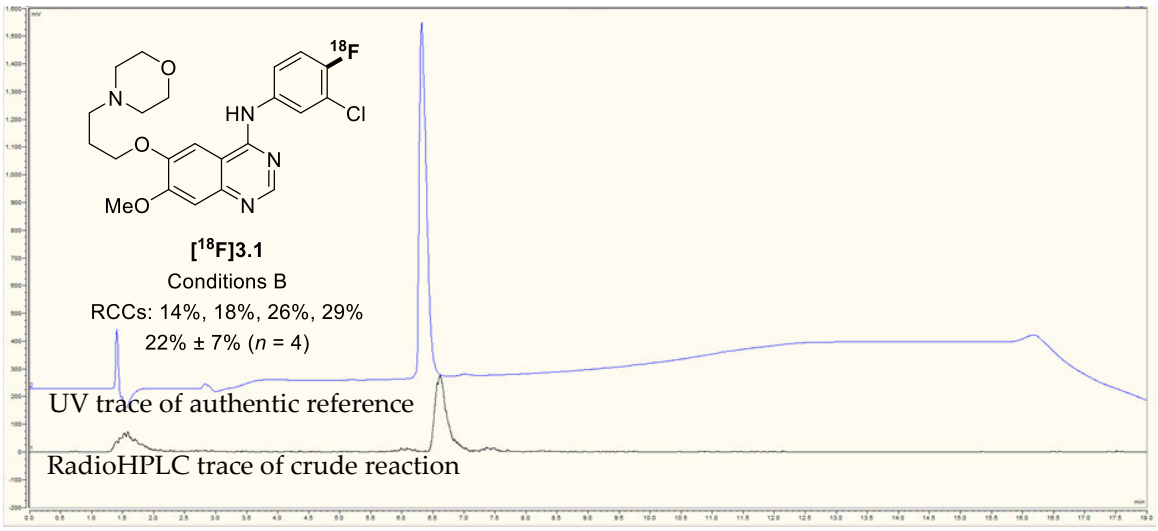


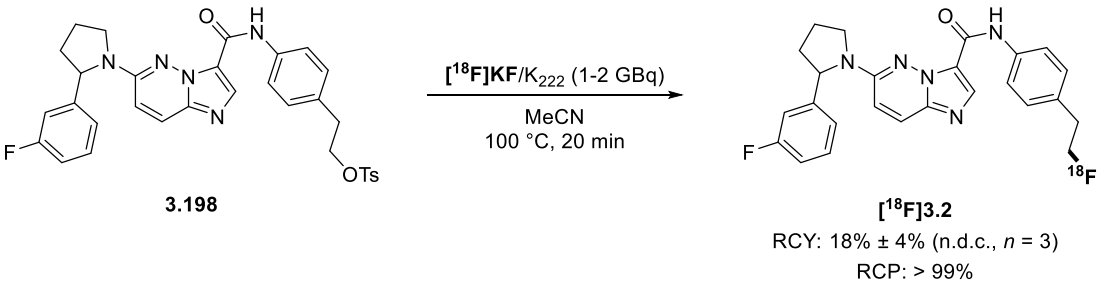
Figure 3.13. Radio-HPLC trace of the crude reaction mixture of the ^{18}F-fluorodeboronation of **3.192**, overlaid with the UV-HPLC trace of gefitinib **3.1**.

3.5.2 ^{18}F-Labelling of IPMICF10

Tropomyosin receptor kinases (Trk) are a group of three structurally-related tyrosine kinases which play crucial roles in the development and maintenance of the mammalian nervous system.[35], [36] TrkA occurs within cholinergic neurons of the basal forebrain and dorsal root ganglion; reduction of TrkA density at early stages of Alzheimer's disease is associated with cognitive decline.[37], [38] TrkB and TrkC are expressed in most brain regions.[39] Dysregulation of TrkB has been implicated in Alzheimer's disease, Parkinson's disease, Huntingdon's disease, schizophrenia and traumatic brain injury.[40]–[44] In addition, Trk are recognised to be involved in pathogenesis of carcinomas, myelomas and lymphoid tumours, in addition to contributing to the development of resistance to cytotoxic drugs.[45], [46]

Development of selective positron emission tomography radiotracers would allow non-invasive monitoring of levels of TrkA/B/C in both the brain and in

cancerous tissue. Bernard-Gauthier and co-workers recently reported optimisation of a (2-pyrrolidin-1-yl)imidazo[1,2-*b*]pyridazine lead compound in order to develop ^{18}F-labelled pan-Trk inhibtors with subnanomolar affinity for TrkB and TrkC.[36] Although all compounds contained an aryl fluoride, the optimisation was partially guided by introduction of a second fluorinated group which would be amenable to ^{18}F-labelling via well-established S$_N$2 methods. The most promising compound, IPMICF10 **3.2**, had potencies of 99 pM and 127 pM for TrkB and TrkC respectively, as well as ≥1000-fold selectivity for TrkB/C versus other kinases expressed in the nervous system.



3.198

[^{18}F]3.2
RCY: 18% ± 4% (n.d.c., *n* = 3)
RCP: > 99%

Scheme 3.9. ^{18}F-Labelling of IPMICF10 via S$_N$2 displacement of tosylate precursor **3.198**

^{18}F-Labelling of IPMICF10 was achieved starting from tosylate precursor **3.198** (Scheme 3.9). Heating with azeotropically-dried [^{18}F]KF/K$_{222}$ complex in MeCN afforded [^{18}F]IPMICF10 **[^{18}F]3.2** in 18% ± 4% radiochemical yield (n.d.c., *n* = 3) and > 99% radiochemical purity. In-vitro autoradiograms confirmed specific binding to brain regions rich in TrkB/C. In addition, in-vitro stability in human plasma was shown to be high, with <5% [^{18}F]fluoride being observed after one hour incubation at 37 °C. ^{18}F-Labelling of IPMICF10 at the aryl fluoride site was considered to be a

good test of the ability of our screening experiment to guide ^{18}F-fluorodeboronation of a complex, heterocycle-containing target.

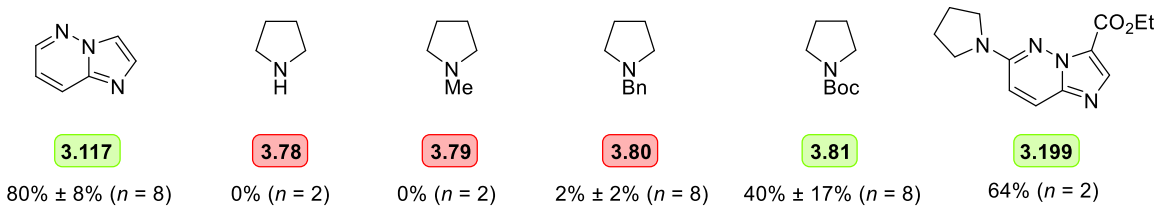
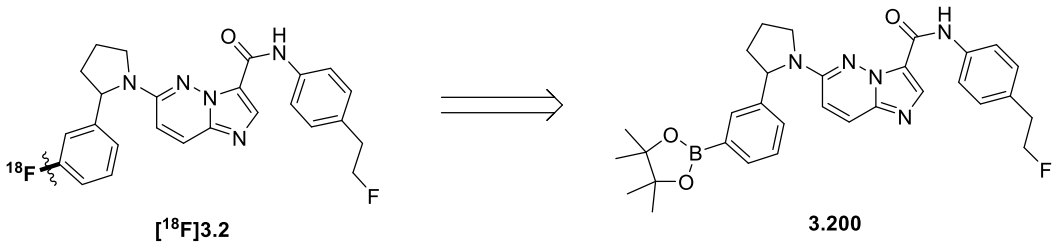


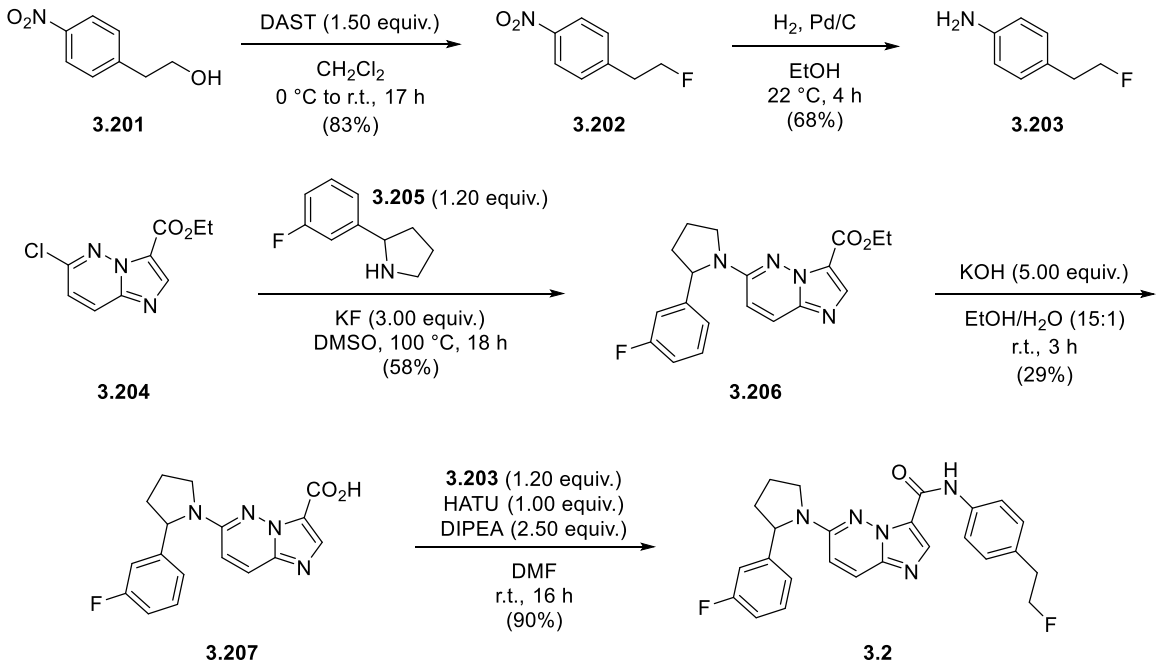
Figure 3.14. Key screening results relevant to the ^{18}F-labelling of IPMICF10

The screening experiment had shown that imidazo[1,2-*b*]pyridazine **3.117**, which features in the core of IPMICF10, had a beneficial effect on the model ^{18}F-fluorodeboronation (Figure 3.14). Pyrrolidines **3.78** to **3.81** had given mixed results, but none of these was a good model for this target. Thus, fragment **3.199**, incorporating pyrrolidine and carbonyl groups into their respective positions on the imidazo[1,2-*b*]pyridazine core, was designed as a better model. This was synthesised and screened; pleasingly, **3.199** also exhibited a beneficial effect on the model reaction (RCC = 64%). This gave us a degree of confidence that final-stage ^{18}F-fluorodeboronation of boronic ester **3.200** would be a successful strategy (Scheme 3.10).



Scheme 3.10. Retro-radiosynthesis of [^{18}F]IPMICF10 **[^{18}F]3.2**

^{19}F-Reference **3.2** was synthesised following the route of Schirrmacher.[36] Fluoroaniline **3.203** was first prepared in two steps from alcohol **3.201** (Scheme 3.11). Deoxyfluorination of **3.201** with DAST proceeded smoothly, affording **3.202** in 83% yield. Palladium-catalysed reduction of the nitro group formed aniline **3.203** in 68% yield. Nucleophilic aromatic substitution of the chloride in **3.204** with pyrrolidine **3.205** afforded **3.206** in 58% yield. Ester hydrolysis was low yielding due to difficulties in isolation of acid **3.207**. Nonetheless, HATU coupling with aniline **3.203** afforded a sufficient quantity of reference **3.2**.

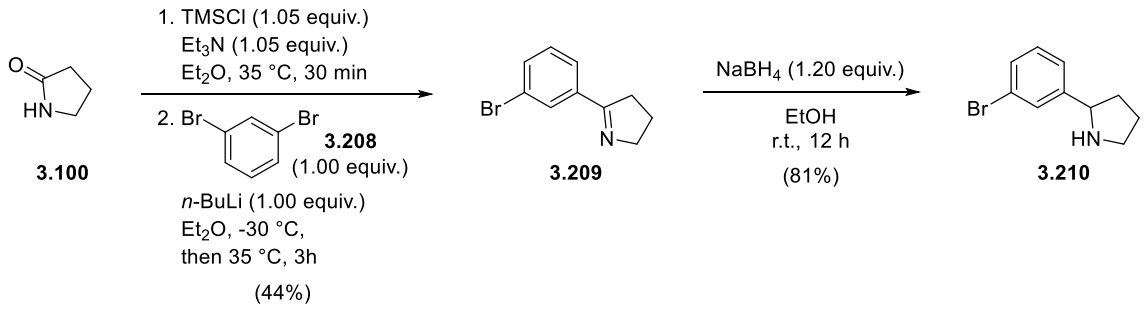


3.201 3.202 3.203 3.204 3.206 3.207 3.2

Scheme 3.11. Synthesis of reference **3.2**

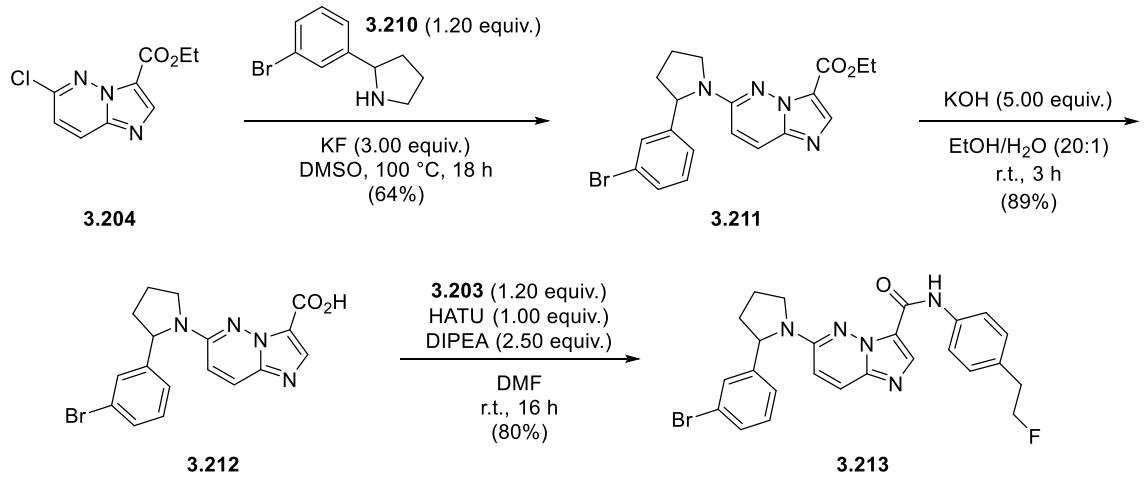
The initial route to boronic ester **3.200** was analogous to that used for reference **3.2**. It was anticipated that replacing the aryl fluoride with the corresponding aryl bromide would allow for a late-stage Miyaura borylation. To that end, pyrrolidine **3.210** was prepared as detailed in Scheme 3.12. 2-Pyrrolidinone **3.100** was first silylated with trimethylsilyl chloride and triethylamine. An aryllithium reagent

derived from 1,3-dibromobenzene **3.208** was then added, affording pyrroline **3.209** in 44% yield.[47] This was reduced with sodium borohydride to form pyrrolidine **3.210**.[48]



Scheme 3.12. Synthesis of pyrrolidine **3.210**

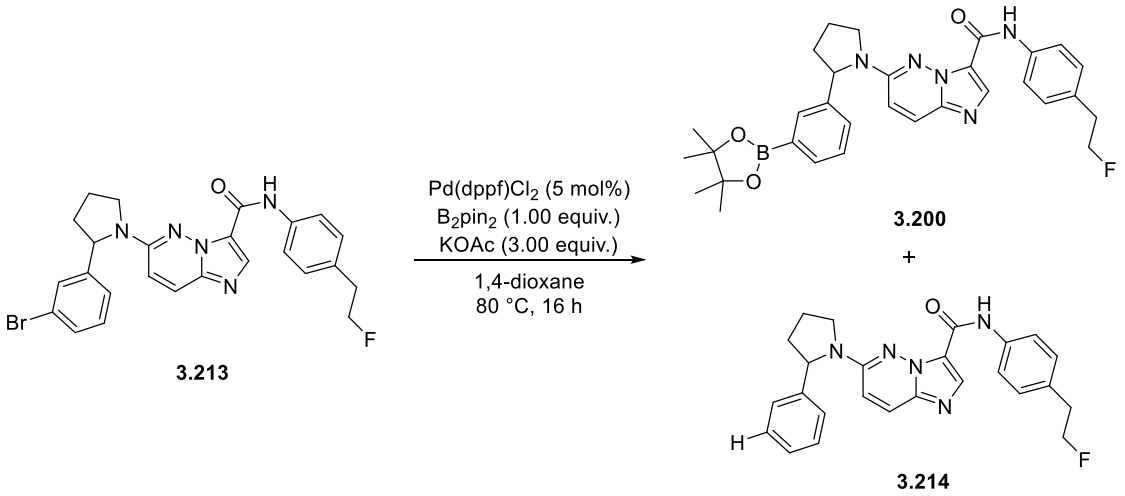
Synthesis of bromide **3.213** was successful using the same route used for reference **3.2** (Scheme 3.13). Substitution of chlorimidazo[1,2-*b*]pyridazine **3.204** with pyrrolidine **3.210** afforded imidazo[1,2-*b*]pyridazine **3.211** in 64% yield. Ester hydrolysis and HATU coupling with aniline **3.203** proceeded smoothly.



Scheme 3.13. Synthesis of bromide **3.213**

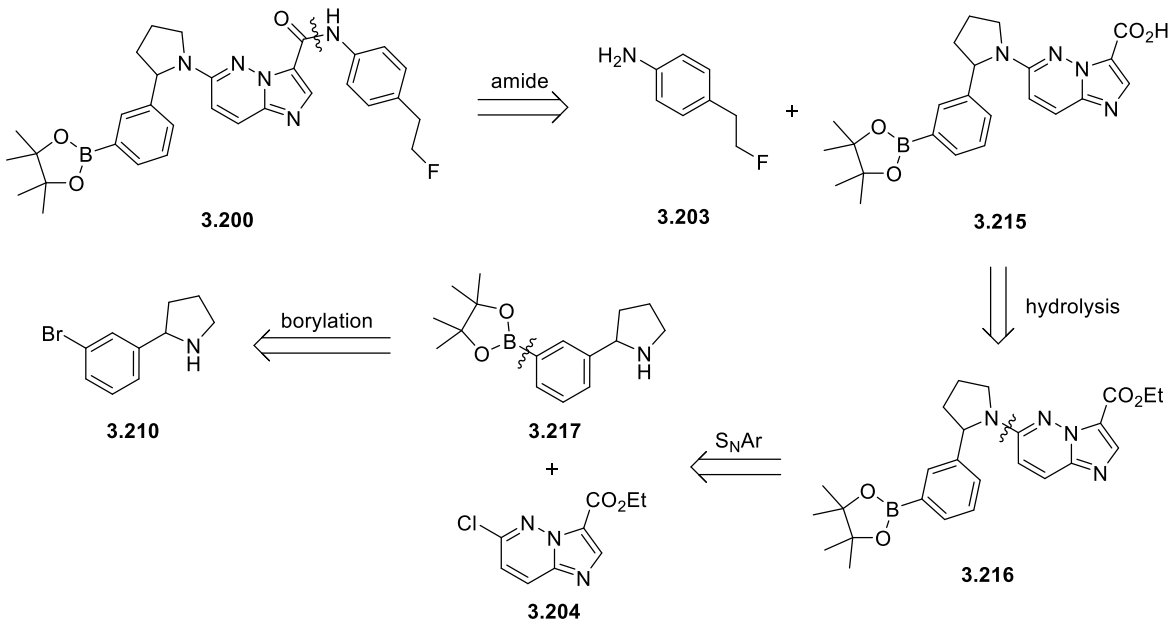
Miyaura borylation of **3.213** was problematic (Scheme 3.14). Although the major product after the reaction was the desired boronic ester **3.200**, it was not possible to separate this from unreacted starting material **3.213** and debromination

by-product **3.214** by silica gel chromatography due to their very similar polarity. Recrystallisation attempts were also unsuccessful and poor solubility in water, methanol and acetonitrile precluded separation by preparative reverse-phase HPLC. Borylation of intermediate ester **3.211** was also attempted, but this suffered from the same problems. It was decided that the borylation step should take place on a less polar intermediate in order to facilitate purification.



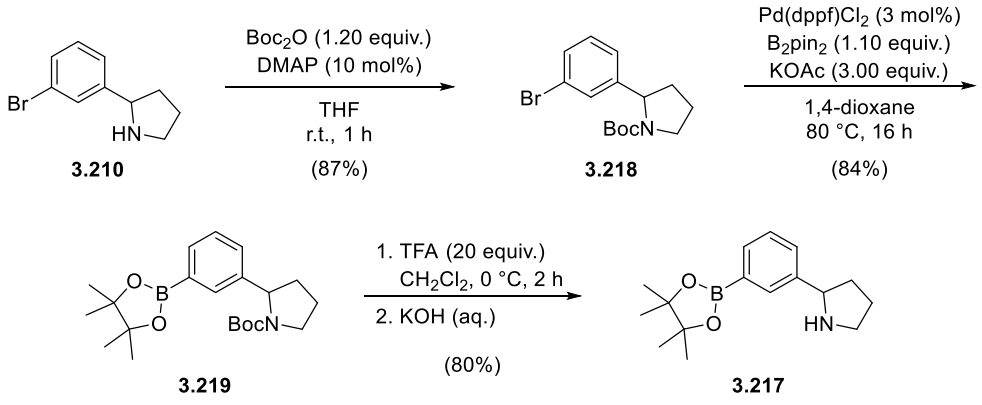
Scheme 3.14. Attempted borylation of bromide **3.213**

A different route to **3.200** was then designed which featured introduction of the boronic ester at a much earlier stage (Scheme 3.15). From a retrosynthetic point of view, amide **3.200** was first disconnected to aniline **3.203**, which had been used in the previous route, and acid **3.215**, which had not. Acid **3.215** could be formed by hydrolysis of ester **3.216**, which in turn was formed in the coupling of pyrrolidine **3.217** with chloroimidazo[1,2-*b*]pyridazine **3.204**. Boronic ester **3.217** could be synthesised from bromide **3.210**.



Scheme 3.15. Alternative retrosynthesis of **3.200** avoiding late-stage borylation

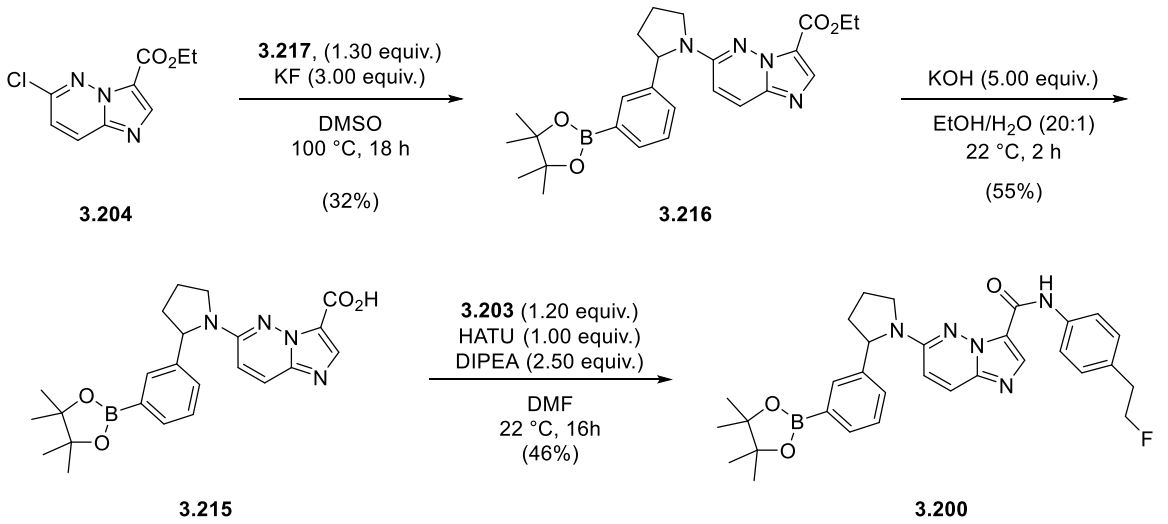
In a forward sense, **3.210** was first Boc-protected, in 87% yield (Scheme 3.16). This was done to reduce the polarity and enable more facile purification by silica gel chromatography. Miyaura borylation proceeded well, affording protected boronic ester **3.219** in 84% yield. Boc-deprotection with trifluoroacetic acid afforded pyrrolidine **3.217**.



Scheme 3.16. Synthesis of pyrrolidine **3.217**

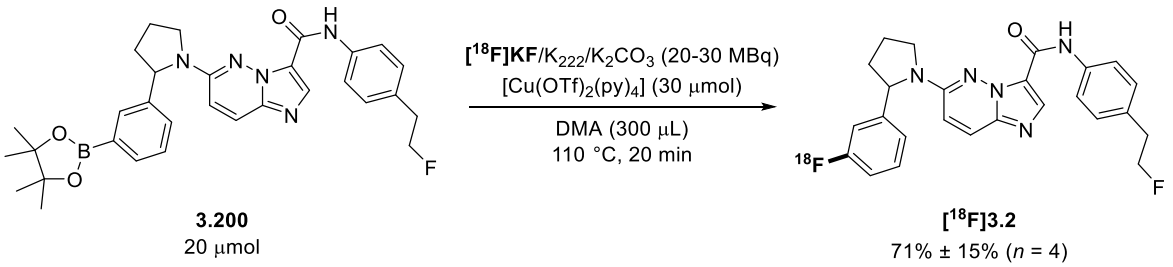
Pyrrolidine **3.217** was then coupled with chloroimidazo[1,2-*b*]pyridazine **3.204** (Scheme 3.17). The low yield of the nucleophilic substitution may be due to

instability of the boronic ester groups in **3.217** and **3.216** under the reaction conditions. Hydrolysis and amide coupling proceeded as planned, albeit in relatively low yields. Despite the low yields of the later steps of the synthesis, enough material was obtained for ^{18}F-labelling studies.



Scheme 3.17. Synthesis of boronic ester **3.200**

The ^{18}F-fluorodeboronation of **3.200** proceeded very well under conditions B (Scheme 3.18); target compound [^{18}F]IPMICF10 **[^{18}F]3.2** was formed in 71% RCC (n = 4).



Scheme 3.18. ^{18}F-Fluorodeboronation of **3.200** to afford [^{18}F]IPMICF10 **[^{18}F]3.2**

Figure 3.15 shows the radio-HPLC trace of the crude reaction mixture, overlaid with the UV-HPLC trace of the ^{19}F-reference. Despite difficulties in accessing

boronic ester **3.200**, the screening experiment correctly predicted that this final-stage ^{18}F-fluorodeboronation would be successful.

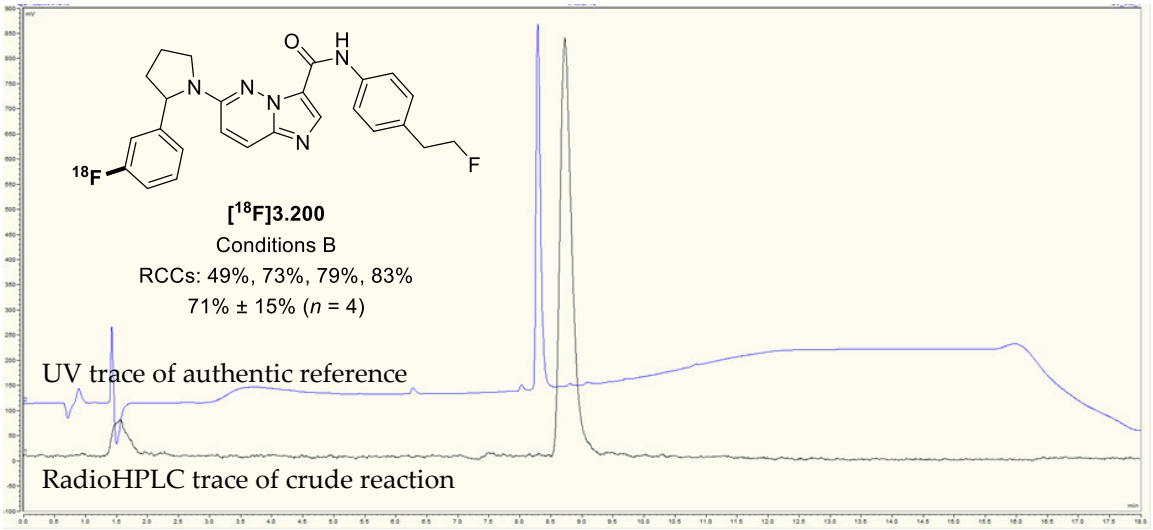


Figure 3.15. Radio-HPLC trace of the crude reaction mixture of the ^{18}F-fluorodeboronation of **3.200**, overlaid with the UV-HPLC trace of IPMICF10 **3.2**.

3.5.3 ^{18}F-Labelling of Rufinamide

Rufinamide **3.186** is an anticonvulsant which was approved by the FDA in 2008 as an adjunctive treatment of seizures associated with Lennox-Gastaut syndrome.[49], [50] It has also been shown to be effective in reducing frequency of partial seizures in adults and adolescents.[51] Although it has been reported to prolong the inactivation of sodium channels of isolated neurons, limiting the frequency of action potential firing, other studies have suggested that there were no effects on sodium channels.[52] Since rufinamide's mechanism of action is poorly understood, ^{18}F-labelling for PET studies is of interest.

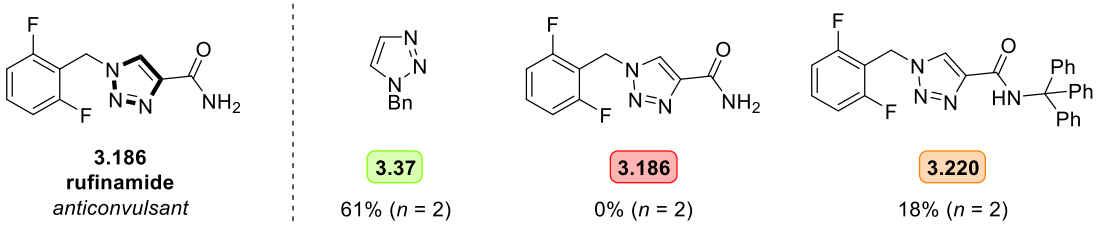
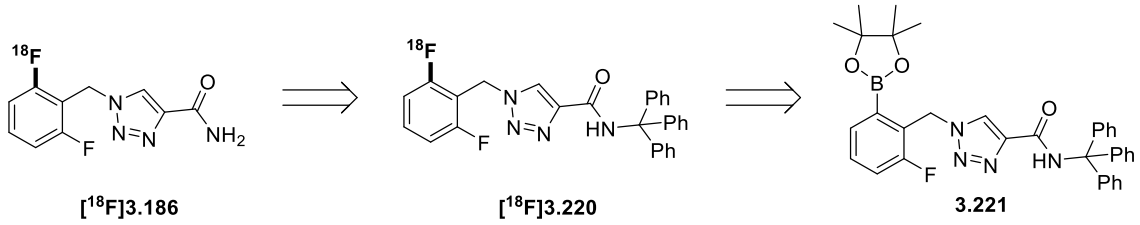


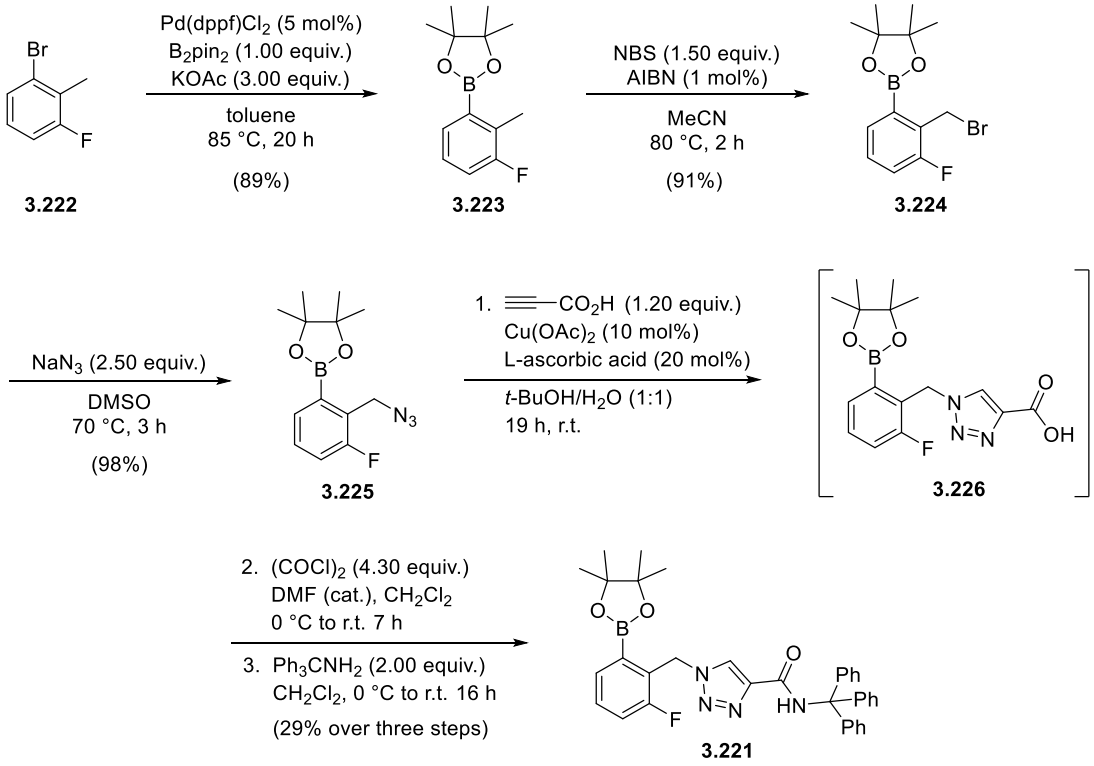
Figure 3.16. Key screening results relevant to the ^{18}F-labelling of rufinamide

The screening experiment had shown that *N*-benzylated triazole **3.37** was not detrimental to the model ^{18}F-fluorodeboronation (Figure 3.16). Based on previous results (section 2.2.4), it was suspected that the free amide would be problematic; a screening experiment with rufinamide **3.186** itself confirmed this to be the case. The partial deprotection observed with the bis-*N*-Boc protected [^{18}F]FDOPA intermediate (Chapter 2, section 2.3.1) suggested that molecules bearing two electron-withdrawing substituents on the same nitrogen atom may undergo deprotection under the reaction conditions. Thus, a carbamate or sulfonamide was not chosen to protect the amide nitrogen. A screening experiment with *N*-trityl-rufinamide **3.200** showed that this was only slightly detrimental and suggested that this was a good compromise between stability and ease of removal. The retro-radiosynthetic scheme was therefore as shown in Scheme 3.19; in a forward sense, ^{18}F-fluorodeboronation of **3.221** would be followed by deprotection of the trityl group of **[^{18}F]3.220** to afford [^{18}F]rufinamide **[^{18}F]3.186**.



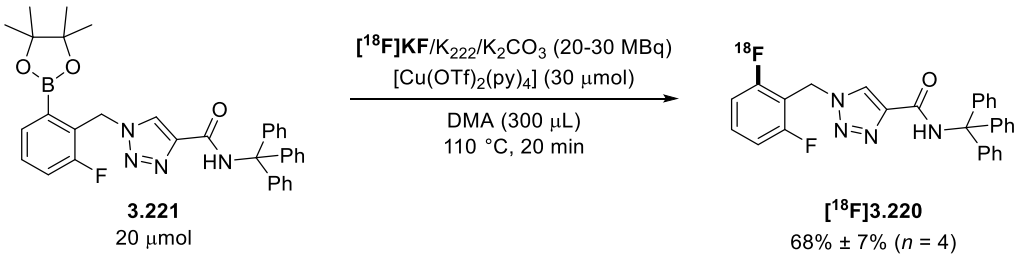
Scheme 3.19. Retro-radiosynthesis of [^{18}F]rufinamide **[^{18}F]3.186**

Boronic ester **3.221** was synthesised by Dr. Enrico Emer (Scheme 3.20). Miyaura borylation of aryl bromide **3.222** afforded boronic ester **3.223** in 89% yield. **3.223** was brominated at the benzylic position in 91% yield using NBS, with AIBN as radical initiator. The benzylic bromide was substituted with azide to form **3.225**, which was subjected to Huisgen CuAAC conditions with propiolic acid.[53] Crude acid **3.226** was transformed into the acid chloride, then substituted with triphenylmethylamine to afford the required boronic ester **3.221**.



Scheme 3.20. Synthesis of boronic ester **3.221**, carried out by Dr. Enrico Emer

^{18}F-Fluorodeboronation of **3.221** under conditions B (Scheme 3.21) afforded protected ^{18}F-rufinamide **[^{18}F]3.220** in 68% RCC (n = 4). The radio-HPLC trace of the crude reaction mixture, overlaid with the UV-HPLC trace of the ^{19}F-reference, is given in Figure 3.17.



Scheme 3.21. ^{18}F-Fluorodeboronation of **3.221** followed by deprotection to afford **[^{18}F]3.220**

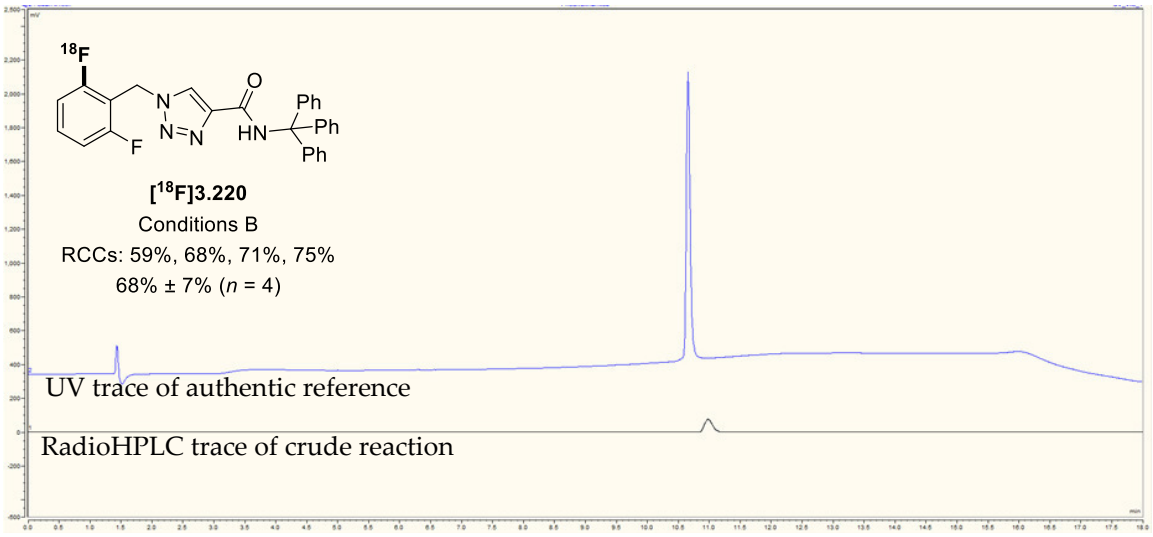
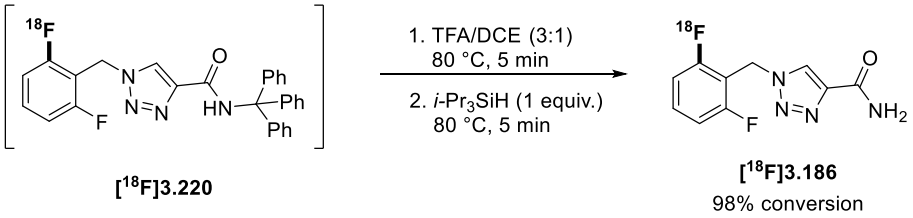


Figure 3.17. Radio-HPLC trace of the crude reaction mixture of the ^{18}F-fluorodeboronation of **3.221**, overlaid with the UV-HPLC trace of reference **3.220**.

Rapid deprotection of the trityl group was achieved using TFA/DCE, followed by *i*-Pr$_3$SiH, affording ^{18}F-rufinamide **[^{18}F]3.186** in 98% conversion from **[^{18}F]3.220** (Scheme 3.22). Figure 3.18 shows the radio-HPLC trace of the crude reaction mixture, overlaid with the UV-HPLC trace of authentic rufinamide **3.186**.



Scheme 3.22. Deprotection of **[^{18}F]3.220** to afford **[^{18}F]3.186**

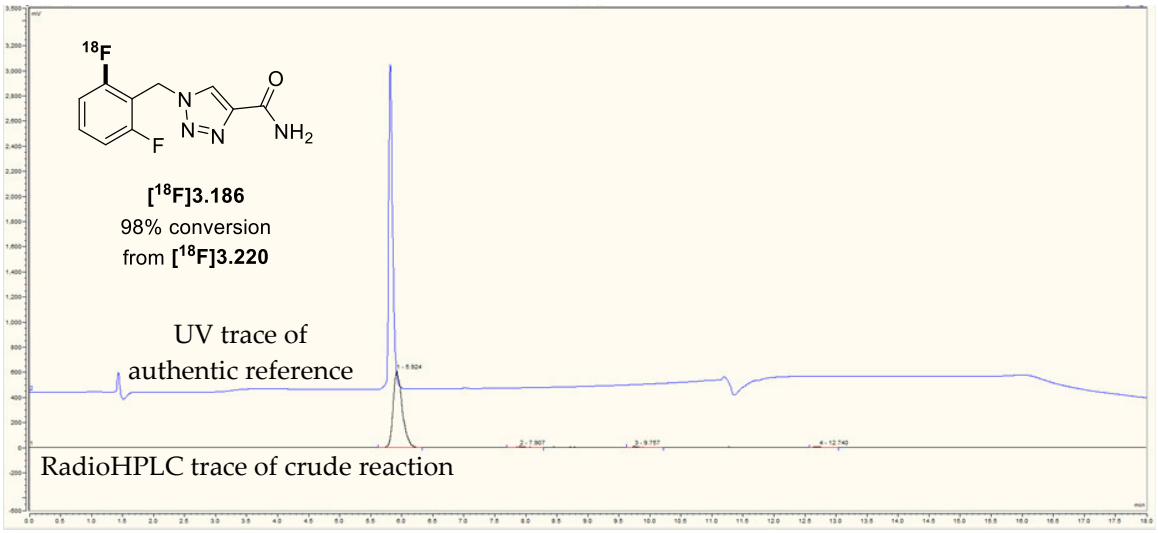


Figure 3.18. Radio-HPLC trace of the crude reaction mixture after deprotection of **[^{18}F]3.220**, overlaid with the UV-HPLC trace of authentic rufinamide **3.186**.

3.5.4 ^{18}F-Labelling of Flutemetamol

Alzheimer's disease is a progressive neurodegenerative disorder characterised by memory loss and cognitive decline.[54] It is the leading cause of dementia in the elderly, and despite a large amount of research in the area, there is no cure. The pathological hallmarks of the disease include intracellular neurofibrillary tangles and extracellular amyloid plaques.[55] These plaques consist of aggregates of amyloid β-peptide, the formation of which is thought to result in neurodegenerative events leading to synaptic dysfunction and neuronal death.[56] β-Amyloid accumulation has been shown to begin several years before the appearance of detectable symptoms; observation at an early stage thus offers an opportunity for early intervention.

Pittsburgh compound B **[^{11}C]3.227** is an amyloid-specific carbon-11 labelled PET ligand derived from the dye thioflavin T **3.228** (Figure 3.19).[57] Whilst

[^{11}C]3.227 has been used to visualise β-amyloid in the brains of Alzheimer's patients, its use in clinical diagnosis is very limited due to the short half-life of carbon-11. For this reason, ^{18}F-labelled analogues of **[^{11}C]3.227** have been developed. Three such analogues approved by the FDA for use in imaging of β-amyloid are flutemetamol **[^{18}F]3.187**, florbetapir **[^{18}F]3.229** and florbetaben **[^{18}F]3.230.**

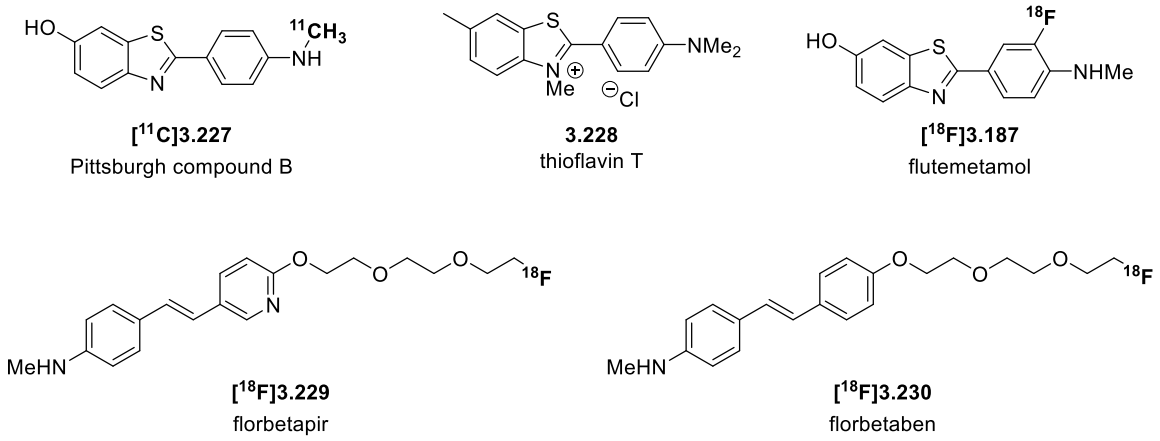
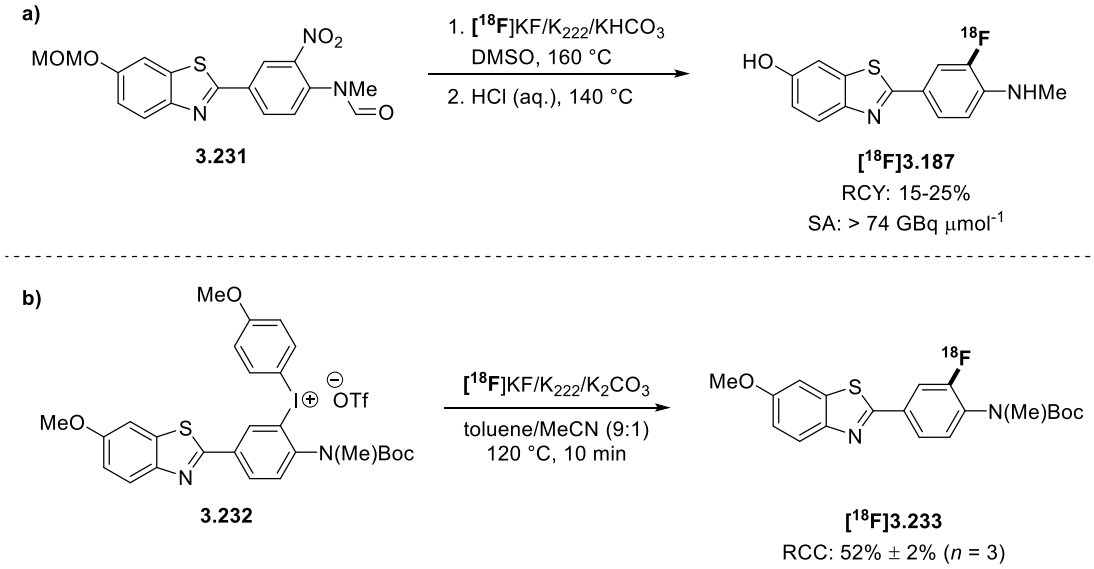


Figure 3.19. Thioflavin T and derivatives used in the imaging of β-amyloid

Flutemetamol **[^{18}F]3.187** was developed by GE Healthcare and was approved by the FDA in 2013.[58]–[61] The radiosynthesis involved displacement of the nitro group of precursor **3.231**, followed by acidic hydrolysis (Scheme 3.23a).[62] Recently, DiMagno and co-workers reported the successful ^{18}F-labelling of a protected flutemetamol **[^{18}F]3.233** via the thermal decomposition of iodonium precursor **3.232** (Scheme 3.23b).[63] However, deprotection was not carried out.



Scheme 3.23. **a)** Radiosynthesis of [^{18}F]flutemetamol via substitution of nitro precursor **3.231**. **b)** Radiosynthesis of protected ^{18}F-labelled flutemetamol **[^{18}F]3.233** from iodonium **3.232**.

Key screening and previous radiolabelling results relevant to the radiosynthesis of [^{18}F]flutemetamol using our ^{18}F-fluorodeboronation are given in Figure 3.20. Whilst screening of **3.69** and successful ^{18}F-labelling of **[^{18}F]3.153** showed that the benzothiazole moiety was well-tolerated, the ^{18}F-labelling of phenol **[^{18}F]2.76** proceeded in only 7% RCC. In contrast, ether **2.77** and veratrole **2.62** were ^{18}F-labelled in 43% and 54% RCCs, respectively, suggesting that protection of the phenol as an ether would be suitable.

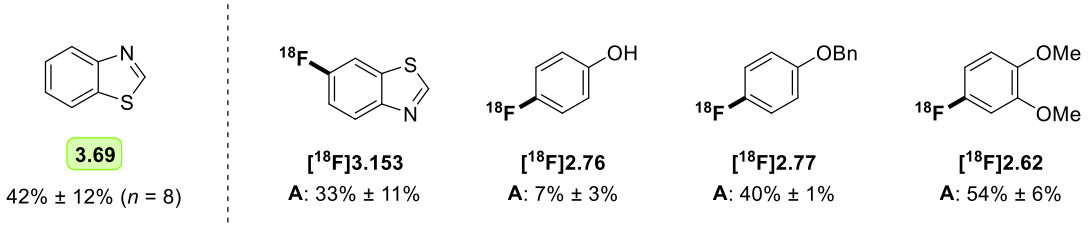
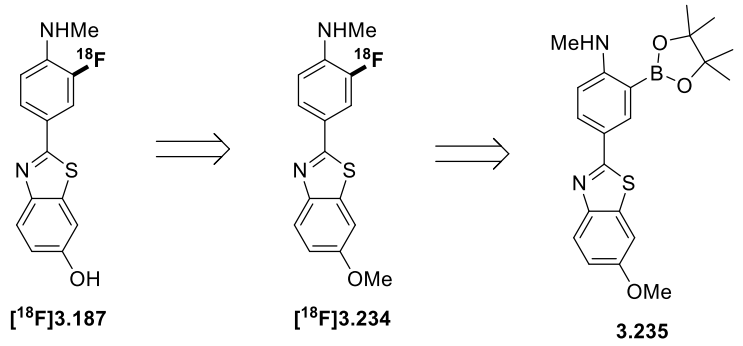


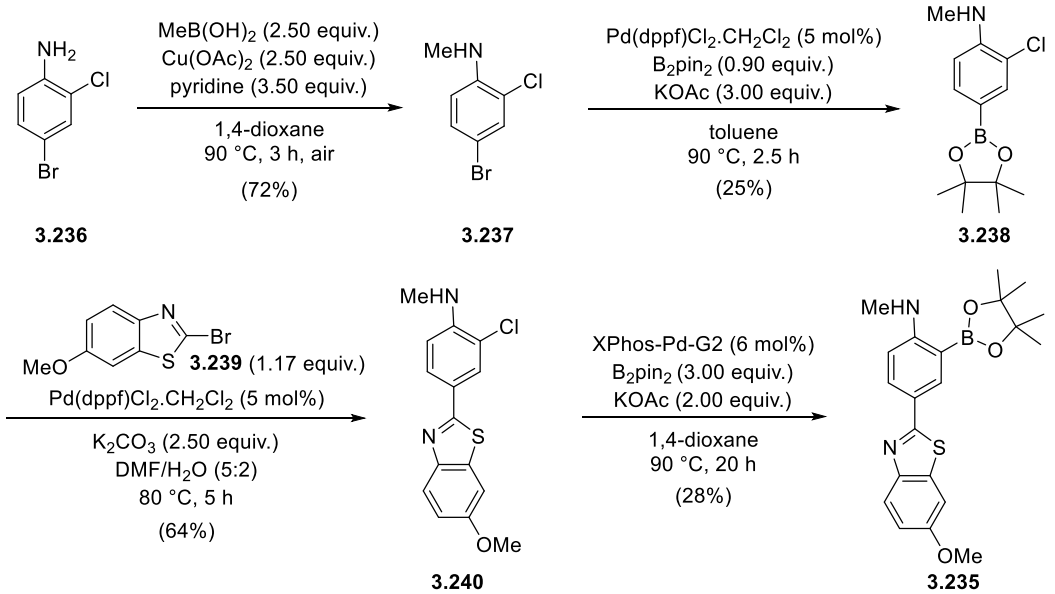
Figure 3.20. Key screening results for the synthesis of [^{18}F]flutemetamol by ^{18}F-fluorodeboronation

Based on the results in Figure 3.20, the retro-radiosynthesis is as shown in Scheme 3.24. In the forward sense, ^{18}F-fluorodeboronation of boronic ester **3.235** would be followed by demethylation to afford [^{18}F]flutemetamol **[^{18}F]3.187**.



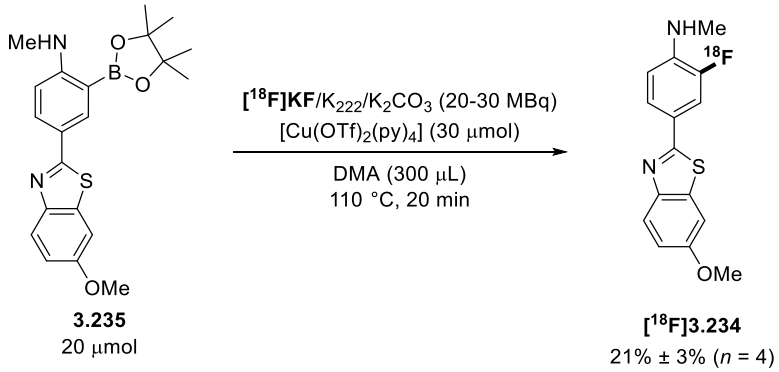
Scheme 3.24. Retro-radiosynthesis of [^{18}F]flutemetamol **[^{18}F]3.187**

Boronic ester **3.235** was synthesised by Dr. Sean Preshlock (Scheme 3.25). Aniline **3.236** was first methylated under Chan-Lam conditions to afford mono-methylated aniline **3.237** in 72% yield. Miyaura borylation was followed by Suzuki coupling of boronic ester **3.238** with bromobenzothiazole **3.239**. The final step was borylation of the aryl chloride; this challenging coupling required use of the Buchwald precatalyst XPhos-Pd-G2.



Scheme 3.25. Synthesis of boronic ester **3.235**, carried out by Dr. Sean Preshlock

Subjecting boronic ester **3.235** to ^{18}F-fluorodeboronation conditions B resulted in formation of desired product **[^{18}F]3.234** in 21% RCC (n = 4, Scheme 3.26). The RCC was relatively low but sufficient for our purposes. This was not unexpected; previous studies had shown aryl boronic esters bearing coordinating groups in an *ortho* position to be challenging substrates (Chapter 2, section 2.2.4).



Scheme 3.26. ^{18}F-Fluorodeboronation of **3.235** to afford **[^{18}F]3.234**

Figure 3.21 shows the radio-HPLC trace of **[^{18}F]3.234**, overlaid with the UV trace of the authentic ^{19}F-reference compound.

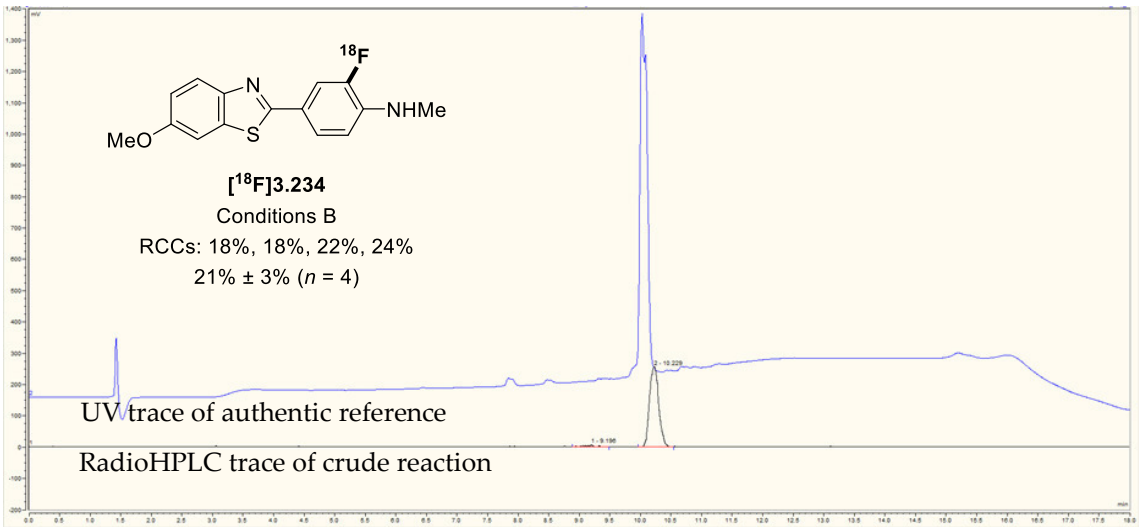


Figure 3.21. Radio-HPLC trace of the crude reaction mixture for the ^{18}F-fluorodeboronation of **3.235**, overlaid with the UV-HPLC trace of ^{19}F-reference **3.234**.

Following purification of **[^{18}F]3.234** by Sep-Pak cartridge, deprotection of the anisole was successful using BBr_3 in a mixture of DCE and CH_2Cl_2 (2:1) at 80 °C. This was not selective; at least five radiolabelled products were observed, with the peak corresponding to [^{18}F]flutemetamol **[^{18}F]3.187** corresponding to 43% of the area (Figure 3.22). The radiolabelled side-products were not identified.

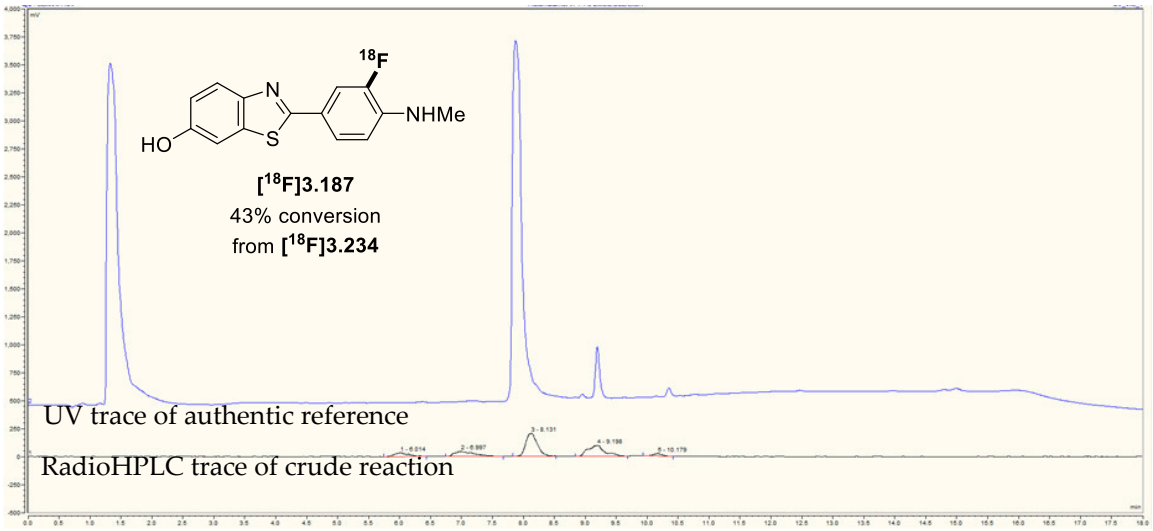
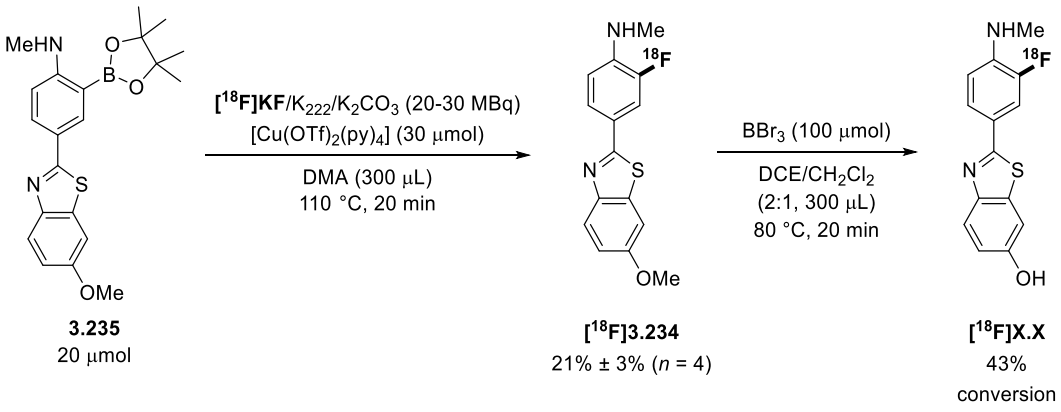


Figure 3.22. Radio-HPLC trace of the crude reaction mixture after deprotection of **[^{18}F]3.234**, overlaid with the UV-HPLC trace of ^{19}F-reference **3.187**.

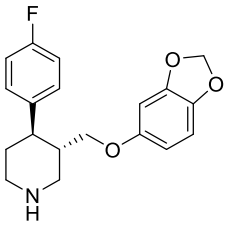
The overall radiosynthesis of [^{18}F]flutemetamol is given in Scheme 3.27.



Scheme 3.27. Radiosynthesis of [^{18}F]flutemetamol via ^{18}F-fluorodeboronation

3.5.5 ^{18}F-Labelling of Paroxetine

Paroxetine **3.3** (Figure 3.23) is a selective serotonin reuptake inhibitor (SSRI), developed by SmithKline Beecham and approved by the FDA in 1992 for the treatment of depression.[64], [65] Although it is prescribed widely, the distribution of paroxetine binding in the human brain is unknown.[66]



3.3
paroxetine
SSRI antidepressant

Figure 3.23. Structure of paroxetine **3.3**

SmithKline Beecham radiochemists attempted to label paroxetine with fluorine-18 from triazene and diazosulfide precursors **3.241** and **3.242** (Figure 3.24a), as well as via use of a temporary *ortho*-aldehyde group to activate displacement of a trimethylammonium triflate.[67] Unfortunately, all of these approaches failed to deliver [^{18}F]paroxetine in acceptable radiochemical yield and specific activity. Scheffel and co-workers successfully labelled a paroxetine derivative, *N*-3-([^{18}F]fluoropropyl)paroxetine **[^{18}F]3.244** (Figure 3.24b), with fluorine-18, but in vitro binding assays showed that the structural change had reduced the affinity for the serotonin binding site by three orders of magnitude.[68]

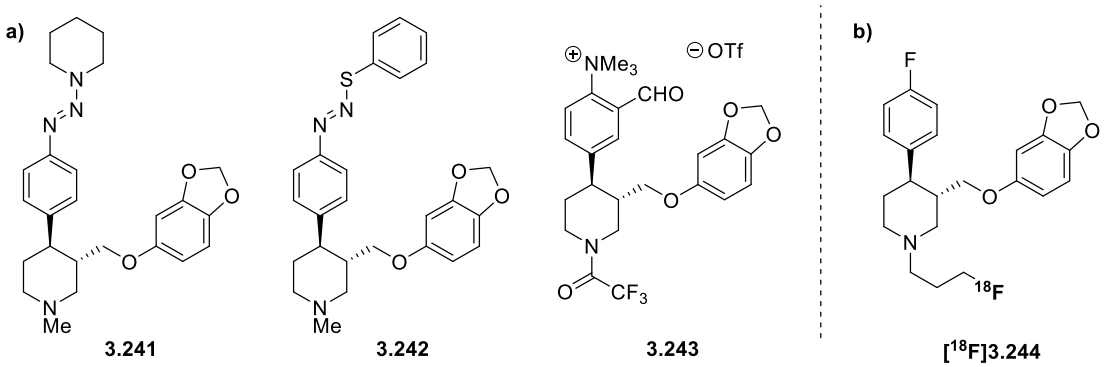
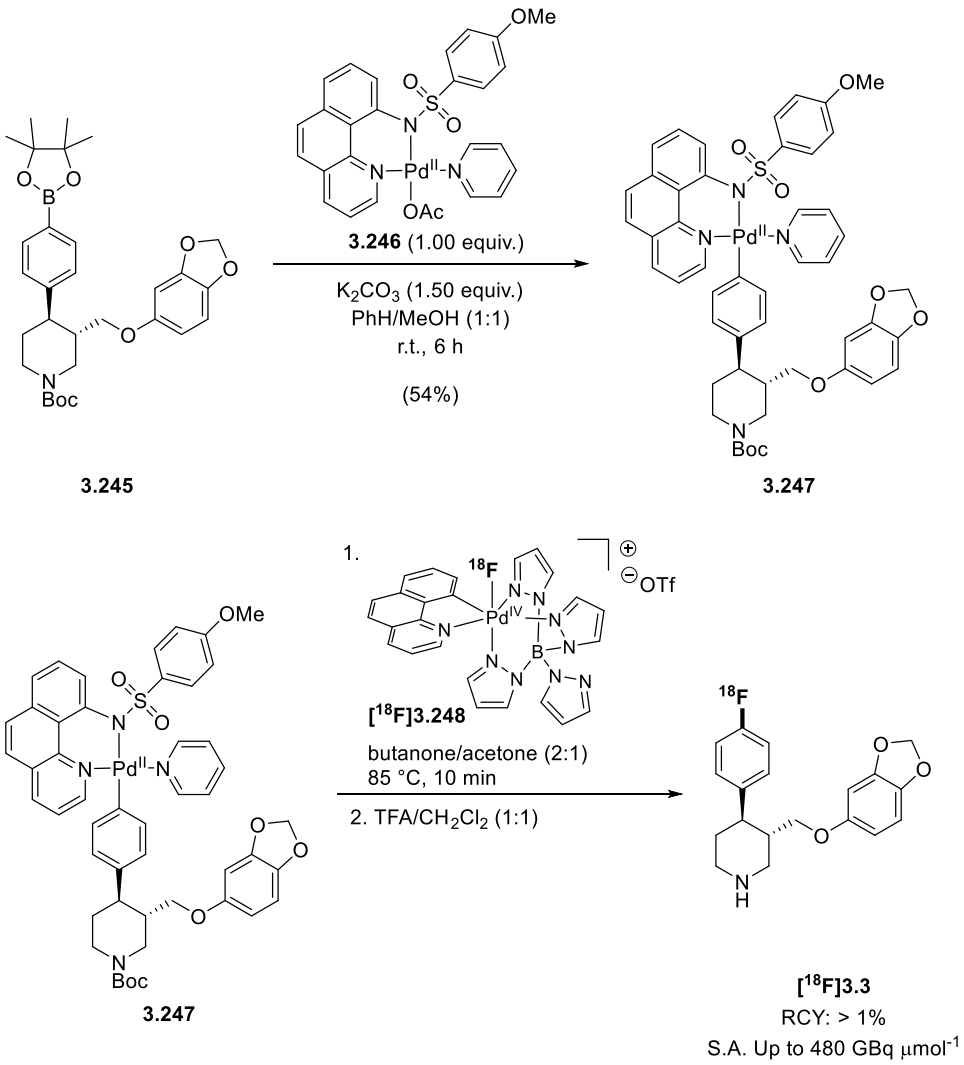


Figure 3.24. a) Precursors unsuccessfully employed for the ^{18}F-labelling of paroxetine. **b)** ^{18}F-Labelled derivative of paroxetine.

Prior to this work, the only successful ^{18}F-labelling of paroxetine was that reported by Ritter and Hooker in 2013.[66] The precursor used was Pd(II) complex **3.247**, prepared from boronic ester **3.245** and Pd(II) complex **3.246** (Scheme 3.28). Reaction of this with Pd(IV) complex **[^{18}F]3.248**, derived from [^{18}F]fluoride, followed by Boc-deprotection, resulted in formation of [^{18}F]paroxetine **[^{18}F]3.3**. Although the radiochemical yield was poor, the specific activity and radiochemical purity after semi-preparative HPLC purification were both high. By starting with approximately 37 GBq [^{18}F]fluoride, the authors prepared sufficient [^{18}F]paroxetine for an imaging study in baboons. This revealed modest brain penetration, slow washout kinetics and a high degree of non-specific binding. The authors suggested that despite these challenges, evaluation of brain pharmacokinetics and distribution in humans was warranted.



Scheme 3.28. Synthesis of [^{18}F]paroxetine **[^{18}F]3.3** via palladium-mediated ^{18}F-fluorination

In the context of ^{18}F-fluorodeboronation, the free piperidine in paroxetine was of concern, since the screening experiment had shown that **3.82** was highly detrimental to the model reaction (Figure 3.25a). Whilst benzyl protection did not raise tolerance to an acceptable level to proceed with ^{18}F-fluorodeboronation, screening of Boc-piperidine **3.85** did not result in reduction of the RCC. In addition, **[^{18}F]3.133**, bearing a piperidine ring in which the nitrogen atom is substituted with an electron-withdrawing group, was successfully ^{18}F-labelled in 80% RCC (Figure 3.25b).

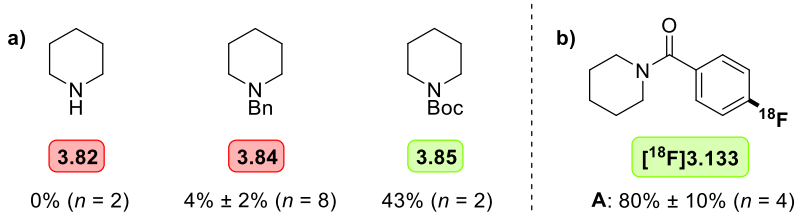
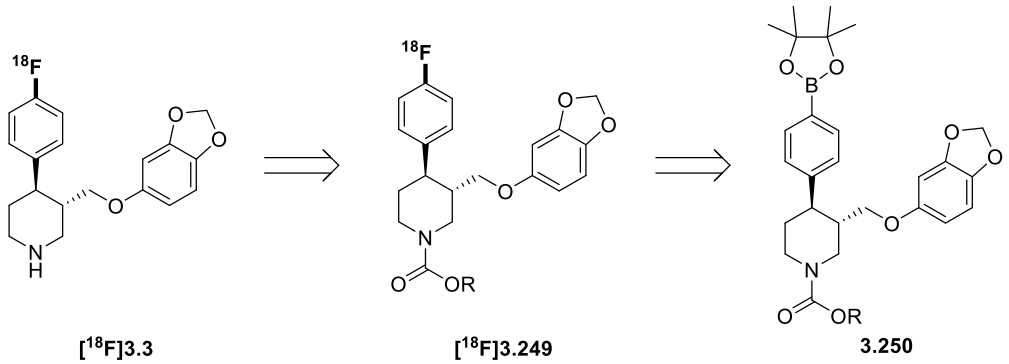


Figure 3.25. **a)** Key screening results relevant to the ^{18}F-labelling of paroxetine. **b)** Successful labelling of piperidine **[^{18}F]3.133** bearing an electron-withdrawing group via ^{18}F-fluorodeboronation

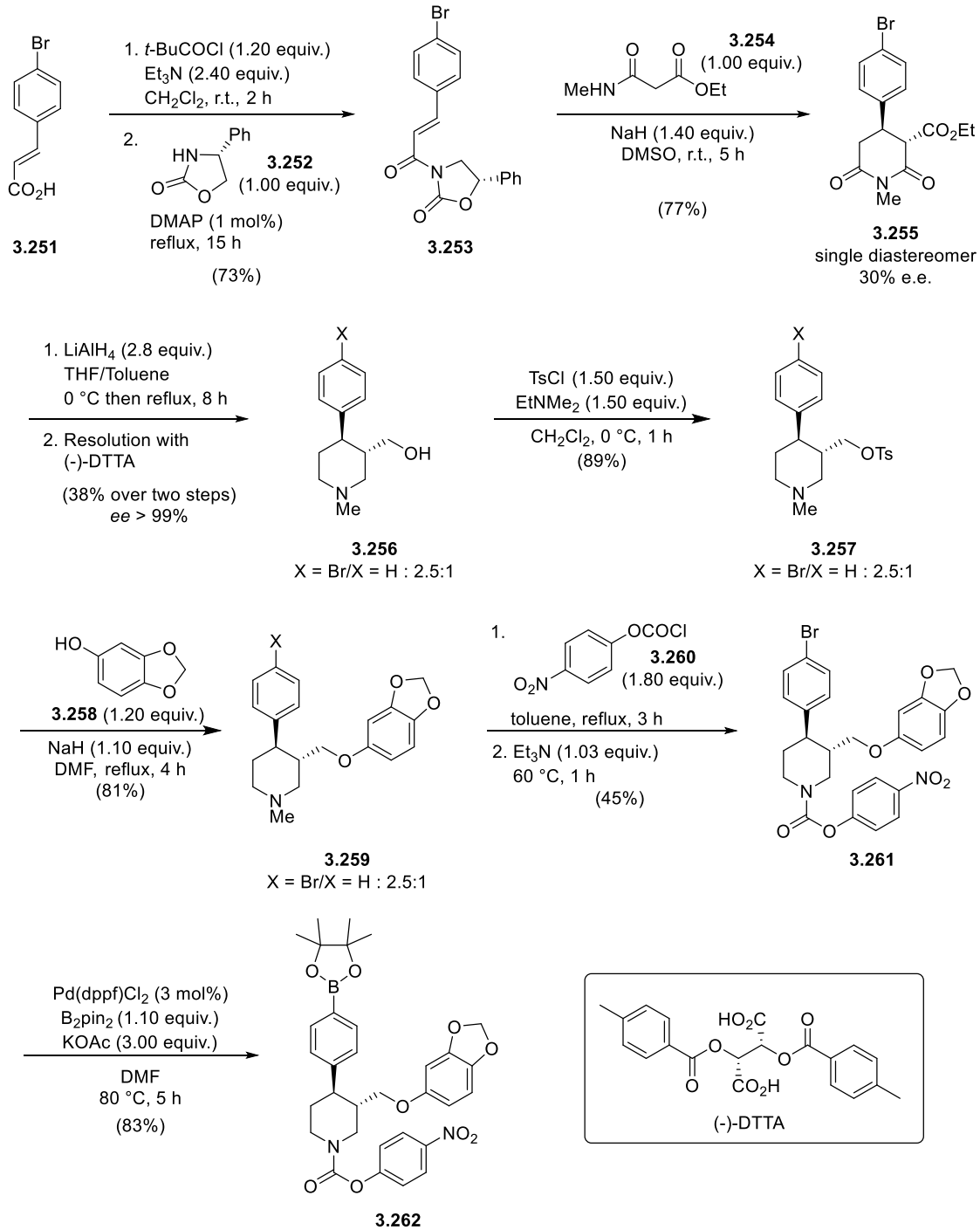
These results suggested that paroxetine should be amenable to ^{18}F-labelling via ^{18}F-fluorodeboronation, providing that the nitrogen atom were protected by an electron-withdrawing group, such as a carbamate. This would require deprotection following ^{18}F-fluorodeboronation, leading to the retro-radiosynthesis given in Scheme 3.29.



Scheme 3.29. Retro-radiosynthesis of [^{18}F]paroxetine **[^{18}F]3.3**

Boronic ester **3.262**, (**3.250** with R = *p*-NO_2-C_6H_4) was synthesised by Dr. Enrico Emer using a chiral auxiliary approach, based on literature procedures for paroxetine (Scheme 3.30).[69]–[73] 4-Bromocinammic acid **3.251** was first activated with pivaloyl chloride to form the mixed anhydride, which reacted with oxazolidinone **3.252** to form **3.253**. Conjugate addition of the sodium enolate of ethyl *N*-methyl malonamide **3.254**, followed by cyclisation, formed diketopiperidine

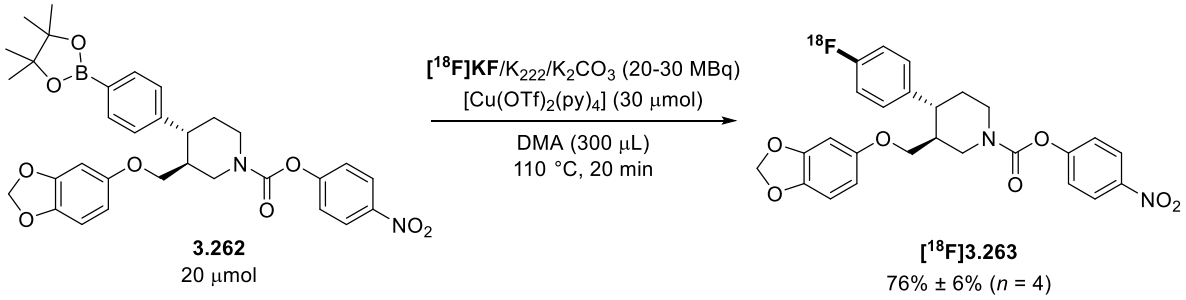
3.255 in 77% yield and with complete diastereoselectivity, albeit only 30% enantiomeric excess.



Scheme 3.30. Synthesis of boronic ester **3.262**, carried out by Dr. Enrico Emer

$LiAlH_4$ reduction was not completely selective for the carbonyl groups, resulting in an inseparable 2.5:1 mixture of the desired (X = Br) and *des*-bromo (X = H) piperidines **3.256**. Resolution of the enantiomers with (-)-DTTA increased the

enantiomeric excess to > 99%. The mixture was tosylated, then substituted with sesamol **3.258**, again affording an inseparable mixture. The *N*-methyl group of **3.259** was then substituted with a *para*-nitrophenyl carbamate via treatment with the corresponding chloroformate **3.260**, followed by triethylamine. At this stage, the desired compound could be isolated cleanly in 45% yield. Miyaura borylation proceeded smoothly, affording boronic ester **3.262** in 83% yield.



Scheme 3.31. ^{18}F-Fluorodeboronation of **3.262** to afford **[^{18}F]3.263**

Pleasingly, subjecting boronic ester **3.262** to ^{18}F-fluorodeboronation conditions B afforded carbamate **[^{18}F]3.263** in 76% ± 6% RCC (Scheme 3.31).

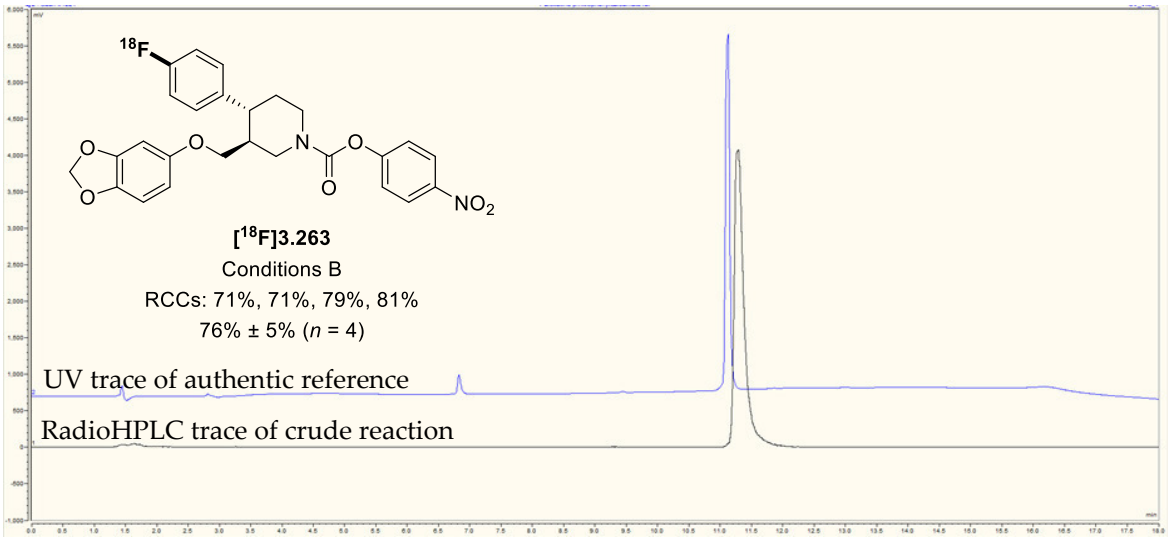
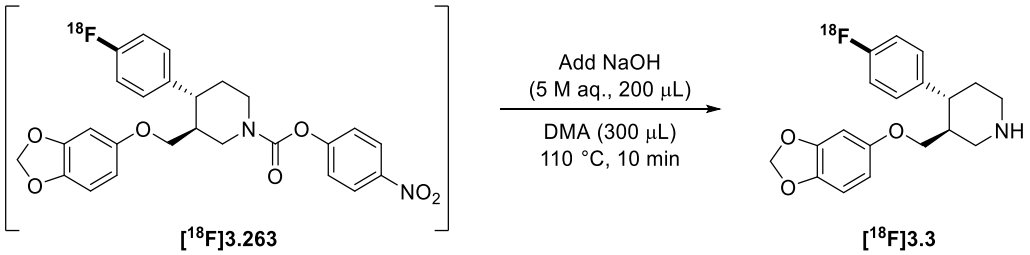


Figure 3.26. Radio-HPLC trace of the crude reaction mixture for the ^{18}F-fluorodeboronation of **3.262**, overlaid with the UV-HPLC trace of ^{19}F-reference **3.263**.

Figure 3.26 shows the radio-HPLC trace of the crude reaction mixture, overlaid with the UV trace of the corresponding ^{19}F-reference compound. Removal of the carbamate with aqueous NaOH was virtually quantitative, affording [^{18}F]paroxetine **[^{18}F]3.3** in 98% conversion, as shown in Scheme 3.32.



Scheme 3.32. Deprotection of **[^{18}F]3.263** to afford **[^{18}F]3.3**

The radio-HPLC trace after deprotection, overlaid with the UV trace of authentic paroxetine **3.3**, is given in Figure 3.27.

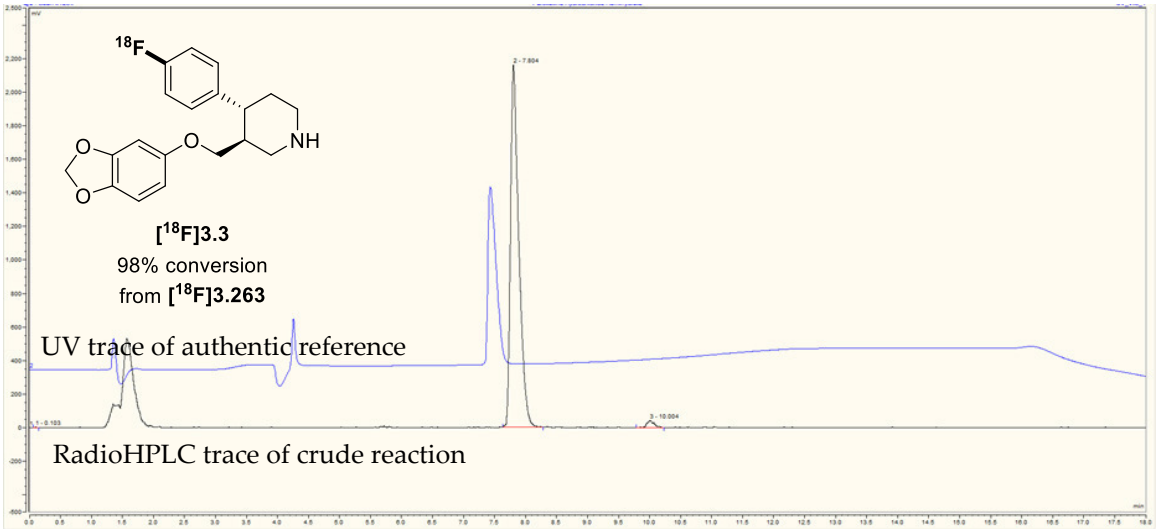
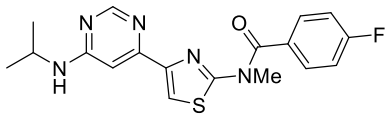


Figure 3.27. Radio-HPLC trace of the crude reaction mixture after deprotection of **[^{18}F]3.263**, overlaid with the UV-HPLC trace of authentic **3.3**.

3.5.6 ^{18}F-Labelling of FITM

The neurotransmitter glutamate plays important roles in the central nervous system.[74] One family of glutamate receptors are the G-protein coupled receptors known as metabotropic glutamate receptors (mGluRs), which modulate the excitability of neurones and efficiency of synapses.[75] The eight subtypes of mGluR are divided into three groups based on sequence homology, pharmacology and signal transduction mechanism. Group I consists of mGluR1 and mGluR5, which are involved in brain development, learning and neuroprotection.[76] mGluR1 and mGluR5 have been implicated in the pathophysiology of Parkinson's disease, anxiety, schizophrenia and epilepsy.[77]–[79]

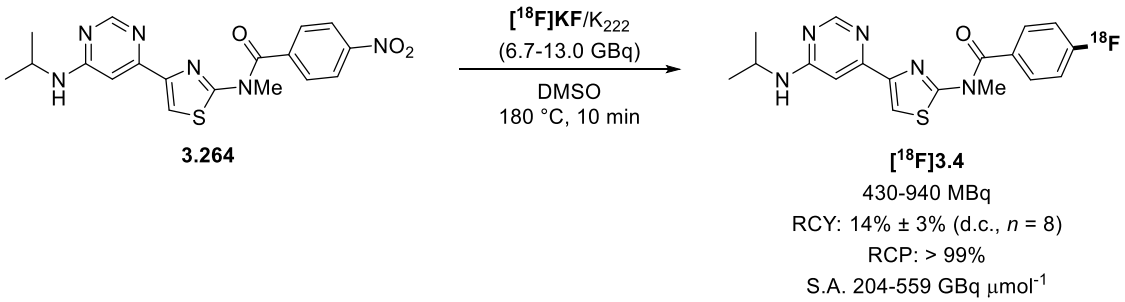


3.4
FITM
mGluR1 inhibitor

Figure 3.28. Structure of FITM

FITM **3.4** was developed by Kawamoto and co-workers as an allosteric antagonist for mGluR1 (Figure 3.28).[80] FITM had a potency of 5 nM against human mGluR1 and showed excellent selectivity over other subtypes, with an IC_{50} value of 7 μM for mGluR5 and > 10 μM for mGluR2 and mGluR8. Zhang and co-workers subsequently labelled FITM with fluorine-18 via nucleophilic aromatic substitution of nitroarene precursor **3.264** (Scheme 3.33). Starting from 6.7 to 13.0 GBq [^{18}F]fluoride afforded 430-940 MBq **[^{18}F]3.4** at end of synthesis, corresponding to a decay-corrected radiochemical yield of 14%. Both radiochemical purity and

specific activity were shown to be high enough for animal imaging. Autoradiography experiments showed that [^{18}F]FITM accumulated in regions of the rat brain known to be rich in mGluR1. Competition experiments with mGluR1 and mGluR5 antagonists (JNJ16259685 and MPEP, respectively) showed that [^{18}F]FITM was selective for mGluR1.



Scheme 3.33. ^{18}F-Labelling of FITM via SNAr displacement of nitro precursor **3.264**

More recently, the Zhang and Pike groups have developed derivatives of [^{18}F]FITM, labelled with fluorine-18 or carbon-11, in order to improve washout kinetics and reduce non-specific binding.[81]–[83]

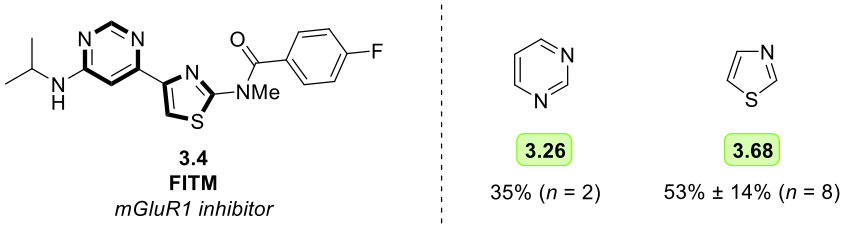
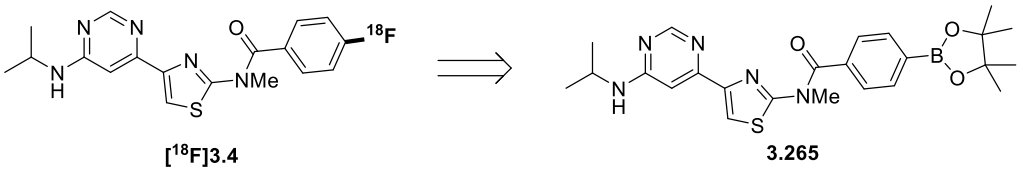


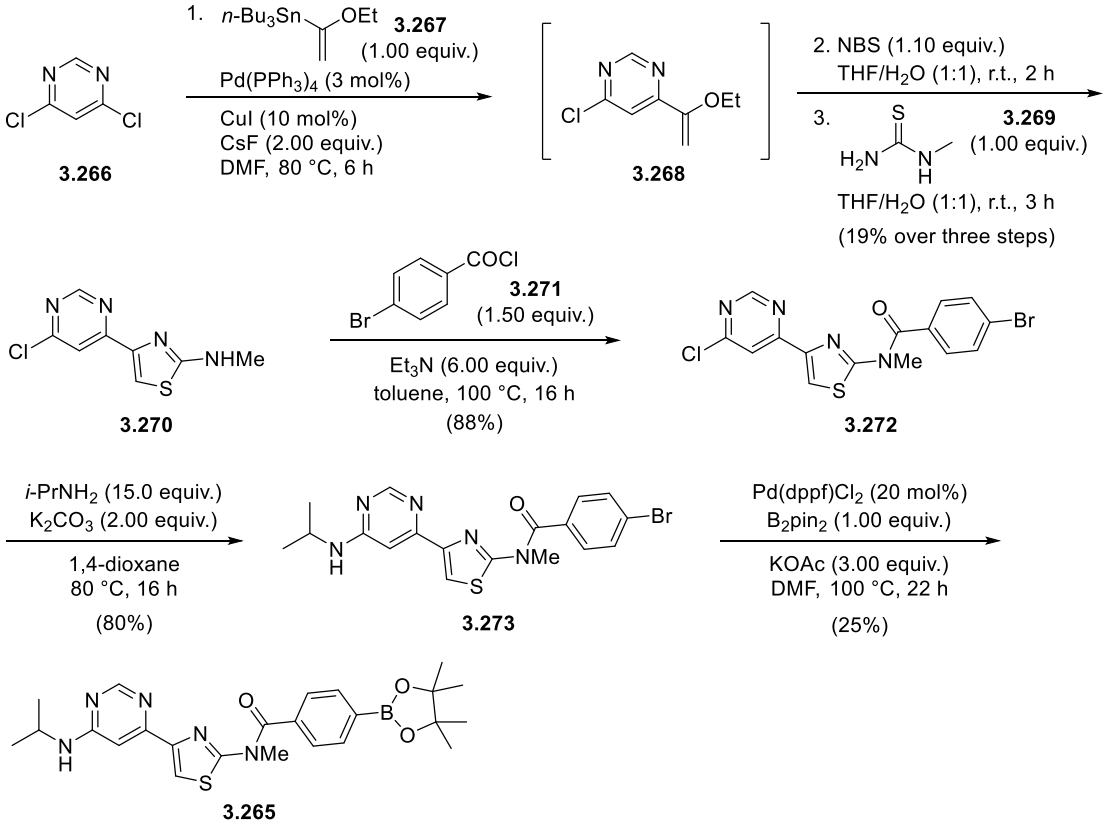
Figure 3.29. Key screening results relevant to the ^{18}F-labelling of FITM

Our screening experiment had shown that both pyrimidine **3.26** and thiazole **3.68** were tolerated in the model ^{18}F-fluorodeboronation (Figure 3.29). For this reason, a final-stage ^{18}F-fluorodeboronation of boronic ester **3.265** seemed appropriate for this target (Scheme 3.34).



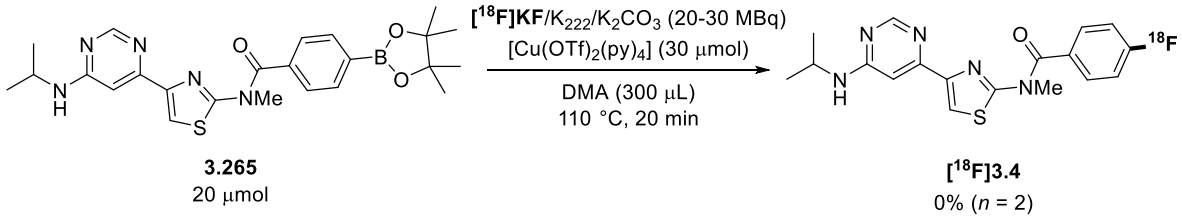
Scheme 3.34. Retro-radiosynthesis of [^{18}F]FITM **[^{18}F]3.4**

Bromide **3.273** was synthesised following the procedure of Zhang (Scheme 3.35).[83] Stille coupling of 4,6-dichloropyrimidine 3.266 with vinylstannane **3.267** afforded enol ether **3.268**. Bromination followed by aminothiazole formation with *N*-methylthiourea **3.269** formed **3.270** in 19% yield over three steps. Acylation with *para*-bromobenzoyl chloride **3.271** afforded amide **3.272** in 88% yield. Substitution of the second chlorine with a large excess of *iso*-propylamine afforded **3.273** in 80% yield. Miyaura borylation of **3.273** was successful, albeit in low yield and with a high catalyst loading.



Scheme 3.35. Synthesis of boronic ester **3.265**

When boronic ester **3.265** was subjected to ^{18}F-fluorodeboronation conditions B, [^{18}F]FITM **[^{18}F]3.4** was not observed (Scheme 3.36). Since both pyrimidine **3.26** and thiazole **3.68** were tolerated in the screening experiment, this failure was surprising.



Scheme 3.36. Attempted ^{18}F-fluorodeboronation of boronic ester **3.265**

In the interest of understanding the discrepancy between the predicted success based on the screening experiment and the observed failure of boronic ester **3.265** to afford [^{18}F]FITM **[^{18}F]3.4**, FITM **3.4** itself was screened in the model ^{18}F-fluorodeboronation of **3.20** (Figure 3.30). In this case, **[^{18}F]3.21** was not observed, suggesting that **3.4** has a severely detrimental effect on the ^{18}F-fluorodeboronation. In order to determine whether the free N–H of **3.4** was the cause of this, tetra-alkylated diamine **3.274** was also screened. This bore no free N–H groups and yet was also severely detrimental to the model reaction. At this point, it became clear that the combination of the pyrimidine and thiazole rings must be the cause of the detrimental effects. It is feasible that nitrogen atoms of the two rings could coordinate to a copper centre in a bidentate fashion, forming an unreactive copper species.

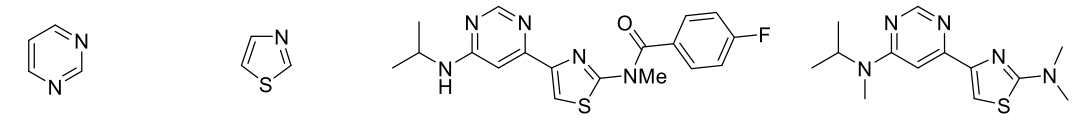
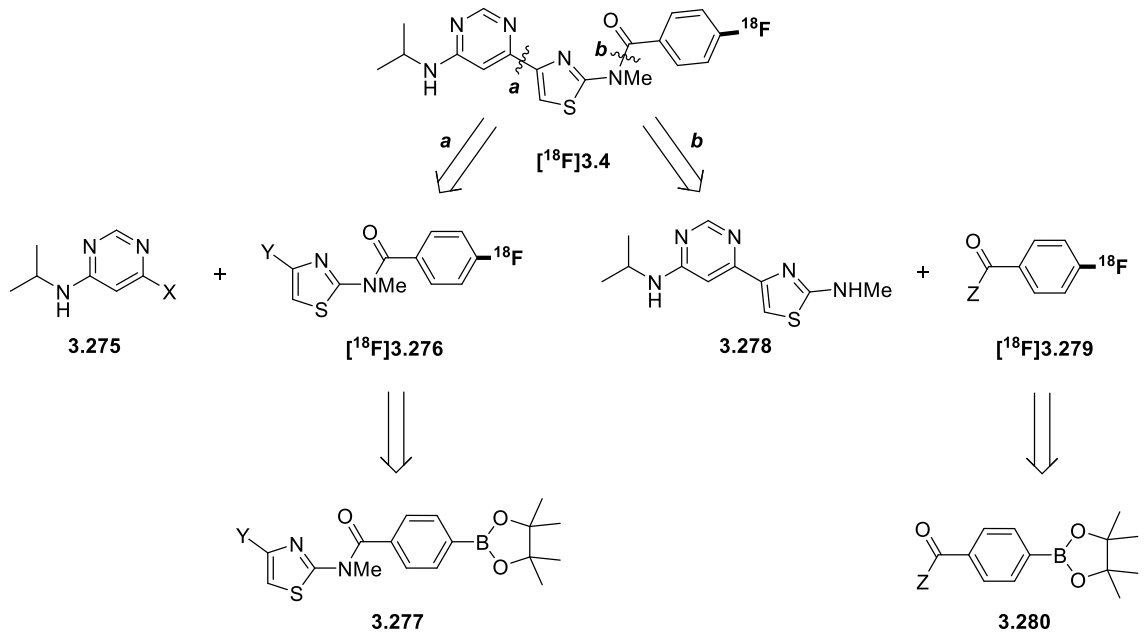


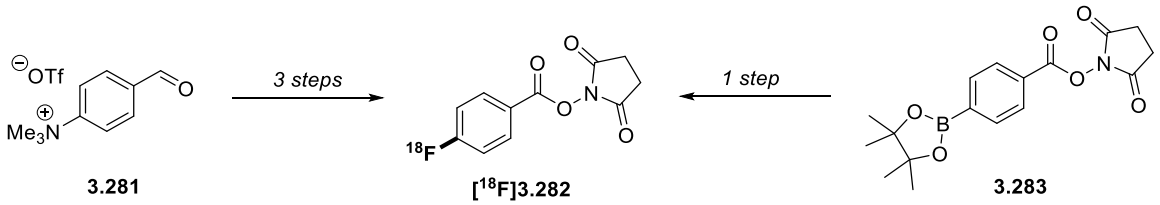
Figure 3.30. Key screening results relevant to the ^{18}F-labelling of FITM

Given this new information, alternative retro-radiosyntheses were considered in which the pyrimidine and thiazole rings were not both present in the ^{18}F-fluorodeboronation step (Scheme 3.37). Disconnection ***a*** involves ^{18}F-fluorodeboronation of thiazole-containing fragment **3.277**, in which Y is a halogen or organometallic group such as a boronic acid derivative, a stannane or a silane. This would be followed by reaction with pyrimidine **3.275**, in which X is a halogen or organometallic group, in a C–C bond forming step. Whilst palladium-catalysed C_{sp2}–C_{sp2} coupling under radiochemical conditions has been reported,[84], [85] this heteroaryl-heteroaryl coupling is unlikely to be trivial and would likely require the correct selection of groups X and Y as well as significant optimisation. Disconnection ***b***, on the other hand, is an acylation of diamine **3.278**, containing both heterocycles, with an ^{18}F-labelled carbonyl compound **3.279**. This route requires selective acylation of the thiazole-amine over the pyrimidine-amine. In addition, the group Z must be carefully chosen, as this must be stable enough to survive the ^{18}F-fluorodeboronation, whilst being reactive enough to acylate diamine **3.278**.



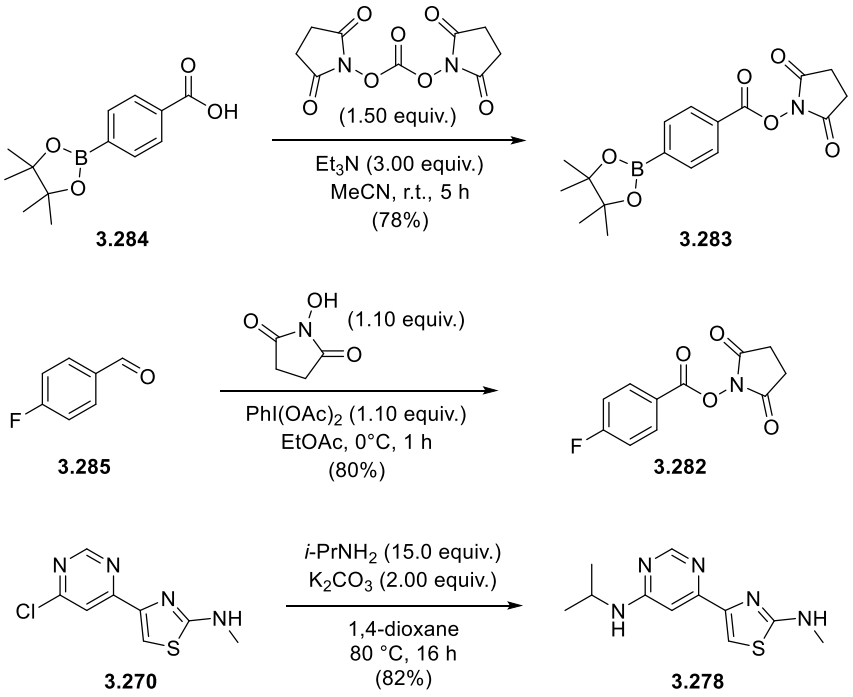
Scheme 3.37. Second generation retro-radiosynthesis of [18F]FITM **[18F]3.4**

Although both routes presented challenges, route ***b*** was chosen, since the post-18F-labelling step appeared to be more facile. For acylating agent **3.279**, an acyl chloride and an anhydride were thought to be too reactive to survive the 18F-fluorodeboronation, whilst a simple alkyl ester probably would not be reactive enough to acylate **3.278**. Our attention was drawn to succinimide-derived active ester **[18F]3.282** (Scheme 3.38), which had been used extensively for the 18F-labelling of peptides and monoclonal antibodies.[86]–[88] Whilst **[18F]3.282** was originally prepared in a three-step sequence from trimethylammonium salt **3.281**, we believed that 18F-fluorodeboronation of **3.283** could be a viable alternative.



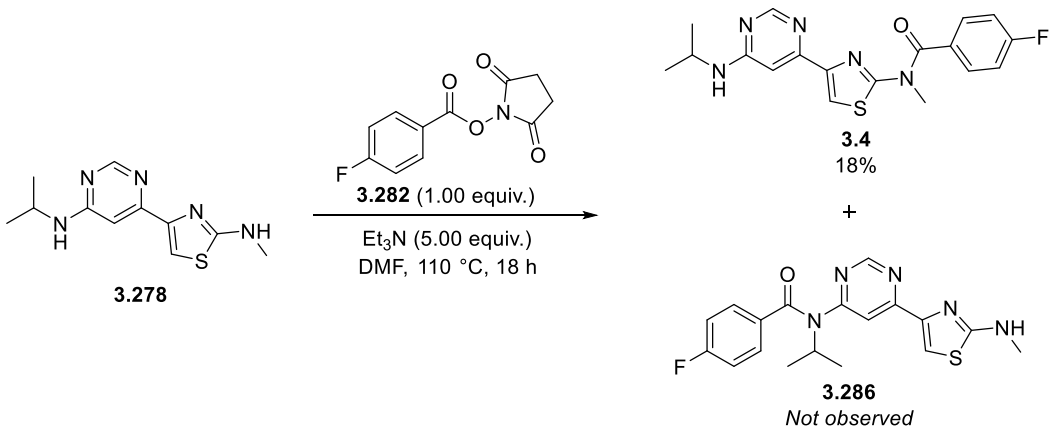
Scheme 3.38. Routes to succinimide ester **[18F]3.282**

In order to investigate this route, boronic ester **3.283** was synthesised from commercially-available boronic ester **3.284** (Scheme 3.39).[89] In addition, ^{19}F-reference **3.282** was synthesised following a literature procedure.[90] By analogy with the synthesis of FITM, diamine **3.278** was synthesised from chloropyrimidine **3.270** via reaction with excess *iso*-propylamine.



Scheme 3.39. Syntheses of boronic ester **3.283**, reference **3.282** and diamine **3.278**

Diamine **3.278** was then acylated with succinimide ester **3.282** in order to determine the selectivity of the acylation (Scheme 3.40). FITM **3.4** was isolated in only 18% yield but the alternative product **3.286** was not observed. Identity of **3.4** was confirmed by HMBC (Figure 3.31); a correlation was observed between the protons of the *N*-methyl group (*H*10) and the carbonyl carbon (*C*11). This would not be present in **3.286**.



Scheme 3.40. Acylation of diamine **3.278** with active ester **3.282**.

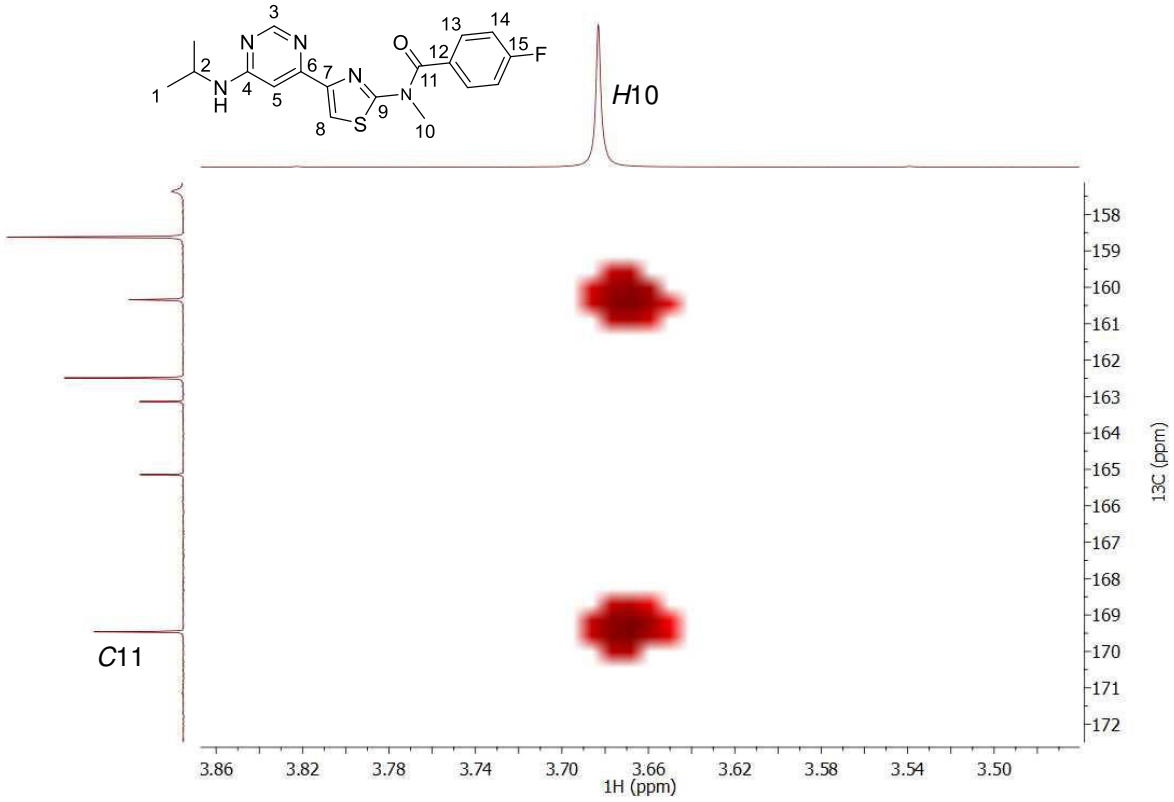
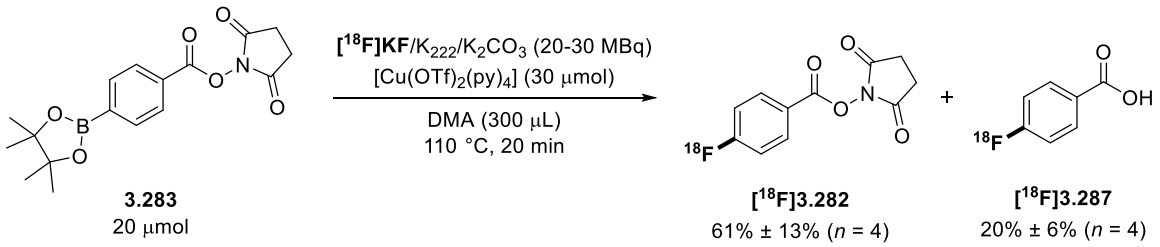


Figure 3.31. Excerpt of HMBC spectrum of **3.4** isolated from reaction of **3.278** with **3.282**.

^{18}F-Fluorodeboronation of boronic ester **3.283** proceeded smoothly; **[^{18}F]3.282** was formed in 61% RCC (n = 4, Scheme 3.41 and Figure 3.32). A radiolabelled impurity; identified as acid **[^{18}F]3.287**, was also formed in 20% RCC (n = 4). However, it was not possible to determine whether this formed during the reaction, during the aqueous quench, or during the analytical HPLC run itself.



Scheme 3.41. ^{18}F-Fluorodeboronation of boronic ester **3.283** to form active ester **[^{18}F]3.282**

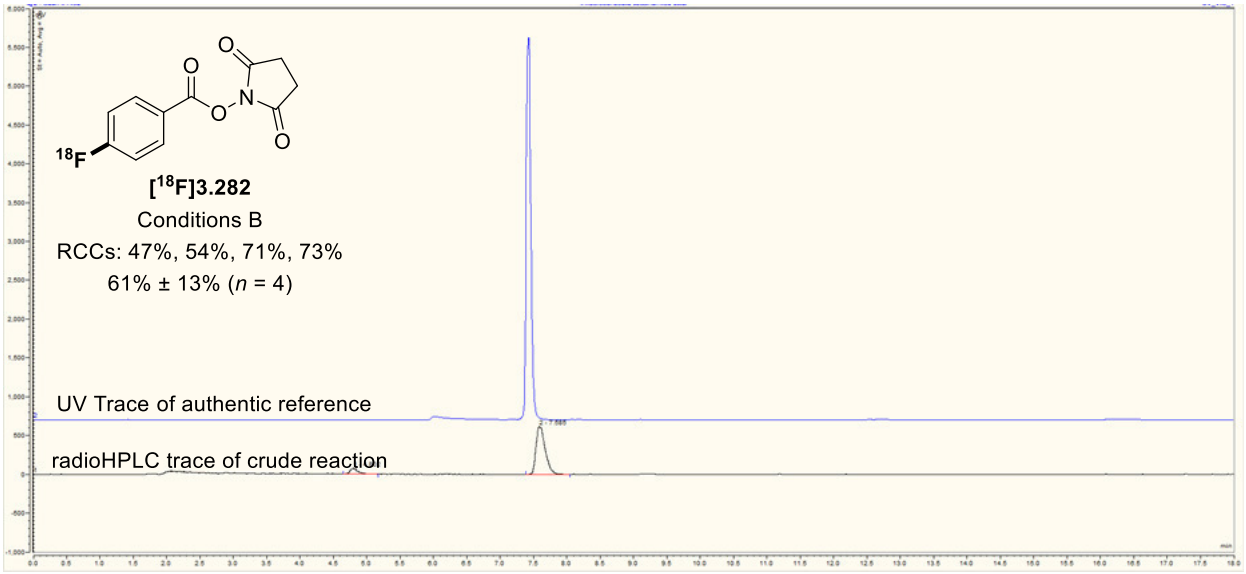
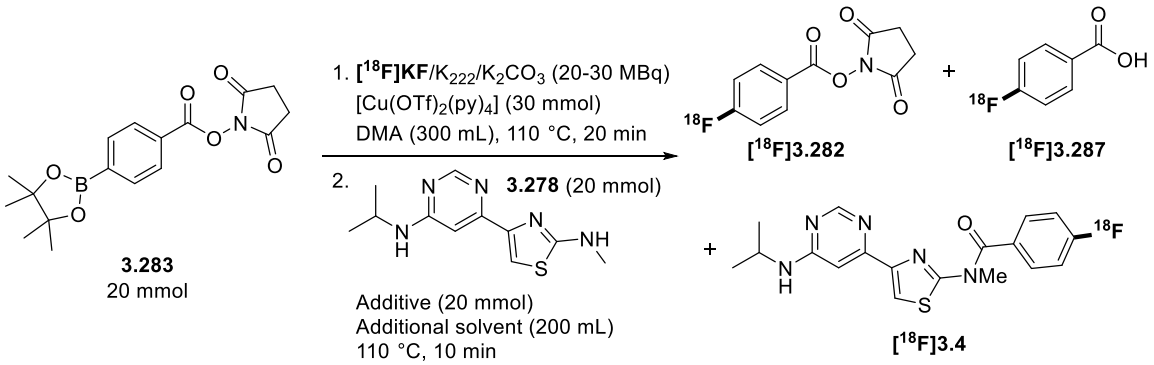


Figure 3.32. Radio-HPLC trace of the crude reaction mixture for the ^{18}F-fluorodeboronation of **3.283**, overlaid with the UV-HPLC trace of ^{19}F-reference **3.282**.

Coupling of **[^{18}F]3.282** with diamine **3.278** proved to be more challenging. Directly adding **3.278** in a solution of DMA and triethylamine resulted in only formation of hydrolysis product **[^{18}F]3.287** (Table 3.19, entry 1). Intermediate purification of **[^{18}F]3.282** by means of a Sep Pak to remove copper salts and unreacted [^{18}F]fluoride resulted in formation of traces of desired product **[^{18}F]3.4**, but acid **[^{18}F]3.287** was still the major product (entry 2). In order to check that the product was not trapped as a copper complex, the standard aqueous quench was replaced with an aqueous solution of EDTA (entry 3), however only traces of **[^{18}F]3.4** were observed. The temperature and time of the coupling reaction were then

increased to 150 °C and 20 minutes, respectively, but this offered no improvement (entry 4).

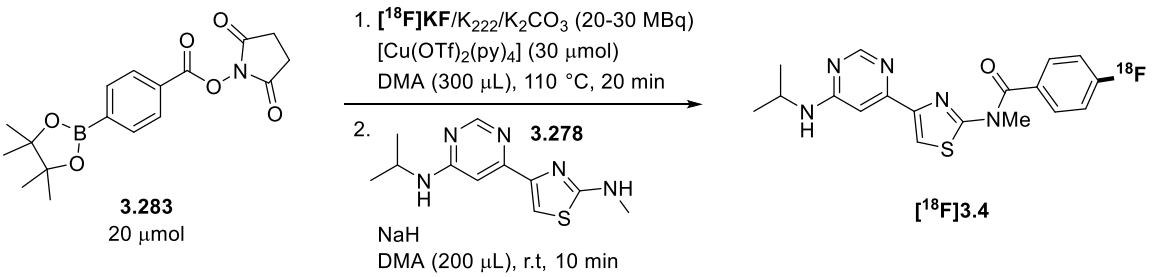


Entry	Solvent Added	Additive	Run	[18F]3.282 / RCC %	[18F]3.287 / RCC %	[18F]3.4 / RCC %
1	DMA/Et3N (1:1)	-	1	1	54	0
			2	1	51	0
2[a]	DMA/Et3N (1:1)	-	1	2	46	3
			2	0	32	6
3[b]	DMA/Et3N (1:1)	-	1	1	50	3
			2	1	64	2
4[c]	DMA/Et3N (1:1)	-	1	3	41	0
			2	3	44	0
5	DMA	-	1	41	21	0
			2	41	24	0
6	DMA/Et3N (1:1)	DMAP	1	1	49	0
			2	1	49	0
7	DMA/Et3N (1:1)	HATU	1	9	32	6
			2	8	44	2
8	DMA/Et3N (1:1)	Cyanuric chloride	1	7	46	0
			2	6	35	2
9[d]	DMA	LiCl	1	56	8	0
			2	60	8	0
10[e]	DMA	TiCl4	1	39	4	0
			2	49	4	0

Table 3.19. Screen of conditions for acylation of **3.278** with **[18F]3.282**. Conditions: **3.283** (20 μmol), [Cu(OTf)2(py)4] (30 μmol), [18F]KF/K222 (20-30 MBq.), DMA (300 μL), air, 110 °C, 20 mins, then add a solution of **3.278** (20 μmol) and additive (20 μmol) in solvent (200 μL), stir at 110 °C for 10 mins. Quench with water (300 μL) and determine yield by radio-TLC and radio-HPLC. [a] Sep-Pak purification was carried out before the coupling step, eluting with DMA (500 μL). [b] Reaction was quenched with Na2EDTA.2H2O (5 wt% aq., 300 μL). [c] Coupling reaction was carried out at 150 °C for 20 mins. [d] A 1% w/v solution of LiCl in DMA (200 μL) was used as the coupling solvent. [e] A 0.1 M solution of TiCl4 in DMA (200 μL) was used as the coupling solvent.

The coupling step was then attempted without added base (entry 5); this resulted in an approximately 2:1 mixture of active ester **[^{18}F]3.282** and acid **[^{18}F]3.287**. No acylation product was observed. The original conditions (entry 1) were then repeated with the addition of DMAP as nucleophilic catalyst (entry 6), but again, **[^{18}F]3.4** was not observed. Use of the coupling reagents HATU and cyanuric chloride (entries 7 and 8) resulted in only trace product formation. Returning to the base-free conditions, the Lewis-acids LiCl (entry 9) and $TiCl_4$ (entry 10) were also screened as additives. Both suppressed hydrolysis of active ester **[^{18}F]3.282**, but coupled product **[^{18}F]3.4** was not formed.

Under all of the conditions given in Table 3.19, hydrolysis of active ester **[^{18}F]3.282** to acid **[^{18}F]3.287** out-competed the desired acylation of diamine **3.278**. In order to increase the nucleophilicity of **3.278**, it was decided to first pre-form the sodium salt. This was done by stirring a mixture of **3.278** and NaH at room temperature for 10 minutes, followed by addition of the crude reaction mixture from the ^{18}F-fluorodeboronation (Table 3.20, entry 1). This formed **[^{18}F]3.4** in 11% RCC; significantly, unreacted active ester **[^{18}F]3.282** remained in 33% RCC. In order to increase the rate of the acylation, the concentration of deprotonated **3.278** was increased (entry 2). These conditions afforded **[^{18}F]3.4** in 26% RCC (n = 2). It was subsequently discovered that the order of addition could be reversed (entry 3); not only did addition of the deprotonated **3.278** solution to the crude reaction mixture from the ^{18}F-fluorodeboronation avoid a transfer of radioactivity, this also resulted in formation of **[^{18}F]3.4** in a higher RCC of 40% ± 13% (n = 4).



Entry	3.278 μmol	NaH μmol	Addition	Run	[18F]3.4 / RCC %	[18F]3.4 / Overall RCC %
1[a]	30	30	Active ester to deprotonated diamine	1	11	11
2[a]	100	120	Active ester to deprotonated diamine	1	33	26 (n = 2)
				2	18	
3[b]	100	120	Deprotonated diamine to active ester	1	38	40 (n = 4)
				2	23	
				3	50	
				4	51	

Table 3.20. Acylation of **3.278** with **[18F]3.282** via initial deprotonation of **3.278** with NaH. 18F-Fluorodeboronation conditions: **3.283** (20 μmol), [Cu(OTf)2(py)4] (30 μmol), [18F]KF/K222 (20-30 MBq.), DMA (300 μL), air, 110 °C, 20 mins. In parallel, stir a suspension of **3.278** and NaH in DMA at r.t. for 10 mins. [a] Add crude 18F-fluorodeboronation solution to deprotonated diamine solution and stir at r.t. for 10 mins, then quench with water (300 μL) and analyse by radio-TLC and radio-HPLC. [b] Add deprotonated diamine solution to crude 18F-fluorodeboronation solution and stir at r.t. for 10 mins, then quench with water (300 μL) and analyse by radio-TLC and radio-HPLC.

Figure 3.33 shows the radio-HPLC trace of the crude reaction mixture after coupling of **[18F]3.282** and **3.278** under the conditions shown in Table 3.20, entry 3, overlaid with the UV-HPLC trace of authentic FITM **3.4**.

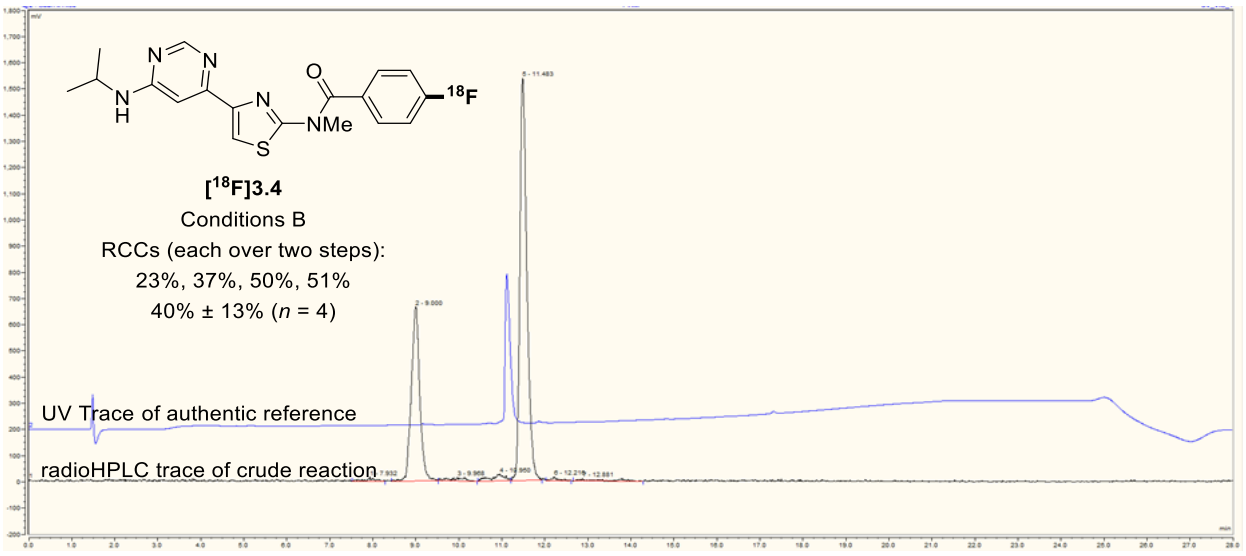


Figure 3.33. Radio-HPLC trace of the crude reaction mixture after the coupling of **[18F]3.282** with **3.278**, overlaid with the UV-HPLC trace of 19F-reference **3.4**.

3.5.7 ^{18}F-Labelling of Risperidone

The antispsychotic drug risperidone **3.5** (Figure 3.34a) was developed by Janssen Pharma and was approved by the FDA in 1993.[91], [92] It is on the World Health Organisation's List of Essential Medicines and it is prescribed for schizophrenia, bipolar mania and irritability associated with autism.[93] The mechanism of action is not well understood, although tritium labelling studies have shown that when compared to other atypical antispsychotics, risperidone shows increased occupancy of the $5HT_{2A}$ receptor and more gradual occupancy of the D_2 receptor.[94] Risperidone has never been labelled with fluorine-18.

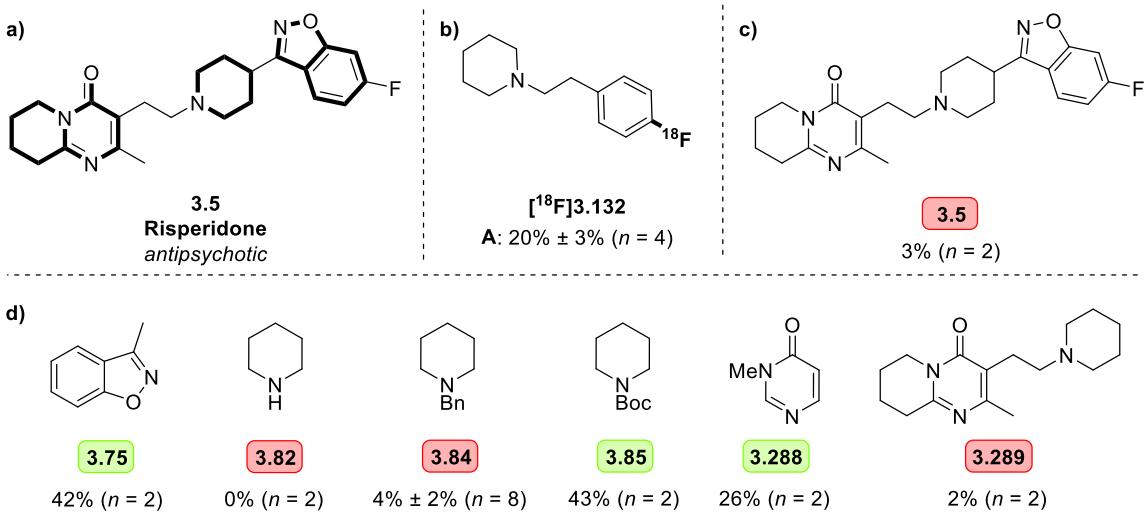
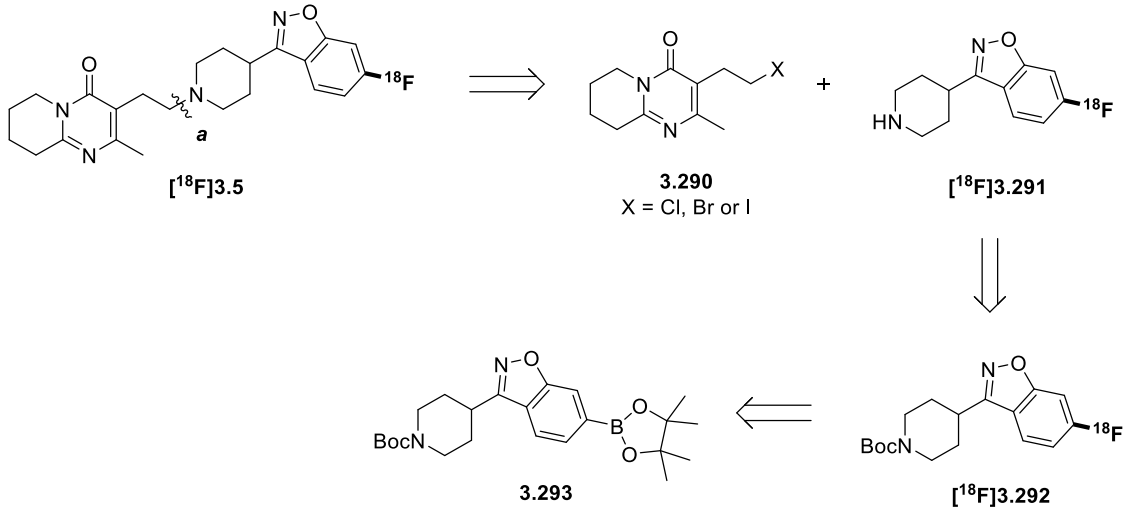


Figure 3.34. **a)** Structure of risperidone **3.5**. **b)** Successful ^{18}F-labelling of phenethylpiperidine **[^{18}F]3.132**. **c)** Screening of risperidone **3.5** in the model ^{18}F-fluorodeboronation. **d)** Other screening results relevant to the ^{18}F-labelling of risperidone.

When considering how to approach the ^{18}F-labelling of risperidone via ^{18}F-fluorodeboronation, it was noted that the screening experiment had shown *N*-alkylated piperidines to be challenging substrates, yet phenethylpiperidine **[^{18}F]3.132** had been successfully ^{18}F-labelled (Scheme 3.34b). In addition, our work on the ^{18}F-labelling of FITM had shown that interactions between heterocycles in a

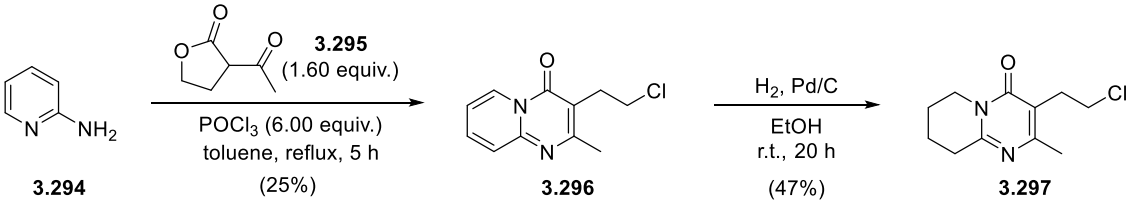
given molecule can be important. For this reason, we supplemented the heterocycle screening data already obtained with that for risperidone **3.5** itself (Figure 3.34c). **3.5** was highly detrimental to the model ^{18}F-fluorodeboronation, suggesting that final stage ^{18}F-fluorodeboronation was unlikely to be a successful strategy.

In order to develop a better retro-radiosynthesis, it was necessary to determine which part of the structure of risperidone was responsible for the detrimental effect on the model ^{18}F-fluorodeboronation. Both 3-methylbenzisoxazole **3.75** and pyrimidinone **3.288** were tolerated (Figure 3.34d), suggesting that these heterocycles were unlikely be the cause of the detrimental effects. In contrast, benzylpiperidine **3.84** was highly detrimental, as was **3.289**, which contained the pyrimidinone and piperidine heterocycles in an appropriate arrangement. This suggested that the initial disconnection of the retro-radiosynthesis should be of C–N bond ***a*** (Scheme 3.42). Direct ^{18}F-labelling of piperidine **3.291**, bearing a free N–H, would probably not be feasible, since piperidine **3.291** itself was not tolerated in the screening experiment (Figure 3.34d). However, *N*-Boc-piperidine **3.85** was tolerated, suggesting that a successful route to [^{18}F]risperidone **[^{18}F]3.4** could consist of ^{18}F-fluorodeboronation of *N*-Boc-piperidine **3.293**, followed by Boc-deprotection of **[^{18}F]3.292** and alkylation of piperidine **[^{18}F]3.291** with halide **3.290** (Scheme 3.42).



Scheme 3.42. Retro-radiosynthesis of [18F]risperidone **[18F]3.5**

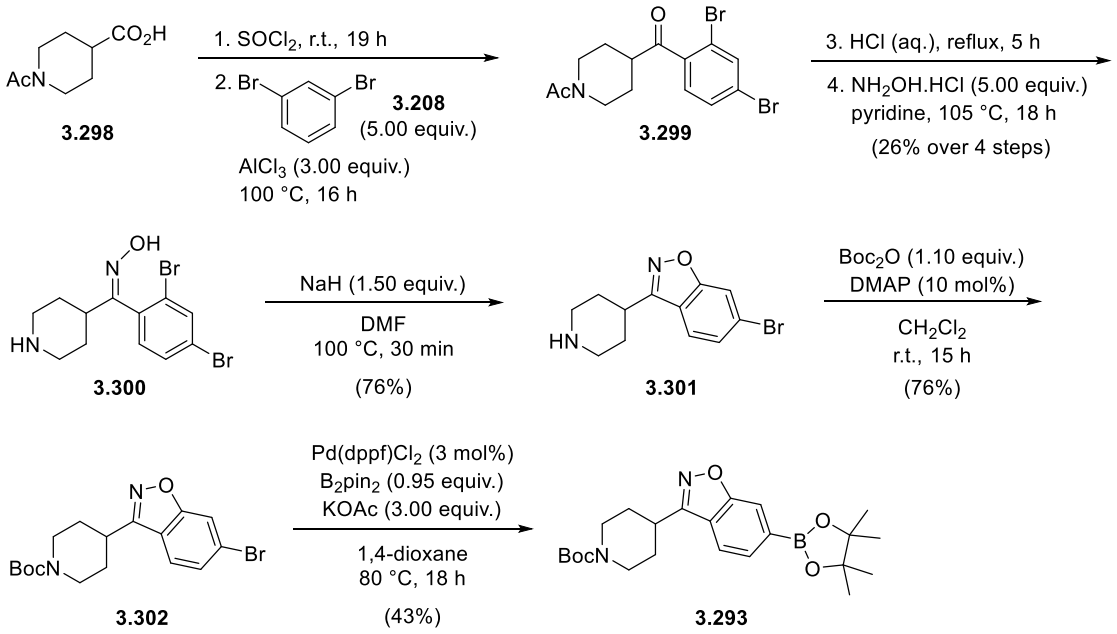
Chloride **3.297** (**3.290** with X = Cl) was synthesised by Dr. Michael Schedler following a literature procedure (Scheme 3.43). Reaction of 2-aminopyridine **3.294** with 2-acetylbutyrolactone **3.295** in the presence of phosphorus(V) oxychloride resulted in formation of pyrido[1,2-*a*]pyrimidinone **3.296** in 25% yield. Partial hydrogenation afforded chloride **3.297** in 47% yield.



Scheme 3.43. Synthesis of chloride **3.297**, carried out by Dr. Michael Schedler

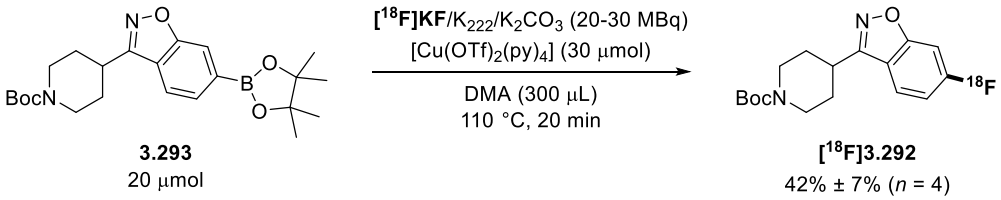
Bromide **3.301** (Scheme 3.44) was also prepared by Dr. Michael Schedler following a literature procedure.[95] *N*-Acetylisonipecotic acid **3.298** was reacted with thionyl chloride to form the acyl chloride, which was then used in a Friedel-Crafts acylation of 1,3-dibromobenzene **3.208** to form ketone **3.299**. Acidic hydrolysis of the amide was followed by oxime formation with hydroxylamine to

afford **3.300** in 26% yield over four steps. Treatment of **3.300** with sodium hydride followed by heating resulted in ring closure to form benzisoxazole **3.301** in 76% yield.



Scheme 3.44. Synthesis of boronic ester **3.293**

I carried out the final two steps of the synthesis of boronic ester **3.293**. Bromide **3.301** was first Boc-protected, in 76% yield (Scheme 3.44). Borylation of **3.302** proceeded in relatively low yield, partially due to instability of the product **3.293**. This was unstable on silica; isolation of **3.293** required preparative HPLC, followed by extraction into ethyl acetate and careful concentration, keeping the temperature below 30 °C. Subjecting boronic ester **3.293** to ^{18}F-fluorodeboronation conditions B resulted in formation of **[^{18}F]3.292** in 42% ± 7% RCC (*n* = 4, Scheme 3.45).



Scheme 3.45. ^{18}F-Fluorodeboronation of boronic ester **3.293** to form benzisoxazole **[^{18}F]3.292**

The radio-HPLC trace of **[^{18}F]3.292**, overlaid with the UV trace of the authentic ^{19}F-reference, is given in Figure 3.35.

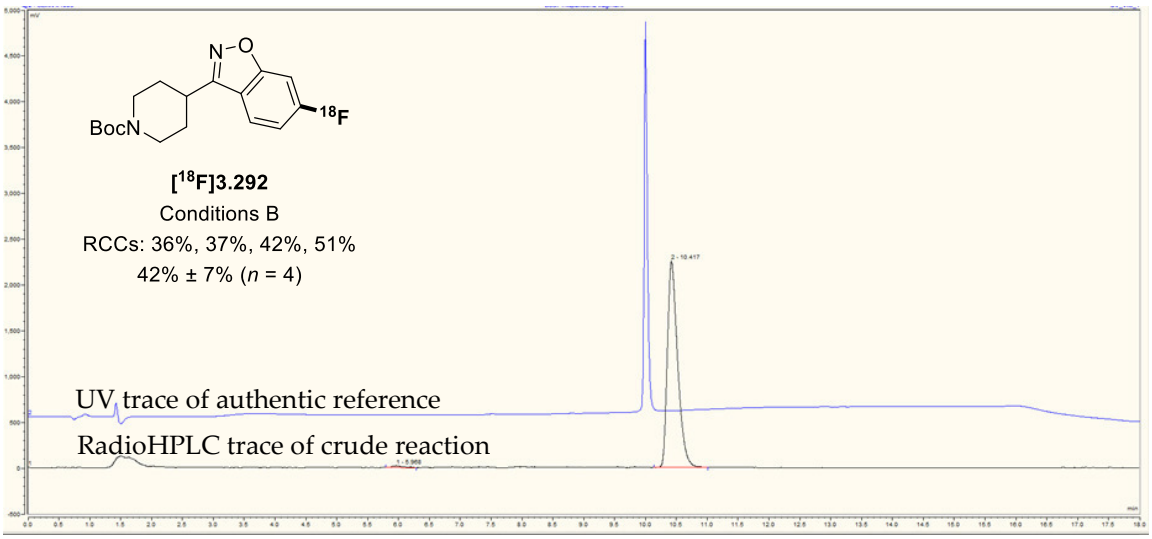
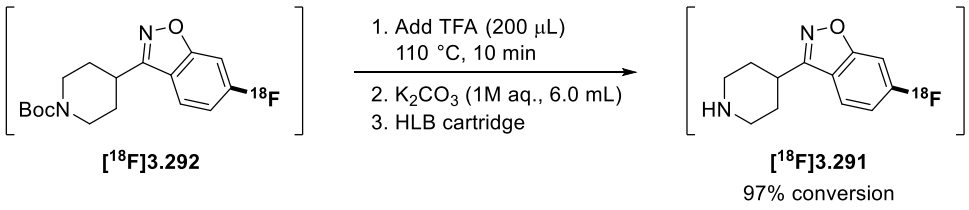


Figure 3.35. Radio-HPLC trace of the crude reaction mixture for the ^{18}F-fluorodeboronation of **3.293**, overlaid with the UV-HPLC trace of ^{19}F-reference **[^{18}F]3.292**.

In order to hydrolyse the Boc group of **[^{18}F]3.292**, trifluoroacetic acid (200 μL) was added to the reaction mixture, which was stirred at 110 °C for a further 10 minutes (Scheme 3.46). Quenching with aqueous potassium carbonate solution, followed by purification with a C18 cartridge, resulted in 97% conversion to piperidine **[^{18}F]3.291**.



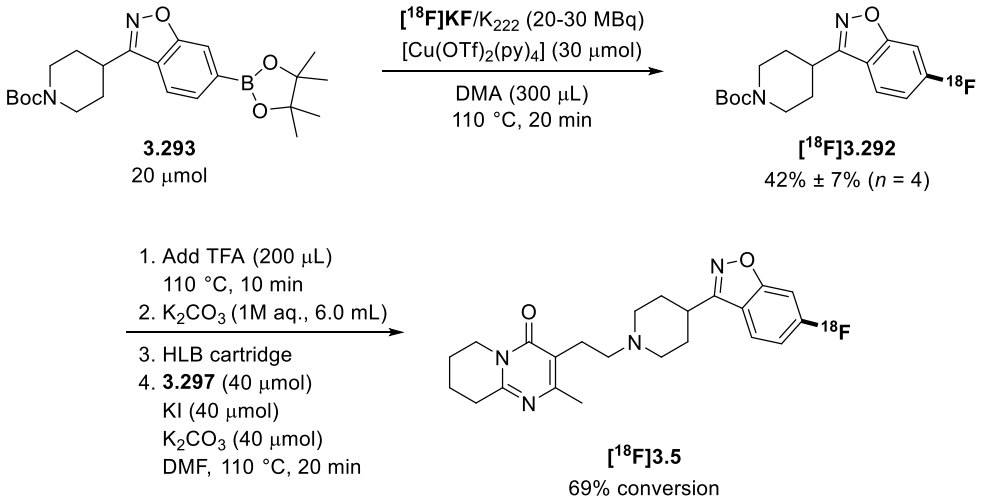
Scheme 3.46. Acidic hydrolysis to form piperidine **[^{18}F]3.291**

Figure 3.36 shows the radio-HPLC trace after this step, overlaid with the UV trace of the authentic ^{19}F-reference.



Figure 3.36. Radio-HPLC trace for the crude mixture for the hydrolysis of **[^{18}F]3.292** to **[^{18}F]3.291**

Having developed a route to prepare piperidine **[^{18}F]3.291**, the final step was alkylation with chloride **3.297**. This was achieved by stirring at 110 °C for 20 minutes with KI and K_2CO_3 in DMF. [^{18}F]Risperidone **[^{18}F]3.5** was formed in 69% conversion from ^{18}F-fluorodeboronation product **[^{18}F]3.292**; the overall radiosynthesis is given in Scheme 3.47.



Scheme 3.47. Synthesis of [^{18}F]risperidone **[^{18}F]3.5** via ^{18}F-fluorodeboronation

Figure 3.37 shows the radio-HPLC trace of **[^{18}F]3.5**, overlaid with the UV trace of the crude reaction mixture. The UV trace of the crude reaction mixture spiked with authentic risperidone **3.5** is also overlaid.

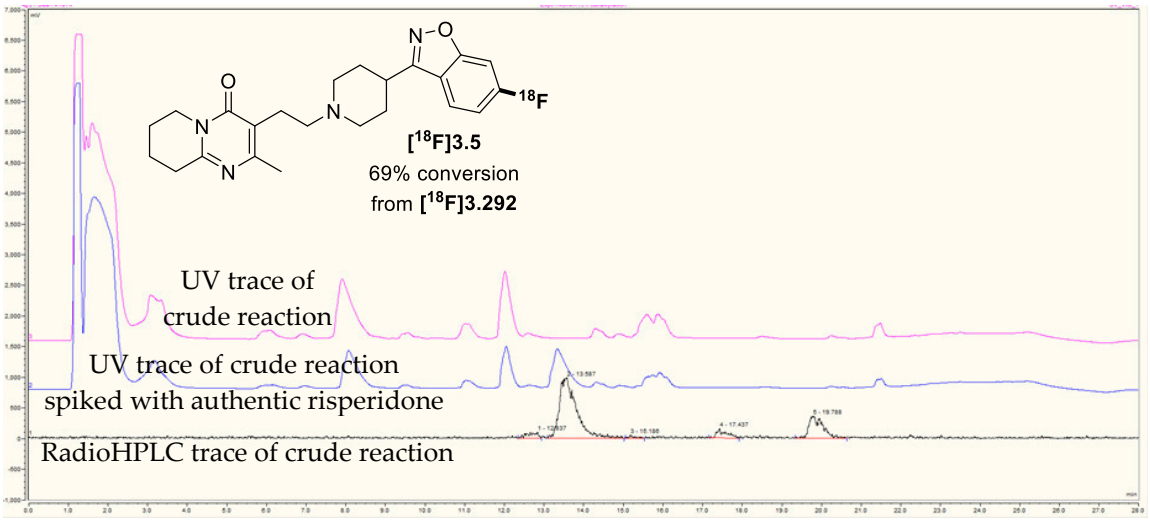


Figure 3.37. Radio-HPLC trace of the crude reaction mixture after coupling of **[^{18}F]3.291** with **3.297** (black line), overlaid with the UV-HPLC trace of the same mixture (pink line) and the UV-HPLC trace of the crude reaction mixture spiked with authentic risperidone **3.5** (blue line).

Although the route to [^{18}F]risperidone seems less efficient than a final-stage ^{18}F-fluorination, no such route has been reported; this is the first reported radiosynthesis. One advantage of this route is that by changing the final coupling partner, the related antipsychotic drugs paliperidone **3.303** and iloperidone **3.304** (Figure 3.38) could potentially be labelled from same intermediate **[^{18}F]3.291**.

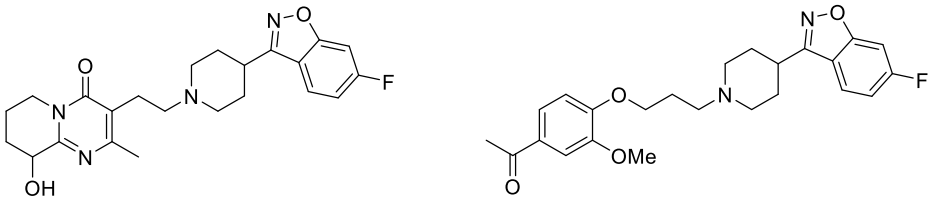
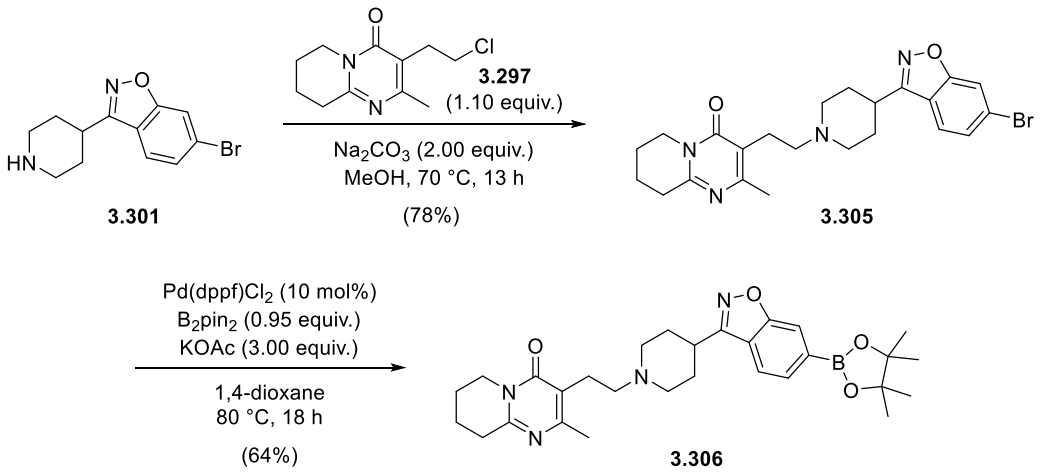


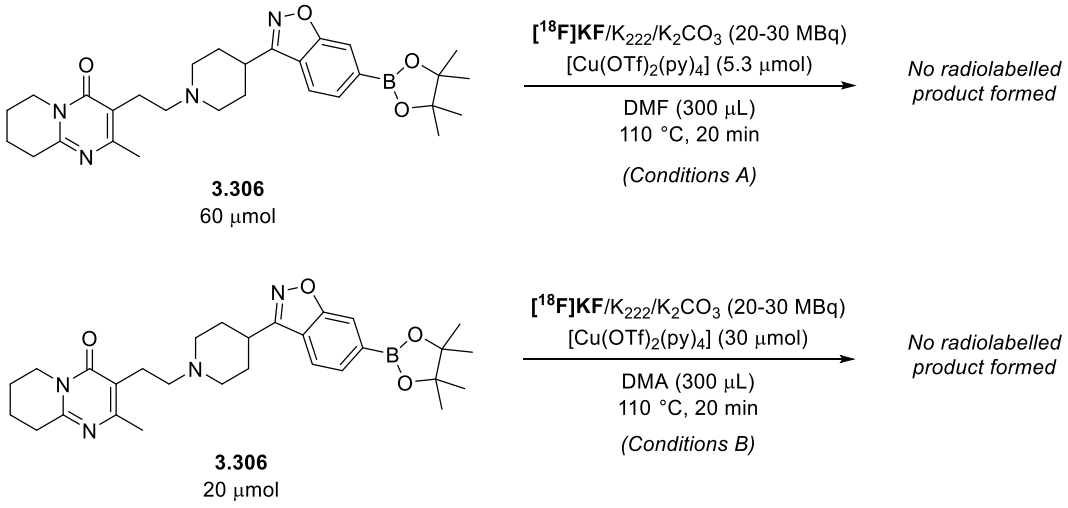
Figure 3.38. Related antipsychotic drugs which could be labelled from **[^{18}F]3.291**

In order to check that the screening experiment had correctly predicted that final-stage ^{18}F-fluorodeboronation was not a feasible route to [^{18}F]risperidone, boronic ester **3.306** was prepared by Dr. Michael Schedler (Scheme 3.48).



Scheme 3.48. Synthesis of boronic ester **3.306,** carried out by Dr. Michael Schedler

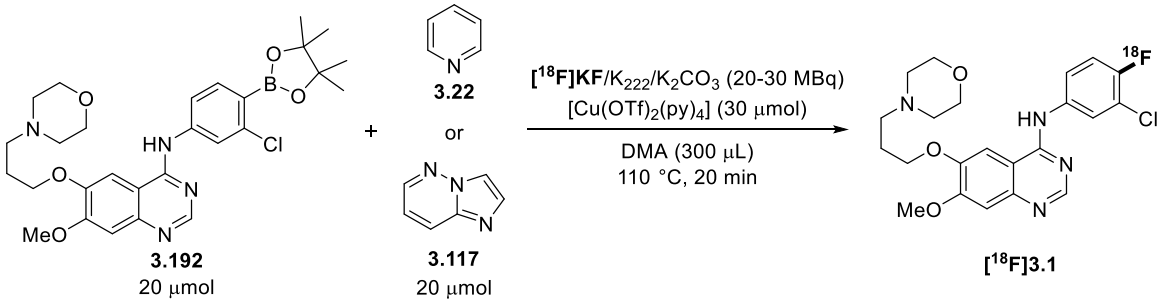
Subjecting boronic ester **3.306** to ^{18}F-fluorodeboronation conditions A or B did not result in formation of [^{18}F]risperidone (Scheme 3.49). The screening experiment correctly predicted that final-stage ^{18}F-fluorodeboronation was not a suitable route in this case.



Scheme 3.49. Attempted ^{18}F-Fluorodeboronation of boronic ester **3.306**

3.5.8 Use of Beneficial Heterocycles to Improve RCC

It was noted during the heterocycle screening study that certain heterocycles had a beneficial effect on the ^{18}F-fluorodeboronation of model boronic ester **3.20**. We sought to take advantage of this observation in order to improve the ^{18}F-fluorodeboronation of drug targets. Taking [^{18}F]gefitinib **[^{18}F]3.1** as the target, we initially investigated the addition of either pyridine **3.22** or imidazo[1,2-*b*]pyridazine **3.117** to the ^{18}F-fluorodeboronation of boronic ester **3.192** (Table 3.21). We were disappointed to observe no significant increase in RCC using pyridine as additive (entry 2) and a slight decrease in RCC when using imidazo[1,2-*b*]pyridazine (entry 3).

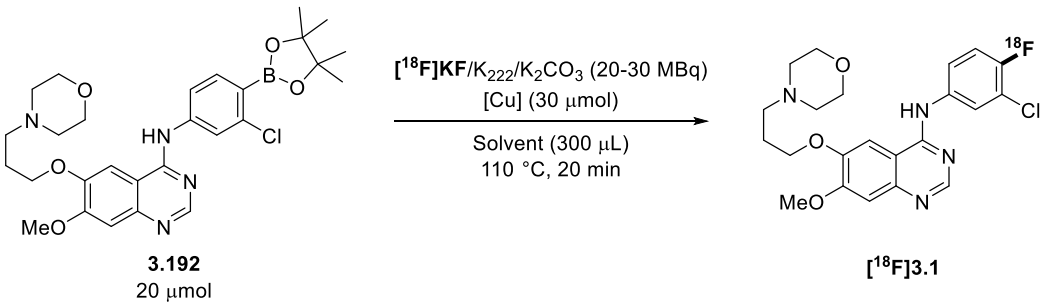


Entry	Additive	RCC Values	Overall RCC
1	None	14%, 18%, 26%, 29%	22% ± 7% (*n* = 4)
2	Pyridine	23%, 27%	25% (*n* = 2)
3	Imidazo[1,2-*b*]pyridazine	16%, 18%	17% (*n* = 2)

Table 3.21. Attempted use of heterocyclic additives to improve the ^{18}F-fluorodeboronation of **3.192**

Since the screening experiment had shown imidazo[1,2-*b*]pyridazine to be more beneficial than pyridine (RCC of **[^{18}F]3.21** improved to 80% and 69%, respectively), we decided to substitute the copper complex with [Cu(OTf)$_2$(impy)$_4$] **3.307** (impy = imidazo[1,2-*b*]pyridazine), in which all four pyridine ligands were

replaced by imidazo[1,2-*b*]pyridazine molecules. This complex was prepared from $Cu(OTf)_2$ and imidazo[1,2-*b*]pyridazine and was analysed by elemental analysis. Replacement of $[Cu(OTf)_2(py)_4]$ with $[Cu(OTf)_2(impy)_4]$ in the ^{18}F-fluorodeboronation of boronic ester **3.192** resulted in a slight increase in RCC (Table 3.22, entries 1 and 2). Simultaneous replacement of the solvent DMA with 1,3-dimethylimidazolidinone (DMI) resulted in a significant increase in RCC; [^{18}F]gefitinib was formed in 43% RCC (n = 2, entry 4). Use of DMI did not result in a significant improvement over DMA when the original copper complex, $[Cu(OTf)_2(py)_4]$, was employed (entry 3).



Entry	[Cu]	Solvent	RCC Values	Overall RCC
1	$[Cu(OTf)_2(py)_4]$	DMA	14%, 18%, 26%, 29%	22% ± 7% (n = 4)
2	$[Cu(OTf)_2(impy)_4]$	DMA	28%, 30%	29% (n = 2)
3	$[Cu(OTf)_2(py)_4]$	DMI	23%, 24%	24% (n = 2)
4	$[Cu(OTf)_2(impy)_4]$	DMI	41%, 45%	43% (n = 2)

Table 3.22. Use of $[Cu(OTf)_2(impy)_4$ and DMI to improve the ^{18}F-fluorodeboronation of **3.192**

3.6 Conclusions

The aim of this project was to aid users of the copper-mediated ^{18}F-fluorodeboronation of boronic esters in planning feasible radiosyntheses of heterocyclic target molecules of medicinal relevance. This was done by means of a screening experiment, in which we monitored fluctuation in the RCC of a model reaction carried out in the presence of heterocyclic additives. This allowed heterocycles to be categorised as compatible or not compatible with the ^{18}F-fluorodeboronation. This, combined with the ^{18}F-fluorodeboronation of more than fifty (hetero)aryl boronic esters, provides a starting point for future users of the method to develop low-risk routes to their target molecules. Use of our screening data, as well as further screening experiments appropriate to the molecule in question, enables the rational design of radiosyntheses using the ^{18}F-fluorodeboronation. This is advantageous over a trial-and-error approach, since it minimises the risk of wasted resources in synthesising boronic ester precursors which are incompatible with the desired reaction.

The de-risking approach to retro-radiosynthesis was demonstrated via the successful use of ^{18}F-fluorodeboronation to label seven drug molecules with fluorine-18. Three common scenarios were exemplified. In the first, final stage ^{18}F-fluorodeboronation was predicted to be successful (gefitinib, IPMICF10). A second class of targets required deprotection following ^{18}F-fluorodeboronation (rufinamide, flutemetamol, paroxetine). In the final case, a fragment of the molecule was first ^{18}F-labelled, which was then coupled to the rest of the structure (FITM,

risperidone). Screening of the unlabelled target molecule itself was shown to have the most predictive value in determining the success of the desired ^{18}F-labelling, but in the event that the target molecule was not tolerated, an understanding of the effects of individual heterocycles within the structure was required in order to design feasible radiosyntheses. The work in this chapter was published in the Journal of the American Chemical Society.[96]

3.7 Future Work

Much of the future work in this area will involve use of the ^{18}F-fluorodeboronation method to label complex targets for PET imaging studies. Several groups have already used the method, based on the initial disclosure in Angewandte Chemie, in order to prepare ^{18}F-labelled compounds for PET imaging studies; examples are given in Figure 3.39.[97]–[101]

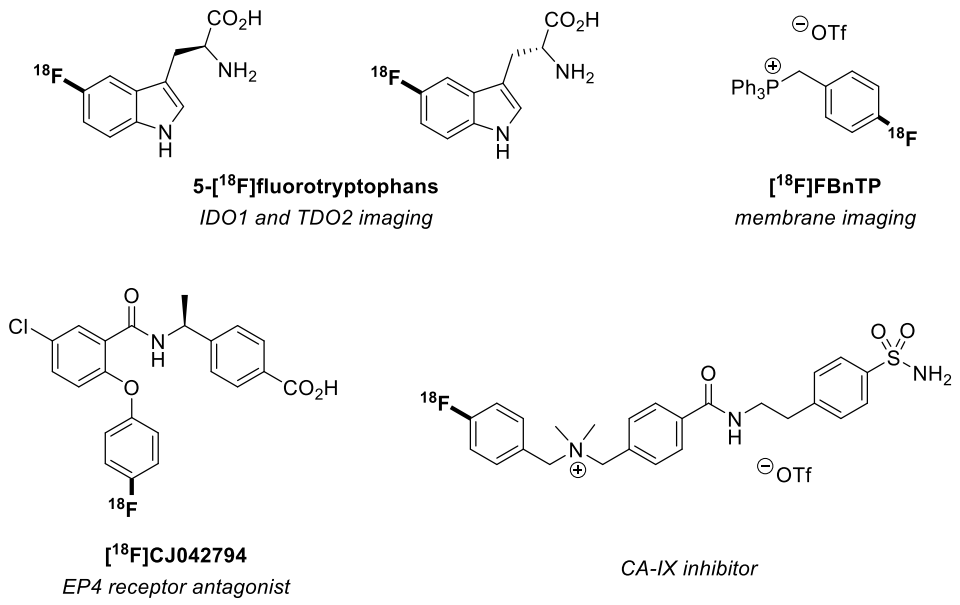


Figure 3.39. Compounds labelled with fluorine-18 by other groups using the ^{18}F-fluorodeboronation method and investigated by PET

Our own group will also use the ^{18}F-fluorodeboronation, following the de-risking approach described in this chapter, in order to prepare complex targets for imaging studies. In addition to use of screening experiments to determine a low-risk radiosynthesis, this will involve optimisation of the reaction conditions for the target molecule in question. Variables such as copper complex, solvent, stoichiometry, temperature and time could all be modified in order to develop a

radiosynthesis which produces suitable quantities of ^{18}F-labelled target for PET imaging studies.

To aid in the use of ^{18}F-fluorodeboronation to label complex targets, parallel studies in the Gouverneur group will focus on the development of improved reaction conditions for challenging classes of substrates. Two examples include substrates bearing a potentially-coordinating group in an *ortho*-position and substrates in which the ^{18}F-fluorodeboronation must take place directly on a heteroaromatic ring. The discovery that $[Cu(OTf)_2(impy)_4]$ can in some cases give superior results to $[Cu(OTf)_2(py)_4]$ suggests that other related copper(II) triflate complexes ought to be investigated. The most beneficial heterocycles from the screening experiment provide an ideal starting point (Figure 3.40a). Synthesis of electronically and sterically-diverse derivatives would allow for structure-activity relationships to be determined; examples of such derivatives of imidazo[1,2-*b*]pyridazine are given in Figure 3.40b.

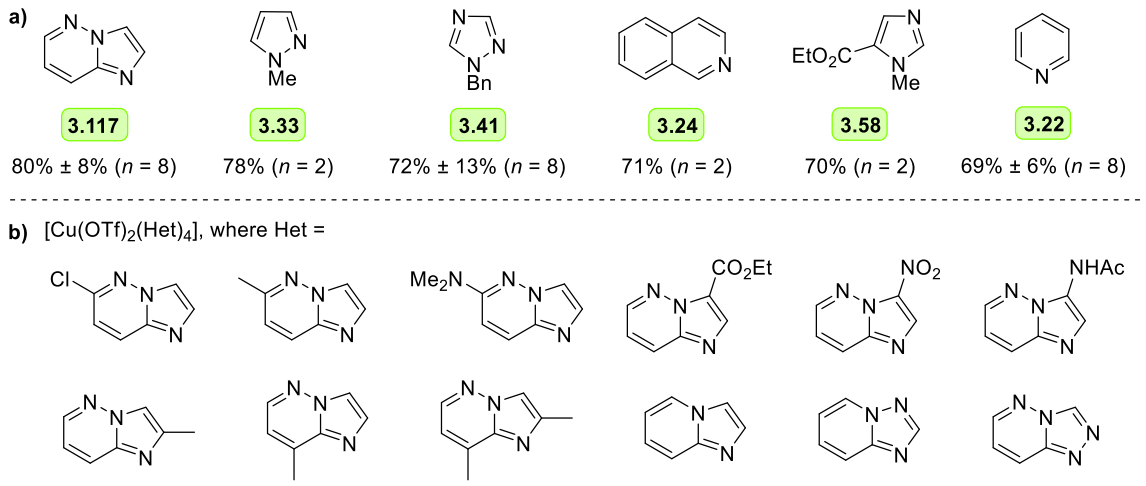


Figure 3.40. **a)** Most beneficial heterocycles from screening experiment. **b)** Imidazo[1,2-*b*]pyridazine derivatives which could be involved in a copper complex structure-activity relationship study

The screening study thus far was largely limited to unsubstituted heterocycles and derivatives in which any N–H groups were protected. Another simple extension of the work could be to expand the screening study to include sterically- and electronically-diverse substituted heterocycles. This would probably be limited to the most prevalent heterocycles in FDA-approved drugs. Examples for pyridines and piperidines are given in Figure 3.41a and Figure 3.41b, respectively.

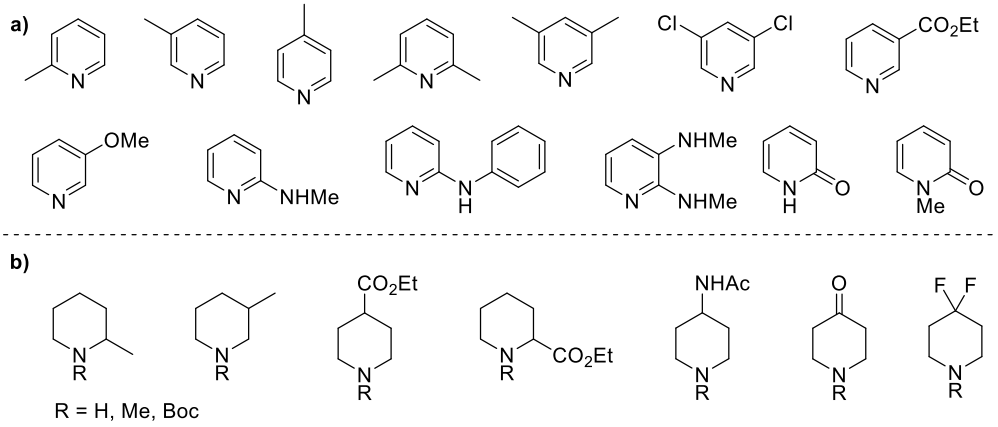


Figure 3.41. **a)** Sterically- and electronically-diverse pyridine derivatives. **b)** Sterically- and electronically-diverse piperidine derivatives.

3.8 References

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Chapter 4

Experimental Data

Chapter 4: Experimental Data

4.1 General Experimental Information

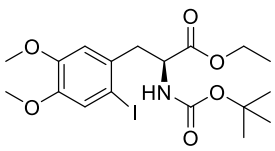
All NMR spectra were recorded on Bruker DPX200, AV400 and AV500 spectrometers. Proton and carbon-13 NMR spectra are reported as chemical shifts (δ) in parts per million (ppm) relative to the solvent peak using the Bruker internal referencing procedure (edlock). Fluorine-19 NMR spectra are referenced relative to $CFCl_3$ in $CDCl_3$. Coupling constants (*J*) are reported in units of hertz (Hz). The following abbreviations are used to describe multiplicities – s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br. (broad). High resolution mass spectra (HRMS, *m*/*z*) were recorded on a Bruker MicroTOF spectrometer using positive electrospray ionization (ESI^+), on a Micromass GCT spectrometer using filed ionization (FI^+) or chemical ionization (CI^+), or on a Waters GCT Classic GCMS using electron impact ionisation (EI). Infrared spectra were recorded either as the neat compound or in a solution using a Bruker Tensor 27 FT-IR spectrometer. Absorptions are reported in wavenumbers (cm^{-1}). Melting points of solids were measured on a Griffin apparatus and are uncorrected. Solvents were purchased from Sigma-Aldrich, Honeywell or Fisher. When dry solvents were required they were purified by expression through an activated alumina column built according to the procedures described by Pangborn and Grubbs. Chemicals were purchased from Acros, Alfa Aesar, Fisher, Fluorochem, Sigma-Aldrich and used as received. Reactions were monitored by thin-layer chromatography (TLC) carried out on

Merck Kiesegel 60 F254 plates, silica gel column chromatography was performed over Merck silica gel C60 (40-60 μm).

Experimental procedures and characterisation are provided in this chapter only for compounds which I made. Experimental procedures and characterisation for compounds made by co-workers are given in the Appendix.

4.2 Experimental Procedures and Characterisation for Compounds in Chapter 2

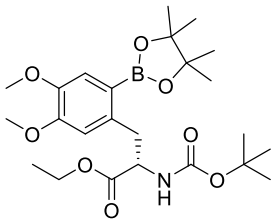
Ethyl *(S)*-2-((*tert*-butoxycarbonyl)amino)-3-(2-iodo-4,5-dimethoxyphenyl) propanoate (2.116)



The title compound was synthesised following a reported procedure.[1] Flash column chromatography (hexane/EtOAc 80:20 to 75:25) afforded ethyl (*S*)-2-((*tert*-butoxycarbonyl)amino)-3-(2-iodo-4,5-dimethoxyphenyl)propanoate as a white solid (**2.116**, 3.15 g, 6.57 mmol, 33% over four steps).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.21 (s, 1H), 6.72 (s, 1H), 5.05 (d, *J* = 8.5 Hz, 1H), 4.62-4.53 (m, 1H), 4.23–4.13 (m, 2H), 3.84 (s, 6H), 3.20 (dd,*J* = 14.0, 6.0 Hz, 1H), 3.04 (dd, *J* = 14.0, 8.0 Hz, 1H), 1.39 (s, 9H), 1.23 (t, *J* = 7.0 Hz, 3H); **MS** (ESI): for $C_{18}H_{26}INNaO_6$ $[M+Na]^+$ requires 502.3 found 502.1. Analytical data was consistent with literature values.[1]

Ethyl *(S)*-2-((*tert*-butoxycarbonyl)amino)-3-(2-4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl-4,5-dimethoxyphenyl)propanoate (2.109)

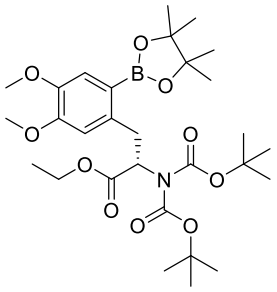


The title compound was synthesised following a reported procedure.[1] Bis(pinacolato)diboron (698 mg, 2.75 mmol, 1.1 equiv.), $Pd(dppf)Cl_2.CH_2Cl_2$ (102 mg, 0.125 mmol, 0.05 equiv.) and potassium acetate (736 mg, 7.5 mmol, 3.0 equiv.) were placed in a dry flask under N_2. DMF (15 mL) was added and the mixture purged with N_2 for 15 minutes. Ethyl (*S*)-2-((*tert*-butoxycarbonyl)amino)-3-(2-iodo-4,5-dimethoxyphenyl) propanoate (**2.106**, 1.20 g, 2.5 mmol, 1,0 equiv.) was added and the mixture was heated to 80 °C and stirred at this temperature for 18 hours. The reaction mixture was allowed to cool to room temperature and brine (20 mL) was added, followed by extraction with Et_2O (3 x 20 mL). The combined organic extracts were washed with brine (30 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. Flash column chromatography (hexane/EtOAc 90:10 to 75:25) afforded ethyl 2-((*tert*-butoxycarbonyl)amino)-3-(2-4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl-4,5-dimethoxyphenyl)propanoate as a white solid (**2.109**, 740 mg, 1.54 mmol, 62%).

Two rotamers present in CD_2Cl_2 solution at 25 °C in an 81:19 ratio. **^{1}H NMR** (400 MHz, CD_2Cl_2): δ = 7.25 (s, 1H), 6.75 (s, 1H), 5.94 (d, *J* = 7.9 Hz, 0.81H), 5.37 (br. s), 4.28-4.15 (m, 3H), 3.85 (s, 3H), 3.84 (s, 3H), 3.24-3.13 (m, 2H), 1.38 (s, 6H), 1.37 (s, 6H), 1.34-1.23 (m, 12H); **^{13}C NMR** (100 MHz, CD_2Cl_2): δ = 172.7, 155.5, 151.6, 147.3, 137.9, 118.2, 113.2, 84.0, 78.9, 60.9, 56.5, 55.8, 55.6, 36.6, 28.0, 24.8, 24.4, 14.0; **^{11}B NMR**

(128 MHz, CD_2Cl_2) δ = 31 (br. s); **HRMS** (ESI): for $C_{24}H_{38}BNNaO_8$ $[M+Na]^+$ requires 502.2587 found 502.2590; **IR** (ATR, neat): ν (cm^{-1}) = 3316, 1730, 1608, 1533, 1464, 1410, 1368, 1346, 1317; **M.P.**: 35-36 °C.

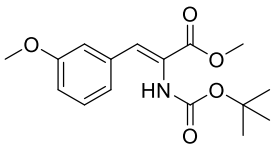
Ethyl (*S*)-2-((di-*tert*-butoxycarbonyl)amino)-3-(2-4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl-4,5-dimethoxyphenyl)propanoate (2.118)



To a solution of ethyl (*S*)-2-((*tert*-butoxycarbonyl)amino)-3-(4,5-dimethoxy-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) phenyl)propanoate (**2.109**, 240 mg, 0.5 mmol, 1 equiv.) in MeCN (2 mL) was added di-*tert*-butyl dicarbonate (328 mg, 1.50 mmol, 3.0 equiv.), *N*,*N*-dimethylaminopyridine (12 mg, 0.10 mmol, 0.20 equiv.) and Et_3N (210 μL, 1.50 mmol, 3.0 equiv.). The mixture was stirred at room temperature under N_2 for 18 hours. The solvent was removed under reduced pressure. The residue was dissolved in EtOAc (5 mL) and washed with NH_4Cl (sat. aq. solution, 5 mL), water (5 mL) and brine (5 mL). The organic extract was dried ($MgSO_4$), filtered and concentrated under reduced pressure. Silica gel column chromatography (hexane/EtOAc 85:15 to 75:25) afforded impure title compound (189 mg). This was purified by preparative reverse phase HPLC to afford ethyl (*S*)-2-((di-*tert*-butoxycarbonyl)amino)-3-(2-4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl-4,5-dimethoxyphenyl)propanoate (**2.118**, 153 mg, 0.26 mmol, 52%).

^{1}H NMR (400 MHz, CD_2Cl_2): δ = 7.22 (s, 1H), 6.56 (s, 1H), 5.18 (dd, *J* = 11.2, 3.9 Hz, 1H), 4.21 (m, 2H), 3.95 (dd, *J* = 13.4, 3.9, 1H), 3.81 (s, 3H), 3.80 (s, 3H), 3.05 (dd, *J* = 13.4, 11.4, 1H) 1.33 (s, 24H), 1.31 (s, 6H), 1.28 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (100 MHz, CD_2Cl_2): δ = 170.9, 152.7, 151.6, 147.6, 139.3, 119.3, 115.0, 84.0, 82.8, 61.6, 60.9, 56.5, 56.0, 35.6, 28.2, 25.2, 14.7; **^{11}B NMR** (128 MHz, CD_2Cl_2): δ = 31 (br. s); **HRMS** (ESI): for $C_{29}H_{46}BNNaO_{10}$ $[M+Na]^+$ requires 602.3112 found 602.3113; **IR** (ATR, neat): ν (cm^{-1}) = 1743, 1700, 1601, 1520, 1450, 1368, 1352; **M.P.**: 58-60 °C.

Methyl 2-(*tert*-butoxycarbonyl)amino-3-(3-methoxyphenyl)acrylate (2.124)

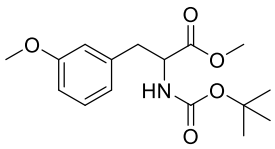


To a solution of (±)-Boc-α-phosphonoglycine trimethyl ester (**2.110**, 1.78 g, 6.0 mmol) in CH_2Cl_2 (5 mL) was added DBU (823 μL, 5.5 mmol). After stirring at room temperature for 10 minutes, a solution of 3-methoxybenzaldehyde (610 μL, 5 mmol) in CH_2Cl_2 (5 mL) was added slowly. The reaction mixture was stirred at room temperature for 2.5 hours and then at reflux for 1 hour. After cooling to room temperature, the solvent was removed under reduced pressure. The residue was dissolved in EtOAc (20 mL), washed successively with 1 M HCl (aq, 20 mL) and brine (20 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. Flash column chromatography (hexane/EtOAc 80:20) afforded methyl 2-(*tert*-butoxycarbonyl)amino-3-(3-methoxyphenyl)acrylate (**2.124**, 1.09 g, 3.55 mmol, 71%) as a clear oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.28 (t, *J* = 8.0 Hz, 1H), 7.22 (s, 1H), 7.13 (d, *J* = 8.0 Hz, 1H), 7.10 (s, 1H), 6.88 (d, *J* = 8.0 Hz, 1H), 6.20 (br s, 1H), 3.86 (s, 3H), 3.81 (s, 3H),

1.41 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 166.0, 159.5, 152.7, 135.3, 129.9, 129.4, 124.9, 122.2, 115.1, 114.6, 80.9, 55.2, 52.5, 28.1; **HRMS** (ESI): for $C_{16}H_{21}NNaO_5$ $[M+Na]^+$ requires 330.1312, found 330.1307; **IR** (ATR, neat): ν (cm^{-1}) = 3346, 1716, 1642, 1578, 1489, 1436, 1367.

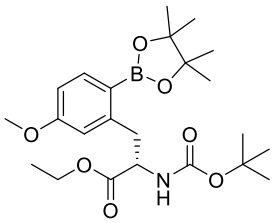
Methyl *N*-(*tert*-butoxycarbonyl)-3-methoxyphenylalaninate (2.125)



To a flask containing 10 % Pd/C (107 mg) was added EtOH (10 mL), followed by methyl-2-[(*tert*-butoxycarbonyl)amino]-3-(3-methoxyphenyl)prop-2-enoate (**2.124**, 1.04 g, 3.4 mmol, 1.0 equiv.) in EtOH (20 mL). The reaction was then allowed to stir under an atmosphere of H_2 for 12 hours. The reaction was purged with N_2, filtered over Celite and the solvent removed under reduced pressure. Flash column chromatography (hexane/EtOAc 80:20) afforded methyl *N*-(*tert*-butoxycarbonyl)-3-methoxyphenylalaninate (**2.125**, 1.00 g, 3.23 mmol, 95%).

^{1}H NMR (400 MHz, CD_2Cl_2): δ = 7.20 (t, *J* = 8 Hz, 1H), 6.79 (dd, *J* = 2, 8 Hz, 1H), 6.70 (d, *J* = 8 Hz, 1H), 6.65-6.67 (m, 1H), 4.97 (d, *J* = 8 Hz, 1H), 4.54-4.72 (m, 1H + rotamer), 3.78 (s, 3H), 3.72 (s, 3H), 2.86-3.14 (m, 2H + rotamer), 1.42 (s, 9H); **MS** (ESI): for $C_{16}H_{23}NNaO_5$ $[M+Na]^+$ requires 332.1, found 332.2. The analytical data were in accordance with the literature. [2]

Methyl 2-(*tert*-butoxycarbonyl)amino-3-[5-methoxy-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]propanoate (2.127)



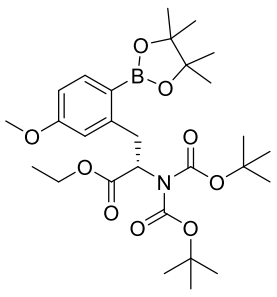
To a stirred solution of methyl 2-((*tert*-butoxycarbonyl) amino)-3-(3-methoxyphenyl)propanoate (**2.125**, 993 mg, 3.20 mmol, 1.0 equiv.) in CH_2Cl_2 (50 mL) at 0 °C was added [bis(trifluoroacetoxy)iodo]benzene (1.65 g, 3.84 mmol, 1.2 equiv.) and iodine (812 mg, 3.20 mmol, 1.0 equiv.). After 15 minutes, the reaction was allowed to warm to room temperature and allowed to stir for 3 hours. Sodium sulfite (1M aq solution, 40 mL) was added and the layers separated. The organic phase was washed successively with water (40 mL) and brine (40 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. Flash column chromatography (hexane/EtOAc 80:20) afforded a complex mixture, including methyl 2-[bis(*tert*-butoxycarbonyl)amino]-3-(2-iodo-5-methoxyphenyl)propanoate. To this was added bis(pinacolato)diboron (2.32 g, 9.15 mmol, 3.0 equiv.), $Pd(dppf)Cl_2.CH_2Cl_2$ (122 mg, 0.15 mmol, 0.05 equiv.) and potassium acetate (1.20 g, 12.20 mmol, 4.0 equiv.). The flask was purged with N_2 for 10 minutes and degassed DMF (20 mL) was added. The mixture was heated to 80 °C for 4 hours, cooled to room temperature and filtered. Et_2O (100 mL) was added and the organic phase washed successively with water (3 x 100 mL), LiCl (5% w/v aq. solution, 100 mL) and brine (100 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. Flash column chromatography (hexane/EtOAc 90:10 to 80:20) afforded methyl 2-(*tert*-butoxycarbonyl)amino-3-[5-methoxy-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-

yl)phenyl]propanoate (**2.127**, 811 mg, 1.86 mmol, 58 % over two steps) as a clear gum.

Compound exists as a 4:1 ratio of rotamers in $CDCl_3$ at 25 °C. Peaks assigned to minor rotamer where possible denoted with *.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.75 (d, *J* = 9.0 Hz, 1H), 7.19 (t, *J* = 8.0 Hz, 1H*), 6.77 (s, 2H), 6.70 (d, *J* = 7.5 Hz, 1H*), 6.66 (s, 1H*), 5.97 (d, *J* = 7.5 Hz, 1H), 5.50 (s, 1H*), 4.98 (d, *J* = 5.5 Hz, 1H*), 4.57 (d, *J* = 6.0 Hz, 1H*), 4.41–4.32 (m, 1H), 3.80 (s, 3H), 3.77 (s, 3H*), 3.74 (s, 3H), 3.71 (s, 3H*), 3.30–3.12 (m, 2H), 3.12-2.98 (m, 2H*), 1.41 (s, 2H), 1.38 – 1.30 (m, 21H), 1.28-1.21 (m, 7H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 173.3, 172.3*, 162.1, 159.7*, 155.6, 145.9, 138.0, 137.5*, 129.5*, 121.6, 115.4, 114.9*, 112.4*, 112.0, 83.8, 83.4*, 79.2*, 74.9*, 56.3, 55.1*, 55.1, 52.2*, 52.0, 37.1, 28.2, 28.0, 25.0, 24.8*, 24.6*, 24.6; **^{11}B NMR** (128 MHz, $CDCl_3$): δ = 31 (br. s); **HRMS** (ESI): for $C_{22}H_{34}BNNaO_7$ $[M+Na]^+$ requires 458.2321, found 458.2314; **IR** (ATR, neat): ν (cm^{-1}) = 3382, 1719, 1602, 1508, 1453, 1349.

Methyl 2-[bis(*tert*-butoxycarbonyl)amino]-3-[5-methoxy-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]propanoate (2.128)

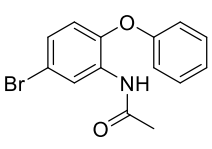


To a stirred solution of methyl 2-(*tert*-butoxycarbonyl)amino-3-[5-methoxy-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) phenyl]propanoate (**2.127**, 756 mg, 1.74 mmol) in MeCN (7 mL) was added di-*tert*-butyl dicarbonate (1.14 g, 5.22 mmol),

(*N*,*N*-dimethylamino)pyridine (213 mg, 1.74 mmol) and triethylamine (728 μL, 5.22 mmol). The mixture was heated to 50 °C for 9 hours, then allowed to cool to room temperature. The solvent was removed under reduced pressure and the residue was dissolved in EtOAc (20 mL). The organic phase was washed successively with NH_4Cl (sat. aq. solution, 20 mL), water (20 mL) and brine (20 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. Silica gel column chromatography (hexane/EtOAc 90:10 to 80:20) afforded a clear gum containing impure title compound (629 mg). Further purification by preparative HPLC afforded methyl 2-[bis(*tert*-butoxycarbonyl)amino]-3-[5-methoxy-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]propanoate (**2.128**, 397 mg, 0.72 mmol, 43 %) as an off-white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.71 (d, *J* = 8.5 Hz, 1H), 6.72 (dd, *J* = 8.5, 2.0 Hz, 1H), 6.58 (s, 1H), 5.30 (dd, *J* = 11.0, 3.5 Hz, 1H), 4.04 (dd, *J* = 13.5, 3.5 Hz, 1H), 3.76 (s, 3H), 3.75 (s, 3H), 3.13–3.02 (m, 1H), 1.33 (s, 18H), 1.31 (s, 6H), 1.30 (s, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 170.9, 161.6, 151.7, 146.8, 138.0, 116.2, 111.7, 83.3, 82.4, 59.9, 55.0, 52.0, 36.0, 27.8, 24.9, 24.8; **^{11}B NMR** (128 MHz, $CDCl_3$): δ = 30 (br. s); **HRMS** (ESI) for $C_{27}H_{42}BNNaO_9$ $[M+Na]^+$ requires 558.2845, found 558.2843; **IR** (ATR, neat): ν (cm^{-1}) = 1748, 1699, 1602, 1368, 1349, 1301, 1270; **M.P.**: 98-99 °C.

_N_-(5-Bromo-2-phenoxyphenyl)acetamide (2.145)



According to a literature procedure,[3] a mixture of 5-bromo-2-fluoronitrobenzene (**2.142**, 4.40 g, 20.0 mmol, 1.00 eq.), phenol (2.07

g, 22.0 mmol, 1.10 eq.) and potassium carbonate (2.76 g, 20.0 mmol, 1.00 eq.) in dry DMF (40 mL) was stirred at 80 °C for 3 hours. The mixture was concentrated under reduced pressure and the residue was partitioned between EtOAc and water. The phases were separated, and the organic phase was washed with 1 M aqueous HCl and brine. The organic phase was dried ($MgSO_4$), filtered and concentrated to afford 5-bromo-2-phenoxynitrobenzene (**2.143**, 5.84 g, 19.8 mmol, 99%) as a yellow oil, which was used without further purification.

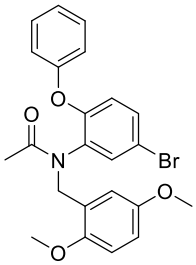
According to a literature procedure,[3] a mixture of 5-bromo-2-phenoxynitrobenzene (**2.143**, 5.79 g, 19.7 mmol, 1.00 eq.), Fe powder (3.53 g, 63.0 mmol, 3.20 eq.) and NH_4Cl (527 mg, 9.85 mmol, 0.50 eq.) in ethanol (60 mL) and water (20 mL) was stirred at 80 °C for 5 hours. The mixture was filtered through filter paper to remove Fe. EtOAc and water were added to the filtrate and the phases were separated. The organic layer was washed with water, dried ($MgSO_4$) and filtered. Concentration under reduced pressure afforded 5-bromo-2-phenoxyaniline (**2.144**, 4.40 g, 16.7 mmol, 85%) as a yellow oil, which was used without further purification.

According to a literature procedure,[3] to a solution of 5-bromo-2-phenoxyaniline (**2.144**, 4.16 g, 15.8 mmol, 1.00 eq.) and Et_3N (2.85 mL, 20.5 mmol, 1.30 eq.) in dry CH_2Cl_2 (30 mL) was added acetyl chloride (1.35 mL, 19.0 mmol, 1.2 eq.) dropwise at 0 °C. The mixture was allowed to warm to room temperature and stirred at room temperature for 3 hours. The mixture was concentrated under reduced pressure. The residue was partitioned between EtOAc and water. The phases were separated

and the organic phase was washed with brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. Flash column chromatography (hexane/EtOAc 85:15) afforded *N*-(5-bromo-2-phenoxyphenyl)acetamide (**2.145**, 3.39 g, 11.1 mmol, 56% over three steps) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.66 (br s, 1H), 7.71 (br s, 1H), 7.38 (t, *J* = 7.9 Hz, 2H), 7.18 (t, *J* = 7.4 Hz, 1H), 7.10 (dd, *J* = 8.7, 2.1 Hz, 1H), 7.01 (d, *J* = 8.0 Hz, 2H), 6.68 (d, *J* = 8.7 Hz, 1H), 2.18 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 168.3, 155.9, 144.6, 130.8, 130.1, 126.6, 124.4, 123.4, 118.9, 118.6, 116.5, 24.9; **MS** (ESI^+): for $C_{14}H_{12}{}^{79}BrNO_2^+$ $[M + H]^+$ requires m/z = 306.0, found 306.0. The analytical data were in accordance with the literature values.[3]

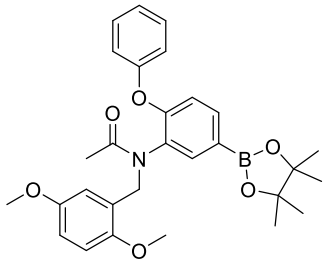
_N_-(5-bromo-2-phenoxyphenyl)-_N_-(2,5-dimethoxybenzyl)acetamide (2.146)



Based on a literature procedure,[3] to a solution of *N*-(5-bromo-2-phenoxyphenyl)acetamide (**2.145**, 3.27 g, 10.7 mmol, 1.00 eq.) in dry DMF (20 mL) was added NaH (60% in mineral oil, 856 mg, 21.4 mmol, 2.00 eq.). The mixture was stirred at room temperature for one hour. 2,5-Dimethoxybenzyl chloride (2.80 g, 15.0 mmol, 1.4 eq.) was added and the mixture was stirred at room temperature for two hours. The mixture was poured into water and extracted three times with EtOAc. The combined organic phases were washed with 1 M aqueous HCl and brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. Flash column chromatography

(hexane/EtOAc 75:25) afforded *N*-(5-bromo-2-phenoxyphenyl)-*N*-(2,5-dimethoxybenzyl)acetamide (**2.146**, 4.05 g, 8.88 mmol, 83%) as a white solid. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.33 (t, *J* = 7.8 Hz, 2H), 7.29 – 7.25 (m, 1H), 7.21 (d, *J* = 2.1 Hz, 1H), 7.14 (t, *J* = 7.4 Hz, 1H), 6.95 (d, *J* = 2.8 Hz, 1H), 6.84 (d, *J* = 8.2 Hz, 2H), 6.77 – 6.65 (m, 3H), 5.05 (d, *J* = 14.4 Hz, 1H), 4.73 (d, *J* = 14.4 Hz, 1H), 3.65 (s, 3H), 3.55 (s, 3H), 1.97 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 170.6, 155.5, 153.4, 153.0, 151.7, 134.3, 133.2, 131.8, 129.9, 126.0, 124.4, 119.3, 116.5, 114.4, 113.7, 111.2, 55.7, 55.6, 46.0, 22.2; **MS** (ESI^+): for $C_{23}H_{22}{}^{79}BrNO_4^+$ $[M + H]^+$ requires m/z = 456.1, found 456.1. The analytical data were in accordance with the literature values.[3]

_N_-(2,5-Dimethoxybenzyl)-_N_-(2-phenoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetamide (2.147)



To an oven-dry flask with a magnetic stirrer was added *N*-(5-bromo-2-phenoxyphenyl)-*N*-(2,5-dimethoxybenzyl) acetamide (**2.146**, 1.44 g, 3.15 mmol, 1.05 eq), bis(pinacolato)diboron (762 mg, 3.00 mmol, 1.00 eq.), $Pd(dppf)Cl_2$ (110 mg, 0.15 mmol, 0.05 eq.) and potassium acetate (882 mg, 9.00 mmol, 3.00 eq). A rubber septum was added, and the flask was evacuated and back-filled with argon three times. Dry, degassed DMF (15 mL) was added. The mixture was heated to 80 °C and stirred at this temperature for 18 hours. After cooling to room temperature, the mixture was diluted with EtOAc and filtered through a short plug of SiO_2, eluting with EtOAc. The solvent was removed under reduced pressure

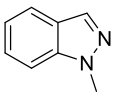
to afford crude **2.147**. Flash column chromatography (pet 40-60/EtOAc 70:30) afforded *N*-(2,5-dimethoxybenzyl)-*N*-(2-phenoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetamide (**2.147**, 743 mg, 1.48 mmol, 49% yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.61 – 7.55 (m, 2H), 7.32 (t, *J* = 7.9 Hz, 2H), 7.14 (t, *J* = 7.4 Hz, 1H), 6.99 (d, *J* = 3.0 Hz, 1H), 6.84 (d, *J* = 7.7 Hz, 2H), 6.74 (d, *J* = 8.6 Hz, 1H), 6.68 (dd, *J* = 8.9, 3.0 Hz, 1H), 6.62 (d, *J* = 8.9 Hz, 1H), 4.99 (d, *J* = 14.5 Hz, 1H), 4.89 (d, *J* = 14.5 Hz, 1H), 3.63 (s, 3H), 3.50 (s, 3H), 1.97 (s, 3H), 1.32 (s, 6H), 1.31 (s, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 171.1, 156.3, 155.4, 153.5, 151.9, 137.0, 135.5, 132.5, 129.8, 126.5, 124.3, 119.7, 116.8, 116.4, 113.7, 111.3, 83.9, 55.7, 55.7, 46.4, 25.0, 24.9, 24.7, 22.3; **^{11}B NMR** (128 MHz, $CDCl_3$): δ = 31.2; **MS** (ESI^+): for $C_{29}H_{34}BNNaO_6^+$ [M + Na]$^+$ requires m/z = 526.2376, found 526.2380; **IR** (ATR, neat): ν (cm^{-1}) = 1662, 1587, 1500, 1466, 1419, 1382, 1356, 1319, 1264, 1244, 1223; **M.P.**: 143-145 °C.

4.3 Experimental Procedures and Characterisation for Compounds in Chapter 3

4.3.1 Heterocycles for Screening

1-Methyl-1*H*-indazole (3.35)

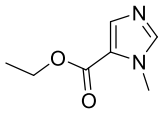


To a solution of 1*H*-indazole (236 mg, 2.00 mmol, 1.00 equiv.) in acetone (2.5 mL) at 0 °C was added KOH (336 mg, 6.00 mmol, 3.00 equiv.). The mixture was stirred at 0 °C for one hour and then allowed to warm to room temperature. MeI (187 μL, 3.00 mmol, 15.0 equiv.) was added and the mixture was stirred at room temperature for 18 hours. The solvent was removed under reduced

pressure. Flash column chromatography (*n*-hexane/EtOAc 85:15) afforded 1-methyl-1H-indazole (**3.35**, 103 mg, 0.78 mmol, 39%) as an off-white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.98 (s, 1H), 7.73 (d, *J* = 8.1 Hz, 1H), 7.42 – 7.36 (m, 2H), 7.19 – 7.11 (m, 1H), 4.08 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 139.9, 132.7, 126.2, 124.0, 121.0, 120.4, 108.9, 35.4; **MS** (ESI^+): for $C_8H_9N_2^+$ $[M + H]^+$ requires m/z = 133.1, found 133.1. The analytical data were in accordance with the literature.[4]

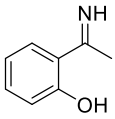
Ethyl 1-methyl-1*H*-imidazole-5-carboxylate (3.58)



Based on a literature procedure,[5] to a solution of ethyl 1*H*-imidazole-4-carboxylate (420 mg, 3.00 mmol, 1.00 equiv.) in dry MeOH (25 mL) was added a solution of MeI (374 µL, 6.00 mmol, 2.00 equiv) in dry MeOH (5 mL). The mixture was heated at reflux for 65 hours. The mixture was cooled to room temperature and all volatiles were removed under reduced pressure. Flash column chromatography (CH_2Cl_2/MeOH/Et_3N 99:1:0.1 to 98:2:0.1) afforded ethyl 1-methyl-1*H*-imidazole-4-carboxylate (**3.58**, 72 mg, 0.467 mmol, 16%) as a pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.71 (s, 1H), 7.52 (s, 1H), 4.31 (q, *J* = 7.1 Hz, 2H), 3.89 (s, 3H), 1.35 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 160.4, 142.4, 137.5, 123.3, 60.4, 34.0, 14.3. **MS** (ESI^+): for $C_7H_{11}N_2O_2^+$ $[M+H]^+$ requires m/z = 155.2, found 155.2. The analytical data were in accordance with the literature.[6]

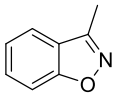
2′-Hydroxyacetophenone imine



Based on a literature procedure,[7] 2′-hydroxyacetophenone (2.40 mL, 20.0 mmol, 1.00 equiv.) was dissolved in 7 M NH_3 in MeOH (14 mL) and the mixture was stirred at room temperature for 2 hours. Removal of volatiles under reduced pressure afforded 2′-hydroxyacetophenone imine (2.62 g, 19.4 mmol, 97%) as a yellow solid.

^{1}H NMR (400 MHz, CD_2Cl_2): δ = 15.04 (br. s, 1H), 9.27 (br. s, 1H), 7.53 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.33 (ddd, *J* = 8.6, 7.2, 1.7 Hz, 1H), 6.91 (dd, *J* = 8.4, 1.1 Hz, 1H), 6.82 (ddd, *J* = 8.2, 7.3, 1.2 Hz, 1H), 2.48 (s, 3H); **^{13}C NMR** (101 MHz, CD_2Cl_2): δ = 179.3, 163.9, 133.8, 129.7, 119.4, 118.7, 118.0, 26.4; **MS** (ESI^+): for $C_8H_{10}NO^+$ $[M + H]^+$ requires m/z = 136.1, found 136.0. The analytical data were in accordance with the literature.[7]

3-Methylbenzisoxazole (3.75)

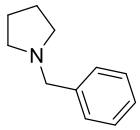


Based on a literature procedure,[7] a suspension of 2′-hydroxyacetophenone imine (675 mg, 5.00 mmol, 1.00 equiv.), *N*-chlorosuccinimide (1.00 g, 7.50 mmol, 1.50 equiv.) and K_2CO_3 (1.38 g, 10.0 mmol, 2.00 equiv.) in THF (15 mL) was stirred at room temperature for 12 hours. H_2O (20 mL) was added to quench the reaction. The mixture was transferred to a separating funnel and extracted with EtOAc (3 x 20 mL). The combined organic phases were washed with brine (40 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford crude title compound. Flash column chromatography (pet 40°-

60°C/EtOAc 99:1 to 98:2) afforded 3-methylbenzisoxazole (**3.75**, 413 mg, 3.11 mmol, 62%) as a pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.62 (dt, *J* = 7.9, 0.9 Hz, 1H), 7.56 – 7.50 (m, 2H), 7.34 – 7.25 (m, 1H), 2.58 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 162.8, 154.9, 129.7, 123.1, 122.2, 121.1, 109.8, 10.0; **HRMS** (ESI^+) for $C_8H_8NO^+$ $[M+H]^+$ requires m/z = 134.0600, found 134.0600. The analytical data were in accordance with the literature.[8]

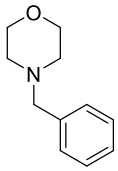
1-Benzylpyrrolidine (3.80)



Following a literature procedure,[9] to a solution of pyrrolidine (417 μL, 5.0 mmol, 1.0 equiv.) and benzyl bromide (595 μL, 5.0 mmol, 1.0 equiv.) in EtOH (10 mL) was added KOH (308 mg, 5.5 mmol, 1.1 equiv.). The mixture was stirred at room temperature for 24 hours, after which the solvent was removed under reduced pressure. The residue was partitioned between EtOAc and H_2O and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated to afford crude title compound. Flash column chromatography (*n*-hexane/EtOAc/Et_3N 95:4:1) afforded 1-benzylpyrrolidine (**3.80**, 463 mg, 2.88 mmol, 58%) as a pale straw-coloured oil.

^{1}H NMR (400 MHz, $CDCl_3$): *δ* = 7.39–7.31 (m, 4H), 7.30–7.24 (m, 1H), 3.65 (s, 2H), 2.57–2.51 (m, 4H), 1.87–1.76 (m, 4H); **^{13}C NMR** (101 MHz, $CDCl_3$): *δ* = 139.4, 128.9, 128.2, 126.8, 60.7, 54.2, 23.4; **MS** (ESI^+): for $C_{11}H_{16}N^+$ $[M + H]^+$ requires m/z = 162.1, found 162.1. The analytical data were in accordance with the literature.[9]

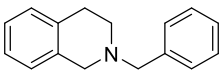
4-Benzylmorpholine (3.93)



Based on a literature procedure,[9] to a solution of morpholine (437 μL, 5.0 mmol, 1.0 equiv.) and benzyl bromide (595 μL, 5.0 mmol, 1.0 equiv.) in EtOH (10 mL) was added KOH (308 mg, 5.5 mmol, 1.1 equiv.). The mixture was stirred at room temperature for 24 hours, after which the solvent was removed under reduced pressure. The residue was partitioned between EtOAc and H_2O and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated to afford crude title compound. Flash column chromatography (*n*-hexane/EtOAc/Et_3N 85:14:1) afforded 4-benzylmorpholine (**3.93**, 715 mg, 4.04 mmol, 81%) as a clear oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39–7.25 (m, 5H), 3.77–3.70 (m, 4H), 3.53 (s, 2H), 2.51–2.43 (m, 4H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 137.8, 129.2, 128.2, 127.1, 67.0, 63.5, 53.6; **MS** (ESI^+): for $C_{11}H_{16}NO^+$ $[M + H]^+$ requires m/z = 178.1, found 178.1. The analytical data were in accordance with the literature.[10]

2-Benzyl-1,2,3,4-tetrahydroisoquinoline (3.95)

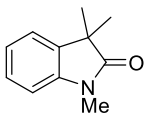


Based on a literature procedure,[9] to a solution of 1,2,3,4-tetrahydroisoquinoline (625 μL, 5.0 mmol, 1.0 equiv.) and benzyl bromide (595 μL, 5.0 mmol, 1.0 equiv.) in EtOH (10 mL) was added KOH (308 mg, 5.5 mmol, 1.1 equiv.). The mixture was stirred at room temperature for 24 hours, after which the solvent was removed under reduced pressure. The residue was partitioned between EtOAc and H_2O and the aqueous layer was extracted with EtOAc. The combined

organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated to afford crude title compound. Flash column chromatography (*n*-hexane/EtOAc/Et_3N 95:4:1) afforded 2-benzyl-1,2,3,4-tetrahydroisoquinoline (**3.95**, 628 mg, 2.82 mmol, 56%) as a pale straw-coloured oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.42–7.37 (m, 2H), 7.33 (t, *J* = 7.3 Hz, 2H), 7.29–7.23 (m, 1H), 7.14–7.05 (m, 3H), 6.97 (d, *J* = 7.3 Hz, 1H), 3.68 (s, 2H), 3.63 (s, 2H), 2.89 (t, *J* = 5.9 Hz, 2H), 2.74 (t, *J* = 5.9 Hz, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 138.4, 134.9, 134.4, 129.1, 128.7, 128.3, 127.1, 126.6, 126.1, 125.5, 62.8, 56.1, 50.6, 29.2; **MS** (ESI^+): for $C_{16}H_{18}N^+$ $[M + H]^+$ requires m/z = 224.1, found 224.1. The analytical data were in accordance with the literature.[10]

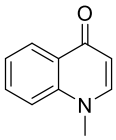
1,3,3-Trimethylindolin-2-one (3.104)



To a solution of indolin-2-one (378 mg, 2.5 mmol, 1.0 equiv.) in dry THF at 0 °C was added NaH (60% in mineral oil, 350 mg, 8.75 mmol, 3.5 equiv.). The resulting suspension was stirred at 0 °C for 30 minutes. MeI (498 μL, 8.0 mmol, 3.2 equiv.) was added and the mixture was stirred at 0 °C for 1 hour. H_2O (1 mL) was added dropwise and the mixture was allowed to warm to room temperature. Volatiles were removed under reduced pressure. The residue was redissolved in EtOAc, washed with water and brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford crude title compound. Flash column chromatography (*n*-hexane/EtOAc 88:12) afforded 1,3,3-trimethylindolin-2-one (**3.104**, 298 mg, 1.54 mmol, 62%) as a pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.27 (t, *J* = 7.7 Hz, 1H), 7.21 (d, *J* = 7.3 Hz, 1H), 7.07 (t, *J* = 7.5 Hz, 1H), 6.85 (d, *J* = 7.8 Hz, 1H), 3.22 (s, 3H), 1.38 (s, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 181.4, 142.7, 135.9, 127.6, 122.4, 122.2, 108.00, 44.1, 26.2, 24.4; **MS** (ESI^+): for $C_{11}H_{13}NNaO^+$ $[M + Na]^+$ requires m/z = 198.1, found 198.1. The analytical data were in accordance with the literature.[11]

1-Methylquinolin-4(1*H*)-one (3.106)

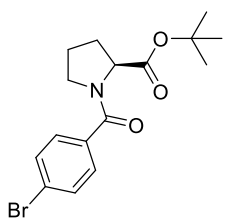


To a solution of quinolin-4-ol (725 mg, 5.0 mmol, 1.0 equiv.) in DMF (10 mL) was added NaH (60% in mineral oil, 300 mg, 7.5 mmol, 1.5 equiv.) and the mixture was stirred at room temperature for 2 hours. Iodomethane (623 μL, 10.0 mmol, 2.0 equiv.) was added and the mixture was heated to 80 °C and stirred at this temperature for 16 hours. The mixture was allowed to cool to room temperature. CH_2Cl_2 (50 mL) was added and the mixture was stirred for 30 minutes, filtered and concentrated under reduced pressure to afford crude title compound. Flash column chromatography (CH_2Cl_2/MeOH 95:5) afforded 1-methylquinolin-4(1*H*)-one (**3.106**, 639 mg, 4.02 mmol, 80%) as a pale brown solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.43 (dd, *J* = 8.3, 1.5 Hz, 1H), 7.69–7.61 (m, 1H), 7.48 (d, *J* = 7.7 Hz, 1H), 7.40–7.34 (m, 2H), 6.22 (d, *J* = 7.7 Hz, 1H), 3.77 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 178.1, 143.6, 140.6, 132.1, 127.0, 126.9, 123.6, 115.3, 110.0, 40.5; **MS** (ESI^+): for $C_{10}H_{10}NO^+$ $[M + H]^+$ requires m/z = 160.1, found 160.1. The analytical data were in accordance with the literature.[12]

4.3.2 Boronic Ester Substrates and ^{19}F-References for Tables 3.17 and 3.18

tert-Butyl (4-bromobenzoyl)-L-prolinate

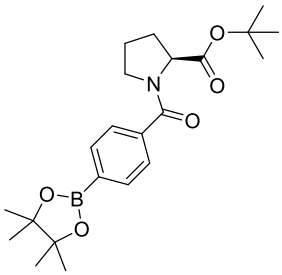


To a solution of *tert*-butyl L-prolinate (1.71 g, 10.0 mmol, 1.00 eq.) in pyridine (30 mL) was added 4-bromobenzoyl chloride (2.20 g, 10.0 mmol, 1.00 eq.). The mixture was stirred at room temperature for 16 hours. The solvent was removed under reduced pressure. The residue was partitioned between EtOAc and water. The phases were separated and the aqueous phase was extracted twice with EtOAc. The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. Flash column chromatography (pet 40°-60°C/EtOAc 70:30) afforded *tert*-butyl (4-bromobenzoyl)-L-prolinate (1.79 g, 5.06 mmol, 51%) as a white solid.

2.5:1 mixture of rotamers observed in $CDCl_3$ solution. Peaks belonging to minor rotamer denoted with *. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.54 (d, *J* = 8.4 Hz, 2H), 7.49 (d, *J* = 8.2 Hz, 2H*), 7.44 (d, *J* = 8.4 Hz, 2H), 7.29 (d, *J* = 8.2 Hz, 2H*), 4.53 (dd, *J* = 8.2, 5.5 Hz, 1H), 4.19 (dd, *J* = 8.2, 2.1 Hz, 1H*), 3.76 (t, *J* = 6.9 Hz, 2H*), 3.60 (dt, *J* = 9.9, 6.9 Hz, 1H), 3.52 – 3.43 (m, 1H), 2.37 – 2.25 (m, 1H), 2.25 – 2.15 (m, 1H*), 2.09 – 1.93 (m, 2H + 3H*), 1.92 – 1.79 (m, 1H), 1.49 (s, 9H), 1.33 (s, 9H*); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 171.2 (1C + 1C*), 169.4 (1C*), 168.4 (1C), 135.9 (1C*), 135.3 (1C), 131.5 (2C + 2C*), 128.9 (2C), 128.5 (2C*), 124.4 (1C), 124.0 (1C*), 82.0 (1C*), 81.4 (1C), 62.0 (1C*), 60.0 (1C), 49.9 (1C), 46.8 (1C*), 31.6 (1C*), 29.4 (1C), 28.0 (3C), 27.7 (3C*), 25.3 (1C), 22.6 (1C*); **HRMS** (ESI^+) for $C_{16}H_{21}O_3NBr^+$ $[M+H]^+$ requires m/z = 354.0699, found

354.0698; **IR** (ATR, neat): ν (cm^{-1}) = 2977, 2879, 1737, 1635, 1592, 1416, 1391, 1367, 1222, 1154, 1068, 1012; **M.P.**: 100-102 °C.

***tert*-Butyl (4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoyl)-L-prolinate (3.129-Bpin)**

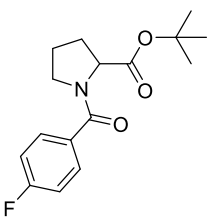


To an oven-dry round bottom flask with a magnetic stirrer was added *tert*-butyl (4-bromobenzoyl)-L-prolinate (743 mg, 2.10 mmol, 1.05 eq.), bis(pinacolato)diboron (508 mg, 2.00 mmol, 1.00 eq.), $Pd(dppf)Cl_2$ (44 mg, 0.06 mmol, 0.03 eq.) and potassium acetate (588 mg, 6.00 mmol, 3.00 eq). A rubber septum was added, and the flask was evacuated and backfilled with N_2 three times. Dry, degassed 1,4-dioxane (10 mL) was added. The mixture was heated to 80 °C and stirred at this temperature for 18 hours. After cooling to room temperature, the mixture was diluted with EtOAc and filtered through a short plug of SiO_2, eluting with EtOAc. The solvent was removed under reduced pressure to afford crude title compound. Flash column chromatography (pet 40°-60°C/EtOAc 75:25) afforded *tert*-butyl (4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoyl)-L-prolinate (**3.129-Bpin**, 409 mg, 1.02 mmol, 51%) as an off-white solid.

2.7:1 mixture of rotamers observed in $CDCl_3$ solution. Peaks belonging to minor rotamer denoted with *. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.82 (d, *J* = 7.8 Hz, 2H), 7.78 (d, *J* = 7.7 Hz, 2H*), 7.52 (d, *J* = 7.9 Hz, 2H), 7.39 (d, *J* = 7.7 Hz, 2H*), 4.53 (dd, *J* = 8.1, 5.3 Hz, 1H), 4.19 (br d, *J* = 8.3 Hz, 1H*), 3.85 – 3.70 (m, 2H*), 3.63 – 3.52 (m, 1H), 3.49

– 3.38 (m, 1H), 2.35 – 2.22 (m, 1H), 2.22 – 2.10 (m, 1H*), 2.06 – 1.91 (m, 2H + 3H*), 1.90 – 1.77 (m, 1H), 1.49 (s, 9H), 1.34 (br s, 12H + 21H*); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 171.4 (1C + 1C*), 170.3 (1C*), 169.5 (1C), 139.5 (1C*), 139.0 (1C), 134.7 (2C*), 134.6 (2C), 126.3 (2C), 125.9 (2C*), 84.0 (2C + 2C*), 81.8 (1C*), 81.3 (1C), 62.0 (1C*), 59.8 (1C), 49.8 (1C), 46.5 (1C*), 31.5 (1C*), 29.4 (1C), 28.0 (3C), 27.8 (3C*), 25.3 (1C), 24.8 (4C + 4C*), 22.5 (1C*). Carbon adjacent to boron was not observed; **^{11}B NMR** (128 MHz, $CDCl_3$): δ = 31.0; **HRMS** (ESI^+): for $C_{22}H_{33}BNO_5^+$ $[M+H]^+$ requires m/z = 402.2446, found 402.2440; **IR** (ATR, neat): ν (cm^{-1}) = 2976, 2934, 1737, 1636, 1555, 1512, 1417, 1393, 1358, 1324, 1268, 1215, 1143, 1087, 1022; **M.P.** 152-154 °C.

***tert*-Butyl (4-fluorobenzoyl)-D/L-prolinate (3.129)**

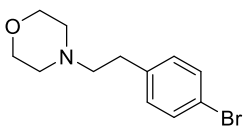


To a solution of D/L-proline (1.15 g, 10.0 mmol, 1.0 eq.) and K_2CO_3 (4.97 g, 36.0 mmol, 3.6 eq.) in H_2O (50 mL) was added a solution of 4-fluorobenzoyl chloride (1.24 mL, 10.5 mmol, 1.05 eq.) in THF (10 mL). The mixture was warmed to 60 °C and stirred at this temperature for 5 hours, before being allowed to cool to room temperature. The mixture was acidifed with 2M HCl and extracted three times with $CHCl_3$. The combined organic extracts were dried ($MgSO_4$) and concentrated to afford a pale pink gum. This intermediate was dissolved in *t*-BuOH (30 mL). Boc_2O (2.62 g, 12.0 mmol, 1.2 eq.) and DMAP (122 mg, 1.0 mmol, 0.1 eq.) were added. The mixture was heated to 50 °C and stirred at this temperature for 24 hours. The solvent was removed under reduced pressure to afford crude **3.129**. Flash column chromatography (pet 40°-60°C/EtOAc 75:25 to

60:40) afforded *tert*-butyl (4-fluorobenzoyl)-D/L-prolinate (**3.129**, 2.09 g, 7.14 mmol, 71% over two steps) as a white solid.

2.5:1 mixture of rotamers observed in $CDCl_3$ solution. Peaks belonging to minor rotamer denoted with *. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.58 (dd, *J* = 8.2, 5.6 Hz, 2H), 7.42 (m, 2H*), 7.11 – 7.01 (m, 2H + 2H*), 4.53 (dd, *J* = 7.9, 5.8 Hz, 1H), 4.21 (d, *J* = 7.1 Hz, 1H*), 3.81 – 3.73 (m, 2H*), 3.66 – 3.58 (m, 1H), 3.54 – 3.46 (m, 1H), 2.38 – 2.14 (m, 1H + 1H*), 2.07 – 1.92 (m, 2H + 3H*), 1.92 – 1.78 (m, 1H), 1.49 (s, 9H), 1.32 (s, 9H*); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 171.3 (s, 1C + 1C*), 169.5 (s, 1C*), 168.4 (s, 1C), 163.6 (d, *J* = 249.9 Hz, 1C), 163.3 (d, *J* = 250.6 Hz, 1C*), 133.2 (d, *J* = 3.1 Hz, 1C*), 132.5 (d, *J* = 3.2 Hz, 1C), 129.5 (d, *J* = 8.6 Hz, 2C), 129.0 (d, *J* = 8.5 Hz, 2C*), 115.2 (d, *J* = 21.8 Hz, 2C + 2C*), 81.8 (s, 1C*), 81.3 (s, 1C), 62.0 (s, 1C*), 60.0 (s, 1C), 50.0 (s, 1C), 46.7 (s, 1C*), 31.5 (s, 1C*), 29.3 (s, 1C), 27.9 (s, 3C), 27.7 (s, 3C*), 25.3 (s, 1C), 22.5 (s, 1C*); **^{19}F NMR** (376 MHz, $CDCl_3$): δ = -109.85 – -109.97 (m, 1F), -110.49 (m, 1F*); **HRMS** (ESI^+): for $C_{16}H_{21}FNO_3^+$ $[M+H]^+$ requires m/z = 294.1500, found 294.1498; **IR** (ATR, neat): ν (cm^{-1}) = 2977, 1738, 1626, 1603, 1425, 1366, 1227, 1211, 1141, 847, 764, 722; **M.P.** 73-75 °C.

4-(4-Bromophenethyl)morpholine

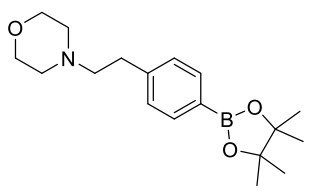


To a suspension of K_2CO_3 (1.66 g, 12.0 mmol, 1.2 equiv.) in DMF (20 mL) was added morpholine (873 μL, 10.0 mmol, 1.0 equiv.) and 4-bromophenethyl bromide (1.53 mL, 10.0 mmol, 1.0 equiv.). The mixture was heated to 80 °C and stirred at this temperature for 14 hours. The mixture was

allowed to cool to room temperature. EtOAc was added and the organic phase was washed three times with brine, dried ($MgSO_4$) and concentrated under reduced pressure. Flash column chromatography (pet 40°-60°C/EtOAc/Et_3N 50:49:1) afforded 4-(4-bromophenethyl)morpholine (1.94 g, 7.18 mmol, 72%) as an off-white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39 (d, *J* = 8.3 Hz, 2H), 7.07 (d, *J* = 8.3 Hz, 2H), 3.76 – 3.69 (m, 4H), 2.74 (dd, *J* = 9.5, 6.4 Hz, 2H), 2.56 (dd, *J* = 9.5, 6.5 Hz, 2H), 2.52 – 2.47 (m, 4H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 139.1, 131.4, 130.4, 119.8, 66.9, 60.4, 53.6, 32.7; **MS** (ESI^+): for $C_{12}H_{17}BrNO^+$ $[M + H]^+$ requires m/z = 270.0, found 270.0. The analytical data were in accordance with the literature.[13]

4-(4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)phenethyl)morpholine (3.137-Bpin)

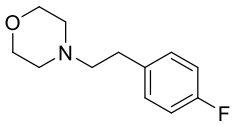


To an oven-dry round bottom flask with a magnetic stirrer was added 4-(4-bromophenethyl)morpholine (851 mg, 3.15 mmol, 1.05 equiv.), bis(pinacolato)diboron (762 mg, 3.00 mmol, 1.00 equiv.), $Pd(dppf)Cl_2$ (66 mg, 0.09 mmol, 0.03 equiv.) and potassium acetate (882 mg, 9.00 mmol, 3.00 equiv.). A rubber septum was added, and the flask was evacuated and backfilled with N_2 three times. Dry, degassed 1,4-dioxane (15 mL) was added. The mixture was heated to 80 °C and stirred at this temperature for 18 hours. After cooling to room temperature, the mixture was diluted with EtOAc and filtered through a short plug of SiO_2, eluting with EtOAc. The solvent was

removed under reduced pressure to afford crude title compound. Flash column chromatography (pet 40°-60°C /EtOAc/Et_3N 60:39:1) afforded partially-purified material. Recrystallisation from hexane afforded 4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenethyl)morpholine (**3.137-Bpin**, 229 mg, 0.72 mmol, 24%) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.74 (d, *J* = 7.9 Hz, 2H), 7.21 (d, *J* = 7.8 Hz, 2H), 3.77 – 3.69 (m, 4H), 2.85 – 2.78 (m, 2H), 2.63 – 2.56 (m, 2H), 2.54 – 2.48 (m, 4H), 1.33 (s, 12H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 143.6, 134.9, 128.1, 83.7, 67.0, 60.6, 53.7, 33.5, 24.8. Carbon adjacent to boron was not observed; **^{11}B NMR** (128 MHz, $CDCl_3$): δ = 31.4; **HRMS** (ESI^+): for $C_{18}H_{29}BNO_3^+$ $[M+H]^+$ requires m/z = 318.2235, found 318.2237; **IR** (ATR, neat): ν (cm^{-1}) = 2933, 2854, 2807, 1612, 1398, 1360, 1321, 1271, 1144, 1118, 1090; **M.P.** 85-86 °C.

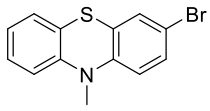
4-(4-Fluorophenethyl)morpholine (3.137)



To a suspension of K_2CO_3 (331 mg, 2.4 mmol, 1.2 equiv.) in DMF (4 mL) was added morpholine (175 μL, 2.0 mmol, 1.0 equiv.) and 4-fluorophenethyl bromide (280 μL, 2.0 mmol, 1.0 equiv.). The mixture was heated to 80 °C and stirred at this temperature for 14 hours. The mixture was allowed to cool to room temperature. EtOAc was added and the organic phase was washed three times with brine, dried ($MgSO_4$) and concentrated under reduced pressure. Flash column chromatography (pet 40°-60°C/EtOAc/Et_3N 55:44:1) afforded 4-(4-fluorophenethyl)morpholine (**3.137**, 329 mg, 1.57 mmol, 79%) as a pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.15 (dd, *J* = 7.8, 5.6 Hz, 2H), 6.96 (t, *J* = 8.6 Hz, 2H), 3.78 – 3.70 (m, 4H), 2.82 – 2.73 (m, 2H), 2.61 – 2.47 (m, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 161.4 (d, *J* = 243.9 Hz), 135.7 (d, *J* = 3.2 Hz), 130.0 (d, *J* = 7.8 Hz), 115.1 (d, *J* = 21.1 Hz), 66.9, 60.8, 53.7, 32.4; **^{19}F NMR** (376 MHz, $CDCl_3$): δ = -117.24 – -117.37 (m); **MS** (ESI^+): for $C_{12}H_{17}FNO^+$ $[M + H]^+$ requires m/z = 210.1, found 210.1. The analytical data were in accordance with the literature.[14]

3-Bromo-10-methyl-10*H*-phenothiazine

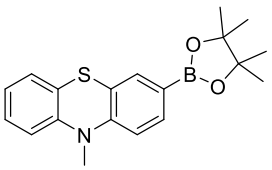


Based on a literature procedure,[15] a NaOAc buffer was prepared by dissolving powdered NaOH (1.20 g, 30.0 mmol, 3.00 equiv.) in AcOH (glacial, 70 mL). To this stirred solution at room temperature was added 10-methyl-10H-phenothiazine (2.13 g, 10.0 mmol, 1.00 equiv.) and CH_2Cl_2 (15 mL). A solution of Br_2 (769 μL, 15.0 mmol, 1.50 equiv.) in AcOH (15 mL) was added dropwise over one hour. The addition funnel was rinsed with CH_2Cl_2 (5 mL) and the reaction mixture was stirred for a further hour at room temperature. The solvents were removed under reduced pressure. The dark red residue was dissolved in CH_2Cl_2 (50 mL), carefully washed with aq. $NaHCO_3$ solution (1% w/v, 50 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. Flash column chromatography (pet 40°-60°C/EtOAc 97:3 to 90:10) afforded 3-bromo-10-methyl-10*H*-phenothiazine (559 mg, 1.91 mmol, 19%) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.28 – 7.22 (m, 2H), 7.18 (td, *J* = 7.9, 1.4 Hz, 1H), 7.13 (dd, *J* = 7.6, 1.3 Hz, 1H), 6.94 (td, *J* = 7.5, 0.9 Hz, 1H), 6.81 (d, *J* = 8.1 Hz, 1H), 6.67 –

6.61 (m, 1H), 3.34 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 145.4, 145.0, 130.0, 129.3, 127.7, 127.2, 125.7, 122.8, 122.7, 115.2, 114.6, 114.2, 35.4; **HRMS** (EI^+): for $C_{13}H_{10}BrNS^+$ $[M]^+$ requires m/z = 290.9717, found 230.9717. The analytical data were in accordance with the literature.[16]

10-Methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-10*H*-phenothiazine (3.138-Bpin)

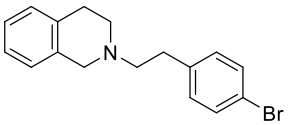


To an oven-dry round bottom flask with a magnetic stirrer was added 3-bromo-10-methyl-10*H*-phenothiazine (460 mg, 1.58 mmol, 1.05 equiv.), bis(pinacolato)diboron (381 mg, 1.50 mmol, 1.00 equiv.), $Pd(dppf)Cl_2$ (33 mg, 0.045 mmol, 0.03 equiv.) and potassium acetate (441 mg, 4.50 mmol, 3.00 equiv). A rubber septum was added, and the flask was evacuated and backfilled with N_2 three times. Dry, degassed 1,4-dioxane (7.5 mL) was added. The mixture was heated to 80 °C and stirred at this temperature for 18 hours. After cooling to room temperature, the mixture was diluted with EtOAc and filtered through a short plug of SiO_2, eluting with EtOAc. The solvent was removed under reduced pressure to afford crude title compound. Flash column chromatography (pet 40°-60°C/EtOAc 90:10) afforded 10-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-10*H*-phenothiazine (**3.138-Bpin**, 272 mg, 0.80 mmol, 53%) as an off-white solid.

^{1}H NMR (400 MHz, CD_2Cl_2): δ = 7.56 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.49 (d, *J* = 1.4 Hz, 1H), 7.17 (ddd, *J* = 8.1, 7.4, 1.5 Hz, 1H), 7.12 (dd, *J* = 7.6, 1.5 Hz, 1H), 6.93 (td, *J* = 7.5, 1.2

Hz, 1H), 6.85 – 6.80 (m, 2H), 3.37 (s, 3H), 1.31 (s, 12H); **^{13}C NMR** (101 MHz, CD_2Cl_2): δ = 148.7, 145.7, 134.7, 133.6, 127.8, 127.4, 123.7, 123.0, 122.7, 114.7, 113.9, 84.1, 35.7, 25.1; **^{11}B NMR** (128 MHz, CD_2Cl_2): δ = 30.1; **HRMS** (ESI^+): for $C_{19}H_{23}BNO_2S^+$ $[M+H]^+$ requires m/z = 339.1573, found 339.1540. The analytical data were in accordance with the literature.[17]

2-(4-Bromophenethyl)-1,2,3,4-tetrahydroisoquinoline

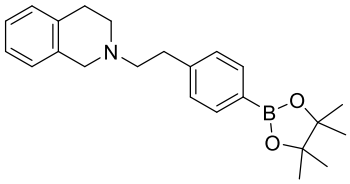


To a suspension of K_2CO_3 (1.66 g, 12.0 mmol, 1.20 equiv.) in DMF (20 mL) was added 1,2,3,4-tetrahydroisoquinoline (1.25 mL, 10.0 mmol, 1.00 equiv.) and 4-bromophenethyl bromide (1.53 mL, 10.0 mmol, 1.00 equiv.). The mixture was heated to 80 °C and stirred at this temperature for 14 hours. The mixture was allowed to cool to room temperature. EtOAc was added and the organic phase was washed three times with brine, dried ($MgSO_4$) and concentrated under reduced pressure. Flash column chromatography (*n*-Hexane/EtOAc/Et_3N 95:4:1 to 90:9:1) afforded 2-(4-bromophenethyl)-1,2,3,4-tetrahydroisoquinoline (2.18 g, 6.91 mmol, 69%) as an off-white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.44 – 7.38 (m, 2H), 7.17 – 7.08 (m, 5H), 7.07 – 7.01 (m, 1H), 3.71 (s, 2H), 2.93 (t, *J* = 5.9 Hz, 2H), 2.90 – 2.84 (m, 2H), 2.80 (t, *J* = 5.9 Hz, 2H), 2.78 – 2.72 (m, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 139.4, 134.6, 134.2, 131.4, 130.5, 128.7, 126.6, 126.2, 125.6, 119.8, 59.9, 56.1, 51.0, 33.4, 29.1; **HRMS** (ESI^+): for $C_{17}H_{19}BrN^+$ $[M+H]^+$ requires m/z = 316.0695, found 316.0696; **IR** (ATR, neat): ν (cm^-

[1]) = 2918, 2794, 2752, 1690, 1485, 1456, 1240, 1127, 1097, 1069, 1008, 935, 868, 856, 810, 748; **M.P.** 88-90 °C.

2-(4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)phenethyl)-1,2,3,4-tetrahydroisoquinoline (3.139-Bpin)

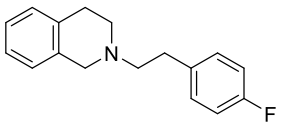


To an oven-dry round bottom flask with a magnetic stirrer was added 2-(4-bromophenethyl)-1,2,3,4-tetrahydroisoquinoline (995 mg, 3.15 mmol, 1.05 equiv.), bis(pinacolato)diboron (762 mg, 3.00 mmol, 1.00 equiv.), $Pd(dppf)Cl_2$ (66 mg, 0.09 mmol, 0.03 equiv.) and potassium acetate (882 mg, 9.00 mmol, 3.00 equiv.). A rubber septum was added, and the flask was evacuated and backfilled with N_2 three times. Dry, degassed 1,4-dioxane (15 mL) was added. The mixture was heated to 80 °C and stirred at this temperature for 18 hours. After cooling to room temperature, the mixture was diluted with EtOAc and filtered through a short plug of SiO_2, eluting with EtOAc. The solvent was removed under reduced pressure to afford crude title compound. Flash column chromatography (pet 40°-60°C/EtOAc/Et_3N 80:19:1) afforded partially-purified title compound. Recrystallisation from hexane afforded 2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenethyl)-1,2,3,4-tetrahydroisoquinoline (**3.139-Bpin**, 660 mg, 1.82 mmol, 60%) as a beige crystalline solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.75 (d, *J* = 7.8 Hz, 2H), 7.26 (d, *J* = 7.8 Hz, 2H), 7.16 – 7.08 (m, 3H), 7.06 – 7.01 (m, 1H), 3.72 (s, 2H), 2.97 – 2.90 (m, 4H), 2.84 – 2.75 (m,

4H), 1.34 (s, 12H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 143.8, 135.0, 134.7, 134.3, 128.6, 128.2, 126.6, 126.1, 125.6, 83.7, 60.1, 56.1, 51.0, 34.2, 29.1, 24.9. Carbon adjacent to boron was not observed; **^{11}B NMR** (128 MHz, $CDCl_3$): δ = 31.7; **HRMS** (ESI^+): for $C_{23}H_{31}BNO_2^+$ $[M+H]^+$ requires m/z = 364.2442, found 364.2441; **IR** (ATR, neat): ν (cm^{-1}) = 2976, 2926, 2799, 1611, 1398, 1359, 1321, 1271, 1143, 1089; **M.P.** 111-113 °C.

2-(4-Fluorophenethyl)-1,2,3,4-tetrahydroisoquinoline (3.139)

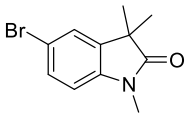


To a suspension of K_2CO_3 (331 mg, 2.40 mmol, 1.20 equiv.) in DMF (4 mL) was added 1,2,3,4-tetrahydroisoquinoline (250 μL, 2.00 mmol, 1.00 equiv.) and 4-fluorophenethyl bromide (280 μL, 2.00 mmol, 1.00 equiv.). The mixture was heated to 80 °C and stirred at this temperature for 14 hours. The mixture was allowed to cool to room temperature. EtOAc was added and the organic phase was washed three times with brine, dried ($MgSO_4$) and concentrated under reduced pressure. Flash column chromatography (pet 40°-60°C/EtOAc/Et_3N 95:4:1) afforded 2-(4-fluorophenethyl)-1,2,3,4-tetrahydroisoquinoline (**3.139**, 320 mg, 1.25 mmol, 63%) as an off-white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.20 (dd, *J* = 8.4, 5.5 Hz, 2H), 7.15 – 7.09 (m, 3H), 7.06 – 7.02 (m, 1H), 6.98 (t, *J* = 8.7 Hz, 2H), 3.72 (s, 2H), 2.96 – 2.86 (m, 4H), 2.82 (t, *J* = 5.9 Hz, 2H), 2.78 – 2.72 (m, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 161.4 (d, *J* = 243.6 Hz), 136.0 (d, *J* = 3.1 Hz), 134.6, 134.2, 130.1 (d, *J* = 7.8 Hz), 128.7, 126.6, 126.2, 125.7, 115.1 (d, *J* = 21.1 Hz), 60.2, 56.1, 51.0, 33.1, 29.1; **^{19}F NMR** (376 MHz, $CDCl_3$): δ = -117.34 – -117.47 (m); **HRMS** (ESI^+): for $C_{17}H_{19}FN^+$ $[M+H]^+$ requires m/z = 256.1496,

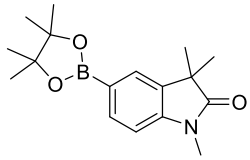
found 256.1498; **IR** (ATR, neat): ν (cm^{-1}) = 2958, 2812, 2770, 1508, 1218, 1129, 1094, 934, 875, 836, 824, 743; **M.P.** 54-56 °C.

5-Bromo-1,3,3-trimethylindolin-2-one



To a solution of 5-bromoindolin-2-one (1.06 g, 5.00 mmol, 1.00 eq.) in dry THF at 0 °C was added NaH (60% in mineral oil, 700 mg, 17.5 mmol, 3.50 eq.). The resulting suspension was stirred at 0 °C for 30 minutes. MeI (996 μL, 16.0 mmol, 3.20 eq.) was added and the mixture was stirred at 0 °C for one hour. H_2O (2 mL) was added dropwise and the mixture was allowed to warm to room temperature. The mixture was concentrated under reduced pressure to remove THF. The residue was redissolved in EtOAc, washed with water and brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford crude title compound. Flash column chromatography (*n*-hexane/EtOAc 85:15) afforded 5-bromo-1,3,3-trimethylindolin-2-one (780 mg, 3.07 mmol, 61%) as a pale pink solid. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.38 (d, *J* = 8.2 Hz, 1H), 7.31 (s, 1H), 6.71 (d, *J* = 8.2 Hz, 1H), 3.19 (s, 3H), 1.36 (s, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 180.7, 141.7, 137.9, 130.5, 125.7, 115.2, 109.4, 44.4, 26.3, 24.3; **HRMS** (ESI^+): for $C_{11}H_{13}BrNO^+$ $[M+H]^+$ requires m/z = 254.0175, found 254.0176; **IR** (ATR, neat): ν (cm^{-1}) = 2966, 2927, 1702, 1606, 1487, 1467, 1416, 1383, 1362, 1342, 1264, 1241, 1196, 1125, 1077, 1060, 1043; **M.P.** 99-100 °C.

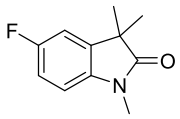
1,3,3-Trimethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)indolin-2-one (3.142-Bpin)



To an oven-dry round bottom flask with a magnetic stirrer was added 5-bromo-1,3,3-trimethylindolin-2-one (533 mg, 2.10 mmol, 1.05 equiv.), bis(pinacolato)diboron (508 mg, 2.00 mmol, 1.00 equiv.), $Pd(dppf)Cl_2$ (44 mg, 0.06 mmol, 0.03 equiv.) and KOAc (588 mg, 6.00 mmol, 3.00 equiv.). A rubber septum was added, and the flask was evacuated and backfilled with N_2 three times. Dry, degassed toluene (10 mL) was added. The mixture was heated to 80 °C and stirred at this temperature for 18 hours. After cooling to room temperature, the mixture was diluted with EtOAc and filtered through a short plug of SiO_2, eluting with EtOAc. The solvent was removed under reduced pressure to afford crude title compound. Flash column chromatography (*n*-hexane/EtOAc 80:20) afforded 1,3,3-trimethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)indolin-2-one (**3.142-Bpin**, 435 mg, 1.45 mmol, 73%) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.76 (dd, *J* = 7.8, 0.9 Hz, 1H), 7.63 (s, 1H), 6.85 (d, *J* = 7.8 Hz, 1H), 3.22 (s, 3H), 1.38 (s, 6H), 1.35 (s, 12H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 181.7, 145.5, 135.2, 135.1, 128.2, 107.5, 83.7, 44.0, 26.2, 24.9, 24.4. Carbon adjacent to boron was not observed; **^{11}B NMR** (128 MHz, $CDCl_3$): δ = 31.5; **HRMS** (ESI^+): for $C_{17}H_{25}BNO_3^+$ $[M+H]^+$ requires m/z = 302.1922, found 302.1923; **IR** (ATR, neat): ν (cm^{-1}) = 2976, 2929, 1718, 1613, 1469, 1440, 1381, 1353, 1314, 1262, 1246, 1214, 1145, 1091; **M.P.** 131-133 °C.

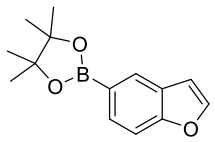
5-Fluoro-1,3,3-trimethylindolin-2-one (3.142)



To a solution of 5-fluoroindolin-2-one (378 mg, 2.5 mmol, 1.00 equiv.) in dry THF at 0 °C was added NaH (60% in mineral oil, 350 mg, 8.75 mmol, 3.50 equiv.). The resulting suspension was stirred at 0 °C for 30 minutes. MeI (498 μL, 8.00 mmol, 3.20 equiv.) was added and the mixture was stirred at 0 °C for one hour. H_2O (1 mL) was added dropwise and the mixture was allowed to warm to room temperature. The mixture was concentrated under reduced pressure to remove THF. The residue was redissolved in EtOAc, washed with water and brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford crude title compound. Flash column chromatography (*n*-hexane/EtOAc 80:20) afforded 5-fluoro-1,3,3-trimethylindolin-2-one (**3.142**, 298 mg, 1.54 mmol, 62%) as a dark red oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.98–6.91 (m, 2H), 6.75 (dd, *J* = 9.2, 4.1 Hz, 1H), 3.20 (s, 3H), 1.36 (s, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 180.9, 159.4 (d, *J* = 240.4 Hz), 138.5 (d, *J* = 1.7 Hz), 137.5 (d, *J* = 7.8 Hz), 113.7 (d, *J* = 23.5 Hz), 110.5 (d, *J* = 24.5 Hz), 108.4 (d, *J* = 8.1 Hz), 44.6, 26.3, 24.3; **^{19}F NMR** (376 MHz, $CDCl_3$): δ = -120.9 (td, *J* = 8.6, 4.1 Hz); **HRMS** (ESI^+): for $C_{11}H_{13}FNO^+$ $[M+H]^+$ requires m/z = 194.0976, found 194.0977; **IR** (ATR, neat): ν (cm^{-1}) = 3052, 2929, 1707, 1613, 1493, 1470, 1442, 1384, 1349, 1274, 1243, 1189, 1114, 1046.

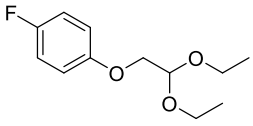
2-(Benzofuran-5-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.145-Bpin)



To an oven-dry flask with a magnetic stirrer was added B_2pin_2 (508 mg, 2.00 mmol, 1.00 equiv.), $Pd(dppf)Cl_2.CH_2Cl_2$ (49 mg, 0.06 mmol, 0.03 equiv.) and KOAc (588 mg, 6.00 mmol, 3.00 equiv). A rubber septum was added, and the flask was purged with argon. Dry, degassed toluene (10 mL) was added, followed by 5-bromobenzofuran (263 μL, 2.10 mmol, 1.05 equiv.). The mixture was heated to 80 °C and stirred at this temperature for 18 hours. After cooling to room temperature, the mixture was diluted with EtOAc and filtered through a short plug of SiO_2, eluting with EtOAc. The solvent was removed under reduced pressure to afford crude title compound. Flash column chromatography (*n*-hexane/EtOAc 95:5) afforded 2-(benzofuran-5-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**3.145-Bpin**, 156 mg, 0.64 mmol, 32% yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.11 (s, 1H), 7.76 (dd, *J* = 8.3, 1.1 Hz, 1H), 7.62 (d, *J* = 2.2 Hz, 1H), 7.50 (dt, *J* = 8.3, 0.8 Hz, 1H), 6.77 (dd, *J* = 2.2, 1.0 Hz, 1H), 1.37 (s, 12H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 157.0, 144.9, 130.7, 128.6, 127.1, 110.9, 106.6, 83.7, 24.9. Carbon adjacent to boron was not observed; **^{11}B NMR** (128 MHz, $CDCl_3$): δ = 31.1; **HRMS** (Probe EI/FI): for $C_{14}H_{17}BO_3$ $[M]^+$ requires m/z = 244.1273, found 244.1279 (M^+); **IR** (ATR, neat): ν (cm^{-1}) = 2978, 1611, 1539, 1477, 1432, 1354, 1290, 1266, 1168, 1144, 1131, 1111, 1069, 1030; **M.P.**: 64-66 °C.

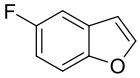
2-(4-Fluorophenoxy)acetaldehyde diethyl acetal



Based on a literature procedure,[18] to a suspension of NaH (60 wt% in mineral oil, 1.07 g, 26.8 mmol, 1.50 equiv.) in dry DMF (20 mL) was added 4-fluorophenol (2.00 g, 17.9 mmol, 1.00 equiv.) at 0 °C. The mixture was stirred at 0 °C for 30 minutes, at which time no further hydrogen evolution was observed. Bromoacetaldehyde diethyl acetal (3.37 mL, 22.4 mmol, 1.25 equiv.) was added and the mixture was heated at reflux (oil bath temperature 170 °C) for 18 hours. The mixture was allowed to cool to room temperature and was then poured into ice cold water and extracted three times with EtOAc. Combined organic extracts were washed three times with 1 M NaOH solution and three times with brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford crude title compound. Flash column chromatography (pet 40°-60°C/EtOAc 95:5 to 90:10) afforded 2-(4-fluorophenoxy)acetaldehyde diethyl acetal (4.89 g, 17.0 mmol, 95% yield) as a clear oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.99–6.92 (m, 2H), 6.89–6.83 (m, 2H), 4.81 (t, *J* = 5.2 Hz, 1H), 3.97 (d, *J* = 5.2 Hz, 2H), 3.76 (dq, *J* = 9.4, 7.1 Hz, 2H), 3.63 (dq, *J* = 9.4, 7.0 Hz, 2H), 1.24 (t, *J* = 7.1 Hz, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 157.4 (d, *J* = 238.4 Hz), 154.8 (d, *J* = 2.0 Hz), 115.8 (d, *J* = 20.8 Hz), 115.7 (d, *J* = 10.2 Hz), 100.5, 69.2, 62.6, 15.3; **^{19}F NMR** (377 MHz, $CDCl_3$): δ = -123.7 (tt, *J* = 8.4, 4.4 Hz); **MS** (ESI^+): for $C_{12}H_{17}FNaO_3^+$ $[M + Na]^+$ requires m/z = 251.1, found 251.1. The analytical data were in accordance with the literature.[18]

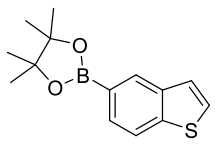
5-Fluorobenzofuran (3.145)



Based on a literature procedure,[18] to a mixture of pyrophosphoric acid (0.78 g, 4.39 mmol, 1.00 equiv.) in toluene (20 mL) was added a solution of 2-(4-fluorophenoxy)acetaldehyde diethyl acetal (1.00 g, 4.39 mmol, 1.00 equiv.) in toluene (5 mL). The mixture was heated to reflux with vigorous stirring for 2.5 hours, after which it was allowed to cool to ambient temperature. The toluene solution was decanted from the pyrophosphoric acid residue and concentrated under reduced pressure to afford crude title compound. Flash column chromatography (*n*-hexane) afforded 5-fluorobenzofuran (**3.145**, 185 mg, 1.36 mmol, 31% yield) as a pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.66 (d, *J* = 2.2 Hz, 1H), 7.43 (dd, *J* = 8.9, 4.1 Hz, 1H), 7.26 (dd, *J* = 8.5, 2.6 Hz, 1H), 7.02 (td, *J* = 9.0, 2.6 Hz, 1H), 6.75 (dd, *J* = 2.2, 0.9 Hz, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 159.2 (d, *J* = 237.9 Hz), 151.2, 146.6, 128.2 (d, *J* = 10.9 Hz), 112.0 (d, *J* = 26.5 Hz), 112.0 (d, *J* = 9.7 Hz), 106.8 (d, *J* = 3.9 Hz), 106.6 (d, *J* = 25.0 Hz); **^{19}F NMR** (377 MHz, $CDCl_3$): δ = -121.4 (td, *J* = 8.8, 4.1 Hz); **HRMS** (EI^+): for $C_8H_5FNO^+$ $[M]^+$ requires m/z = 136.0324, found 136.0320. The analytical data were in accordance with the literature.[18]

2-(Benzo[b]thiophen-5-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.147-Bpin)

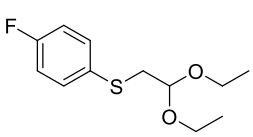


To an oven-dry flask with a magnetic stirrer was added 5-bromobenzo[b]thiophene (447 mg, 2.10 mmol, 1.05 equiv.), B_2pin_2 (508 mg, 2.00 mmol, 1.00 equiv.), $Pd(dppf)Cl_2.CH_2Cl_2$ (49 mg, 0.06 mmol, 0.03 equiv.)

and KOAc (588 mg, 6.00 mmol, 3.00 equiv.). A rubber septum was added, and the flask was purged with argon. Dry, degassed toluene (10 mL) was added. The mixture was heated to 80 °C and stirred at this temperature for 17 hours. After cooling to room temperature, the mixture was diluted with EtOAc and filtered through a short plug of SiO_2, eluting with EtOAc. The solvent was removed under reduced pressure to afford crude title compound. Flash column chromatography (pet 40°–60°C/EtOAc 98:2) afforded 2-(benzo[b]thiophen-5-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaboroane (**3.147-Bpin**, 287 mg, 1.10 mmol, 55%) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.32 (s, 1H), 7.89 (d, *J* = 8.1 Hz, 1H), 7.76 (d, *J* = 8.1 Hz, 1H), 7.42 (d, *J* = 5.4 Hz, 1H), 7.36 (d, *J* = 5.4 Hz, 1H), 1.38 (s, 12H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 142.7, 139.2, 130.7, 129.7, 126.0, 124.1, 121.8, 83.8, 24.9. Carbon adjacent to boron was not observed; **^{11}B NMR** (128 MHz, $CDCl_3$): δ = 31.2; **HRMS** (EI^+): for $C_{14}H_{17}BO_2S^+$ $[M]^+$ requires m/z = 260.1042, found 260.1040; **IR** (ATR, neat): ν (cm^{-1}) = 2977, 1600, 1509, 1441, 1417, 1353, 1330, 1310, 1283, 1259, 1214, 1190, 1143, 1081, 1047; **M.P.**: 73-75 °C.

(2,2-Diethoxyethyl)(4-fluorophenyl)sulfane

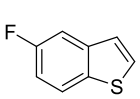


Based on a literature procedure,[18] to a suspension of NaH (60 wt% in mineral oil, 600 mg, 15.0 mmol, 1.50 equiv.) in dry DMF (10 mL) at 0 °C was added 4-fluorothiophenol (1.07 mL, 10.0 mmol, 1.00 equiv.). The mixture was stirred at 0 °C for one hour, after which it was allowed to warm to ambient temperature. Bromoacetaldehyde diethyl acetal (1.88 mL, 12.5 mmol, 1.25

equiv.) was added and the mixture was heated at reflux (oil bath temperature 170 °C) for 18 hours. The mixture was then allowed to cool to ambient temperature, poured into cold water and extracted three times with EtOAc. The combined organic phases were washed three times with 1 M NaOH and three times with brine, dried ($MgSO_4$) and concentrated under reduced pressure to afford crude title compound. Flash column chromatography (pet 40°-60°C/EtOAc 97:3 to 96:4) afforded (2,2-diethoxyethyl)(4-fluorophenyl)sulfane (1.43 g, 5.86 mmol, 59%) as a clear oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.43–7.36 (m, 2H), 7.02–6.94 (m, 2H), 4.61 (t, *J* = 5.5 Hz, 1H), 3.65 (dq, *J* = 9.1, 7.1 Hz, 2H), 3.52 (dq, *J* = 9.2, 7.1 Hz, 2H), 3.07 (d, *J* = 5.5 Hz, 2H), 1.18 (t, *J* = 7.0 Hz, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 161.8 (d, *J* = 246.4 Hz), 132.4 (d, *J* = 8.0 Hz), 131.3 (d, *J* = 3.3 Hz), 115.9 (d, *J* = 21.9 Hz), 101.8, 62.1, 38.6, 15.2; **^{19}F NMR** (376 MHz, $CDCl_3$): δ = -115.64 (tt, *J* = 8.6, 5.2 Hz); **HRMS** (ESI^+): for $C_{12}H_{17}FNaO_2S^+$ $[M+H]^+$ requires m/z = 267.0825, found 267.0825; **IR** (ATR, neat): ν (cm^{-1}) = 2976, 1590, 1491, 1444, 1372, 1343, 1294, 1226, 1157, 1123, 1091, 1057, 1014.

5-Fluorobenzo[*b*]thiophene (3.147)

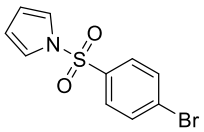


To a mixture of pyrophosphoric acid (1.49 g, 8.37 mmol, 2.00 equiv.) in toluene (20 mL) was added a solution of (2,2-diethoxyethyl)(4-fluorophenyl)sulfane (1.00 g, 4.39 mmol, 1.00 equiv.) in toluene (5 mL). The mixture was heated to reflux with vigorous stirring for 2.5 h, after which it was allowed to cool to ambient temperature. The toluene solution was decanted from the

pyrophosphoric acid residue and concentrated under reduced pressure to afford crude title compound. Flash column chromatography (*n*-pentane) afforded 5-fluorobenzo[*b*]thiophene (**3.147**, 309 mg, 2.03 mmol, 49%) as a low-melting colourless crystalline solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.80 (dd, *J* = 8.8, 4.8 Hz, 1H), 7.52 (d, *J* = 5.4 Hz, 1H), 7.49 (dd, *J* = 9.5, 2.4 Hz, 1H), 7.29 (d, *J* = 5.4 Hz, 1H), 7.11 (td, *J* = 8.8, 2.5 Hz, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 160.8 (d, *J* = 241.2 Hz), 140.6 (d, *J* = 9.5 Hz), 135.1, 128.8, 123.6 (d, *J* = 3.7 Hz), 123.5 (d, *J* = 9.1 Hz), 113.1 (d, *J* = 25.4 Hz), 109.0 (d, *J* = 22.9 Hz); **^{19}F NMR** (376 MHz, $CDCl_3$): δ = -119.3 (td, *J* = 9.1, 4.9 Hz); **HRMS** (EI^+): for $C_8H_5FS^+$ $[M]^+$ requires m/z = 152.0096; found 152.0088; **IR** (ATR, neat): ν (cm^{-1}) = 3105, 1597, 1566, 1503, 1436, 1423, 1318, 1248, 1234, 1139, 1125, 1093, 1053; **M.P.** Not determined – compound melted on attempt to transfer to melting point tube at room temperature.

1-((4-Bromophenyl)sulfonyl)-1*H*-pyrrole

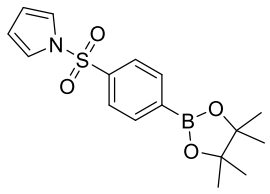


A solution of lithium bis(trimethylsilyl)amide (1M in THF, 5.50 mL, 5.50 mmol, 1.10 equiv.) was added dropwise to a solution of pyrrole (347 µL, 5.00 mmol, 1.00 equiv.) in dry THF (10 mL) at −78 °C. The mixture was stirred at this temperature for 30 minutes. A solution of 4-bromobenzenesulfonyl chloride (1.53 g, 6.00 mmol, 1.20 equiv.) in dry THF (5 mL) was added dropwise at −78 °C. The mixture was allowed to warm to ambient temperature and was stirred for 20 hours. The solvent was removed under reduced pressure. The residue was

dissolved in EtOAc and washed sequentially with 1 M aq. HCl, sat. aq. $NaHCO_3$ and brine, dried ($MgSO_4$) and concentrated under reduced pressure. Flash column chromatography (pet 40°–60°C/EtOAc 96:4) afforded 1-((4-bromophenyl)sulfonyl)-1*H*-pyrrole (738 mg, 2.58 mmol, 52%) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.71 (d, *J* = 8.7 Hz, 1H), 7.63 (d, *J* = 8.7 Hz, 1H), 7.17–7.11 (m, 1H), 6.34–6.29 (m, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 138.1, 132.7, 129.1, 128.2, 120.8, 114.1; **MS** (ESI^+): for $C_{10}H_8BrNNaO_2S^+$ $[M + Na]^+$ requires m/z = 307.9, found 308.0. The analytical data were in accordance with the literature.[19]

1-((4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)sulfonyl)-1*H*-pyrrole (3.156-Bpin)

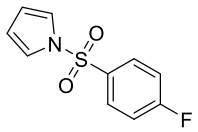


To an oven-dry flask with a magnetic stirrer was added 1-((4-bromophenyl)sulfonyl)-1*H*-pyrrole (901 mg, 3.15 mmol, 1.05 equiv.), B_2pin_2 (762 mg, 3.00 mmol, 1.00 equiv.), $Pd(dppf)Cl_2$ (66 mg, 0.09 mmol, 0.03 equiv.) and KOAc (882 mg, 9.00 mmol, 3.00 eq). A rubber septum was added, and the flask was purged with argon. Dry, degassed DMF (15 mL) was added. The mixture was heated to 80 °C and stirred at this temperature for 18 hours. After cooling to room temperature, the mixture was diluted with EtOAc and filtered through a short plug of SiO_2, eluting with EtOAc. The solvent was removed under reduced pressure to afford crude title compound. Flash column chromatography (pet 40°–60°C/EtOAc 90:10) afforded 1-((4-(4,4,5,5-tetramethyl-

1,3,2-dioxaborolan-2-yl)phenyl)sulfonyl)-1*H*-pyrrole (**3.156-Bpin**, 649 mg, 1.95 mmol, 65%) as an off-white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.83 (d, *J* = 8.0 Hz, 2H), 7.75 (d, *J* = 8.0 Hz, 2H), 7.10 – 7.05 (m, 2H), 6.22 – 6.18 (m, 2H), 1.25 (s, 12H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 141.1, 135.5, 125.7, 120.8, 113.7, 84.5, 24.8. Carbon adjacent to boron was not observed; **^{11}B NMR** (128 MHz, $CDCl_3$): δ = 30.4; **HRMS** (ESI^+): for $C_{16}H_{21}BNO_4S^+$ $[M+H]^+$ requires m/z = 334.1279, found 334.1280; **IR** (ATR, neat): ν (cm^{-1}) = 3143, 2925, 1600, 1455, 1394, 1360, 1272, 1191, 1171, 1143, 1098, 1077, 1057, 1033, 1018; **M.P.**: 114-116 °C.

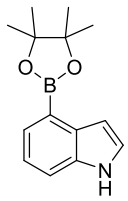
1-((4-Fluorophenyl)sulfonyl)-1*H*-pyrrole (3.156)



A solution of lithium bis(trimethylsilyl)amide (1 M in THF, 2.20 mL, 2.20 mmol, 1.10 equiv.) was added dropwise to a solution of pyrrole (139 µL, 2.00 mmol, 1.00 equiv.) in dry THF (4 mL) at −78 °C. The mixture was stirred at this temperature for 30 minutes. A solution of 4-fluorobenzenesulfonyl chloride (467 mg, 2.40 mmol, 1.20 equiv.) in dry THF (2 mL) was added dropwise at −78 °C. The mixture was allowed to warm to ambient temperature and was stirred for 20 hours. The solvent was removed under reduced pressure. The residue was dissolved in EtOAc and washed sequentially with 1M aq. HCl, sat. aq. $NaHCO_3$ and brine, dried ($MgSO_4$) and concentrated under reduced pressure. Flash column chromatography (*n*-hexane/EtOAc 95:5) afforded 1-((4-fluorophenyl)sulfonyl)-1*H*-pyrrole (**3.156**, 143 mg, 0.64 mmol, 32%) as a pale brown solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.91–7.84 (m, 2H), 7.20–7.13 (m, 4H), 6.33–6.29 (m, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 165.7 (d, *J* = 257.1 Hz), 135.2 (d, *J* = 3.3 Hz), 129.7 (d, *J* = 9.7 Hz), 120.8, 116.7 (d, *J* = 22.9 Hz), 113.9; **^{19}F NMR** (376 MHz, $CDCl_3$): δ = -102.8 (tt, *J* = 8.1, 4.9 Hz); **HRMS** (EI^+): for $C_{10}H_8FNO_2S^+$ $[M]^+$ requires m/z = 225.0260, found 225.0252; **IR** (ATR, neat): ν (cm^{-1}) = 3145, 3103, 3067, 1588, 1492, 1449, 1407, 1372, 1293, 1171, 1155, 1099, 1089, 1073, 1058, 1034, 1011; **M.P.** 95-97 °C.

4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indole (3.157-Bpin)

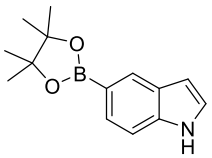


To an oven-dry flask with a magnetic stirrer was added B_2pin_2 (762 mg, 3.00 mmol, 1.00 equiv.), $Pd(dppf)Cl_2.CH_2Cl_2$ (73 mg, 0.09 mmol, 0.03 equiv.) and KOAc (882 mg, 9.00 mmol, 3.00 equiv.). A rubber septum was added, and the flask was purged with argon. Dry, degassed toluene (15 mL) was added, followed by 4-bromoindole (395 μL, 3.15 mmol, 1.05 equiv.). The mixture was heated to 80 °C and stirred at this temperature for 18 hours. After cooling to room temperature, the mixture was diluted with EtOAc and filtered through a short plug of SiO_2, eluting with EtOAc. The solvent was removed under reduced pressure to afford crude title compound. Flash column chromatography (petrol 40°C-60°C/EtOAc 90:10) afforded 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indole (**3.157-Bpin**, 595 mg, 2.45 mmol, 82% yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.20 (br s, 1H), 7.68 (d, *J* = 7.0 Hz, 1H), 7.51 (d, *J* = 8.1 Hz, 1H), 7.29–7.20 (m, 2H), 7.09 (s, 1H), 1.43 (s, 12H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 135.1, 132.5, 127.9, 124.6, 121.3, 114.0, 104.6, 83.4, 25.0. Carbon adjacent to boron

was not observed; **^{11}B NMR** (128 MHz, $CDCl_3$): δ 31.2; **MS** (ESI^+): for $C_{14}H_{19}BNO_2^+$ $[M + H]^+$ requires m/z = 244.2, found 244.2. The analytical data were in accordance with the literature.[20]

5-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indole (3.158-Bpin)

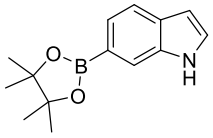


To an oven-dry flask with a magnetic stirrer was added 5-bromoindole (980 mg, 5.00 mmol, 1.05 equiv.), B_2pin_2 (1.21 g, 4.76 mmol, 1.00 equiv.), $Pd(dppf)Cl_2.CH_2Cl_2$ (122 mg, 0.15 mmol, 0.03 equiv.) and KOAc (1.47g, 15.0 mmol, 3.00 eq). A rubber septum was added, and the flask was purged with argon. Dry, degassed toluene (25 mL) was added. The mixture was heated to 80 °C and stirred at this temperature for 18 hours. After cooling to room temperature, the mixture was diluted with EtOAc and filtered through a short plug of SiO_2, eluting with EtOAc. The solvent was removed under reduced pressure to afford crude title compound. Flash column chromatography (*n*-hexane/EtOAc 85:15) afforded partially purified material, which was recrystallized from *n*-hexane to afford 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indole (**3.158-Bpin**, 573 mg, 2.36 mmol, 47% yield) as white needles.

^{1}H NMR (400 MHz, $CDCl_3$): = δ 8.24 (br s, 1H), 8.21 (s, 1H), 7.66 (d, *J* = 8.2 Hz, 1H), 7.37 (d, *J* = 8.2 Hz, 1H), 7.17 (br s, 1H), 6.57 (br s, 1H), 1.38 (s, 12H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 137.8, 128.6, 128.0, 127.6, 124.2, 110.5, 103.1, 83.4, 24.9. Carbon adjacent to boron was not observed; **^{11}B NMR** (128 MHz, $CDCl_3$): δ = 31.2; **MS** (ESI^+):

for $C_{14}H_{19}BNO_2^+$ $[M + H]^+$ requires m/z = 244.2, found 244.2. The analytical data were in accordance with the literature.[20]

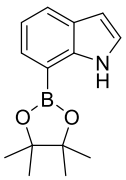
6-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indole (3.159-Bpin)



To an oven-dry flask with a magnetic stirrer was added 6-bromoindole (617 mg, 3.15 mmol, 1.05 equiv.), B_2pin_2 (762 mg, 3.00 mmol, 1.00 equiv.), $Pd(dppf)Cl_2.CH_2Cl_2$ (73 mg, 0.09 mmol, 0.03 equiv.) and KOAc (882 mg, 9.00 mmol, 3.00 equiv.). A rubber septum was added, and the flask was purged with argon. Dry, degassed toluene (15 mL) was added. The mixture was heated to 80 °C and stirred at this temperature for 18 hours. After cooling to room temperature, the mixture was diluted with EtOAc and filtered through a short plug of SiO_2, eluting with EtOAc. The solvent was removed under reduced pressure to afford crude title compound. Flash column chromatography (petrol 40°C-60°C/EtOAc 85:15) afforded 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indole (**3.159-Bpin**, 536 mg, 2.21 mmol, 74% yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.36 (br s, 1H), 7.96 (s, 1H), 7.71 (d, *J* = 7.7 Hz, 1H), 7.63 (d, *J* = 7.7 Hz, 1H), 7.24 (s, 1H), 6.59 (s, 1H), 1.43 (s, 12H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 135.5, 130.4, 125.6, 125.5, 120.0, 118.1, 102.6, 83.5, 24.9. Carbon adjacent to boron was not observed; **^{11}B NMR** (128 MHz, $CDCl_3$): δ = 29.9; **MS** (ESI^+): for $C_{14}H_{19}BNO_2^+$ $[M + H]^+$ requires m/z = 244.2, found 244.1. The analytical data were in accordance with the literature.[21]

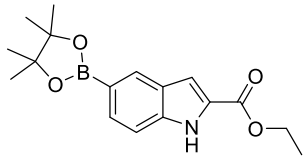
7-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indole (3.160-Bpin)



To an oven-dry flask with a magnetic stirrer was added 7-bromoindole (617 mg, 3.15 mmol, 1.05 equiv.), B_2pin_2 (762 mg, 3.00 mmol, 1.00 equiv.), $Pd(dppf)Cl_2.CH_2Cl_2$ (73 mg, 0.09 mmol, 0.03 equiv.) and KOAc (882 mg, 9.00 mmol, 3.00 equiv.). A rubber septum was added, and the flask was purged with argon. Dry, degassed toluene (15 mL) was added. The mixture was heated to 80 °C and stirred at this temperature for 18 hours. After cooling to room temperature, the mixture was diluted with EtOAc and filtered through a short plug of SiO_2, eluting with EtOAc. The solvent was removed under reduced pressure to afford crude title compound. Flash column chromatography (petrol 40°C-60°C/EtOAc 95:5) afforded 7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indole (**3.160-Bpin**, 424 mg, 1.74 mmol, 58% yield) as an off-white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.27 (br s, 1H), 7.81 (d, *J* = 7.9 Hz, 1H), 7.70 (d, *J* = 6.9 Hz, 1H), 7.29 (br s, 1H), 7.17 (t, *J* = 7.5 Hz, 1H), 6.58 (br s, 1H), 1.43 (s, 12H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 141.0, 129.2, 126.8, 124.2, 124.0, 119.3, 101.9, 83.8, 25.0. Carbon adjacent to boron was not observed; **^{11}B NMR** (128 MHz, $CDCl_3$): δ = 31.0; **MS** (ESI^+): for $C_{14}H_{19}BNO_2^+$ $[M + H]^+$ requires m/z = 244.2, found 244.1. The analytical data were in accordance with the literature.[22]

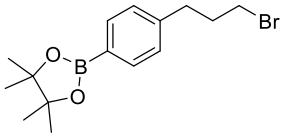
Ethyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indole-2-carboxylate (3.161-Bpin)



To an oven-dry flask with a magnetic stirrer was added ethyl 5-bromo-1*H*-indole-2-carboxylate (844 mg, 3.15 mmol, 1.05 equiv.), B_2pin_2 (762 mg, 3.00 mmol, 1.00 equiv.), $Pd(dppf)Cl_2.CH_2Cl_2$ (73 mg, 0.09 mmol, 0.03 equiv.) and KOAc (882 mg, 9.00 mmol, 3.00 equiv.). A rubber septum was added, and the flask was purged with argon. Dry, degassed toluene (15 mL) was added. The mixture was heated to 80 °C and stirred at this temperature for 18 hours. After cooling to room temperature, the mixture was diluted with EtOAc and filtered through a short plug of SiO_2, eluting with EtOAc. The solvent was removed under reduced pressure to afford crude title compound. Flash column chromatography (petrol 40°C-60°C/EtOAc 88:12) afforded ethyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indole-2-carboxylate (**3.161-Bpin**, 791 mg, 2.51 mmol, 84% yield) as an off-white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.01 (br s, 1H), 8.22 (d, *J* = 0.7 Hz, 1H), 7.75 (dd, *J* = 8.3, 0.9 Hz, 1H), 7.41 (d, *J* = 8.3 Hz, 1H), 7.23 (dd, *J* = 2.0, 0.9 Hz, 1H), 4.42 (q, *J* = 7.1 Hz, 2H), 1.42 (t, *J* = 7.1 Hz, 3H), 1.37 (s, 12H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 162.0, 138.7, 131.1, 130.7, 127.7, 127.3, 111.2, 109.2, 83.7, 61.1, 24.9, 14.4; **^{11}B NMR** (128 MHz, $CDCl_3$): δ = 31.2; **HRMS** (ESI^+): for $C_{17}H_{23}BNO_4^+$ $[M+H]^+$ requires m/z = 316.1715, found 316.1717; **IR** (ATR, neat): ν (cm^{-1}) = 3308, 2978, 2932, 1691, 1615, 1574, 1540, 1479, 1379, 1358, 1329, 1301, 1274, 1251, 1194, 1146, 1069, 1024**; M.P.**: 141-143 °C.

2-(4-(3-Bromopropyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane



To a suspension of $LiAlH_4$ (9.12 g, 240 mmol, 3.00 equiv.) in dry Et_2O (800 mL) was added 4-bromocinnamic acid (18.16 g, 80.0 mmol, 1.00 equiv.) in 500 mg portions over 35 minutes under a N_2 blanket. The mixture was stirred at room temperature for a further 90 minutes, then cooled to 0 °C. Cold H_2O (10 mL) was added slowly over 20 minutes; gas was evolved. NaOH (15% aq. solution, 10 mL) was added, followed by a further portion of H_2O (30 mL). The mixture was allowed to warm to room temperature and was stirred for 15 minutes. $MgSO_4$ was added and the suspension was stirred for 10 minutes. The mixture was filtered through Celite, eluting with Et_2O. The filtrate was concentrated under reduced pressure to afford crude 3-(4-bromophenyl)propan-1-ol (15.59 g) as a pale yellow oil, which was taken on without further purification.

To an oven-dry flask with a magnetic stirrer was added B_2pin_2 (17.42 g, 68.6 mmol, 0.95 equiv.), $Pd(dppf)Cl_2.CH_2Cl_2$ (1.77 g, 2.17 mmol, 0.03 equiv.) and KOAc (21.23 g, 217 mmol, 3.00 equiv.). A rubber septum was added, and the flask was purged with argon. Dry, degassed toluene (300 mL) was added. A solution of crude 3-(4-bromophenyl)propan-1-ol (15.54 g) in dry degassed toluene (60 mL) was added. The mixture was heated to 80 °C and stirred at this temperature for 8 hours. After cooling to room temperature, the mixture was diluted with EtOAc and filtered through a short plug of SiO_2, eluting with EtOAc. The filtrate was concentrated to afford crude 3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)propan-1-ol (28.12 g) as a yellow oil, which was taken on without further purification.

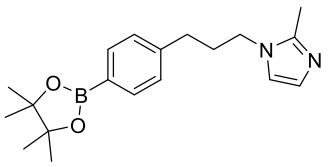
The crude 3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)propan-1-ol (28.07 g) was redissolved in EtOH (400 mL). Pd/C (10%, 200 mg) was added. The mixture was evacuated until bubbles were observed, then back-filled with H_2. This process was repeated twice more. The mixture was stirred at room temperature under a balloon of H_2 for 3 hours. The solvent was then removed under reduced pressure. The residue was suspended in EtOAc and filtered through a plug of Celite, eluting with EtOAc. The filtrate was concentrated under reduced pressure. Flash column chromatography (petrol 40°C-60°C/EtOAc 70:30) afforded partially-purified 3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)propan-1-ol (20.41 g) as a yellow oil, which was taken on without further purification.

To a solution of partially-purified 3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)propan-1-ol (20.41 g) in dry CH_2Cl_2 (400 mL) at 0 °C was added PPh_3 (30.6 g, 117 mmol, 1.50 equiv.) followed by NBS (20.8 g, 117 mmol, 1.50 equiv.). The mixture was stirred at 0 °C for one hour. The mixture was allowed to warm to room temperature and the solvent was removed under reduced pressure. Flash column chromatography (petrol 40°C-60°C/EtOAc 96:4) afforded 2-(4-(3-bromopropyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (11.55 g, 35.5 mmol, 44% over four steps) as a clear oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.75 (d, *J* = 8.0 Hz, 1H), 7.22 (d, *J* = 8.0 Hz, 1H), 3.38 (t, *J* = 6.6 Hz, 1H), 2.79 (t, *J* = 7.4 Hz, 1H), 2.17 (dq, *J* = 13.7, 6.7 Hz, 1H), 1.34 (s, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 143.9, 135.0, 128.0, 83.7, 34.2, 34.0, 33.0, 24.8. Carbon adjacent to boron was not observed; **^{11}B NMR** (128 MHz, $CDCl_3$): δ = 30.2; **HRMS**

(EI): for $C_{15}H_{22}BBrO_2^+$ $[M]^+$ requires m/z = 324.0896; found 324.0907; **IR** (ATR, neat) $\tilde{\nu}$ (cm^{-1}) = 2979, 1612, 1518, 1398, 1359, 1320, 1144, 1089, 1022, 962, 859, 658.

2-Methyl-1-(3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)propyl)-1H-imidazole (3.165-Bpin)

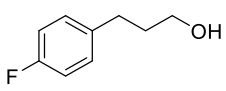


A suspension of 2-methylimidazole (821 mg, 10.0 mmol, 1.00 equiv.), 2-(4-(3-bromopropyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.25 g, 10.0 mmol, 1.00 equiv.) and K_2CO_3 (4.14 g, 30.0 mmol, 3.00 equiv.) in dry DMF (20 mL) was heated at 80 °C for 2 hours. The mixture was allowed to cool to room temperature. The mixture was diluted with EtOAc (100 mL) and H_2O (100 mL) and the phases were separated. The organic phase was washed with brine (3 x 100 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. Flash column chromatography (CH_2Cl_2/MeOH 96:4) afforded 2-methyl-1-(3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)propyl)-1H-imidazole (**3.165-Bpin**, 2.61 mmol, 26%) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.75 (d, *J* = 8.0 Hz, 2H), 7.17 (d, *J* = 8.0 Hz, 2H), 6.91 (d, *J* = 1.2 Hz, 1H), 6.80 (d, *J* = 1.3 Hz, 1H), 3.81 (t, *J* = 7.2 Hz, 2H), 2.65 (t, *J* = 7.6 Hz, 2H), 2.32 (s, 3H), 2.12 – 2.02 (m, 2H), 1.34 (s, 12H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 144.4, 143.7, 135.1, 127.7, 127.2, 118.9, 83.8, 45.2, 32.7, 31.7, 24.8, 13.0. Carbon adjacent to boron was not observed; **^{11}B NMR** (128 MHz, $CDCl_3$) δ = 31.3; **HRMS** (ESI^+): for $C_{19}H_{28}BN_2O_2^+$ $[M+H]^+$ requires m/z = 327.2238; found 327.2238; **IR** (ATR, neat) $\tilde{\nu}$

(cm^{-1}) = 2980, 1612, 1522, 1398, 1360, 1322, 1275, 1145, 1090, 1021, 963, 859, 659; **M.P.**: 105-108 °C.

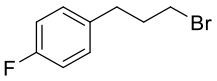
3-(4-Fluorophenyl)propan-1-ol



To a suspension of $LiAlH_4$ (5.70 g, 150 mmol, 3.00 equiv.) in dry Et_2O (250 mL) was added a suspension of 4-fluorocinnamic acid (8.30 g, 50.0 mmol, 1.00 equiv.) in dry Et_2O (250 mL) and dry CH_2Cl_2 (70 mL) over one hour. The mixture was stirred at room temperature for 3 hours, then cooled to 0 °C. Cold H_2O (6.0 mL) was added slowly over 20 minutes; gas was evolved. NaOH (15% aq. solution, 6.0 mL) was added, followed by a further portion of H_2O (18 mL). The mixture was allowed to warm to room temperature and was stirred for 15 minutes. $MgSO_4$ was added and the suspension was stirred for 5 minutes. The mixture was filtered through Celite, eluting with Et_2O. All volatiles were removed under reduced pressure to afford a pale yellow oil, which was redissolved in EtOH (200 mL). Pd/C (10%, 1.00 g) was added. The mixture was evacuated until bubbles were observed, then back-filled with H_2. This process was repeated twice more. The mixture was stirred at room temperature under a balloon of H_2 for 3 hours. The solvent was then removed under reduced pressure. The residue was suspended in EtOAc and filtered through a plug of Celite, eluting with EtOAc. The filtrate was concentrated under reduced pressure. Flash column chromatography (petrol 40°C-60°C/EtOAc 70:30) afforded 3-(4-fluorophenyl)propan-1-ol (5.61 g, 36.4 mmol, 73% over two steps) as a clear oil.

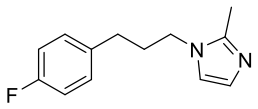
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.18 – 7.11 (m, 2H), 7.00 – 6.93 (m, 2H), 3.66 (t, *J* = 6.4 Hz, 2H), 2.74 – 2.64 (m, 2H), 1.92 – 1.81 (m, 2H), 1.56 (s, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 161.2 (d, *J* = 243.3 Hz), 137.4 (d, *J* = 3.2 Hz), 129.7 (d, *J* = 7.7 Hz), 115.1 (d, *J* = 21.1 Hz), 63.0 (s), 34.3 (s), 31.2 (s); **^{19}F NMR** (376 MHz, $CDCl_3$): δ = -117.68 – -117.80 (m). The analytical data were in accordance with the literature values. **HRMS** (EI): for $C_9H_{11}FO^+$ $[M]^+$ requires m/z = 154.0794; found 154.0798.[23]

1-(3-Bromopropyl)-4-fluorobenzene



To a solution of 3-(4-fluorophenyl)propan-1-ol (2.31 g, 15.0 mmol, 1.00 equiv.) in dry CH_2Cl_2 (75 mL) at 0 °C was added PPh_3 (5.90 g, 22.5 mmol, 1.50 equiv.) followed by NBS (4.01 g, 22.5 mmol, 1.50 equiv.). The mixture was stirred at 0 °C for one hour. The mixture was allowed to warm to room temperature and the solvent was removed under reduced pressure. Flash column chromatography (petrol 40°C-60°C/EtOAc 99.5:0.5) afforded 1-(3-bromopropyl)-4-fluorobenzene (2.79 g, 12.6 mmol, 84%) as a clear oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.19 – 7.12 (m, 2H), 7.02 – 6.94 (m, 2H), 3.38 (t, *J* = 6.5 Hz, 2H), 2.76 (t, *J* = 7.3 Hz, 2H), 2.18 – 2.10 (m, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 161.4 (d, *J* = 243.9 Hz), 136.1 (d, *J* = 3.2 Hz), 129.9 (d, *J* = 7.8 Hz), 115.2 (d, *J* = 21.2 Hz), 34.2 (s), 33.1 (s), 32.8 (s); **^{19}F NMR** (376 MHz, $CDCl_3$): = δ -117.12 – -117.23 (m); **HRMS** (EI): for $C_9H_{10}BrF^+$ $[M]^+$ requires m/z = 215.9950; found 215.9961; **IR** (ATR, neat) $\tilde{\nu}$ (cm^{-1}) = 2940, 1601, 1509, 1221, 1158, 1092, 830, 819.

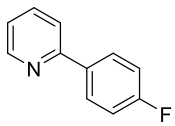
1-(3-(4-Fluorophenyl)propyl)-2-methyl-1H-imidazole (3.165)



A suspension of 2-methylimidazole (164 mg, 2.00 mmol, 1.00 equiv.), 1-(3-bromopropyl)-4-fluorobenzene (343 mg, 2.00 mmol, 1.00 equiv.) and K_2CO_3 (828 mg, 6.00 mmol, 3.00 equiv.) in dry DMF (4 mL) was heated at 80 °C for 2 hours. The mixture was allowed to cool to room temperature. The mixture was diluted with EtOAc (30 mL) and H_2O (30 mL) and the phases were separated. The organic phase was washed with brine (3 x 40 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. Flash column chromatography (CH_2Cl_2/MeOH 97:3) afforded 1-(3-(4-fluorophenyl)propyl)-2-methyl-1H-imidazole (**3.165**, 114 mg, 0.522 mmol, 26%) as a pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.13 – 7.06 (m, 2H), 7.01 – 6.94 (m, 2H), 6.91 (s, 1H), 6.80 (s, 1H), 3.81 (t, *J* = 7.2 Hz, 2H), 2.63 – 2.56 (m, 2H), 2.31 (s, 3H), 2.08 – 1.98 (m, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 161.4 (d, *J* = 244.2 Hz), 144.4 (s), 136.0 (d, *J* = 3.3 Hz), 129.6 (d, *J* = 7.8 Hz), 127.2 (s), 118.8 (s), 115.3 (d, *J* = 21.2 Hz), 45.1 (s), 32.0 (s), 31.7 (s), 13.0 (s); **^{19}F NMR** (376 MHz, $CDCl_3$): δ = -116.81 – -116.92 (m); **HRMS** (ESI^+): for $C_{13}H16FN_2^+$ $[M+H]^+$ requires m/z = 219.1292; found 219.1292; **IR** (ATR, neat) $\tilde{\nu}$ (cm^{-1}) = 3364, 2948, 1601, 1509, 1423, 1279, 1221, 1158, 823, 733, 678.

2-(4-Fluorophenyl)pyridine (3.172)

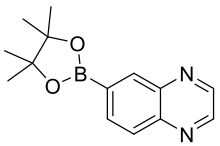


Based on a literature procedure,[24] to a mixture of 4-fluorophenylboronic acid (420 mg, 3.00 mmol, 1.50 equiv.), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol, 0.015 equiv.) and K_2CO_3 (552 mg, 4.00 mmol, 2.00 equiv.) in

EtOH/H_2O (3:1, 32 mL) was added 2-bromopyridine (191 μL, 2.00 mmol, 1.00 equiv.). The mixture was stirred at 80 °C for one hour. The mixture was allowed to cool to room temperature. Brine was added and the mixture was extracted three times with EtOAc. Combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. Flash column chromatography (*n*-hexane/EtOAc 90:10) afforded 2-(4-fluorophenyl)pyridine (**3.172**, 81 mg (0.47 mmol, 24%) as a crystalline white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.68 (d, *J* = 4.6 Hz, 1H), 8.02 – 7.95 (m, 2H), 7.75 (td, *J* = 7.8, 1.7 Hz, 1H), 7.68 (d, *J* = 7.9 Hz, 1H), 7.23 (dd, *J* = 6.7, 5.4 Hz, 1H), 7.19 – 7.12 (m, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 163.6 (d, *J* = 248.4 Hz), 156.5, 149.6, 136.9, 135.5 (d, *J* = 3.1 Hz), 128.7 (d, *J* = 8.3 Hz), 122.0, 120.2, 115.7 (d, *J* = 21.6 Hz); **^{19}F NMR** (376 MHz, $CDCl_3$): δ = -113.1 – -113.2 (m); **MS** (ESI^+): for $C_{11}H_9FN^+$ $[M + H]^+$ requires m/z = 174.1, found 174.1. The analytical data were in accordance with the literature.[25]

6-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)quinoxaline (3.182-Bpin)

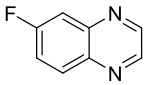


To an oven-dry flask with a magnetic stirrer was added 6-bromoquinoxaline (437 mg, 2.10 mmol, 1.05 equiv.), B_2pin_2 (508 mg, 2.00 mmol, 1.00 equiv.), $Pd(dppf)Cl_2.CH_2Cl_2$ (49 mg, 0.06 mmol, 0.03 equiv.) and KOAc (588 mg, 6.00 mmol, 3.00 equiv.). A rubber septum was added, and the flask was purged with argon. Dry, degassed toluene (10 mL) was added. The mixture was heated to 80 °C and stirred at this temperature for 18 hours. After cooling to

room temperature, the mixture was diluted with EtOAc and filtered through a short plug of SiO_2, eluting with EtOAc. The solvent was removed under reduced pressure to afford crude title compound. Flash column chromatography (petrol 40°C-60°C/EtOAc 70:30) afforded 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinoxaline (**3.182-Bpin**, 296 mg, 1.16 mmol, 58% yield) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.86 (d, *J* = 1.8 Hz, 1H), 8.85 (d, *J* = 1.8 Hz, 1H), 8.59 (s, 1H), 8.13 (dd, *J* = 8.4, 1.3 Hz, 1H), 8.07 (d, *J* = 8.4 Hz, 1H), 1.39 (s, 12H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 145.6, 145.1, 144.5, 142.5, 137.4, 134.8, 128.5, 84.4, 24.9. Carbon adjacent to boron was not observed; **^{11}B NMR** (128 MHz, $CDCl_3$): δ = 30.9; **MS** (ESI^+): for $C_{14}H_{18}BN_2O_2^+$ $[M + H]^+$ requires m/z =257.1, found 257.1. The analytical data were in accordance with the literature.[26]

6-Fluoroquinoxaline (3.182)



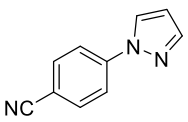
To a solution of 4-fluorobenzene-1,2-diamine (630 mg, 5.0 mmol, 1.00 equiv.) in MeOH (25 mL) was added aqueous glyoxal solution (40%, 1.43 mL, 12.5 mmol, 2.5 equiv.). The mixture was stirred at room temperature for 20 hours, after which the solvent was removed under reduced pressure to afford crude title compound. Flash column chromatography (CH_2Cl_2/EtOAc 99:1) afforded 6-fluoroquinoxaline (**3.182**, 168 mg, 1.14 mmol, 23% yield) as a pale brown crystalline solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.85 (d, *J* = 1.7 Hz, 1H), 8.82 (d, *J* = 1.7 Hz, 1H), 8.12 (dd, *J* = 9.2, 5.7 Hz, 1H), 7.74 (dd, *J* = 9.1, 2.8 Hz, 1H), 7.57 (ddd, *J* = 9.2, 8.2, 2.8 Hz,

1H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 162.7 (d, *J* = 252.7 Hz), 145.7, 144.3 (d, *J* = 3.1 Hz), 143.8 (d, *J* = 13.1 Hz), 140.3, 131.7 (d, *J* = 10.0 Hz), 120.6 (d, *J* = 26.1 Hz), 113.0 (d, *J* = 21.5 Hz); **^{19}F NMR** (376 MHz, $CDCl_3$): δ = -107.7 (td, *J* = 8.5, 5.8 Hz); **MS** (ESI^+): for $C_8H_6FN_2^+$ $[M + H]^+$ requires m/z = 149.0, found 149.0. The analytical data were in accordance with the literature.[26]

4.3.3 C–N Coupling Product 3.52

4-(1*H*-Pyrazol-1-yl)benzonitrile (3.52)



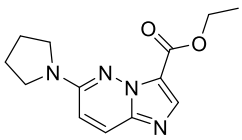
Based on a literature procedure,[27] suspension of 4-fluorobenzonitrile (605 mg, 5.00 mmol, 1.00 equiv.), pyrazole (408 mg, 6.00 mmol, 1.20 equiv.) and K_2CO_3 (1.73 g, 12.5 mmol, 2.50 equiv.) in dry DMSO (10 mL) was heated at 120 °C for 18 hours. The mixture was allowed to cool to room temperature. The mixture was transferred to a separating funnel and diluted with EtOAc (100 mL) and water (100 mL). The phases were separated and the organic phase was washed with brine (3 x 100 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. Flash column chromatography (pet 40°-60°C/EtOAc 75:25) afforded 4-(1*H*-pyrazol-1-yl)benzonitrile (**3.52**, 737 mg, 4.36 mmol, 87%) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.99 (d, *J* = 2.6 Hz, 1H), 7.86 – 7.81 (m, 2H), 7.77 (d, *J* = 1.5 Hz, 1H), 7.76 – 7.72 (m, 2H), 6.53 (dd, *J* = 2.4, 1.9 Hz, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 142.9, 142.4, 133.6, 126.8, 118.9, 118.4, 109.6, 109.0; **MS** (ESI^+) for $C_{10}H_8N_3^+$

[M+H]$^+$ requires m/z = 170.1, found 170.2. The analytical data were in accordance with the literature values.[28]

4.3.4 IPMICF10

Ethyl 6-(pyrrolidin-1-yl)imidazo[1,2-*b*]pyridazine-3-carboxylate (3.199)

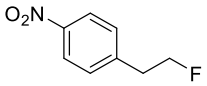


Modifying a literature procedure,[29] to a suspension of ethyl 6-chloroimidazo[1,2-*b*]pyridazine-3-carboxylate (451 mg, 2.00 mmol, 1.00 equiv.) and potassium fluoride (348 mg, 6.00 mmol, 3.00 equiv.) in dry DMSO (4 mL) was added pyrrolidine (200 μL, 2.40 mmol, 1.20 equiv.). The mixture was heated at 100 °C for 16 hours. The mixture was allowed to cool to room temperature. EtOAc (20 mL) and H_2O (20 mL) were added and the phases were separated. The aqueous phase was extracted with EtOAc (2 x 20 mL). The combined organic phases were washed with brine (3 x 50 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford crude title compound. Flash column chromatography (pet 40°-60°C/EtOAc/Et_3N 50:49:1 to 20:79:1) afforded ethyl 6-(pyrrolidin-1-yl)imidazo[1,2-*b*]pyridazine-3-carboxylate (**3.199**, 473 mg, 1.82 mmol, 91%) as a beige solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.10 (s, 1H), 7.71 (d, *J* = 9.8 Hz, 1H), 6.71 (d, *J* = 9.8 Hz, 1H), 4.39 (q, *J* = 7.1 Hz, 2H), 3.59 – 3.51 (m, 4H), 2.08 – 2.00 (m, 4H), 1.40 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 159.3, 153.2, 139.3, 138.6, 125.7, 119.4, 111.6, 60.2, 47.0, 25.4, 14.4; **HRMS** (NH_3 CI) for $C_{13}H_{16}N_4O_2^+$ [M+H]$^+$ requires m/z =

261.1346, found 261.1353; **IR** (ATR, neat): ν (cm^{-1}) = 3108, 3037, 2963, 2859, 1678, 1611, 1558, 1512, 1473, 1458, 1426, 1309, 1270, 1199, 1125, 1112, 1055, 1019, 906, 817, 763; **M.P.**: 134-136 °C.

1-(2-Fluoroethyl)-4-nitrobenzene (3.202)

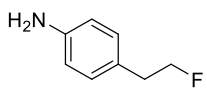


Based on a literature procedure,[30] DAST (5.88 mL, 44.9 mmol, 1.5 equiv.) was added at 0 °C to a solution of 2-(4-nitrophenyl)ethanol (**3.201**, 5.00 g, 29.9 mmol, 1.00 equiv.) in CH_2Cl_2 (125 mL). The mixture was allowed to warm to room temperature and stirred for 17 hours. The remaining DAST was quenched by careful addition of aqueous Na_2CO_3 solution (sat., 100 mL). The mixture was stirred at room temperature for 5 minutes. The mixture was transferred to a separating funnel containing $CHCl_3$ (500 mL), H_2O (300 mL) and aqueous Na_2CO_3 solution (sat., 400 mL). The phases were separated. The organic phase was washed with brine (500 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford crude title compound. Flash column chromatography (pet 40°-60°C/EtOAc 90:10 to 85:15) afforded 1-(2-fluoroethyl)-4-nitrobenzene (**3.202**, 4.20 g, 24.9 mmol, 83%) as a pale yellow crystalline solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.18 (d, *J* = 8.7 Hz, 2H), 7.41 (d, *J* = 8.6 Hz, 2H), 4.68 (dt, *J* = 46.9, 6.0 Hz, 2H), 3.12 (dt, *J* = 25.7, 6.0 Hz, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 146.9, 145.1 (d, *J* = 4.0 Hz), 129.8, 123.7, 83.0 (d, *J* = 170.2 Hz), 36.7 (d, *J* = 20.6 Hz); **^{19}F NMR** (376 MHz, $CDCl_3$): δ = -217.0 (tt, *J* = 46.9, 25.7 Hz); **HRMS** (NH_3 CI^+) for

$C_8H_8FNO_2^+$ [M+H]$^+$ requires m/z = 170.0612, found 170.0617. The analytical data were in accordance with the literature.[30]

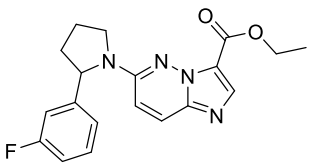
4-(2-Fluoroethyl)aniline (3.203)



Based on a literature procedure,[30] a suspension of 1-(2-fluoroethyl)-4-nitrobenzene (**3.202**, 3.38 g, 20.0 mmol, 1.00 equiv.) and 10% Pd/C (750 mg) in EtOH (200 mL) was stirred under an atmosphere of H_2 (balloon) for 4 hours. All volatiles were then removed under reduced pressure. EtOAc was added to the residue, which was filtered through a plug of Celite, eluting with EtOAc. The mixture was concentrated under reduced pressure to afford crude title compound as a brown oil. Flash column chromatography (pet 40°-60°/EtOAc 80:20) afforded 4-(2-fluoroethyl)aniline (**3.203**, 1.89 g, 13.6 mmol, 68%) as a pale orange oil which turned brown on standing.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.05 – 7.00 (m, 2H), 6.68 – 6.63 (m, 2H), 4.57 (dt, *J* = 47.2, 6.8 Hz, 2H), 3.45 (br. s, 2H), 2.92 (dt, *J* = 22.2, 6.8 Hz, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 145.0, 129.8, 126.8 (d, *J* = 7.3 Hz), 115.3, 84.5 (d, *J* = 168.7 Hz), 36.0 (d, *J* = 20.2 Hz); **^{19}F NMR** (377 MHz, $CDCl_3$): δ = -214.5 (tt, *J* = 47.2, 22.2 Hz); **HRMS** (ESI$^+$): for $C_8H_{11}NF^+$ [M+H]$^+$ requires m/z = 140.0870, found 140.0868. The analytical data were in accordance with the literature.[30]

Ethyl 6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-*b*]pyridazine-3-carboxylate (3.206)

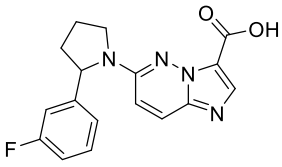


Based on a literature procedure,[29] a stirred suspension of ethyl 6-chloroimidazo[1,2-*b*]pyridazine-3-carboxylate (630 mg, 2.79 mmol, 1.00 equiv.), 2-(3-fluorophenyl)pyrrolidine (553 mg, 3.35 mmol, 1.20 equiv.) and KF (485 mg, 8.37 mmol, 3.00 equiv.) in dry DMSO (4 mL) was heated at 100 °C for 20 hours. The mixture was allowed to cool to room temperature. EtOAc (25 mL) and H_2O (25 mL) were added and the phases were separated. The aqueous phase was extracted with EtOAc (2 x 25 mL). The combined organic phases were washed with brine (3 x 50 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford crude title compound. Flash column chromatography (pet 40°-60°C/EtOAc/Et_3N 19:80:1) afforded ethyl 6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-*b*]pyridazine-3-carboxylate (**3.206**, 572 mg, 1.62 mmol, 58%) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.11 (s, 1H), 7.59 (d, *J* = 9.9 Hz, 1H), 7.31 – 7.23 (m, 1H), 7.01 (d, *J* = 7.7 Hz, 1H), 6.97 – 6.88 (m, 2H), 6.47 (d, *J* = 9.9 Hz, 1H), 5.03 – 4.94 (m, 1H), 4.39 (q, *J* = 7.1 Hz, 2H), 3.98 (ddd, *J* = 10.9, 7.2, 4.1 Hz, 1H), 3.86 – 3.76 (m, 1H), 2.55 – 2.41 (m, 1H), 2.14 – 1.96 (m, 3H), 1.39 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 163.1 (d, *J* = 246.9 Hz), 159.2, 152.9, 145.9 (d, *J* = 6.3 Hz), 139.3, 138.8, 130.4 (d, *J* = 8.2 Hz), 125.7, 121.3 (d, *J* = 2.8 Hz), 119.5 (s), 114.2 (d, *J* = 21.2 Hz), 112.7 (d, *J* = 22.0 Hz), 111.8, 61.9 (d, *J* = 1.6 Hz), 60.2, 48.5, 36.0, 22.8, 14.4; **^{19}F NMR** (376 MHz, $CDCl_3$): δ = -112.1 – -112.4 (m); **MS** (ESI^+) for $C_{19}H_{20}FN_4O_2^+$ $[M+H]^+$ requires

m/z = 355.2, found 355.2. The analytical data were in accordance with the literature.[29]

6-(2-(3-Fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-*b*]pyridazine-3-carboxylic acid (3.207)

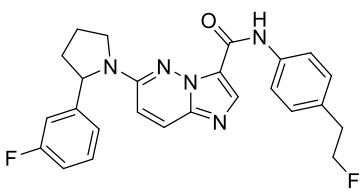


Based on a literature procedure,[29] to a solution of ethyl 6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-*b*]pyridazine-3-carboxylate (**3.206**, 529 mg, 1.49 mmol, 1.00 equiv.) in EtOH (15 mL) and H_2O (1 mL) was added powdered KOH (417 mg, 7.45 mmol, 5.00 eq.). The mixture was stirred at room temperature for 3 hours. The solvent was removed under reduced pressure and the residue was re-dissolved in H_2O (5 mL). 5M aq. HCl was added dropwise until pH 5-6. The aqueous phase was extracted with EtOAc (5 x 10 mL). The combined organic phases were washed with brine (40 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford 6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-*b*]pyridazine-3-carboxylic acid (**3.207**, 140 mg, 0.43 mmol, 29%) as an off-white solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.01 (s, 1H), 7.89 (d, *J* = 9.9 Hz, 1H), 7.39 – 7.31 (m, 1H), 7.19 – 7.09 (m, 2H), 7.08 – 7.01 (m, 1H), 6.80 (d, *J* = 8.7 Hz, 1H), 5.16 (dd, *J* = 7.8, 2.0 Hz, 1H), 3.97 – 3.86 (m, 1H), 3.69 – 3.60 (m, 1H), 2.48 – 2.38 (m, 1H), 2.06 – 1.94 (m, 2H), 1.91 – 1.82 (m, 1H); **^{13}C NMR** (101 MHz, DMSO-d_6): δ = 162.3 (d, *J* = 243.7 Hz), 159.3, 152.3, 146.7 (d, *J* = 6.5 Hz), 138.6, 138.1, 130.5 (d, *J* = 8.4 Hz), 126.1,

121.9 (d, *J* = 2.1 Hz), 119.0, 113.8 (d, *J* = 21.1 Hz), 113.0 (d, *J* = 21.8 Hz), 112.8, 61.1, 48.3, 35.2, 22.6; **^{19}F NMR** (376 MHz, DMSO-d_6): δ = -113.0 (br. s); **MS** (ESI^+) for $C_{17}H_{16}FN_4O_2^+$ $[M+H]^+$ requires m/z = 327.1, found 327.2. The analytical data were in accordance with the literature.[29]

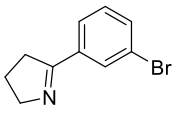
***N*-(4-(2-Fluoroethyl)phenyl)-6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-*b*]pyridazine-3-carboxamide (3.2)**



Based on a literature procedure,[29] to a solution of 6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-*b*]pyridazine-3-carboxylic acid (**3.207**, 70 mg, 0.21 mmol, 1.0 equiv.) in dry DMF (3 mL) was added DIPEA (92 μL, 0.53 mmol, 2.5 equiv.). To this was added a solution of HATU (80 mg, 0.21 mmol, 1.0 equiv.) in dry DMF (1 mL), followed by a solution of 4-(2-fluoroethyl)aniline (**3.203**, 35 mg, 0.25 mmol, 1.2 equiv.) in dry DMF (1 mL). The mixture was stirred at room temperature for 16 hours. The mixture was transferred to a separating funnel and diluted with EtOAc (25 mL), then washed with brine (3 x 30 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford crude title compound. Flash column chromatography (CH_2Cl_2/MeOH/Et_3N 98:2:0.1) afforded *N*-(4-(2-fluoroethyl)phenyl)-6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-*b*]pyridazine-3-carboxamide (**3.2**, 85 mg, 0.19 mmol, 90%) as a white solid. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 10.54 (br. s, 1H), 8.27 (s, 1H), 7.66 (d, *J* = 9.8 Hz, 1H), 7.58 – 7.42 (m, 2H), 7.32 – 7.25 (m, 1H), 7.21 (d, *J* = 8.3 Hz, 2H), 7.03 – 6.93 (m, 2H), 6.90 (d,

J = 9.6 Hz, 1H), 6.51 (d, *J* = 9.5 Hz, 1H), 5.08 (d, *J* = 7.9 Hz, 1H), 4.63 (dt, *J* = 47.1, 6.5 Hz, 2H), 4.01 – 3.92 (m, 1H), 3.81 – 3.72 (m, 1H), 3.00 (dt, *J* = 23.5, 6.5 Hz, 2H), 2.67 – 2.48 (m, 1H), 2.22 – 2.04 (m, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 163.2 (d, *J* = 247.6 Hz), 157.1, 152.0, 144.8 (d, *J* = 6.3 Hz), 137.9, 136.5, 133.0 (d, *J* = 6.1 Hz), 130.7 (d, *J* = 8.3 Hz), 129.5, 127.0, 122.4, 121.1 (d, *J* = 2.8 Hz), 120.5, 114.6 (d, *J* = 21.2 Hz), 112.6 (d, *J* = 22.1 Hz), 110.9, 84.1 (d, *J* = 169.0 Hz), 62.0, 48.6, 36.4 (d, *J* = 20.3 Hz), 35.8, 22.7; **^{19}F NMR** (376 MHz, $CDCl_3$): δ = -111.5 – -111.7 (m), -215.39 (tt, *J* = 47.1, 23.5 Hz); **MS** (ESI^+) for $C_{25}H_{24}F_2N_5O^+$ $[M+H]^+$ requires m/z = 448.2, found 448.2. The analytical data were in accordance with the literature.[29]

5-(3-Bromophenyl)-3,4-dihydro-2*H*-pyrrole (3.209)

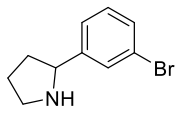


Based on a literature procedure,[31] a stirred solution of 2-pyrrolidinone (19.0 mL, 250 mmol, 1.00 equiv.) and Et_3N (36.6 mL, 263 mmol, 1.05 eq.) in Et_2O (500 mL) was cooled to 0 °C under argon. TMSCl (33.3 mL, 263 mmol, 1.05 eq.) was added. The mixture was heated to reflux and stirred for 30 minutes. The mixture was allowed to cool to room temperature and was then filtered under argon into a second flask. The solid in the original flask was washed with Et_2O (3 x 50 mL) and the washings were added to the second flask. The solution in the second flask was cooled to -30 °C under argon. A solution of 1,3-dibromobenzene (30.2 mL, 250 mmol, 1.00 equiv.) in Et_2O (200 mL) was cooled to -78 °C under argon. *n*-BuLi (2.5 M solution in hexanes, 100 mL, 250 mmol, 1.00 eq.) was added *via* canula. The solution was stirred at -78 °C for 10 minutes. This

aryllithium solution was added *via* canula to the stirred solution in the second flask at -30 °C. This solution was then allowed to warm to room temperature. The solution was heated to reflux and stirred for 3 hours. The solution was allowed to cool to room temperature. The reaction was quenched by addition of aqueous HCl (1 M, 800 mL) and was stirred at room temperature for 5 minutes. The mixture was transferred to a separating funnel and the phases were separated. The aqueous phase was washed with Et_2O (800 mL). The aqueous phase was then basified by addition of NaOH (10% w/v aq. solution, 300 mL). The basic aqueous phase was extracted with Et_2O (2 x 700 mL). These two organic extracts were combined, dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford crude title compound as a red oil. Flash column chromatography (pet 40°-60°C /EtOAc/Et_3N 95:4:1 to 85:14:1) afforded 5-(3-bromophenyl)-3,4-dihydro-2*H*-pyrrole (**3.209**, 24.9 g, 111 mmol, 44%) as a pale orange crystalline solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.00 (t, *J* = 1.8 Hz, 1H), 7.76 – 7.72 (m, 1H), 7.54 (ddd, *J* = 8.0, 1.9, 1.0 Hz, 1H), 7.27 (t, *J* = 7.9 Hz, 1H), 4.07 (tt, *J* = 7.5, 2.1 Hz, 2H), 2.94 – 2.87 (m, 2H), 2.09 – 2.00 (m, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 172.00, 136.6, 133.1, 130.6, 129.9, 126.1, 122.6, 61.6, 34.9, 22.6; **MS** (ESI^+): for $C_{10}H_{11}{}^{79}BrN^+$ $[M + H]^+$ requires m/z = 224.0, found 224.0. The analytical data were in accordance with the literature.[31]

2-(3-Bromophenyl)pyrrolidine (3.210)

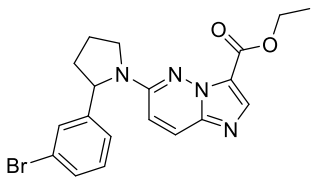


Based on a literature procedure,[32] $NaBH_4$ (4.97 g, 132 mmol, 1.20 equiv.) was added portionwise to a solution of 5-(3-bromophenyl)-3,4-dihydro-2*H*-pyrrole (**3.209**, 24.5 g, 110 mmol, 1.00 equiv.) in EtOH (110 mL) at 0 °C. The solution was allowed to warm to room temperature and was stirred at room temperature for 12 hours. The solution was cooled to 0 °C and was quenched by careful addition of 2M aq. HCl solution. The solution was then acidified to pH 1 by addition of 6M aq. HCl solution. The solution was allowed to warm to room temperature and was stirred at room temperature for one hour. The mixture was cooled to 0 °C and 10% w/v aq. NaOH solution was added until pH > 10. The mixture was transferred to a separating funnel and extracted with CH_2Cl_2 (3 x 400 mL). The combined organic phases were washed with brine (800 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford crude title compound as a yellow oil. Flash column chromatography (pet 40°-60°C/EtOAc/Et_3N 80:19:1 to 20:79:1) afforded 2-(3-bromophenyl)pyrrolidine (**3.210**, 20.0 g, 88.4 mmol, 81%) as a pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.53 (t, *J* = 1.7 Hz, 1H), 7.34 (ddd, *J* = 7.9, 1.8, 1.2 Hz, 1H), 7.27 (d, *J* = 7.6 Hz, 1H), 7.16 (t, *J* = 7.8 Hz, 1H), 4.09 (t, *J* = 7.7 Hz, 1H), 3.17 (ddd, *J* = 10.1, 7.6, 5.3 Hz, 1H), 3.01 (ddd, *J* = 10.0, 8.2, 6.7 Hz, 1H), 2.17 (tdd, *J* = 8.2, 7.7, 4.9 Hz, 1H), 1.96 – 1.76 (m, 3H), 1.62 (ddt, *J* = 12.4, 9.1, 7.8 Hz, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 147.7, 129.8, 129.7, 129.5, 125.1, 122.5, 61.8, 46.9, 34.4, 25.5; **HRMS** (ESI^+)

for $C_{10}H_{13}BrN^+$ $[M+H]^+$ requires m/z = 226.0226, found 226.0227. The analytical data were in accordance with the literature.[33]

Ethyl 6-(2-(3-bromophenyl)pyrrolidin-1-yl)imidazo[1,2-*b*]pyridazine-3-carboxylate (3.211)

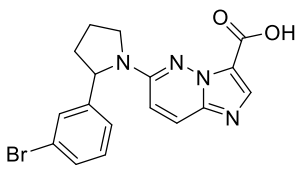


Based on a literature procedure,[29] a stirred suspension of ethyl 6-chloroimidazo[1,2-*b*]pyridazine-3-carboxylate (790 mg, 3.50 mmol, 1.00 equiv.), 2-(3-bromophenyl)pyrrolidine (870 mg, 3.85 mmol, 1.10 equiv.) and KF (609 mg, 10.5 mmol, 3.00 equiv.) in dry DMSO (5 mL) was heated at 100 °C for 22 hours. The mixture was allowed to cool to room temperature. EtOAc (50 mL) and H_2O (50 mL) were added and the phases were separated. The aqueous phase was extracted with EtOAc (2 x 50 mL). The combined organic phases were washed with brine (3 x 100 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford crude title compound. Flash column chromatography (pet 40°-60°C/EtOAc/Et_3N 19:80:1) afforded ethyl 6-(2-(3-bromophenyl)pyrrolidin-1-yl)imidazo[1,2-*b*]pyridazine-3-carboxylate (**3.211**, 933 mg, 2.25 mmol, 64%) as a white foam.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.12 (s, 1H), 7.61 (d, *J* = 9.8 Hz, 1H), 7.42 – 7.36 (m, 2H), 7.21 – 7.14 (m, 2H), 6.48 (d, *J* = 9.9 Hz, 1H), 4.97 (dd, *J* = 8.2, 2.2 Hz, 1H), 4.40 (q, *J* = 7.1 Hz, 2H), 3.98 (ddd, *J* = 11.0, 7.2, 4.2 Hz, 1H), 3.81 (dt, *J* = 11.1, 7.7 Hz, 1H), 2.54 – 2.42 (m, 1H), 2.17 – 1.97 (m, 3H), 1.40 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 159.3, 152.8, 145.6, 139.4, 138.9, 130.5, 130.4, 128.9, 125.9, 124.4, 123.0, 119.5, 111.8,

61.9, 60.3, 48.6, 36.0, 22.9, 14.4; **IR** (ATR, neat): ν (cm^{-1}) = 2975, 1719, 1688, 1618, 1557, 1456, 1421, 1310, 1189, 1174, 1049, 917, 805, 781, 760; **M.P.**: 82-85 °C.

6-(2-(3-Bromophenyl)pyrrolidin-1-yl)imidazo[1,2-*b*]pyridazine-3-carboxylic acid (3.212)

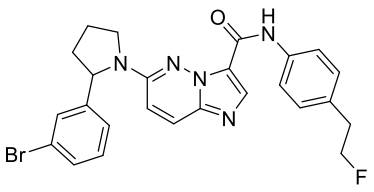


Based on a literature procedure,[29] to a solution of ethyl 6-(2-(3-bromophenyl)pyrrolidin-1-yl)imidazo[1,2-*b*]pyridazine-3-carboxylate (**3.211**, 893 mg, 2.15 mmol, 1.00 equiv.) in EtOH (20 mL) and H_2O (1 mL) was added powdered KOH (602 mg, 10.8 mmol, 5.00 equiv.). The mixture was stirred at room temperature for three hours. The solvent was removed under reduced pressure and the residue was re-dissolved in H_2O (10 mL) and acidifed to pH 5-6 with 6 M aqueous HCl. The aqueous phase was extracted with EtOAc (4 x 20 mL). The combined organic phases were washed with brine (80 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford 6-(2-(3-bromophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazine-3-carboxylic acid (**3.212**, 742 mg, 1.92 mmol, 89%) as a beige solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.53 (br. s, 1H), 8.04 (s, 1H), 7.90 (d, *J* = 9.9 Hz, 1H), 7.51 (s, 1H), 7.45 – 7.39 (m, 1H), 7.31 – 7.24 (m, 2H), 6.81 (d, *J* = 8.6 Hz, 1H), 5.15 (dd, *J* = 8.1, 2.7 Hz, 1H), 3.96 – 3.88 (m, 1H), 3.65 (dt, *J* = 10.5, 7.8 Hz, 1H), 2.48 – 2.39 (m, 1H), 2.06 – 1.94 (m, 2H), 1.92 – 1.84 (m, 1H); **^{13}C NMR** (101 MHz, DMSO-d_6): δ = 159.2, 152.4, 146.4, 138.4, 137.7, 130.7, 129.9, 128.7, 125.9, 125.0, 121.9, 119.1, 112.9, 60.9, 48.4, 35.2, 22.6; **HRMS** (ESI$^+$) for $C_{17}H_{16}{}^{79}BrN_4O_2^+$ $[M+H]^+$ requires m/z =

387.0451, found 387.0447; **IR** (ATR, neat): ν (cm^{-1}) = 2973, 1678, 1562, 1471, 1335, 1258, 1190, 1146, 925, 757, 705; **M.P.**: 182 °C (decomp.)

6-(2-(3-Bromophenyl)pyrrolidin-1-yl)-*N*-(4-(2-fluoroethyl)phenyl)imidazo[1,2-*b*]pyridazine-3-carboxamide (3.213)

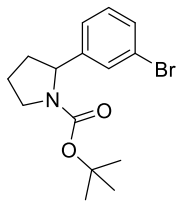


Based on a literature procedure,[29] to a solution of 6-(2-(3-bromophenyl)pyrrolidin-1-yl)imidazo[1,2-*b*]pyridazine-3-carboxylic acid (**3.212**, 555 mg, 1.43 mmol, 1.00 equiv.) in dry DMF (30 mL) was added DIPEA (662 μL, 3.58 mmol, 2.50 equiv.). To this was added a solution of HATU (543 mg, 1.43 mmol, 1.00 equiv.) in dry DMF (5 mL), followed by a solution of 4-(2-fluoroethyl)aniline (239 mg, 1.72 mmol, 1.20 equiv.) in dry DMF (5 mL). The mixture was stirred at room temperature for 22 hours. The mixture was transferred to a separating funnel and diluted with EtOAc (200 mL), then washed with brine (4 x 300 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford crude title compound. Flash column chromatography (CH_2Cl_2/MeOH/Et_3N 98:2:0.1) afforded 6-(2-(3-bromophenyl)pyrrolidin-1-yl)-*N*-(4-(2-fluoroethyl)phenyl)imidazo[1,2-*b*]pyridazine-3-carboxamide (**3.213**, 586 mg, 1.15 mmol, 80%) as an off-white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.55 (br. s, 1H), 8.31 (s, 1H), 7.74 (d, *J* = 9.9 Hz, 1H), 7.57 – 7.45 (br. m, 2H), 7.42 (d, *J* = 7.9 Hz, 1H), 7.37 (s, 1H), 7.24 (d, *J* = 8.4 Hz, 2H), 7.20 (t, *J* = 7.8 Hz, 1H), 7.12 (d, *J* = 7.7 Hz, 1H), 6.56 (d, *J* = 9.3 Hz, 1H), 5.08 (d, *J* = 8.2 Hz, 1H), 4.64 (dt, *J* = 47.1, 6.5 Hz, 2H), 4.04 – 3.97 (m, 1H), 3.85 – 3.76 (m, 1H),

3.02 (dt, *J* = 23.3, 6.5 Hz, 2H), 2.62 – 2.49 (m, 1H), 2.20 – 2.08 (m, 3H).; **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 157.0, 152.0, 144.4, 138.0, 137.9, 136.5, 133.0 (d, *J* = 6.2 Hz), 130.8, 130.6, 129.6, 128.6, 127.1, 124.1, 123.2, 122.4, 120.5, 110.9, 84.1 (d, *J* = 169.0 Hz), 61.9, 48.6, 36.4 (d, *J* = 20.3 Hz), 35.9, 22.7; **^{19}F NMR** (376 MHz, $CDCl_3$): δ = -215.3 (tt, *J* = 47.2, 23.5 Hz); **HRMS** (ESI^+) for $C_{25}H_{23}{}^{79}BrFN_5O^+$ $[M+H]^+$ requires m/z = 508.1143, found 508.1139; **IR** (ATR, neat): ν (cm^{-1}) = 2980, 1655, 1624, 1601, 1563, 1544, 1469, 1426, 1317, 1177, 1057, 995, 922, 804, 705; **M.P.**: 193-196 °C.

***tert*-Butyl 2-(3-bromophenyl)pyrrolidine-1-carboxylate (3.218)**

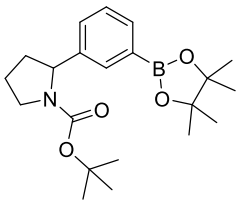


To a solution of 2-(3-bromophenyl)pyrrolidine (**3.210**, 9.04 g, 40.0 mmol, 1.00 equiv.) in THF (80 mL) was added DMAP (488 mg, 1.33 mmol, 0.10 equiv.) and Boc_2O (10.5 g, 48.0 mmol, 1.20 equiv.). The mixture was stirred at room temperature for one hour. The solvent was removed under reduced pressure to afford crude title compound. Flash column chromatography (pet 40°-60°C/EtOAc 90:10 to 85:15) afforded *tert*-butyl 2-(3-bromophenyl)pyrrolidine-1-carboxylate (**3.218**, 11.3 g, 34.6 mmol, 87%) as a white solid.

2:1 mixture of rotamers observed in $CDCl_3$ solution. Peaks belonging to minor rotamer denoted with *. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.37 – 7.28 (m, 2H + 2H*), 7.16 (t, *J* = 7.7 Hz, 1H + 1H*), 7.09 (br. d, *J* = 7.7 Hz, 1H + 1H*), 4.90 (s, 1H*), 4.70 (s, 1H), 3.56 (m, 1H + 1H*), 2.32 (br. s, 1H + 1H*), 1.98 – 1.73 (m, 3H + 3H*), 1.45 (s, 9H*), 1.20 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 154.4 (1C + 1C*), 147.5 (1C), 146.6 (1C*),

129.8 (1C + 1C*), 129.6 (1C + 1C*), 128.7 (1C), 128.5 (1C*), 124.2 (1C + 1C*), 122.3 (1C +1C*), 79.5 (1C), 77.2 (1C*), 60.9 (1C), 60.4 (1C*), 47.1 (1C + 1C*), 35.9 (1C), 34.8 (1C*), 28.4 (1C*), 28.2 (1C), 23.4 (1C*), 23.2 (1C); **HRMS** (NH_3 CI) for $C_{15}H_{21}BrNO_2^+$ $[M+H]^+$ requires m/z = 326.0750, found 326.0759; **IR** (ATR, neat) $\tilde{\nu}$ (cm^{-1}) = 2974, 1691, 1595, 1570, 1476, 1389, 1365, 1255, 1158, 1114, 1071; **M.P.**: 67-68 °C.

***tert*-Butyl 2-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)pyrrolidine-1-carboxylate (3.219)**

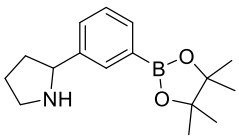


To an oven-dry flask with a magnetic stirrer was added *tert*-butyl 2-(3-bromophenyl)pyrrolidine-1-carboxylate (**3.218**, 5.22 g, 16.0 mmol, 1.00 equiv.), B_2pin_2 (4.47 g, 17.6 mmol, 1.10 equiv.), $Pd(dppf)Cl_2$ (392 mg, 0.48 mmol, 0.03 equiv.) and KOAc (4.70 g, 48.0 mmol, 3.00 equiv.). A rubber septum was added, and the flask was purged with argon. Dry, degassed 1,4-dioxane (80 mL) was added. The mixture was heated to 80 °C and stirred at this temperature for 16 hours. After cooling to room temperature, the mixture was diluted with EtOAc and filtered through a short plug of SiO_2, eluting with EtOAc. The solvent was removed under reduced pressure to afford crude title compound. Flash column chromatography (pet 40°-60°C/EtOAc 85:15 to 80:20) afforded *tert*-butyl 2-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)pyrrolidine-1-carboxylate (**3.219**, 5.02 g, 13.5 mmol, 84%) as a white solid.

3:1 mixture of rotamers observed in $CDCl_3$ solution. Peaks belonging to minor rotamer denoted with *. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.65 (d, *J* = 7.1 Hz, 1H +

1H*), 7.61 (s, 1H + 1H*), 7.29 (t, *J* = 7.4 Hz, 1H + 1H*), 7.24 (dt, *J* = 7.9, 1.6 Hz, 1H + 1H*), 4.94 (br. s, 1H*), 4.76 (br. s, 1H), 3.70 – 3.42 (m, 2H + 2H*), 2.39 – 2.20 (m, 1H + 1H*), 1.97 – 1.77 (m, 3H + 3H*), 1.47 (br. s, 9H*), 1.33 (s, 12H + 12H*), 1.16 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 154.7 (1C + 1C*), 144.1 (1C + 1C*), 133.0 (1C + 1C*), 132.1 (1C + 1C*), 128.4 (1C + 1C*), 127.5 (1C + 1C*), 83.7 (2C + 2C*), 79.2 (1C + 1C*), 61.2 (1C), 60.8 (1C*), 47.1 (1C + 1C*), 36.0 (1C), 34.9 (1C*), 28.4 (3C*), 28.1 (3C), 24.8 (4C), 24.8 (4C*), 23.3 (1C + 1C*); Carbon adjacent to boron was not observed; **^{11}B NMR** (128 MHz, $CDCl_3$): δ = 31.5; **HRMS** (NH_3 CI) for $C_{21}H_{33}BNO_4^+$ $[M+H]^+$ requires m/z = 374.2497, found 374.2508; **IR** (ATR, neat): ν (cm^{-1}) = 2976, 1693, 1389, 1359, 1311, 1144, 1113, 1078, 965, 910, 860, 709; **M.P.**: 85-87. °C.

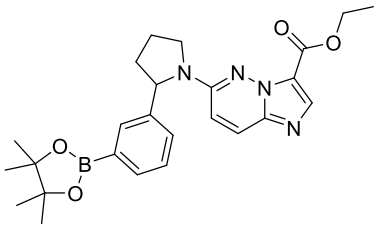
2-(3-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)pyrrolidine (3.217)



To a solution of *tert*-butyl 2-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)pyrrolidine-1-carboxylate (**3.219**, 4.48 g, 12.0 mmol, 1.00 equiv.) in CH_2Cl_2 (120 mL) at 0 °C was added trifluoroacetic acid (18.4 mL, 240 mmol, 20.0 equiv.). The mixture was stirred at 0 °C for two hours. The mixture was then basified by addition of aq. NaOH solution (2M, 125 mL) and transferred to a separating funnel. The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (2 x 100 mL). The combined organic phases were washed with brine (300 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford 2-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)pyrrolidine (**3.217**, 2.63 g, 9.63 mmol, 80%) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.77 (s, 1H), 7.69 (d, *J* = 7.3 Hz, 1H), 7.51 (d, *J* = 7.7 Hz, 1H), 7.33 (t, *J* = 7.5 Hz, 1H), 4.17 (t, *J* = 7.8 Hz, 1H), 3.64 (br. s, 2H), 3.22 (ddd, *J* = 10.4, 7.7, 5.9 Hz, 1H), 3.03 (ddd, *J* = 10.3, 8.3, 6.5 Hz, 1H), 2.26 – 2.16 (m, 1H), 2.00 – 1.68 (m, 3H), 1.34 (s, 12H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 142.2, 133.7, 133.0, 129.7, 128.0, 83.8, 62.7, 46.6, 33.9, 25.3, 24.9; **^{11}B NMR** (128 MHz, $CDCl_3$): δ = 30.8; **HRMS** (NH_3 CI) for $C_{16}H_{25}BNO_2^+$ $[M+H]^+$ requires m/z = 274.1973, found 274.2002; **IR** (ATR, neat) $\tilde{\nu}$ (cm^{-1}) = 2978, 1619, 1476, 1457, 1430, 1359, 1319, 1272, 1167, 1144, 1078, 965, 852, 709, 678.

Ethyl 6-(2-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)pyrrolidin-1-yl)imidazo[1,2-*b*]pyridazine-3-carboxylate (3.216)

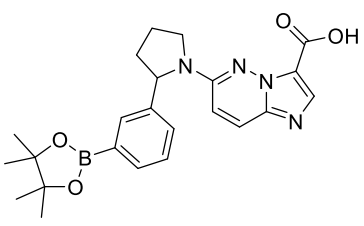


Based on a literature procedure,[29] a stirred suspension of ethyl 6-chloroimidazo[1,2-*b*]pyridazine-3-carboxylate (902 mg, 4.00 mmol, 1.00 equiv.), 2-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)pyrrolidine (**3.217**, 1.42 g, 5.20 mmol, 1.30 equiv.) and KF (696 mg, 12.0 mmol, 3.00 equiv.) in dry DMSO (8 mL) was heated at 100 °C for 18 hours. The mixture was allowed to cool to room temperature. EtOAc (50 mL) and H_2O (50 mL) were added and the phases were separated. The aqueous phase was extracted with EtOAc (2 x 50 mL). The combined organic phases were washed with brine (3 x 100 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford crude title compound. Flash column chromatography (pet 40°-60°C/EtOAc/Et_3N 60:40:0.1 to 20:80:0.1) afforded ethyl 6-

(2-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)pyrrolidin-1-yl)imidazo[1,2-*b*]pyridazine-3-carboxylate (**3.216**, 584 mg, 1.26 mmol, 32%) as a white foam.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.12 (s, 1H), 7.73 – 7.68 (m, 2H), 7.54 (d, *J* = 9.9 Hz, 1H), 7.33 – 7.25 (m, 2H), 6.46 (d, *J* = 9.8 Hz, 1H), 4.95 (dd, *J* = 8.2, 1.9 Hz, 1H), 4.41 (q, *J* = 7.1 Hz, 2H), 4.05 – 3.97 (m, 1H), 3.86 (dt, *J* = 11.3, 7.3 Hz, 1H), 2.56 – 2.42 (m, 1H), 2.18 – 1.97 (m, 3H), 1.41 (t, *J* = 7.1 Hz, 3H), 1.34 (s, 12H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 159.4, 153.2, 142.4, 139.4 (br.), 138.7, 133.9, 132.0, 128.4, 128.2, 125.5, 119.5 (br.), 112.3, 83.9, 62.6, 60.3, 48.6, 36.4, 24.9, 22.8, 14.4; Carbon adjacent to boron was not observed. **^{11}B NMR** (128 MHz, $CDCl_3$): δ = 31.5; **HRMS** (ESI^+) for $C_{25}H_{32}BN_4O_4^+$ $[M+H]^+$ requires m/z = 463.2511, found 463.2503; **IR** (ATR, neat): ν (cm^{-1}) = 2979, 1722, 1693, 1608, 1558, 1459, 1358, 1311, 1273, 1192, 1143, 1052, 805, 760, 711, 675; **M.P.**: 78-80 °C.

6-(2-(3-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)pyrrolidin-1-yl)imidazo[1,2-*b*]pyridazine-3-carboxylic acid (3.215)

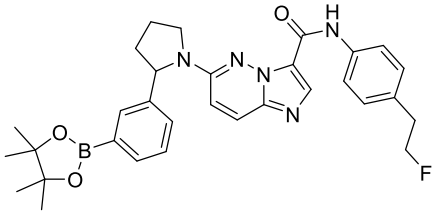


Based on a literature procedure,[29] to a solution of ethyl 6-(2-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)pyrrolidin-1-yl)imidazo[1,2-*b*]pyridazine-3-carboxylate (**3.216**, 269 mg, 0.58 mmol, 1.00 equiv.) in EtOH (6 mL) and H_2O (300 μL) was added powdered KOH (162 mg, 2.90 mmol, 5.00 equiv.). The mixture was stirred at room temperature for two hours. The solvent was removed under reduced

pressure and the residue was re-dissolved in H_2O (3 mL), acidifed with 6M aqueous HCl and neutralised to pH 5-6 with saturated aqueous $NaHCO_3$. The precipitated solid was filtered off and dried under vacuum, affording 6-(2-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)pyrrolidin-1-yl)imidazo[1,2-*b*]pyridazine-3-carboxylic acid (**3.215**, 140 mg, 0.32 mmol, 55%) as an off-white solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.59 (br. s, 1H), 8.07 (s, 1H), 7.87 (d, *J* = 9.9 Hz, 1H), 7.60 (s, 1H), 7.55 (d, *J* = 6.9 Hz, 1H), 7.40 – 7.27 (m, 2H), 6.75 (br. d, *J* = 6.4 Hz, 1H), 5.18 (dd, *J* = 8.0, 2.7 Hz, 1H), 3.89 (ddd, *J* = 11.0, 7.3, 3.9 Hz, 1H), 3.69 (dt, *J* = 10.8, 7.8 Hz, 1H), 2.47 – 2.41 (m, 1H), 2.05 – 1.90 (m, 2H), 1.89 – 1.80 (m, 1H), 1.28 (s, 12H); **^{13}C NMR** (101 MHz, DMSO-d_6): δ = 159.1, 152.6, 143.0, 138.2, 137.2, 133.2, 131.5, 128.9, 128.2, 125.6, 119.2, 113.2, 83.7, 61.4, 48.4, 35.7, 24.7, 24.7, 22.5; Carbon adjacent to boron was not observed. **^{11}B NMR** (128 MHz, DMSO-d_6): δ = 34.8; **HRMS** (ESI^+) for $C_{23}H_{28}BN_4O_4^+$ $[M+H]^+$ requires m/z = 435.2198, found 435.2195; **IR** (ATR, neat): ν (cm^{-1}) = 3145, 2978, 1772, 1670, 1504, 1421, 1359, 1271, 1225, 1206, 1141, 817, 771, 756, 706, 672; **M.P.**: 206-208 °C.

_N_-(4-(2-Fluoroethyl)phenyl)-6-(2-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)pyrrolidin-1-yl)imidazo[1,2-*b*]pyridazine-3-carboxamide (3.200)



Based on a literature procedure,[29] to a solution of 6-(2-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazine-3-carboxylic acid (**3.215**, 140 mg, 0.32 mmol, 1.00 equiv.) in dry DMF

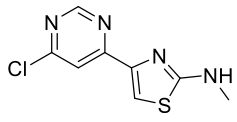
(4 mL) was added DIPEA (139 μL, 0.80 mmol, 2.50 equiv.). To this was added a solution of HATU (122 mg, 0.32 mmol, 1.00 equiv.) in dry DMF (1 mL), followed by a solution of 4-(2-fluoroethyl)aniline (53 mg, 0.38 mmol, 1.20 equiv.) in dry DMF (1 mL). The mixture was stirred at room temperature for 16 hours. The mixture was transferred to a separating funnel and diluted with EtOAc (40 mL), then washed with brine (3 x 40 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford crude title compound. Flash column chromatography (CH_2Cl_2/MeOH/Et_3N 98:2:0.1) afforded *N*-(4-(2-fluoroethyl)phenyl)-6-(2-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)pyrrolidin-1-yl)imidazo[1,2-*b*]pyridazine-3-carboxamide (**3.200**, 82 mg, 0.15 mmol, 46%) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.74 (br. s, 1H), 8.30 (s, 1H), 7.74 (d, *J* = 7.3 Hz, 1H), 7.71 (s, 1H), 7.67 (d, *J* = 9.8 Hz, 1H), 7.57 (br. s, 2H), 7.32 (t, *J* = 7.5 Hz, 1H), 7.25 – 7.21 (m, 3H), 6.53 (d, *J* = 8.1 Hz, 1H), 5.09 (d, *J* = 7.2 Hz, 1H), 4.63 (dt, *J* = 47.1, 6.6 Hz, 2H), 4.08 – 3.99 (m, 1H), 3.87 – 3.78 (m, 1H), 3.01 (dt, *J* = 23.2, 6.6 Hz, 2H), 2.64 – 2.47 (m, 1H), 2.23 – 2.09 (m, 3H), 1.35 (s, 12H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 157.1, 152.3, 141.3, 137.9 (br.), 137.6, 136.8, 134.2, 132.8 (d, *J* = 6.3 Hz), 131.9, 129.6, 128.4, 128.1, 126.8, 122.5 (br.), 120.4, 111.5, 84.1 (d, *J* = 169.1 Hz), 84.0, 62.7, 48.7, 36.4 (d, *J* = 20.4 Hz), 36.1, 24.9, 22.7. Carbon adjacent to boron was not observed; **^{19}F NMR** (376 MHz, $CDCl_3$): δ = -215.0 – -215.5 (m); **^{11}B NMR** (128 MHz, $CDCl_3$): δ = 32.2; **HRMS** (ESI^+) for $C_{31}H_{36}BFN_5O_3^+$ $[M+H]^+$ requires m/z = 556.2890, found 556.2891; **IR** (ATR, neat):

ν (cm^{-1}) = 2978, 1663, 1603, 1564, 1544, 1471, 1427, 1359, 1317, 1171, 1144, 805, 732, 712; **M.P.**: 235-237 °C.

4.3.5 FITM

4-(6-Chloropyrimidin-4-yl)-*N*-methylthiazol-2-amine (3.270)



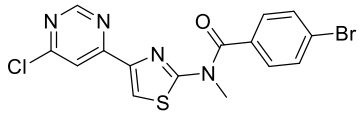
Based on a literature procedure,[34] to a flame-dried flask was added 4,6-dichloropyrimidine (10.4 g, 70.0 mmol, 1.00 equiv.), $Pd(PPh_3)_4$ (2.43 g, 2.10 mmol, 0.03 equiv.), CuI (1.33 g, 7.00 mmol, 0.10 equiv.) and CsF (21.3 g, 140 mmol, 2.00 equiv.). A rubber septum was added and the flask was evacuated and back-filled with argon; this was repeated twice more. Degassed DMF (200 mL) was added, followed by tributyl(1-ethoxyvinyl)stannane (23.6 mL, 70.0 mmol, 1.00 equiv.). The stirred solution was heated to 80 °C and stirred at this temperature for 6 hours. Then solution was then allowed to cool to room temperature, diluted with CH_2Cl_2 (800 mL) and filtered through Celite. H_2O (1 L) was added to the filtrate and the phases were separated. The organic phase was dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford crude 4-chloro-6-(1-ethoxyvinyl)pyrimidine **3.268**. Flash column chromatography (pet 40°-60°C/EtOAc 96:4) afforded partially purified 4-chloro-6-(1-ethoxyvinyl)pyrimidine (**3.268**, 6.31 g) as a pale yellow solid, which was carried through to the next step without further purification.

To a solution of this enol ether in THF/H_2O (1:1, 100 mL) was added *N*-bromosuccinimide (6.57 g, 36.9 mmol, 1.10 equiv). The mixture was stirred at

room temperature for two hours. *N*-Methylthiourea (3.02 g, 33.5 mmol, 1.00 equiv.) was added and the mixture was stirred at room temperature for a further three hours. The THF was removed under reduced pressure. The residue was partitioned between $CHCl_3$ (350 mL) and H_2O (300 mL). The aqueous phase was extracted with $CHCl_3$ (4 x 350 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford crude title compound. Flash column chromatography ($CHCl_3$/*i*-PrOH/Et_3N 99:1:0.1 to 97:3:0.1) afforded 4-(6-chloropyrimidin-4-yl)-*N*-methylthiazol-2-amine (**3.270**, 3.04 g, 13.4 mmol, 19% over three steps) as a beige solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.89 (s, 1H), 7.90 (s, 1H), 7.60 (s, 1H), 5.35 (br. s, 1H), 3.05 (d, *J* = 5.0 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 170.7, 162.2, 160.4, 158.5, 148.3, 117.5, 111.1, 32.1; **HRMS** (ESI^+) for $C_8H_8ClN_4S^+$ $[M+H]^+$ requires m/z = 227.0153, found 227.0152; **IR** (ATR, neat): ν (cm^{-1}) = 3297, 3121, 3091, 1578, 1561, 1538, 1488, 1458, 1439, 1357, 1294, 1097, 1040, 985, 760, 736, 715; **M.P.**: 170-172 °C. ^{1}H NMR data were in accordance with the literature.[34]

4-Bromo-*N*-(4-(6-chloropyrimidin-4-yl)thiazol-2-yl)-*N*-methylbenzamide (3.272)

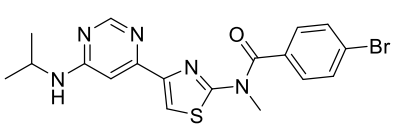


Based on a literature procedure,[35] to a solution of 4-(6-chloropyrimidin-4-yl)-*N*-methylthiazol-2-amine (**3.270**, 1.36 g, 6.00 mmol, 1.00 equiv.) and Et_3N (5.02 mL, 36.0 mmol, 6.00 equiv.) in toluene (30 mL) was added 4-bromobenzoyl chloride (1.98 g, 9.00 mmol, 1.50 equiv.). The mixture was heated to 100 °C and stirred at this temperature for 16 hours. After

cooling to room temperature, the mixture was partitioned between $CHCl_3$ (200 mL) and water (200 mL). The phases were separated and the organic phase dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford crude title compound. Flash column chromatography ($CHCl_3$/EtOAc/Et_3N 100:0:0.1 to 90:10:0.1) afforded 4-bromo-*N*-(4-(6-chloropyrimidin-4-yl)thiazol-2-yl)-*N*-methylbenzamide (**3.272**, 2.16 g, 5.27 mmol, 88%) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.94 (s, 1H), 8.12 (s, 1H), 8.04 (s, 1H), 7.67 (d, *J* = 8.4 Hz, 2H), 7.47 (d, *J* = 8.4 Hz, 2H), 3.75 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 169.6, 162.3, 160.7, 160.4, 158.7, 146.2, 132.8, 132.1, 129.2, 125.9, 118.8, 117.4, 38.4; **HRMS** (NH_3 CI): for $C_{15}H_{11}BrClN_4OS^+$ $[M+H]^+$ requires m/z = 408.9520; found 408.9530; **IR** (ATR, neat): ν (cm^{-1}) = 3122, 1637, 1569, 1547, 1500, 1482, 1440, 1422, 1368, 1351, 1300, 1289, 1275, 1100, 1071, 1008; **M.P.** 212-214 °C. ^{1}H NMR data were in accordance with the literature.[35]

4-Bromo-*N*-(4-(6-(*iso*-propylamino)pyrimidin-4-yl)thiazol-2-yl)-*N*-methylbenzamide (3.273)

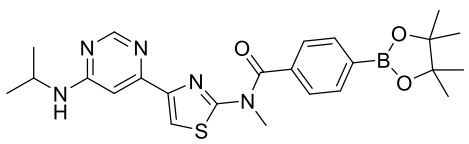


Based on a literature procedure,[35] to a suspension of 4-bromo-*N*-(4-(6-chloropyrimidin-4-yl)thiazol-2-yl)-*N*-methylbenzamide (**3.272**, 1.85 g, 4.50 mmol, 1.00 equiv.) and K_2CO_3 (1.24 g, 9.00 mmol, 2.00 equiv.) in 1,4-dioxane (45 mL) was added *iso*-propylamine (5.79 mL, 67.5 mmol, 15.0 equiv.). The mixture was heated to 80 °C and stirred at this

temperature for 16 hours. After cooling to room temperature, the mixture was partitioned between EtOAc (250 mL) and water (250 mL). The phases were separated and the organic phase was washed with brine (250 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford crude title compound. Flash column chromatography (CH_2Cl_2/EtOAc/Et_3N 60:40:0.1 to 40:60:0.1) afforded 4-bromo-*N*-(4-(6-(*iso*-propylamino)pyrimidin-4-yl)thiazol-2-yl)-*N*-methylbenzamide (**3.273**, 1.47 g, 3.59 mmol, 80%) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.57 (s, 1H), 7.92 (s, 1H), 7.65 (d, *J* = 8.4 Hz, 2H), 7.46 (d, *J* = 8.5 Hz, 2H), 7.04 (s, 1H), 4.86 (br. s, 1H), 4.11 (br. s, 1H), 3.73 (s, 3H), 1.28 (d, *J* = 6.4 Hz, 7H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 169.5, 162.4, 160.3, 157.5, 155.8 (br.), 146.8, 133.1, 132.1, 132.0, 129.3, 125.7, 116.8, 99.7 (br.), 43.1, 38.4, 22.7; **HRMS** (NH_3 CI): for $C_{18}H_{19}BrN_5OS^+$ $[M+H]^+$ requires m/z = 432.0488; found 432.0497; **IR** (ATR, neat): ν (cm^{-1}) = 3260, 2971, 1645, 1600, 1498, 1424, 1347, 1177, 1093, 1072, 1009; **M.P.** 169-171 °C. The analytical data were in accordance with the literature.[35]

_N_-(4-(6-(Isopropylamino)pyrimidin-4-yl)thiazol-2-yl)-_N_-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (3.265)

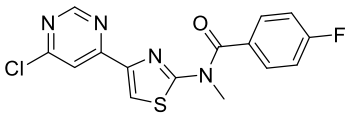


4-Bromo-*N*-(4-(6-(isopropylamino)pyrimidin-4-yl)thiazol-2-yl)-*N*-methylbenzamide (**3.273**, 300 mg, 0.694 mmol, 1.05 equiv.), B_2pin_2 (168 mg, 0.661 mmol, 1.0 equiv.), $Pd(dppf)Cl_2$ (97.0 mg, 0.132 mmol, 0.20 equiv.) and KOAc (204 mg, 1.98 mmol, 3.0 equiv.) were suspended in anhydrous and degassed DMF (5 mL). The mixture was stirred for 22

h at 100 °C. The mixture was allowed to cool to room temperature, diluted with CH_2Cl_2 and filtered through Celite. The mixture was concentrated under reduced pressure to afford crude title compound. Flash column chromatography (*n*-pentane/EtOAc 67:33 to 0:100) afforded *N*-(4-(6-(isopropylamino)pyrimidin-4-yl)thiazol-2-yl)-*N*-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (**126**, 80.7 mg, 0.168 mmol, 25%) as a slightly brown solid. A small amount was further purified by recrystallisation from CH_2Cl_2/hexane; analytical data is based on this sample.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.57 (s, 1H), 7.95 – 7.92 (m, 2H), 7.92 (s, 1H), 7.57 – 7.54 (m, 2H), 7.05 (d, *J* = 1.0 Hz, 1H), 4.85 (br. s, 1H), 4.11 (br. s, 1H), 3.70 (s, 3H), 1.37 (s, 12H), 1.28 (d, *J* = 6.4 Hz, 6H); **^{13}C NMR** (126 MHz, $CDCl_3$): δ = 170.4, 162.5, 160.2, 158.6, 157.4, 148.0, 136.7, 134.9, 131.9 (br.), 126.6, 115.9, 99.5 (br.), 84.2, 42.8, 38.3, 24.9, 22.8; **^{11}B NMR** (128 MHz, $CDCl_3$): *δ* = 32.0; **HRMS** (ESI^+) for $C_{24}H_{31}BN_5O_3S^+$ $[M+H]^+$ requires m/z = 480.22352, found 480.22351; **IR** (ATR, neat) $\tilde{\nu}$ (cm^{-1}) = 2972, 2361, 2340, 1602, 1498, 1354, 1144, 1093, 1016, 856, 803, 670; **M.P.**: 197 °C.

_N_-(4-(6-Chloropyrimidin-4-yl)thiazol-2-yl)-4-fluoro-_N_-methylbenzamide

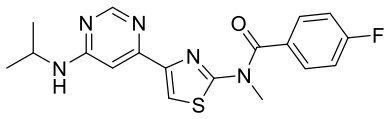


Based on a literature procedure,[36] to a solution of 4-(6-chloropyrimidin-4-yl)-*N*-methylthiazol-2-amine (**3.270**, 680 mg, 3.00 mmol, 1.00 equiv.) and Et_3N (2.51 mL, 18.0 mmol, 6.00 equiv.) in toluene (15 mL) was added 4-fluorobenzoyl chloride (530 μL, 4.50 mmol, 1.50 equiv.). The mixture was heated to 100 °C and stirred at this temperature for 16

hours. After cooling to room temperature, the mixture was partitioned between $CHCl_3$ (100 mL) and water (100 mL). The phases were separated and the organic phase dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford crude title compound. Flash column chromatography (CH_2Cl_2/EtOAc/Et_3N 100:0:0.1 to 90:10:0.1) afforded *N*-(4-(6-chloropyrimidin-4-yl)thiazol-2-yl)-4-fluoro-*N*-methylbenzamide (880 mg, 2.53 mmol, 84%) as an off-white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.98 (s, 1H), 8.28 (s, 1H), 8.08 (s, 1H), 7.65 – 7.60 (m, 2H), 7.25 – 7.17 (m, 2H), 3.77 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 169.7, 164.3 (d, *J* = 253.1 Hz), 163.0, 161.0, 159.4, 157.9, 145.1, 130.2 (d, *J* = 8.8 Hz), 129.9 (d, *J* = 3.5 Hz), 120.1, 117.5, 116.0 (d, *J* = 22.1 Hz), 38.6; **^{19}F NMR** (376 MHz, $CDCl_3$): δ = -107.1 (tt, *J* = 8.5, 5.2 Hz); **HRMS** (NH_3 CI): for $C_{15}H_{11}FClN_4OS^+$ $[M+H]^+$ requires m/z = 349.0321; found 349.0329; **IR** (ATR, neat): ν (cm^{-1}) = 1650, 1601, 1562, 1504, 1424, 1348, 1281, 1227, 1160, 1100, 1090, 1027, 1013; **M.P.** 192-194 °C.

4-Fluoro-*N*-(4-(6-(*iso*-propylamino)pyrimidin-4-yl)thiazol-2-yl)-*N*-methylbenzamide (3.4)

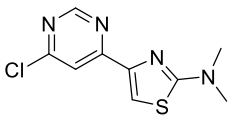


To a solution of *N*-(4-(6-chloropyrimidin-4-yl)thiazol-2-yl)-4-fluoro-*N*-methylbenzamide (174 mg, 0.50 mmol, 1.0 equiv.) and K_2CO_3 (138 mg, 1.00 mmol, 2.00 equiv.) in 1,4-dioxane (5 mL) was added *iso*-propylamine (643 μL, 7.50 mmol, 15.0 equiv.). The mixture was heated to 80 °C and stirred at this temperature for 18 hours. The mixture was allowed to cool to room temperature and all volatiles were removed under reduced

pressure. The crude product was purified by flash column chromatography on silica (CH_2Cl_2/EtOAc 50:50) to afford 4-fluoro-*N*-(4-(6-(*iso*-propylamino)pyrimidin-4-yl)thiazol-2-yl)-*N*-methylbenzamide (**3.4**, 134 mg, 0.36 mmol, 72%) as an off-white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.54 (s, 1H), 7.88 (s, 1H), 7.57 (dd, *J* = 8.5, 5.2 Hz, 2H), 7.15 (t, *J* = 8.5 Hz, 2H), 7.03 (s, 1H), 5.11 (bs, 1H), 4.08 (bs, 1H), 3.70 (s, 3H), 1.25 (d, *J* = 6.4 Hz, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 169.5, 164.2 (d, *J* = 252.4 Hz), 162.6, 160.4, 158.7, 157.4, 148.2, 130.5 (d, *J* = 3.6 Hz), 130.2 (d, *J* = 8.8 Hz), 116.0 (d, *J* = 22.0 Hz), 115.9, 99.6 (br.), 42.9, 38.5, 22.9; **^{19}F NMR** (376 MHz, $CDCl_3$): δ = −107.7 (ddd, *J* = 13.7, 8.6, 5.1 Hz); **HRMS** (ESI^+) for $C_{18}H_{19}ON_5FS^+$ $[M+H]^+$ requires m/z = 372.12889, found 372.12860; **IR** (ATR, neat) $\tilde{\nu}$ (cm^{-1}) = 3226, 2970, 1650, 1597, 1538, 1504, 1466, 1424, 1342, 1286, 1223, 1161, 1093, 1012, 976, 853, 791, 753, 713, 656, 631; **M.P.**: 174 °C.

4-(6-Chloropyrimidin-4-yl)-*N*,*N*-dimethylthiazol-2-amine

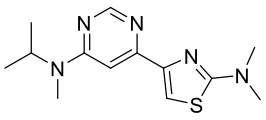


To a suspension of NaH (60 wt% in mineral oil, 90 mg, 2.25 mmol, 1.50 equiv.) in dry DMF (7 mL) was added a solution of 4-(6-chloropyrimidin-4-yl)-*N*-methylthiazol-2-amine (341 mg, 1.50 mmol, 1.00 equic.) in dry DMF (7 mL). The mixture was stirred at room temperature for 30 minutes. MeI (280 μL, 4.50 mmol, 3.00 eq.) was added and the mixture was stirred at room temperature for 20 hours. The mixture was partitioned between $CHCl_3$ (100 mL) and brine (100 mL) and the phases were separated. The organic phase was washed

with brine (2 x 100 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. Flash column chromatography ($CHCl_3$/Et_3N 100:0.1 afforded 4-(6-chloropyrimidin-4-yl)-*N*,*N*-dimethylthiazol-2-amine (147 mg, 0.61 mmol, 41%) as a beige solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.86 (d, *J* = 0.8 Hz, 1H), 7.96 (d, *J* = 0.7 Hz, 1H), 7.58 (s, 1H), 3.15 (s, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 171.0, 162.1, 160.7, 158.4, 148.7, 117.6, 111.0, 40.2; **HRMS** (NH_3 CI) for $C_9H_{10}ClN_4S^+$ $[M+H]^+$ requires m/z = 241.0309, found 241.0308; **IR** (ATR, neat) $\tilde{\nu}$ (cm^{-1}) = 3093, 1577, 1557, 1540, 1489, 1456, 1410, 1363, 1098, 760, 723; **M.P.**: 117-119 °C.

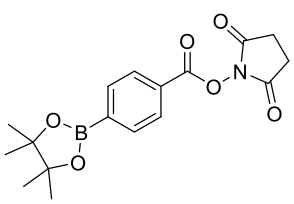
4-(6-(*iso*-Propyl(methyl)amino)pyrimidin-4-yl)-*N*,*N*-dimethylthiazol-2-amine (3.274)



To a suspension of 4-(6-chloropyrimidin-4-yl)-*N*,*N*-dimethylthiazol-2-amine (124 mg, 0.52 mmol, 1.0 equiv.) and K_2CO_3 (144 mg, 1.04 mmol, 2.0 equiv.) in 1,4-dioxane (2.5 mL) was added *N*-iso-propylmethylamine (812 μL, 7.80 mmol, 15.0 equiv.). The mixture was heated to 80 °C and stirred at this temperature for 18 hours. The mixture was allowed to cool to room temperature and all volatiles were removed under reduced pressure. Flash column chromatography ($CHCl_3$/Et_3N 99:1) afforded 4-(6-(*iso*-propyl(methyl)amino)pyrimidin-4-yl)-*N*,*N*-dimethylthiazol-2-amine (**3.274**, 85 mg, 0.31 mmol, 60%) as a yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.55 (s, 1H), 7.43 (s, 1H), 7.13 (s, 1H), 4.94 (br. s, 1H), 3.15 (s, 6H), 2.94 (s, 3H), 1.20 (d, *J* = 6.7 Hz, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 170.9, 162.4, 157.7, 157.3, 150.7, 108.0, 98.7, 45.5, 40.2, 27.9, 19.6; **HRMS** (ESI^+) for $C_{13}H_{20}N_5S^+$ $[M+H]^+$ requires m/z = 278.1434, found 278.1430; **IR** (ATR, neat): ν (cm^{-1}) = 3090, 2978, 2923, 1568, 1529, 1500, 1405, 1350, 1322, 1129, 1054, 988, 942, 860, 835, 784, 766, 727; **M.P.**: 74-77 °C.

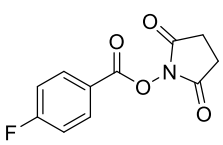
2,5-Dioxopyrrolidin-1-yl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate (3.283)



Following a literature procedure,[37] to a solution of 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoic acid (1.24 g, 5.00 mmol, 1.00 equiv.) in MeCN (50 mL) was added Et_3N (2.09 mL, 15.0 mmol, 3.00 equiv.) and *N,N'*-disuccinimidyl carbonate (1.92 g, 7.50 mmol, 1.50 equiv.). The mixture was stirred at room temperature for 5 hours. The solvent was removed under reduced pressure, keeping the water bath temperature below 35 °C. The residue was dissolved in CH_2Cl_2 (100 mL) and washed with saturated aq. $NaHCO_3$ solution (100 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated under reduced pressure, keeping the water bath temperature below 35 °C. Flash column chromatography (pet 40°-60°C/EtOAc 50:50) afforded 2,5-dioxopyrrolidin-1-yl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate (**3.283**, 1.35 g, 3.91 mmol, 78%) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.10 (d, *J* = 8.2 Hz, 2H), 7.92 (d, *J* = 8.2 Hz, 2H), 2.90 (s, 4H), 1.36 (s, 12H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 169.2, 161.9, 135.0, 129.5, 127.1, 84.4, 25.7, 24.9. Carbon adjacent to boron was not observed; **^{11}B NMR** (128 MHz, $CDCl_3$): δ = 31.1; **MS** (ESI^+): for $C_{17}H_{20}BNNaO_6^+$ $[M + Na]^+$ requires m/z = 368.1, found 368.2. The analytical data were consistent with the literature values.[37]

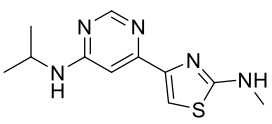
2,5-Dioxopyrrolidin-1-yl 4-fluorobenzoate (3.282)



Following a literature procedure,[38] to a solution of 4-fluorobenzaldehyde (1.07 mL, 10.0 mmol, 1.00 equiv.) and (diacetoxy)iodobenzene (3.54 g, 11.0 mmol, 1.10 equiv.) in EtOAc (20 mL) at 0 °C was added *N*-hydroxysuccinimide (1.27 g, 11.0 mmol, 1.10 equiv.). The mixture was stirred at 0 °C for one hour. The solvent was removed under reduced pressure. Flash column chromatography (heptane/EtOAc 75:25) afforded 2,5-dioxopyrrolidin-1-yl 4-fluorobenzoate (**3.282**, 1.89 g, 7.97 mmol, 80%) as a crystalline white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.21 – 8.13 (m, 2H), 7.25 – 7.16 (m, 2H), 2.91 (s, 4H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 169.1, 166.9 (d, *J* = 257.8 Hz), 160.9, 133.4 (d, *J* = 9.8 Hz), 121.4 (d, *J* = 3.1 Hz), 116.3 (d, *J* = 22.3 Hz), 25.6; **MS** (ESI^+): for $C_{11}H_8FNNaO_4^+$ $[M + Na]^+$ requires m/z = 260.0, found 260.0. The analytical data were consistent with literature.[38]

4-(6-(Isopropylamino)pyrimidin-4-yl)-*N*-methylthiazol-2-amine (3.278)

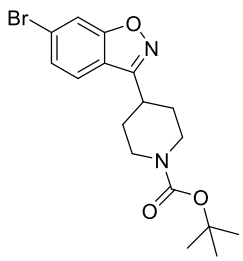


To a suspension of 4-(6-chloropyrimidin-4-yl)-*N*-methylthiazol-2-amine (**3.270**, 1.36 g, 6.00 mmol, 1.00 equiv.) and K_2CO_3 (1.66 g, 12.0 mmol, 2.00 equiv.) in 1,4-dioxane (30 mL) was added isopropylamine (7.72 mL, 90.0 mmol, 15.0 equiv.). The mixture was heated to 80 °C and stirred at this temperature for 18 hours. After cooling to room temperature, the mixture was partitioned between EtOAc (200 mL) and water (200 mL). The phases were separated and the aqueous phase was extracted twice with EtOAc (2 x 200 mL). The combined organic phases were washed with brine (400 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford crude title compound. Flash column chromatography ($CHCl_3$/*i*-PrOH/Et_3N 95:5:0.1 afforded 4-(6-(isopropylamino)pyrimidin-4-yl)-*N*-methylthiazol-2-amine (**3.278**, 1.22 g, 4.90 mmol, 82%) as a beige solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.50 (s, 1H), 7.46 (s, 1H), 6.93 (s, 1H), 5.54 (br. s, 1H), 5.14 (br. s, 1H), 4.05 (br. s, 1H), 3.00 (d, *J* = 3.7 Hz, 3H), 1.24 (d, *J* = 6.4 Hz, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 170.6, 162.5, 157.9 (br.), 156.8, 149.6, 108.5, 99.5 (br.), 42.9, 32.1, 22.7; **HRMS** (ESI^+) for $C_{11}H_{16}N_5S^+$ $[M+H]^+$ requires m/z = 250.1121, found 250.1122; **IR** (ATR, neat): ν (cm^{-1}) = 3252, 2971, 1599, 1514, 1465, 1409, 1340, 1223, 1179; **M.P.** 151-153 °C.

4.3.6 Risperidone

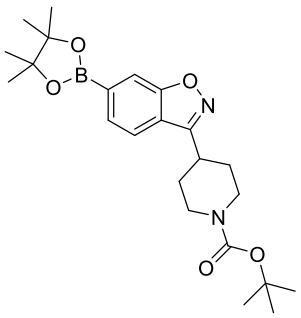
tert-Butyl 4-(6-bromobenzo[d]isoxazol-3-yl)piperidine-1-carboxylate (3.302)



To a solution of 6-bromo-3-(piperidin-4-yl)benzo[d]isoxazole (**3.301**, 1.50 g, 5.34 mmol, 1.00 equiv.) in CH_2Cl_2 (25 mL) was added Boc_2O (1.28 g, 5.87 mmol, 1.10 equiv.) and DMAP (65 mg, 0.53 mmol, 0.10 equiv.). The mixture was stirred at room temperature for 15 hours. The solvent was removed under reduced pressure. Flash column chromatography (pet 40°-60°C/EtOAc 85:15 to 60:40) afforded *tert*-butyl 4-(6-bromobenzo[d]isoxazol-3-yl)piperidine-1-carboxylate (**3.301**, 1.55 g, 4.07 mmol, 76%) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.77 (d, *J* = 1.1 Hz, 1H), 7.55 (d, *J* = 8.4 Hz, 1H), 7.43 (dd, *J* = 8.4, 1.4 Hz, 1H), 4.22 (br. s, 2H), 3.23 (tt, *J* = 11.4, 3.8 Hz, 1H), 2.96 (br. t, *J* = 11.9 Hz, 2H), 2.06 (br. d, *J* = 10.1 Hz, 2H), 1.99 – 1.86 (m, 2H), 1.49 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 163.6, 160.7, 154.7, 126.9, 124.3, 122.2, 119.8, 113.6, 79.8, 43.6, 34.4, 30.2, 28.4; **HRMS** (ESI^+) for $C_{17}H_{21}BrN_2NaO_3^+$ $[M+Na]^+$ requires m/z = 403.0628, found 403.0625; **IR** (ATR, neat): ν (cm^{-1}) = 2974, 2856, 1677, 1605, 1426, 1226, 1159, 1123, 1022, 986, 948, 909, 846, 812, 771; **M.P.**: 174-176 °C.

***tert*-Butyl 4-(6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[d]isoxazol-3-yl)piperidine-1-carboxylate (3.293)**

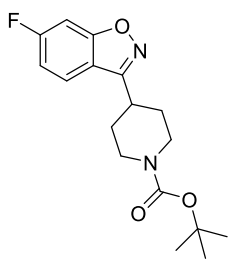


To an oven-dry round bottom flask with a magnetic stirrer was added *tert*-butyl 4-(6-bromobenzo[d]isoxazol-3-yl)piperidine-1-carboxylate (**3.302**, 200 mg, 0.525 mmol, 1.05 equiv.), B_2pin_2 (127 mg, 0.50 mmol, 1.00 equiv.), $Pd(dppf)Cl_2$ (12.2 mg, 0.015 mmol, 0.03 equiv.) and KOAc (147 mg, 1.50 mmol, 3.00 equiv.). A rubber septum was added, and the flask was evacuated and backfilled with N_2 three times. Dry, degassed 1,4-dioxane (2.5 mL) was added. The mixture was heated to 80 °C and stirred at this temperature for 18 hours. After cooling to room temperature, the mixture was diluted with EtOAc and filtered through a short plug of Celite, eluting with EtOAc. The solvent was removed under reduced pressure to afford crude title compound. The residue was dissolved in MeCN (15 mL) and purified by preparative HPLC. The resulting MeCN/H_2O solution was diluted with H_2O and extracted with EtOAc. The organic phase was dried ($MgSO_4$), filtered and concentrated under reduced pressure, keeping the water bath temperature below 30 °C, to afford *tert*-butyl 4-(6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[d]isoxazol-3-yl)piperidine-1-carboxylate (**3.293**, 91.7 mg, 0.214 mmol, 43%) as an off-white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.01 (s, 1H), 7.72 – 7.66 (m, 2H), 4.32 – 4.14 (m, 2H), 3.26 (tt, *J* = 11.4, 3.8 Hz, 1H), 2.96 (br. t, *J* = 10.8 Hz, 2H), 2.07 (br. d, *J* = 11.6 Hz, 2H), 2.02 – 1.89 (m, 2H), 1.49 (s, 9H), 1.37 (s, 12H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 163.0,

160.7, 154.8, 128.8, 122.7, 120.6, 116.3, 84.3, 79.7, 43.5 (br.), 34.6, 30.1, 28.5, 24.9. Carbon adjacent to boron was not observed. **HRMS** (NH_3 CI) for $C_{23}H_{33}BN_2O_5^+$ $[M+H]^+$ requires m/z = 428.2483, found 428.2589; **IR** (ATR, neat): ν (cm^{-1}) = 2980, 2929, 1686, 1491, 1392, 1364, 1347, 1228, 1170, 1141, 1121, 854, 963; **M.P.**: 158-160 °C.

***tert*-Butyl 4-(6-fluorobenzo[d]isoxazol-3-yl)piperidine-1-carboxylate (3.292)**



To a solution of 6-fluoro-3-(piperidin-4-yl)benzo[d]isoxazole (440 mg, 2.00 mmol, 1.00 equiv.) in CH_2Cl_2 (10 mL) was added Boc_2O (480 mg, 2.20 mmol, 1.10 equiv.) and DMAP (24 mg, 0.20 mmol, 0.10 equiv.). The mixture was stirred at room temperature for 16 hours. The solvent was then removed under reduced pressure. Flash column chromatography (pet 40°-60°C/EtOAc 70:30) afforded *tert*-butyl 4-(fluorobenzo[d]isoxazol-3-yl)piperidine-1-carboxylate (**3.292**, 578 mg, 1.81 mmol, 91%) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.63 (dd, *J* = 8.7, 5.1 Hz, 1H), 7.25 (dd, *J* = 8.4, 1.7 Hz, 1H), 7.06 (td, *J* = 8.8, 2.1 Hz, 1H), 4.23 (br. d, *J* = 8.4 Hz, 2H), 3.23 (tt, *J* = 11.5, 3.8 Hz, 1H), 2.95 (br. t, *J* = 12.0 Hz, 2H), 2.05 (br. d, *J* = 12.0 Hz, 2H), 1.99 – 1.86 (m, 2H), 1.48 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 164.1 (d, *J* = 250.9 Hz), 163.9 (d, *J* = 13.6 Hz), 160.6, 154.7, 122.3 (d, *J* = 11.1 Hz), 117.14, 112.5 (d, *J* = 25.4 Hz), 97.5 (d, *J* = 26.7 Hz), 79.75, 43.7 (br.), 34.4, 30.2, 28.4; **^{19}F NMR** (376 MHz, $CDCl_3$): δ = -109.3 (td, *J* = 8.7, 5.1 Hz); **HRMS** (ESI^+) for $C_{17}H_{21}BrN_2NaO_3^+$ $[M+Na]^+$ requires m/z = 403.0628, found

403.0625; **IR** (ATR, neat): ν (cm^{-1}) = 2980, 2861, 1679, 1608, 1426, 1226, 1167, 1120, 1091, 1022, 841, 820, 648; **M.P.**: 104-106 °C.

4.3.7 $[Cu(OTf)_2(impy)_4]$ Complex 3.307

A solution of imidazo[1,2-b]pyridazine (758 mg, 6.36 mmol, 10 equiv.) in MeOH (1 mL) was added dropwise at 55 °C to a solution of $Cu(OTf)_2$ (230 mg, 0.636 mmol, 1.0 equiv.) in MeOH (1 mL). The blue precipitate which formed was washed with Et_2O (3 x 2 mL), then recrystallised from hot MeOH to afford $[Cu(OTf)_2(impy)_4]$ (**3.307**, 324 mg, 0.387 mmol, 61%).

Anal. Calcd. for $C_{26}H_{20}CuF_6N_{12}O_6S_2$: C, 37.26; H, 2.41; N, 20.05. Found: C, 37.07; H, 2.33; N, 19.91; **IR** (ATR, neat): ν (cm^{-1}) = 2981, 1620, 1541, 1503, 1374, 1352, 1306, 1281, 1241, 1221, 1149, 1071, 1027, 950, 918, 879, 801, 755, 733, 632.

4.4 Radiochemistry

4.4.1 Working Procedures in SOMIL

Whilst working in SOMIL, a minimum of two trained researchers were present in order to ensure that work was carried out in a safe manner. When carrying out small-scale "aliquot" reactions (most of the reactions discussed in this thesis), two or three researchers worked together in order to make efficient use of the [^{18}F]fluoride. Reactions were carried out in duplicate (n = 2), from which a mean RCC was determined. For many reactions, two pairs were carried out, where possible on separate days, giving rise to n = 4 for these reactions. Each reaction underwent several steps:

1. Weighing of solid reagents into vial.
2. Dispensing aliquot of [^{18}F]fluoride into vial.
3. Adding solvent (or solution of reagent in solvent) and putting reaction into heating block.
4. Removing reaction from heating block and quenching.
5. Preparing samples for radio-TLC and radio-HPLC analysis.
6. Injecting radio-HPLC sample.
7. Running radio-TLC plate and analysing using moving bed detector.

Reactions in SOMIL were carried out in collaboration with Dr. Matt Tredwell, Dr. Sean Preshlock, Dr. Michael Schedler and Dr. Stefan Verhoog. I carried out steps 1,

6 and 7, as well as planning the reactions and analysing the results in collaboration with the other researchers.

4.4.2 General Information

General information for radiochemical procedures at the Chemistry Research Laboratory, University of Oxford

[^{18}F]Fluoride was produced by Alliance Medical (UK) via the ^{18}O(p,n)^{18}F reaction and delivered as [^{18}F]fluoride in ^{18}O-enriched-water. Radiosynthesis and azeotropic drying was performed on a NanoTek microfluidic device (Advion).

Procedure for preparation of a solution of [^{18}F]KF/K$_{222}$ in MeCN

A solution of Kryptofix 222 (15 mg) and K_2CO_3 (3 mg) in 1 mL of MeCN/H_2O, 4:1 was freshly prepared. [^{18}F]Fluoride (3.0-4.0 GBq) was separated from ^{18}O-enriched-water using a Chromafix PS-HCO_3 ^{18}F separation cartridge (45 mg) and subsequently released with 900 μL (in 6 x 150 μL portions) of the K$_{222}$/K_2CO_3 solution into a 5 mL V-vial containing a magnetic stir bar in the concentrator. The solution was dried with five cycles of azeotropic drying with MeCN (5 x 200 μl) under a flow of N_2 at 105 °C. The dried [^{18}F]KF/K$_{222}$ residue was redissolved in anhydrous MeCN (500–1000 μL).

General procedure for ^{18}F-fluorodeboronation of aryl boronic esters (Conditions A)

A solution of [^{18}F]KF/K_{222} in MeCN (20-30 MBq, 10-50 μL) was dispensed into a V-vial containing $Cu(OTf)_2(py)_4$ (5.3 μmol), aryl pinacol boronate (60 μmol) and a magnetic stirrer bar. Air (20 mL) was flushed through the reaction vial using a syringe and then DMF (300 μL) was added via syringe. The sealed vial was heated at 110 °C for 20 minutes. The reaction was quenched by addition of water (200 μL). An aliquot was removed for analysis by radioTLC and HPLC for radiochemical conversion and product identity. Analysis was performed using the gradient **A** or **B** given below with a Waters Nova-Pak C18 column (4 μm, 3.9 x 150 mm) at a flow rate 1ml/min. Radio-TLC was performed on Merck Kiesegel 60 F254 plates, using as eluent either *n*-hexane/EtOAc (1:1) or CH_2Cl_2/MeOH (9:1) as appropriate. Analysis was performed using a plastic scintillator/PMT detector.

General procedure for ^{18}F-fluorodeboronation of aryl boronic esters (Conditions B)

A solution of [^{18}F]KF/K_{222} in MeCN (20-30 MBq, 10-50 μL) was dispensed into a V-vial containing $Cu(OTf)_2(py)_4$ (30 μmol), aryl pinacol boronate (20 μmol) and a magnetic stirrer bar. Air (20 mL) was flushed through the reaction vial using a syringe and then DMA (300 μL) was added via syringe. The sealed vial was heated at 110 °C for 20 minutes. The reaction was quenched by addition of water (200 μL). An aliquot was removed for analysis by radioTLC and HPLC for radiochemical

conversion and product identity. Analysis was performed using the gradient **A** or **B** given below with a Waters Nova-Pak C18 column (4 μm, 3.9 x 150 mm) at a flow rate 1ml/min. Radio-TLC was performed on Merck Kiesegel 60 F254 plates, using as eluent either *n*-hexane/EtOAc (1:1) or CH_2Cl_2/MeOH (9:1) as appropriate. Analysis was performed using a plastic scintillator/PMT detector.

General procedure for heterocyclic additive screening experiments with 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzonitrile 3.20

A solution of [^{18}F]KF/K_{222} in MeCN (20-30 MBq, 10-50 μL) was dispensed into a V-vial containing $Cu(OTf)_2(py)_4$ (5.3 μmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzonitrile (**3.20**, 60 μmol) and a magnetic stirrer bar. Air (20 mL) was flushed through the reaction vial using a syringe and then a solution containing the heterocycle (60 μmol) in DMF (300 μL) was added via syringe. The sealed vial was heated at 110 °C for 20 minutes. The reaction was quenched by addition of water (200 μL). An aliquot was removed for analysis by radioTLC and HPLC for radiochemical conversion and product identity. Analysis was performed using the gradient **A** or **B** given below with a Waters Nova-Pak C18 column (4 μm, 3.9 x 150 mm) at a flow rate 1ml/min. Radio-TLC was performed on Merck Kiesegel 60 F254 plates, using *n*-hexane/EtOAc (1:1) as eluent. Analysis was performed using a plastic scintillator/PMT detector.

4.4.3 HPLC Gradients

Gradient **A**:

Water/MeCN, 1 mL/min
Waters Nova-Pak C18 Column, 4 μm, 3.9 x 150 mm
0-1 min (5% MeCN) isocratic
1-10 min (5% MeCN to 95% MeCN) linear increase
10-14 min (95% MeCN) isocratic
14-15 min (95% MeCN to 5% MeCN) linear decrease
15-17 min (5% MeCN) isocratic

Gradient **B**:

HPLC gradient: water with 0.1% TFA (v/v)/MeCN with 0.1% TFA (v/v), 1 mL/min
Waters Nova-Pak C18 Column, 4 μm, 3.9 x 150 mm
0-1 min (5% MeCN with 0.1% TFA) isocratic
1-10 min (5% MeCN with 0.1% TFA to 95% MeCN with 0.1% TFA) linear increase
10-14 min (95% MeCN with 0.1% TFA) isocratic
14-15 min (95% MeCN with 0.1% TFA to 5% MeCN with 0.1% TFA) linear decrease
15-17 min (5% MeCN with 0.1% TFA) isocratic

Gradient **C**:

HPLC gradient: water with 0.1% TFA (v/v)/MeCN with 0.1% TFA (v/v), 1 mL/min,
Waters Nova-Pak C18 Column, 4 μm, 3.9 x 150 mm
0-1 min (5% MeCN with 0.1% TFA) isocratic
1-19 min (5% MeCN with 0.1% TFA to 95% MeCN with 0.1% TFA) linear increase
19-23 min (95% MeCN with 0.1% TFA) isocratic
25-27 min (95% MeCN with 0.1% TFA to 5% MeCN with 0.1% TFA) linear decrease
27-28 min (5% MeCN with 0.1% TFA) isocratic

Gradient **D**:

HPLC gradient: water with 0.1% TFA (v/v)/MeCN with 0.1% TFA (v/v), 1 mL/min,
Waters Nova-Pak C18 Column, 4 μm, 3.9 x 150 mm
0-1 min (5% MeCN with 0.1% TFA) isocratic
1-19 min (5% MeCN with 0.1% TFA to 40% MeCN with 0.1% TFA) linear increase
19-21 min (40% MeCN with 0.1% TFA to 95% MeCN with 0.1% TFA) linear increase
21-23 min (95% MeCN with 0.1% TFA) isocratic
23-25 min (95% MeCN with 0.1% TFA to 5% MeCN with 0.1% TFA) linear decrease
25-27 min (5% MeCN with 0.1% TFA) isocratic

4.4.4 Procedure for ^{18}F-Fluorination of Copper Complex 2.6

A solution of [^{18}F]KF/K_{222} in MeCN (20-30 MBq, 10-50 μL) was dispensed into a V-vial containing **2.6** (3.6 mg, 0.0053 mmol), TBAF·2Pin (2.6 mg, 0.0053 mmol) and a magnetic stirrer bar. Air (20 mL) was flushed through the reaction vial using a syringe and then DMF (300 μL) was added via syringe. The sealed vial was heated at 110 °C for 20 minutes. The reaction was quenched by addition of aqueous NH_4OH (35 %, 200 μL). An aliquot was removed for analysis by radioTLC and HPLC for radiochemical conversion and product identity. Analysis was performed using the gradient **B** given in section 4.4.3 with a Waters Nova-Pak C18 column (4 μm, 3.9 x 150 mm) at a flow rate 1ml/min. Radio-TLC was performed on Merck Kiesegel 60 F254 plates, using CH_2Cl_2/MeOH (9:1) as eluent. Analysis was performed using a plastic scintillator/PMT detector.

4.4.7 Procedure for ^{18}F-Fluorodeboronation of 3.138-Bpin

[^{18}F]3.138 was synthesised from boronic ester **3.138-Bpin** following **General procedure for ^{18}F-fluorodeboronation of aryl boronic esters (Conditions A)** except that the reaction was quenched by addition of water (200 μL) and MeOH (200 μL).

4.4.8 Procedure for ^{18}F-Fluorodeboronation of 3.182-Bpin

[^{18}F]3.182 was synthesised from boronic ester **3.182-Bpin** following **General procedure for ^{18}F-fluorodeboronation of aryl boronic esters (Conditions A)** except

that **3.182-Bpin** (60 μmol) was not initially present in the reaction vial and was instead added as a solution in the reaction solvent (300 μL DMF).

4.4.9 Procedure for S_NAr Control Experiments

A solution of [^{18}F]KF/K_{222} in MeCN (20-30 MBq, 10-50 μL) was dispensed into a V-vial containing $Cu(OTf)_2(py)_4$ (20.3 mg, 30 μmol), 2,4-dichloropyridine (**3.184**, 3.0 mg, 20 μmol) and a magnetic stirrer bar. Air (20 mL) was flushed through the reaction vial using a syringe and then DMA (300 μL) was added via syringe. The sealed vial was heated at 110 °C for 20 minutes. The reaction was quenched by addition of water (200 μL). An aliquot was removed for analysis by radioTLC and HPLC for radiochemical conversion and product identity. Analysis was performed using the gradient **B** given in section 4.4.3 with a Waters Nova-Pak C18 column (4 μm, 3.9 x 150 mm) at a flow rate 1ml/min. Radio-TLC was performed on Merck Kiesegel 60 F254 plates, using CH_2Cl_2/MeOH (9:1) as eluent. Analysis was performed using a plastic scintillator/PMT detector.

The experiment was repeated omitting the $Cu(OTf)_2(py)_4$ and the results were compared.

4.4.10 Procedure for Synthesis of [^{18}F]Gefitinib [^{18}F]3.1

[^{18}F]3.1 was synthesised from boronic ester **3.192** following **General procedure for ^{18}F-fluorodeboronation of aryl boronic esters (Conditions B)** as described in section 4.4.2**.** HPLC analysis was carried out using gradient **B**, Waters Nova-Pak C18 Column, 4 μm, 3.9 x 150 mm.

4.4.11 Procedure for Synthesis of [^{18}F]IPMICF10 [^{18}F]3.2

[^{18}F]3.2 was synthesised from boronic ester **3.200** following **General procedure for ^{18}F-fluorodeboronation of aryl boronic esters (Conditions B)** as described in section 4.4.2. HPLC analysis was carried out using gradient **B**, Waters Nova-Pak C18 Column, 4 μm, 3.9 x 150 mm.

4.4.12 Procedure for Synthesis of *N*-Trityl-[^{18}F]rufinamide [^{18}F]3.220

[^{18}F]3.220 was synthesised from boronic ester **3.221** following **General procedure for ^{18}F-fluorodeboronation of aryl boronic esters (Conditions B)** as described in section 4.4.2, except that the reaction was quenched by addition of a solution of EtOH/H_2O (3:1, 200 μL)**.** HPLC analysis was carried out using gradient **B**, Waters Nova-Pak C18 Column, 4 μm, 3.9 x 150 mm.

4.4.13 Procedure for Synthesis of [^{18}F]Rufinamide [^{18}F]3.186

A solution of [^{18}F]KF/K_{222} in MeCN (20-30 MBq, 10-50 μL) was dispensed into a V-vial containing $Cu(OTf)_2(py)_4$ (30 μmol), **3.221** (20 μmol) and a magnetic stirrer bar.

Air (20 mL) was flushed through the reaction vial using a syringe and DMA (300 μL) was added via syringe. The sealed vial was heated at 110 °C for 20 minutes. The reaction was quenched with the addition of 500 μL EtOH. The reaction solution was further diluted with 6 mL of a 4:1 EtOH:H_2O solution and loaded onto a Sep-Pak Plus C-18 Cartridge (Part No. WAT020515, Waters). The cartridge was then flushed with 2 mL water, followed by 2 mL air. The protected-product was then eluted into a 5 mL V-vial containing a magnetic stir bar with 2 mL DCM followed with 1 mL air. The DCM was evaporated under a flow of N_2 at 80 °C. The residue was then dissolved in 800 μL of a 3:1 TFA:DCE solution. The reaction was heated at 80 °C for 5 min. A solution containing 41 μL $^{i}Pr_3SiH$ and 150 μL DCE was added the reaction mixture and heated at 80 °C for 5 min. The reaction was then quenched with 400 μL EtOH and 200 μL of a 1:1 mixture of H_2O:MeCN. An aliquot was removed for analysis by HPLC to determine conversion of the deprotection step. Analysis was performed using the gradient **B** described in section 4.4.3 with a Waters Nova-Pak C18 column (4 μm, 3.9 x 150 mm) at a flow rate 1ml/min.

4.4.14 Procedure for Synthesis of *O*-Methyl-[^{18}F]flutemetamol [^{18}F]3.234

[^{18}F]3.234 was synthesised from boronic ester **3.235** following **General procedure for ^{18}F-fluorodeboronation of aryl boronic esters (Conditions B)** as described in section 4.4.2. HPLC analysis was carried out using gradient **B**, Waters Nova-Pak C18 Column, 4 μm, 3.9 x 150 mm.

4.4.15 Procedure for Synthesis of Flutemetamol [^{18}F]3.187

A solution of [^{18}F]KF/K_{222} in MeCN (20-30 MBq, 10-50 μL) was dispensed into a V-vial containing $Cu(OTf)_2(py)_4$ (30 μmol), **3.235** (20 μmol) and a magnetic stirrer bar. Air (20 mL) was flushed through the reaction vial using a syringe and DMA (300 μL) was added via syringe. The sealed vial was heated at 110 °C for 20 minutes. The reaction solution was diluted with 6 mL de-ionized water and loaded onto a Sep-Pak Plus C-18 Cartridge (Part No. WAT020515, Waters). The cartridge was then flushed with 2 mL water, followed by 2 mL air. Protected product **3.234** was then eluted into a 5 mL V-vial containing a magnetic stir bar with 2 mL MeCN followed with 1 mL air. The MeCN was evaporated under a flow of N_2 at 110 °C and the residue was azeotropically dried with the addition of 3x500 μL MeCN. The residue was then dissolved in 200 μL DCE and 100 μL of a 1 M BBr_3 solution in CH_2Cl_2 was added. The reaction was heated at 80 °C for 20 min. A 50 μL aliquot was removed and diluted in 200 μL EtOH for analysis by HPLC to determine conversion of the deprotection step. Analysis was performed using the gradient **B** described in section 4.4.3 with a Waters Nova-Pak C18 column (4 μm, 3.9 x 150 mm) at a flow rate 1ml/min.

4.4.16 Procedure for Synthesis of *N*-(4-Nitrophenoxycarbonyl)-[^{18}F]paroxetine [^{18}F]3.263

[^{18}F]3.263 was synthesised from boronic ester **3.262** following **General procedure for ^{18}F-fluorodeboronation of aryl boronic esters (Conditions B)** as described in

section 4.4.2. HPLC analysis was carried out using gradient **B**, Waters Nova-Pak C18 Column, 4 μm, 3.9 x 150 mm.

4.4.17 Procedure for Synthesis of [^{18}F]Paroxetine [^{18}F]3.3

A solution of [^{18}F]KF/K_{222} in MeCN (20-30 MBq, 10-50 μL) was dispensed into a V-vial containing $Cu(OTf)_2(py)_4$ (30 μmol), **3.262** (20 μmol) and a magnetic stirrer bar. Air (20 mL) was flushed through the reaction vial using a syringe and DMA (300 μL) was added via syringe. The sealed vial was heated at 110 °C for 20 minutes. The reaction vial was allowed to cool to room temperature and then 200 μL of 5 M $NaOH_{(aq)}$ solution was added via syringe. The reaction was stirred at 110 °C for 10 minutes. An aliquot was removed for analysis by HPLC to determine the conversion of the deprotection step. Analysis was performed using the gradient **B** described in section 4.4.3 with a Waters Nova-Pak C18 column (4 μm, 3.9 x 150 mm) at a flow rate 1ml/min.

4.4.18 Procedure for Synthesis of *N*-succinimidyl-4-[^{18}F]fluorobenzoate [^{18}F]3.282

[^{18}F]3.282 was synthesised from boronic ester **3.283** following **General procedure for ^{18}F-fluorodeboronation of aryl boronic esters (Conditions B)** as described in section 4.4.2. HPLC analysis was carried out using gradient A, Waters Nova-Pak C18 Column, 4 μm, 3.9 x 150 mm.

4.4.19 Procedure for the Synthesis of [^{18}F]FITM [^{18}F]3.4

A solution of [^{18}F]KF/K_{222} in MeCN (20-30 MBq, 10-50 μL) was dispensed into a V-vial containing $Cu(OTf)_2(py)_4$ (30 μmol), **3.283** (20 μmol) and a magnetic stirrer bar. Air (20 mL) was flushed through the reaction vial using a syringe and DMA (300 μL) was added via syringe. The sealed vial was heated at 110 °C for 20 minutes. While the reaction is heating, NaH (38.4 mg, 0.96 mmol) was added to a separate vial containing **3.278** (199 mg, 0.80 mmol) in DMA (1.60 mL). The reaction mixture was agitated and allowed to stand at room temperature for 15 min. The reaction vial containing **[^{18}F]3.282**was allowed to cool to room temperature and then 200 μL of the deprotonated **3.278** solution was added via syringe. The reaction was stirred for 10 min at room temperature. The reaction was then quenched with 300 μL water and an aliquot was removed for analysis by radioTLC and HPLC to determine RCC after two steps. Analysis was performed using the gradient **C**, described in section 4.4.3, with a Waters Nova-Pak C18 column (4 μm, 3.9 x 150 mm) at a flow rate 1ml/min. Radio-TLC was performed on Merck Kiesegel 60 F254 plates. Analysis was performed using a plastic scintillator/PMT detector.

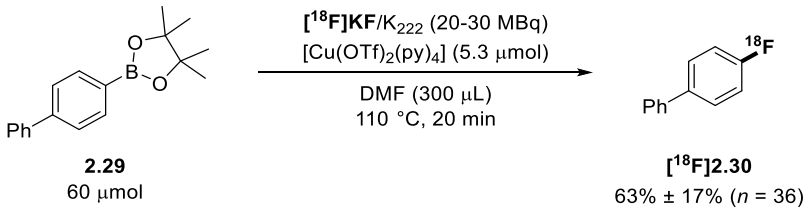
4.4.20 Procedure for ^{18}F-Fluorodeboronation of 3.293

[^{18}F]3.292 was synthesised from boronic ester **3.293** following **General procedure for ^{18}F-fluorodeboronation of aryl boronic esters (Conditions B)** as described in section 4.4.2. HPLC analysis was carried out using gradient B, Waters Nova-Pak C18 Column, 4 μm, 3.9 x 150 mm.

4.4.21 Procedure for Synthesis of [^{18}F]Risperidone [^{18}F]3.5

A solution of [^{18}F]KF/K_{222} in MeCN (20-30 MBq, 10-50 μL) was dispensed into a V-vial containing $Cu(OTf)_2(py)_4$ (30 μmol), **3.293** (20 μmol) and a magnetic stirrer bar. Air was flushed through the reaction vial using a syringe and then a solution containing DMA (300 μL) was added via syringe. The sealed vial was heated at 110 °C for 20 minutes. 200 μL of TFA was added and the reaction was heated for an additional 10 min at 110 °C. The reaction solution was diluted with 6 mL 1 M $K_2CO_{3(aq)}$ and loaded onto an Oasis HLB Plus LP extraction cartridge. The cartridge was then flushed with 2 mL water, followed by 2 mL air. Deprotected fragment **[^{18}F]3.291** was then eluted into a 5 mL V-vial containing K_2CO_3 (40 μmol), KI (40 μmol) and a magnetic stir bar with 2 mL MeCN followed with 1 mL air. The MeCN was evaporated under a flow of N_2 at 110 °C and the residue was azeotropically dried with the addition of 3x500μL MeCN. **3.297** (9 mg, 40 μmol) was then added to the reaction mixture as a solution in 500 μL DMF. The reaction was heated at 110 °C for 20 min. An aliquot was removed for analysis by HPLC to determine conversion of the alkylation step. Analysis was performed using the gradient **D** given in section 4.4.3 with a Waters Nova-Pak C18 column (4 μm, 3.9 x 150 mm) at a flow rate 1 ml/min.

4.4.22 RCC Data for ^{18}F-Fluorodeboronation of 2.29



2.29
60 μmol

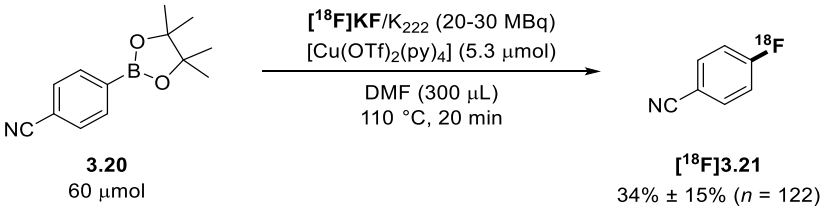
[^{18}F]2.30
63% ± 17% (*n* = 36)

RCC values obtained:

21%	41%	51%	58%	60%	69%	75%	79%	81%	85%
30%	42%	53%	59%	68%	71%	77%	80%	82%	87%
35%	45%	54%	59%	68%	73%	77%	81%	83%	88%
39%	47%	55%	60%	69%	73%				

Overall, 63% ± 17% (*n* = 36).

4.4.23 RCC Data for ^{18}F-Fluorodeboronation of 3.20 in the Absence of a Heterocyclic Additive



3.20
60 μmol

[^{18}F]3.21
34% ± 15% (*n* = 122)

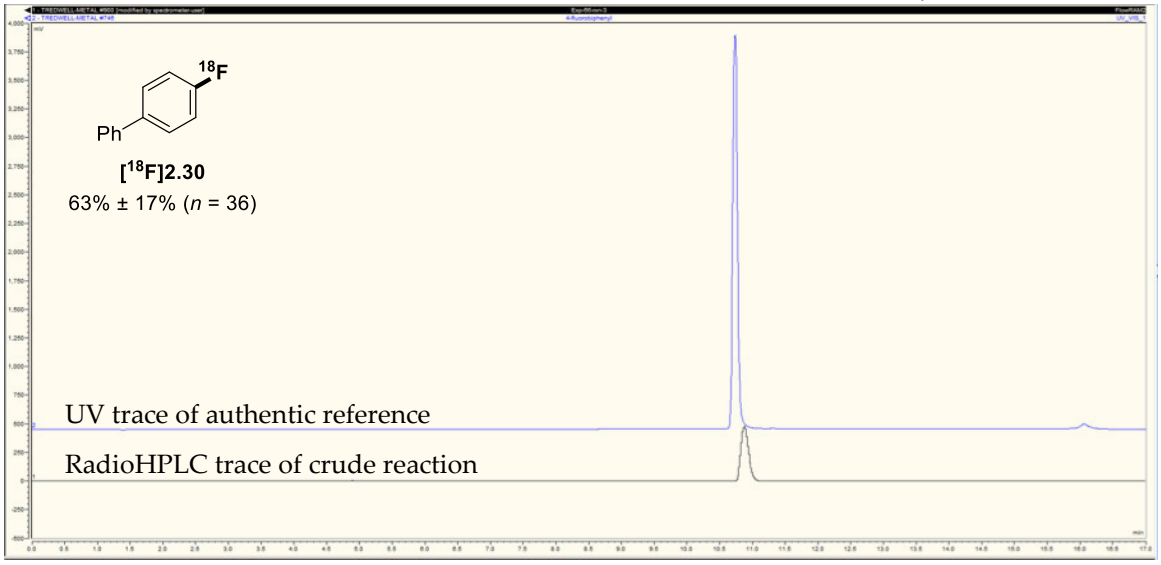
RCC values obtained:

3%	18%	21%	25%	28%	32%	35%	42%	47%	54%
4%	18%	22%	25%	29%	32%	36%	42%	48%	54%
5%	18%	22%	26%	29%	33%	36%	42%	48%	55%
5%	19%	23%	26%	29%	33%	37%	43%	48%	56%
6%	19%	23%	27%	30%	33%	37%	43%	49%	57%
11%	19%	23%	27%	30%	33%	37%	43%	50%	59%
12%	20%	24%	27%	30%	34%	37%	44%	51%	64%
15%	20%	24%	27%	30%	34%	38%	45%	51%	66%
16%	20%	25%	27%	31%	34%	39%	45%	52%	66%
16%	21%	25%	28%	31%	35%	40%	45%	52%	67%
17%	21%	25%	28%	32%	35%	40%	47%	52%	70%
17%	21%	25%	28%	32%	35%	41%	47%	53%	73%
18%	21%								

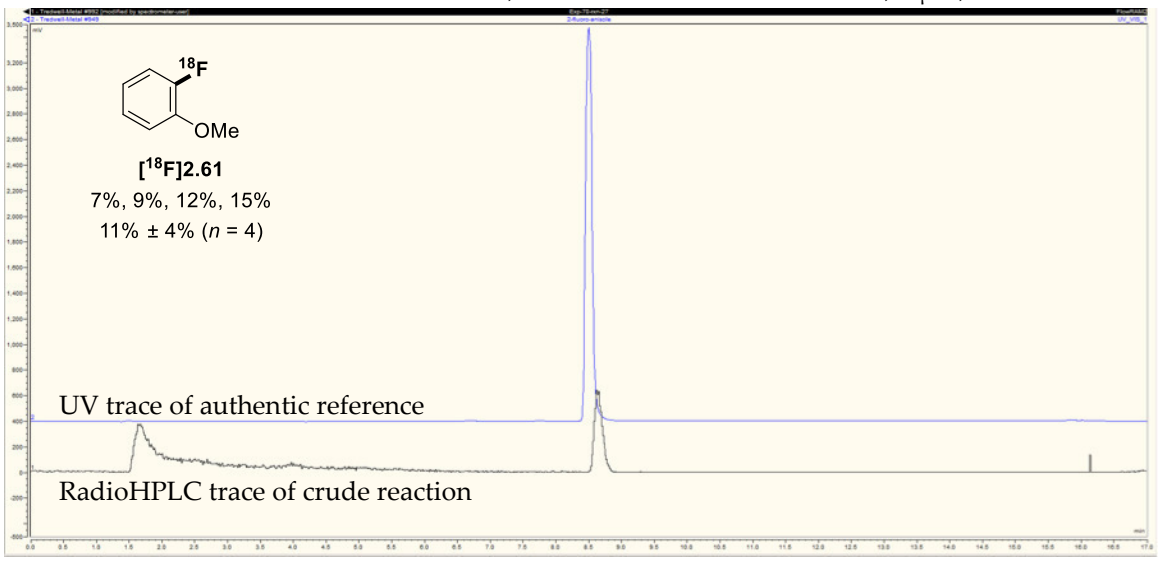
Overall, 34% ± 15% (*n* = 122).

4.4.24 Radio-HPLC Traces for Compounds in Table 2.9

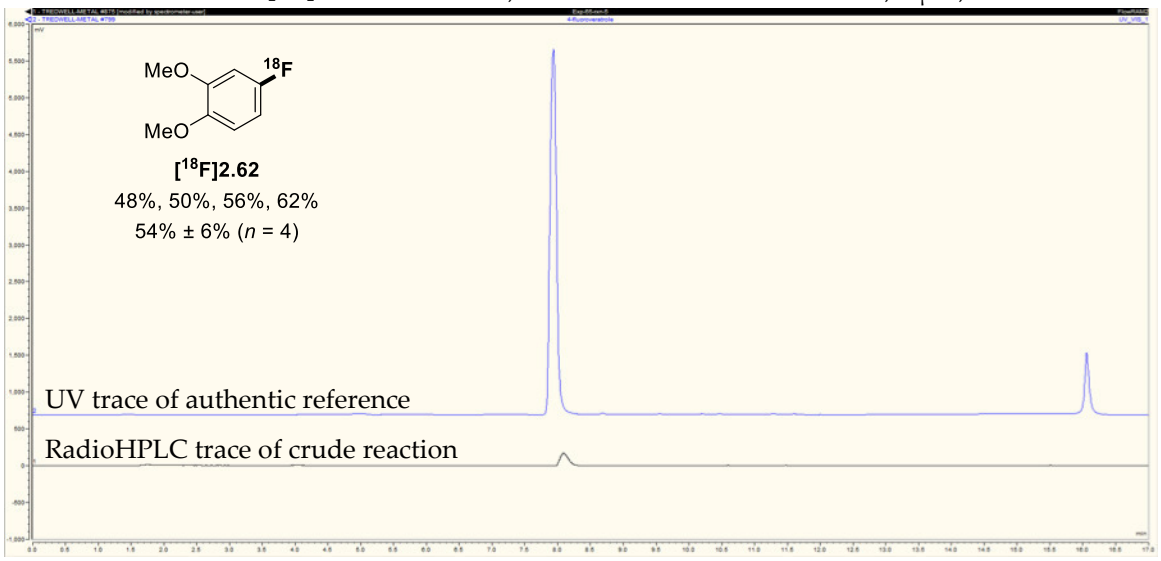
RadioHPLC Trace for **[^{18}F]2.30**. Gradient **A**, Waters Nova-Pak C18 Column, 4 µm, 3.9 x 150 mm.



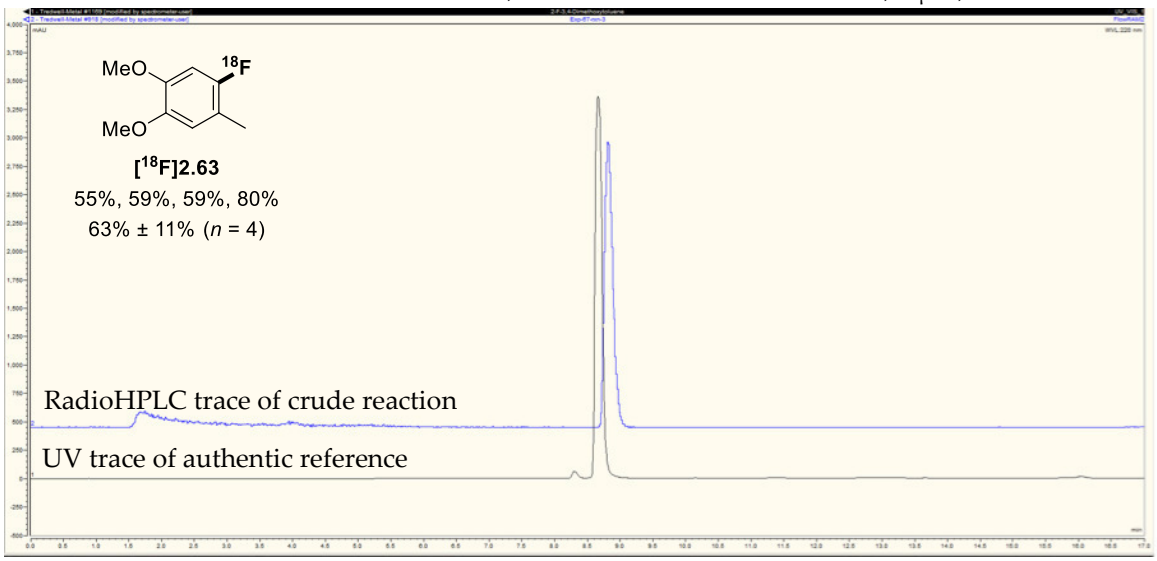
RadioHPLC Trace for **[^{18}F]2.61**. Gradient **A**, Waters Nova-Pak C18 Column, 4 µm, 3.9 x 150 mm.



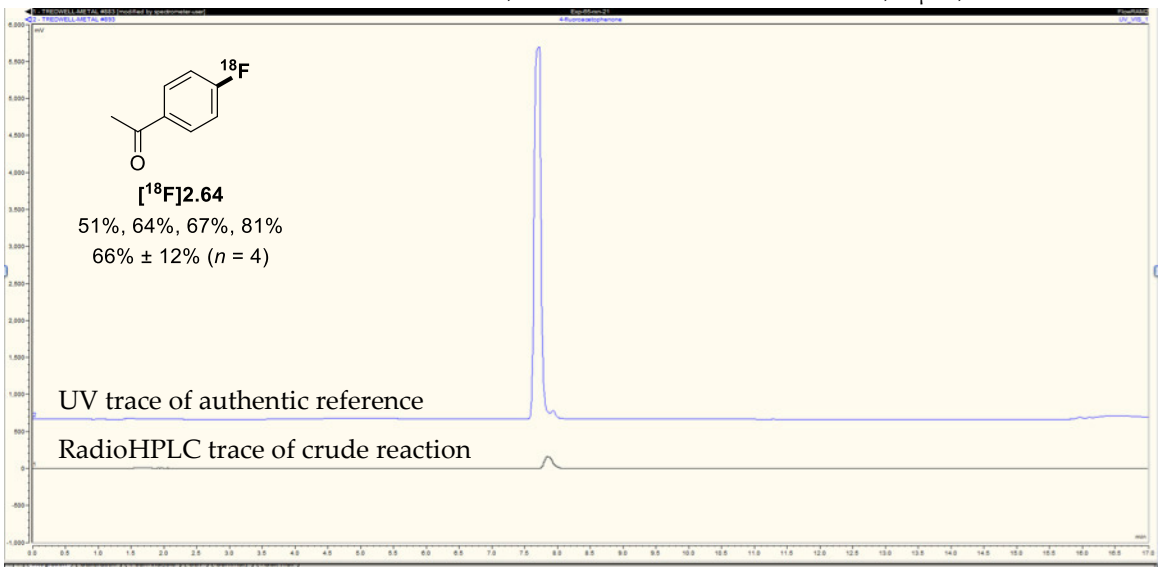
RadioHPLC Trace for **[^{18}F]2.62**. Gradient **A**, Waters Nova-Pak C18 Column, 4 µm, 3.9 x 150 mm.



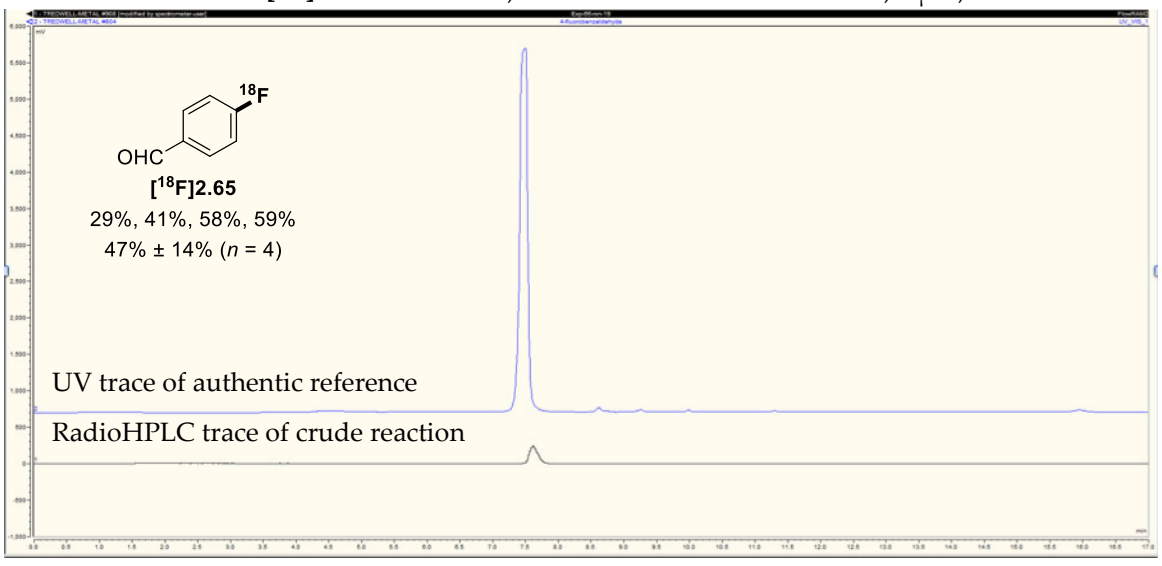
RadioHPLC Trace for **[^{18}F]2.63**. Gradient **A**, Waters Nova-Pak C18 Column, 4 μm, 3.9 x 150 mm.



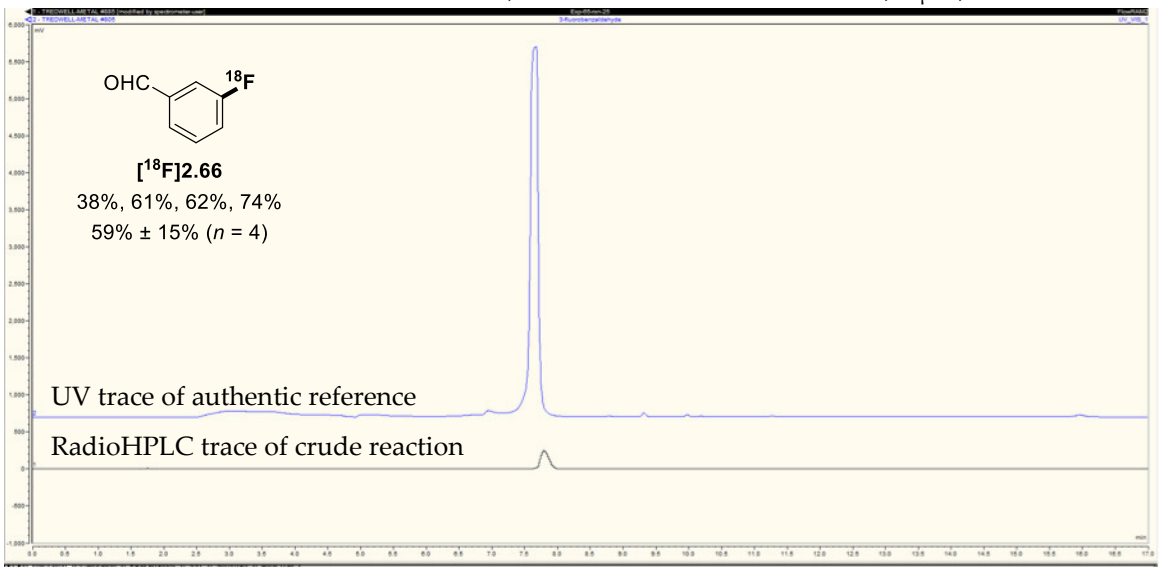
RadioHPLC Trace for **[^{18}F]2.64**. Gradient **A**, Waters Nova-Pak C18 Column, 4 μm, 3.9 x 150 mm.



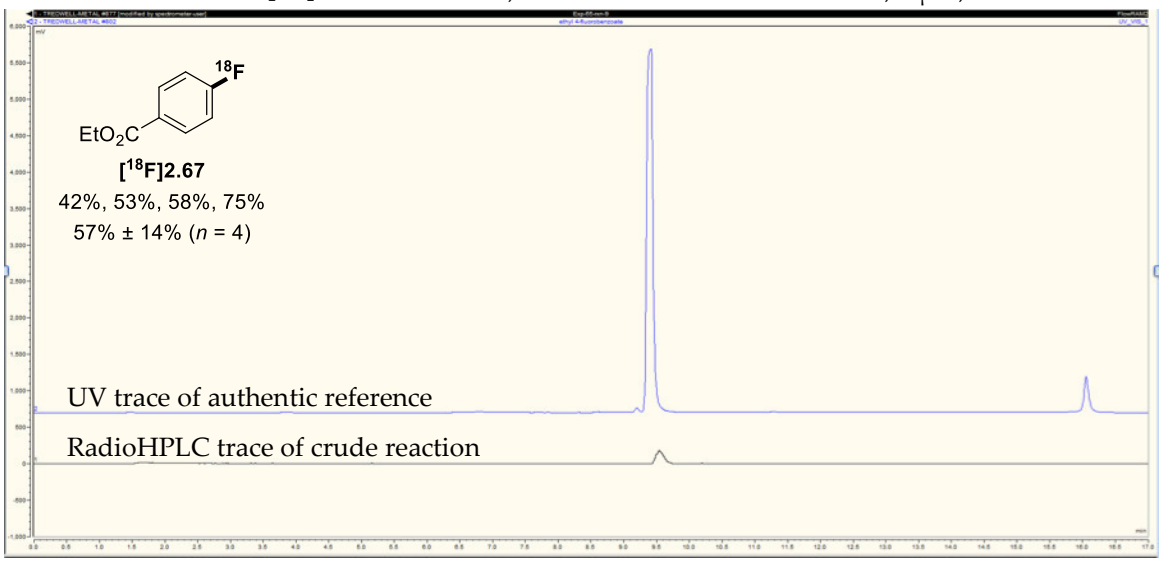
RadioHPLC Trace for **[^{18}F]2.65**. Gradient **A**, Waters Nova-Pak C18 Column, 4 μm, 3.9 x 150 mm.



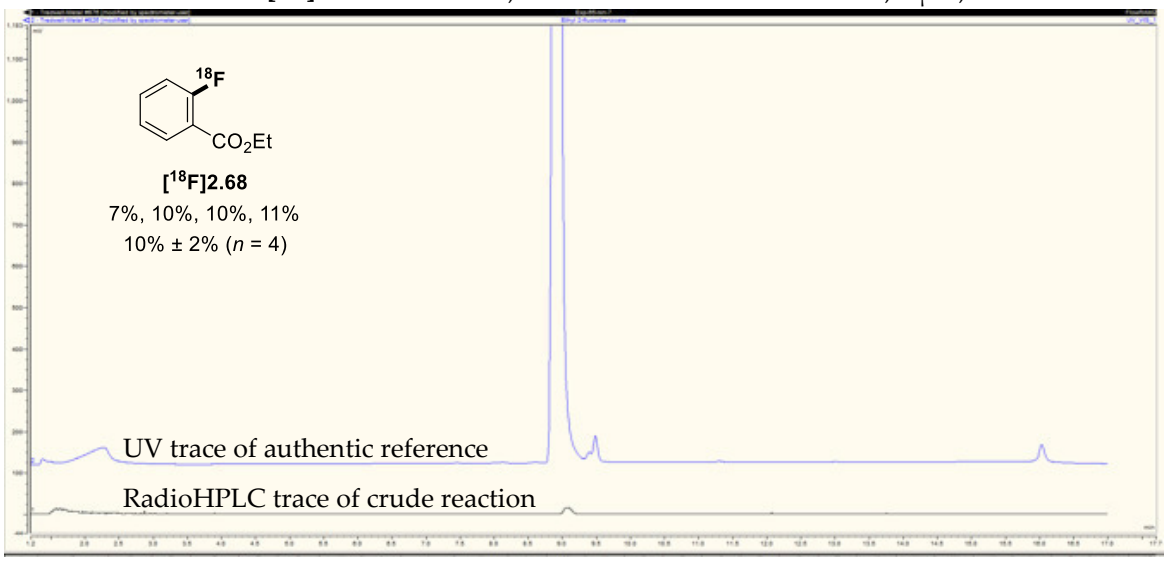
RadioHPLC Trace for **[^{18}F]2.66**. Gradient **A**, Waters Nova-Pak C18 Column, 4 µm, 3.9 x 150 mm.



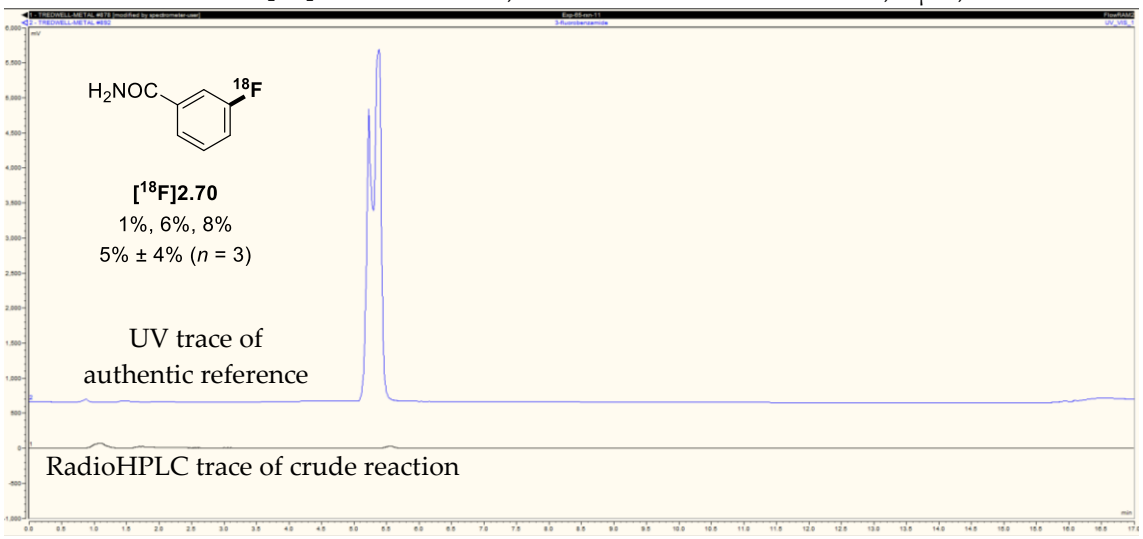
RadioHPLC Trace for **[^{18}F]2.67**. Gradient **A**, Waters Nova-Pak C18 Column, 4 µm, 3.9 x 150 mm.



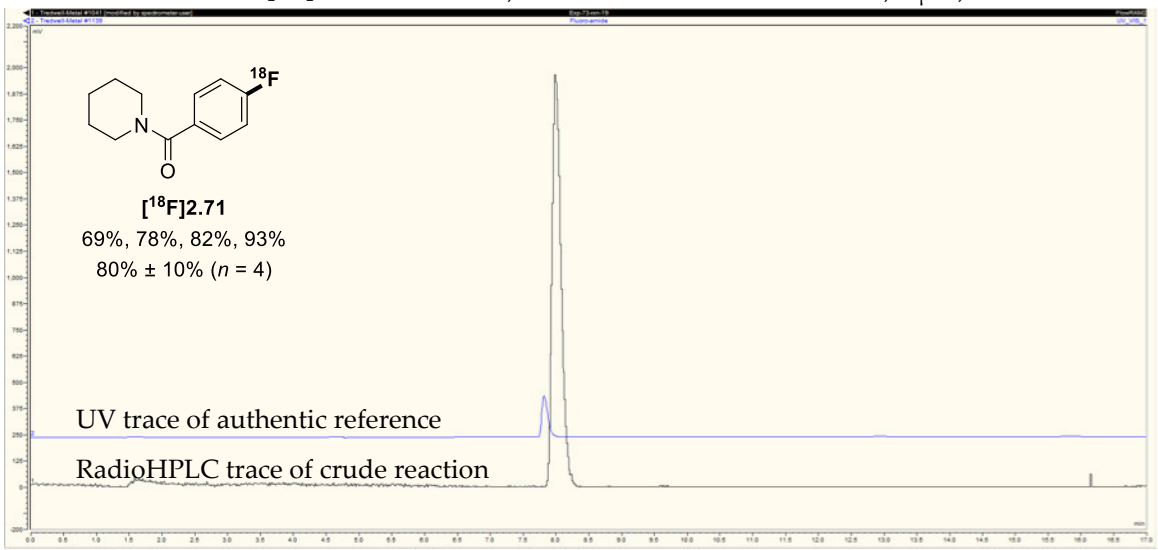
RadioHPLC Trace for **[^{18}F]2.68**. Gradient **A**, Waters Nova-Pak C18 Column, 4 µm, 3.9 x 150 mm.



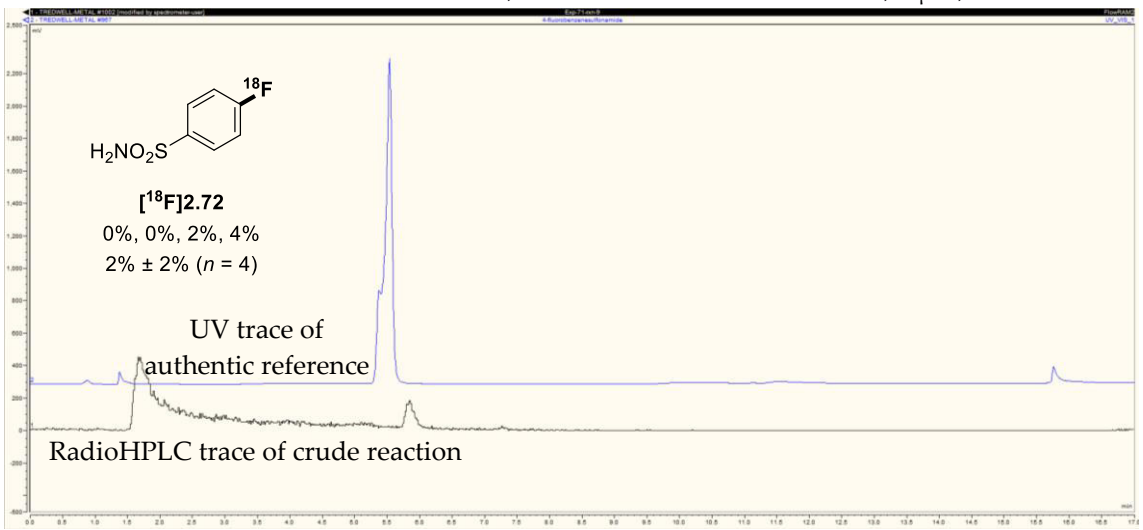
RadioHPLC Trace for **[^{18}F]2.70**. Gradient **A**, Waters Nova-Pak C18 Column, 4 μm, 3.9 x 150 mm.



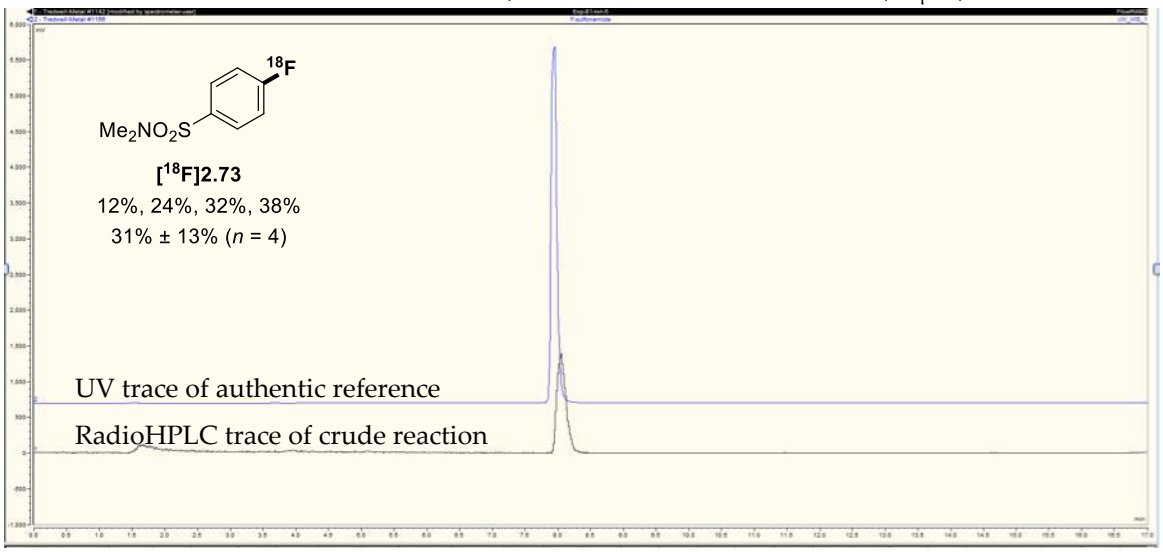
RadioHPLC Trace for **[^{18}F]2.71**. Gradient **A**, Waters Nova-Pak C18 Column, 4 μm, 3.9 x 150 mm



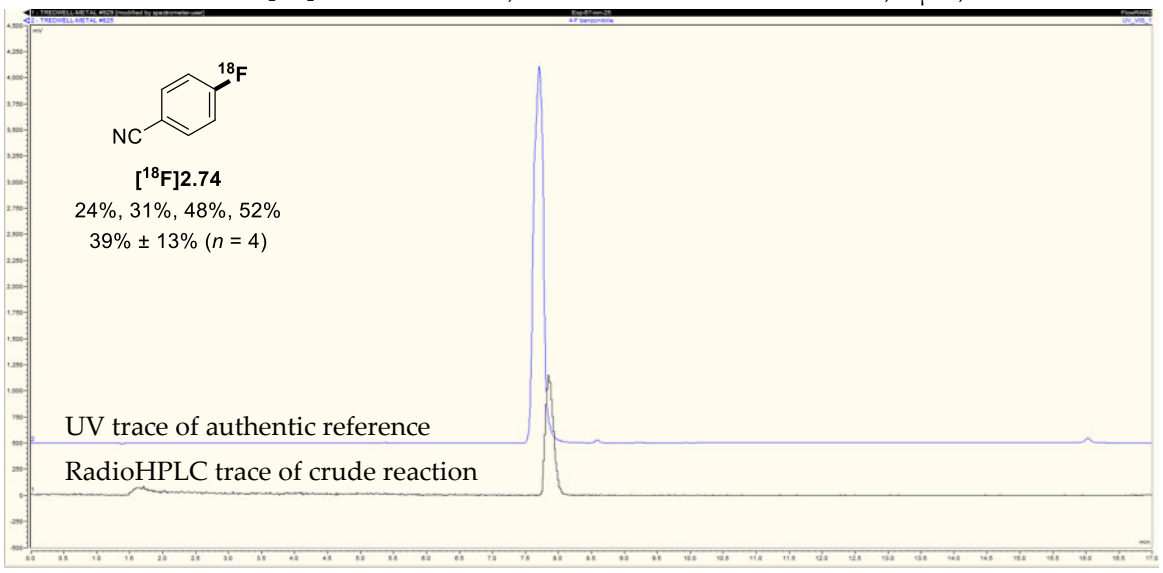
RadioHPLC Trace for **[^{18}F]2.72**. Gradient **A**, Waters Nova-Pak C18 Column, 4 μm, 3.9 x 150 mm.



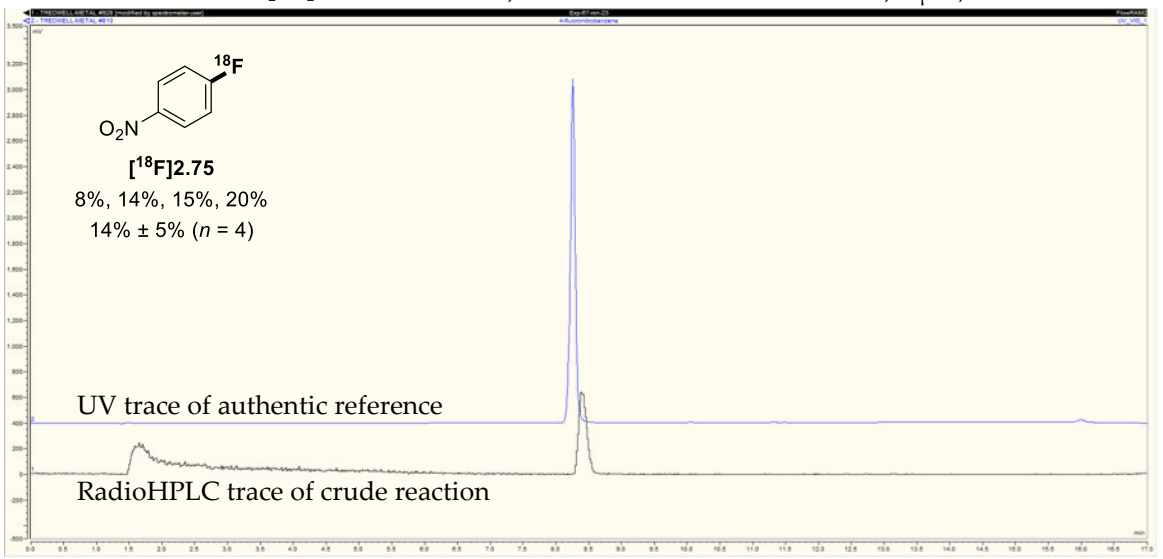
RadioHPLC Trace for **[^{18}F]2.73**. Gradient **A**, Waters Nova-Pak C18 Column, 4 µm, 3.9 x 150 mm



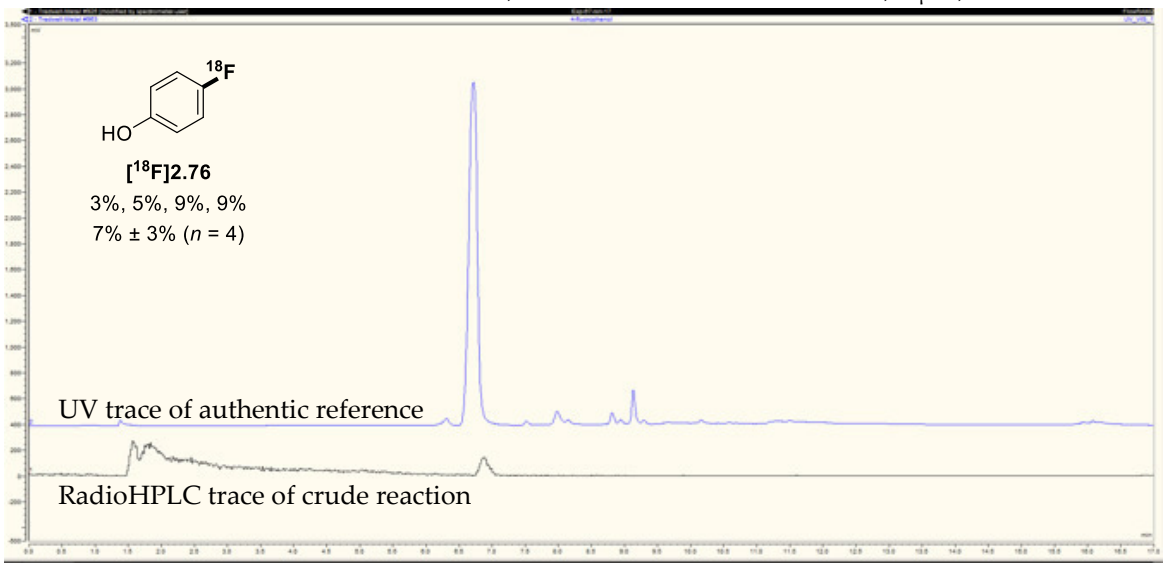
RadioHPLC Trace for **[^{18}F]2.74**. Gradient **A**, Waters Nova-Pak C18 Column, 4 µm, 3.9 x 150 mm



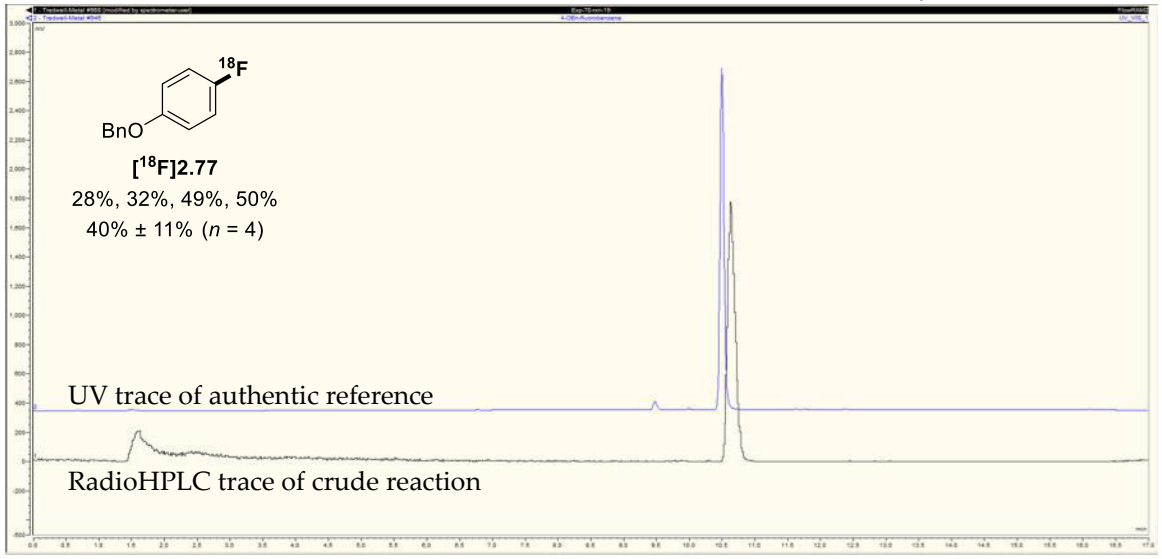
RadioHPLC Trace for **[^{18}F]2.75**. Gradient **A**, Waters Nova-Pak C18 Column, 4 µm, 3.9 x 150 mm



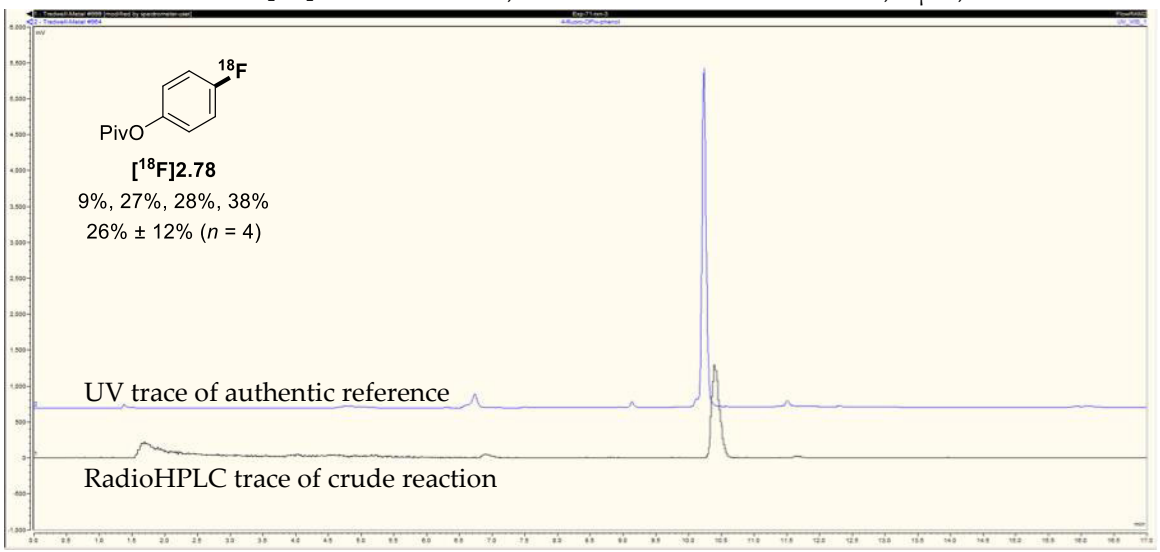
RadioHPLC Trace for **[^{18}F]2.76**. Gradient **A**, Waters Nova-Pak C18 Column, 4 μm, 3.9 x 150 mm



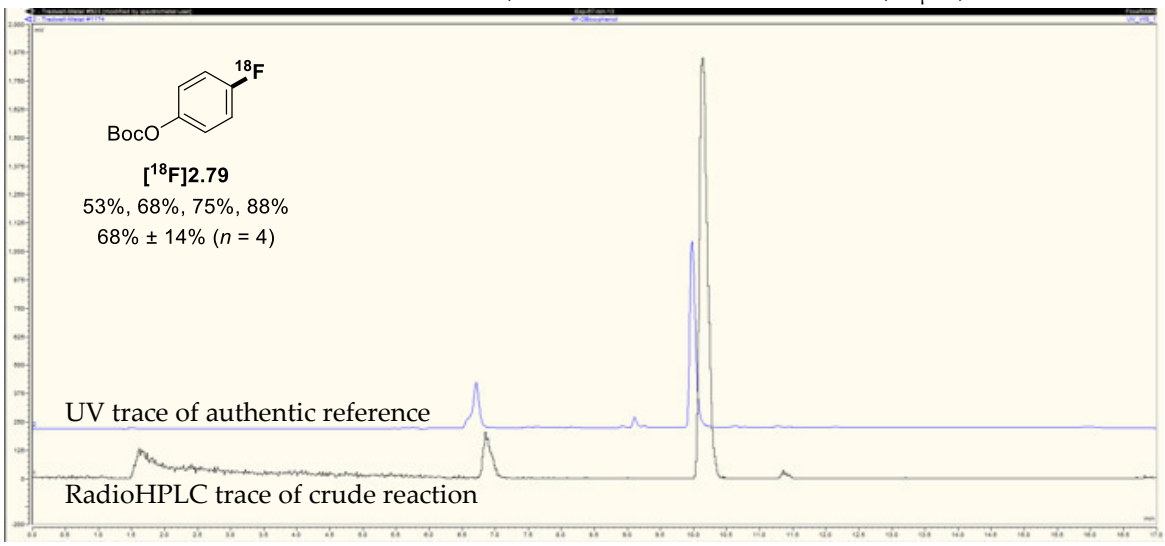
RadioHPLC Trace for **[^{18}F]2.77**. Gradient **A**, Waters Nova-Pak C18 Column, 4 μm, 3.9 x 150 mm



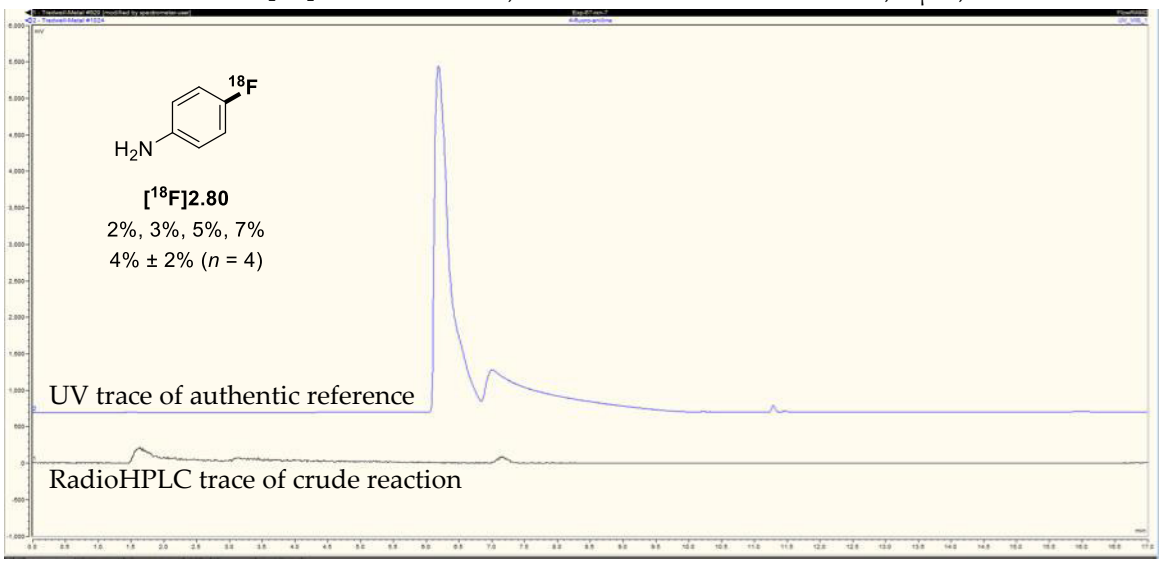
RadioHPLC Trace for **[^{18}F]2.78**. Gradient **A**, Waters Nova-Pak C18 Column, 4 μm, 3.9 x 150 mm



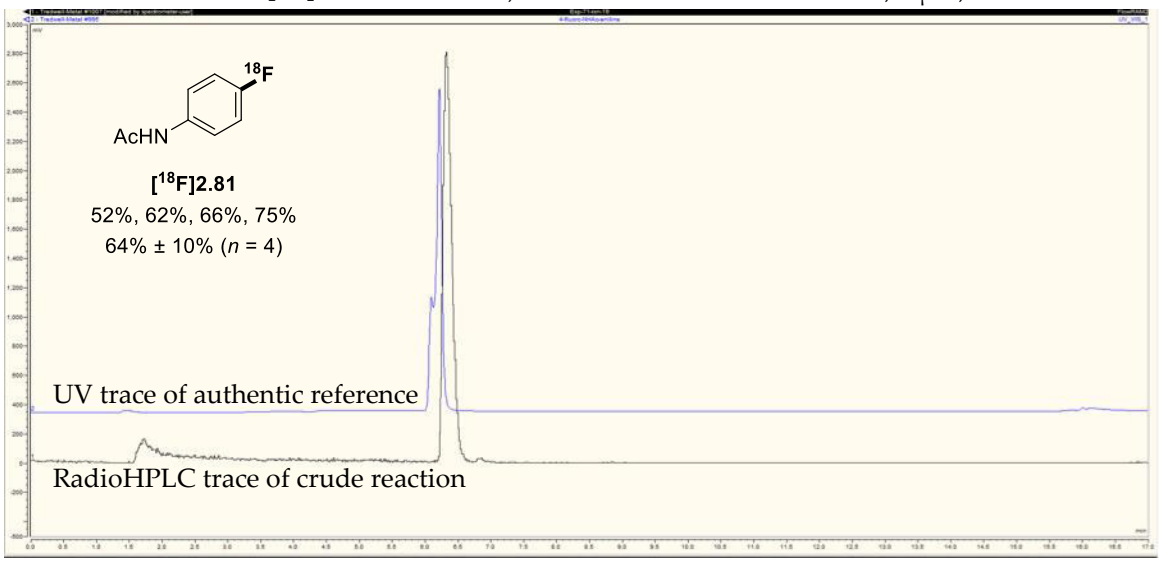
RadioHPLC Trace for **[^{18}F]2.79**. Gradient **A**, Waters Nova-Pak C18 Column, 4 μm, 3.9 x 150 mm



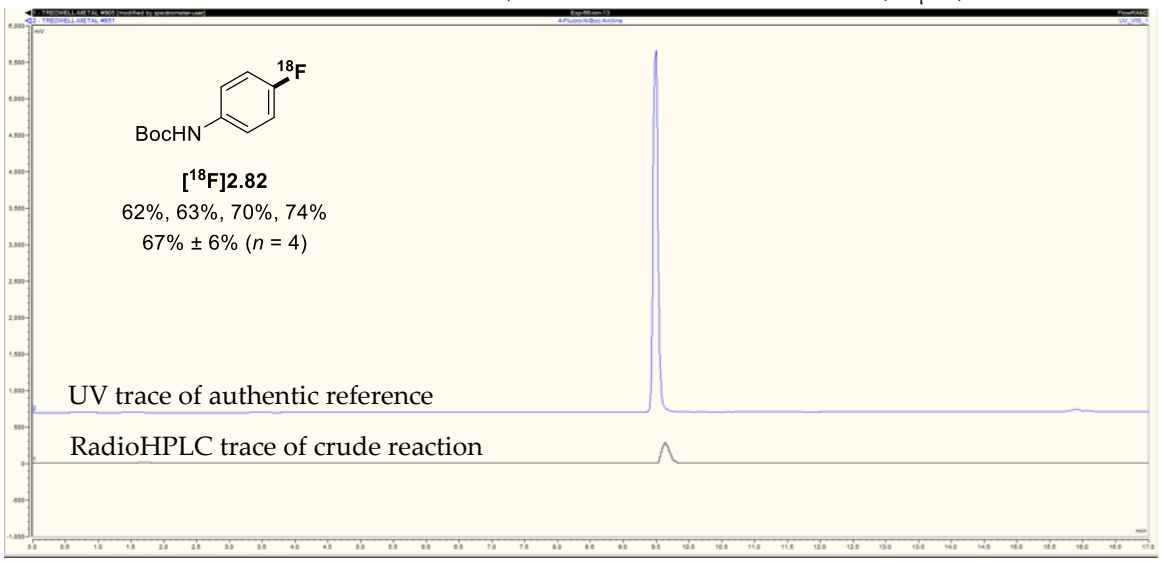
RadioHPLC Trace for **[^{18}F]2.80**. Gradient **A**, Waters Nova-Pak C18 Column, 4 μm, 3.9 x 150 mm



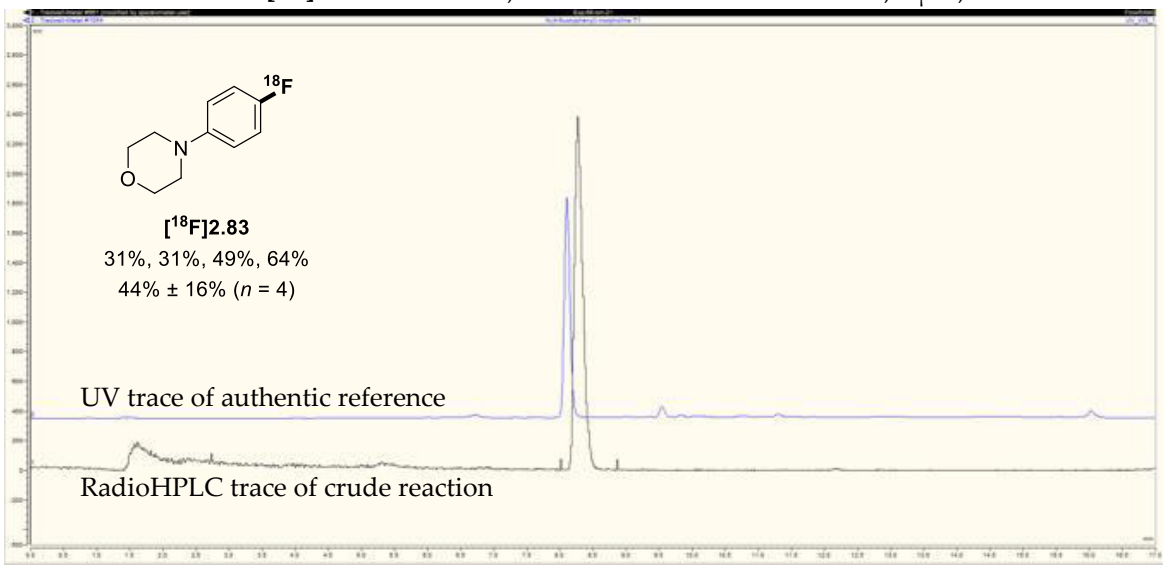
RadioHPLC Trace for **[^{18}F]2.81**. Gradient **A**, Waters Nova-Pak C18 Column, 4 μm, 3.9 x 150 mm



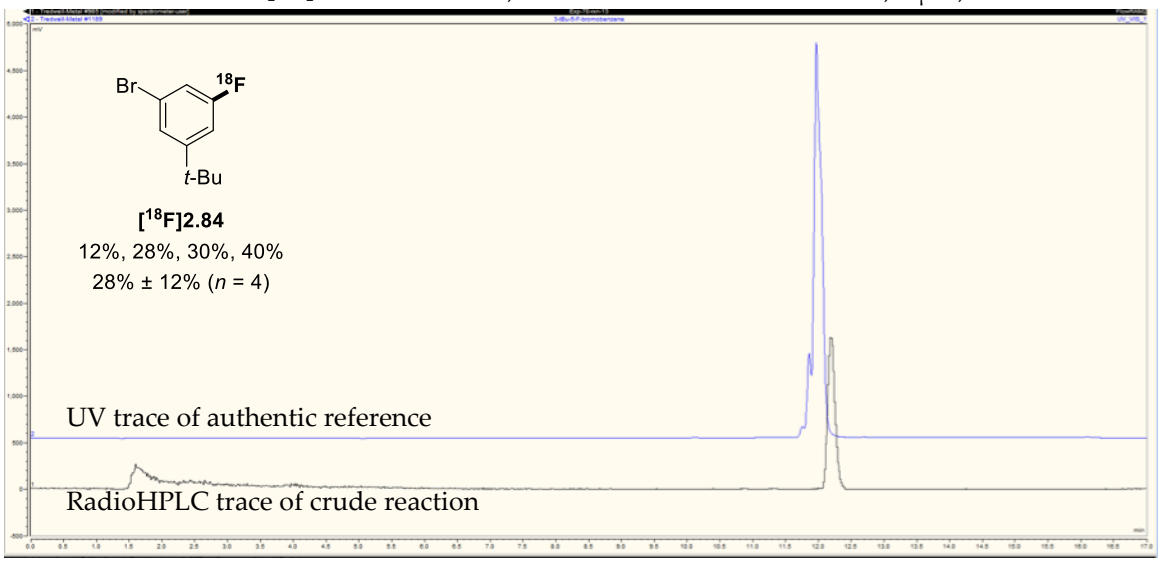
RadioHPLC Trace for **[^{18}F]2.82**. Gradient **A**, Waters Nova-Pak C18 Column, 4 μm, 3.9 x 150 mm



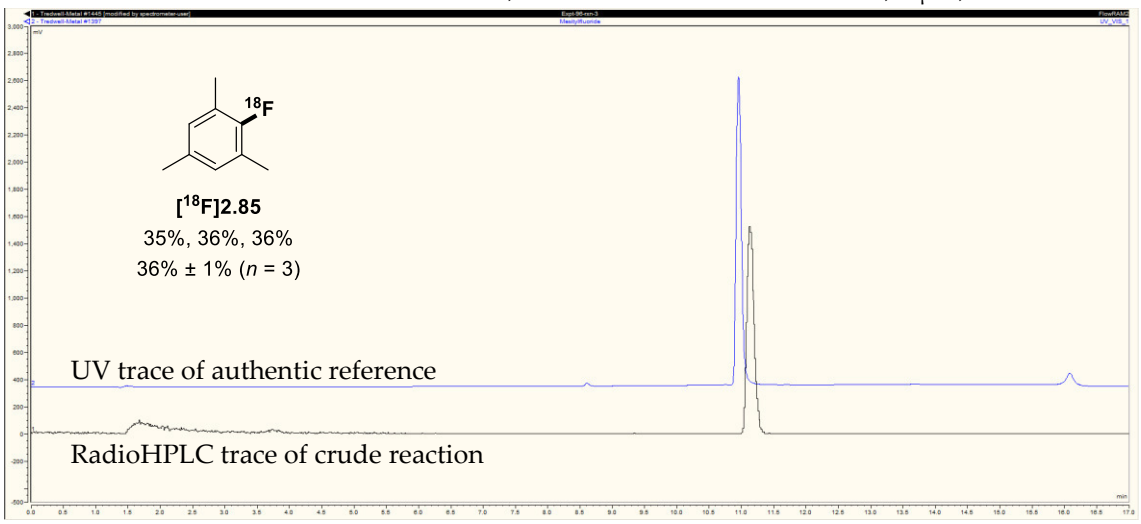
RadioHPLC Trace for **[^{18}F]2.83**. Gradient **A**, Waters Nova-Pak C18 Column, 4 μm, 3.9 x 150 mm



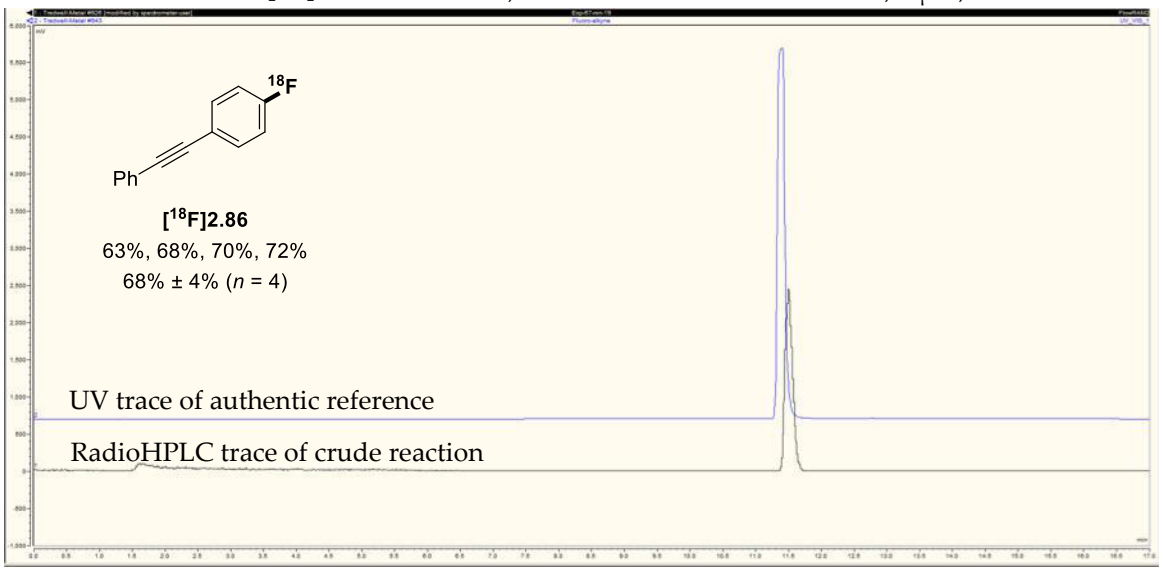
RadioHPLC Trace for **[^{18}F]2.84**. Gradient **A**, Waters Nova-Pak C18 Column, 4 μm, 3.9 x 150 mm



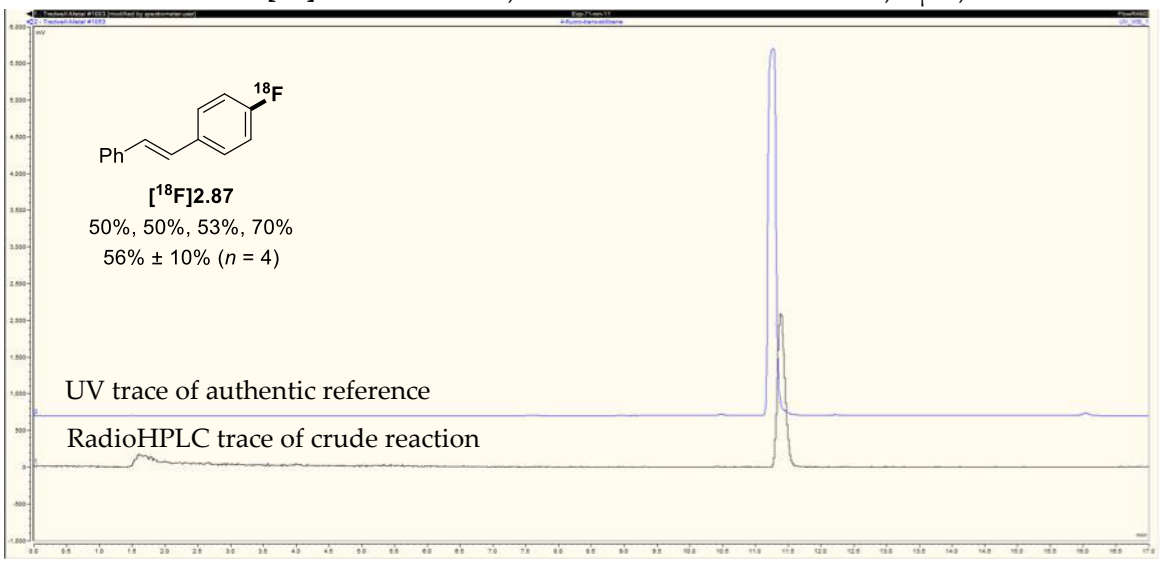
RadioHPLC Trace for **[^{18}F]2.85**. Gradient **A**, Waters Nova-Pak C18 Column, 4 µm, 3.9 x 150 mm



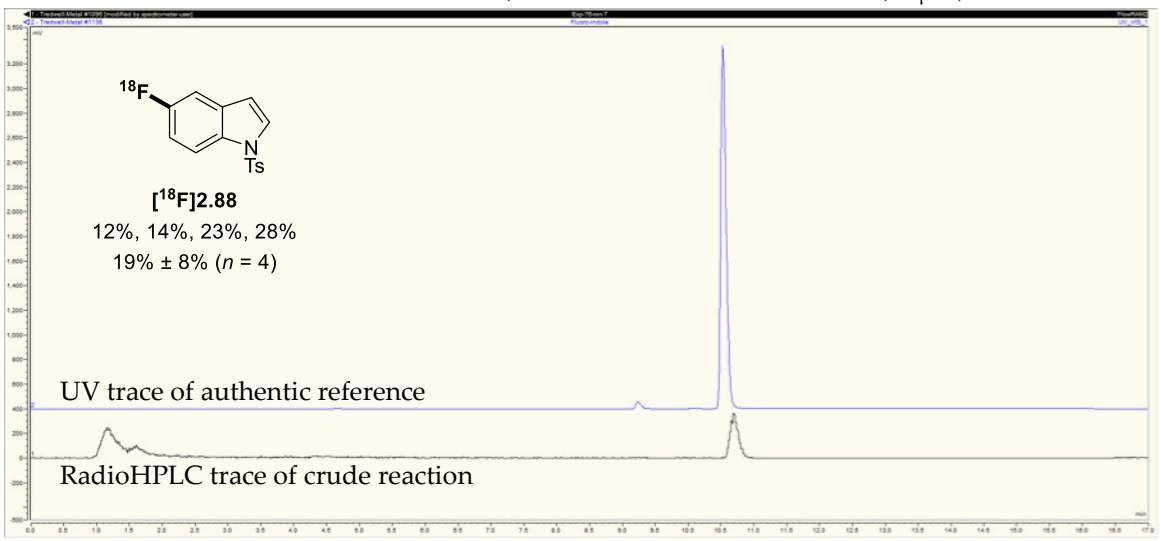
RadioHPLC Trace for **[^{18}F]2.86**. Gradient **A**, Waters Nova-Pak C18 Column, 4 µm, 3.9 x 150 mm



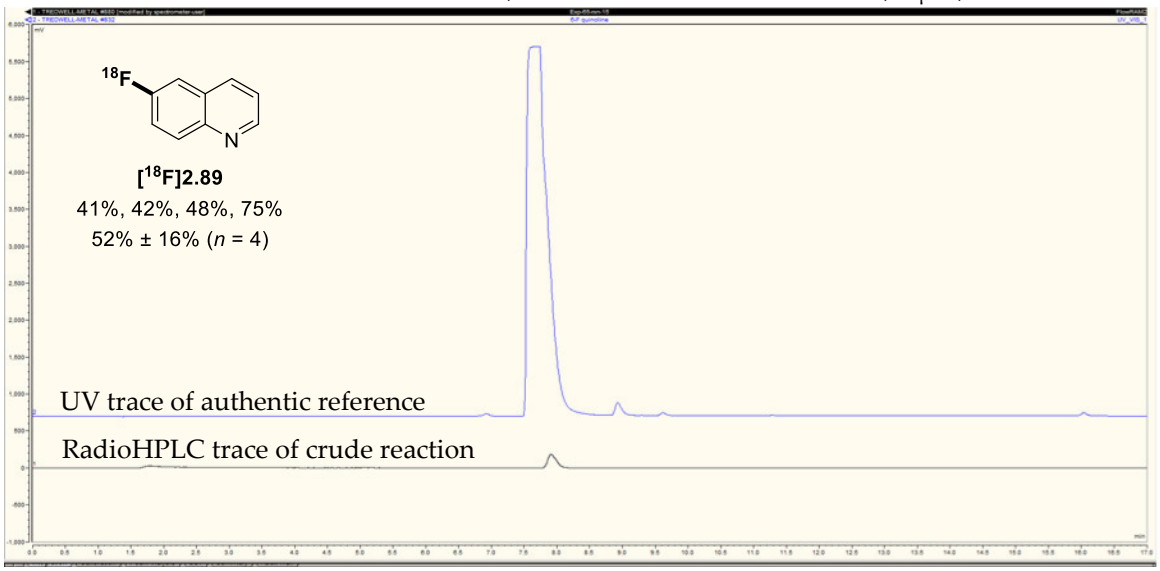
RadioHPLC Trace for **[^{18}F]2.87**. Gradient **A**, Waters Nova-Pak C18 Column, 4 µm, 3.9 x 150 mm



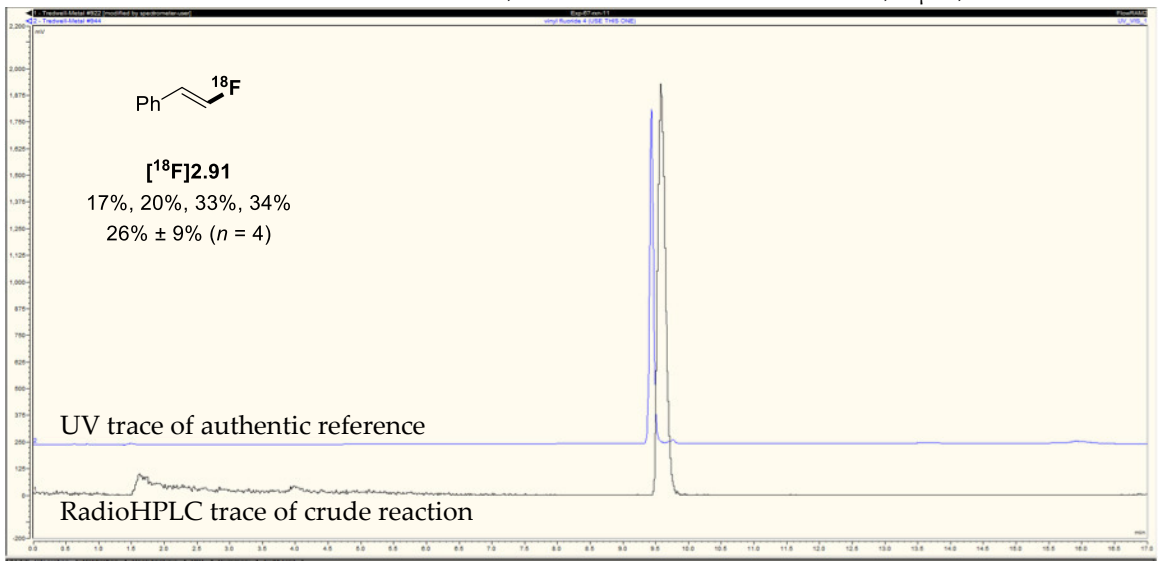
RadioHPLC Trace for **[^{18}F]2.88**. Gradient **A**, Waters Nova-Pak C18 Column, 4 μm, 3.9 x 150 mm



RadioHPLC Trace for **[^{18}F]2.89**. Gradient **A**, Waters Nova-Pak C18 Column, 4 μm, 3.9 x 150 mm

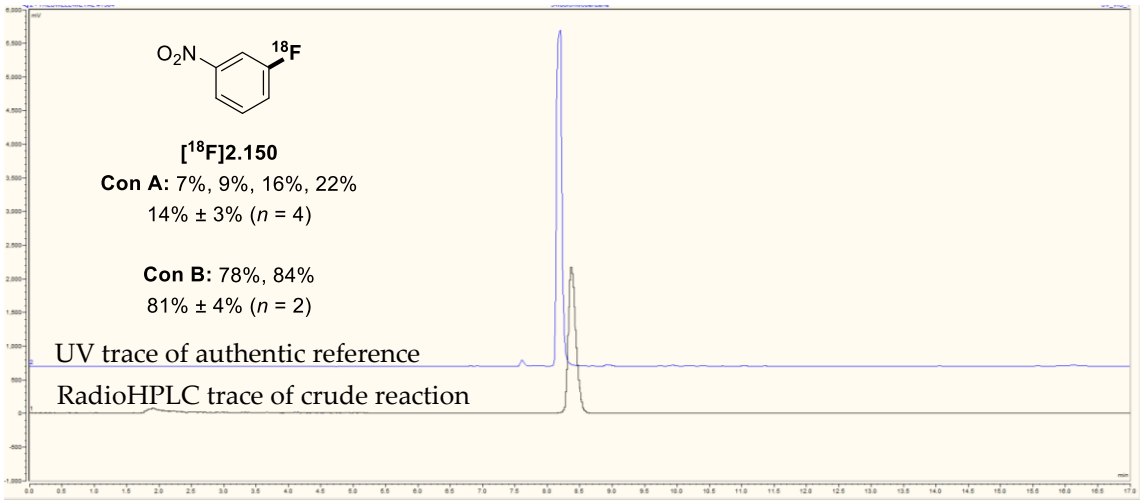


RadioHPLC Trace for **[^{18}F]2.91**. Gradient **A**, Waters Nova-Pak C18 Column, 4 μm, 3.9 x 150 mm

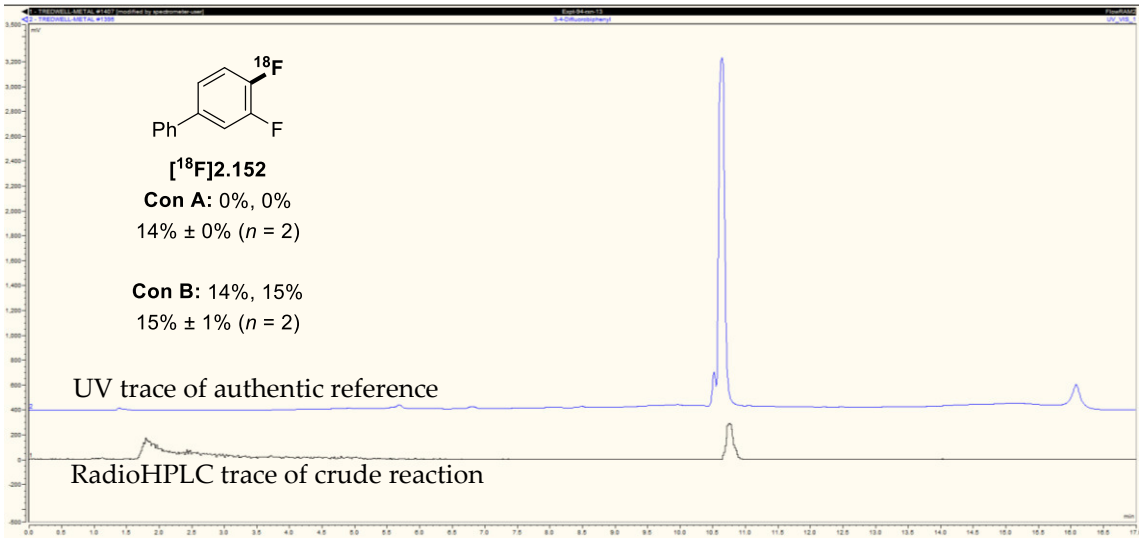


4.4.25 Radio-HPLC Traces for Compounds in Table 2.12

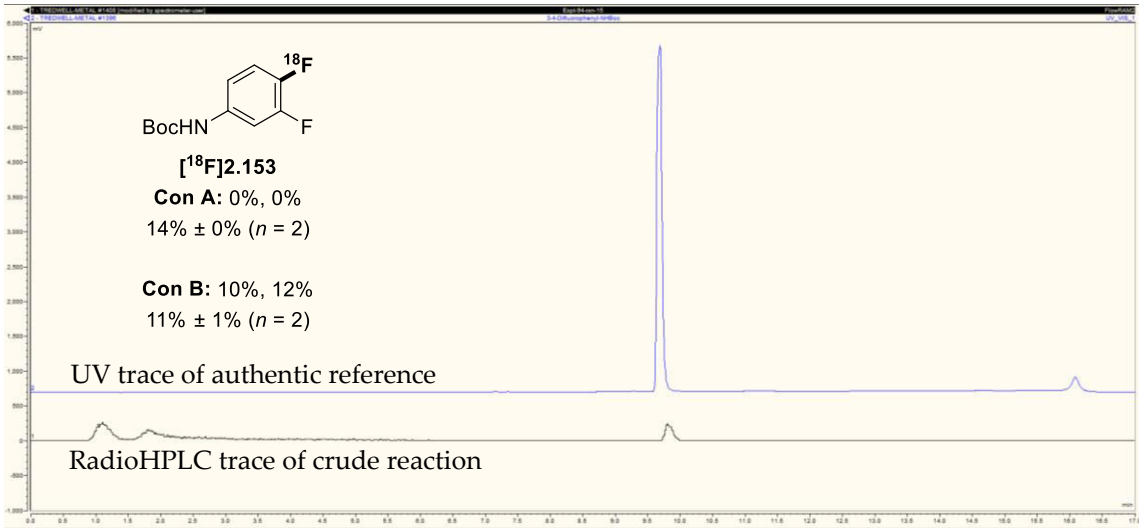
RadioHPLC Trace for **[^{18}F]2.150**. Gradient **A**, Waters Nova-Pak C18 Column, 4 µm, 3.9 x 150 mm



RadioHPLC Trace for **[^{18}F]2.152**. Gradient **A**, Waters Nova-Pak C18 Column, 4 µm, 3.9 x 150 mm

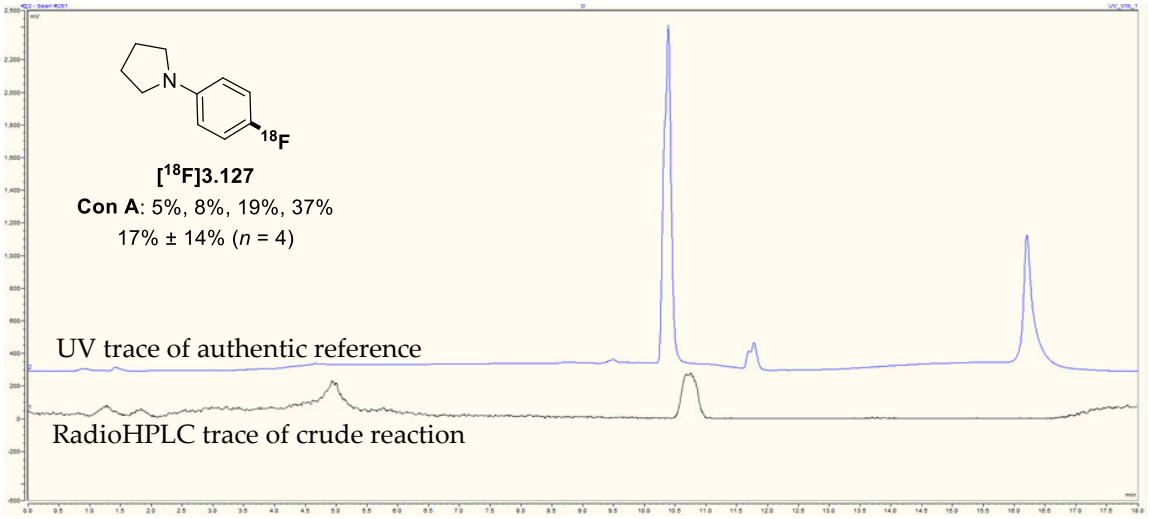


RadioHPLC Trace for **[^{18}F]2.153**. Gradient **A**, Waters Nova-Pak C18 Column, 4 µm, 3.9 x 150 mm

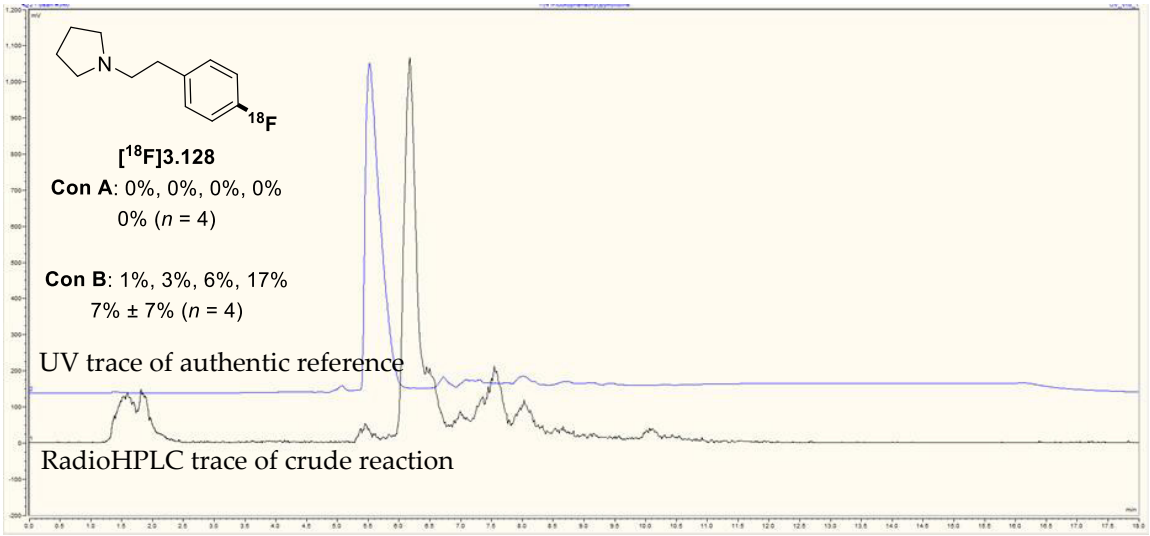


4.4.26 Radio-HPLC Traces for Compounds in Tables 3.17 and 3.18

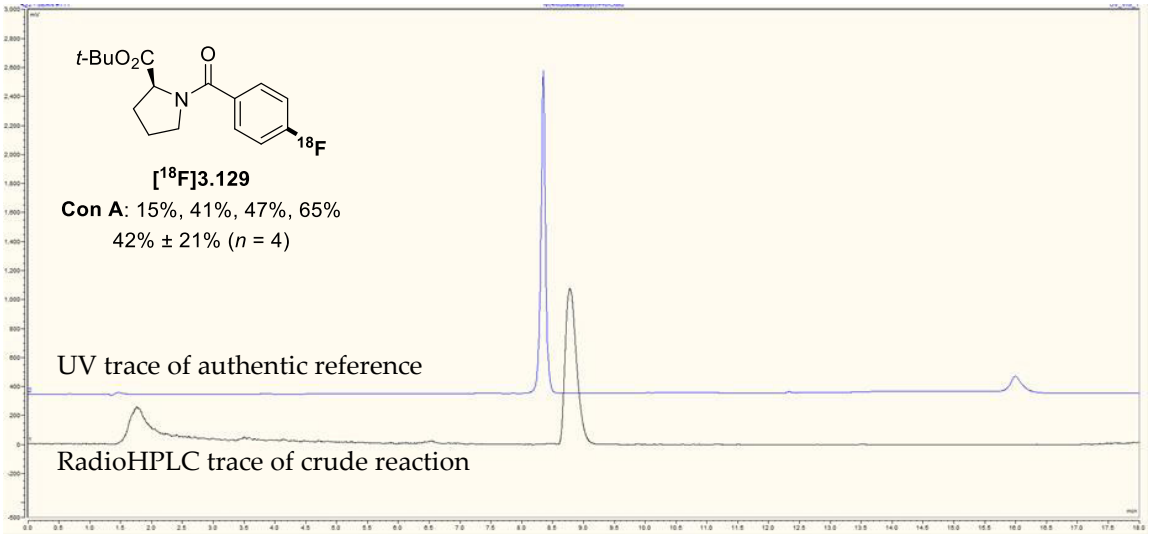
RadioHPLC Trace for **[^{18}F]3.127**. Gradient **A**, Waters Nova-Pak C18 Column, 4 μm, 3.9 x 150 mm.



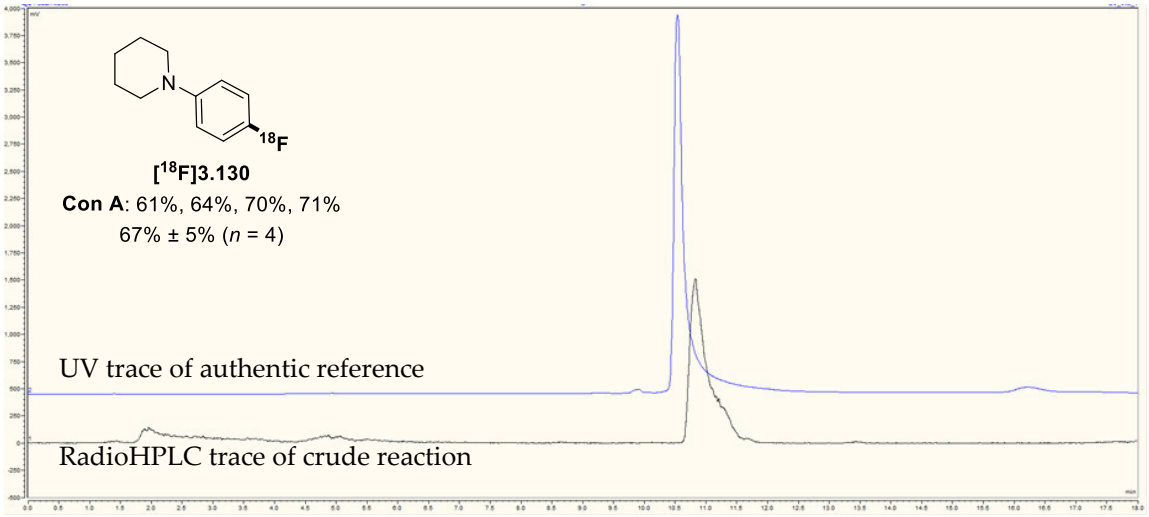
RadioHPLC Trace for **[^{18}F]3.128**. Gradient **A**, Waters Nova-Pak C18 Column, 4 μm, 3.9 x 150 mm.



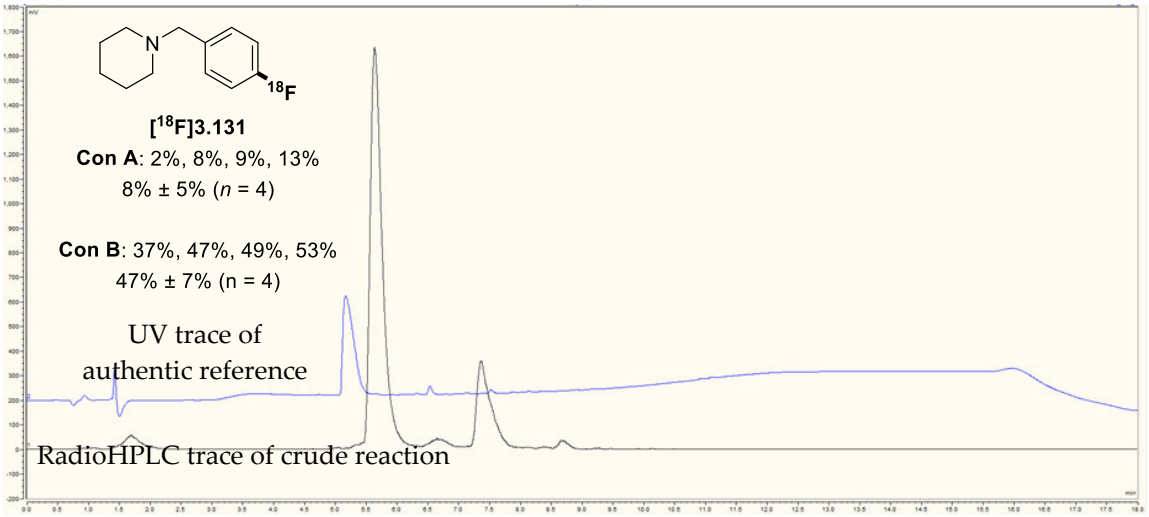
RadioHPLC Trace for **[^{18}F]3.129**. Gradient **A**, Waters Nova-Pak C18 Column, 4 μm, 3.9 x 150 mm.



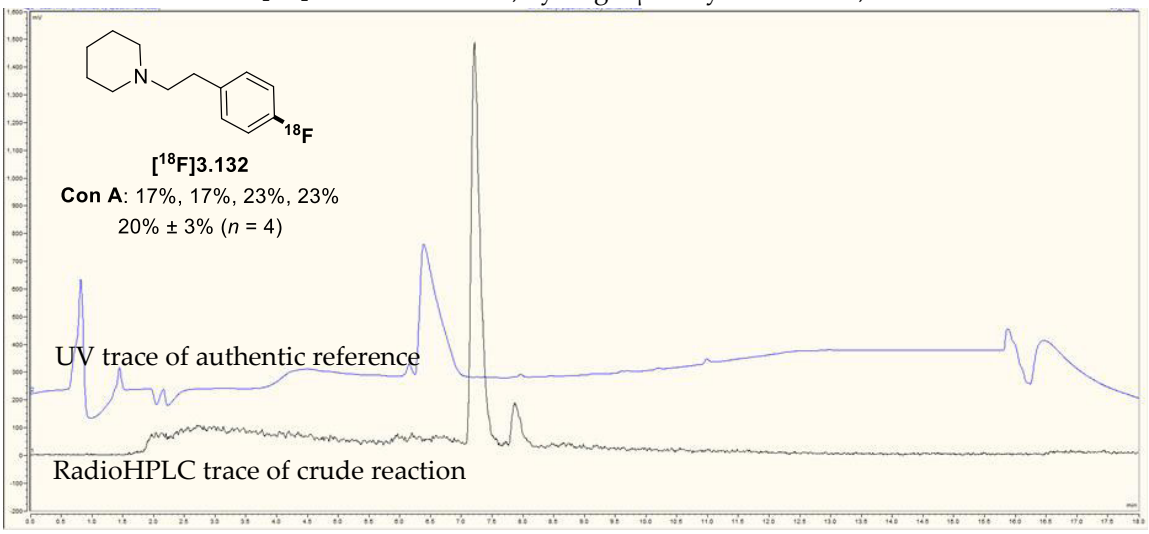
RadioHPLC Trace for **[^{18}F]3.130**. Gradient **A**, Waters Nova-Pak C18 Column, 4 μm, 3.9 x 150 mm.



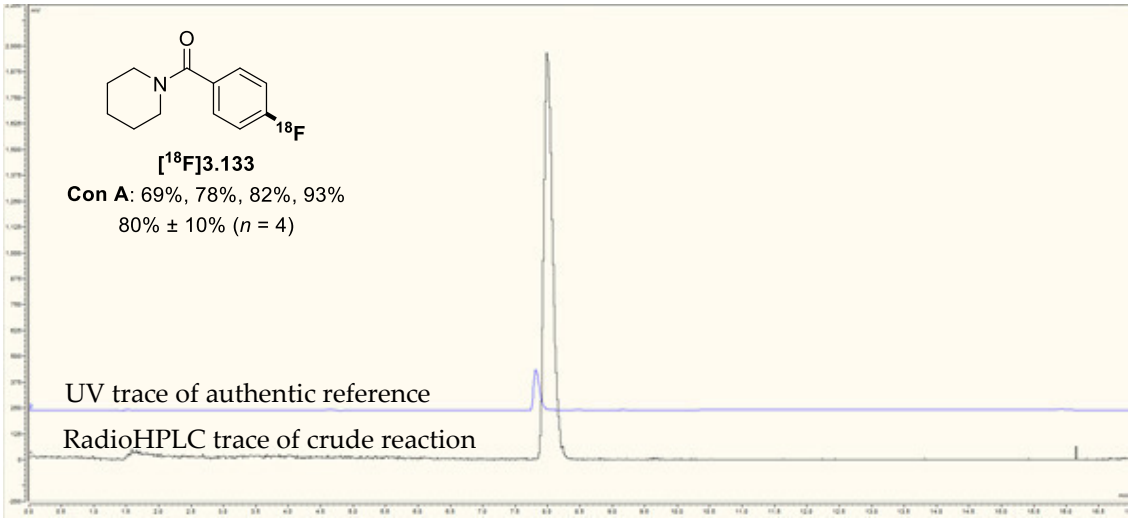
RadioHPLC Trace for **[^{18}F]3.131**. Gradient **B**, Waters Nova-Pak C18 Column, 4 μm, 3.9 x 150 mm.



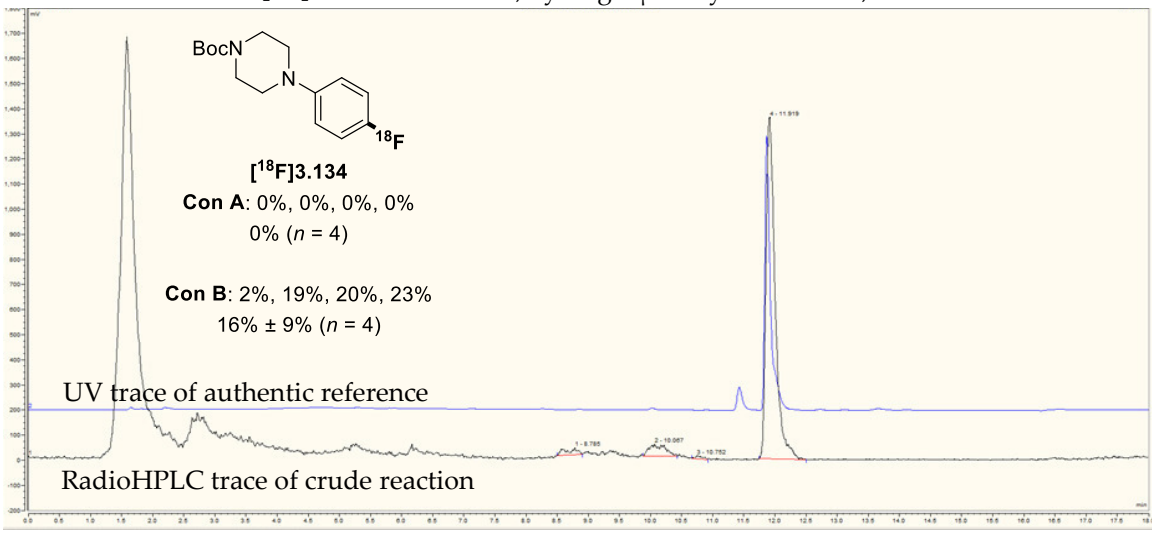
RadioHPLC Trace for **[^{18}F]3.132**. Gradient **B**, Synergi 4μm Hydro-RP 80A, 150 x 4.6 mm.



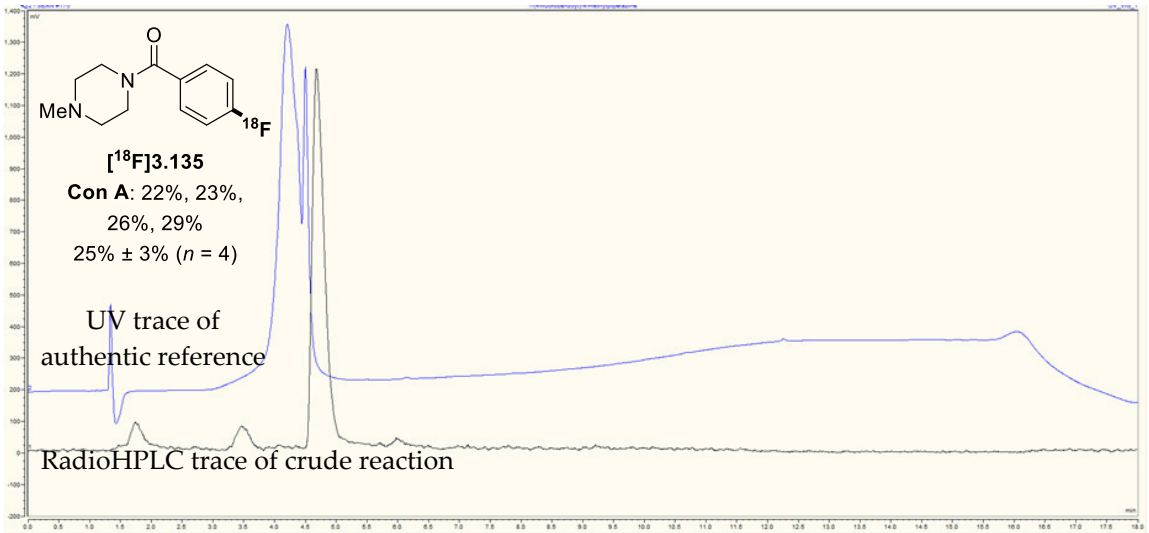
RadioHPLC Trace for **[^{18}F]3.133**. Gradient **A**, Waters Nova-Pak C18 Column, 4 μm, 3.9 x 150 mm.



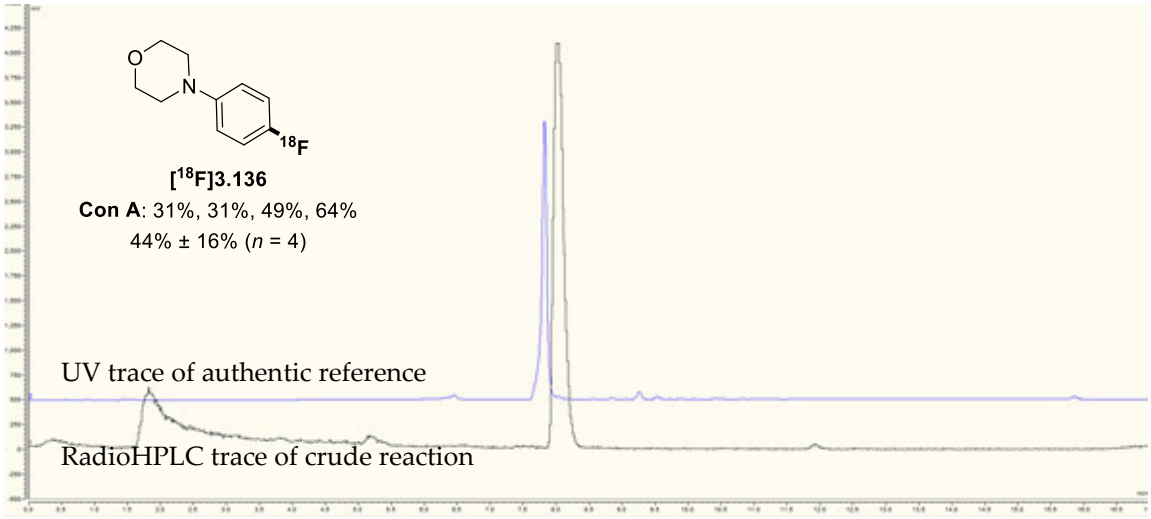
RadioHPLC Trace for **[^{18}F]3.134.** Gradient **A**, Synergi 4μm Hydro-RP 80A, 150 x 4.6 mm.



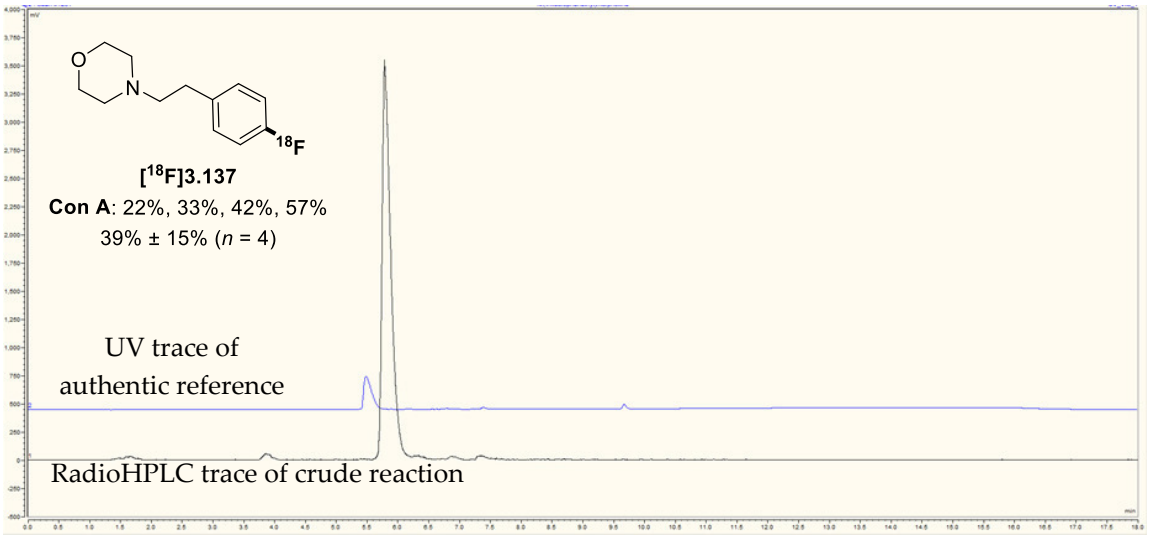
RadioHPLC Trace for **[^{18}F]3.135**. Gradient **B**, Waters Nova-Pak C18 Column, 4 μm, 3.9 x 150 mm.



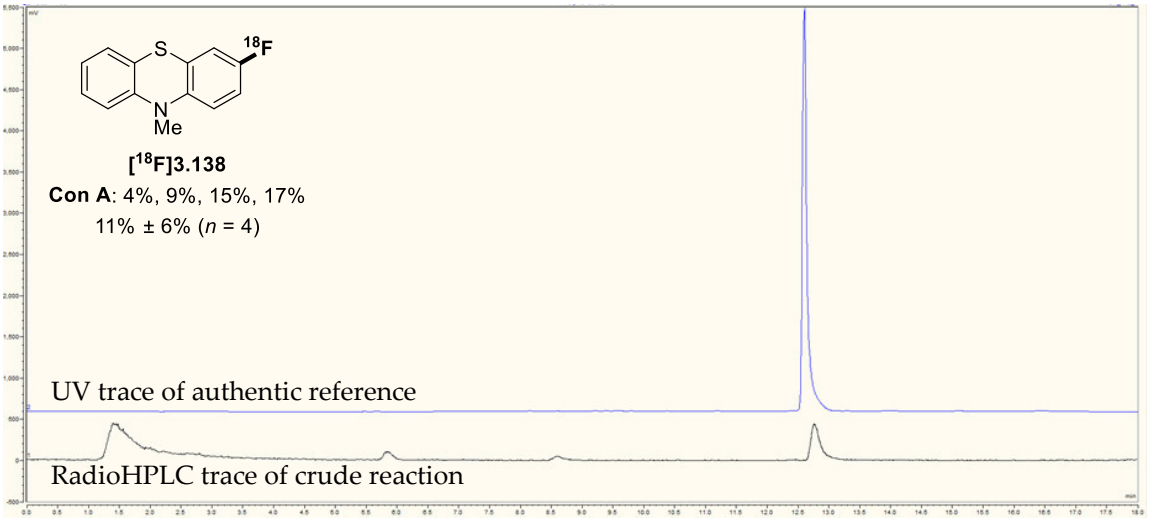
RadioHPLC Trace for **[^{18}F]3.136**. Gradient **A**, Waters Nova-Pak C18 Column, 4 µm, 3.9 x 150 mm.



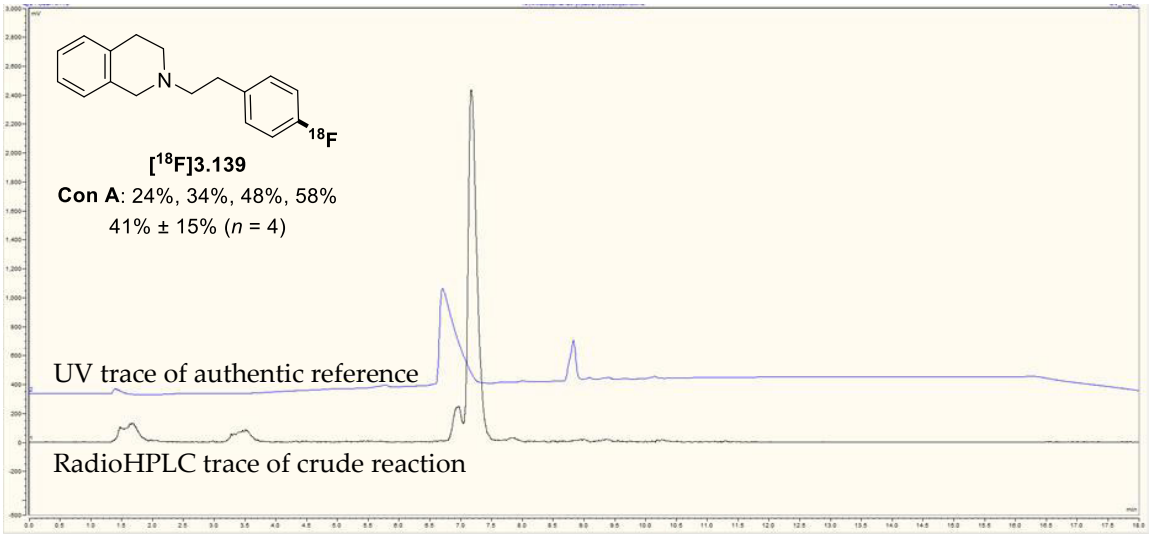
RadioHPLC Trace for **[^{18}F]3.137**. Gradient **B**, Waters Nova-Pak C18 Column, 4 µm, 3.9 x 150 mm.



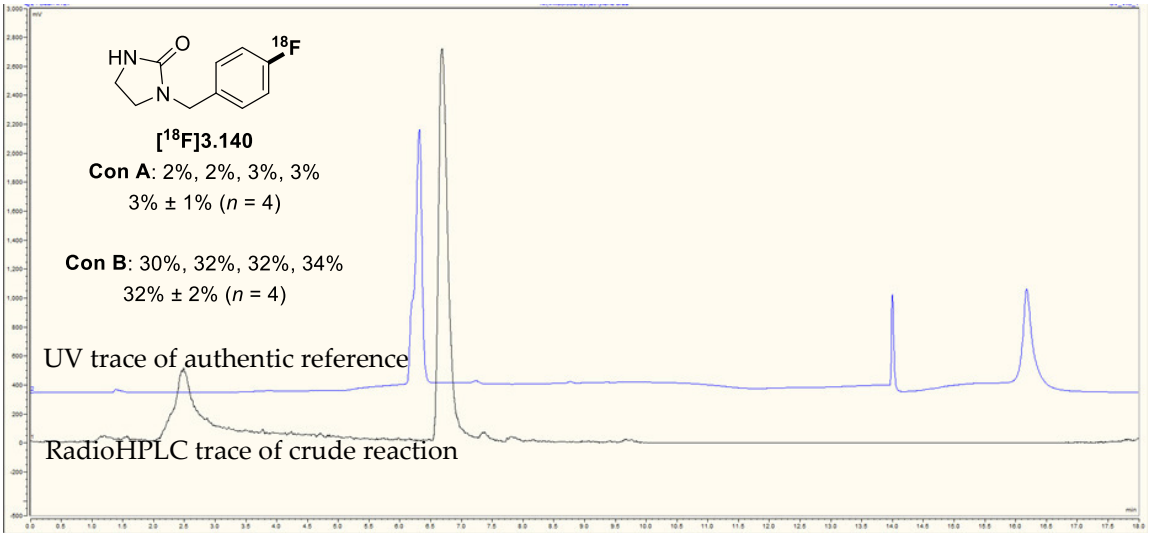
RadioHPLC Trace for **[^{18}F]3.138**. Gradient **A**, Synergi 4µm Hydro-RP 80A, 150 x 4.6 mm.



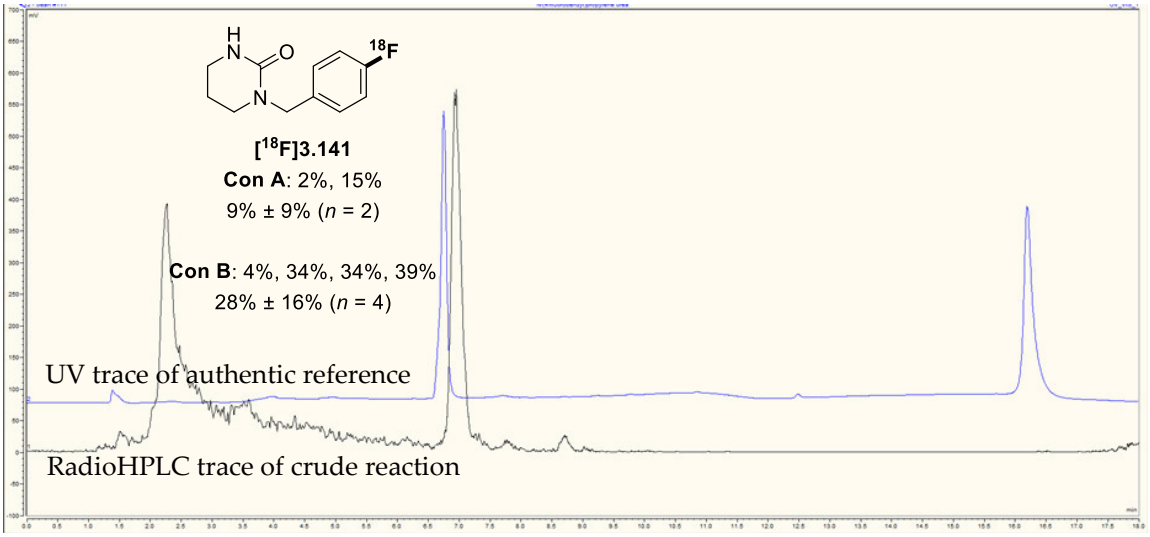
RadioHPLC Trace for **[^{18}F]3.139**. Gradient **B**, Waters Nova-Pak C18 Column, 4 μm, 3.9 x 150 mm.



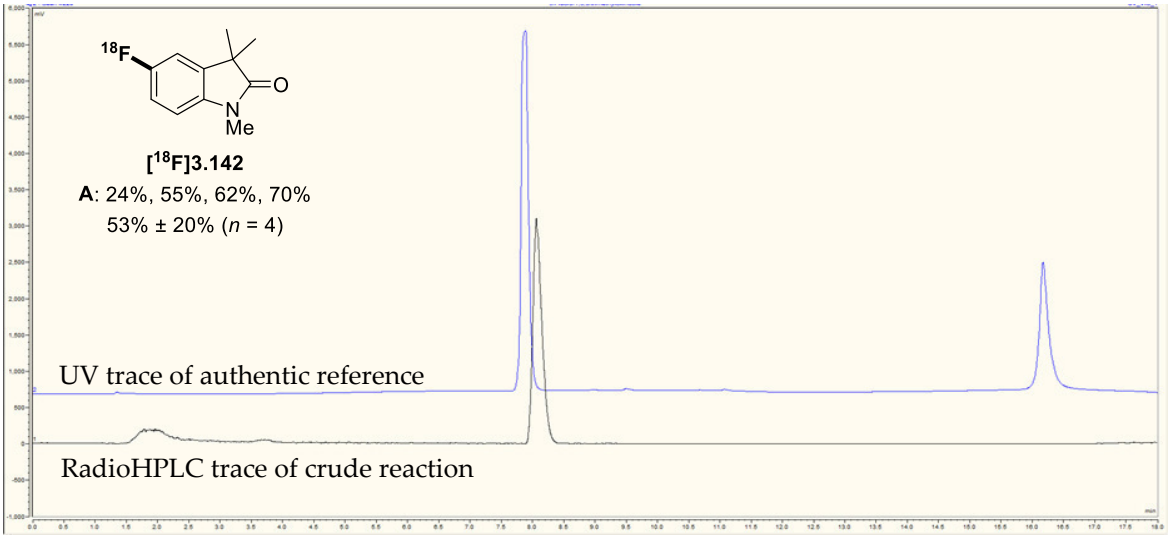
RadioHPLC Trace for **[^{18}F]3.140**. Gradient **A**, Waters Nova-Pak C18 Column, 4 μm, 3.9 x 150 mm.



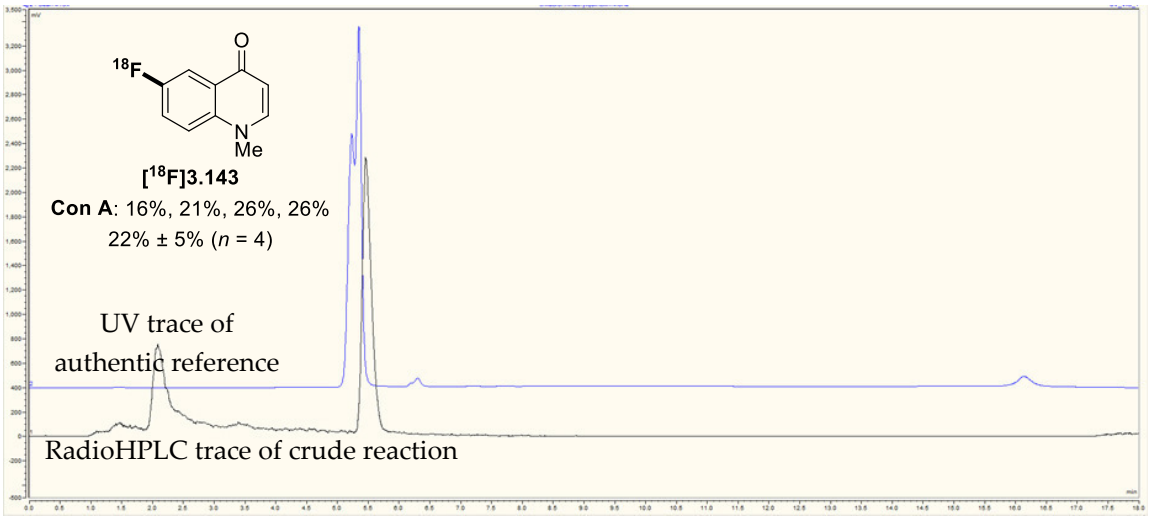
RadioHPLC Trace for **[^{18}F]3.141**. Gradient **A**, Waters Nova-Pak C18 Column, 4 μm, 3.9 x 150 mm.



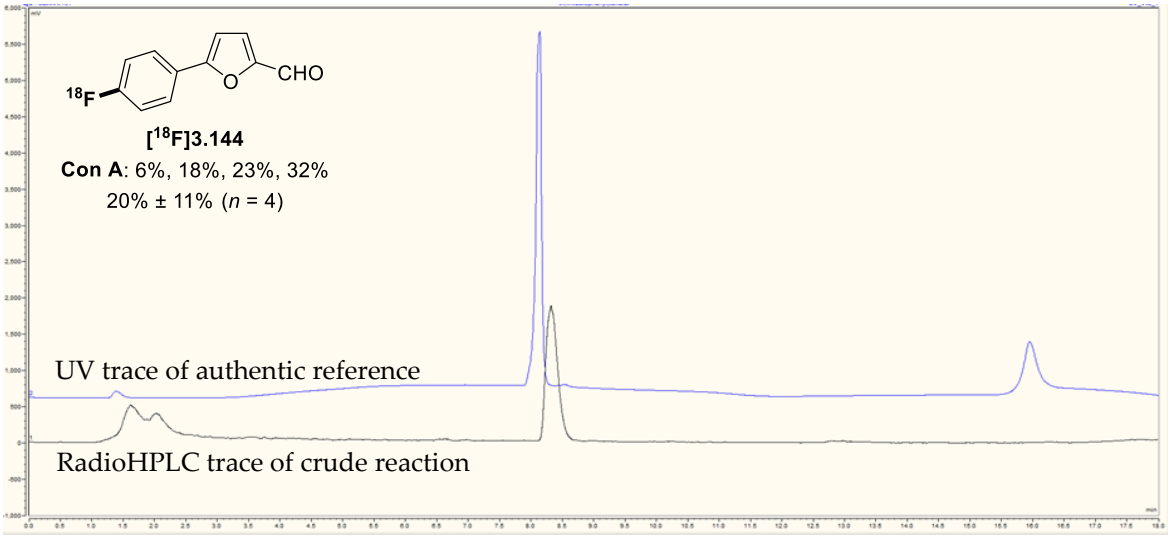
RadioHPLC Trace for **[^{18}F]3.142**. Gradient **A**, Waters Nova-Pak C18 Column, 4 µm, 3.9 x 150 mm.



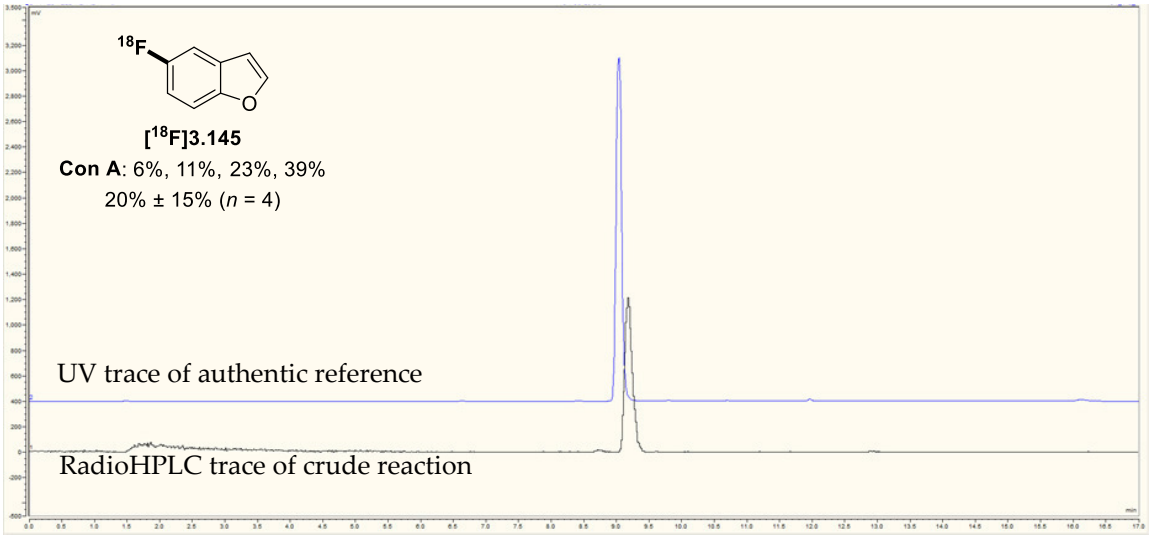
RadioHPLC Trace for **[^{18}F]3.143**. Gradient **A**, Waters Nova-Pak C18 Column, 4 µm, 3.9 x 150 mm.



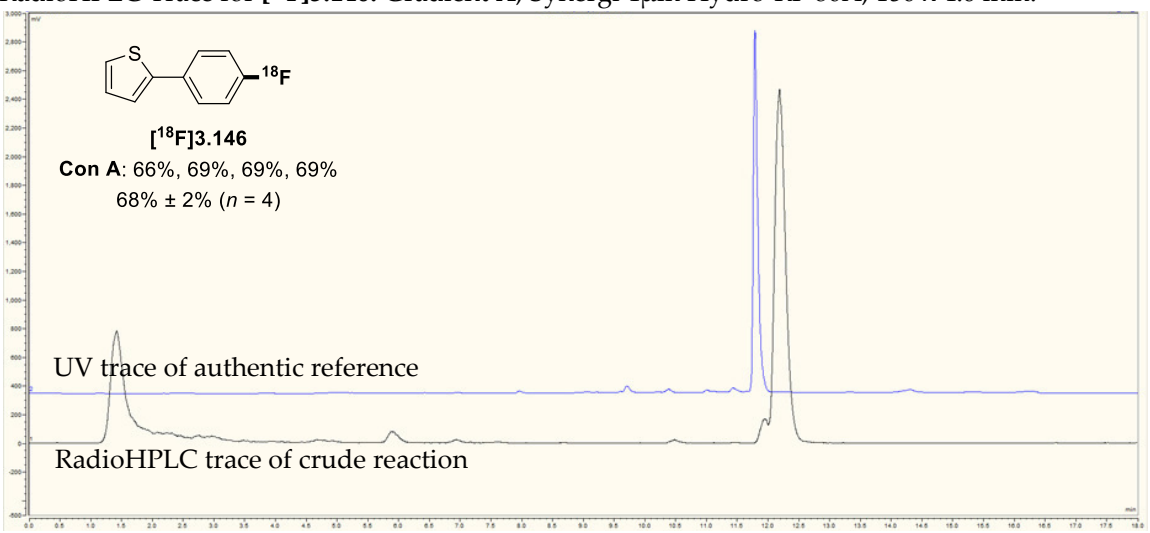
RadioHPLC Trace for **[^{18}F]3.144**. Gradient **A**, Waters Nova-Pak C18 Column, 4 µm, 3.9 x 150 mm.



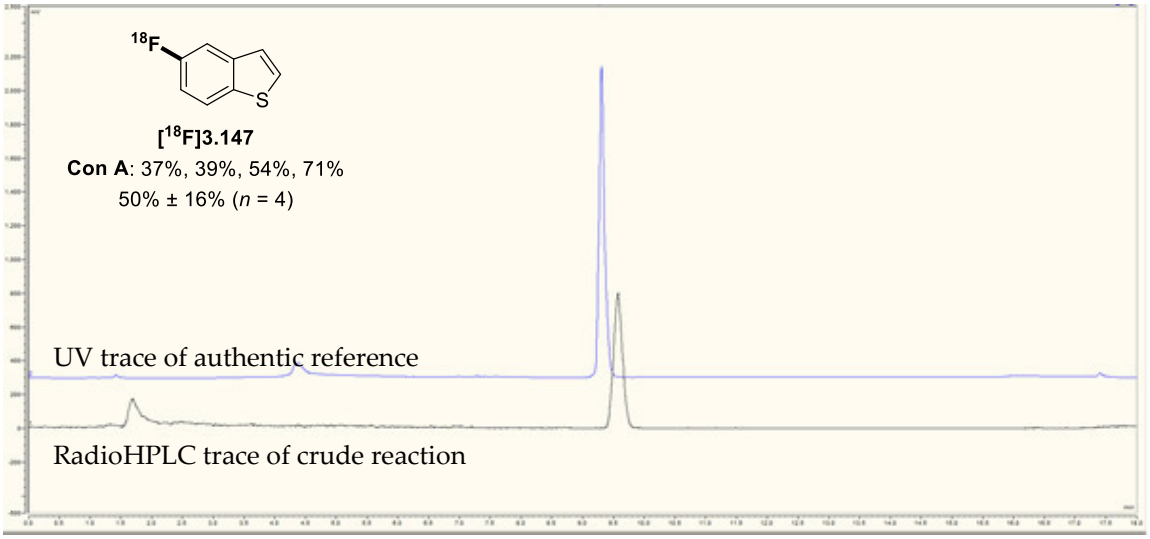
RadioHPLC Trace for **[^{18}F]3.145**. Gradient **A**, Waters Nova-Pak C18 Column, 4 μm, 3.9 x 150 mm.



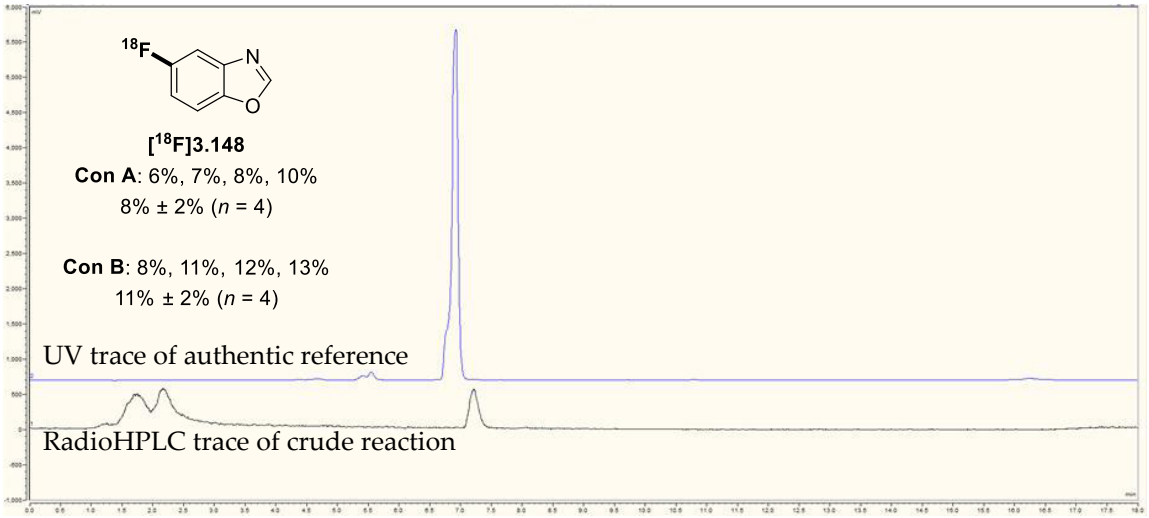
RadioHPLC Trace for **[^{18}F]3.146.** Gradient **A**, Synergi 4μm Hydro-RP 80A, 150 x 4.6 mm.



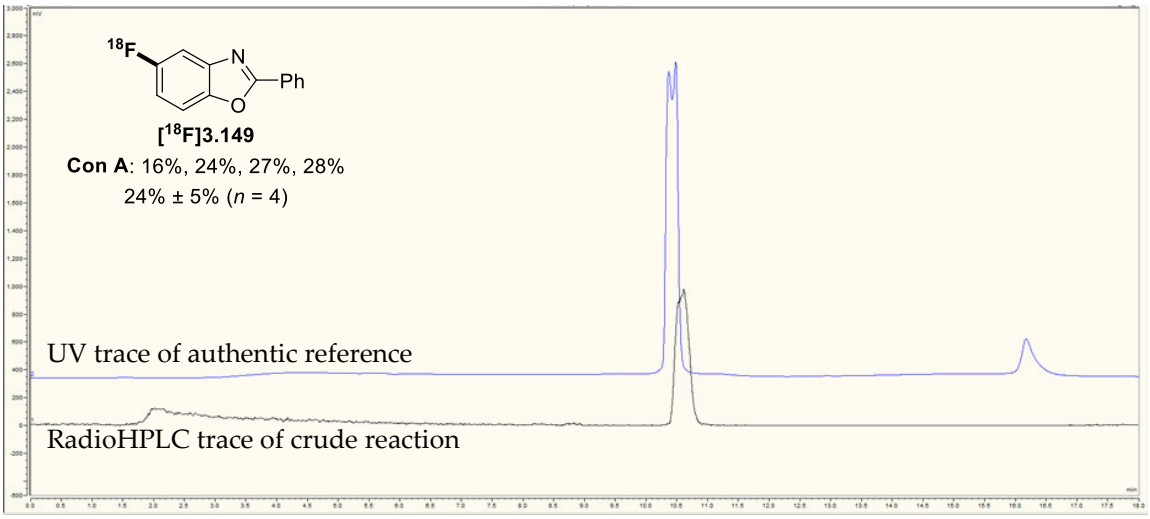
RadioHPLC Trace for **[^{18}F]3.147**. Gradient **A**, Waters Nova-Pak C18 Column, 4 μm, 3.9 x 150 mm.



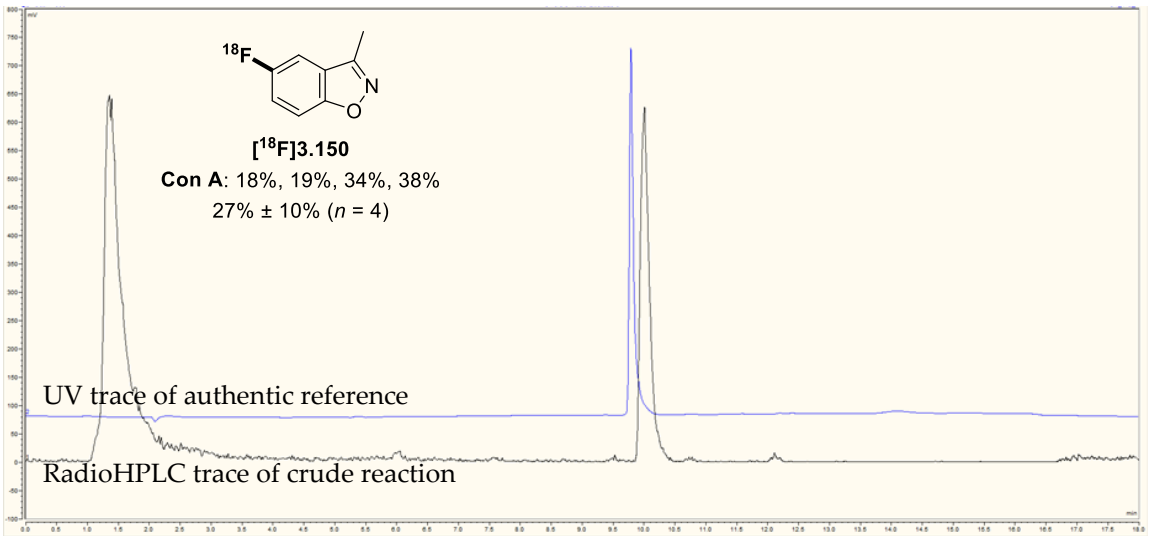
RadioHPLC Trace for **[^{18}F]3.148**. Gradient **A**, Waters Nova-Pak C18 Column, 4 µm, 3.9 x 150 mm.



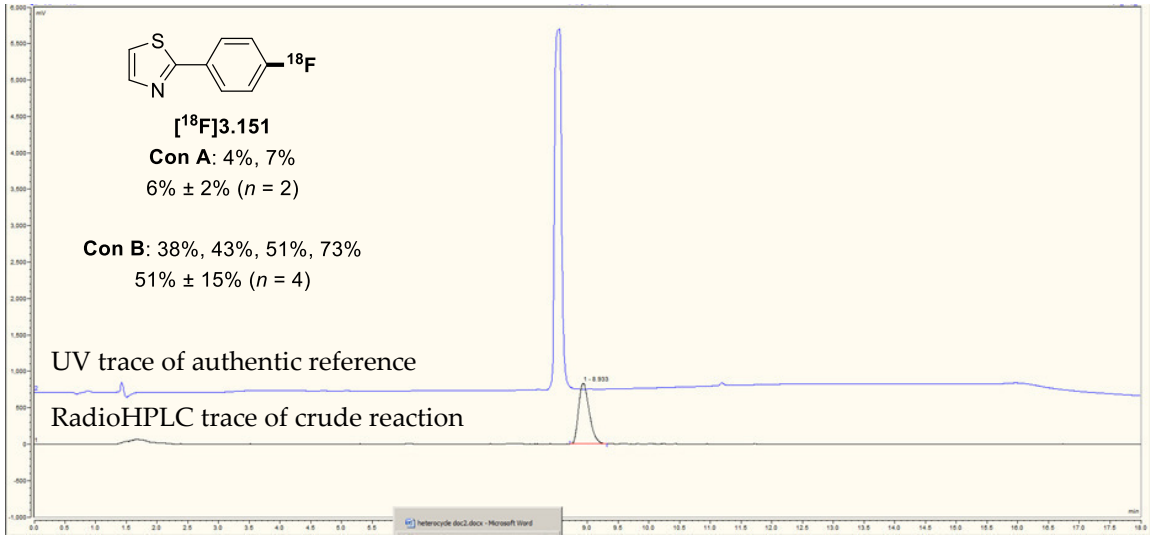
RadioHPLC Trace for **[^{18}F]3.149**. Gradient **A**, Waters Nova-Pak C18 Column, 4 µm, 3.9 x 150 mm.



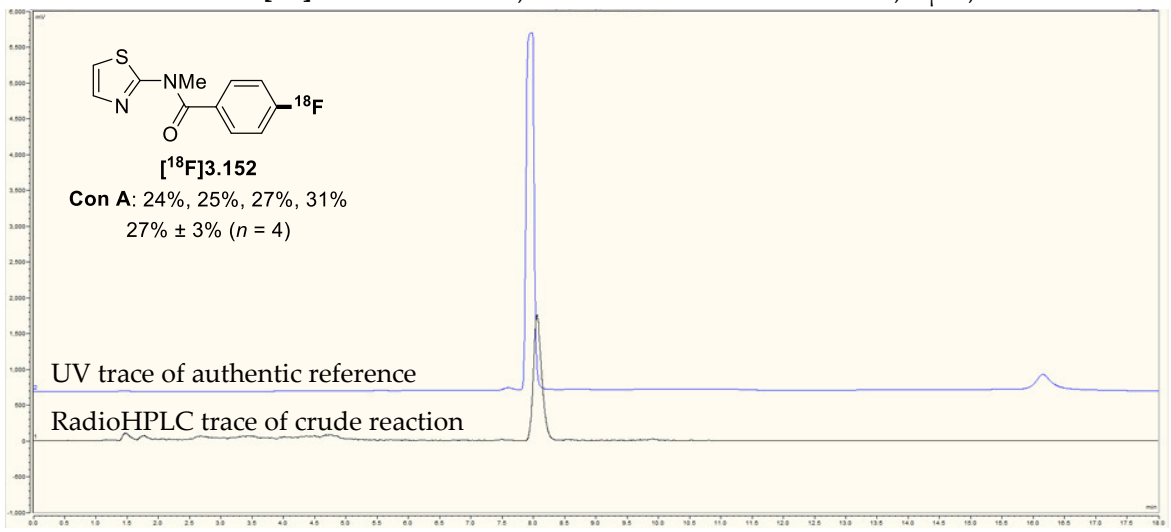
RadioHPLC Trace for **[^{18}F]3.150.** Gradient **A**, Synergi 4µm Hydro-RP 80A, 150 x 4.6 mm.



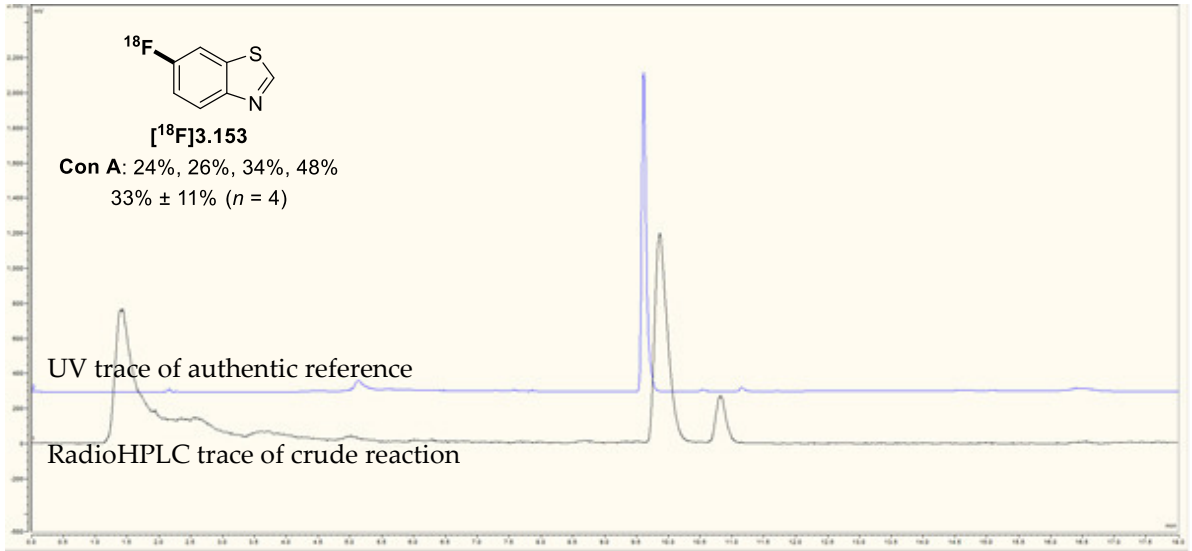
RadioHPLC Trace for **[^{18}F]3.151**. Gradient **B**, Waters Nova-Pak C18 Column, 4 µm, 3.9 x 150 mm.



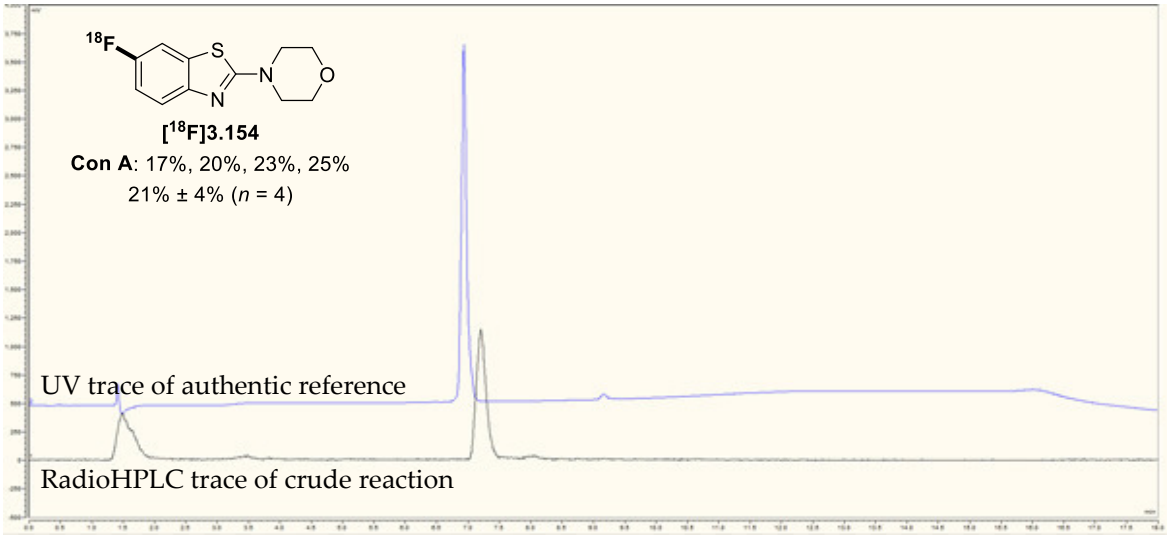
RadioHPLC Trace for **[^{18}F]3.152**. Gradient **A**, Waters Nova-Pak C18 Column, 4 µm, 3.9 x 150 mm.



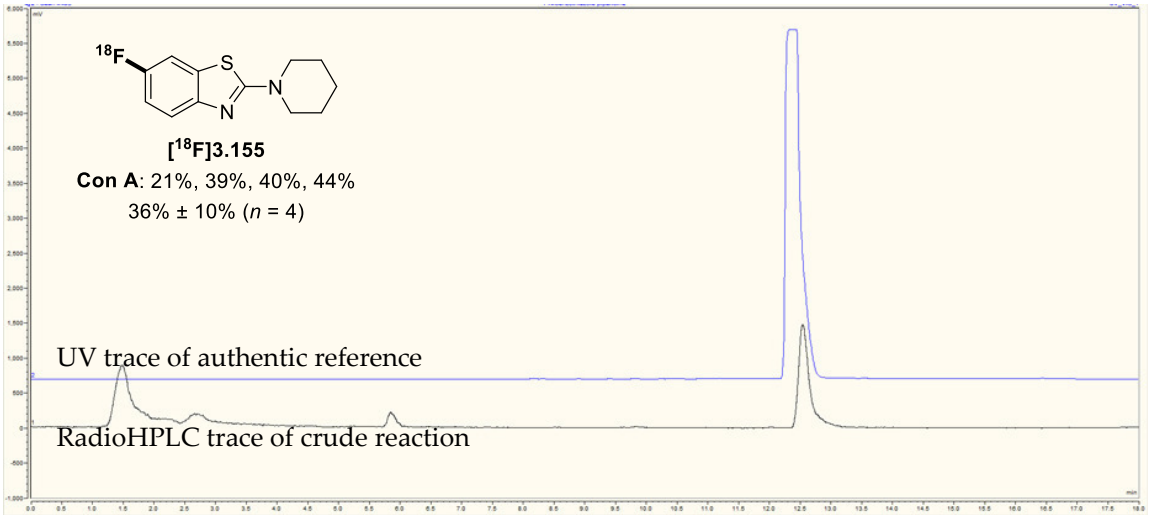
RadioHPLC Trace for **[^{18}F]3.153.** Gradient **A**, Synergi 4µm Hydro-RP 80A, 150 x 4.6 mm.



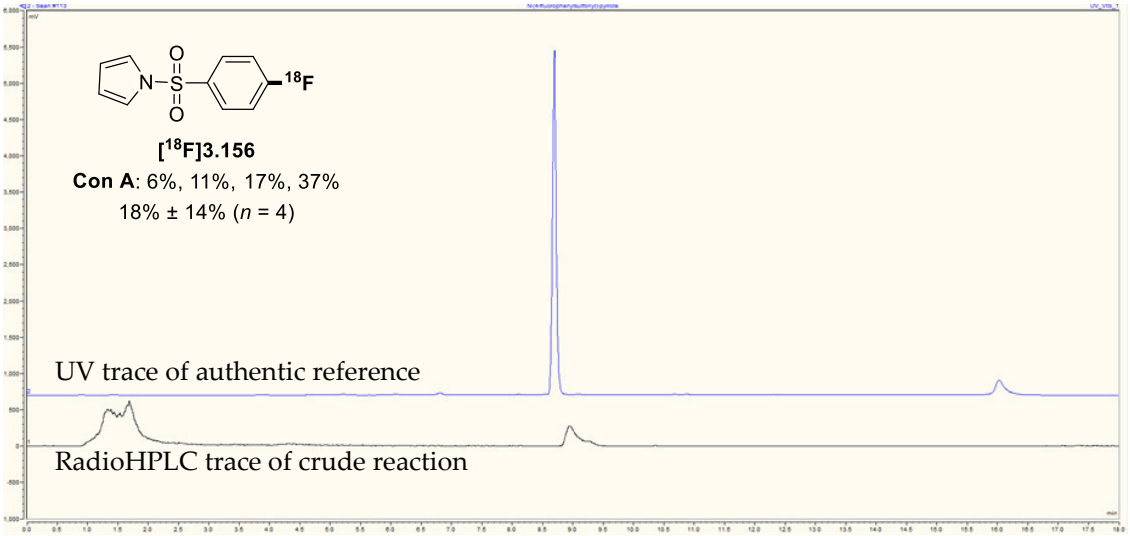
RadioHPLC Trace for **[^{18}F]3.154**. Gradient **B**, Waters Nova-Pak C18 Column, 4 µm, 3.9 x 150 mm.



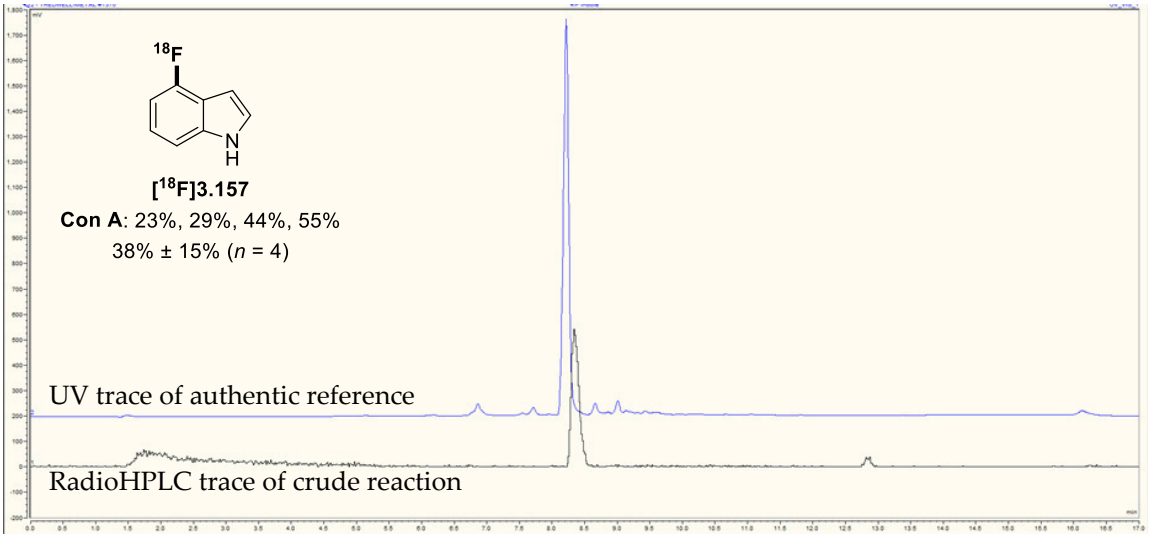
RadioHPLC Trace for **[^{18}F]3.155.** Gradient **A**, Synergi 4µm Hydro-RP 80A, 150 x 4.6 mm.



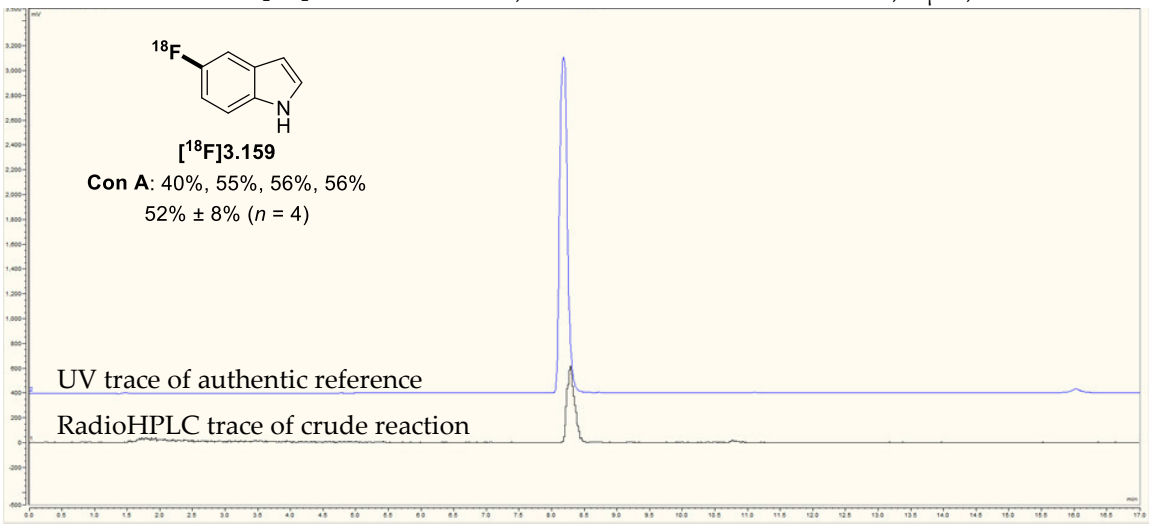
RadioHPLC Trace for **[^{18}F]3.156**. Gradient **A**, Waters Nova-Pak C18 Column, 4 µm, 3.9 x 150 mm.



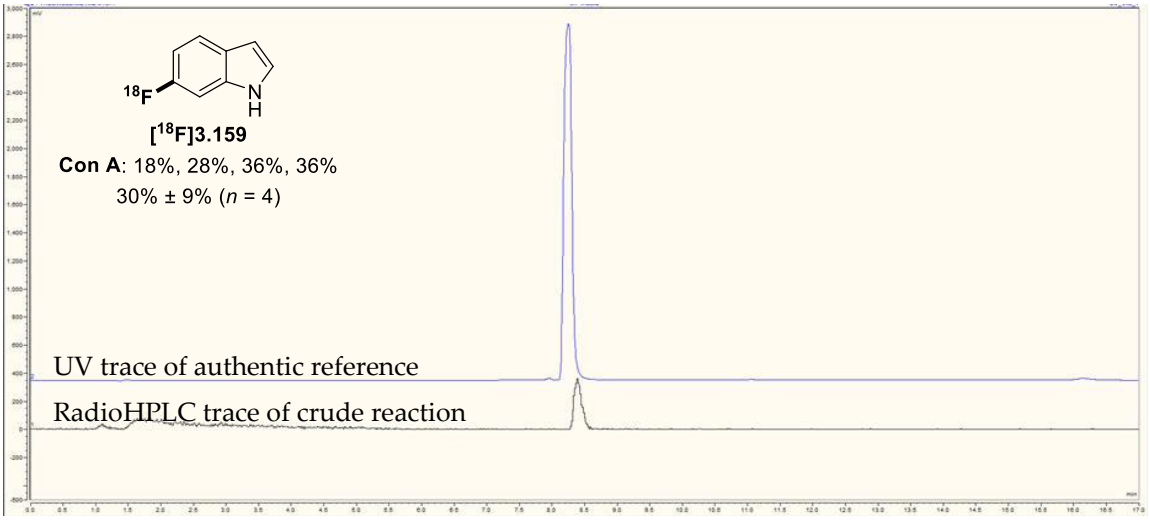
RadioHPLC Trace for **[^{18}F]3.157**. Gradient **A**, Waters Nova-Pak C18 Column, 4 μm, 3.9 x 150 mm.



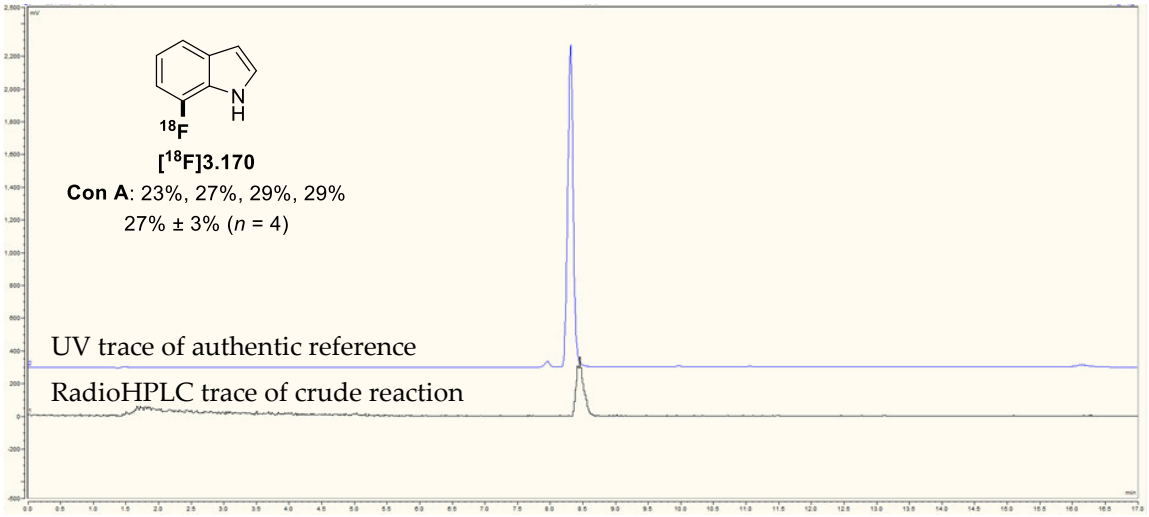
RadioHPLC Trace for **[^{18}F]3.158**. Gradient **A**, Waters Nova-Pak C18 Column, 4 μm, 3.9 x 150 mm.



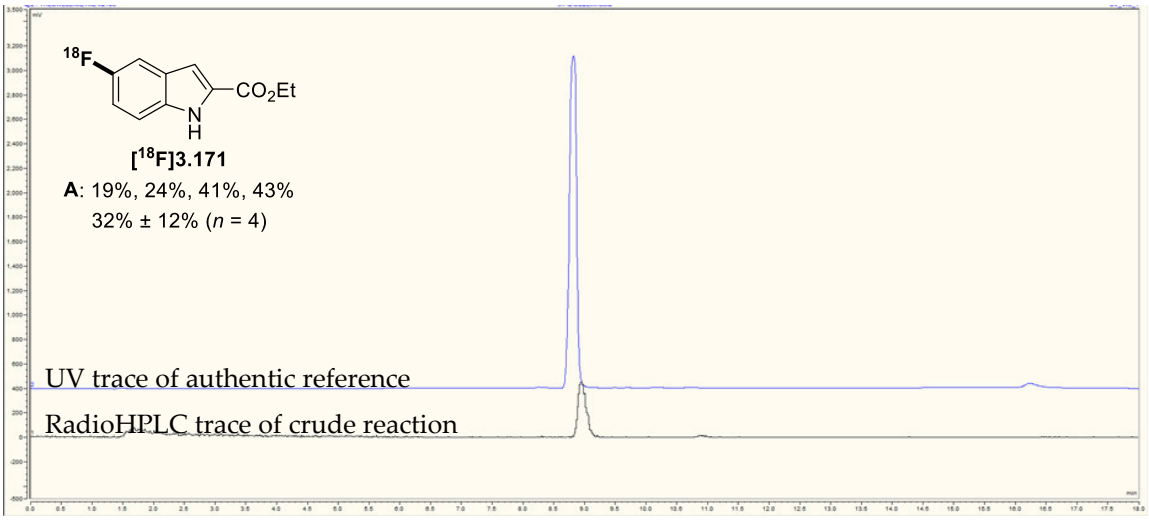
RadioHPLC Trace for **[^{18}F]3.159**. Gradient **A**, Waters Nova-Pak C18 Column, 4 μm, 3.9 x 150 mm.



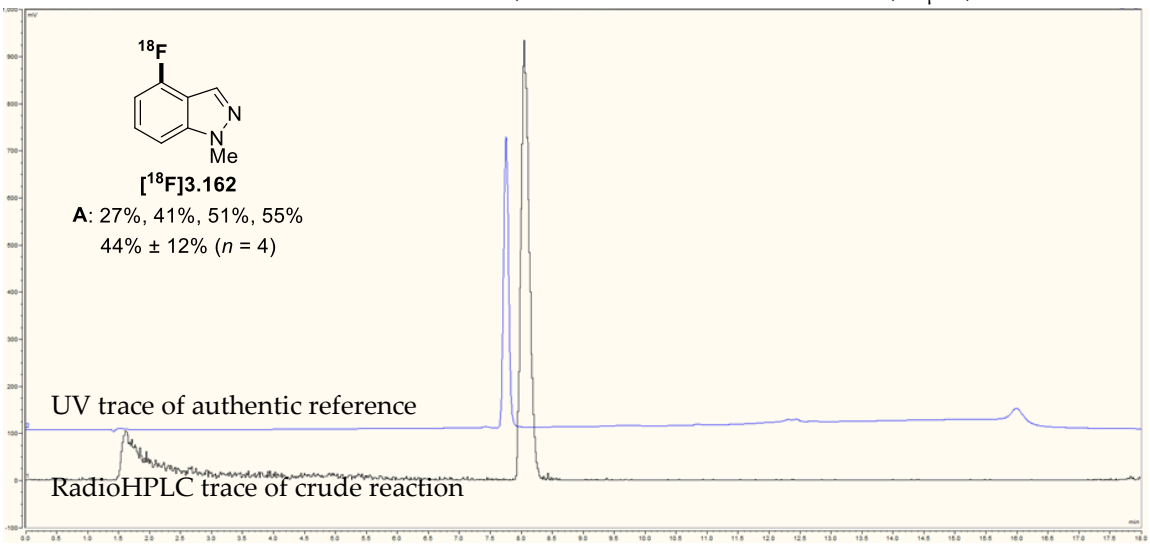
RadioHPLC Trace for **[^{18}F]3.160**. Gradient **A**, Waters Nova-Pak C18 Column, 4 μm, 3.9 x 150 mm.



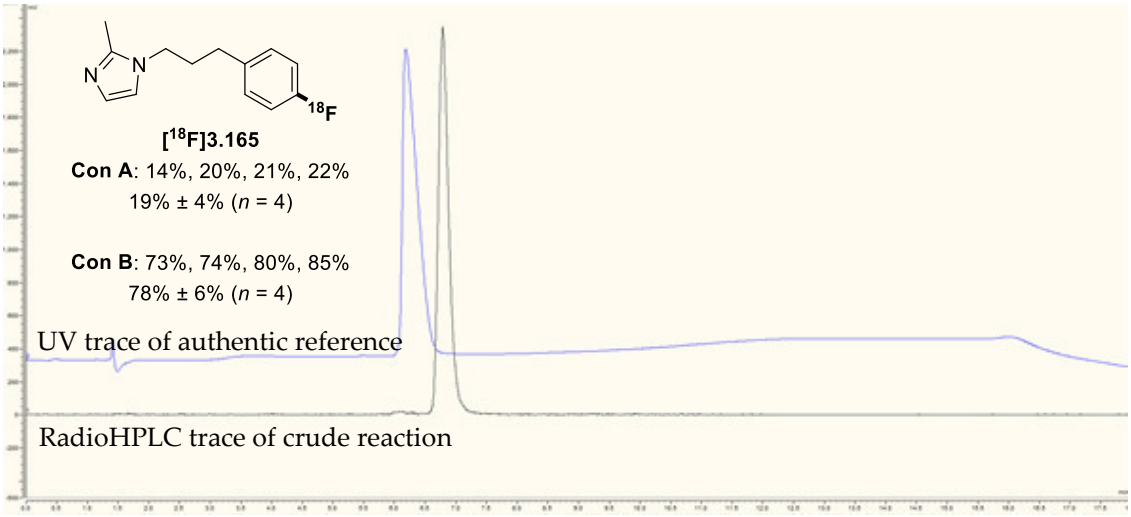
RadioHPLC Trace for **[^{18}F]3.161**. Gradient **A**, Waters Nova-Pak C18 Column, 4 μm, 3.9 x 150 mm.



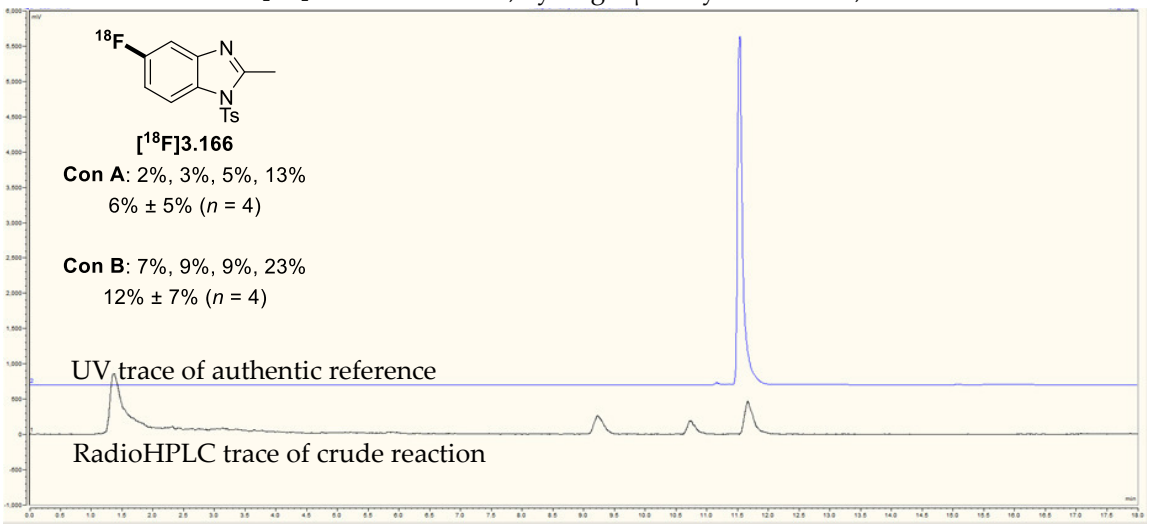
RadioHPLC Trace for **[^{18}F]3.162**. Gradient **A**, Waters Nova-Pak C18 Column, 4 μm, 3.9 x 150 mm.



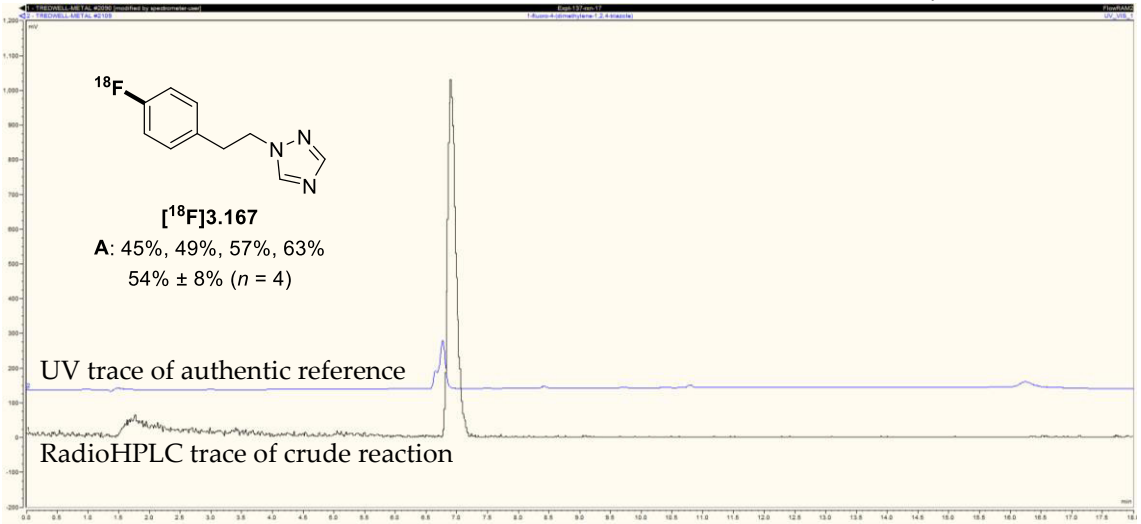
RadioHPLC Trace for **[^{18}F]3.165**. Gradient **B**, Waters Nova-Pak C18 Column, 4 μm, 3.9 x 150 mm.



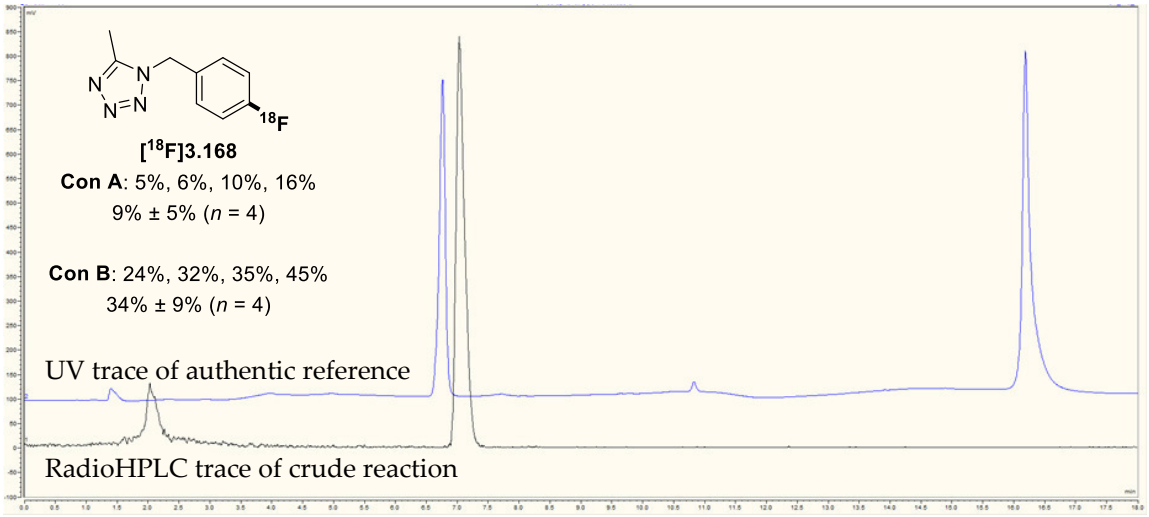
RadioHPLC Trace for **[^{18}F]3.166** Gradient **A**, Synergi 4μm Hydro-RP 80A, 150 x 4.6 mm.



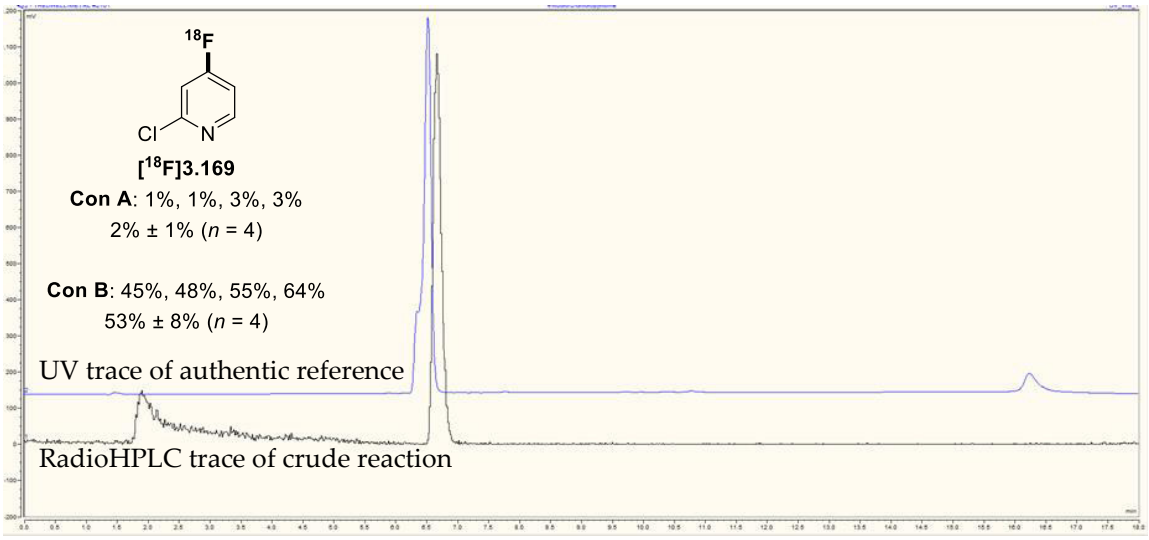
RadioHPLC Trace for **[^{18}F]3.167**. Gradient **A**, Waters Nova-Pak C18 Column, 4 μm, 3.9 x 150 mm.



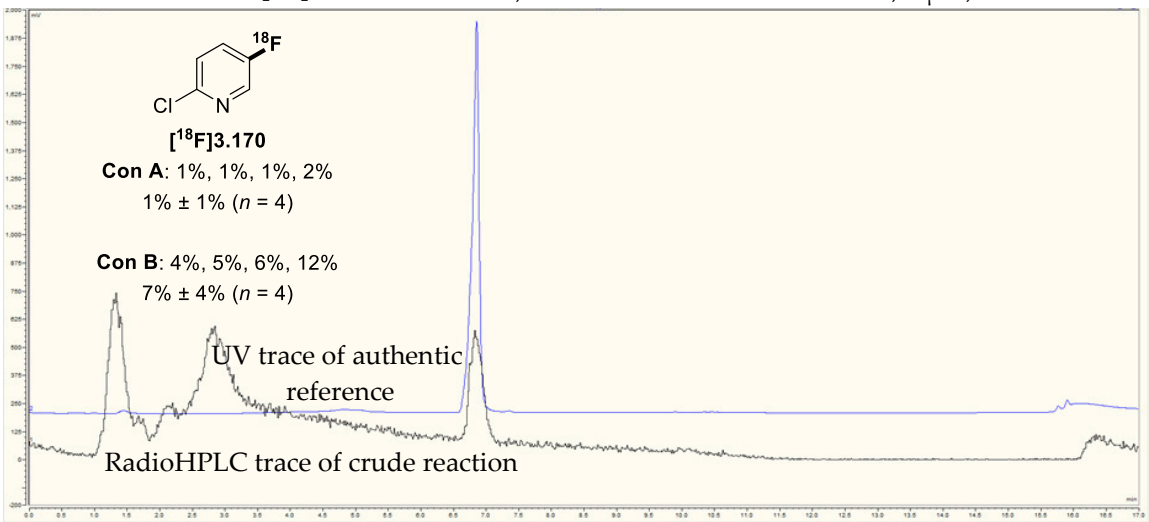
RadioHPLC Trace for **[^{18}F]3.168**. Gradient **A**, Waters Nova-Pak C18 Column, 4 µm, 3.9 x 150 mm.



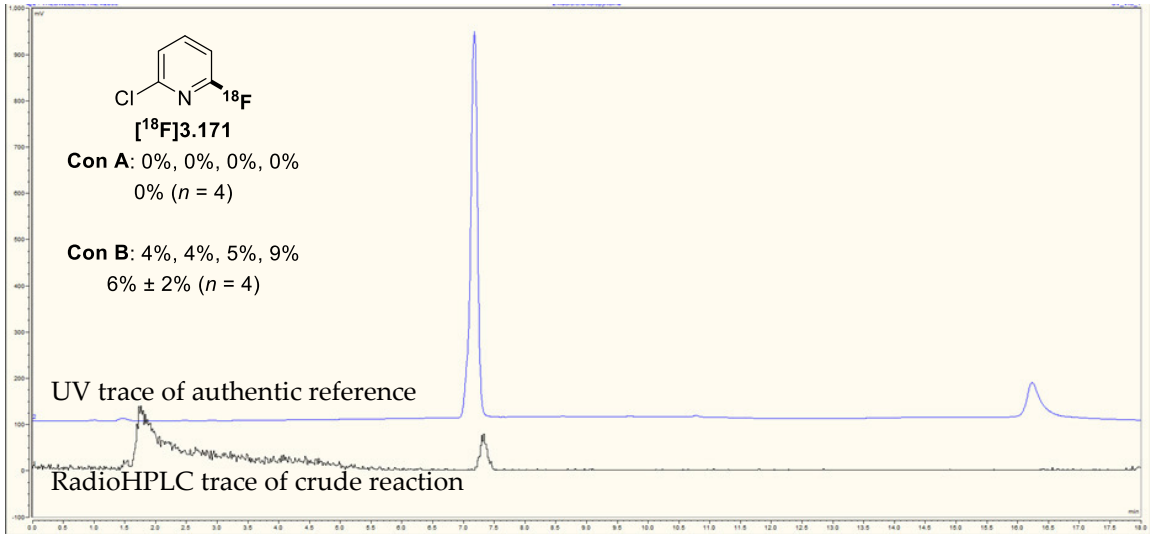
RadioHPLC Trace for **[^{18}F]3.169**. Gradient **A**, Waters Nova-Pak C18 Column, 4 µm, 3.9 x 150 mm.



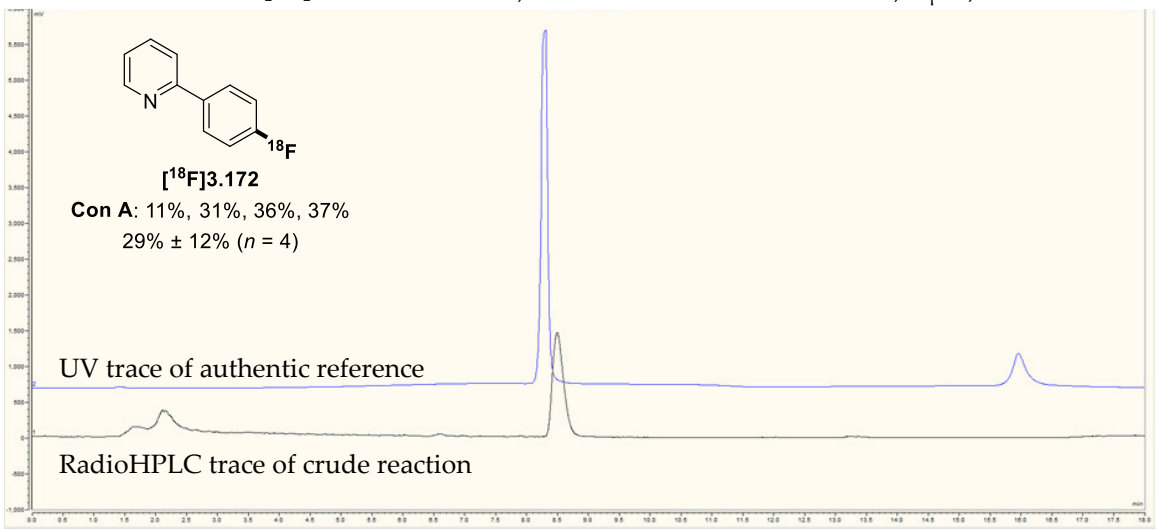
RadioHPLC Trace for **[^{18}F]3.170**. Gradient **A**, Waters Nova-Pak C18 Column, 4 µm, 3.9 x 150 mm.



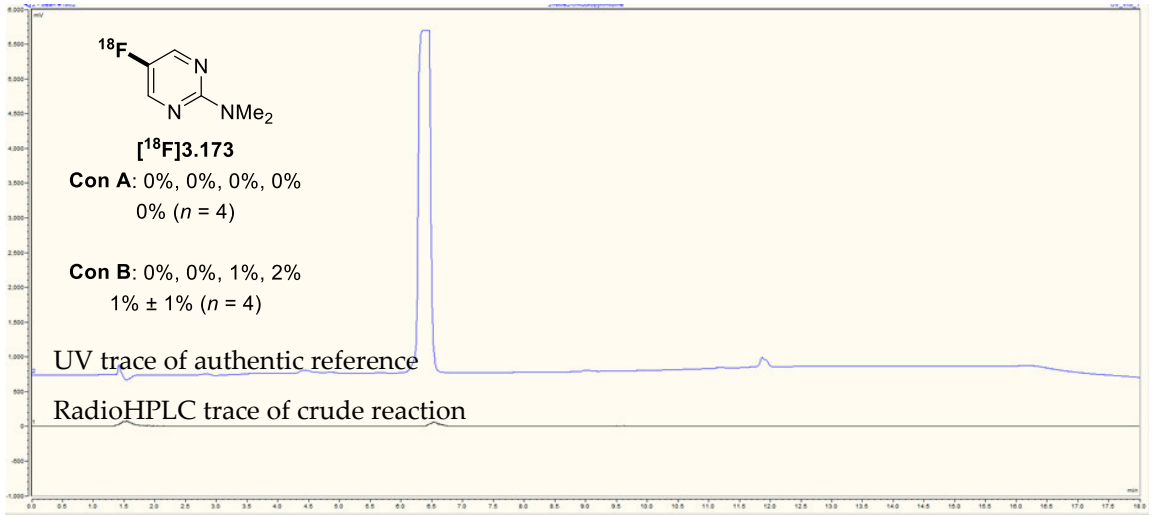
RadioHPLC Trace for **[^{18}F]3.171**. Gradient **A**, Waters Nova-Pak C18 Column, 4 μm, 3.9 x 150 mm.



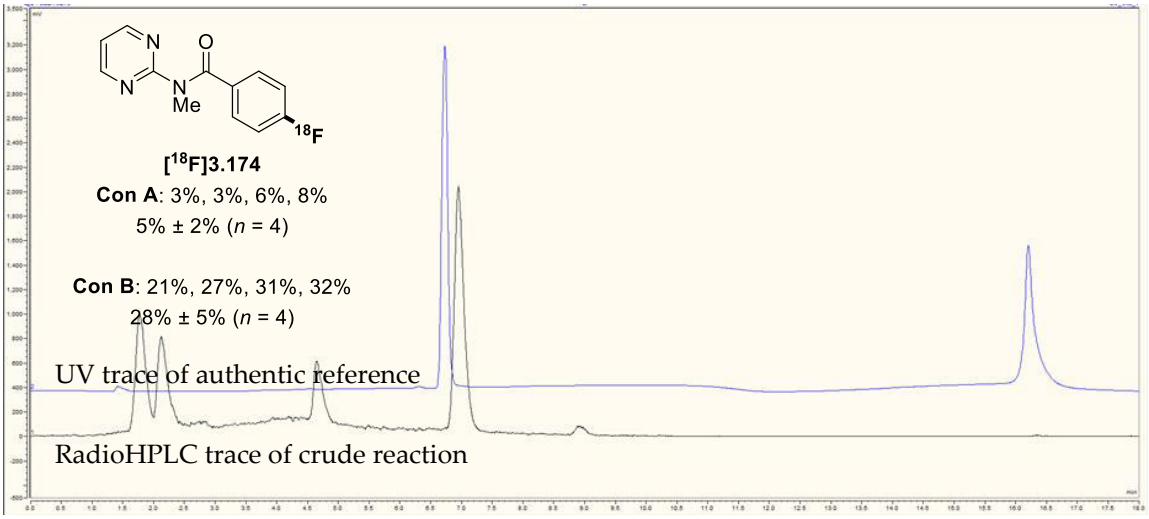
RadioHPLC Trace for **[^{18}F]3.172**. Gradient **A**, Waters Nova-Pak C18 Column, 4 μm, 3.9 x 150 mm.



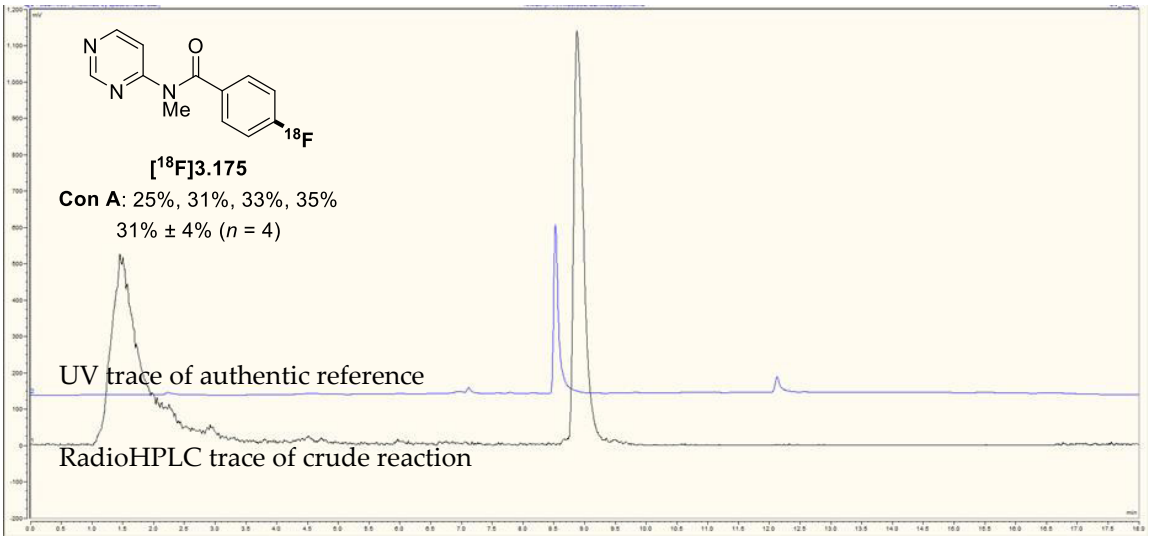
RadioHPLC Trace for **[^{18}F]3.173**. Gradient **B**, Waters Nova-Pak C18 Column, 4 μm, 3.9 x 150 mm.



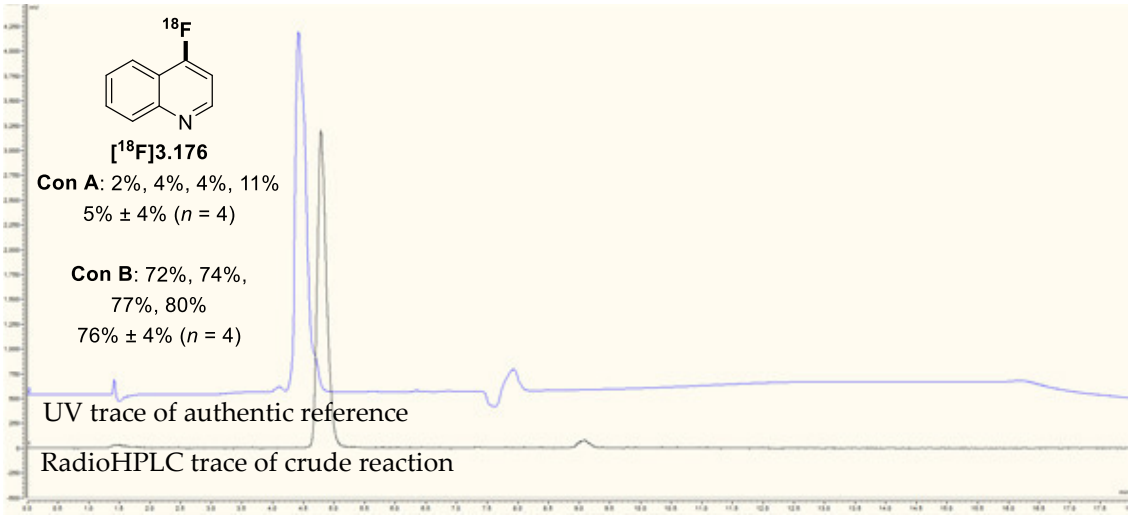
RadioHPLC Trace for **[^{18}F]3.174**. Gradient **A**, Waters Nova-Pak C18 Column, 4 µm, 3.9 x 150 mm.



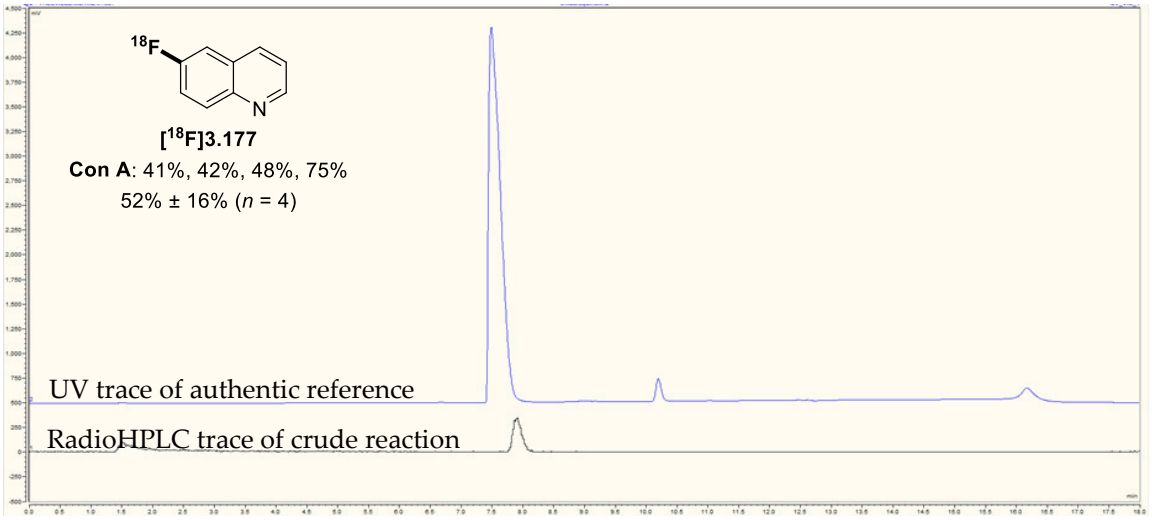
RadioHPLC Trace for **[^{18}F]3.175.** Gradient **B**, Synergi 4µm Hydro-RP 80A, 150 x 4.6 mm.



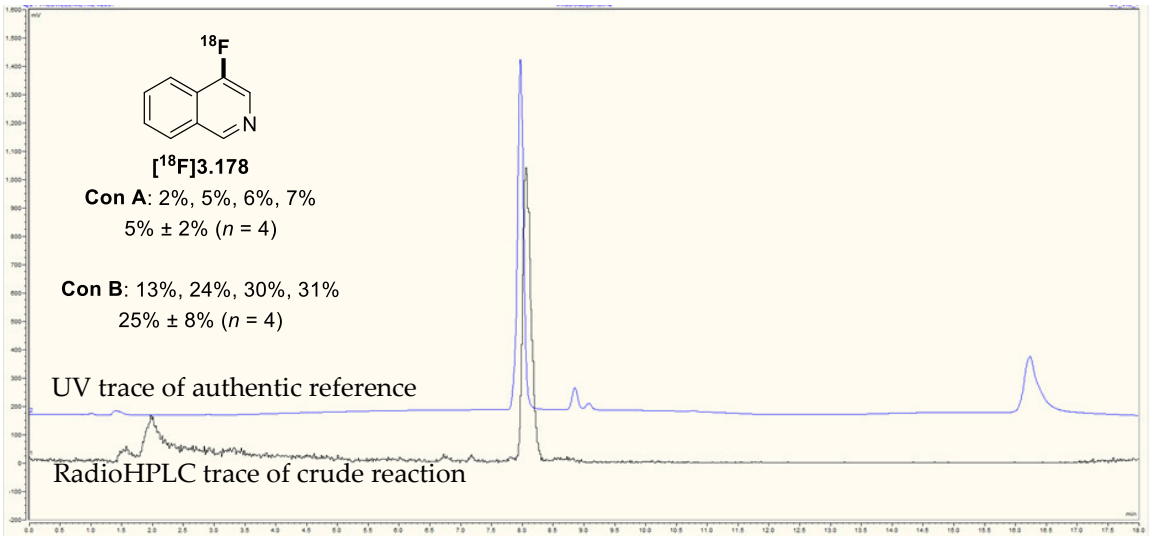
RadioHPLC Trace for **[^{18}F]3.176**. Gradient **B**, Waters Nova-Pak C18 Column, 4 µm, 3.9 x 150 mm.



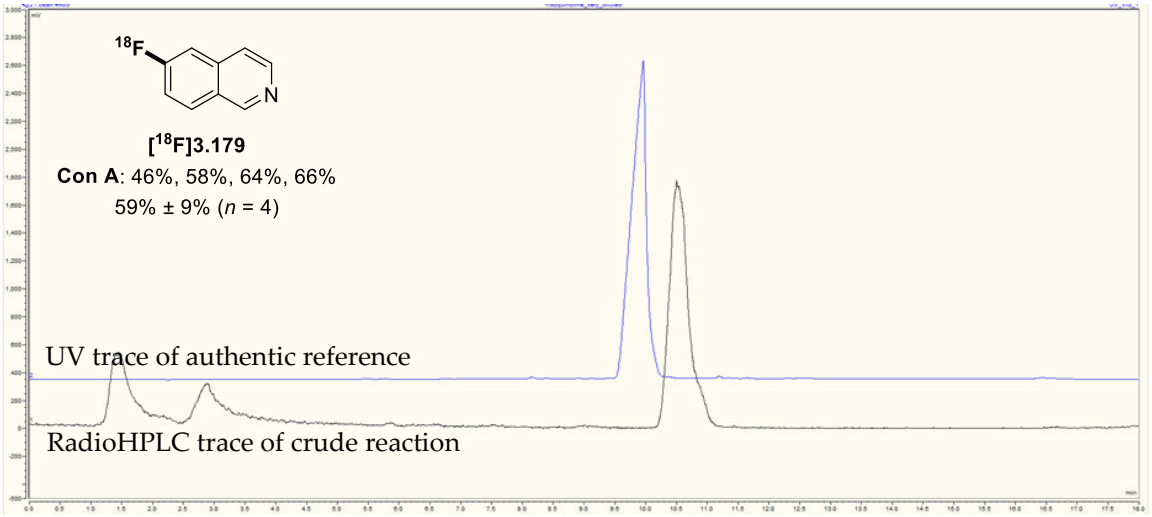
RadioHPLC Trace for **[^{18}F]3.177**. Gradient **A**, Waters Nova-Pak C18 Column, 4 μm, 3.9 x 150 mm.



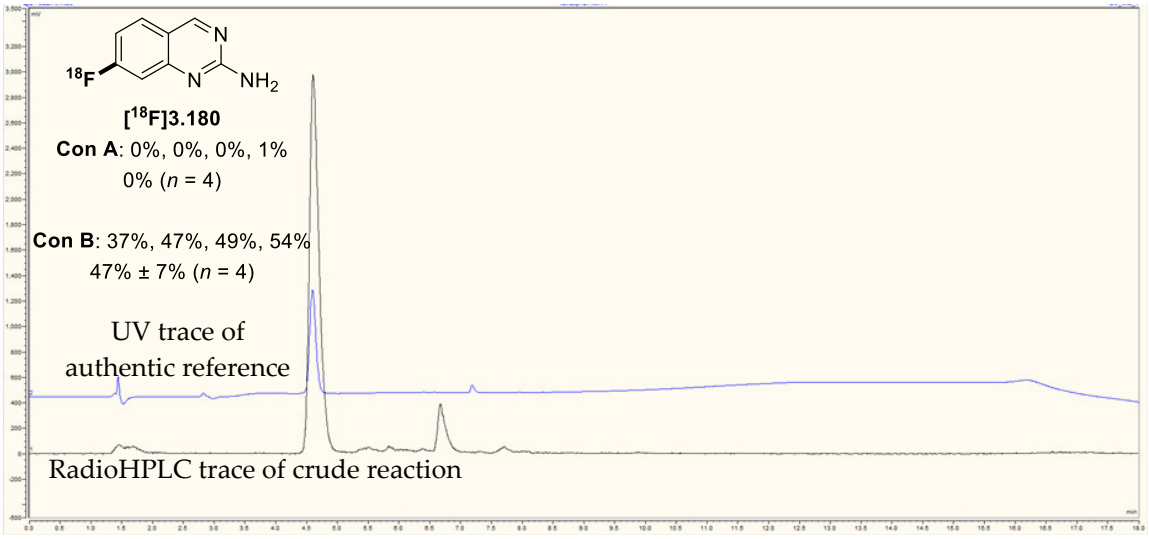
RadioHPLC Trace for **[^{18}F]3.178**. Gradient **A**, Waters Nova-Pak C18 Column, 4 μm, 3.9 x 150 mm.



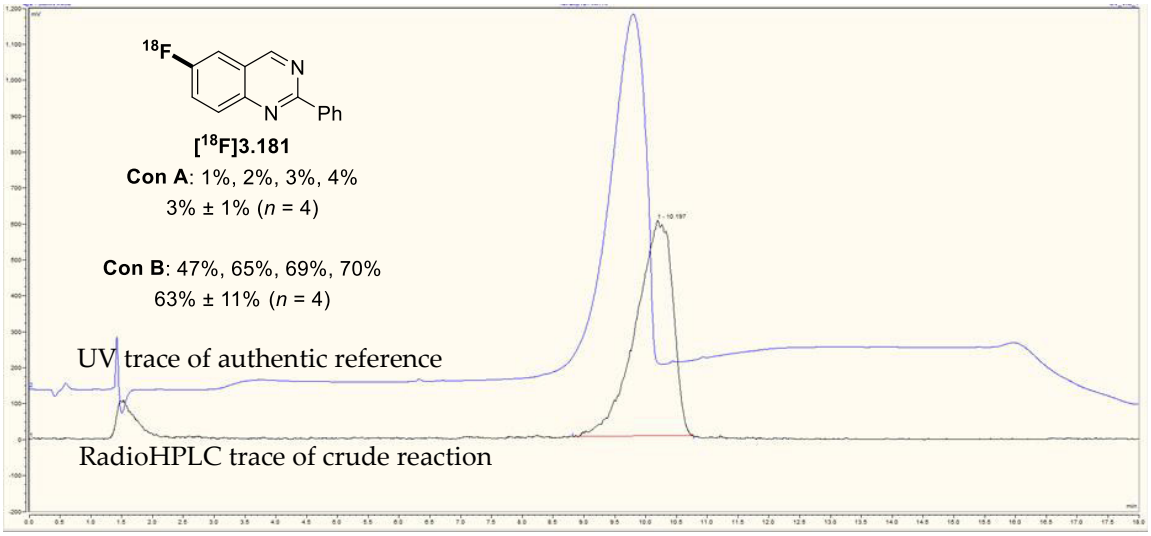
RadioHPLC Trace for **[^{18}F]3.179**. Gradient **A**, Synergi 4μm Hydro-RP 80A, 150 x 4.6 mm.



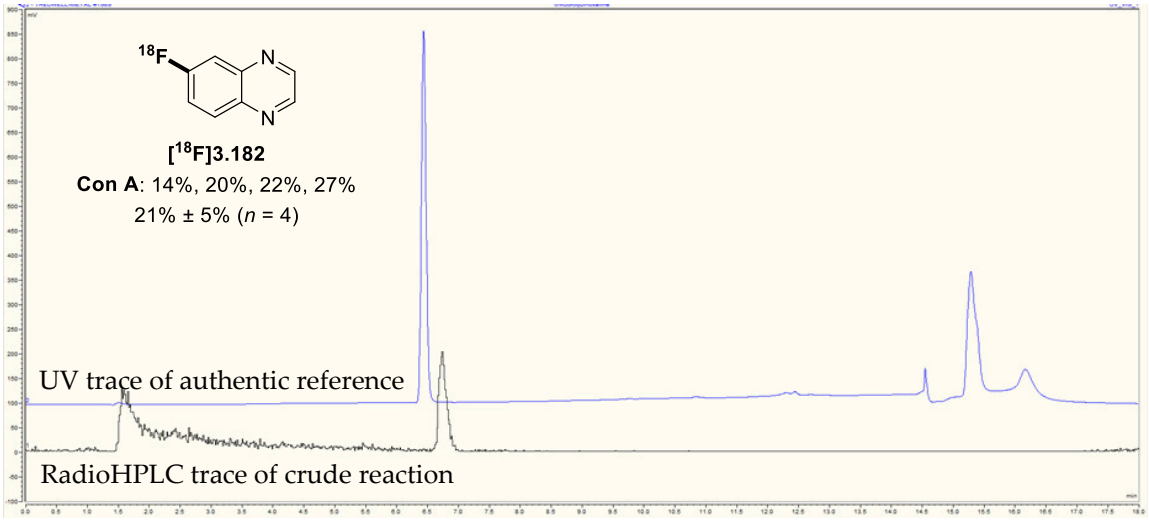
RadioHPLC Trace for **[^{18}F]3.180**. Gradient **B**, Waters Nova-Pak C18 Column, 4 μm, 3.9 x 150 mm.



RadioHPLC Trace for **[^{18}F]3.181**. Gradient **B**, Waters Nova-Pak C18 Column, 4 μm, 3.9 x 150 mm.



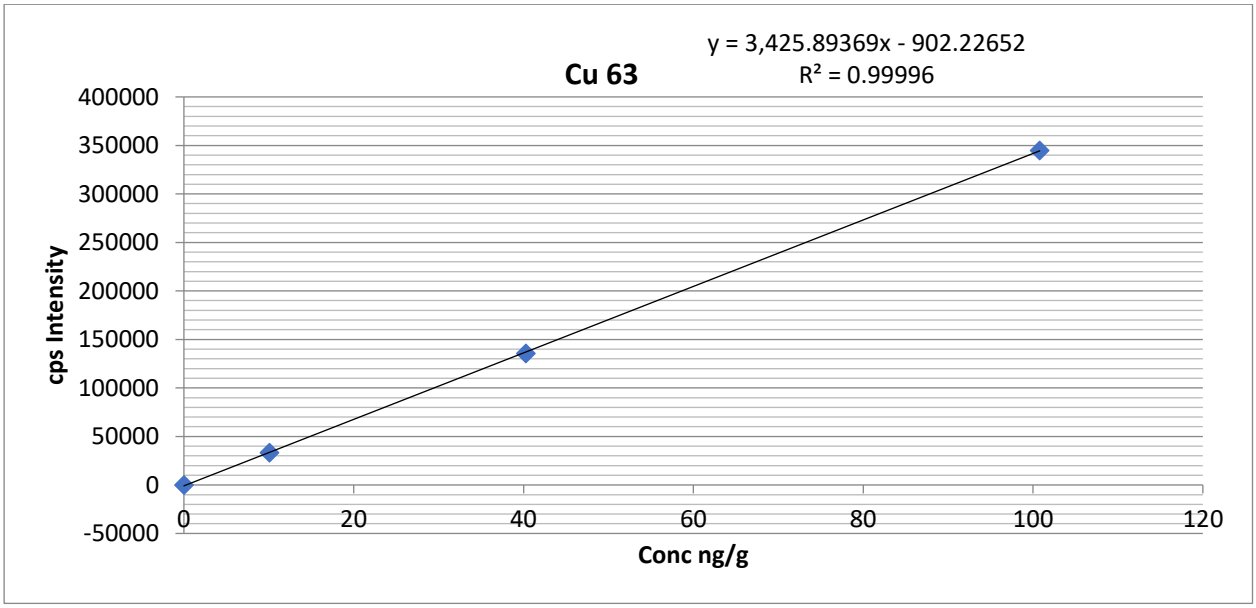
RadioHPLC Trace for **[^{18}F]3.182**. Gradient **A**, Waters Nova-Pak C18 Column, 4 μm, 3.9 x 150 mm.



4.4.27 ICP-MS analysis of [^{18}F]2.30

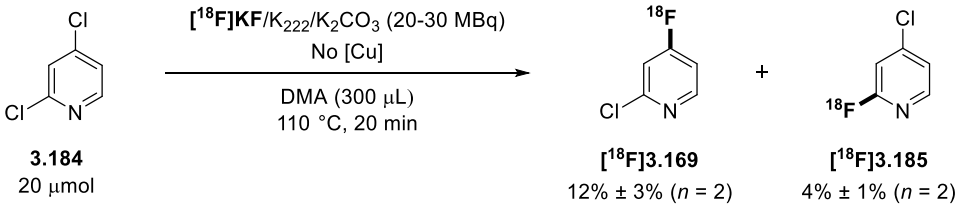
[^{18}F]**2.30** was prepared following the general procedure. At the end of the synthesis the entire sample was purified directly by HPLC. The fraction corresponding to [^{18}F]-4-fluorobiphenyl was collected. A portion of the sample was analysed by ICP-MS to determine copper content. The copper content was determined by comparison to a standard curve generated by a series of dilutions of a known copper concentration. From this method the quantity of copper-63 was determined to be 2.07 ppm (n = 4).

Standard Curve of Ion Count versus Copper-63 concentration (ppb):



ICP-MS sample preparation was carried out by P. Holdship (Department of Earth Sciences, University of Oxford. Analysis was carried out by Phosphonics.

4.4.28 Radio-HPLC Trace for S_NAr Control Experiment (section 3.4)

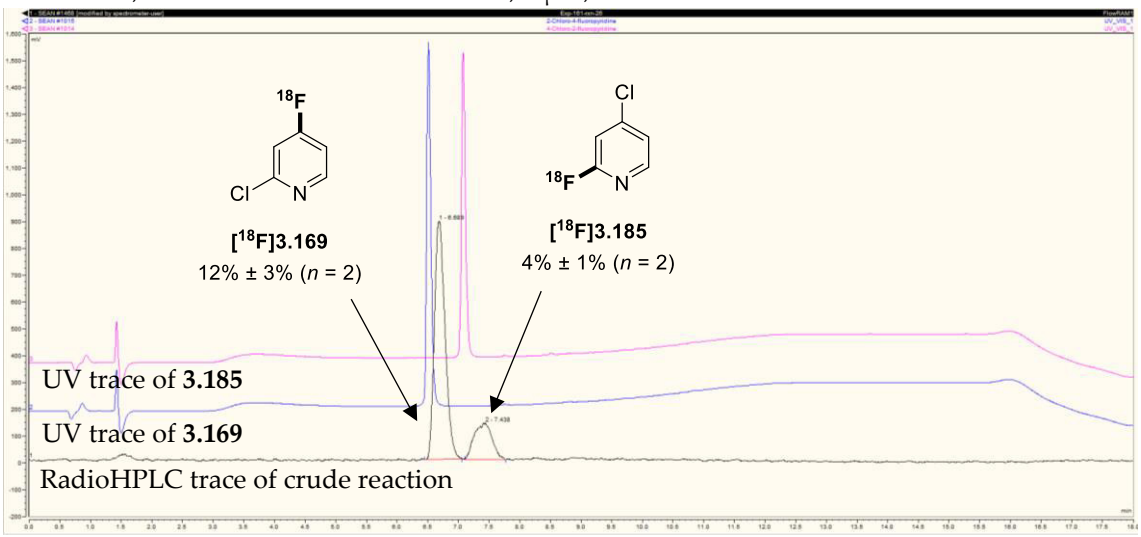


3.184
20 μmol

[^{18}F]3.169
12% ± 3% (*n* = 2)

[^{18}F]3.185
4% ± 1% (*n* = 2)

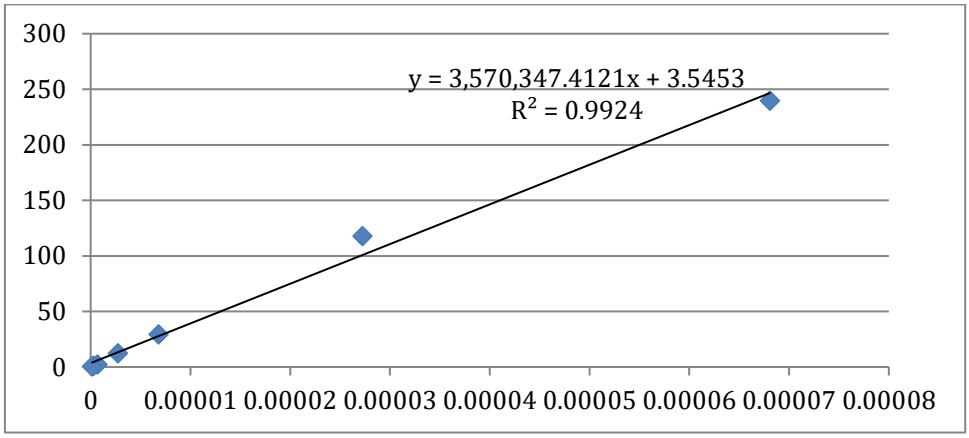
RadioHPLC Trace for the above reaction.
Gradient **B**, Waters Nova-Pak C18 Column, 4 μm, 3.9 x 150 mm.



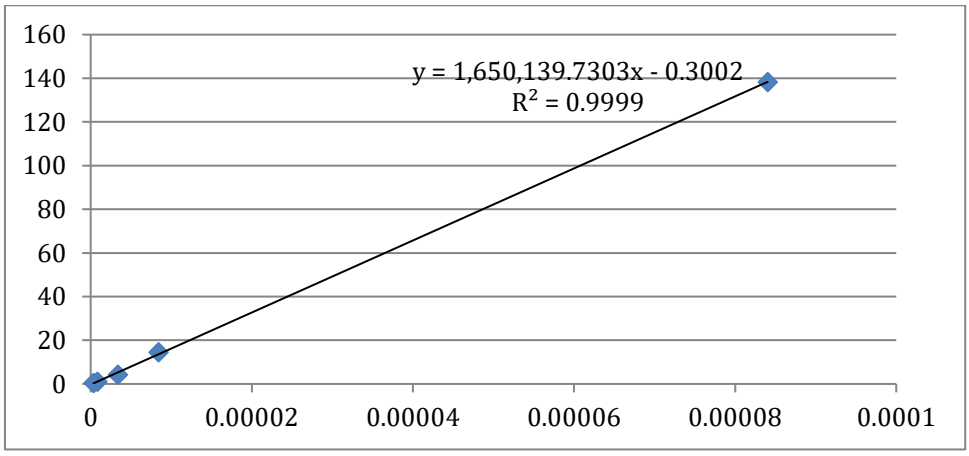
When the reaction was repeated with the addition of $[Cu(OTf)_2(py)_4]$ (30 μmol), organic radiolabelled products were not observed.

4.4.29 Calibration Curves for Product Distribution Experiment (section 3.3.6)

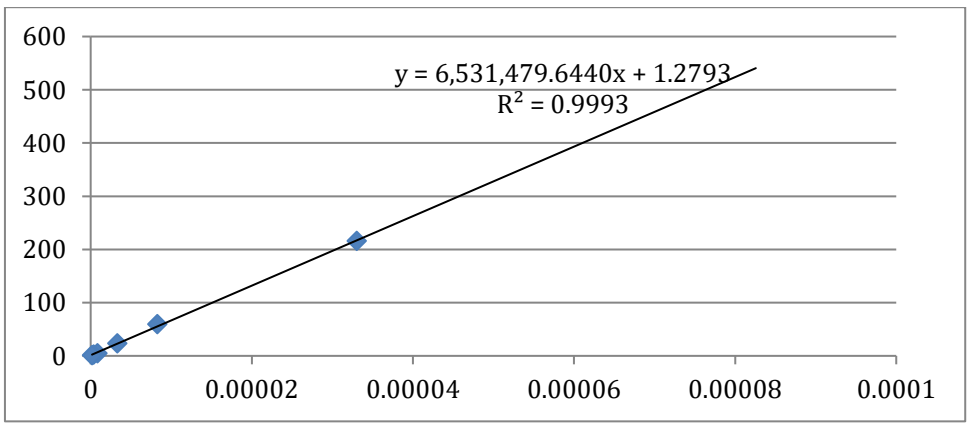
(4-Cyanophenyl)boronic acid (3.48)



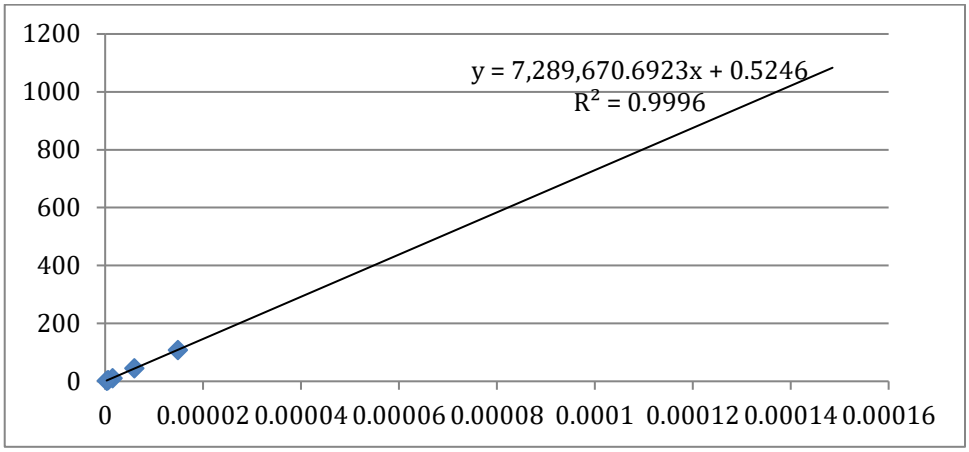
4-Cyanophenol (3.49)



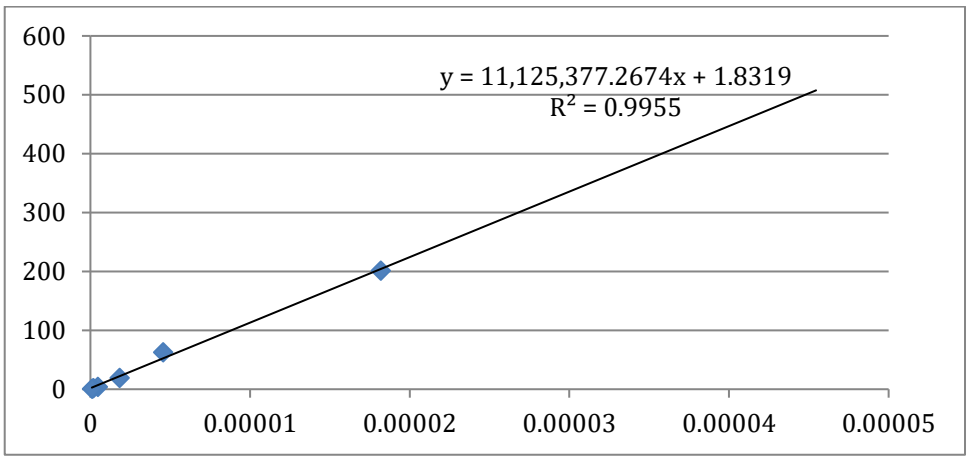
4-Fluorobenzonitrile (3.21)



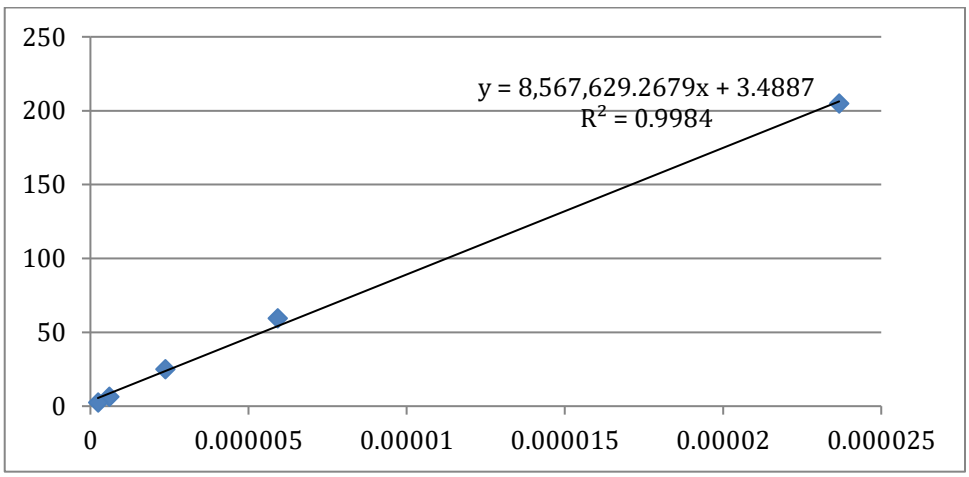
Benzonitrile (3.50)



4,4'-Oxydibenzonitrile (3.51)



4-(1*H*-Pyrazol-1-yl)benzonitrile (3.52)



4.4.30 Specific Activity Calculation (Performed by Mickael Huiban at Imanova)

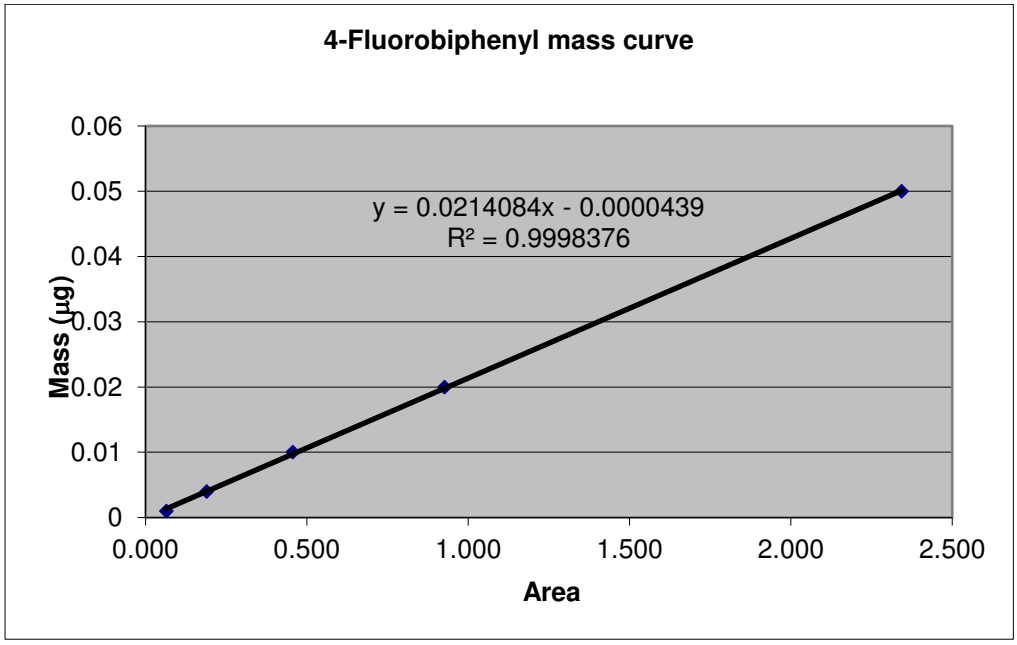
The [^{18}F]fluoride was trapped on an ion exchange cartridge (DW-TRC-L Trap & Release Column) and released using 0.7 mL of a solution consisting of 800 μL of acetonitrile, 200 μL of water, 13 mg of K_{222} and 2.5 mg of potassium carbonate into a dried 5 mL wheaton V-vial. The content of the reactor was evaporated a first time (under a stream of argon). The evaporation process was repeated 2 times following the addition of 1 mL of dry acetonitrile each time.

The reaction vessel was cooled down to 50 °C, and a solution of $Cu(OTf)_2(py)_4$ (14 mg) and precursor **2.29** (17 mg) in anhydrous DMF (300 μL) was added to the dried [^{18}F]fluoride. The vial was heated to 110 °C for 20 minutes, and then cooled down to 50 °C. The crude mixture was diluted with 4 mL of the HPLC mobile phase (Eluent A = Ammonium Formate 50 mM pH 8.0, Eluent B = Acetonitrile, A:B = 50:50) and passed through a frit (empty 3 mL SPE tube and frit, from Macherey-Nagel) to remove particles in suspension. The reaction vessel and frit were further rinsed with 1.5 mL of HPLC mobile phase, which were added to the filtered crude mixture. The resulting solution was loaded on a semi-prep HPLC for purification. Product was eluted through an Agilent Eclipse XDB C18, 250 x 9.4 mm, 5 μm column with the HPLC mobile phase at a flow of 8 mL/min. UV (254 nm) and radioactivity traces were monitored and the fraction corresponding to [^{18}F]-4-fluorobiphenyl was collected.

Analysis was performed on an Agilent Eclipse XDB C18, 150 x 4.6 mm, 5 μm column. The analytical column was eluted at 2 mL/min with a mixture of

acetonitrile and ammonium formate buffer, 50 mM, pH 8 (buffer/acetonitrile = 55/45). Radiochemical purity was assessed by injecting the radiotracer alone; Specific activity was derived from that injection. Identity of the radiolabelled product was also confirmed by co-injection with the unlabelled reference standard.

Starting from 12 GBq of [^{18}F]fluoride, a dose of 1.378 GBq of [^{18}F]-4-fluorobiphenyl, this corresponds to a 21% radiochemical yield, decay-corrected. Specific activity on that dose was 112 GBq/µmol at End Of Synthesis.



4.5 References

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Appendix

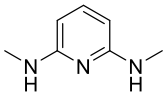
Appendix

A.1 Experimental Procedures and Characterisation for Compounds in Chapter 2

Synthesised by Co-workers

N,N'- Dimethyl-2,6-diaminopyridine (2.26)

Prepared by Dr. Enrico Emer.

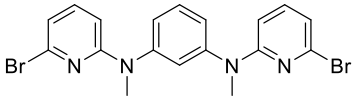


Adapting a known procedure,[1] a mixture of 2,6-dibromopyridine (3.00 g, 12.7 mmol) in aqueous methylamine solution (40%, 15 mL) was heated in a sealed tube at 190 °C for 17 hours. After cooling to room temperature, the solution was filtered and the filtrate was diluted with water (50 mL), then extracted with CH_2Cl_2 (2 x 50 mL). The combined organic phases were washed with brine, dried with $MgSO_4$, filtered and all volatiles were removed *in vacuo*. Flash column chromatography (*n*-hexane/EtOAc 70:30) afforded *N,N'*-dimethyl-2,6-diaminopyridine (**2.26**, 1.25 g, 9.09 mmol, 72%) as a brown solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.29 (1H, t, *J* = 8.0 Hz), 5.74 (2H, d, *J* = 7.9 Hz), 4.29 (2H, brs), 2.86 (6H, d, *J* = 5.3 Hz); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 159.0, 139.1, 94.0, 29.2. The analytical data were in accordance with the literature.[1]

N^1,*N*^{3}-Bis(6-bromopyridin-2-yl)-*N*^{1},*N*^{3}-dimethylbenzene-1,3-diamine (2.28)

Prepared by Dr. Enrico Emer.



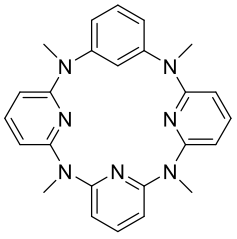
Adapting a known procedure,[2] a fine powder of benzene-1,3-diamine (457 mg, 4.2 mmol, 1.0 equiv.), 2,6-dibromopyridine (3.0 g, 12.7 mmol, 3.0 equiv.), and potassium *tert*-butoxide (4.74 g,

42.2 mmol, 10 equiv.) was stirred vigorously at room temperature under argon for 30 minutes. Dry THF (38 mL) was the added and an exothermic reaction took place immediately, to give an olive solution. After 1.5 hours, the reaction mixture was warmed to 66 °C and a solution of MeI (2.10 mL, 33.8 mmol, 8.0 equiv.) was added in two portions and the resulting mixture was stirred for a further 1.5 hours. The mixture was then cooled to room temperature and the solvent was removed *in vacuo*. The residue was dissolved in EtOAc (100 mL) and washed with brine, dried with $MgSO_4$, filtered and all volatiles were removed *in vacuo*. Flash column chromatography (petrol 30°-40°C/EtOAc 83:17) afforded N^1,N^3-bis(6-bromopyridin-2-yl)-N^1,N^3-dimethylbenzene-1,3-diamine (**2.28**, 1.49 g, 3.28 mmol, 78%) as a light yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.44 (1H, t, *J* = 7.9 Hz), 7.19 (2H, dd, *J* = 8.3, 7.4 Hz), 7.17 (1H, d, *J* = 1.9 Hz), 7.13 (2H, dd, *J* = 8.0, 2.2 Hz), 6.79 (2H, dd, *J* = 7.4, 0.5 Hz), 6.53 (2H, dd, *J* = 8.4, 0.6 Hz), 3.47 (6H, s); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 158.4, 147.1, 140.0, 138.8, 130.9, 124.0, 123.1, 116.5, 107.1, 38.5. The analytical data were in accordance with the literature.[2]

Azacalix[1]arene[3]pyridine (2.5)

Prepared by Dr. Enrico Emer.

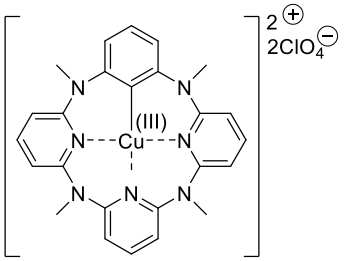


Adapting a known procedure,[3] a mixture of *N*,*N'*-dimethyl-2,6-diaminopyridine (**2.26**, 152 mg, 1.1 mmol, 1.0 equiv.), N^1,N^3-bis(6-bromopyridin-2-yl)-N^1,N^3-dimethylbenzene-1,3-diamine (**2.28**,

500 mg, 1.1 mmol, 1.0 equiv.), $Pd_2(dba)_3$ (151 mg, 0.165 mmol, 0.15 equiv), dppp (136 mg, 0.33 mmol, 0.30 equiv) and NaO*t*-Bu (317 mg, 3.3 mmol, 3.0 equiv.) in anhydrous 1,4-dioxane (200 mL) was refluxed under argon for 3 hours. After cooling to room temperature, the mixture was filtered through a Celite pad. The solvent was removed under reduced pressure and the residue was dissolved in CH_2Cl_2 and washed with brine. The organic layer was dried with $MgSO_4$, filtered and all volatiles were removed *in vacuo*. Flash column chromatography on basic alumina (petrol 30º-40ºC/EtOAc 94:6), followed by recrystallization from *n*-hexane afforded azacalix[1]arene[3]pyridine (**2.5**, 112 mg, 0.26 mmol, 24%) as a white solid. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.42 (2H, t, *J* = 8.0 Hz), 7.17 (2H, dt, *J* = 15.0, 7.6 Hz), 6.80 (2H, dd, *J* = 7.9, 1.9 Hz), 6.63-6.59 (3H, m), 6.05 (4H, dd, *J* = 7.9, 6.3 Hz), 3.25 (s, 6H), 3.17 (s, 6H); **MS** (ESI^+): for $C_{25}H_{25}N_7H$ $[M+H]^+$ requires m/z = 424.2, found 424.2. The analytical data were in accordance with the literature.[3]

Cu(III) Complex 2.6

Prepared by Dr. Enrico Emer.



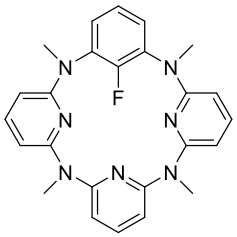
Adapting a known procedure,[3] azacalix[1]arene[3]pyridine (**2.5**, 112.1 mg, 0.26 mmol, 1.0 equiv.) and $Cu(ClO_4)_2{\cdot}6H_2O$ (145 mg, 0.39 mmol, 1.5 equiv.) were dissolved in a mixture of $CHCl_3$ (10 mL) and MeOH (10 mL). The solution turned dark green and then turned light brown with the formation of a brown/green precipitate. After one hour, the precipitate was

filtered and dried *in vacuo* to afford **2.6** as an olive green crystalline solid (177 mg, 0.26 mmol, 99%).

^{1}H NMR (400 MHz, CD_3CN): δ = 8.17 (1H, t, *J* = 8.1 Hz), 8.10 (2H, t, *J* = 8.1 Hz), 7.51 (1H, t, *J* = 7.6 Hz), 7.39 (2H, dd, *J* = 8.3, 0.9 Hz), 7.32 (2H, d, *J* = 8.1 Hz), 7.19 (2H, dd, *J* = 7.8, 0.9 Hz), 7.07 (2H, d, *J* = 7.7 Hz), 3.68 (6H, s), 3.53 (6H, s); **MS** (ESI$^+$): for $C_{25}H_{25}ClCuN_7O_4$ $[M\text{-}ClO_4]^+$ requires m/z = 585.1, found 585.0, for $C_{25}H_{25}CuN_7$ $[M\text{-}2ClO_4]^{2+}$ requires m/z = 243.1, found 242.6. The analytical data were in accordance with the literature.[3]

Fluorinated Product 2.7

Prepared by Dr. Enrico Emer.



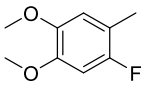
Adapting a known procedure,[4] to a solution of copper complex **2.6** (19.5 mg, 0.05 mmol, 1.0 equiv.) in MeCN (3 mL) was added KF (5.8 mg, 0.1 mmol, 2.0 equiv.). The reaction mixture was heated at reflux for 3 hours, then allowed to cool to room temperature. The reaction was quenched with aqueous ammonia solution and extracted with CH_2Cl_2. The organic phase was wash with brine, dried with $MgSO_4$ and concentrated *in vacuo*. Purification by preparative TLC (SiO_2, petrol 30º-40ºC/EtOAc/CH_2Cl_2 77:8:15) afforded **2.7** as a light yellow solid (8.5 mg, 0.02 mmol, 38%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.42 (2H, t, *J* = 8.0 Hz), 7.19 (1H, t, *J* = 7.7 Hz), 6.87 (3H, m), 6.62 (2H, d, *J* = 7.7 Hz), 6.08 (2H, d, *J* = 8.0 Hz), 6.04 (2H, d, *J* = 8.0 Hz), 3.23 (6H, s), 3.14 (6H, s); **^{19}F NMR** (376 MHz, $CDCl_3$): δ = -130.7; **MS** (ESI$^+$): for $C_{25}H_{25}FN_7$

[M+H]$^+$ requires m/z = 442.1, found 442.1. The analytical data were in accordance with the literature.[4]

1-Fluoro-4,5-dimethoxy-2-methylbenzene (2.62)

Prepared by Dr. Matthew Tredwell.

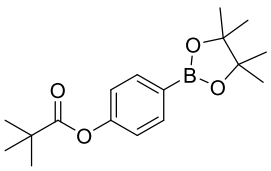


The title compound was synthesised following a reported procedure.[5] Preparative reverse phase HPLC afforded 1-fluoro-4,5-dimethoxy-2-methylbenzene (**2.62**, 2 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.64 (d, *J* = 8 Hz, 1H), 6.59 (d, *J* = 11 Hz, 1H), 3.84 (s, 3H), 3.83 (s, 3H), 2.20 (d, *J* = 2 Hz); **^{13}C NMR** (125.8 MHz, $CDCl_3$): δ = 154.1 (d, *J* = 237 Hz), 146.6 (d, *J* = 10 Hz), 143.8 (d, *J* = 3 Hz), 113.9 (d, *J* = 18 Hz), 112.7 (d, *J* = 6 Hz), 98.9 (d, *J* = 28 Hz), 55.4, 55.1, 12.9; **^{19}F {^{1}H} NMR** (376 MHz, $CDCl_3$): δ = − 125.18; **HRMS** (FI) for $C_9H_{11}FO_2$ [M]$^+$ requires 10.0743 found 170.0738; **IR** (ATR, neat): ν (cm^{-1}) = 2917, 2849, 1516, 1465, 1222, 1110.

4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl pivalate (2.78-Bpin)

Prepared by Dr. Sean Preshlock.



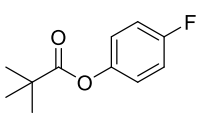
To a solution of 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (358 mg, 1.6 mmol, 1.0 equiv.) in CH_2Cl_2 (15 mL) was added pivaloyl chloride (196 μL, 1.6 mmol) and pyridine (525 μL, 6.5 mmol). The

mixture was stirred at room temperature for 3 days. The mixture was diluted with Et_2O, passed through a short plug of SiO_2 and concentrated in vacuo. Recrystallisation from MeOH/H_2O afforded 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl pivalate (**2.78-Bpin**, 171 mg, 0.56 mmol, 35%) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.83 (d, *J* = 8.4 Hz, 1H), 7.07 (d, *J* = 8.4 Hz, 1H), 1.37 (s, 9H), 1.35 (s, 12H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 176.5, 153.4, 135.8, 120.5, 83.5, 38.8, 26.8, 24.5; **^{11}B NMR** (128 MHz, $CDCl_3$): δ = 31 (br s); **HRMS** (ESI): for $C_{17}H_{25}BNaO_4$ $[M+Na]^+$ requires 327.1741 found 327.1745; **IR** (ATR, neat): ν (cm^{-1}) = 1754, 1602, 1479, 1398, 1360, 1320, 1199, 1115, 1085; **M.P.**: 120-122 °C.

4-Fluorophenyl pivalate (2.78)

Prepared by Dr. Sean Preshlock.

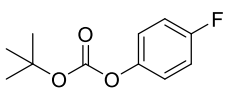


4-Fluorophenol (1.35 g, 12 mmol) was added to a 250 mL round bottom flask, to which was added 75 mL of CH_2Cl_2, pivaloyl chloride (1.47 mL, 12 mmol) and pyridine (4 mL, 49 mmol). The mixture was stirred at room temperature for 3 days before diluting with H_2O. The organic layer was separated and washed with brine and dried over $MgSO_4$. Volatiles were removed under reduced pressure and the product was redissolved in pentane and passed through a short plug of SiO_2. (742 mg, 32%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.04 (m, 4H), 1.37 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 177.1, 160.1 (d, *J* = 244.3 Hz), 146.9 (d, *J* = 2.2 Hz), 122.8 (d, *J* = 8.1 Hz), 115.9 (d, *J* = 23.5 Hz); 39.1, 27.1; **^{19}F NMR** (376 MHz, $CDCl_3$): δ = -117.5 (m); **HRMS** (EI/FI) for $C_{11}H_{13}FO_2$ $[M]^+$ requires 196.0900 found 196.0894; **IR** (ATR, neat): 1750, 1504, 1482, 1277, 1183, 1109.

***tert*-Butyl (4-fluorophenyl) carbonate (2.79)**

Prepared by Dr. Sean Preshlock.



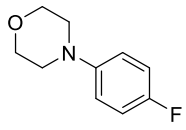
4-Fluorophenol (448 mg, 4 mmol) and 4-dimethylaminopyridine (488 mg, 4 mmol) were weighed into a 50 mL round bottom flask, to which was added 15 mL of DCM. Di-*tert*-butyl carbonate (872 mg, 4 mmol) was added. The mixture was stirred at room temperature for 24 h under a N_2 atmosphere. The reaction mixture was washed with water, brine and dried over Na_2SO_4. Volatiles were removed under reduced pressure and the product was purified by silica gel column chromatography (hexanes/EtOAc.) White solid (637 mg, 75% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.14 (m, 2H), 7.05 (m, 2H), 1.57 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 160.1 (d, $J_{C\text{-}F}$ = 244.3 Hz) 151.9, 122.7 (d, $J_{C\text{-}F}$ = 8.1 Hz), 116.0 (d, $J_{C\text{-}F}$ = 23.5 Hz), 83.7, 27.7; **^{19}F {^{1}H} NMR** (376 MHz, $CDCl_3$): δ = −117.16; **M.P.**: 38-39 °C

Data consistent with literature values.[6]

4-(4-Fluorophenyl)morpholine (2.83)

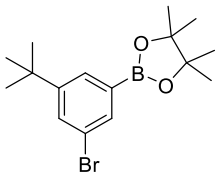
Prepared by Dr. Matthew Tredwell.



The title compound was prepared according to a literature procedure.[7], [8] **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 6.98 (t, J = 8.7 Hz, 2H), 6.92-6.83 (m, 2H), 3.87 (t, J = 4.4 Hz, 4H), 3.09 (t, J = 4.4 Hz, 4H); **^{19}F {^{1}H} NMR** (376 MHz, CDCl3): δ = –124.2. The analytical data were consistent with literature values.[9]

2-(3-Bromo-5-(*tert*-butyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2.84-Bpin)

Prepared by Dr. Sean Preshlock.



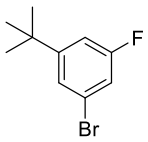
B_2Pin_2 (355 mg, 1.40 mmol, 1.4 equiv.), $[Ir(OMe)COD]_2$ (20 mg, 0.030 mmol, 1.5 mol%) and 4,4′-di-*tert*-butyl-2,2′-bipyridine (16 mg, 0.060 mmol, 3.0 mol%) were added to a 25 mL Schlenk flask and the reaction vessel was sealed and purged with N_2 for 1 hour. Degassed heptane (4 mL) was added to the reaction vessel via syringe followed by 1-bromo-3-(*tert*-butyl)benzene (340 μL, 2.0 mmol, 1.0 equiv.) and the reaction mixture was the stirred at 60 °C for 8 hours. The reaction mixture was allowed to return to room temperature and volatiles were removed *in vacuo*. The product was redissolved in Et_2O and passed through a short plug of SiO_2. Recrystallisation from MeOH/H_2O

afforded 2-(3-bromo-5-(*tert*-butyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2.84-Bpin, 389 mg, 1.15 mmol, 58 %) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.76 (s, 1H), 7.73 (s, 1H), 7.61 (s, 1H), 1.35 (s, 12H), 1.33 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 152.9, 134.6, 131.4, 130.0, 122.4, 84.0, 34.9, 31.2, 24.9; **^{11}B NMR** (128 MHz, $CDCl_3$) δ = 31 (br. s); **HRMS** (EI/FI) m/z calculated for $C_{16}H_{24}BBrO_2$ $[M]^+$ required 338.1056, found 338.1051; **M.P.**: 85-86 °C.

1-Bromo-3-(*tert*-butyl)-5-fluorobenzene (2.84)

Prepared by Dr. Sean Preshlock.

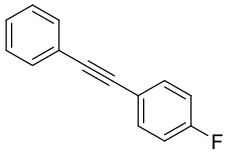


2-(3-Bromo-5-(*tert*-butyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.0 equiv, 604 mg) and potassium *tert*-butoxide (1.0 equiv, 200 mg) were dissolved in MeOH (10 mL) and stirred at room temperature for 2 hours under an atmosphere of N_2. The reaction was cooled to 0 °C and silver(I) triflate (1.3 g) was added. The reaction was stirred at 0 °C for 30 minutes before the volatiles were removed *in vacuo* at 0 °C. The residue was redissolved twice in dry acetone (10 mL, then 5 mL) and dried by co-evaporation. The residue was then redissolved in dry acetone (10 mL) over 3 Å molecular sieves. The reaction was allowed to return to room temperature and stirred for 1 hour. Volatiles were removed *in vacuo*. The product was redissolved in DCM and passed through a short plug of SiO_2. The product was then distilled under vacuum. Product isolated as colorless oil (89 mg, 93:7 mixture product to protodeborylated impurity);

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.30 (s, 1H), 7.05 (m, 2H), 1.31 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 162.6 (d, *J* = 248.7 Hz), 155.6 (d, *J* = 6.6 Hz), 124.6 (d, *J* = 2.9 Hz), 122.2 (d, *J* = 10.3 Hz), 116.1 (d, *J* = 125 Hz), 111.6 (d, *J* = 22 Hz), 35.1, 31.0; **^{19}F {^{1}H}** (NMR, 376 MHz, $CDCl_3$): δ = 111.3 (s); **HRMS** (EI/FI) m/z calculated for $C_{10}H_{12}BrF$ $[M]^+$ 230.0106, found 230.0225; **IR** (ATR, neat): 2966, 1605, 1578, 1424, 1365, 1276.

1-Fluoro-4-(phenylethynyl)benzene (2.86)

Prepared by Dr. Matthew Tredwell.

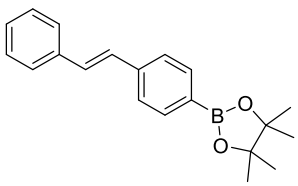


The title compound was synthesised from 1-bromo-4-fluorobenzene and phenylacetylene following a reported procedure; (33 mg, 33 %).[9]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.49-7.55 (m, 4H), 7.33-7.38 (m, 3H), 7.02-7.08 (m, 2H); **^{19}F {^{1}H} NMR** (376 MHz, $CDCl_3$): δ = −111.0. The analytical data was consistent with the literature.[10]

(*E*)-4,4,5,5-Tetramethyl-2-(4-styrylphenyl)-1,3,2-dioxaborolane (2.87-Bpin)

Prepared by Dr. Stefan Gruber.



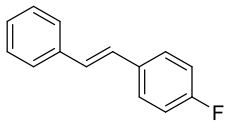
$Pd(dppf)Cl_2{\cdot}CH_2Cl_2$ (141.0 mg, 0.2 mmol, 0.05 equiv.) was added to a mixture of (*E*)-1-bromo-4-styrylbenzene (1.00 g, 3.9 mmol, 1.0 equiv.), potassium acetate (1.10 g, 11.6 mmol,

3.0 equiv.) and 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (1.00 g, 4.1 mmol, 1.05 equiv.) in DMF (3 mL). The mixture was stirred at 130° C under nitrogen for 16 hours. The insoluble solid was removed by filtration through a Celite pad (eluted with EtOAc). The filtrate was diluted with H_2O (30 mL) and extracted with EtOAc (3 x 30 mL). The combined organic extracts were washed with brine (30 mL), dried over $MgSO_4$ and concentrated *in vacuo* to give the crude product. The residue was dissolved in EtOAc (30 mL) and then activated-carbon powder and silica-gel were added and the mixture was shaken, sonicated and filtered through silica-gel/Celite pad (eluted with EtOAc). The filtrate was concentrated *in vacuo* and the residue was further purified by crystallization from hot hexane and dried under vacuum to afford (*E*)-4,4,5,5-tetramethyl-2-(4-styrylphenyl)-1,3,2-dioxaborolane (**2.87-Bpin**, 818 mg, 2.7 mmol, 69 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.84 (d, *J* = 8.0 Hz, 2H), 7.56-7.54 (d, *J* = 8.0 Hz, 4H), 7.38 (t, *J* = 7.5 Hz, 2H), 7.29 (d, *J* = 7.5 Hz, 1H), 7.21 (d, *J* = 16.3 Hz, 1H), 7.14 (d, *J* = 16.3 Hz, 1H), 1.38 (s, 12H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 140.1, 137.3, 135.3, 129.8, 128.8, 128.7, 127.9, 126.7, 125.9, 83.8, 25.0. The analytical data were consistent with literature values.[11]

(*E*)-4-Fluorostilbene (2.87)

Prepared by Dr. Matthew Tredwell.

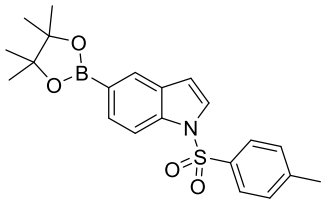


The title compound was prepared according to a literature procedure.[12]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.52-7.46 (m, 4H), 7.38-7.34 (m, 2H), 7.28-7.25 (m, 1H), 7.10-7.00 (m, 4H); **^{13}C NMR** (101 MHz, CD_2Cl_2): δ = 162.5 (d, *J* = 247 Hz), 137.3, 133.7 (d, J = 3 Hz), 128.9, 128.7 (d, *J* = 2 Hz), 128.1 (d, *J* = 8 Hz), 127.8, 127.6, 126.6, 115.8 (d, *J* = 22 Hz); **^{19}F {^{1}H} NMR** (376 MHz, $CDCl_3$): δ = –114.3. The analytical data were consistent with the literature values.[13]

5-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-1-tosyl-1*H*-indole (2.88-Bpin)

Prepared by Dr. Stefan Gruber.



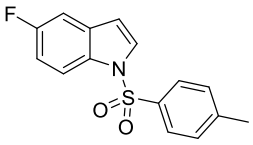
4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indole (500 mg, 2.0 mmol, 1.0 equiv.) was added to a 100 mL round bottom flask, to which was added 50 mL of anhydrous THF under N_2. NaH (60 wt% in mineral oil, 128 mg, 3.2 mmol, 1.6 equiv.) was added and stirred for 30 min. The reaction mixture was then cooled to 0 °C and tosyl chloride (456 mg, 2.4 mmol, 1.2 equiv.) was added. The mixture was allowed to come to room temperature and stirred for 24 hours. Volatiles were then removed under reduced pressure. The residue was then redissolved in CH_2Cl_2 and washed with water, then brine and dried over $MgSO_4$. Volatiles were again removed *in vacuo*

and the product was recrystallized from Et_2O/pentane to afford 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-tosyl-1*H*-indole (**2.88-Bpin**, 794 mg, 83% yield) as a white solid.

^{1}H NMR (400 MHz, C_6D_6): δ = 8.32 (d, *J* = 8.3 Hz, 1H), 8,27 (s, 1H), 8.14 (d, *J* = 8.3 Hz, 1H), 7.57 (d, *J* = 8.3 Hz, 2H), 7.43 (d, *J* = 3.7 Hz, 1H), 6.44 (d, *J* = 8.2 Hz, 2H), 6.24 (d, *J* = 3.5 Hz, 1H), 1.63 (s, 3H), 1.12 (s, 12H); **^{13}C NMR** (100 MHz, C_6D_6): δ = 144.7, 137.9, 136.4, 131.8, 131.4, 130.1, 129.9, 127.3, 127.2, 113.9, 109.9, 84.7, 25.3, 21.3; **^{11}B NMR** (128 MHz, C_6D_6): δ = 32 (br. s); **HRMS** (ESI) for $C_{21}H_{24}BNNaO_4S$ $[M+Na]^+$ requires 420.1415 found 420.1416; **IR** (ATR, neat): ν (cm^{-1}) = 1608, 1432, 1356, 1300, 1192, 1169, 1129; **M.P.**: 136 °C.

5-Fluoro-1-[(4-methylphenyl)sulfonyl]-1*H*-indole (2.88)

Prepared by Dr. Stefan Gruber.



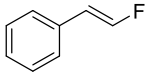
5-Fluoro-1*H*-indole (500 mg, 3.7 mmol) was weighed into a 50 mL Schlenk tube and purged with N_2. 10 mL dry THF was added via syringe. NaH (60 wt% in mineral oil, 128 mg, 3.2 mmol) was added as a solid portion and the reaction was stirred for 30 min. Tosyl chloride (456 mg, 2.4 mmol) was added at 0 °C and the reaction was allowed to come to room temperature and stirred overnight. 10 mL MeOH was added to quench the reaction and volatiles were removed under reduced pressure. The residue was redissolved

in DCM and washed with water, brine and dried over $MgSO_4$. The crude material purified by silica gel column chromatography. (323 mg, 47 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.95 (dd, *J* 4, 9 Hz, 1H), 7.73-7.77 (m, 2H), 7.60 (d, *J* = 4 Hz, 1H), 7.19-7.23 (m, 2H), 7.17 (dd, *J* = 2, 9 Hz, 1H), 7.04 (td, *J* = 2, 9 Hz, 1H), 6.61 (dd, *J* = 1, 4 Hz, 1H), 2.32 (s, 3H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ = 160.0 (d, *J* = 238 Hz), 145.6, 135.5, 132.2 (d, *J* = 10 Hz), 131.6, 130.4, 128.5, 127.2, 115.0 (d, *J* = 9 Hz), 113.0 (d, *J* = 26 Hz), 109.4 (d, *J* = 4 Hz), 107.3 (d, *J* = 24 Hz), 22.0; **^{19}F {^{1}H} NMR** (376 MHz, $CDCl_3$): δ = − 119.9; **HRMS** (ESI) for $C_{15}H_{12}FNNaO_2S$ $[M+Na]^+$ requires 312.0465 found 312.0468; **IR** (ATR, neat): ν (cm^{-1}) = 1595, 1460, 1444, 1371, 1171, 1138; **M.P.**: 107-109 °C.

(2-Fluoroethenyl)benzene (2.91)

Prepared by Dr. Matthew Tredwell.

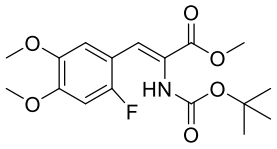


The title compound was synthesised following a reported procedure; (9 %, ^{19}F NMR yield).[5]

^{1}H NMR (400 MHz, CD_2Cl_2): δ = 7.15-.7.25 (m, 5H), 7.12 (dd, *J* = 12, 84 Hz, 1H), 6.32 (dd, *J* = 11, 19 Hz, 1H); ^{19}F {^{1}H} NMR (376 MHz, CD_2Cl_2): δ = −130.8; Data consistent with literature.[14]

Methyl-2-[(*tert*-butoxycarbonyl)amino]-3-(2-fluoro-4,5-dimethoxyphenyl)prop-2-enoate (2.111)

Prepared by Dr. Matthew Tredwell.

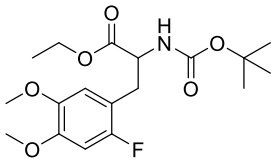


To a solution of (±)-Boc-α-phosphonoglycine trimethyl ester (1.78 g, 6 mmol) in CH_2Cl_2 (5 mL) at rt, was added 1,8-diazabicyclo[5.4.0]undec-7-ene (823 μL, 5.5 mmol) and allowed to stir for 10 minutes. 2-Fluoro-4,5-dimethoxybenzaldehyde (921 mg, 5 mmol) in DCM (5 mL) was added dropwise. The solvent was removed *in vacuo*, the residue was re-dissolved in EtOAc (10 mL) and washed with 1M $HCl_{(aq)}$ and brine. The organic phase was separated, dried over Na_2SO_4 and the solvent removed *in vacuo*. The crude material was recrystallized from hexane/ethyl acetate. (1.353 g, 76 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39 (s, 1H), 7.19 (d, *J* = 7 Hz, 1H), 6.61 (d, *J* = 12 Hz, 1H), 3.87 (s, 3H), 3.84 (s, 3H), 3.82 (s, 3H) 1.33 (bs, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 165.9, 155.8 (d, *J* = 246 Hz), 152.8, 151.0 (d, *J* = 10 Hz), 145.0 (d, *J* = 2 Hz), 123.9, 122.2 (d, *J* = 4 Hz), 113.2 (d, *J* = 13 Hz), 110.7 (d, *J* = 3 Hz), 99.6 (d, *J* = 28 Hz), 80.9, 56.2, 56.1, 52.6, 28.1; **^{19}F {^{1}H} NMR** (376 MHz, $CDCl_3$): δ = −118.9 (broad singlet); **HRMS** (ESI) for $C_{17}H_{22}FNNaO_6$ $[M+Na]^+$ requires 378.1323 found 378.1323; **IR** (ATR, neat): ν (cm^{-1}) = 3332, 2977, 1716, 1515, 1258; **M.P.**: 137-139 °C.

Ethyl-2-[(*tert*-butoxycarbonyl)amino]-3-(2-fluoro-4,5-dimethoxyphenyl)propanoate (2.112)

Prepared by Dr. Matthew Tredwell.



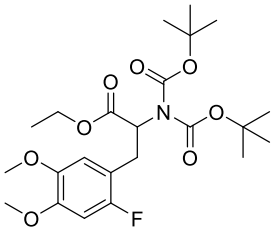
To a flask containing 10 % Pd/C (33 mg) was added EtOH (1 mL), followed by methyl-2-[(*tert*-butoxycarbonyl)amino]-3-(2-fluoro-4,5-dimethoxyphenyl)prop-2-enoate (**2.111**, 355 mg, 1 mmol) in EtOH (9 mL). The reaction was then allowed to stir under an atmosphere of H_2 for 5 hours. The reaction was purged with N_2, filtered over celite and the solvent removed *in vacuo*. The crude material was dissolved in THF (4 mL) and treated with 2.5 M LiOH (4 mL). The reaction was allowed to stir at rt for 12 hours. The solvent was removed *in vacuo* and the aqueous layer was washed with diethyl ether and then acidified with 1 M HCl. The aqueous layer was extracted with EtOAc. The solvent was removed *in vacuo*. The crude material was dissolved in DMF (5 mL). To this solution was added $NaHCO_3$ (168 mg, 2 mmol) and ethyl iodide (0.4 mL, 5 mmol) and the reaction allowed to stir at rt for 24 hours. The reaction was partitioned between EtOAc and H_2O. The aqueous phase was extracted with EtOAc. The combined organic fractions were dried over Na_2SO_4 and the solvent removed *in vacuo*. The crude material purified by silica gel column chromatography. (304 mg, 82 %).

Two rotamers present in an 85:15 ratio in $CDCl_3$ at 25 °C. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 6.51-6.56 (m, 2H), 5.02 (d, *J* = 8 Hz, 0.88H), 4.69-4.86 (bs, 0.14H, rotamer), 4.41-4.48 (m, 0.89H), 4.22-4.32 (bs, 0.16H, rotamer), 4.06-4.14 (m, 2H), 3. 77 (s, 3H), 3.76 (s, 3H), 2.81-3.07 (m, 2H, + rotamer), 1.34 (s, 9H), 1.18 (t, *J* = 7 Hz, 3H); **^{13}C NMR**

(100 MHz, $CDCl_3$): δ = 171.8, 155.4 (d, *J* = 232 Hz), 155.0, 148.8 (d, *J* = 15 Hz), 145.1, 113.5 (d, *J* = 3 Hz), 113.4 (d, *J* = 20 Hz), 99.9 (d, *J* = 29 Hz), 79.8, 61.4, 56.3, 56.1, 53.8, 31.4, 28.3, 14.1; **^{19}F {^{1}H} NMR** (376 MHz, $CDCl_3$): δ = −124.8; **HRMS** (ESI) for $C_{18}H_{26}FNNaO_6$ $[M+Na]^+$ requires 394.1636 found 394.1640; **IR** (ATR, neat): ν (cm^{-1}) = 2978, 1713, 1626, 1516, 1226; **M.P.** 89-90 °C.

Ethyl-2-[bis(*tert*-butoxycarbonyl)amino]-3-(2-fluoro-4,5-dimethoxyphenyl)propanoate (2.113)

Prepared by Dr. Matthew Tredwell.



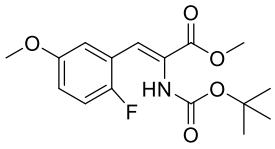
To a solution of ethyl-2-[(*tert*-butoxycarbonyl)amino]-3-(2-fluoro-4,5-dimethoxyphenyl)propanoate (**2.112**, 100 mg, 0.27 mmol) in MeCN (3 mL) was added 4-(dimethylamino)pyridine (33 mg, 0.27 mmol) followed by di-*tert*-butyl dicarbonate (177 mg, 0.81 mmol). The reaction was allowed to stir for 36 hours at rt. The reaction was diluted with EtOAc, and washed with sat. $NH_4Cl_{(aq)}$ and brine. The organic fraction was dried over Na_2SO_4 and the solvent removed *in vacuo*. The crude material was purified by silica gel column chromatography. (113 mg, 89 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.50-6.55 (m, 2H), 5.07 (dd, *J* = 5, 11 Hz, 1H), 4.12-4.17 (m, 2H), 3.75 (s, 6H), 3.31-3.36 (m, 1H), 3.10-3.17 (m, 1H), 1.33 (s, 18H), 1.21 (t, *J* = 7 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 170.2, 155.4 (d, *J* = 239 Hz), 151.7, 148.6 (d, *J* = 10 Hz), 144.9 (d, *J* = 2 Hz), 114.9 (d, *J* = 17 Hz), 113.8 (d, *J* = 6 Hz), 99.9 (d, *J* =

28 Hz), 82.8, 61.3, 58.3, 56.2, 56.1, 28.9, 27.8, 14.1; **^{19}F {^{1}H} NMR** (376 MHz, $CDCl_3$): δ = −125.0; **HRMS** (ESI) for $C_{23}H_{34}FNNaO_0$ $[M+Na]^+$ requires 494.2161 found 494.2168; **IR** (ATR, neat): 2980, 1741, 1700, 1517, 1367, 1226; **M.P.**: 86-88 °C.

Methyl-2-[(*tert*-butoxycarbonyl)amino]-3-(2-fluoro-5-methoxyphenyl)prop-2-enoate (2.130)

Prepared by Dr. Matthew Tredwell.



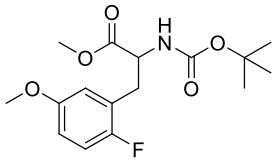
To a solution of (±)-Boc-α-phosphonoglycine trimethyl ester (1.78 g, 6 mmol) in CH_2Cl_2 (5 mL) at rt, was added 1,8-diazabicyclo[5.4.0]undec-7-ene (823 μL, 5.5 mmol) and allowed to stir for 10 minutes. 2-Fluoro-5-methoxybenzaldehyde (623 μL, 5 mmol) in CH_2Cl_2 (5 mL) was added dropwise. The solvent was removed *in vacuo*, the residue was re-dissolved in EtOAc (10 mL) and washed with 1M $HCl_{(aq)}$ and brine. The organic phase was separated, dried over Na_2SO_4 and the solvent removed *in vacuo*. The crude material was recrystallized from hexane/ethyl acetate. (1.03 g, 63 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.21 (s, 1H), 7.02-7.06 (m, 1H), 6.91 (t, *J* = 10 Hz, 1H), 6.73-6.78 (m, 1H), 6.36 (bs, 1H), 3.79 (s, 3H), 3.68 (s, 3H), 1.31 (bs, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 165.6, 155.3, 155.1 (d, *J* = 244 Hz), 152.4, 126.3, 122.7 (d, *J* = 15 Hz), 120.9 (d, *J* = 4 Hz), 116.4 (d, *J* = 8 Hz), 116.2 (d, *J* = 24 Hz), 113.6 (d, *J* = 2 Hz), 81.1, 55.7, 52.7, 28.0; **^{19}F {^{1}H} NMR** (376 MHz, $CDCl_3$): δ = −123.1 (br s); **HRMS** (ESI) for

$C_{16}H_{20}FNNaO_5$ [M+Na]$^+$ requires 348.1218 found 348.1219; **IR** (ATR, neat): 2979, 1709, 1494, 1368, 1245, 1210; **M.P.**: 89-93 °C.

Methyl *N*-(*tert*-butoxycarbonyl)-2-fluoro-5-methoxyphenylalaninate (2.131)

Prepared by Dr. Matthew Tredwell.

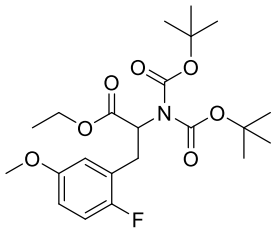


To a flask containing 10 % Pd/C (33 mg) was added EtOH (1 mL), followed by methyl-2-[(*tert*-butoxycarbonyl)amino]-3-(2-fluoro-5-methoxyphenyl)prop-2-enoate (**2.130**, 325 mg, 1 mmol) in EtOH (9 mL). The reaction was then allowed to stir under an atmosphere of H_2 for 5 hours. The reaction was purged with N_2, filtered over celite and the solvent removed *in vacuo*. The crude product was purified by column chromatography. (321 mg, 98 %).

Two rotamers present in an 4:1 ratio in $CDCl_3$ at 25 °C. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 6.93 (t, *J* = 9 Hz, 1H), 6.70-6.74 (m, 1H), 6.30-6.70 (m, 1H), 5.07 (d, *J* = 8 Hz, 0.8H), 4.80 (br s, 0.2H, rotamer), 4.53-4.60 (m, 0.8H), 4.41 (br s, 0.2H), 3.75 (s, 3H), 3.72 (s, 3H), 2.86-3.19 (m, 2H, + rotamer), 1.40 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 172.2, 155.8 (d, *J* = 238 Hz), 155.5, 155.0, 123.8 (d, *J* = 18 Hz), 116.4 (d, *J* = 4 Hz), 115.8 (d, *J* = 24 Hz), 113.7 (d, *J* = 8 Hz), 79.9, 55.7, 53.6, 52.4, 32.1, 28.3; **^{19}F {^{1}H} NMR** (376 MHz, $CDCl_3$): δ = −128.6; **HRMS** (ESI) for $C_{16}H_{22}FNNaO_5$ [M+Na]$^+$ requires 350.1374 found 350.1385; **IR** (ATR, neat): 1713, 1501, 1366, 1165.

Methyl-2-[bis(*tert*-butoxycarbonyl)amino]-3-(2-fluoro-5-methoxyphenyl)propanoate (2.132)

Prepared by Dr. Matthew Tredwell.

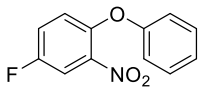


To a solution of methyl-2-[(*tert*-butoxycarbonyl)amino]-3-(2-fluoro-5-methoxyphenyl)propanoate (**2.132**, 300 mg, 0.92 mmol) in MeCN (10 mL) was added 4-(dimethylamino)pyridine (112 mg, 0.92 mmol) followed by di-*tert*-butyl dicarbonate (610 mg, 2.8 mmol). The reaction was allowed to stir for 16 hours at rt. The reaction was diluted with EtOAc, and washed with sat. $NH_4Cl_{(aq)}$ and brine. The organic fraction was dried over Na_2SO_4 and the solvent removed *in vacuo*. The crude material was purified by silica gel column chromatography (365 mg, 93 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.88 (t, *J* = 8 Hz, 1H), 6.64-6.70 (m, 1H), 6.60-6.64 (m, 1H), 5.17 (dd, *J* = 4, 11, Hz, 1H), 3.73 (s, 3H), 3.71 (s, 3H), 3.40-3.46 (m, 1H), 3.16-3.25 (m, 1H), 1.36 (s, 18H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 170.6, 155.9 (d, *J* = 238 Hz), 155.4, 151.4, 125.1 (d, *J* = 18 Hz), 116.6 (d, *J* = 4 Hz), 115.6 (d, *J* = 24 Hz), 113.4 (d, *J* = 8 Hz), 83.0, 58.0, 55.6, 52.3, 29.8, 27.8; **^{19}F {^{1}H} NMR** (376 MHz, $CDCl_3$): δ = −128.5; **HRMS** (ESI) for $C_{21}H_{30}FNNaO_7$ $[M+Na]^+$ requires 450.1899 found 450.1881; **IR** (ATR, neat): 1747, 1699, 1502, 1367, 1140.

5-Fluoro-2-phenoxynitrobenzene (2.138)

Prepared by Dr. Matthew Tredwell.



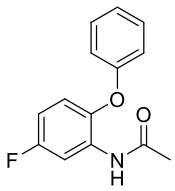
The title compound was synthesised following a reported procedure.[15]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.72 (dd, *J* = 3, 8 Hz, 1H), 7.37-7.43 (m, 2H), 7.26-7.32 (m, 1H), 7.18-7.23 (m, 1H), 7.02-7.10 (m, 3H); **^{19}F {^{1}H} NMR** (376 MHz, $CDCl_3$): δ = − 116.3; **MS** (ESI): $C_{12}H_8FNNaO_3^+$ $[M+Na]^+$ requires 256.0, found 256.1 $[M+Na]^+$. The analytical data was consistent with literature values.[16]

***N*-(5-fluoro-2-phenoxyphenyl)acetamide (2.140)**

Prepared by Dr. Matthew Tredwell.

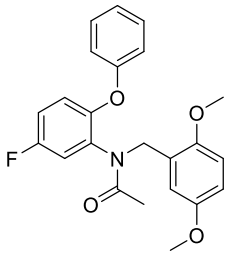
The title compound was synthesised following a reported procedure.[15]



^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.21 (dd, *J* = 3, 10 Hz, 1H), 7.65-7.75 (bs, 1H), 7.25-7.30 (m, 2H), 7.04-7.08 (m, 1H), 6.88-6.92 (m, 2H), 6.73 (dd, *J* = 5, 9, Hz, 1H), 6.56-6.65 (m, 1H), 2.08 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 168.5, 158.8 (d, *J* = 241 Hz), 156.7, 141.0 (d, *J* = 2 Hz), 131.0 (d, *J* = 12 Hz), 130.1, 123.9, 118.8 (d, *J* = 9 Hz), 118.1, 110.0 (d, *J* = 24 Hz), 108.1 (d, *J* = 30 Hz), 24.9; **^{19}F {^{1}H} NMR** (376 MHz, $CDCl_3$): δ = − 116.3; **HRMS** (ESI) for $C_{14}H_{12}FNNaO_2$ $[M+Na]^+$ requires 268.0744, found 268.0750; IR (ν / cm^{-1}) 1676, 1616, 1527, 1469, 1433, 1211; Data consistent with literature.[17]

_N_-(5-Fluoro-2-phenoxyphenyl)-_N_-(2,5-dimethoxybenzyl)acetamide (2.94)

Prepared by Dr. Matthew Tredwell.



The title compound was synthesised following a reported procedure.[4] (104 mg, 78 %).[15]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.28-7.33 (m, 2H), 7.08-7.14 (m, 1H), 6.65-6.95 (m, 8H), 5.11 (d, *J* = 14 Hz, 1H), 4.64 (d, *J* = 14 Hz, 1H), 3.65 (s, 3H), 3.55 (s, 3H), 1.96 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 170.6, 157.7 (d, *J* = 244 Hz), 156.4, 153.5, 151.8, 149.7 (d, *J* = 3 Hz), 134.4 (d, *J* = 10 Hz), 129.9, 126.2, 123.9, 119.7 (d, *J* = 9 Hz), 118.7, 117.2 (d, *J* = 23 Hz), 116.4, 115.6 (d, *J* = 23 Hz), 113.5, 111.4, 55.7, 55.6, 45.9, 22.2; **^{19}F {^{1}H} NMR** (376 MHz, $CDCl_3$): δ = − 118.74; **HRMS** (ESI): for $C_{23}H_{22}FNNaO_4$ $[M+Na]^+$ requires 418.1425 found 418.1431. The analytical data was consistent with literature values.[18]

3,4-Difluoro-1,1'-biphenyl (2.152)

Nitrogen was bubbled through a mixture of 4-bromo-1,2-difluorobenzene (260 mg, 0.86 mmol), phenylboronic acid (1.49 g, 11.40 mmol), K_2CO_3 (2.86 g, 20.73 mmol), $Pd(dppf)Cl_2.CH_2Cl_2$ (0.21 g, 0.26 mmol) and H_2O (4 mL) for 10 min. Then the reaction was heated at 80 °C for 2 h, cooled to room temperature and diluted with H_2O (5 mL), and extracted with hexane (3 x 10 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated in vacuum to give a residue which

was purified by crystallization from hot hexane (placed in the freezer) to afford the product as a white solid (758 mg, 17%).

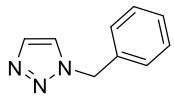
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.54-7.51 (m, 2H), 7.47-7.35 (m, 4H), 7.32-7.35 (m, 1H), 7.25-7.19 (m, 1H); **^{19}F{^{1}H} NMR**, 376 MHz, $CDCl_3$): δ = –137.7 (d, *J* = 20 Hz), –140.4 (d, *J* = 20 Hz). The analytical data was consistent with literature values.[19]

A.2 Experimental Procedures and Characterisation for Compounds in Chapter 3 Synthesised by Co-workers

A.2.1 Heterocycles for Screening

1-Benzyl-1*H*-1,2,3-triazole (3.37)

Prepared by Dr. Michael Schedler.

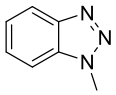


Adapting a known procedure,[20] 1,2,3-triazole (420 μL, 7.24 mmol, 1.0 equiv.) was dissolved in anhydrous THF (20 mL) and DBU (1.29 mL, 8.69 mmol, 1.2 equiv.) and benzyl bromide (0.945 mL, 7.96 mmol, 1.1 equiv.) were added. The mixture was stirred for 18 hours at room temperature and then quenched by addition of H_2O (20 mL). The mixture was extracted with CH_2Cl_2 (3 x 20 mL) and the combined organic phases were washed with brine, dried ($MgSO_4$) and filtered. All volatiles were removed *in vacuo*. The crude product was purified by flash column chromatography on silica (*n*-pentane/EtOAc 50:50) yielding 1-benzyl-1*H*-1,2,3-triazole (**3.37**, 330 mg, 2.08 mmol, 29%) as a colourless solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.70 (br s, 1H), 7.46 (br s, 1H), 7.40–7.32 (m, 3H), 7.27–7.25 (m, 2H), 5.56 (s, 2H); **MS** (ESI^+): for $C_9H_{10}N_3^+$ $[M+H]^+$ requires m/z = 160.1, found 160.1. Analytical data were in accordance with the literature.[21]

1-Methylbenzotriazole (3.39)

Prepared by Dr. Enrico Emer.

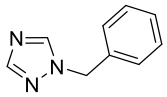


Adapting a known procedure,[22] to a stirred solution of benzotriazole (5.0 g, 42.0 mmol, 1.0 equiv.) in MeCN (75 mL) was added aq. NaOH solution (8 mL, 25%), followed by a solution of MeI (3.14 mL, 50.4 mmol, 1.2 equiv.) in MeCN (8 mL). The reaction mixture was stirred at room temperature for 48 hours, concentrated *in vacuo* and extracted with $CHCl_3$ (4 x 25 mL). The combined organic extracts were washed with brine (2 x 25 mL), dried ($MgSO_4$) and the solvent was removed *in vacuo*. Recrystallization afforded 1-methylbenzotriazole (**3.39**, 3.1 g, 23.2 mmol, 55%) as white crystals.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.06-8.04 (m, 1H), 7.53-7.47 (m, 2H), 7.41-7.35 (m, 1H), 4.29 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 146.1, 133.6, 127.3, 123.8, 119.9, 109.1, 34.2. The analytical data were in accordance with the literature.[23]

1-Benzyl-1*H*-1,2,4-triazole (3.41)

Prepared by Dr. Michael Schedler.



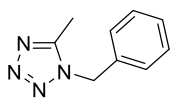
Following a known procedure,[20] 1,2,4-triazole (1.00 g, 14.5 mmol, 1.0 equiv.) and benzyl chloride (1.69 mL, 16.0 mmol, 1.1 equiv.) were

dissolved in anhydrous THF (10 mL). A solution of DBU (2.60 mL, 17.4 mmol, 1.2 equiv.) in anhydrous THF (5 mL) was added slowly and the reaction was stirred for 16h at room temperature. The reaction was then poured into H_2O (50 mL) and this mixture was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic phases were dried ($MgSO_4$), filtered and all volatiles were removed *in vacuo*. The resulting residue was purified by flash column chromatography on silica (*n*-pentane/EtOAc 33:67 to 20:80) yielding 1-benzyl-1*H*-1,2,4-triazole (**3.41**, 1.37 g, 8.61 mmol, 59%) as a colourless solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.14 (br s, 1H), 8.01 (br s, 1H), 7.41–7.33 (m, 3H), 7.27–7.25 (m, 2H), 5.36 (s, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 152.2, 134.5, 129.0, 128.6, 127.9, 53.5; **MS** (ESI^+): for $C_9H_{10}N_3^+$ $[M+H]^+$ requires m/z = 160.1, found 160.1. Analytical data were in accordance with the literature.[20]

1-Benzyl-5-methyl-1*H*-tetrazole (3.43)

Prepared by Dr. Michael Schedler.



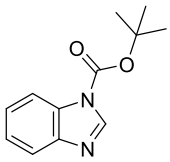
Adapting a known procedure,[24] 5-methyl-1*H*-tetrazole (500 mg, 5.95 mmol, 1.0 equiv.) and K_2CO_3 (987 mg, 7.14 mmol, 1.2 equiv.) were suspended in acetone (20 mL). Benzyl bromide (850 µL, 7.14 mmol, 1.2 equiv.) was added and the mixture was stirred at 50 °C for 1.5 hours. Afterwards, all volatiles were removed *in vacuo* and the residue was dissolved in EtOAc (30 mL) and brine (30 mL). The organic phase was separated and dried with $MgSO_4$, filtered and all volatiles were removed *in vacuo*. The residue was purified by flash column

chromatography on silica (*n*-pentane/EtOAc 50:50) yielding 1-benzyl-5-methyl-1*H*-tetrazole (**3.43**, 484 mg, 2.78 mmol, 47%) as a colourless solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.30–7.23 (m, 3H), 7.14–7.10 (m, 2H), 5.43 (s, 2H), 2.37 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 151.7, 133.1, 129.1, 128.8, 127.4, 50.7, 8.9; **HRMS** (ESI^+): for $C_9H_{11}N_4^+$ $[M+H]^+$ requires m/z = 175.0978, found 175.0979; **IR** (ATR, neat): $\tilde{\nu}$ (cm^{-1}) = 1492, 1407, 1203, 1082, 719, 693, 664. **M.P.**: 44°C.

tert-Butyl benzo[d]imidazole-1-carboxylate (3.63)

Prepared by Dr. Michael Schedler.

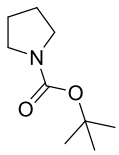


Benzimidazole (250 mg, 2.12 mmol, 1.0 equiv.), Boc_2O (506 mg, 2.32 mmol, 1.1 equiv.) and DMAP (25.9 mg, 0.212 mmol, 0.10 equiv.) were dissolved in anhydrous CH_2Cl_2 (10 mL) and stirred at room temperature for 16 hours. All volatiles of the reaction mixture were removed *in vacuo* and the resulting residue was purified by flash column chromatography on silica (*n*-pentane/EtOAc 80:20) yielding *tert*-butyl benzimidazole-1-carboxylate (**3.63**, 418 mg, 1.91 mmol, 90%) as a colourless solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.44 (s, 1H), 8.01–7.98 (m, 1H), 7.80–7.78 (m, 1H), 7.41–7.33 (m, 2H), 1.70 (s, 9H); **MS** (ESI^+): for $C_{12}H_{14}N_2NaO_2^+$ $[M+Na]^+$ requires m/z = 241.1, found 241.1. Analytical data were in accordance with the literature.[25]

tert-Butyl pyrrolidine-1-carboxylate (3.81)

Prepared by Dr. Michael Schedler.

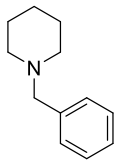


Pyrrolidine (577 µL, 7.03 mmol, 1.0 equiv.), Boc_2O (1.69 g, 7.74 mmol, 1.1 equiv.) and DMAP (86 mg, 0.703 mmol, 0.10 equiv.) were dissolved in anhydrous CH_2Cl_2 (25 mL) and stirred at room temperature for 17 hours. All volatiles of the reaction mixture were removed *in vacuo* and the resulting residue was purified by flash column chromatography on silica (*n*-pentane/ethyl acetate 90:10), yielding *tert*-butyl pyrrolidine-1-carboxylate (**3.81**, 1.19 g, 6.94 mmol, 99%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.36–3.23 (m, 4H), 1.85–1.79 (m, 4H), 1.46 (s, 9H); **MS** (ESI^+): for $C_{18}H_{34}N_2NaO_4^+$ $[2M+Na]^+$ requires m/z = 365.2, found 365.2. The analytical data were in accordance with the literature.[26]

1-Benzylpiperidine (3.84)

Prepared by Dr. Enrico Emer.



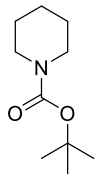
Adapting a known procedure,[27] piperidine (5.8 mL, 58.7 mmol, 2.5 equiv.) was added at 0 °C to a solution of benzyl bromide (2.8 mL, 23.5 mmol, 1.0 equiv.) in CH_2Cl_2 (100 mL). The reaction mixture was stirred overnight at room temperature, then concentrated *in vacuo* and aqueous HCl (50 mL, 2M) was added. The mixture was extracted with *n*-hexane (3 x 40 mL). The aqueous layer was made strongly basic by adding solid sodium hydroxide and the resulting solution was extracted with diethyl ether (3 x 40 mL). The combined

organic phase was dried over $MgSO_4$, filtered and solvents were removed in vacuo. 1-Benzylpiperidine (**3.84**, 3.84 g, 21.8 mmol, 93%) was isolated by flash column chromatography (*n*-hexane/EtOAc 80:20) as a light yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.23-7.22 (m, 4H), 7.17-7.14 (m, 1H), 3.39 (s, 2H), 2.29 (s, 4H), 1.48 (dq, J = 10.9, 5.4 Hz, 4H), 1.35 (q, J = 5.5 Hz, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 138.6, 129.2, 128.0, 126.7, 63.9, 54.5, 25.9, 24.4. The analytical data were in accordance with the literature.[28]

tert-Butyl piperidine-1-carboxylate (3.85)

Prepared by Dr. Michael Schedler.

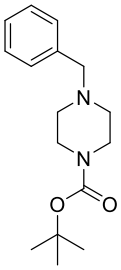


Piperidine (580 µL, 5.87 mmol, 1.0 equiv.), Boc_2O (1.41 g, 6.46 mmol, 1.1 equiv.) and DMAP (72 mg, 0.59 mmol, 0.10 equiv.) were dissolved in anhydrous CH_2Cl_2 (25 mL) and stirred at room temperature for 17 hours. All volatiles of the reaction mixture were removed *in vacuo* and the resulting residue was purified by flash column chromatography on silica (*n*-pentane/ethyl acetate 95:5) yielding *tert*-butyl piperidine-1-carboxylate (**3.85**, 935 mg, 5.05 mmol, 86%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.36–3.34 (m, 4H), 1.65–1.47 (m, 6H), 1.45 (s, 9H); **MS** (ESI^+) for $C_{20}H_{38}N_2NaO_4^+$ $[2M+Na]^+$ requires m/z = 393.3, found 393.3. Analytical data were in accordance with the literature.[29]

***tert*-Butyl 4-benzylpiperazine-1-carboxylate (3.91)**

Prepared by Dr. Michael Schedler.

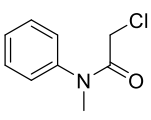


Following a known procedure,[30] 1-benzylpiperazine (1.00 g, 5.67 mmol, 1.0 equiv.), Boc_2O (1.36 g, 6.24 mmol, 1.1 equiv.) and DMAP (69.3 mg, 0.567 mmol, 0.10 equiv.) were dissolved in anhydrous CH_2Cl_2. The reaction mixture was stirred for 18 hours at room temperature and was stopped by addition of H_2O (25 mL). The mixture was extracted with CH_2Cl_2 (3 x 25 mL) and the combined organic phases were washed with brine, dried with $MgSO_4$, filtered and all volatiles were removed *in vacuo*. The residue was purified by flash column chromatography on silica (*n*-pentane/EtOAc 90:10 to 80:20) yielding *tert*-butyl 4-benzylpiperazine-1-carboxylate (**3.91**, 1.39 g, 5.04 mmol, 89%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.14 (br s, 1H), 8.01 (br s, 1H), 7.34–7.24 (m, 5H), 3.51 (s, 2H) , 3.43 (t, J = 5.1 Hz, 4H) , 2.39 (t, J = 5.1 Hz, 4H), 1.45 (s, 9H); **MS** (ESI^+): for $C_{16}H_{25}N_2O_2^+$ $[M+H]^+$ requires m/z = 277.2, found 277.2 Analytical data were in accordance with the literature.[30]

2-Chloro-*N*-methyl-*N*-phenylacetamide

Prepared by Dr. Michael Schedler.



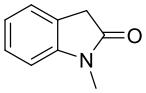
Following a known procedure,[31] a mixture of an aqueous KOH solution (1.57 g, 28.0 mmol, 3.0 equiv, dissolved in 10 mL H_2O) and EtOAc (10 mL) was cooled to 0 °C. *N*-Methylaniline (1.00 g, 9.35 mmol, 1.0 equiv.)

was added via syringe to the mixture and the reaction was stirred for 5 minutes. Chloroacetyl chloride (1.11 mL, 14.0 mmol, 1.5 equiv.) was added via syringe slowly and the reaction was stirred for 2 h at 0 °C. Then, the reaction was diluted with 10 mL EtOAc and the aqueous phase was separated. The organic phase was washed with brine, dried with $MgSO_4$, filtered and all volatiles were removed *in vacuo*. The resulting yellow oil was cooled to 0 °C and crystallised. Recrystallisation from EtOH afforded 2-chloro-*N*-methyl-*N*-phenylacetamide (680 mg, 3.70 mmol, 40%) as a colourless solid.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.50–7.35 (m, 3H), 7.28–7.22 (m, 2H), 3.85 (s, 2H), 3.31 (s, 3H); **MS** (ESI^+): for $C_{18}H_{20}Cl_2N_2NaO_2^+$ $(2M+Na)^+$ requires m/z = 389.1, found 389.1. Analytical data were in accordance with the literature.[31]

1-Methylindolin-2-one (3.103)

Prepared by Dr. Michael Schedler.



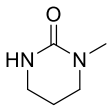
Following a known procedure,[31] 2-chloro-*N*-methyl-*N*-phenylacetamide (367 mg, 0.200 mmol, 1.0 equiv.), $Pd(OAc)_2$ (0.5 mg, 0.002 mmol, 0.01 equiv.) and JohnPhos (1.2 mg, 0.004 mmol, 0.02 equiv.) were dissolved in anhydrous toluene (2 mL) in a flame-dried Schlenk tube. Et_3N (67 µL, 0.30 mmol, 1.5 equiv.) was added to the reaction and the tube was stirred at 80 °C under N_2 for 2.5 h. The reaction mixture was then cooled to room temperature and diluted with EtOAc (20 mL) and filtered through Celite. All volatiles of the filtrate were removed *in vacuo* and the resulting yellow solid was purified by flash column

chromatography on silica (*n*-pentane/EtOAc 80:20) yielding 1-methylindolin-2-one (**3.103**, 169 mg, 1.14 mmol, 77%) as a colourless solid.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.31–7.23 (m, 2H), 7.04 (td, J = 7.5, 1.0 Hz, 1H), 6.82 (d, J = 6.8 Hz, 1H), 3.52 (s, 2H), 3.21 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 175.2, 145.4, 128.0, 124.6, 124.4, 122.5, 108.2, 35.9, 26.3; **MS** (ESI^+): for $C_9H_9NNaO^+$ $[M+Na]^+$ requires m/z = 170.1, found 170.1. Analytical data were in accordance with the literature.[31]

1-Methyltetrahydropyrimidin-2(1*H*)-one (3.111)

Prepared by Dr. Michael Schedler.

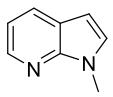


Propylene urea (1.00 g, 10.0 mmol, 1.0 equiv.) and K_2CO_3 (1.38 mg, 10.0 mmol, 1.0 equiv.) were suspended in anhydrous DMF (5 mL). MeI (0.626 mL, 10.0 mmol, 1.0 equiv.) was added and the reaction was stirred at 100 °C for 2 hours. The reaction mixture was cooled to room temperature and quenched by the addition of H_2O (10 mL). The mixture was washed with CH_2Cl_2 (3 x 20 mL) and the organic phases were discarded. All volatiles of the aqueous phase were removed *in vacuo* and the resulting solid residue was extracted with CH_2Cl_2 (3 x 100 mL). These organic phases were filtered and all volatiles were removed *in vacuo*. Flash column chromatography on silica (CH_2Cl_2/MeOH 95:5) afforded 1-methyltetrahydro-pyrimidin-2(1*H*)-one (**3.111**, 230.0 mg, 2.02 mmol, 20%) was obtained as a colourless, crystalline solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.50 (s, 1H), 3.23 (td, J = 5.8, 2.5 Hz, 2H), 3.18 (t, J = 6.0 Hz, 2H), 2.86 (s, 3H), 1.87 (p, J = 5.9 Hz, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 157.0, 47.5, 40.5, 35.0, 22.3; **HRMS** (ESI^+): for $C_5H_{11}N_2O^+$ $[M+H]^+$ requires m/z = 115.0868, found 115.0867; **IR** (ATR, neat): $\tilde{\nu}$ (cm^{-1}) = 3290, 3215, 3061, 2928, 1641, 1528, 1444, 1400, 1376, 1348, 1316, 1266, 1197, 1124, 1100, 1066, 980, 756, 670; **M.P.:** 74 °C.

_N_-Methyl-7-azaindole (3.115)

Prepared by Dr. Enrico Emer.

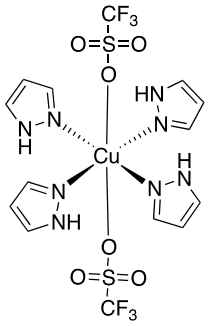


Adapting a known procedure,[32] to a solution of 7-azaindole (1.0 g, 8.46 mmol, 1.00 equiv.) in anhydrous DMF (5 mL) was added NaH (60% in mineral oil, 244 mg, 10.2 mmol, 1.20 equiv.) under N_2, and the mixture was stirred at 0 °C for one hour. MeI (580 μL, 9.30 mmol, 1.10 equiv.) was added slowly. The mixture was allowed to warm to room temperature and was stirred for a further 12 hours. H_2O (50 mL) was added, and the product was extracted with EtOAc. The EtOAc extract was washed with H_2O (3 x 50 mL), dried over anhydrous $MgSO_4$, and the solvent was removed *in vacuo*. *N*-Methyl-7-azaindole (**3.115**, 971 mg, 7.35 mmol, 87%) was obtained without further purification as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.35 (dd, J = 4.7, 1.5 Hz, 1H), 7.91 (dd, J = 7.8, 1.6 Hz, 1H), 7.19 (d, J = 3.5 Hz, 1H), 7.06 (dd, J = 7.8, 4.7 Hz, 1H), 6.46 (d, J = 3.5 Hz, 1H), 3.91 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 147.8, 142.8, 129.0, 128.7, 120.5, 115.5, 99.2, 31.23. The analytical data were in accordance with the literature.[32]

A.2.2 [Cu(OTf)$_2$(Hpz)$_4$] Complex

Prepared by Dr. Enrico Emer.

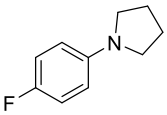


$Cu(OTf)_2$ (1.0 g, 2.76 mmol, 1.0 equiv.) was dissolved in hot MeOH (10 mL). An excess of pyrazole (3.8 g, 55.3, 20 equiv.) was added and the resulting dark blue solution was stirred at room temperature for 20 minutes. On standing at -20 °C overnight, a blue crystalline solid resulted, which was isolated by filtration and washed with cold MeOH. [Cu(OTf)$_2$(Hpz)$_4$] was formed in 86% yield as intensely blue crystals. The structure was determined by X ray analysis and was consistent with the literature.[33]

A.2.3 Boronic Ester Substrates and ^{19}F-References for Compounds in Tables 3.17 and 3.18

1-(4-Fluorophenyl)pyrrolidine (3.127)

Prepared by Dr. Michael Schedler.



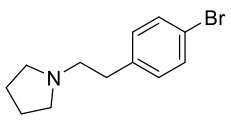
Adapting a known procedure,[34] CuI (29.0 mg, 0.150 mmol, 1.50 equiv.) and dried, ground K_3PO_4 (1.28 g, 6.00 mmol, 2.00 equiv.) were suspended in *i*-PrOH (3 mL). Ethylene glycol (336 μL, 6.0 mmol, 2.0- equiv.), pyrrolidine (368 μL, 4.50 mmol, 1.5- equiv.) and 4-fluoro-iodobenzene (345 μL, 3.00 mmol, 1.00 equiv.) were added to the reaction. The reaction tube was sealed and stirred at 80 °C for 9 hours. The reaction was stopped by addition of H_2O (5 mL) and the mixture was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic phases

were washed with brine, dried with $MgSO_4$, filtered and all volatiles were removed in vacuo. The residue was purified by flash column chromatography on silica (*n*-pentane/EtOAc 100:0 to 95:5) yielding 1-(4-fluorophenyl)-pyrrolidine (**3.127**, 155 mg, 0.939 mmol, 31%) was obtained as colourless solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.93 (t, *J* = 8.7 Hz, 2H), 6.48 (dd, *J* = 9.0, 4.3 Hz, 2H), 3.26–3.23 (m, 4H), 2.02–1.99 (m, 4H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 154.9 (d, *J* = 233.1 Hz), 145.0 (d, *J* = 1.4 Hz), 115.5 (d, *J* = 21.9 Hz), 112.2 (d, *J* = 7.2 Hz), 48.2 (s), 25.6 (s); **^{19}F NMR** (376 MHz, $CDCl_3$): δ = –131.0 (tt, *J* = 8.6, 4.3 Hz); **MS** (ESI^+) for $C_{10}H_{13}FN^+$ $[M+H]^+$ requires m/z = 166.1, found 166.1. The analytical data were in accordance with the literature.[35]

1-(4-Bromophenethyl)pyrrolidine

Prepared by Dr. Michael Schedler.



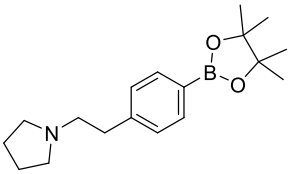
Pyrrolidine (821 µL, 10.0 mmol, 1.0 equiv.), 4-bromophenethyl bromide (1.53 mL, 10.0 mmol, 1.00 equiv.) and triethylamine (1.39 ml, 10.0 mmol, 1.00 equiv.) were dissolved in anhydrous MeCN (20 mL) and the mixture was stirred at room temperature for 24 hours. After removing all volatiles *in vacuo*, the residue was purified by flash column chromatography on silica (CH_2Cl_2/Et_3N 99:1 to 98:2) yielding 1-(4-bromophenethyl)pyrrolidine (1.23 g, 4.84 mmol, 48%) as a colourless crystalline solid.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.42–7.35 (m, 2H), 7.11–7.04 (m, 2H), 2.83–2.49 (m, 8H), 1.88–1.70 (m, 4H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ =139.6, 131.4, 130.4, 119.8, 58.1,

54.3, 35.3, 23.6; **MS** (ESI$^+$) for $C_{12}H_{17}{}^{81}BrN^+$ $[M+H]^+$ requires m/z = 256.0, found 256.1.The analytical data were in accordance with the literature.[36]

1-(4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)phenethyl)pyrrolidine (3.128-Bpin)

Prepared by Dr. Michael Schedler.



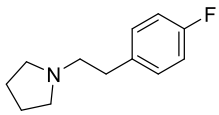
Modifying a known procedure,[37] 1-(4-bromophenethyl)pyrrolidine (500 mg, 1.97 mmol, 1.05 equiv.), B_2pin_2 (475 mg, 1.87 mmol, 1.00 equiv.), $Pd(dppf)Cl_2$ (43 mg, 0.056 mmol, 0.03 equiv.) and KOAc (550 mg, 5.62 mmol, 3.00 equiv.) were suspended in anhydrous and degassed 1,4-dioxane (10 mL). The mixture was stirred at 80 °C for 15 hours, then diluted with CH_2Cl_2 and filtered. All volatiles were removed *in vacuo* and the residue was purified by flash column chromatography on neutralized silica (CH_2Cl_2/Et_3N 99.5:0.5) yielding 1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenethyl)pyrrolidine (**3.128-Bpin**, 198 mg, 0.658 mmol, 33%) as a colourless solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.73 (d, J = 7.7 Hz, 2H), 7.22 (d, J = 7.7 Hz, 2H), 2.87–2.82 (m, 2H), 2.71–2.67 (m, 2H), 2.59–2.53 (m, 4H), 1.83–1.76 (m, 4H), 1.33 (s, 12H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ =144.1, 135.0, 128.2, 83.8, 58.3, 54.4, 36.2, 25.0, 23.6; **^{11}B NMR** (128 MHz, $CDCl_3$): δ = 31.0; **HRMS** (ESI$^+$) for $C_{18}H_{29}O_2NB^+$ $[M+H]^+$ requires

m/z = 302.22859, found 302.22873; **IR** (ATR, neat) $\tilde{\nu}$ (cm^{-1}) = 2970, 2944, 801, 1611, 1357, 1141, 1090, 883, 655; **M.P**.: 74 °C.

1-(4-Fluorophenethyl)pyrrolidine (**3.128)**

Prepared by Dr. Michael Schedler.

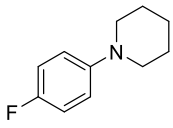


Pyrrolidine (164 μL, 2.00 mmol, 1.00 equiv.), 4-fluorophenethyl bromide (280 μL, 2.00 mmol, 1.00 equiv.) and Et_3N (278 μL, 2.00 mmol, 1.00 equiv.) were dissolved in anhydrous MeCN (4 mL) and the mixture was stirred at room temperature for 40 hours. All volatiles were removed in vacuo and the residue was purified by flash column chromatography on silica (CH_2Cl_2/Et_3N 98:2) yielding 1-(4-fluorophenethyl)pyrrolidine (**3.128**, 195 mg, 1.01 mmol, 51%) as a slightly yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.17–7.12 (m, 2H), 6.97–6.91 (m, 2H), 2.81–2.77 (m, 2H), 2.67–2.63 (m, 2H), 2.58–2.52 (m, 4H), 1.83–1.74 (m, 4H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ =161.5 (d, J = 243.7 Hz), 136.3 (d, J = 3.3 Hz), 130.0 (d, J = 7.7 Hz), 115.2 (d, J = 21.2 Hz), 58.5, (d, J = 1.4 Hz), 54.3 (s), 35.2 (s), 23.6 (s); **^{19}F NMR** (376 MHz, $CDCl_3$): δ = –117.6 (ddd, J = 14.3, 9.2, 5.5 Hz); **HRMS** (ESI^+) for $C_{12}H_{17}NF^+$ $[M+H]^+$ requires m/z = 194.13395, found 194.13391; **IR** (ATR, neat) $\tilde{\nu}$ (cm^{-1}) = 2960, 2932, 2786, 1509, 1459, 1350, 1221, 1152, 1122, 883, 825, 763.

1-(4-Fluorophenyl)piperidine (3.130)

Prepared by Dr. Michael Schedler.

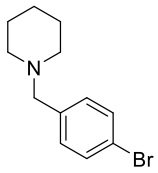


Adapting a known procedure,[34] CuI (29 mg, 0.150 mmol, 1.50 equiv.) and dried, ground K_3PO_4 (1.28 g, 6.00 mmol, 2.00 equiv.) were suspended in *i*-PrOH (3 mL). Ethylene glycol (336 µL, 6.00 mmol, 2.00 equiv.), piperidine (446 µL, 4.50 mmol, 1.50 equiv.) and 4-fluoro-iodobenzene (345 µL, 3.00 mmol, 1.00 equiv.) were added to the reaction. The reaction tube was sealed and stirred at 80 °C for 9 hours. The reaction was stopped by addition of water (5 mL) and the mixture was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic phases were washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica (*n*-pentane/EtOAc 98:2) yielding 1-(4-fluorophenyl)-piperidine (**3.130**, 292 mg, 1.63 mmol, 54%) was obtained as colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.96–6.86 (m, 4H), 3.06 (t , J = 5.5 Hz, 4H), 1.74–1.69 (m, 4H), 1.58–1.55 (m, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 157.0 (d, J = 238.1 Hz), 149.1 (s), 118.3 (d, J = 7.8 Hz), 115.3 (d, J = 22.1 Hz), 51.8 (s), 26.0 (s), 24.2 (s); **^{19}F NMR** (376 MHz, $CDCl_3$): δ = −152.2– −152.3 (m); **MS** (ESI^+) for $C_{11}H_{15}FN^+$ $[M+H]^+$ requires m/z = 180.1, found 180.1. The analytical data were in accordance with the literature.[38]

1-(4-Bromobenzyl)piperidine

Prepared by Dr. Enrico Emer.

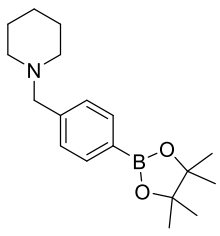


Adapting a known procedure,[27] piperidine (5.8 mL, 58.7 mmol, 25.0 equiv.) was added at 0 °C to a solution of 1-bromo-4-(bromomethyl)benzene (5.9 g, 23.5 mmol, 1.0 equiv.) in CH_2Cl_2 (100 mL). After the reaction mixture was stirred overnight at rt, the crude was concentrated under vacuo and aqueous HCl (50 mL, 2M) was added. The mixture was extracted with *n*-hexane (3 x 40 mL). The aqueous layer was made strongly basic by adding solid sodium hydroxide and the resulting solution was extracted with Et_2O (3 x 40 mL). The combined organic phase was dried over $MgSO_4$, filtered and solvents were removed in vacuo. 1-(4-Bromobenzyl)piperidine (5.92 g, 23.3 mmol, 99%) was obtained without further purification as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.43 (d, *J* = 8.4, 2H), 7.20 (d, *J* = 8.5 Hz, 2H), 3.41 (s, 2H), 2.35 (br s, 4H), 1.57 (dt, *J* = 11.2, 5.6 Hz, 4H), 1.44 (q, *J* = 5.6 Hz, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 137.7, 131.1, 130.7, 120.5, 63.0, 54.4, 25.9, 24.3. The analytical data were in accordance with the literature.[39]

1-(4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)piperidine (3.131-BPin)

Prepared by Dr. Enrico Emer.



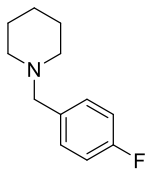
$Pd(dppf)Cl_2$ (161 mg, 0.197 mmol, 0.05 equiv.) was added to a mixture of 1-(4-bromobenzyl)piperidine (1.0 mg, 3.94 mmol, 1.00 equiv.), KOAc (1.16 g, 11.8 mmol, 3.00 equiv.) and B_2pin_2 (1.10 g,

4.33 mmol, 1.10 equiv.) in DMF (5 mL). The mixture was stirred at 130 °C under N_2 for 5 hours. The insoluble solid was removed by filtration through a pad of Celite (eluting with CH_2Cl_2). The filtrate was diluted with H_2O (30 mL) and extracted with CH_2Cl_2 (3 x 30 mL). The combined organic extracts were washed with brine (30 mL), dried over $MgSO_4$ and concentrated in vacuo to give the crude product. Flash column chromatography (*n*-hexane/EtOAc 80:20 to 70:30) afforded 1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)piperidine (**3.131-BPin**, 918 mg, 3.05 mmol, 77%) as a light green oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.76 (d, *J* = 7.8, 2H), 7.33 (d, *J* = 7.8 Hz, 2H), 3.49 (s, 2H), 2.36 (br s, 4H), 1.56 (dd, *J* = 10.6, 5.2 Hz, 4H), 1.48-1.38 (m, 2H), 1.24 (s, 12H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 141.8, 134.6, 128.6, 83.6, 63.8, 54.4, 25.9, 24.8, 24.3. The analytical data were in accordance with the literature.[40]

1-(4-Fluorobenzyl)piperidine (3.131)

Prepared by Dr. Enrico Emer.



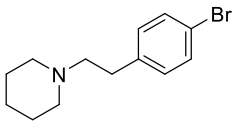
Adapting a known procedure,[27] piperidine (5.80 mL, 58.7 mmol, 25.0 equiv.) was added at 0 °C to a solution of 1-(bromomethyl)-4-fluorobenzene (5.9 g, 23.5 mmol, 1.0 equiv.) in CH_2Cl_2 (100 mL). After the reaction mixture was stirred overnight at room temperature, the crude was concentrated under vacuo and aqueous HCl (50 mL, 2M) was added. The mixture was extracted with *n*-hexane (3 x 40 mL). The aqueous layer was made strongly basic by adding solid sodium hydroxide and the resulting solution was extracted

with Et_2O (3 x 40 mL). The combined organic phase was dried over $MgSO_4$, filtered and solvents were removed *in vacuo*. Flash column chromatography (*n*-hexane/EtOAc 80:20) afforded 1-(4-fluorobenzyl)piperidine (**3.131**, 868 mg, 4.47 mmol, 89%) as a light yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.28 (dd, *J* = 8.6, 5.6 Hz, 2H), 7.02-6.97 (t, *J* = 8.6 Hz, 2H), 3.44 (s, 2H), 2.36 (br s, 4H), 1.58 (q, *J* = 5.6 Hz, 4H), 1.44 (dd, *J* = 6.8, 4.0 Hz, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 163.1, 134.2, 130.5 (d, *J* = 7.90 Hz), 114.9, 114.7, 63.0, 54.4, 25.9, 24.3; **^{19}F NMR** (376 MHz, $CDCl_3$): δ = –116.3. The analytical data were in accordance with the literature.[41]

1-(4-Bromophenethyl)piperidine

Prepared by Dr. Michael Schedler.

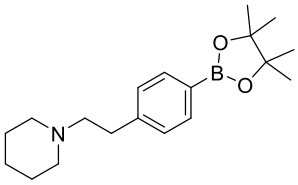


Piperidine (1.00 mL, 10.0 mmol, 1.0 equiv.), 4-bromophenethyl bromide (1.53 mL, 10.0 mmol, 1.0 equiv.) and Et_3N (1.39 ml, 10.0 mmol, 1.0 equiv.) were dissolved in anhydrous MeCN (20 mL) and the mixture was stirred at room temperature for 15 hours. The reaction was stopped by addition of H_2O (20 mL) and the mixture was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic phases were dried with $MgSO_4$, filtered and all volatiles were removed *in vacuo*. The residue was purified by flash column chromatography on silica (CH_2Cl_2/MeOH 95:5) yielding 1-(4-bromophenethyl)piperidine (1.47 g, 5.50 mmol, 55%) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40–7.37 (m, 2H), 7.08–7.06 (m, 2H), 2.77–2.73 (m, 2H), 2.54–2.51 (m, 2H), 2.44 (br t, J = 5.4 Hz, 4H), 1.61 (p, J = 5.6 Hz, 4H), 1.45 (p, J = 6.0 Hz, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 139.9, 131.5, 130.6, 119.8, 61.2, 54.7, 33.2, 26.2, 24.6; **MS** (ESI^+) for $C_{13}H_{19}{}^{81}BrN^+$ $[M+H]^+$ requires m/z = 270.1, found 270.0. The analytical data were in accordance with the literature.[42]

1-(4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)phenethyl)piperidine (3.132-BPin)

Prepared by Dr. Michael Schedler.



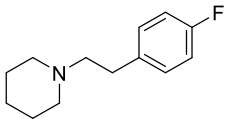
Modifying a known procedure,[37] 1-(4-bromo-phenethyl)piperidine (400 mg, 1.49 mmol, 1.00 equiv.), B_2pin_2 (378 mg, 1.49 mmol, 1.00 equiv.), $Pd(dppf)Cl_2.CH_2Cl_2$ (37 mg, 0.045 mmol, 0.030 equiv.) and KOAc (439 mg, 4.48 mmol, 3.00 equiv.) were suspended in anhydrous and degassed DMF (6 mL). The mixture was stirred at 80 °C for 16 hours. The mixture was allowed to cool to room temperature, diluted with CH_2Cl_2 and filtered through Celite. All volatiles were removed *in vacuo* and the residue was purified by flash column chromatography on silica (*n*-pentane/EtOAc 80:20 to 50:50) yielding 1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenethyl)piperidine (**3.132-BPin**, 109 mg, 0.346 mmol, 23%) as a slightly yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.73 (d, J = 7.7 Hz, 2H), 7.21 (d, J = 7.6 Hz, 2H), 2.84–2.80 (m, 4H), 2.57–2.53 (m, 2H), 2.45 (br t. J = 5.3 Hz, 4H), 1.61 (p, J = 5.6 Hz, 4H), 1.45

(p, *J* = 6.0 Hz, 2H), 1.33 (s, 12H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ =144.3, 135.0, 128.3, 83.8, 61.3, 54.7, 34.0, 26.2, 25.0, 24.6; **^{11}B NMR** (128 MHz, $CDCl_3$): δ = 30.4; **HRMS** (ESI^+) for $C_{19}H_{31}BNO_2^+$ $[M+H]^+$ requires m/z = 316.2442, found 316.2443; **IR** (ATR, neat) $\tilde{\nu}$ (cm^{-1}) = 2980, 2933, 2799, 1612, 1449, 1399, 1359, 1323, 1269, 1142, 1114, 1090, 1022, 964, 859, 824, 766, 738; **M.P.**: 41 °C.

1-(4-Fluorophenethyl)piperidine (3.132)

Prepared by Dr. Michael Schedler.



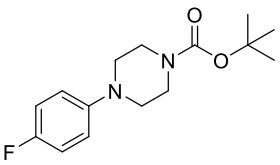
Piperidine (200 µL, 2.00 mmol, 1.00 equiv.), 4-fluorophenethyl bromide (280 µL, 2.00 mmol, 1.00 equiv.) and Et_3N (278 µL, 2.00 mmol, 1.00 equiv.) were dissolved in anhydrous MeCN (10 mL) and the mixture was stirred at room temperature for 16 hours. The reaction was stopped by addition of H_2O (20 mL) and the mixture was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic phases were dried with $MgSO_4$, filtered and all volatiles were removed *in vacuo.* The residue was purified by flash column chromatography on silica (CH_2Cl_2/MeOH 97.5:2.5) yielding 1-(4-fluorophenethyl)piperidine (**3.132**, 200 mg, 0.966 mmol, 48%) as a slightly yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.13–7.08 (m, 2H), 6.94–6.88 (m, 2H), 2.77–2.73 (m, 2H), 2.52–2.47 (m, 2H), 2.43 (br t, *J* = 5.4 Hz, 4H), 1.59 (p, *J* = 5.6 Hz, 4H), 1.43 (p, *J* = 6.2 Hz, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 161.4 (d, *J* = 243.6 Hz), 136.2 (d, *J* = 3.1 Hz), 130.2 (d, *J* = 7.7 Hz), 115.1 (d, *J* =21.0 Hz), 61.4 (d, *J* = 1.2 Hz), 54.6 (s), 32.8, 26.0, 24.4; **^{19}F NMR** (376 MHz, $CDCl_3$): δ = –117.5 (ddd, *J* = 14.3, 9.0, 5.4 Hz); **MS** (ESI^+) for

$C_{13}H_{19}NF^+$ $[M+H]^+$ requires m/z = 208.1, found 208.1. The analytical data were in accordance with the literature.[43]

tert-Butyl 4-(4-fluorophenyl)piperazine-1-carboxylate (3.134)

Prepared by Dr. Michael Schedler.

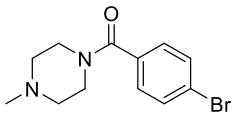


Adapting a known procedure,[38] CuBr (29.0 mg, 0.200 mmol, 0.20 equiv.) and BINOL (42.9 mg, 0.150 mmol, 0.15 equiv.) were dissolved in anhydrous DMF (0.5 mL). The reaction was stirred for 10 minutes at room temperature. *tert*-Butyl piperazine-1-carboxylate (279 mg, 1.50 mmol, 1.5 equiv.), K_3PO_4 (424 mg, 2.00 mmol, 2.0 equiv.) and 4-fluoro-iodobenzene (115 µL, 1.00 mmol, 1.0 equiv.) were added to the reaction mixture. The Schlenk tube was sealed and stirred at 100 °C for 14 hours. The reaction was cooled to room temperature and all volatiles were removed *in vacuo.* The residue was purified by flash column chromatography on silica (*n*-pentane/EtOAc 95:5) to afford *tert*-butyl 4-(4-fluorophenyl)piperazine-1-carboxylate (**3.134**, 143 mg, 0.511 mmol, 51%) as a slightly yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.99–6.95 (m, 2H), 6.90–6.86 (m, 2H), 3.59–3.56 (m, 4H), 3.04 (t, J = 5.1 Hz, 4H), 1.43 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 157.7 (d, J = 239.6 Hz), 154.9 (s), 148.2 (d, J = 2.4 Hz), 118.7 (d, J = 7.7 Hz), 115.8 (d, J = 22.1 Hz), 80.1 (s), 50.6 (s), 44.1 (s), 28.6 (s); **^{19}F NMR** (376 MHz, $CDCl_3$): δ = –123.7––123.8 (m); **MS** (ESI^+) for $C_{15}H_{22}FN_2O_2^+$ $[M+H]^+$ requires m/z = 281.2, found 281.2. The analytical data were in accordance with the literature.[44]

(4-Bromophenyl)(4-methylpiperazin-1-yl)methanone

Prepared by Dr. Michael Schedler.

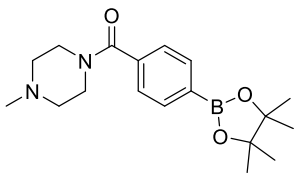


Modifying a known procedure,[45] 1-methylpiperazine (1.11 mL, 9.98 mmol, 1.00 equiv.) was dissolved in anhydrous pyridine (20 mL) and the solution was cooled to 0 °C before 4-bromobenzoyl chloride (2.19 g, 9.98 mmol, 1.00 equiv.) was added. The reaction was warmed to room temperature and stirred for 16 hours. The reaction mixture was poured into H_2O (100 mL) and the mixture was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic phases were dried with $MgSO_4$, filtered and all volatiles were removed in vacuo. The residue was purified by flash column chromatography on silica (CH_2Cl_2/MeOH 95:5) yielding (4-bromophenyl)(4-methylpiperazin-1-yl)methanone (2.06 g, 7.27 mmol, 73%) as a colorless solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.54 (d, J = 8.4 Hz, 2H), 7.28 (d, J = 8.4 Hz, 2H), 3.78 (br s, 2H), 3.45 (br s, 2H), 2.45 (br s, 2H), 2.40 (br s, 2H), 2.33 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ =169.2, 134.7, 131.7, 128.8, 124.0, 55.1, 54.8, 47.7, 46.1, 42.2; **MS** (ESI^+) for $C_{12}H_{16}{}^{81}BrN_2O^+$ $[M+H]^+$ requires m/z = 285.0, found 285.0. The analytical data were in accordance with the literature.[46]

(4-Methylpiperazin-1-yl)(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methanone (3.135-BPin)

Prepared by Dr. Michael Schedler.

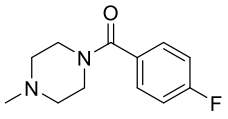


Modifying a known procedure,[40] (4-bromophenyl)(4-methylpiperazin-1-yl)methanone (891 mg, 3.15 mmol, 1.05 equiv.), B_2pin_2 (762 mg, 3.00 mmol, 1.0 equiv.), $Pd(dppf)Cl_2$ (66 mg, 0.090 mmol, 0.030 equiv.) and KOAc (882 mg, 9.00 mmol, 3.00 equiv.) were suspended in anhydrous and degassed 1,4-dioxane (15 mL). The mixture was stirred at 80 °C for 16 hours. The mixture was allowed to cool to room temperature, diluted with CH_2Cl_2 and filtered. All volatiles were removed *in vacuo* and the residue was purified by flash column chromatography on silica (CH_2Cl_2/MeOH 95:5) followed by recrystallization from CH_2Cl_2/*n*-hexane yielding (4-methylpiperazin-1-yl)(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methanone (**3.135-BPin**, 336 mg, 1.02 mmol, 34%) as an off-white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.82 (d, J = 7.7 Hz, 2H), 7.37 (d, J = 7.9 Hz, 2H), 3.78 (br s, 2H), 3.38 (br s, 2H), 2.46 (br s, 2H), 2.30 (m, 5H), 1.33 (s, 12H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 170.3, 138.5, 134.9, 126.3, 84.2, 55.4, 54.9, 47.7, 46.1, 42.1, 25.0; **^{11}B NMR** (128 MHz, $CDCl_3$): δ = 30.9; **HRMS** (ESI^+) for $C_{18}H_{28}BN_2O_3^+$ $[M+H]^+$ requires m/z = 331.21875, found 331.21869; **IR** (ATR, neat) $\tilde{\nu}$ (cm^{-1}) = 2983, 2949, 2803, 1625, 1509, 1436, 1392, 1356, 1332, 1290, 1264, 1168, 1134, 1088, 1006, 963, 853, 823, 774, 734, 709, 658; **M.P.**: 94 °C.

(4-Fluorophenyl)(4-methylpiperazin-1-yl)methanone (3.135)

Prepared by Dr. Michael Schedler.

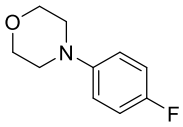


Modifying a known procedure,[45] 1-methylpiperazine (222µL, 2.00 mmol, 1.00 equiv.) was dissolved in anhydrous pyridine (4 mL) and the solution was cooled to 0 °C before 4-fluorobenzoyl chloride (236 µL, 2.00 mmol, 1.00 equiv.) was added. The reaction was warmed to room temperature and stirred for 16 hours. The reaction mixture was poured into H_2O (20 mL) and the mixture was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic phases were dried with $MgSO_4$, filtered and all volatiles were removed *in vacuo*. The residue was purified by flash column chromatography on silica (CH_2Cl_2/MeOH 95:5) yielding (4-fluorophenyl)(4-methylpiperazin-1-yl)methanone (**3.135**, 433 mg, 1.95 mmol, 97%) as a colorless solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.41, (dd, J = 8.5, 5.5 Hz, 2H), 7.09 (t, J = 8.6 Hz, 2H), 3.75 (br s, 2H), 3.48 (br s, 2H), 2.42 (br s, 4H), 2.32 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 169.d (s), 163.5 (d, J = 249.8 Hz), 132.0 (d, J = 3.5 Hz), 129.5 (d, J = 8.5 Hz), 115.7 (d, J = 21.8 Hz), 55.1 (br s), 47.8 (br s), 46.2 (s), 42.4 (br s); **^{19}F NMR** (376 MHz, $CDCl_3$): δ = –110.4 (tt, J = 9.4, 5.4 Hz); **HRMS** (ESI^+) for $C_{12}H_{15}FN_2O^+$ $[M+H]^+$ requires m/z = 223.12412, found 223.12410; **IR** (ATR, neat) $\tilde{\nu}$ (cm^{-1}) = 2993, 2943, 2873, 2847, 2796, 1625, 1597, 1507, 1426, 1361, 1293, 1266, 1239, 1213, 1161, 1137, 1005, 889, 850, 760; **M.P.**: 46 °C.

4-(4-Fluorophenyl)morpholine (3.136)

Prepared by Dr. Matthew Tredwell.

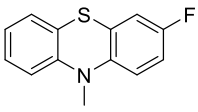


The title compound was prepared according to a literature procedure.[7], [8]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.98 (t, J = 8.7 Hz, 2H), 6.92-6.83 (m, 2H), 3.87 (t, J = 4.4 Hz, 4H), 3.09 (t, J = 4.4 Hz, 4H); **^{19}F {^{1}H} NMR** (376 MHz, CDCl3): δ = –124.2. The analytical data were consistent with literature values.[9]

3-Fluoro-10-methyl-10*H*-phenothiazine (3.138)

Prepared by Dr. Michael Schedler.

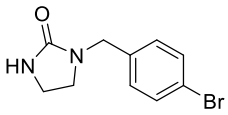


Adapting a known procedure,[47] 2-bromo-thiophenol (361 μL, 3.00 mmol, 1.00 equiv.), 2-bromo-5-fluoro-iodobenzene (393 μL, 3.00 mmol, 1.00 equiv.), $Pd(dba)_2$ (86.2 mg, 0.150 mmol, 0.05 equiv.), dppf (166 mg, 0.300 mmol, 0.10 equiv.) and NaO*t*-Bu (1.15 g, 12.0 mmol, 3.00 equiv.) were suspended in anhydrous toluene (15 mL). Methylamine (2M in THF, 4.5 mL, 9.00 mmol, 3.00 equiv.) was added to the mixture and the pressure tube was sealed under nitrogen. The tube was stirred at 100 °C for 17 hours. The reaction was cooled to room temperature and all volatiles were removed *in vacuo*. The residue was purified by flash column chromatography on silica (*n*-pentane) yielding 2-((2-bromo-5-fluorophenyl)thio)-*N*-methylaniline (151 mg, 0.484 mmol, 16%), that was used directly in the next step.

Adapting a known procedure,[48] 2-((2-bromo-5-fluorophenyl)thio)-*N*-methylaniline (151 mg, 0.484 mmol, 1.00 equiv.), $Pd(dba)_2$ (13.9 mg, 0.0242 mmol, 0.05 equiv.), BINAP (22.6 mg, 0.0363 mmol, 0.075 equiv.) and NaO*t*-Bu (65.1 mg, 0.678 mmol, 1.40 equiv.) were suspended in anhydrous toluene (5 mL) and stirred in a sealed pressure tube at 110 °C for 15 hours. The reaction was cooled to room temperature and water (20 mL) was added. The mixture was extracted with CH_2Cl_2 (3 x 20 mL) and the combined organic phases were dried with $MgSO_4$, filtered and all volatiles were removed *in vacuo*. The residue was purified by flash column chromatography on silica (*n*-pentane) yielding 3-fluoro-10-methyl-10*H*-phenothiazine (**3.138**, 8.9 mg, 0.039 mmol, 1% over two steps) as a colourless solid. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.19 (td, *J* = 7.7, 1.6 Hz, 1H), 7.14 (dd, *J* = 7.6, 1.5 Hz, 1H), 6.94 (td, *J* = 7.5, 1.2 Hz, 1H), 6.91–6.84 (m, 2H), 6.81 (dd, *J* = 8.1, 1.1 Hz, 1H), 6.72 (dd, *J* = 8.8, 4.6 Hz, 1H), 3.35 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ =158.8 (d, *J* = 242.1 Hz), 146.0 (s), 142.3 (d, *J* = 2.2 Hz), 127.9 (s), 127.3 (s), 125.6 (d, *J* = 8.4 Hz), 122.8 (s), 122.7 (s), 114.5 (d, *J* = 8.3 Hz), 114.3 (d, *J* = 24.8 Hz), 114.2 (s), 113.7 (d, *J* = 22.4 Hz), 35.6 (s); **^{19}F NMR** (376 MHz, $CDCl_3$): δ = –122.8 (td, *J* = 8.0, 4.5 Hz); **HRMS** (ESI^+) for $C_{13}H_{11}NFS^+$ $[M+H]^+$ requires m/z =232.0591, found 232.0591; **IR** (ATR, neat) $\tilde{\nu}$ (cm^{-1}) = 3062, 2964, 2891, 1595, 1572, 1495, 1458, 1400, 1328, 1258, 1200, 1165, 1138, 1101, 1034, 906, 870, 842, 811, 760; **M.P.**: 80 °C.

1-(4-Bromobenzyl)imidazolidin-2-one

Prepared by Dr. Michael Schedler.

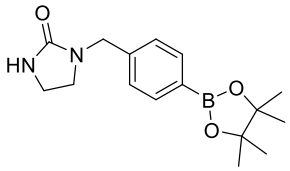


Adapting a known procedure,[49] NaH (60% in mineral oil, 480 mg, 12.0 mmol, 1.20 equiv.) was suspended in anhydrous THF (40 mL) and a solution of imidazolidin-2-one (861 mg, 10.0 mmol, 1.00 equiv.) in anhydrous THF (20 mL) was added slowly. After stirring the reaction mixture for one hour at room temperature, a suspension of 4-bromobenzyl bromide (3.00 g, 12.0 mmol, 1.20 equiv.) in anhydrous THF (20 mL) was added slowly. The mixture was refluxed for 16 hours, cooled to room temperature and quenched by the addition of H_2O (100 mL). The mixture was extracted with CH_2Cl_2 (3 x 50 mL) and the combined organic phases were dried with $MgSO_4$, filtered and all volatiles were removed in vacuo. The residue was purified by flash column chromatography on silica (CH_2Cl_2/MeOH 7.5:2.5) yielding 1-(4-bromobenzyl)imidazolidin-2-one (767 mg, 3.01 mmol, 30%) as a colorless solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.46 (d, J = 8.3 Hz, 2H), 7.16 (d, J = 8.1 Hz, 2H), 4.48 (br s, 1H), 4.32 (s, 2H), 3.41 (dd, J = 9.0, 6.3 Hz, 2H), 3.32–3.28 (m, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 162.9, 136.4, 131.8, 129.9, 121.5, 47.2, 44.7, 38.2; **HRMS** (ESI^+) for $C_{10}H_{12}BrN_2O^+$ $[M+H]^+$ requires m/z = 255.01275, found 255.01268; **IR** (ATR, neat) $\tilde{\nu}$ (cm^{-1}) = 3222, 3084, 2912, 1681, 1492, 1448, 1405, 1365, 1255, 1100, 1067, 1008, 932, 780, 756, 704, 660; **M.P.**: 143 °C.

1-(4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)imidazolidin-2-one (3.140-BPin)

Prepared by Dr. Michael Schedler.

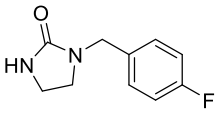


Modifying a known procedure,[37] 1-(4-bromobenzyl)imidazolidin-2-one (536 mg, 2.10 mmol, 1.05 equiv.), B_2pin_2 (508 mg, 2.00 mmol, 1.0 equiv.), $Pd(dppf)Cl_2$ (43.9 mg, 0.0600 mmol, 0.030 equiv.) and KOAc (588 mg, 6.00 mmol, 3.0 equiv.) were suspended in anhydrous and degassed 1,4-dioxane (10 mL). The mixture was stirred for 15 hours at 80 °C. The mixture was allowed to cool to room temperature, diluted with CH_2Cl_2 and filtered. All volatiles were removed *in vacuo* and the residue was purified by recrystallization from CH_2Cl_2/*n*-hexane yielding 1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)imidazolidin-2-one (**3.140-Bpin**, 607 mg, 2.00 mmol, 100%) as a brown solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.78 (d, J = 7.6 Hz, 2H), 7.28 (d, J = 7.7 Hz, 2H), 4.87 (br s, 1H), 4.37 (s, 2H), 3.39 (dd, J = 9.1, 6.5 Hz, 2H), 3.28 (dd, J = 8.8, 6.1 Hz, 2H), 1.34 (12H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 162.9, 140.4, 135.2, 127.6, 83.9, 47.9, 44.6, 38.2, 25.0; **^{11}B NMR** (128 MHz, $CDCl_3$): δ = 30.8; **HRMS** (ESI^+) for $C_{16}H_{24}BN_2O_3^+$ $[M+H]^+$ requires m/z = 303.18745, found 303.18723; **IR** (ATR, neat) $\tilde{\nu}$ (cm^{-1}) = 3233, 2977, 1692, 1613, 1493, 1449, 1402, 1359, 1265, 1141, 1092, 1019, 966, 855, 790, 659; **M.P.**: 162 °C.

1-(4-Fluorobenzyl)imidazolidin-2-one (3.140)

Prepared by Dr. Michael Schedler.

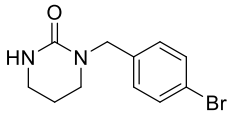


Adapting a known procedure,[49] NaH (60% in mineral oil, 96.0 mg, 2.40 mmol, 1.20 equiv.) was suspended in anhydrous THF (10 mL) and a solution of imidazolidin-2-one (172 mg, 2.00 mmol, 1.00 equiv.) in anhydrous THF (5 mL) was added slowly. After stirring the reaction mixture for one hour at room temperature, 4-fluorobenzyl bromide (289 μL, 2.40 mmol, 1.20 equiv.) was added slowly. The mixture was refluxed for 6 hours, cooled to room temperature and quenched by the addition of H_2O (30 mL). The mixture was extracted with CH_2Cl_2 (3 x 30 mL) and the combined organic phases were dried with $MgSO_4$, filtered and all volatiles were removed in vacuo. The residue was purified by flash column chromatography on silica (CH_2Cl_2/MeOH 97.5:2.5) yielding 1-(4-fluorobenzyl)imidazolidin-2-one (**3.140**, 101 mg, 0.521 mmol, 26%) as a colourless solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.25 (dd, J = 8.4, 5.5 Hz, 2H), 7.01 (t, J = 8.7 Hz, 2H), 4.82 (br s, 1H), 4.33 (s, 2H), 3.40 (dd, J = 9.0, 6.4 Hz, 2H), 3.29 (dd, J = 8.8, 6.1 Hz, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 162.4 (d, J = 245.5 Hz), 162.7 (s), 133.1 (d, J = 3.3 Hz), 129.9 (d, J = 8.1 Hz), 115.6 (d, J = 21.5 Hz), 47.2 (s), 44.6 (s), 38.2 (s); **^{19}F NMR** (376 MHz, $CDCl_3$): δ = –115.2(tt, J =9.2, 5.2 Hz); **HRMS** (ESI^+) for $C_{10}H_{11}FN_2O^+$ $[M+H]^+$ requires m/z = 195.09282, found 195.09288; **IR** (ATR, neat) $\tilde{\nu}$ (cm^{-1}) = 3234, 2917, 1680, 1602, 1502, 1460, 1416, 1368, 1262, 1216, 1156, 1093, 1015, 928, 828, 750, 658; **M.P.**: 120 °C.

1-(4-Bromobenzyl)tetrahydropyrimidin-2(1*H*)-one

Prepared by Dr. Michael Schedler.

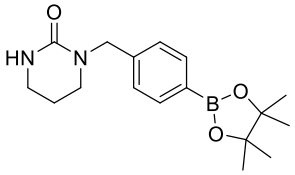


Adapting a known procedure,[50] propylene-urea (262 mg, 2.62 mmol, 1.00 equiv.), 4-bromobenzyl bromide (656 mg, 2.62 mmol, 1.00 equiv.), K_2CO_3 (362 mg, 2.62 mmol, 1.0 equiv.) and KI (217 mg, 1.31 mmol, 0.50 equiv.) were dissolved in anhydrous DMF (5 mL) and heated to 100 °C for 1.5 hours. The reaction mixture was cooled to room temperature and poured into an ice-water-mixture (100 mL). The mixture was extracted with CH_2Cl_2 (3 x 30 mL) and the combined organic phases were dried with $MgSO_4$, filtered and all volatiles were removed *in vacuo*. The residue was purified by flash column chromatography on silica (CH_2Cl_2/MeOH 95:5) yielding 1-(4-bromobenzyl)tetrahydropyrimidin-2(1*H*)-one (267 mg, 0.993 mmol, 38%) as a colourless solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.45–7.42 (2H, m), 7.18–7.15 (m, 2H), 4.85 (br s, 1H), 4.49 (s, 2H), 3.33–3.30 (m, 2H), 3.16–3.14 (m, 2H), 1.93–1.87 (m, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 137.4, 131.8, 129.8, 128.8, 121.2, 50.4, 45.0, 40.8, 22.4; **HRMS** (ESI^+) for $C_{11}H_{14}BrN_2O^+$ $[M+H]^+$ requires m/z = 269.02840, found 269.02856; **IR** (ATR, neat) $\tilde{\nu}$ (cm^{-1}) = 3295, 3207, 3062, 2939, 2865, 1651, 1519, 1485, 1453, 1402, 1350, 1305, 1287, 1208, 1173, 1069, 1012, 966, 797, 758, 678; **M.P.**: 104 °C.

1-(4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)tetrahydropyrimidin-2(1*H*)-one (3.141-Bpin)

Prepared by Dr. Michael Schedler.

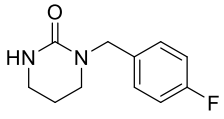


Modifying a known procedure,[37] 1-(4-bromobenzyl)tetrahydropyrimidin-2(1*H*)-one (138 mg, 0.513 mmol, 1.05 equiv.), B_2pin_2 (124 mg, 0.489 mmol, 1.0 equiv.), $Pd(dppf)Cl_2$ (10.7 mg, 0.0147 mmol, 0.030 equiv.) and KOAc (144 mg, 1.47 mmol, 3.00 equiv.) were suspended in anhydrous and degassed 1,4-dioxane (3 mL). The mixture was stirred for 16 hours at 80 °C. The mixture was allowed to cool to room temperature, diluted with CH_2Cl_2 and filtered. All volatiles were removed *in vacuo* and the residue was purified by flash column chromatography on silica (CH_2Cl_2/MeOH 95:5) yielding 1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)tetrahydropyrimidin-2(1*H*)-one (**3.141-Bpin**, 102 mg, 0.323 mmol, 66%) as an off-white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.69 (d, J = 7.6 Hz, 2H), 7.21 (d, J = 7.7 Hz, 2H), 5.03 (br s, 1H), 4.50 (s, 2H), 3.23 (td, J = 5.9, 2.3 Hz, 2H), 3.05 (t, J = 5.9 Hz, 2H), 1.80 (p, J = 5.9 Hz, 2H), 1.26 (s, 12H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 156.6, 141.5, 135.1, 127.4, 83.9. 50.8, 44.8, 40.7, 25.0, 22.4; **^{11}B NMR** (128 MHz, $CDCl_3$): δ = 30.4; **HRMS** (ESI^+) for $C_{17}H_{26}BN_2O_3^+$ $[M+H]^+$ requires m/z = 317.20310, found 317.20263; **IR** (ATR, neat) $\tilde{\nu}$ (cm^{-1}) = 3291, 3221, 2980, 2933, 2864, 1655, 1613, 1515, 1452, 1403, 1359, 1328, 1310, 1282, 1261, 1209, 1165, 1141, 1088, 1019, 962, 857, 827, 792, 756, 727, 674, 657; **M.P.**: 168 °C.

1-(4-Fluorobenzyl)tetrahydropyrimidin-2(1H)-one (3.141)

Prepared by Dr. Michael Schedler.

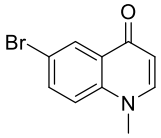


Adapting a known procedure,[50] propylene-urea (262 mg, 2.62 mmol, 1.00 equiv.), 4-fluorobenzyl bromide (326 μL, 2.62 mmol, 1.00 equiv.), K_2CO_3 (362 mg, 2.62 mmol, 1.00 equiv.) and KI (217 mg, 1.31 mmol, 0.50 equiv.) were dissolved in anhydrous DMF (5 mL) and heated to 100 °C for 1.5 hours. The reaction mixture was cooled to room temperature and poured into an ice-water-mixture (100 mL). The mixture was extracted with CH_2Cl_2 (3 x 30 mL) and the combined organic phases were dried with $MgsSO_4$, filtered and all volatiles were removed *in vacuo*. The residue was purified by flash column chromatography on silica (CH_2Cl_2/MeOH 97.5:2.5 to 95:5) yielding 1-(4-fluorobenzyl)tetrahydropyrimidin-2(1*H*)-one (**3.141**, 256 mg, 1.23 mmol, 47%) as a colourless solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.25 (dd, *J* = 8.2, 5.4 Hz, 2H), 7.00 (t, *J* = 8.7 Hz, 2H), 5.20 (br s, 1H), 4.51 (s, 2H), 3.31 (td, *J* = 5.9, 2.5 Hz, 2H), 3.15 (t, *J* = 5.9 Hz, 2H), 1.89 (p, *J* = 5.9 Hz, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 162.2 (d, *J* = 244.8 Hz), 156.6 (s), 134.1 (d, *J* = 3.1 Hz), 129.6 (d, *J* = 8.1 Hz), 115.4 (d, *J* = 21.4 Hz), 50.1 (s), 44.9 (s), 40.7 (s), 22.4 (s); **^{19}F NMR** (376 MHz, $CDCl_3$): δ = –115.8 (ddd, *J* =14.2, 9.0, 5.4 Hz); **HRMS** (ESI^+) for $C_{11}H_{14}FN_2O^+$ $[M+H]^+$ requires m/z = 209.1085, found 209.1084; **IR** (ATR, neat) $\tilde{\nu}$ (cm^{-1}) = 3290, 3208, 3061, 2947, 2853, 1643, 1509, 1453, 1416, 1356, 1297, 1216, 1176, 1153, 1090, 1014, 970, 898, 813, 784, 753, 678; **M.P.**: 122 °C.

6-Bromo-1-methylquinolin-4(1*H*)-one

Prepared by Dr. Michael Schedler.

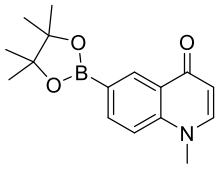


Adapting a known procedure,[51] 6-bromoquinolin-4-ol (500 mg, 2.23 mmol, 1.00 equiv.) and NaH (60% in mineral oil, 134 mg, 3.35 mmol, 1.50 equiv.) were suspended in anhydrous DMF (10 mL) and this mixture was stirred at room temperature for two hours. MeI (278 μL, 4.46 mmol, 2.00 equiv.) was added and the reaction was heated to 80 °C for 6 hours. After cooling back to room temperature, the mixture was diluted with brine (20 mL) and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic phases were dried with $MgSO_4$, filtered and all volatiles were removed in vacuo. The resulting oil was purified by flash column chromatography on silica (CH_2Cl_2/MeOH 95:5) yielding 6-bromo-1-methylquinolin-4(1*H*)-one (487 mg, 2.05 mmol, 92%) as a colourless solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.52 (d, *J* = 2.4 Hz, 1H), 7.70 (dd, *J* = 9.0, 2.4 Hz, 1H), 7.47 (d, *J* = 7.7 Hz, 1H), 7.24 (d, *J* = 9.0 Hz, 1H), 6.21 (d, *J* = 7.7 Hz, 1H), 3.76 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ =176.9, 143.9, 139.5, 135.2, 129.6, 128.4, 117.7, 117.4, 110.5, 40.8; **MS** (ESI^+) for $C_{10}H_9BrNO^+$ $[M+H]^+$ requires m/z = 238.0, found 238.0. The analytical data were in accordance with the literature.[51]

1-Methyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinolin-4(1*H*)-one (3.143-Bpin)

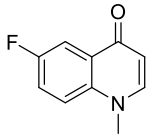
Prepared by Dr. Michael Schedler.



Modifying a known procedure,[37] 6-bromo-1-methylquinolin-4(1*H*)-one (197 mg, 0.828 mmol, 1.05 equiv.), B_2pin_2 (201 mg, 0.791 mmol, 1.00 equiv.), $Pd(dppf)Cl_2$ (17.6 mg, 0.0240 mmol, 0.030 equiv.) and KOAc (231 mg, 2.36 mmol, 3.00 equiv.) were suspended in anhydrous and degassed 1,4-dioxane (5 mL). The mixture was stirred at 80 °C for 20 hours. The mixture was allowed to cool to room temperature, diluted with CH_2Cl_2 and filtered. All volatiles were removed *in vacuo* and the residue was purified by recrystallization from CH_2Cl_2/*n*-hexane yielding 1-methyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinolin-4(1*H*)-one (3.143**-Bpin**, 66.0 mg, 0.232 mmol, 29%) as a pale brown solid. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.90 (s, 1H), 8.00 (d, *J* = 8.5 Hz, 1H), 7.44 (d, *J* = 7.7 Hz, 1H), 7.30 (d, *J* = 8.6 Hz, 1H), 6.20 (d, *J* = 7.8 Hz, 1H), 3.74 (s, 3H), 1.33 (s, 12H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 178.5, 143.8, 142.7, 137.8, 134.9, 126.4, 114.5, 111.0, 84.2, 40.7, 25.1; **^{11}B NMR** (128 MHz, $CDCl_3$): δ = 30.7; **HRMS** (ESI^+) for $C_{16}H_{21}BNO_3^+$ $[M+H]^+$ requires m/z = 286.16090, found 286.16097; **IR** (ATR, neat) $\tilde{\nu}$ (cm^{-1}) = 2977, 1632, 1851, 1497, 1361, 1284, 1146, 1102, 964, 887, 848, 820, 773, 710, 652; **M.P.**: 196 °C.

6-Fluoro-1-methylquinolin-4(1*H*)-one (3.143)

Prepared by Dr. Michael Schedler.

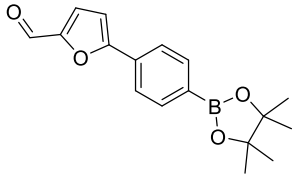


Adapting a known procedure,[51] 6-fluoroquinolin-4-ol (500 mg, 3.07 mmol, 1.00 equiv.) and NaH (60% in mineral oil, 222 mg, 5.55 mmol, 1.50 equiv.) were suspended in anhydrous DMF (10 mL) and this mixture was stirred at room temperature for two hours. MeI (384 μL, 6.13 mmol, 2.00 equiv.) was added to the reaction and the reaction was heated to 80 °C for 5 hours. After cooling back to room temperature, the mixture was diluted with brine (30 mL) and extracted with CH_2Cl_2 (3 x 30 mL). The combined organic phases were washed with brine, dried with $MgSO_4$, filtered and all volatiles were removed *in vacuo*. The resulting oil was purified by flash column chromatography on silica (CH_2Cl_2/MeOH 97.5:2.5) yielding 6-fluoro-1-methylquinolin-4(1*H*)-one (**3.143**, 106 mg, 0.599 mmol, 20%) as a colorless solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.14–8.08 (m, 1H), 7.50 (d, J = 7.7 Hz, 1H), 7.44–7.40 (m, 2H), 6.24 (d, J =7.7 Hz, 1H), 3.81 (s, 3H); **^{19}F NMR** (376 MHz, $CDCl_3$): δ = –117.3 (m); **MS** (ESI^+) for $C_{10}H_9FNO^+$ $[M+H)^+$ requires m/z = 178.1, found 178.1. The analytical data were in accordance with the literature.[51]

5-(4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)furan-2-carbaldehyde (3.144-Bpin)

Prepared by Dr. Michael Schedler.

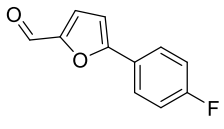


Modifying a known procedure,[37] 5-(4-bromophenyl)furfural (527 mg, 2.10 mmol, 1.05 equiv.), B_2pin_2 (508 mg, 2.00 mmol, 1.00 equiv.), $Pd(dppf)Cl_2$ (43.9 mg, 0.0600 mmol, 0.030 equiv.) and KOAc (588 mg, 6.00 mmol, 3.00 equiv.) were suspended in anhydrous and degassed 1,4-dioxane (10 mL). The mixture was stirred at 80 °C for 16 hours. The mixture was allowed to cool to room temperature, diluted with CH_2Cl_2 and filtered. All volatiles were removed *in vacuo* and the residue was purified by flash column chromatography on silica (toluene/EtOAc 97.5:2.5 to 95:5) yielding 5-(4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)furan-2-carbaldehyde (**3.144-Bpin**, 250 mg, 0.839 mmol, 42%) as an off-white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.67 (s, 1H), 7.88 (d, J = 8.1 Hz, 2H), 7.82 (d, J = 8.3 Hz, 2H), 7.32 (d, J = 3.7 Hz, 1H), 6.90 (d, J = 3.7 Hz, 1H), 1.36 (s, 12H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 177.5, 159.4, 152.4, 135.5, 131.4, 124.5, 123.4, 108.6, 84.2, 25.0; **^{11}B NMR** (128 MHz, $CDCl_3$): δ = 31.4; **HRMS** (ESI^+) for $C_{17}H_{20}BO_4^+$ $[M+H]^+$ requires m/z = 299.14492, found 299.14504; **IR** (ATR, neat) $\tilde{\nu}$ (cm^{-1}) = 2974, 1663, 1532, 1355, 1261, 1140, 1092, 1023, 962, 857, 802, 765, 651; **M.P.**: 113 °C.

5-(4-Fluorophenyl)furan-2-carbaldehyde (3.144)

Prepared by Dr. Michael Schedler.

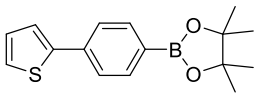


Following a known procedure,[52] 5-bromofurfural (350 mg, 2.00 mmol, 1.00 equiv.), 4-fluorophenylboronic acid (336 mg, 2.40 mmol, 1.20 equiv.), $Pd(PPh_3)_4$ (100 mg, 0.087 mmol, 0.043 equiv.) and $Pd(dppf)Cl_2$ (50 mg, 0.068 mmol, 0.034 equiv.) were dissolved in a degassed solvent mixture (60 mL toluene, 30 mL EtOH and 60 mL 1 M aq. K_2CO_3 solution). The mixture was refluxed for 6 hours. After cooling back to room temperature, the mixture was extracted with CH_2Cl_2 (3 x 150 mL) and the combined organic phases were dried with $MgSO_4$, filtered and all volatiles were removed *in vacuo*. The residue was purified by flash column chromatography on silica (*n*-pentane/ethyl acetate 90:10) yielding 5-(4-fluorophenyl)furan-2-carbaldehyde (**3.144**, 211 mg, 1.11 mmol, 56%) as an off-white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.65 (s, 1H), 7.81 (dd, J = 8.8, 5.4 Hz, 2H), 7.32 (d, J = 7.3 Hz, 1H), 7.14 (t, J = 8.6 Hz, 2H), 6.78 (d, J = 3.7 Hz, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 177.3 (s), 163.7 (d, J = 250.9 Hz), 158.7 (s), 152.3 (s), 127.5 (d, J = 8.5 Hz), 125.5 (d, J = 3.4 Hz), 123.7 (s), 116.4 (d, J = 22.3 Hz), 107.5 (s); **^{19}F NMR** (376 MHz, $CDCl_3$): δ = –110.2 (ddd, J =14.1, 8.5, 5.3 Hz); **MS** (ESI^+) for $C_{11}H_7FNaO^+$ $[M+Na]^+$ requires m/z 213.0, found 213.1. The analytical data were in accordance with the literature.[52]

4,4,5,5-Tetramethyl-2-(4-(thiophen-2-yl)phenyl)-1,3,2-dioxaborolane (3.146-Bpin)

Prepared by Dr. Michael Schedler.

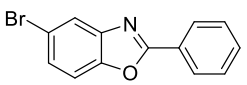


Modifying a known procedure,[40] 2-(4-bromophenyl)-thiophene (502 mg, 2.10 mmol, 1.05 equiv.), B_2pin_2 (508 mg, 2.00 mmol, 1.00 equiv.), $Pd(dppf)Cl_2$ (43.9 mg, 0.0600 mmol, 0.030 equiv.) and KOAc (588 mg, 6.00 mmol, 3.00 equiv.) were suspended in anhydrous and degassed 1,4-dioxane (10 mL). The mixture was stirred at 80 °C for 15 hours. The mixture was allowed to cool to room temperature, diluted with CH_2Cl_2 and filtered through celite. All volatiles were removed *in vacuo* and the residue was purified by flash column chromatography on silica (*n*-pentane/EtOAc 99:1) to afford 4,4,5,5-tetramethyl-2-(4-(thiophen-2-yl)phenyl)-1,3,2-dioxaborolane (**3.146-Bpin**, 301 mg, 1.05 mmol, 53%) as a colourless solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.84 (d, J = 8.2 Hz, 2H), 7.64 (d, J = 8.2 Hz, 2H), 7.39 (dd, J = 3.6, 1.2 Hz, 1H), 7.31 (dd, J = 5.1, 1.2 Hz, 1H), 7.10 (dd, J = 5.1, 3.6 Hz, 1H), 1.37 (s, 12H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 144.4, 137.1, 135.5, 128.2, 125.4, 125.2, 123.7, 84.0, 25.0; **^{11}B NMR** (128 MHz, $CDCl_3$): δ = 30.8; **HRMS** (CI^+) for $C_{16}H_{20}BO_2S^+$ $[M+H]^+$ requires m/z = 287.1272, found 287.1280; **IR** (ATR, neat) $\tilde{\nu}$ (cm^{-1}) = 3101, 2980, 2928, 1605, 1428, 1397, 1359, 1322, 1302, 1262, 1212, 1142, 1091, 1017, 961, 858, 819, 741, 703, 670, 653; **M.P.**: 67 °C.

5-Bromo-2-phenylbenzo[*d*]oxazole

Prepared by Dr. Enrico Emer.

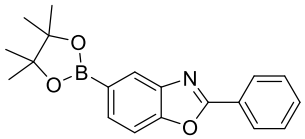


Adapting a known procedure,[53] $Pd(OAc)_2$ (28 mg, 0.13 mmol, 0.025 equiv.) and PPh_3 (131 mg, 0.5 mmol, 0.10 equiv.) were added to a mixture of 5-bromobenzo[*d*]oxazole (1.0 g, 5.04 mmol, 1.00 equiv.), Cs_2CO_3 (3.28 g, 10.0 mmol, 2.00 equiv.) and iodobenzene (11.3 mL, 101 mmol, 20.0 equiv.) in DMF (25 mL). The mixture was stirred at 100 °C under N_2 for 5 hours. The insoluble solid was removed by filtration through a Celite pad (eluting with CH_2Cl_2). The filtrate was diluted with H_2O (50 mL) and extracted with CH_2Cl_2 (3 x 50 mL). The combined organic extracts were washed with brine (50 mL), dried over $MgSO_4$ and concentrated *in vacuo* to give the crude product. The excess of iodobenzene was removed by distillation. Flash column chromatography (*n*-hexane/EtOAc 90:10) afforded 5-bromo-2-phenylbenzo[*d*]oxazole (727 mg, 2.64 mmol, 52%) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.26-8.24 (m, 2H), 7.92 (t, J = 1.2 Hz, 1H), 7.57-7.54 (m, 3H), 7.48 (d, J = 1.3 Hz, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 164.1, 149.7, 143.7, 131.9, 129.0, 128.1, 127.8, 126.6, 123.0, 117.3, 111.8. The analytical data were in accordance with the literature.[54]

2-Phenyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[*d*]oxazole (3.149-BPin)

Prepared by Dr. Enrico Emer.

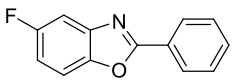


$Pd(dppf)Cl_2$ (65 mg, 0.079 mmol, 0.05 equiv.) was added to a mixture of 5-bromo-2-phenylbenzo[*d*]oxazole (434 mg, 1.58 mmol, 1.0 equiv.), KOAc (465 mg, 4.74 mmol, 3.00 equiv.) and B_2pin_2 (300 mg, 1.18 mmol, 0.75 equiv.) in DMF (3 mL). The mixture was stirred at 80° C under N_2 for 16 hours. The insoluble solid was removed by filtration through a Celite pad (eluting with CH_2Cl_2). The filtrate was diluted with H_2O (30 mL) and extracted with CH_2Cl_2 (3 x 30 mL). The combined organic extracts were washed with brine (30 mL), dried over $MgSO_4$ and concentrated *in vacuo* to give the crude product. Flash column chromatography (*n*-hexane/EtOAc 90:10) afforded 2-phenyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[*d*]oxazole (**3.149-BPin**, 229 mg, 0.71 mmol, 60%) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.14-8.11 (m, 3H), 7.72 (dd, J = 8.1, 1.1 Hz, 1H), 7.44 (dd, J = 8.1, 0.5 Hz, 1H), 7.38-7.36 (m, 3H), 1.24 (s, 12H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 162.9, 152.9, 141.9, 131.7, 131.5, 128.8, 127.7, 127.2, 126.9, 110.1, 83.9, 24.9; **^{11}B NMR** (128 MHz, $CDCl_3$): δ = 33.5 (br s); **HRMS** (ESI^+): for $C_{19}H_{21}BNO_3^+$ $[M+H]^+$ requires m/z = 322.16090; found 322.16097; **IR** (ATR, neat): $\tilde{\nu}$ (cm^{-1}) = 3060, 2978, 2931, 2362, 1623, 1356, 1145, 710; **M.P.**: 79-81 °C.

5-Fluoro-2-phenylbenzo[*d*]oxazole (3.149)

Prepared by Dr. Enrico Emer.

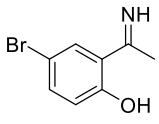


Adapting a known procedure,[53] $Pd(OAc)_2$ (12 mg, 0.055 mmol, 0.025 equiv.) and PPh_3 (57.4 mg, 0.22 mmol, 0.10 equiv.) were added to a mixture of 5-fluorobenzo[*d*]oxazole (300 mg, 2.19 mmol, 1.00 equiv.), Cs_2CO_3 (1.43 g, 4.38 mmol, 2.00 equiv.) and iodobenzene (4.9 mL, 43.8 mmol, 20.0 equiv.) in DMF (10 mL). The mixture was stirred at 100 °C under nitrogen for 5 hours. The insoluble solid was removed by filtration through a Celite pad (eluting with CH_2Cl_2). The filtrate was diluted with H_2O (20 mL) and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic extracts were washed with brine (20 mL), dried over $MgSO_4$ and concentrated *in vacuo* to give the crude product. The excess of iodobenzene was removed by distillation. Flash column chromatography (*n*-hexane/EtOAc 90:10) afforded 5-fluoro-2-phenylbenzo[*d*]oxazole (**3.149**, 223 mg, 1.05 mmol, 48%) as a colourless solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.23-8.21 (m, 2H), 7.54-7.43 (m, 5H), 7.06 (td, J = 9.1, 2.6 Hz, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 164.7, 160.1 (d, J = 240.1 Hz), 147.0, 142.8 (d, J = 17.0 Hz), 131.7, 128.9, 127.6, 126.7, 112.6 (d, J = 26.8 Hz), 110.8 (d, J = 9.7 Hz), 106.31 (d, J = 25.4 Hz); **^{19}F NMR** (376 MHz, $CDCl_3$): δ = -117.7 (td, J = 8.9, 4.2 Hz). The analytical data were in accordance with the literature.[55]

4-Bromo-2-(1-iminoethyl)phenol

Prepared by Dr. Michael Schedler.

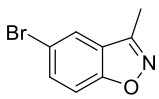


Following a known procedure,[56] 5′-bromo-2′-hydroxyacetophenone (1.98 g, 10.0 mmol, 1.00 equiv.) was dissolved in a solution of ammonia in methanol (7 M, 7 mL, 49.0 mmol, 4.9 equiv.) and the reaction was stirred for 2.5 hours at room temperature. The precipitate was filtered off and washed with methanol. The precipitate was dried *in vacuo* yielding 4-bromo-2-(1-iminoethyl)phenol (1.66 g, 7.76 mmol, 78%) as a bright yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 15.15 (br s, 1H), 9.24 (br s, 1H), 7.59 (d, J = 2.5 Hz, 1H), 7.40 (dd, J = 8.9, 2.5 Hz, 1H), 6.87 (d, J = 8.9 Hz, 1H), 2.47 (d, J = 1.4 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 177.5, 162.9, 136.2, 131.5, 120.8, 120.1, 109.1, 26.1; **MS** (ESI^+) for $C_8H_9{}^{81}BrNO^+$ $[M+H]^+$ requires m/z = 216.0, found 215.9. The analytical data were in accordance with the literature.[57]

5-Bromo-3-methylbenzisoxazole

Prepared by Dr. Michael Schedler.



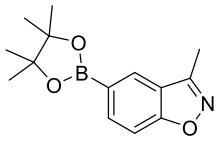
Following a known procedure,[56] 4-bromo-2-(1-iminoethyl)phenol (500 mg, 2.50 mmol, 1.00 equiv.), K_2CO_3 (690 mg, 5.00 mmol, 2.00 equiv.) and NCS (503 mg, 3.75 mmol, 1.50 equiv.) were suspended in anhydrous THF (10 mL). The mixture was stirred for 3 hours at room temperature and quenched by addition of H_2O (20 mL). The mixture was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic phases were dried with $MgSO_4$, filtered and all

volatiles were removed *in vacuo.* The residue was purified by flash column chromatography on silica (*n*-pentane/EtOAc 99:1) yielding 5-bromo-3-methylbenzoisoxazole (331 mg, 1.56 mmol, 62%) as a colourless solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.75 (d, *J* = 1.8 Hz, 1H), 7.61 (dd, *J* = 8.8, 1.9 Hz, 1H), 7.42 (d, *J* = 8.8 Hz, 1H), 2.55 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 161.9, 154.6, 132.9, 124.4, 123.9, 116.1, 111.5, 10.1. The analytical data were in accordance with the literature.[58]

3-Methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzisoxazole (3.150-Bpin)

Prepared by Dr. Michael Schedler.

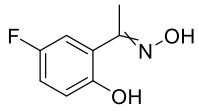


Modifying a known procedure,[37] 5-bromo-3-methylbenzoisoxazole (271 mg, 1.28 mmol, 1.05 equiv.), B_2pin_2 (310 mg, 1.22 mmol, 1.00 equiv.), $Pd(dppf)Cl_2$ (26.7 mg, 0.0365 mmol, 0.030 equiv.) and KOAc (358 mg, 3.65 mmol, 3.00 equiv.) were suspended in anhydrous and degassed 1,4-dioxane (5 mL). The mixture was stirred for 15 hours at 80 °C. The mixture was allowed to cool to room temperature, diluted with CH_2Cl_2 and filtered through Celite. All volatiles were removed *in vacuo* and the residue was purified by flash column chromatography on silica (*n*-pentane/EtOAc 98:2 to 96:4) yielding 3-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzisoxazole (**3.150-Bpin**, 136 mg, 0.525 mmol, 43%) as a colourless solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.14 (t J = 1.0 Hz, 1H), 7.98 (dd, J = 8.5, 1.1 Hz, 1H), 7.53 (dd, J = 8.5, 0.9 Hz, 1H), 2.59 (s, 3H), 1.38 (s, 12H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 164.8, 155.4, 136.1, 129.0, 122.4, 109.4, 84.3, 25.1, 10.3; **^{11}B NMR** (128 MHz, $CDCl_3$): δ = 31.2; **HRMS** (ESI^+) for $C_{14}H_{19}BNO_3^+$ $[M+H]^+$ requires m/z = 260.1453, found 260.1454; **IR** (ATR, neat) $\tilde{\nu}$ (cm^{-1}) = 2988, 1608, 1482, 1359, 1334, 1265, 1229, 1148, 1101, 1054, 965, 903, 854, 815, 764, 723, 700, 682; **M.P.**: 78 °C.

1-(5-Fluoro-2-hydroxyphenyl)ethan-1-one oxime

Prepared by Dr. Michael Schedler.



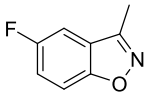
To a solution of 5′-fluoro-2′-hydroxyacetophenone (3.08 g, 20.0 mmol, 1.00 equiv.) in MeOH/pyridine (2:1, 15 mL) was added hydroxylamine hydrochloride (2.22 g, 32.0 mmol, 1.60 equiv.). The mixture was stirred at room temperature for 14 hours, after which the solvent was removed *in vacuo*. The residue was partitioned between Et_2O (150 mL) and H_2O (100 mL). The phases were separated and the organic phase was washed with H_2O (100 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Drying under high vacuum overnight afforded 1-(5-Fluoro-2-hydroxyphenyl)ethan-1-one oxime (3.30 g, 19.5 mmol, 98%) as an off-white solid without further purification.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.95-11.15 (m, 2H), 7.29 (dd, J = 10.2, 3.1 Hz, 1H), 7.11 – 7.05 (m, 1H), 6.87 (dd, J = 9.0, 5.0 Hz, 1H), 2.23 (s, 3H); **^{13}C NMR** (101 MHz, DMSO-d_6): δ = 156.6 (d, J = 2.7 Hz), 155.1 (d, J = 233.2 Hz), 153.3 (d, J = 1.6 Hz), 120.2 (d, J = 7.6 Hz), 117.5 (d, J = 8.1 Hz), 116.6 (d, J = 23.0 Hz), 114.0 (d, J = 24.6 Hz),

11.2 (s). **^{19}F NMR** (376 MHz, DMSO-d_6): δ = -125.30 (ddd, J = 10.2, 8.1, 5.0 Hz); **HRMS** (ESI$^+$) for $C_8H_7FNO_2^-$ $[M–H]^-$ requires m/z = 168.0466, found 168.0465; **IR** (ATR, neat) $\tilde{\nu}$ (cm^{-1}) = 3320, 2981, 1642, 1592, 1506, 1412, 1370, 1326, 1270, 1238, 1189, 1038, 897, 865, 786, 766, 743, 671; **M.P**.: 167-170 °C.

5-Fluoro-3-methylbenzisoxazole (3.150)

Prepared by Dr. Michael Schedler.



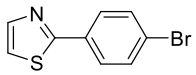
Adapting a known procedure,[59] (*E*)-1-(5-fluoro-2-hydroxyphenyl)ethan-1-one oxime (500 mg, 2.96 mmol, 1.00 equiv.) and PPh_3 (1.32 g, 5.03 mmol, 1.70 equiv.) were dissolved in anhydrous THF (20 mL) and the solution was cooled to 0 °C. A solution of DEAD (788 μL, 5.03 mmol, 1.70 equiv.) in anhydrous THF (10 mL) was added to the reaction and the mixture was stirred at 0 °C for 30 minutes. All volatiles of the reaction were then removed *in vacuo* and the residue was purified by flash column chromatography on silica (*n*-pentane/EtOAc 99.5:0.5) yielding 5-fluoro-3-methylbenzisoxazole (**3.150**, 149 mg, 0.987 mmol, 33%) as a colourless solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.48 (ddd, J = 8.9, 3.8, 0.8 Hz, 1H), 7.30–7.24 (m, 2H), 2.55 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 159.6 (s), 159.2 (d, J = 241.4 Hz), 155.3 (d, J = 4.5 Hz), 123.0 (d, J = 10.3 Hz), 118.5 (d, J = 27.0 Hz), 110.9 (d, J = 9.2 Hz), 106.1 (d, J = 24.9 Hz), 10.2 (s); **^{19}F NMR** (376 MHz, $CDCl_3$): δ = −120.0 (td, J = 8.2, 3.9 Hz); **HRMS** (ESI$^+$) for $C_8H_7FNO^+$ $[M+H]^+$ requires m/z = 152.05062, found 152.05058; **IR**

(ATR, neat) $\tilde{\nu}$ (cm^{-1}) = 1528, 1478, 1446, 1390, 1321, 1189, 874, 856, 813, 759, 680; **M.P.**: 56 °C.

2-(4-Bromophenyl)thiazole

Prepared by Dr. Enrico Emer.

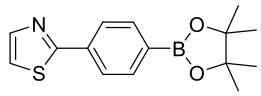


Adapting a known procedure,[60] to a stirred solution of 1-bromo-4-iodobenzene (450 mg, 1.59 mmol, 1.00 equiv.) in 1,4-dioxane (35 ml) was added 2-tributylstannylthiazole (500 μL, 1.59 mmol, 1.00 equiv.), followed by $Pd(PPh_3)_4$ (185 mg, 0.16 mmol, 0.05 equiv.). The solution was stirred at reflux for 1 hour. After cooling the mixture to room temperature, aqueous KF solution (10% w/v, 30 mL) was added and stirring was continued at room temperature for 20 min. The resulting precipitate was filtered and the organic layer was washed with brine (3 x 20 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo* to give the crude product. Flash column chromatography (*n*-hexane/EtOAc 95:5) afforded 2-(4-bromophenyl)thiazole (157 mg, 0.65 mmol, 41%) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.88 (d, *J* = 3.3 Hz, 1H), 7.84 (d, *J* = 8.8 Hz, 2H), 7.58 (d, *J* = 8.8 Hz, 2H), 7.35 (d, *J* = 3.3 Hz, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 166.9, 143.7, 132.4, 132.0, 127.8, 124.1, 119.1. The analytical data were in accordance with the literature.[61]

2-(4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)thiazole (3.151-Bpin)

Prepared by Dr. Enrico Emer.

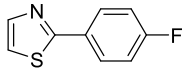


$Pd(dppf)Cl_2$ (26.6 mg, 0.032 mmol, 0.05 equiv.) was added to a mixture of 2-(4-bromophenyl)thiazole (157 mg, 0.65 mmol, 1.00 equiv.), KOAc (192 mg, 1.96 mmol, 3.00 equiv.) and B_2pin_2 (182 mg, 0.72 mmol, 1.10 equiv.) in DMF (3 mL). The mixture was stirred at 80 °C under N_2 for 24 hours. The insoluble solid was removed by filtration through a Celite pad (eluting with CH_2Cl_2). The filtrate was diluted with H_2O (20 mL) and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic extracts were washed with brine (20 mL), dried over $MgSO_4$ and concentrated *in vacuo* to give the crude product. Flash column chromatography (*n*-hexane/EtOAc 95:5) afforded 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[*d*]thiazole (**3.151-Bpin**, 114 mg, 0.4 mmol, 61%) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.98 (d, *J* = 8.4 Hz, 2H), 7.90-7.88 (m, 3H), 7.36 (d, *J* = 3.3 Hz, 1H), 1.37 (s, 12H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 168.3, 143.8, 135.8, 135.4, 125.7, 119.1, 84.0, 24.9; **^{11}B NMR** (128 MHz, $CDCl_3$): δ = 30.9 (br s). The analytical data were in accordance with the literature.[62]

2-(4-Fluorophenyl)thiazole (3.151)

Prepared by Dr. Enrico Emer.



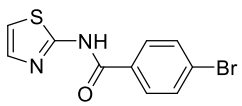
Adapting a known procedure,[63] to a stirred solution of (4-fluorophenyl)boronic acid (512 mg, 3.66 mmol, 1.20 equiv.) in

toluene (5 ml) was added 2-bromothiazole (275 μL, 3.05 mmol, 1.00 equiv.), followed by $Pd(PPh_3)_4$ (176.2 mg, 0.15 mmol, 0.05 equiv.). The reaction mixture was purged with argon, aqueous Na_2CO_3 solution (2M, 5 mL) was added, and the reaction mixture was stirred at 110 °C for 24 hours. The reaction mixture was cooled to room temperature and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic extracts were washed with brine (30 mL), dried over $MgSO_4$ and concentrated *in vacuo* to give the crude product. Flash column chromatography (CH_2Cl_2/*n*-hexane 75:25) afforded 2-(4-fluorophenyl)thiazole (**3.151**, 438 mg, 2.44 mmol, 80%) as a light red liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.98-7.94 (m, 2H), 7.86 (d, J = 3.3 Hz, 1H), 7.33 (dd, J = 3.3, 0.4 Hz, 1H), 7.17-7.12 (m, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 167.2, 163.8 (d, J = 250.1 Hz), 143.7, 129.9 (d, J = 3.8 Hz), 128.5 (d, J = 8.7 Hz), 118.8, 116.0 (d, J = 22.2 Hz); **^{19}F NMR** (376 MHz, $CDCl_3$): δ = -110.6 (m). The analytical data were in accordance with the literature.[63]

4-Bromo-*N*-(thiazol-2-yl)benzamide

Prepared by Dr. Michael Schedler.



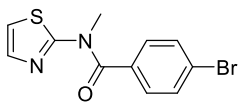
Adapting a known procedure,[45] 2-aminothiazole (1.00 g, 10.0 mmol, 1.00 equiv.) was dissolved in anhydrous pyridine (20 mL) and the solution was cooled to 0 °C. 4-Bromobenzoyl chloride (2.19 g, 10.0 mmol, 1.00 equiv.) was added to the reaction and the mixture was warmed to room temperature and stirred for 15 hours. Afterwards, the reaction was stopped by

addition of H_2O (50 mL) and the mixture was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic phases were dried with $MgSO_4$, filtered and all volatiles were removed *in vacuo*. Purification of the residue by flash column chromatography on silica (*n*-pentane/EtOAc 67:33) yielded 4-bromo-*N*-(thiazol-2-yl)benzamide (1.83 g, 6.47 mmol, 65%) as a colourless solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 12.40 (s, 1H), 7.90–7.88 (m, 2H), 7.68–7.66 (m, 2H), 7.09 (d, J = 3.6 Hz, 1H), 7.00 (d, J = 3.6 Hz, 1H); **MS** (ESI^+) for $C_{10}H_8BrN_2OS^+$ $[M+H]^+$ requires m/z = 282.9, found 283.0. The analytical data were in accordance with the literature.[64]

4-Bromo-*N*-methyl-*N*-(thiazol-2-yl)benzamide

Prepared by Dr. Michael Schedler.



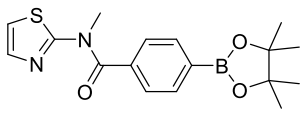
Adapting a known procedure,[65] NaH (60% in mineral oil, 138 mg, 3.45 mmol, 1.30 equiv.) was suspended in anhydrous THF (25 mL) and the suspension was cooled to 0 °C. 4-Bromo-*N*-(thiazol-2-yl)benzamide (750 mg, 2.65 mmol, 1.00 equiv.) was dissolved in anhydrous THF (15 mL) and this solution was added dropwise to the reaction. The reaction was warmed to room temperature and stirred at room temperature for 30 minutes. The reaction was cooled again to 0 °C and MeI (216 µL, 3.45 mmol, 1.30 equiv.) was added. The reaction was warmed to room temperature and stirred for 15 hours. H_2O (50 mL) was then added and the mixture was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic phases were dried with $MgSO_4$, filtered and all volatiles were

removed *in vacuo*. The residue was purified by flash column chromatography on silica (*n*-pentane/EtOAc 50:50 to 33:67) yielding 4-bromo-*N*-methyl-*N*-(thiazol-2-yl)benzamide (237 mg, 0.798 mmol, 30%) as a colourless crystalline solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.23–8.20 (m, 2H), 7.59–7.55 (m, 2H), 7.02 (d, *J* = 4.7 Hz, 1H), 6.71 (d, *J* = 4.7 Hz, 1H), 3.86 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 173.2, 168.2, 136.1, 131.4, 131.0, 126.9, 126.4, 109.4, 36.0; **HRMS** (ESI^+) for $C_{11}H_{10}BrN_2OS^+$ $[M+H]^+$ requires m/z = 296.96917, found 296.96934; **IR** (ATR, neat) $\tilde{\nu}$ (cm^{-1}) = 3142, 3112, 3079, 2947, 1592, 1553, 1495, 1401, 1360, 1282, 1246, 972, 708; **M.P.**: 177 °C.

_N_-Methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-_N_-(thiazol-2-yl)benzamide (3.152-Bpin)

Prepared by Dr. Michael Schedler.

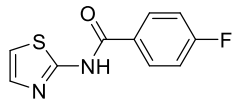


Modifying a known procedure,[37] 4-bromo-*N*-methyl-*N*-(thiazol-2-yl)benzamide (220 mg, 0.741 mmol, 1.05 equiv.), B_2pin_2 (178 mg, 0.706 mmol, 1.00 equiv.), $Pd(dppf)Cl_2$ (15.5 mg, 0.0212 mmol, 0.030 equiv.) and KOAc (208 mg, 2.12 mmol, 3.0 equiv.) were suspended in anhydrous and degassed 1,4-dioxane (5 mL). The mixture was stirred for 19 hours at 80 °C. The mixture was allowed to cool to room temperature, diluted with CH_2Cl_2 and filtered. All volatiles were removed *in vacuo* and the residue was purified by recrystallization from CH_2Cl_2/*n*-hexane yielding *N*-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-*N*-(thiazol-2-yl)benzamide (**3.152-Bpin**, 45.5 mg, 0.132 mmol, 18%) as an off-white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.35–8.32 (m, 2H), 7.90–7.87 (m, 2H), 7.01 (d, J = 4.7 Hz, 1H), 6.70 (d, J = 4.7 Hz, 1H), 3.88 (s, 3H), 1.36 (s, 12H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 173.8, 167.9, 139.3, 134.5, 128.3, 126.9, 109.1, 84.0, 35.8, 24.9; **^{11}B NMR** (128 MHz, $CDCl_3$): δ = 30.2; **HRMS** (ESI^+) for $C_{17}H_{22}BN_2O_3S^+$ $[M+H]^+$ requires m/z = 345.14387, found 345.14392; **IR** (ATR, neat) $\tilde{\nu}$ (cm^{-1}) = 2980, 1857, 1543, 1488, 1405, 1344, 1282, 1168, 1143, 1082, 1018, 969, 857, 810, 776, 709, 652, 631; **M.P.**: 156 °C.

4-Fluoro-*N*-(thiazol-2-yl)benzamide

Prepared by Dr. Michael Schedler.



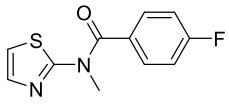
Adapting a known procedure,[45] 2-aminothiazole (735 mg, 7.35 mmol, 1.00 equiv.) was dissolved in anhydrous pyridine (20 mL) and the solution was cooled to 0 °C. 4-Fluorobenzoyl chloride (872 µL, 7.35 mmol, 1.00 equiv.) was added to the reaction and the mixture was warmed to room temperature and stirred for 15 hours. The reaction was then stopped by addition of H_2O (20 mL) and the mixture was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic phases were dried with $MgSO_4$, filtered and all volatiles were removed *in vacuo*. Purification of the residue by flash column chromatography on silica (*n*-pentane/EtOAc 75:25 to 50:50) yielded 4-fluoro-*N*-(thiazol-2-yl)benzamide (1.59 g, 7.16 mol, 97%) as a colourless solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 13.03 (s, 1H), 8.06 (dd, J = 8.6, 5.3 Hz, 2H), 7.19 (t, J = 8.4 Hz, 2H), 6.97 (q, J = 3.7 Hz, 2H); **^{13}C** NMR (101 MHz, $CDCl_3$): δ = 165.6 (d, J = 254.3 Hz), 165.1 (s), 160.8 (s), 137.0 (s), 130.9 (d, J = 9.2 Hz), 129.2 (d, J = 3.1 Hz), 116.1

(d, J = 22.0 Hz), 113.8 (s); **^{9}F NMR** (376 MHz, $CDCl_3$): δ = –105.6(tt, J = 8.2, 5.3 Hz); **HRMS** (ESI^+) for $C_{10}H_8FN_2OS^+$ $[M+H]^+$ requires m/z = 223.03359, found 223.03351; **IR** (ATR, neat) $\tilde{\nu}$ (cm^{-1}) = 3152, 2929, 2851, 2789, 2735, 1668, 1602, 1542, 1511, 1492, 1440, 1409, 1313, 1291, 1229, 1161, 1100, 1061, 1016, 967, 949, 899, 852, 811, 749, 717, 684, 630; **M.P.**: 164 °C.

4-Fluoro-*N*-methyl-*N*-(thiazol-2-yl)benzamide (3.152)

Prepared by Dr. Michael Schedler.

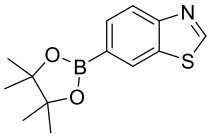


Adapting a known procedure,[65] NaH (60% in mineral oil, 138 mg, 3.45 mmol, 1.30 equiv.) was suspended in anhydrous THF (25 mL) and the suspension was cooled to 0 °C. 4-Fluoro-*N*-(thiazol-2-yl)benzamide (588 mg, 2.65 mmol, 1.00 equiv.) was dissolved in anhydrous THF (15 mL) and this solution was added drop wise to the reaction. The reaction was warmed to room temperature and stirred at room temperature for 30 minutes. The reaction was cooled again to 0 °C and MeI (216 µL, 3.45 mmol, 1.30 equiv.) was added. The reaction was warmed to room temperature and stirred for 16 hours. H_2O (30 mL) was then added and the mixture was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic phases were dried with $MgSO_4$, filtered and all volatiles were removed *in vacuo*. The residue was purified by flash column chromatography on silica (*n*-pentane/EtOAc 67:33 to 50:50) yielding 4-fluoro-*N*-methyl-*N*-(thiazol-2-yl)benzamide (**3.152**, 445 mg, 1:89 mmol, 71%) as a colourless solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.37–8.33 (m, 2H), 7.10 (t, J = 8.7 Hz, 2H), 6.99 (d, J = 4.7 Hz, 1H), 6.67 (d, J = 4.7 Hz, 1H), 3.84 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 173.0 (s), 168.0 (s), 165.2 (d, J = 51.1 Hz), 133.4 (d, J = 2.9 Hz), 131.7 (d, J = 8.9 Hz), 126.8 (s), 115.0 (d, J = 21.6 Hz), 109.2 (s), 35.9 (s); **^{19}F NMR** (376 MHz, $CDCl_3$): δ = –109.4 (tt, J =8.4, 5.7 Hz); **HRMS** (ESI^+) for $C_{11}H_{10}FN_2OS^+$ $[M+H]^+$ requires m/z = 237.04924, found 237.04929; **IR** (ATR, neat) $\tilde{\nu}$ (cm^{-1}) = 3118, 3073, 1604, 1564, 1494, 1407, 1363, 1283, 1257, 12145, 1144, 1120, 1084, 1011, 971, 875, 846, 818, 764, 680, 625; **M.P.**: 112 °C.

6-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[*d*]thiazole (3.153-Bpin)

Prepared by Dr. Enrico Emer.

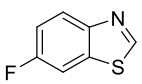


Pd(dppf)Cl_2 (95 mg, 0.12 mmol, 0.05 equiv.) was added to a mixture of 6-bromobenzo[*d*]thiazole (500 mg, 2.33 mmol, 1.00 equiv.), KOAc (686 mg, 6.99 mmol, 3.00 equiv.) and B_2pin_2 (653 mg, 2.57 mmol, 1.10 equiv.) in DMF (4 mL). The mixture was stirred at 80 °C under N_2 for 24 hours. The insoluble solid was removed by filtration through a Celite pad (eluting with CH_2Cl_2). The filtrate was diluted with H2O (30 mL) and extracted with CH_2Cl_2 (3 x 30 mL). The combined organic extracts were washed with brine (30 mL), dried over $MgSO_4$ and concentrated *in vacuo* to give the crude product. Flash column chromatography (*n*-hexane/EtOAc 90:10) afforded 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[*d*]thiazole (**3.153-Bpin**, 434 mg, 1.66 mmol, 71%) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.05 (s, 1H), 8.45 (t, *J* = 0.9 Hz, 1H), 8.13 (dd, *J* = 8.2, 0.7 Hz, 1H), 7.94 (dd, *J* = 8.2, 1.1 Hz, 1H), 1.37 (s, 12H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 155.3, 155.1, 133.2, 131.9, 128.9, 122.8, 84.1, 24.8. The analytical data were in accordance with the literature.[66]

6-Fluorobenzo[*d*]thiazole (3.153)

Prepared by Dr. Enrico Emer.



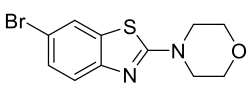
Adapting a known procedure,[67] 6-fluorobenzo[*d*]thiazol-2-amine (500 mg, 2.97 mmol, 1.00 equiv.) was dissolved in 85% H_3PO_4 (20 mL). The resultant homogeneous solution was cooled to -10 °C and a concentrated aqueous solution of $NaNO_2$ (1.23 g, 17.8, 6 equiv.) was added dropwise at a rate that the reaction temperature did not exceed -4 °C. The resultant thick yellow syrup was maintained at -8 °C for one hour, poured into 50% H_3PO_2 (8 mL) at 0 °C and warmed to room temperature over two hours. The solution was diluted with ice-cold water, neutralised with Na_2CO_3, and extracted with $CHCl_3$ three times. The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo* to give the crude product. Flash column chromatography (*n*-hexane/EtOAc 90:10) afforded 6-fluorobenzo[*d*]thiazole (**3.153**, 301 mg, 1.97 mmol, 66%) as a yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.93 (s, 1H), 8.06 (dd, *J* = 9.0, 4.8 Hz, 1H), 7.61 (dd, *J* = 8.1, 2.5 Hz, 1H), 7.24 (td, *J* = 8.9, 2.6 Hz, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 160.8 (d, *J* = 246.2), 153.5 (d, *J* = 3.0), 149.8, 134.7 (d, *J* = 11.5 Hz), 124.4 (d, *J* = 9.5 Hz), 114.9

(d, *J* = 23.9 Hz), 107.8 (d, *J* = 27.0 Hz); **^{19}F NMR** (376 MHz, $CDCl_3$): δ = -115.6 (td, *J* = 8.5, 4.8 Hz). The analytical data were in accordance with the literature.[68]

4-(6-Bromobenzo[*d*]thiazol-2-yl)morpholine

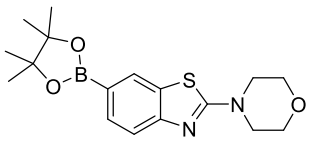
Prepared by Dr. Enrico Emer.



Adapting a known procedure,[69] 2-chloro-6-bromobenzo[*d*]thiazole (1.00 g, 4.02 mmol, 1.00 equiv.), DBU (6.0 µL, 0.04 mmol, 0.01 equiv.) and $NaHCO_3$ (304 mg, 3.62 mmol, 0.90 equiv.) were added in a round-bottom flask. Morpholine (352 µL, 4.02 mmol, 1.00 equiv.) was added and the reaction mixture was stirred with a metal spatula. After standing for 5 minutes at room temperature the white solid was washed with H_2O (4 x 20 mL) and then recrystallized from EtOH. 4-(6-Bromobenzo[*d*]thiazol-2-yl)morpholine (1.16 g, 3.86 mmol, 68%) was obtained without further purification as a white solid. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.73 (t, *J* = 1.2 Hz, 1H), 7.42 (s, 1H), 7.41 (s, 1H), 3.84 (t, *J* = 4.5 Hz, 4H), 3.62 (t, *J* = 4.5 Hz, 4H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 169.0, 151.6, 132.4, 129.4, 123.3, 120.4, 114.0, 66.2, 48.5. The analytical data were in accordance with the literature.[70]

4-(6-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[*d*]thiazol-2-yl)morpholine (3.154-Bpin)

Prepared by Dr. Enrico Emer.

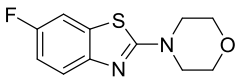


$Pd(dppf)Cl_2$ (111 mg, 0.136 mmol, 0.05 equiv.) was added to a mixture of 4-(6-bromobenzo[*d*]thiazol-2-yl)morpholine (816 mg, 2.72 mmol, 1.00 equiv.), KOAc (801 mg, 8.16 mmol, 3.00 equiv.) and B_2pin_2 (760 mg, 2.99 mmol, 1.10 equiv.) in DMF (4 mL). The mixture was stirred at 130 °C under N_2 for 5 hours. The insoluble solid was removed by filtration through a Celite pad (eluting with CH_2Cl_2). The filtrate was diluted with H_2O (30 mL) and extracted with CH_2Cl_2 (3 x 30 mL). The combined organic extracts were washed with brine (30 mL), dried over $MgSO_4$ and concentrated *in vacuo* to give the crude product. Flash column chromatography (*n*-hexane/EtOAc 80:20) afforded 4-(6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[*d*]thiazol-2-yl)morpholine (**3.154-Bpin**, 461.4 mg, 0.97 mmol, 36%) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.09 (dd, *J* = 1.2, 0.6 Hz, 1H), 7.76 (dd, *J* = 8.1, 1.2 Hz, 1H), 7.55 (dd, *J* = 8.1, 0.5 Hz, 1H), 3.85-3.83 (m, 4H), 3.67-3.64 (m, 4H), 1.36 (s, 12H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 170.1, 155.0, 132.6, 130.2, 127.5, 118.6, 83.7, 66.2, 48.4, 24.9; **^{11}B NMR** (128 MHz, $CDCl_3$): δ = 31.8 (br s); **HRMS** (ESI^+): for $C_{17}H_{24}BN_2O_3S^+$ $[M+H]^+$ requires m/z = 347.15952; found 347.15927; **IR** (ATR, neat): $\tilde{\nu}$ (cm^{-1}) = 2976, 2924, 2857, 2361, 2341, 1558, 1526, 1347, 1144; **M.P.**: 112-116 °C.

4-(6-Fluorobenzo[*d*]thiazol-2-yl)morpholine (3.154)

Prepared by Dr. Enrico Emer.

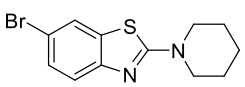


Adapting a known procedure,[69] 2-chloro-6-fluorobenzo[*d*]thiazole (500 mg, 2.70 mmol, 1.00 equiv.), DBU (4.0 μL, 0.027 mmol, 0.01 equiv.) and $NaHCO_3$ (202 mg, 2.4 mmol, 0.90 equiv.) were added in a round-bottom flask. Morpholine (236 μL, 2.70 mmol, 1.00 equiv.) was added and the reaction mixture was stirred with a metal spatula. After standing for 5 minutes at room temperature the white solid was washed with H_2O (4 x 10 mL) and then recrystallized from EtOH. 4-(6-Fluorobenzo[*d*]thiazol-2-yl)morpholine (**3.154**, 220 mg, 0.92 mmol, 34%) was obtained without further purification as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.49 (dd, *J* = 8.8, 4.7 Hz, 1H), 7.34 (dd, *J* = 8.2, 2.6 Hz, 1H), 7.04 (td, *J* = 9.0, 2.7 Hz, 1H), 3.86-3.83 (m, 4H), 3.62-3.60 (m, 4H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 168.6, 158.2 (d, *J* = 240.4 Hz), 148.9, 131.3 (d, *J* = 10.9 Hz), 119.8 (d, *J* = 8.7 Hz), 113.7 (d, *J* = 23.9 Hz), 107.4 (d, *J* = 27.0 Hz), 66.2, 48.5; **^{19}F NMR** (376 MHz, $CDCl_3$): δ = -120.98 (td, *J* = 8.6, 4.7 Hz). The analytical data were in accordance with the literature.[70]

6-Bromo-2-(piperidin-1-yl)benzo[*d*]thiazole

Prepared by Dr. Enrico Emer.



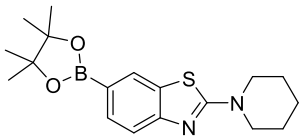
Adapting a known procedure,[69] 2-chloro-6-bromobenzo[*d*]thiazole (1.0 g, 4.02 mmol, 1.00 equiv.), DBU (6.0 μL, 0.04 mmol, 0.01 equiv.) and $NaHCO_3$ (304 mg, 3.62 mmol, 0.9 equiv.) were

added in a round-bottom flask. Piperidine (398 μL, 4.02 mmol, 1.00 equiv.) was added and the reaction mixture was stirred with a metal spatula. After standing for 5 minutes at room temperature the white solid was washed with H_2O (4 x 20 mL) and then recrystallized from EtOH. Flash column chromatography (*n*-hexane/EtOAc 90:10) afforded 6-bromo-2-(piperidin-1-yl)benzo[*d*]thiazole (855 mg, 2.87 mmol, 71%) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.67 (dd, *J* = 1.5, 0.9 Hz, 1H), 7.38-7.33 (m, 2H), 3.57 (bs s, 4H), 1.69 (br s, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 168.8, 151.9, 132.3, 129.0, 123.0, 119.7, 113.1, 49.6, 25.2, 24.1. The analytical data were in accordance with the literature.[70]

2-(Piperidin-1-yl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[*d*]thiazole (3.155-Bpin)

Prepared by Dr. Enrico Emer.



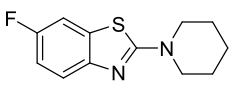
$Pd(dppf)Cl_2$ (90 mg, 0.11 mmol, 0.05 equiv.) was added to a mixture of 6-bromo-2-(piperidin-1-yl)benzo[*d*]thiazole (655 mg, 2.20 mmol, 1.00 equiv.), KOAc (648 mg, 6.60 mmol, 3.00 equiv.) and B_2pin_2 (614 mg, 2.42 mmol, 1.10 equiv.) in DMF (4 mL). The mixture was stirred at 80 °C under N_2 for 18 hours. The insoluble solid was removed by filtration through a Celite pad (eluting with CH_2Cl_2). The filtrate was diluted with H_2O (30 mL) and extracted with CH_2Cl_2 (3 x 30 mL). The combined organic extracts were washed with brine (30 mL), dried over $MgSO_4$ and concentrated *in vacuo* to give the crude product. Flash

column chromatography (*n*-hexane/EtOAc 80:20) afforded 2-(piperidin-1-yl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[*d*]thiazole (**3.155-Bpin**, 556 mg, 1.61 mmol, 73%) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.04 (dd, *J* = 1.1, 0.5 Hz, 1H), 7.73 (dd, *J* = 8.1, 1.2 Hz, 1H), 7.50 (dd, *J* = 8.1, 0.5 Hz, 1H), 3.62 (br s, 4H), 1.68 (br s, 6H), 1.34 (s, 12H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 169.9, 155.4, 132.4, 130.2, 127.2, 118.0, 83.5, 49.5, 25.3, 24.8, 24.1; **^{11}B NMR** (128 MHz, $CDCl_3$): δ = 30.4 (br s); **HRMS** (ESI^+): for $C_{18}H_{26}BN_2O_2S^+$ $[M+H]^+$ requires m/z = 345.18026; found 345.17888; **IR** (ATR, neat): $\tilde{\nu}$ (cm^{-1}) = 2976, 2936, 2855, 2360, 1557, 1524, 1345, 1143, 856; **M.P**.: 120-126 °C.

6-Fluoro-2-(piperidin-1-yl)benzo[*d*]thiazole (3.155)

Prepared by Dr. Enrico Emer.

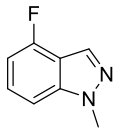


Adapting a known procedure,[69] 2-chloro-6-fluorobenzo[*d*]thiazole (1.00 g, 5.33 mmol, 1.00 equiv.), DBU (8.0 µL, 0.05 mmol, 0.01 equiv.) and $NaHCO_3$ (403 mg, 4.80 mmol, 0.90 equiv.) were added in a round-bottom flask. Piperidine (527 µL, 5.33 mmol, 1.00 equiv.) was added and the reaction mixture was stirred with a metal spatula. After standing for 5 minutes at room temperature the white solid was washed with H_2O (4 x 20 mL) and then recrystallized from ethanol. Flash column chromatography (*n*-hexane/EtOAc 80:20) afforded 6-fluoro-2-(piperidin-1-yl)benzo[*d*]thiazole (**3.155**, 706 mg, 2.97 mmol, 56%) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.44 (dd, *J* = 8.8, 4.7 Hz, 1H), 7.29 (dd, *J* = 8.2, 2.7 Hz, 1H), 6.99 (td, *J* = 9.0, 2.6 Hz, 1H), 3.57 (br s, 4H), 1.70-1.68 (br s, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 168.4, 157.9 (d, *J* = 240.0 Hz), 149.3, 131.3 (d, *J* = 10.8 Hz), 119.0 (d, *J* = 8.8 Hz), 113.4 (d, *J* = 23.1 Hz), 107.3 (d, *J* = 27.1 Hz), 49.5, 25.2, 24.1; **^{19}F NMR** (376 MHz, $CDCl_3$): δ = -121.9 (m). The analytical data were in accordance with the literature.[71]

4-Fluoro-1-methyl-1*H*-indazole (3.162)

Prepared by Dr. Enrico Emer.

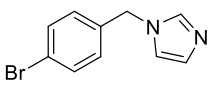


Adapting a known procedure,[72] to a stirred solution of 4-fluoroindazole (300 mg, 2.20 mmol, 1.00 equiv.) and KOH (370 mg, 6.60 mmol, 3.00 equiv.) in acetone (3 mL) at 0 °C was added MeI (206 ◎L, 3.30 mmol, 1.50 equiv.). The reaction mixture was stirred at room temperature for 18 h. The inorganic base was removed by filtration and the volatiles were removed *in vacuo*. Flash column chromatography (*n*-hexane/EtOAc 85:15) afforded 4-fluoro-1-methyl-1*H*-indazole (**3.162**, 173 mg, 1.15 mmol, 53%) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.03 (d, *J* = 0.9 Hz, 1H), 7.27 (ddd, *J* = 8.4, 7.7, 4.9 Hz, 1H), 7.11 (dt, *J* = 7.7, 0.7 Hz, 1H), 6.75 (ddd, *J* = 10.0, 7.7, 0.6 Hz, 1H), 4.03 (s, 3H); **^{19}F {^{1}H} NMR** (376 MHz, $CDCl_3$): δ = -118.2. The analytical data were in accordance with the literature.[73]

1-(4-Bromobenzyl)-1*H*-imidazole

Prepared by Dr. Enrico Emer.

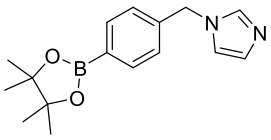


Adapting a known procedure,[74] imidazole (1.50 g, 22.0 mmol, 1.00 equiv.) was added to a solution of NaOH (968 mg, 24.2 mmol, 1.10 equiv.) in DMSO (25 mL). After the reaction mixture was stirred for room temperature for two hours, 1-bromo-4-(bromomethyl)benzene (5.50 mL, 22.0 mmol, 1.00 equiv.) was added and the solution was stirred at room temperature for another 3 hours. After completion, H_2O (25 mL) was added to the mixture and the aqueous solution was extracted with $CHCl_3$ (4 x 25 mL). The combined organic phases were dried over $MgSO_4$, filtered and solvents were removed *in vacuo*. Flash column chromatography (EtOAc) afforded 1-(4-bromobenzyl)-1*H*-imidazole (4.24 g, 17.9 mmol, 81%) as a light yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.56 (s, 1H), 7.49 (d, J = 8.5 Hz, 2H), 7.12 (s, 1H), 7.02 (d, J = 8.6 Hz, 2H), 6.90 (s, 1H), 5.08 (s, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 137.1, 135.0, 131.8, 129.6, 128.6, 121.9, 118.9, 49.7. The analytical data were in accordance with the literature.[75]

1-(4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)-1*H*-imidazole (3.163-Bpin)

Prepared by Dr. Enrico Emer.



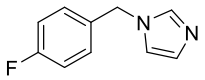
$Pd(dppf)Cl_2$ (172 mg, 0.21 mmol, 0.05 equiv.) was added to a mixture of 1-(4-bromobenzyl)-1*H*-imidazole (1.00 g, 4.22

mmol, 1.33 equiv.), KOAc (1.24 g, 12.6 mmol, 3.00 equiv.) and B_2pin_2 (804 mg, 3.17 mmol, 1.00 equiv.) in DMF (5 mL). The mixture was stirred at 80 °C under N_2 for 14 hours. The insoluble solid was removed by filtration through a Celite pad (eluting with CH_2Cl_2). The filtrate was diluted with H_2O (30 mL) and extracted with CH_2Cl_2 (3 x 30 mL). The combined organic extracts were washed with brine (30 mL), dried over $MgSO_4$ and concentrated *in vacuo* to give the crude product. Flash column chromatography (EtOAc) afforded 1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)-1*H*-imidazole (**3.163-Bpin**, 568 mg, 2.00 mmol, 63%) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.78 (d, J = 8.0 Hz, 2H), 7.60 (s, 1H), 7.20 (s, 1H), 7.13 (d, J = 7.9 Hz, 2H), 7.01 (s, 1H), 5.13 (s, 2H), 1.33 (s, 12H); **^{13}C NMR** (126 MHz, $CDCl_3$): δ = 139.3 (br s), 139.1, 135.3, 130.5 (br s), 128.9 (br s), 126.5, 120.7 (br s), 83.9, 51.1, 24.8; **^{11}B NMR** (128 MHz, $CDCl_3$): δ = 32.0 (br s); **HRMS** (ESI^+): for $C_{16}H_{22}O_2N_2B^+$ $[M+H]^+$ requires m/z = 284.18052; found 284.18076; **IR** (ATR, neat): $\tilde{\nu}$ (cm^{-1}) = 2978.0, 2931.4, 1359.6, 1143.7, 1088.7, 858.0, 656.3; **M.P.**: 118-121 °C.

1-(4-Fluorobenzyl)-1*H*-imidazole (3.163)

Prepared by Dr. Enrico Emer.



Adapting a known procedure,[74] imidazole (3.0 g, 44.1 mmol, 3.00 equiv.) was added to a solution of KOH (11.0 g, 196 mmol, 13.4 equiv.) in DMSO (40 mL). After the reaction mixture was stirred at room temperature for two hours, 1-(bromomethyl)-4-fluorobenzene (1.8 mL, 14.7 mmol, 1.00 equiv.) was added and the solution was stirred for another three hours at room temperature. After

completion, H_2O (40 mL) was added to the mixture and the aqueous solution was extracted with $CHCl_3$ (4 x 40 mL). The combined organic phase was dried over $MgSO_4$, filtered and solvents were removed *in vacuo*. Flash column chromatography (EtOAc) afforded 1-(4-fluorobenzyl)-1*H*-imidazole (**3.163**, 2.00 g, 11.2 mmol, 76%) as a light yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.63 (s, 1H), 7.24-7.19 (m, 2H), 7.13 (s, 1H), 7.11-7.05 (m, 2H), 6.99 (s, 1H), 5.15 (s, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 161.6 (d, J = 246.3 Hz), 136.5 (s), 131.5 (d, J = 3.1 Hz), 128.7 (s), 128.5 (d, J = 8.8 Hz), 118.6 (s), 115.0 (d, J = 20.8 Hz), 49.1 (s); **^{19}F NMR** (376 MHz, $CDCl_3$): δ = -114.0 (m). The analytical data were in accordance with the literature.[76]

1-(4-Bromophenethyl)-2-methyl-1*H*-imidazole

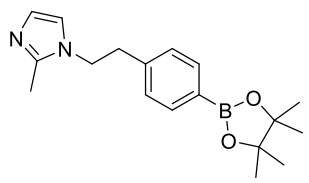
Prepared by Dr. Michael Schedler.

A suspension of 2-methylimidazole (1.64 g, 20.0 mmol, 1.00 equiv.), 4-bromophenethyl bromide (3.00 mL, 20.0 mmol, 1.00 equiv.) and K_2CO_3 (8.30 g, 60.0 mmol, 3.00 equiv.) in dry DMF (15 mL) was heated at 80 °C for two hours. The mixture was allowed to cool to room temperature. H_2O (30 mL) was added and the aqueous phase was extracted with CH_2Cl_2 (3 x 30 mL). Combined organic phases were washed with H_2O (15 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Flash column chromatography (CH_2Cl_2/MeOH 95:5) afforded 1-(4-bromophenethyl)-2-methyl-1*H*-imidazole (1.96 g, 7.40 mmol, 37%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39 (d, *J* = 8.2 Hz, 2H), 6.90 – 6.84 (m, 3H), 6.71 (s, 1H), 4.02 (t, *J* = 6.9 Hz, 2H), 2.93 (t, *J* = 6.9 Hz, 2H), 2.12 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 144.5, 136.5, 131.8, 130.4, 127.4, 120.9, 118.7, 47.2, 36.9, 12.8; **HRMS** (ESI^+): for $C_{12}H_{14}N_2Br^+$ $[M+H]^+$ requires m/z = 265.0335; found 265.0333.

2-Methyl-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenethyl)-1*H*-imidazole (3.164-Bpin)

Prepared by Dr. Michael Schedler.



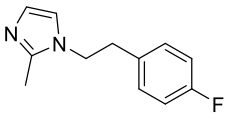
To an oven-dry flask with a magnetic stirrer was added 1-(4-bromophenethyl)-2-methyl-1*H*-imidazole (1.50 g, 5.66 mmol, 1.05 equiv.), B_2pin_2 (1.37 g, 5.39 mmol, 1.00 equiv.), $Pd(dppf)Cl_2.CH_2Cl_2$ (465 mg, 0.57 mmol, 0.10 equiv.) and KOAc (1.66 g, 17.0 mmol, 3.00 equiv.). A rubber septum was added, and the flask was purged with argon. Dry, degassed 1,4-dioxane (25 mL) was added. The mixture was heated to 80 °C and stirred at this temperature for 16 hours. After cooling to room temperature, the mixture was diluted with EtOAc and filtered through a short plug of Celite, eluting with EtOAc. The solvent was removed *in vacuo* to afford crude title compound, which was purified by flash column chromatography (EtOAc/MeOH 100:0 to 90:10) to afford 2-methyl-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenethyl)-1*H*-imidazole (**3.164-Bpin**, 613 mg, 1.96 mmol, 36% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.72 (d, *J* = 7.9 Hz, 2H), 7.05 (d, *J* = 7.9 Hz, 2H), 6.90 (d, *J* = 1.2 Hz, 1H), 6.72 (d, *J* = 1.2 Hz, 1H), 4.06 (t, *J* = 7.1 Hz, 2H), 3.00 (t, *J* = 7.1 Hz,

2H), 2.17 (s, 3H), 1.34 (s, 12H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 144.4, 140.5, 135.2, 128.1, 126.6, 118.8, 83.8, 47.4, 37.6, 24.8, 12.5; **HRMS** (ESI^+): for $C_{18}H_{26}BN_2O_2^+$ $[M+H]^+$ requires m/z = 313.2082; found 313.2076; **IR** (ATR, neat) $\tilde{\nu}$ (cm^{-1}) = 2979, 1612, 1397, 1358, 1322, 1272, 1144, 1090, 858, 658; **M.P.** 89 °C.

1-(4-Fluorophenethyl)-2-methyl-1*H*-imidazole (3.164)

Prepared by Dr. Michael Schedler.



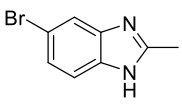
A suspension of 2-methylimidazole (164 mg, 2.00 mmol, 1.0 equiv.), 4-fluorophenethyl bromide (364 μL, 2.60 mmol, 1.30 equiv.) and K_2CO_3 (828 mg, 6.00 mmol, 3.00 equiv.) in dry DMF (2.0 mL) was heated at 80 °C for 18 hours. The mixture was allowed to cool to room temperature. H_2O (10 mL) was added and the aqueous phase was extracted with CH_2Cl_2 (3 x 15 mL). Combined organic phases were washed with H_2O (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Flash column chromatography (CH_2Cl_2/MeOH 95:5) afforded 1-(4-fluorophenethyl)-2-methyl-1*H*-imidazole (**3.164**, 171 mg, 0.84 mmol, 42%) as a colourless solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.98 – 6.91 (m, 4H), 6.88 (s, 1H), 6.71 (s, 1H), 4.01 (t, *J* = 6.9 Hz, 2H), 2.94 (t, *J* = 6.9 Hz, 2H), 2.10 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 161.9 (d, *J* = 245.4 Hz), 144.5, 133.2 (d, *J* = 3.3 Hz), 130.2 (d, *J* = 7.9 Hz), 127.3, 118.7, 115.5 (d, *J* = 21.3 Hz), 47.5, 36.6, 12.7; **^{19}F NMR** (376 MHz, $CDCl_3$): δ = -115.7 – -115.8 (m). **HRMS** (ESI^+): for $C_{12}H_{14}FN_2^+$ $[M+H]^+$ requires m/z = 205.1136; found 205.1133;

IR (ATR, neat) $\tilde{\nu}$ (cm^{-1}) = 2927, 1602, 1510, 1423, 1278, 1220, 1159, 984, 826, 726, 676; **M.P.** 57-58 °C.

5-Bromo-2-methyl-1*H*-benzo[*d*]imidazole

Prepared by Dr. Enrico Emer.

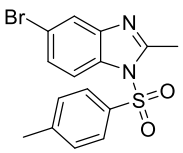


Adapting a known procedure,[77] 4-bromobenzene-1,2-diamine (3.00 g, 16.05 mmol, 1.00 equiv.) and glacial acetic acid (15 mL) were refluxed for two hours. Ice and KOH were added to bring pH to 8.0, and the resulting solid was filtered and collected. 5-Bromo-2-methyl-1*H*-benzo[*d*]imidazole (2.31 g, 10.9 mmol, 68%) was obtained without further purification as an orange solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.38 (br s, 1H), 7.64 (s, 1H), 7.40 (d, J = 8.4 Hz, 1H), 7.23 (dd, J = 8.5, 1.9 Hz, 1H), 2.47 (s, 3H); **^{13}C NMR** (101 MHz, DMSO-d_6): δ = 152.8, 140.8, 137.6, 123.8, 117.1, 115.7, 113.3, 14.6. The analytical data were in accordance with the literature.[78]

5-Bromo-2-methyl-1-tosyl-1*H*-benzo[*d*]imidazole

Prepared by Dr. Enrico Emer.



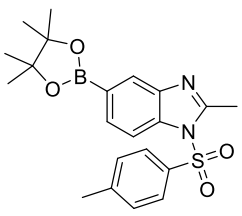
Adapting a known procedure,[79] a solution of 5-bromo-2-methyl-1*H*-benzo[*d*]imidazole (441 mg, 2.10 mmol, 1.00 equiv.) and Et_3N (321 µl, 2.30 mmol, 1.10 equiv.) in acetone (5 mL) was added dropwise to a solution of *p*-toluenesulfonyl chloride (439 mg, 2.30 mmol, 1.10 equiv.) in acetone (8 mL). The

reaction mixture was stirred at room temperature for 4 hours, then concentrated under reduced pressure as a mixture of 6-bromo-2-methyl-1-tosyl-1*H*-benzo[*d*]imidazole and 5-bromo-2-methyl-1-tosyl-1*H*-benzo[*d*]imidazole. Flash column chromatography (*n*-hexane/EtOAc 80:20) followed by recrystallisation from Et_2O/*n*-hexane afforded 5-bromo-2-methyl-1-tosyl-1*H*-benzo[*d*]imidazole (236 mg, 0.64 mmol, 31%) as a white solid.

^{1}H NMR (400 MHz; $CDCl_3$): δ = 8.23 (s, 1H), 7.81 (d, *J* = 8.4 Hz, 2H), 7.50 (d, *J* = 8.5 Hz, 1H), 7.44 (dd, *J* = 8.4, 1.7 Hz, 1H), 7.33 (d, *J* = 8.0 Hz, 2H), 2.77 (s, 3H), 2.42 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$): δ = 146.3, 141.1, 135.1, 130.4, 127.9, 126.8, 120.8, 118.1, 116.6, 21.7, 16.9; two carbon atoms were not observed; **HRMS** (ESI^+): for $C_{15}H_{14}BrN_2O_2S^+$ $[M+H]^+$ requires m/z = 364.99539; found 364.99472 ; **IR** (ATR, neat): $\tilde{\nu}$ (cm^{-1}) = 3103, 3067, 2924, 1608, 1596, 1426, 1372, 1269, 1170, 1090, 1001, 931, 812, 715, 663; **M.P.**: 140-143 °C.

2-Methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-tosyl-1*H*-benzo[*d*]imidazole (3.166-Bpin)

Prepared by Dr. Enrico Emer.



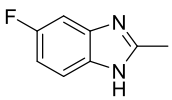
$Pd(dppf)Cl_2$ (94 mg, 0.115 mmol, 0.05 equiv.) was added to a mixture of 5-bromo-2-methyl-1-tosyl-1*H*-benzo[*d*]imidazole (839 mg, 2.30 mmol, 1.00 equiv.), KOAc (676 mg, 6.89 mmol, 3.00 equiv.) and B_2pin_2 (642 mg, 2.53 mmol, 1.10 equiv.) in DMF (8 mL). The mixture was stirred at 80 °C under N_2 for 20 hours. The reaction mixture was cooled to room

temperature and concentrated *in vacuo*. The residue was diluted with H2O (20 mL) and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic extracts were washed with brine (20 mL), dried over $MgSO_4$ and concentrated *in vacuo* to give the crude product. Flash column chromatography (cyclohexane/EtOAc 70:30) afforded 2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-tosyl-1*H*-benzo[*d*]imidazole (**3.166-Bpin**, 190 mg, 0.46 mmol, 20%) as a white solid.

^{1}H NMR (400 MHz; $CDCl_3$): δ = 8.49 (t, *J* = 0.8 Hz, 1H), 7.83 (d, *J* = 8.4 Hz, 2H), 7.78 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.61 (dd, *J* = 8.0, 0.7 Hz, 1H), 7.30 (d, *J* = 8.0 Hz, 2H), 2.80 (s, 3H), 2.39 (s, 3H), 1.38 (s, 12H); **^{13}C NMR** (126 MHz, $CDCl_3$): δ = 152.3, 145.9, 144.2, 135.4, 133.1, 131.0, 130.2, 126.8, 119.7, 118.9, 83.9, 24.9, 21.6, 17.0; carbon adjacent to boron was not observed; **^{11}B NMR** (128 MHz, $CDCl_3$): δ = 31.4 (br s); **HRMS** (ESI^+): for $C_{21}H_{26}BN_2O_4S^+$ $[M+H]^+$ requires m/z = 413.17008; found 413.17010; **IR** (ATR, neat): $\tilde{\nu}$ (cm^{-1}) = 3064, 2979, 2930, 1597, 1547, 1372, 1238, 1216, 1189, 1172, 1144, 857, 710, 664; **M.P.**: 134-136 °C.

5-Fluoro-2-methyl-1*H*-benzo[*d*]imidazole

Prepared by Dr. Enrico Emer.



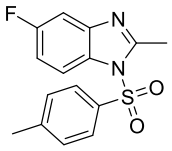
Adapting a known procedure,[77] 4-fluorobenzene-1,2-diamine (1.00 g, 7.94 mmol, 1.00 equiv.) and glacial acetic acid (10 mL) were refluxed for two hours. Ice and KOH were added to bring pH to 8.0, and the resulting solid was filtered and collected. 5-Fluoro-2-methyl-1*H*-benzo[*d*]imidazole

(763 mg, 5.09 mmol, 64%) was obtained without further purification as an orange solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.32-12.26 (m, 1H), 7.43-7.39 (m, 1H), 7.26-7.23 (m, 1H), 6.94 (ddd, J = 9.9, 8.8, 2.4 Hz, 1H), 2.46 (d, J = 6.8 Hz, 3H); **^{19}F NMR** (376 MHz, DMSO-d_6): δ = -122.2. The analytical data were in accordance with the literature.[6]

5-Fluoro-2-methyl-1-tosyl-1*H*-benzo[*d*]imidazole (3.166)

Prepared by Dr. Enrico Emer.



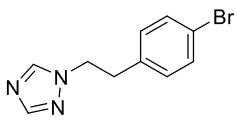
Adapting a known procedure,[79] a solution of 5-fluoro-2-methyl-1*H*-benzo[*d*]imidazole (224 mg, 1.49 mmol, 1.00 equiv.) and Et_3N (230 µl, 1.64 mmol, 1.10 equiv.) in acetone (4 mL) was added dropwise to a solution of *p*-toluenesulfonyl chloride (313 mg, 1.64 mmol, 1.10 equiv.) in acetone (7 mL). The reaction mixture was stirred at room temperature for four hours, then concentrated in vacuo to afford a mixture of 6-fluoro-2-methyl-1-tosyl-1*H*-benzo[*d*]imidazole and 5-fluoro-2-methyl-1-tosyl-1*H*-benzo[*d*]imidazole. Flash column chromatography (*n*-hexane/EtOAc 80:20) followed by recrystallisation from Et_2O/*n*-hexane afforded 5-fluoro-2-methyl-1-tosyl-1*H*-benzo[*d*]imidazole (**3.166**, 150 mg, 0.49 mmol, 33%) as a yellow solid.

^{1}H NMR (400 MHz; $CDCl_3$): δ = 7.71-7.69 (m, 2H), 7.67-7.64 (m, 1H), 7.43 (dd, J = 8.8, 4.9 Hz, 1H), 7.19 (dd, J = 8.6, 0.6 Hz, 2H), 6.94 (ddd, J = 9.2, 8.8, 2.5 Hz, 1H), 2.67 (s, 3H), 2.27 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 160.5 (d, J = 242.0 Hz), 151.6, 146.2,

138.0, 134.9, 133.2 (d, *J* = 12.8 Hz), 130.2, 126.7, 120.1 (d, *J* = 9.7 Hz), 112.4 (d, *J* = 24.3 Hz), 100.9 (d, *J* = 30.2 Hz), 21.5, 16.7; **^{19}F NMR** (377 MHz; $CDCl_3$): δ = -115.8 (td, *J* = 9.2, 4.8 Hz); **HRMS** (ESI^+): for $C_{15}H_{14}FN_2O_2S^+$ $[M+H]^+$ requires m/z = 305.07545; found 305.07538 ; **IR** (ATR, neat): $\tilde{\nu}$ (cm^{-1}) = 3091, 2927, 1620, 1598, 1557, 1478, 1438, 1374, 1275, 1190, 1175, 1147, 813, 705, 665; **M.P**.: 105-110°C.

1-(4-Bromophenethyl)-1*H*-1,2,4-triazole

Prepared by Dr. Michael Schedler.

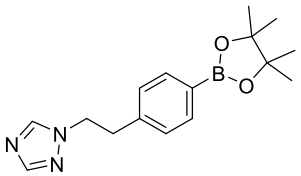


1*H*-1,2,4-Triazole (346 mg, 5.00 mmol, 1.00 equiv.), 4-bromophenethyl bromide (843 µL, 5.50 mmol, 1.10 equiv.) and K_2CO_3 (760 mg, 5.50 mmol, 1.10 equiv.) were suspended in anhydrous THF (10 mL) and stirred at 65 °C for 16 hours. The reaction was stopped by addition of H_2O (50 mL) and extracted with CH_2Cl_2 (3 x 50 mL). The combined organic phases were washed with brine, dried with $MgSO_4$, filtered and all volatiles were removed *in vacuo*. Purification of the residue by flash column chromatography on silica (*n*-pentane/EtOAc 33:67 to 0:100) yielded 1-(4-bromophenethyl)-1*H*-1,2,4-triazole (462 mg, 1.83 mmol, 37%) as a colourless solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.97 (s, 1H), 7.78 (s, 1H), 7.41–7.38 (m, 2H), 6.91–6.88 (m, 2H), 4.37 (t, *J* = 6.9 Hz, 2H), 3.14 (t, *J* = 6.9 Hz, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 152.3, 143.3, 136.2, 132.0, 130.4, 121.1, 50.9, 35.7; **HRMS** (ESI^+) for $C_{10}H_{11}N_3Br^+$ $[M+H]^+$ requires m/z = 252.01309, found 225.01319; **IR** (ATR, neat) $\tilde{\nu}$ (cm^{-1}) = 3124, 2650, 1488, 1265, 1145, 1005, 803, 745, 678, 650; **M.P.**: 71 °C.

1-(4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)phenethyl)-1*H*-1,2,4-triazole (3.167-Bpin)

Prepared by Dr. Michael Schedler.

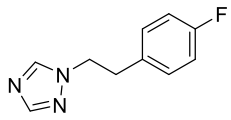


Modifying a known procedure,[37] 1-(4-bromophenethyl)-1*H*-1,2,4-triazole (264 mg, 1.05 mmol, 1.05 equiv.), B_2pin_2 (254 mg, 1.00 mmol, 1.0 equiv.), $Pd(dppf)Cl_2.CH_2Cl_2$ (24.5 mg, 0.030 mmol, 0.030 equiv.) and KOAc (294 mg, 3.00 mmol, 3.00 equiv.) were suspended in anhydrous and degassed 1,4-dioxane (5 mL). The mixture was stirred at 80 °C for 15 hours. The mixture was allowed to cool to room temperature, diluted with CH_2Cl_2 and filtered. All volatiles were removed *in vacuo* and the residue was purified by flash column chromatography on silica (*n*-pentane/EtOAc 50:50 to 33:67) yielding 1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenethyl)-1*H*-1,2,4-triazole (**3.167-Bpin**, 50.6 mg, 0.169 mmol, 16%) as a colourless solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.93 (br s, 1H), 7.72–7.70 (m, 3H), 7.04 (d, J = 7.7 Hz, 2H), 4.38 (t, J = 7.0 Hz, 2H), 3.17 (t, J = 7.0 Hz, 2H), 1.32 (s, 12H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 152.2, 143.3, 140.4, 135.4, 128.1, 83.9, 51.1, 36.5, 25.0; **^{11}B NMR** (128 MHz, $CDCl_3$): δ = 31.0; **HRMS** (ESI^+) for $C_{16}H_{23}O_2N_3B_1^+$ $[M+H]^+$ requires m/z = 300.18778, found 300.18797; **IR** (ATR, neat) $\tilde{\nu}$ (cm^{-1}) = 3110, 2981, 1611, 1508, 1358, 1141, 1087, 858, 653; **M.P.**: 129 °C.

1-(4-Fluorophenethyl)-1*H*-1,2,4-triazole (3.167)

Prepared by Dr. Michael Schedler.

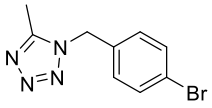


1*H*-1,2,4-Triazole (69.1 mg, 1.00 mmol, 1.00 equiv.), 4-fluorophenethyl bromide (154 µL, 1.10 mmol, 1.10 equiv.) and K_2CO_3 (152 mg, 1.10 mmol, 1.10 equiv.) were suspended in anhydrous THF (2 mL) and stirred at 65 °C for 16 hours. The reaction was stopped by addition of H_2O (10 mL) and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic phases were washed with brine, dried with $MgSO_4$, filtered and all volatiles were removed *in vacuo*. Purification of the residue by flash column chromatography on silica (*n*-pentane/EtOAc 33:67 to 0:100) yielded 1-(4-fluorophenethyl)-1*H*-1,2,4-triazole (**3.167**, 91.8 mg, 0.480 mmol, 48%) as a colourless solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.97 (s, 1H), 7.78 (s, 1H), 7.00–6.93 (m, 4H), 4.37 (t, *J* = 6.9 Hz, 2H), 3.15 (t, *J* = 6.9 Hz, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 162.0 (d, *J* = 245.5 Hz), 152.3 (s), 143.3 (s), 132.9 (d, *J* = 3.4 Hz), 130.2 (d, *J* = 8.0 Hz), 115.8 (d, *J* = 21.5 Hz), 51.2 (s), 35.5 (s); **^{19}F NMR** (376 MHz, $CDCl_3$): δ = –115.5 (tt, *J* = 8.1, 5.9 Hz); **HRMS** (ESI^+) for $C_{10}H_{11}N_3F^+$ $[M+H]^+$ requires m/z = 192.09315, found 192.09318; **IR** (ATR, neat) $\tilde{\nu}$ (cm^{-1}) = 3118, 1506, 1268, 1218, 1142, 858, 827, 791, 678, 647; **M.P.**: 37 °C.

1-(4-Bromobenzyl)-5-methyl-1*H*-tetrazole

Prepared by Dr. Michael Schedler.

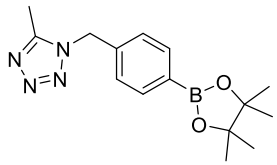


Adapting a known procedure,[24] 5-methyl-1*H*-tetrazole (500 mg, 5.95 mmol, 1.00 equiv.) and K_2CO_3 (987 mg, 7.14 mmol, 1.20 equiv.) were suspended in acetone (20 mL). 4-Bromobenzyl bromide (1.78 g, 7.14 mmol, 1.20 equiv.) was added and the mixture was stirred at 50 °C for two hours. The mixture was allowed to cool to room temperature and all volatiles were removed *in vacuo*. The residue was dissolved in H_2O (50 mL) and the mixture was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic phases were dried with $MgSO_4$, filtered and all volatiles were removed *in vacuo*. The residue was purified by flash column chromatography on silica (*n*-pentane/EtOAc 50:50) yielding 1-(4-bromobenzyl)-5-methyl-1*H*-tetrazole (747 mg, 2.95 mmol, 50%) as an off-white solid.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.77–7.48 (m, 2H), 7.12–7.05 (m, 2H), 5.45 (s, 2H), 2.46 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ =151.7, 132.7, 132.2 129.3, 123.4, 50.4, 9.2; **HRMS** (ESI^+) for $C_9H_{10}N_4Br^+$ $[M+H]^+$ requires m/z = 253.00834, found 253.00847; **IR** (ATR, neat) $\tilde{\nu}$ (cm^{-1}) = 1518, 1488, 1395, 1071, 1011, 761, 659; **M.P.**: 79°C.

5-Methyl-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)-1*H*-tetrazole (3.168-Bpin)

Prepared by Dr. Michael Schedler.

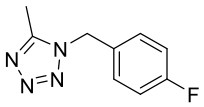


Modifying a known procedure,[37] 1-(4-bromobenzyl)-5-methyl-1*H*-tetrazole (500 mg, 1.98 mmol, 1.05 equiv.), B_2pin_2 (480 mg, 1.89 mmol, 1.00 equiv.), $Pd(dppf)Cl_2$ (41.4 mg, 0.0566 mmol, 0.030 equiv.) and KOAc (555 mg, 5.66 mmol, 3.00 equiv.) were suspended in anhydrous and degassed 1,4-dioxane (10 mL). The mixture was stirred at 80 °C for 16 hours. The mixture was allowed to cool to room temperature, diluted with CH_2Cl_2 and filtered. All volatiles were removed *in vacuo* and the residue was purified by recrystallization from CH_2Cl_2/*n*-hexane yielding 5-methyl-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)-1*H*-tetrazole (**3.168-Bpin**, 491 mg, 1.64 mmol, 87%) as an off-white, grey solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.80 (d, J = 7.8 Hz, 2H), 7.17 (d, J = 7.7 Hz, 2H), 5.51 (s, 2H), 2.41 (s, 3H), 1.33 (s, 12H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 151.8, 136.0, 135.8, 126.8, 84.2, 51.1, 25.0, 9.1; **^{11}B NMR** (128 MHz, $CDCl_3$): δ = 31.0; **HRMS** (ESI^+): for $C_{15}H_{21}BN_2O_2$ $[M+H]^+$ requires m/z = 301.18303; found 301.18309; **IR** (ATR, neat): $\tilde{\nu}$ (cm^{-1}) = 2982, 1402, 1360, 1268, 1142, 1089, 859, 824, 776, 721, 697, 651; **M.P.**: 126 °C.

1-(4-Fluorobenzyl)-5-methyl-1*H*-tetrazole (3.168)

Prepared by Dr. Michael Schedler.

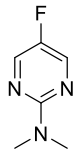


Adapting a known procedure,[24] 5-methyl-1*H*-tetrazole (250 mg, 2.98 mmol, 1.00 equiv.) and K_2CO_3 (493 mg, 3.57 mmol, 1.20 equiv.) were suspended in acetone (10 mL). 4-Fluorobenzyl bromide (444 µL, 3.57 mmol, 1.20 equiv.) was added and the mixture was stirred at 50 °C for two hours. The mixture was allowed to cool to room temperature and all volatiles were removed *in vacuo*. The residue was dissolved in H_2O (20 mL) and the mixture was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic phases were dried with $MgSO_4$, filtered and all volatiles were removed *in vacuo*. The residue was purified by flash column chromatography on silica (*n*-pentane/EtOAc 50:50) yielding 1-(4-fluorobenzyl)-5-methyl-1*H*-tetrazole (**3.168**, 226 mg, 1.27 mmol, 43%) as a colourless solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.22 (dd, J = 8.4, 5.1 Hz, 2H), 7.05 (t , J = 8.5 Hz, 2H), 5.46 (s, 2H), 2,45 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 163.0 (d, J = 248.9 Hz), 151.6 (s), 129.6 (d, J = 8.4 Hz), 129.1 (d, J = 3.4 Hz), 116.4 (d, J = 21.9 Hz). 50.3 (s), 9.1 (s); **^{19}F NMR** (376 MHz, $CDCl_3$): δ = –112.1 (dt, J = 8.6, 4.4 Hz); **HRMS** (ESI$^+$) for $C_9H_{10}FN_4^+$ $[M+H]^+$ requires m/z = 193.08840, found 193.08855; **IR** (ATR, neat) $\tilde{\nu}$ (cm^{-1}) = 3068, 1605, 1532, 1508, 1429, 1362, 1317, 1251, 1218, 1160, 1121, 1084, 1049, 1011, 991, 921, 838, 820; 777; 694, 675, 627; **M.P.**: 61 °C.

5-Fluoro-N,N-dimethylpyrimidin-2-amine (3.173)

Prepared by Dr. Sean Preshlock.

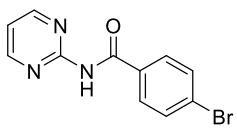


A mixture of 2-chloro-5-fluoropyrimidine (500 mg, 3.8 mmol, 1.0 equiv.) and diethanolamine (994 mg, 9.5 mmol, 2.5 equiv.) in DMF (2 mL) was heated to 130 °C. After 5.5 hours, the product and DMF was distilled under reduced pressure. The collected fraction was diluted in 50 mL of water and loaded onto an Oasis HLB Plus LP Extraction Cartridge. The cartridge was flushed with 2 mL of deionized water and 2 mL of air. The product was eluted with 1 mL $CDCl_3$ and an additional 2 mL of air and the filtrate was concentrated *in vacuo* (bath temp < 30 °C). The residue was re-dissolved in Et_2O and washed three times with brine, dried ($MgSO_4$) and filtered. The filtrated was concentrated *in vacuo* (bath temp < 30 °C) to afford a volatile solid; yield could not be accurately determined.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.19 (s, 2H), 3.15 (s, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 159.5 (s), 151.4 (d, *J* = 246.4 Hz), 145.0 (d, *J* = 21.5 Hz), 37.6 (s); **^{19}F NMR** (376 MHz, $CDCl_3$): δ = –159.16; **HRMS** (ESI) for $C_6H_9N_3F$ $[M+H]^+$ requires 142.07750 found 142.07747; **IR** (ATR, neat) $\tilde{\nu}$ (cm^{-1}) = 2917, 2849, 1556, 1538, 1411, 1386, 1243, 820, 784; **M.P.** Could not be determined due to volatility.

4-Bromo-*N*-(pyrimidin-2-yl)benzamide

Prepared by Dr. Michael Schedler.



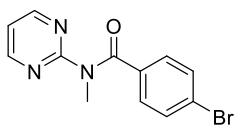
Adapting a known procedure,[45] 2-aminopyrimidine (1.00 g, 10.5 mmol, 1.00 equiv.) was dissolved in anhydrous pyridine (20

mL) and the solution was cooled to 0 °C. 4-Bromobenzoyl chloride (2.30 g, 10.5 mmol, 1.00 equiv.) was added to the reaction and the mixture was warmed to room temperature and stirred for 15 hours. The reaction was then stopped by addition of H_2O (50 mL) and the mixture was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic phases were dried with $MgSO_4$, filtered and all volatiles were removed *in vacuo*. Purification of the residue by flash column chromatography on silica (EtOAc) yielded 4-bromo-*N*-(pyrimidin-2-yl)benzamide (1.88 g, 6.76 mmol, 64%) as an off-white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.82 (br s, 1H), 8.67–8.61 (m, 2H), 7.85–7.78 (m, 2H), 7.66–7.60 (m, 2H), 7.70 (tt, *J* = 4.9, 1,3 Hz, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 164.5, 158.4, 157.8, 133.3 132.0 129.3, 127.2, 117.0; **HRMS** (ESI^+) for $C_{11}H_9BrNO_3^+$ $[M+H]^+$ requires m/z = 277.99235, found 277.99256; **IR** (ATR, neat) $\tilde{\nu}$ (cm^{-1}) = 3305, 3034, 1674, 1569, 1508, .1425, 1274, 794, 657; **M.P.**: 112 °C.

4-Bromo-*N*-methyl-*N*-(pyrimidin-2-yl)benzamide

Prepared by Dr. Michael Schedler.



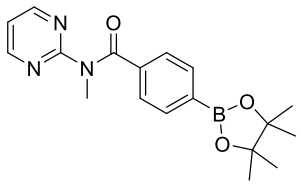
Adapting a known procedure,[80] 4-bromo-*N*-(pyrimidin-2-yl)benzamide (625 mg, 2.25 mmol, 1.00 equiv) and Cs_2CO_3 (734 mg, 2.25 mmol, 1.00 equiv.) were suspended in DMF (25 mL). MeI (281 µL, 5.50 mmol, 2.00 equiv.) was added to the reaction and the mixture was stirred at room temperature for 6 hours. The reaction was stopped by addition of H_2O (60 mL) and the mixture was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic phases

were washed with brine, dried with $MgSO_4$, filtered and all volatiles were removed *in vacuo*. Purification of the residue by flash column chromatography on silica (*n*-pentane/EtOAc 50:50) yielded 4-bromo-*N*-methyl-*N*-(pyrimidin-2-yl)benzamide (490 mg, 1.68 mmol, 75%) as an off-white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.45 (br s, 2H), 7.39–7.36 (m, 2H), 7.24–7.21 (m, 2H), 6.95 (t, *J* = 4.7 Hz, 1H), 3.65 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 171.5, 162.4, 157.9, 136.3, 131.4, 129.8, 124.8, 117.0, 35.0; **HRMS** (ESI^+) for $C_{12}H_{11}BrN_3O^+$ $[M+H]^+$ requires m/z = 292.00800, found 292.00819; **IR** (ATR, neat) $\tilde{\nu}$ (cm−1) = 3077, 3047, 1980, 1898, 1655, 1562, 1477, 1435, 1398, 1338, 1281, 1190, 1136, 1097, 1069, 1007, 950, 884, 827, 749; **M.P.**: 76 °C.

_N_-Methyl-_N_-(pyrimidin-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (3.174-Bpin)

Prepared by Dr. Michael Schedler.



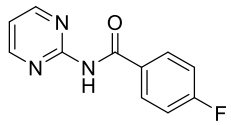
Modifying a known procedure,[37] 4-bromo-*N*-methyl-*N*-(pyrimidin-2-yl)benzamide (242 mg, 0.827 mmol, 1.05 equiv.), B_2pin_2 (200 mg, 0.788 mmol, 1.00 equiv.), $Pd(dppf)Cl_2$ (21.0 mg, 0.0286 mmol, 0.030 equiv.) and KOAc (280 mg, 2.86 mmol, 3.00 equiv.) were suspended in anhydrous and degassed 1,4-dioxane (4 mL). The mixture was stirred at 80 °C for 17 hours. The mixture was allowed to cool to room temperature, diluted with CH_2Cl_2 and filtered. All volatiles were removed *in vacuo* and the residue was purified by recrystallization from CH_2Cl_2/*n*-hexane yielding *N*-methyl-

N-(pyrimidin-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (**3.174-Bpin**, 199 mg, 0.587 mmol, 74%) as a slightly brown solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.39 (d, *J* = 4.9 Hz, 2H), 7.65 (d, *J* = 7.8 Hz, 2H), 7.33 (d, *J* = 7.8 Hz, 2H), 6.89 (t, *J* = 4.9 Hz, 1H), 3.65 (s, 3H), 1.31 (s, 12H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 172.4, 162.6, 157.8, 139.7, 134.4, 137.3, 116.9, 84.1, 34.9, 25.0; **^{11}B NMR** (128 MHz, $CDCl_3$): δ = 30.8; **HRMS** (ESI^+) for $C_{18}H_{23}BN_3O_3^+$ $[M+H]^+$ requires m/z = 340.18270, found 340.18278; **IR** (ATR, neat) $\tilde{\nu}$ (cm^{-1}) = 2979, 1660, 1567, 1445, 1395, 1328, 1271, 1137, 1086, 1007, 959, 849, 811, 742, 659; **M.P.**: 123 °C.

4-Fluoro-*N*-(pyrimidin-2-yl)benzamide

Prepared by Dr. Michael Schedler.

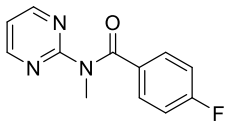


Adapting a known procedure,[45] 2-aminopyrimidine (190 mg, 2.00 mmol, 1.00 equiv.) was dissolved in anhydrous pyridine (4 mL) and the solution was cooled to 0 °C. 4-Fluorobenzoyl chloride (370 mg, 2.00 mmol, 1.00 equiv.) was added to the reaction and the mixture was warmed to room temperature and stirred for 15 hours. Afterwards, the reaction was stopped by addition of H_2O (50 mL) and the mixture was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic phases were dried with $MgSO_4$, filtered and all volatiles were removed *in vacuo*. Purification of the residue by flash column chromatography on silica (EtOAc) yielded 4-fluoro-*N*-(pyrimidin-2-yl)benzamide (332 mg, 1.53 mmol, 76%) as a colourless solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ =8.97 (br s, 1H), 8.58 (d, *J* = 4.9 Hz, 2H), 7.95 (dd, *J* =8.7, 5.4 Hz, 2H), 7.14 (t, *J* = 8.5 Hz, 2H), 7.02 (t, *J* = 4.9 Hz, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 165.3 (d, *J* = 253.6 Hz), 164.2 (s), 158.5 (s), 157.9 (s), 130.6 (d, *J* = 3.1 Hz), 130.2 (d, *J* = 9.1 Hz), 117.0 (s), 116.0 (d, *J* = 22.0 Hz); **^{19}F NMR** (376 MHz, $CDCl_3$): δ = –106.4 (ddd, *J* = 13.5, 8.5, 5.1 Hz); **HRMS** (ESI^+) for $C_{11}H_9ON_3F^+$ $[M+H]^+$ requires m/z = 218.07242, found 218.07248; **IR** (ATR, neat) $\tilde{\nu}$ (cm^{-1}) = 3207, 3058, 1697, 1592, 1503, 1437, 1417, 1330, 1278, 1227, 1154, 1079, 904, 872, 847, 795, 756, 730, 633; **M.P.**: 119 °C.

4-Fluoro-*N*-methyl-*N*-(pyrimidin-2-yl)benzamide (3.174)

Prepared by Dr. Michael Schedler.

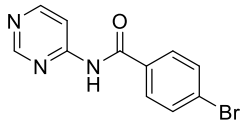


4-Fluoro-*N*-(pyrimidin-2-yl)benzamide (292 mg, 1.35 mmol, 1.00 equiv) and Cs_2CO_3 (439 mg, 1.35 mL, 1.00 equiv.) were suspended in DMF (10 mL). MeI (168 µL, 2.69 mmol, 2.00 equiv.) was added to the mixture and the reaction was stirred at room temperature for two hours. The reaction was then stopped by addition of H_2O (50 mL) and the mixture was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic phases were washed with brine, dried with $MgSO_4$, filtered and all volatiles were removed *in vacuo*. Purification of the residue by flash column chromatography on silica (*n*-pentane/EtOAc 50:50) yielded 4-fluoro-*N*-methyl-*N*-(pyrimidin-2-yl)benzamide (**3.174**, 208 mg, 0.900 mmol, 67%) as a colourless solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.42 (d, J = 4.8 Hz, 2H), 7.37–7.33 (m, 2H), 6.93–6.88 (m, 3H), 3.64 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 171.3 (s), 163.9 (d, J = 248.7 Hz), 162.6 (s), 157.8 (s), 133.3 (d, J = 3.4 Hz), 130.4 (d, J = 8.8 Hz), 116.9 (s), 115.2 (d, J = 21.9 Hz), 35.0 (s); **^{19}F NMR** (376 MHz, $CDCl_3$): δ = –109.5 (ddd, J = 14.1, 9.0, 5.4 Hz); **HRMS** (ESI^+) for $C_{12}H_{11}FN_3O^+$ $[M+H]^+$ requires m/z = 232.08807, found 232.08805; **IR** (ATR, neat) $\tilde{\nu}$ (cm^{-1}) = 3044, 2935, 1644, 1560, 1398, 1358, 1329, 1223, 853, 812, 756; **M.P.**: 81 °C.

4-Bromo-*N*-(pyrimidin-4-yl)benzamide

Prepared by Dr. Michael Schedler.



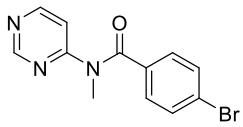
Adapting a known procedure,[45] 4-aminopyrimidine (250 mg, 2.63 mmol, 1.00 equiv.) was dissolved in anhydrous pyridine (5 mL) and the solution was cooled to 0 °C. 4-Bromobenzoyl chloride (576 mg, 2.63 mmol, 1.00 equiv.) was added to the reaction and the mixture was warmed to room temperature and stirred for 15 hours. The reaction was then stopped by addition of H_2O (30 mL) and the mixture was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic phases were dried with $MgSO_4$, filtered and all volatiles were removed *in vacuo*. Purification of the residue by flash column chromatography on silica (*n*-pentane/EtOAc 50:50) yielded 4-bromo-*N*-(pyrimidin-4-yl)benzamide (349 mg, 1.26 mmol, 48%) as a colourless solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.88 (br s, 1H), 8.70–8.65 (m, 2H), 8.31 (dd, J = 5.8, 1.3 Hz, 1H), 7.81–7.77 (m, 2H), 7.69–7.65 (m, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ =

165.4, 158.8, 158.6, 157.3, 132.5, 132.2, 129.0, 128.2, 110.6; **HRMS** (ESI^+) for $C_{11}H_9BrN_3O^+$ $[M+H]^+$ requires m/z = 277.99235, found 277.99240; **IR** (ATR, neat) $\tilde{\nu}$ (cm^{-1}) = 3213, 3152, 3063, 1681, 1572, 1508, 1483, 1391, 1299, 1262, 1181, 1100, 1070, 1010; 993; 890; 836; 775; 742; 671; **M.P.**: 142 °C.

4-Bromo-*N*-methyl-*N*-(pyrimidin-4-yl)benzamide

Prepared by Dr. Michael Schedler.



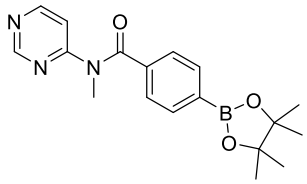
Adapting a known procedure,[80] 4-bromo-*N*-(pyrimidin-4-yl)benzamide (967 mg, 3.48 mmol, 1.00 equiv) and Cs_2CO_3 (1.25 g, 3.83 mmol, 1.10 equiv.) were suspended in DMF (25 mL). MeI (435 µL, 6.96 mmol, 2.00 equiv.) was added to the reaction and the mixture was stirred at room temperature for 17 hours. The reaction was stopped by addition of water (30 mL) and the mixture was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic phases were dried with $MgSO_4$, filtered and all volatiles were removed *in vacuo*. Purification of the residue by flash column chromatography on silica (*n*-pentane/EtOAc 33:67) yielded 4-bromo-*N*-methyl-*N*-(pyrimidin-4-yl)benzamide (352 mg, 1.21 mmol, 35%) as an off-white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.28 (br s, 1H), 8.11–8.08 (m, 2H), 7.98 (d, J = 6.6 Hz, 1H), 7.87 (dd, J = 6.6, 1.1 Hz, 1H), 7.57–7.53 (m, 2H), 3.75 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 175.2, 158.2, 153.0, 151.1, 136.5, 131.4, 131.3, 126.9, 114.3, 37.9; **HRMS** (ESI^+) for $C_{12}H_{11}BrN_3O^+$ $[M+H]^+$ requires m/z = 292.00800, found 292.00812; **IR** (ATR,

neat) $\tilde{\nu}$ (cm−1) = 3148, 3027, 1914, 1636, 1601, 1586, 1526, 1414, 1384, 1342, 1281, 1262, 1198, 1156, 1096, 1079, 1065, 1008, 882, 864, 833, 795, 757; **M.P.**: 102 °C.

_N_-Methyl-_N_-(pyrimidin-4-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (3.175-Bpin)

Prepared by Dr. Michael Schedler.



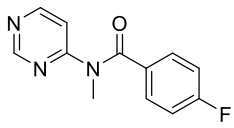
Modifying a known procedure,[37] 4-bromo-*N*-methyl-*N*-(pyrimidin-4-yl)benzamide (352 mg, 1.21 mmol, 1.05 equiv.), B_2pin_2 (919 mg, 3.62 mmol, 3.00 equiv.), $Pd(dppf)Cl_2$ (88.6 mg, 0.121 mmol, 0.10 equiv.) and KOAc (354 mg, 3.62 mmol, 3.00 equiv.) were suspended in anhydrous and degassed 1,4-dioxane (5 mL). The mixture was stirred at 80 °C for 21 hours. The mixture was allowed to cool to room temperature, diluted with CH_2Cl_2 and filtered through Celite. All volatiles were removed *in vacuo* and the residue was purified by flash column chromatography on silica (EtOAc) yielding *N*-methyl-*N*-(pyrimidin-4-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaboro-lan-2-yl)benzamide (**3.175-Bpin**, 184 mg, 0.543 mmol, 45%) as a slightly grey solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.25 (s, 1H), 8.20 (d, J = 8.1 Hz, 2H), 7.94 (d, J = 6.6 Hz, 1H), 7.9 (d, 8.2 Hz, 2H), 7.80 (dd, J = 6.7, 1.1 Hz, 1H), 3.75 (s, 3H), 1.36 (s, 12H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 176.4, 157.7, 152.6, 151.2, 139.7, 134.6, 128.8, 114.2, 84.1, 37.8, 25.0; **^{11}B NMR** (128 MHz, $CDCl_3$): δ = 31.5; **HRMS** (ESI^+) for $C_{18}H_{23}BN_3O_3^+$ $[M+H]^+$ requires m/z = 340.18270, found 340.18275; **IR** (ATR, neat) $\tilde{\nu}$ (cm^{-1}) = 1629,

1597, 1523, 1502, 1419, 1389, 1356, 1276, 1257, 1137, 1111, 1077, 857, 780, 712, 652; **M.P.**: 173 °C.

4-Fluoro-*N*-methyl-*N*-(pyrimidin-4-yl)benzamide (3.175)

Prepared by Dr. Michael Schedler.

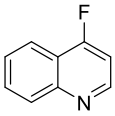


Adapting a known procedure,[45] 4-aminopyrimidine (241 mg, 2.53 mmol, 1.00 equiv.) was dissolved in anhydrous pyridine (10 mL) and the solution was cooled to 0 °C. 4-Fluorobenzoyl chloride (300 µL, 2.53 mmol, 1.00 equiv.) was added to the reaction and the mixture was warmed to room temperature and stirred for 16 hours. The reaction was then stopped by addition of H_2O (30 mL) and the mixture was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic phases were dried with $MgSO_4$, filtered and all volatiles were removed *in vacuo*. Purification of the residue by flash column chromatography on silica (*n*-pentane/EtOAc 50:50) yielded partially purified 4-fluoro-*N*-(pyrimidin-4-yl)benzamide, that was used directly in the next step.
The partially purified 4-fluoro-*N*-(pyrimidin-4-yl)benzamide was dissolved in anhydrous DMF (10 mL) and Cs_2CO_3 (907 mg, 2.78 mmol, 1.10 equiv.) was added. MeI (317 µL, 5.06 mmol, 2.00 equiv.) was added to the mixture and the reaction was stirred for 19 hours at room temperature. The reaction was quenched by addition of water (20 mL) and the mixture was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic phases were washed with brine, dried with $MgSO_4$, filtered and all volatiles were removed *in vacuo*. Purification of the residue by flash column chromatography

on silica (*n*-pentane/EtOAc 50:50) yielded 4-fluoro-*N*-methyl-*N*-(pyrimidin-4-yl)benzamide (**3.175**, 18.3 mg, 0.0792 mmol, 3% over two steps) as a colourless solid. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.27–8.23 (m, 3H), 7.96 (d, *J* = 6.6 Hz, 1H), 7.84 (dd, *J* = 6.6, 1.0 Hz, 1H), 7.09 (t, *J* = 8.7 Hz, 2H), 3.75 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 175.1 (s), 165.4 (d, *J* = 251.9 Hz), 157.9 (s), 151.2 (s), 152.8 (s), 133.8 (s), 132.1 (d, *J* = 9.1 Hz), 115.1 (d, *J* = 21.6 Hz), 114.2 (s), 37.8 (s); **^{19}F NMR** (376 MHz, $CDCl_3$): δ = –108.2 (tt, *J* = 8.7, 5.6 Hz); **HRMS** (ESI^+) for $C_{12}H_{11}FN_3O^+$ $[M+H]^+$ requires m/z = 232.08807, found 232.08817; **IR** (ATR, neat) $\tilde{\nu}$ (cm^{-1}) = 2960, 2921, 1632, 1611, 1588, 1521, 1497, 1406, 1390, 1324, 1302, 1281, 1261, 1211, 1158, 1142, 1105, 1080, 1013, 886, 843, 809, 769; **M.P.**: 116 °C.

4-Fluoroquinoline (3.176)

Prepared by Dr. Michael Schedler.



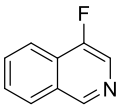
Adapting a known procedure,[81] 4-aminoquinoline (500 mg, 3.47 mmol, 1.00 equiv.) was dissolved in HBF_4 (48% in H_2O, 3 mL) and the mixture was cooled to −10 °C. A solution of $NaNO_2$ (159 mg, 7.98 mmol, 2.30 equiv.) in H_2O (0.5 mL) was slowly added at −10 °C. After the reaction was kept at −10 °C for further 10 min, the mixture was filtered using a pre-cooled sintered glass funnel. The precipitate was washed with cold *n*-pentane and transferred to a beaker. Anhydrous diethyl ether (10 mL) was added to the precipitate and gas was evolved. The mixture was kept at room temperature for 30 minutes before H_2O (10 mL) was added. The mixture was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic

phases were dried with $MgSO_4$, filtered and all volatiles were removed *in vacuo*. The residue was purified by flash column chromatography on silica (*n*-pentane/EtOAc 9:1) yielding 4-fluoroquinoline (**3.176**, 17.0 mg, 0.116 mmol, 3% over two steps) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.86 (dd, J = 8.4, 5.0 Hz, 1H), 8.14–8.08 (m, 2H), 7.77 (ddd, J = 8.5, 6.9, 1.5 Hz, 1H), 7.60 (ddd, J = 8.1, 6.8, 1.1 Hz, 1H), 7.09 (dd, J = 9.7, 5.0 Hz, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 165.4 (d, J = 268.6 Hz), 151.6 (d, J = 8.0 Hz), 150.6 (d, J = 4.6 Hz), 130.7 (s), 129.3 (d, J = 3.8 Hz), 127.0 (d, J = 1.7 Hz), 120.6 (d, J = 5.2 Hz), 119.7 (d, J = 13.1 Hz), 105.8 (d, J = 14.6 Hz) ; **^{19}F NMR** (376 MHz, $CDCl_3$): δ = −112.7–−112.8 (m); **MS** (ESI^+) for $C_9H_7NF^+$ $[M+H]^+$ requires m/z = 148.1, found 148.1. The analytical data were in accordance with the literature.[82]

4-Fluoroisoquinoline (3.178)

Prepared by Dr. Michael Schedler.



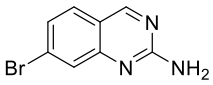
Following a known procedure,[83] 4-aminoisoquinoline (150 mg, 1.04 mmol, 1.00 equiv.) was dissoled in HBF_4 (48% in H_2O, 1 mL) and the mixture was cooled to −10 °C. A solution of $NaNO_2$ (73.9 mg, 1.07 mmol, 1.03 equiv.) in H_2O (0.5 mL) was slowly added at −10 °C. The reaciton was stirred at −8 °C for one hour. All volatiles of the mixture were removed *in vacuo*. The residue was suspended in toluene (20 mL) and the suspension was heated to 90 °C for 1 h. The mixture was cooled back to room temperature and was filtered. The precipitate was dissolved in a mixture of CH_2Cl_2 (25 mL) and $NaHCO_3$ solution (sat. aq., 25 mL).

The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 25 mL). The combined organic phases were dried with Na_2SO_4, filtered and all volatiles were removed *in vacuo*. The resulting brown oil was purified by flash column chromatography on silica (*n*-pentane/EtOAc 90:10 to 80:20) yielding 4-fluoroisoquinoline (**3.178**, 12.5 mg, 0.0850 mmol, 8%) as a yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.03 (s, 1H), 8.33 (s, 1H), 8.03 (dq, *J* = 8.4, 0.9 Hz, 1H), 7.96 (ddt, 8.3, 2.0, 1.0 Hz, 1H), 7.72 (ddd, *J* = 8.2, 6.9, 1.2 Hz, 1H), 7.62 (ddd, *J* = 8.2, 7.0, 1.2 Hz, 1H); **^{19}F NMR** (376 MHz, $CDCl_3$): δ = −139.9 (br s). The analytical data were in accordance with the literature.[73]

7-Bromoquinazolin-2-amine

Prepared by Dr. Michael Schedler.



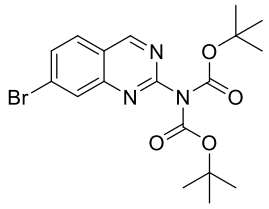
Applying a known procedure,[84] guanidine carbonate salt (2.34 g, 13.0 mmol, 1.30 equiv.) and DIPEA (4.42 mL, 26.0 mmol, 2.60 equiv.) were dissolved in NMP (20 mL) and the mixture was heated to 160 °C. A solution of 4-bromo-2-fluoro-benzaldehyde (2.03 g, 10.0 mmol, 1.00 equiv.) in NMP (5 mL) was added slowly to the hot reaction mixture. After stirring the reaction at 160 °C for two hours, it was cooled below 100 °C and an ice-water mixture (100 mL) was added. The mixture was stirred at room temperature for 30 minutes. A golden precipitate formed, that was filtered off and washed with H_2O (20 mL) and EtOH (20 mL). The precipitate was then stirred with EtOH (20 mL) for one hour and filtered off again. After washing the solid with EtOH (20 ml), an EtOH/toluene

mixture (20 mL, 1:1) and toluene (20 mL), the precipitate was dried *in vacuo*, yielding 7-bromoquinazolin-2-amine (961 mg, 4.29 mmol, 43%) as a brown solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.12 (s, 1H), 7.74 (d, J = 8.5 Hz, 1H), 7.59 (d, J = 1.8 Hz 1H), 7.35 (dd, J = 8.5, 1.9 Hz, 1H), 7.04 (br s, 2H); **^{13}C NMR** (101 MHz, DMSO-d_6): δ = 162.5, 161.2, 152.7, 129.8, 127.8, 126.4, 124.9, 118.1; **HRMS** (ESI$^+$) for $C_8H_7BrN_3^+$ $[M+H]^+$ requires m/z = 223.98179, found 223.98183; **IR** (ATR, neat) $\tilde{\nu}$ (cm^{-1}) = 3314, 3165, 1662, 1612, 1548, 1490, 1417, 1195, 1052, 932, 860, 781, 713, 637; **M.P.** > 250 °C.

tert-Butyl-_N_-(_tert_-butoxycarbonyl)-(7-bromoquinazolin-2-yl)carbamate

Prepared by Dr. Michael Schedler.



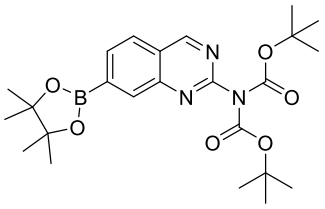
7-Bromoquinazolin-2-amine (800 mg, 3.57 mmol, 1.00 equiv.) and DMAP (1.31 g, 10.7 mmol, 3.00 equiv.) were dissolved in anhydrous THF (20 mL). Boc_2O (3.12 g, 14.3 mmol, 4.00 equiv.) and Et_3N (1.98 ml, 14.3 mmol, 4.00 equiv.) were added to the reaction and it was stirred for 4 days. All volatiles were removed *in vacuo* and the residue was purified by flash column chromatography on silica (*n*-pentane/EtOAc 80:20 to 60:40) yielding *tert*-butyl-*N*-(*tert*-butoxycarbonyl)-(7-bromoquinazolin-2-yl)carbamate (1.07 g, 2.53 mmol, 71%) as a yellowish solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.38 (s, 1H), 8.21 (d, J = 1.7 Hz, 1H), 7.83 (d, J = 8.7 Hz, 1H), 7.76 (dd, J = 8.7, 1.7 Hz, 1H), 1.46 (s, 18 H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 162.1, 156.0, 152.0, 151.0, 132.0, 130.8, 129.7, 128.3, 121.7, 83.7, 28.00; **HRMS** (ESI$^+$) for $C_{18}H_{23}BrN_3O_4^+$ $[M+H]^+$ requires m/z = 424.08665, found 424.08635; **IR** (ATR, neat)

$\tilde{\nu}$ (cm^{-1}) = 2977, 1751, 1726, 1608, 1553, 1474, 1400, 1368, 1280, 1159, 1116, 1057, 945, 907, 865, 778; **M.P.**: 124 °C.

tert-Butyl-_N_-(_tert_-butoxycarbonyl)-(7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinazolin-2-yl)carbamate (3.180-Bpin)

Prepared by Dr. Michael Schedler.



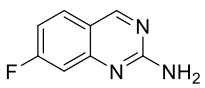
Modifying a known procedure,[37] *tert*-butyl-*N*-(*tert*-butoxycarbonyl)-(7-bromoquinazolin-2-yl)carbamate (533 mg, 1.26 mmol, 1.05 equiv.), B_2pin_2 (305 mg, 1.20 mmol, 1.00 equiv.), $Pd(dppf)Cl_2$ (26.3 mg, 0.0359 mmol, 0.030 equiv.) and KOAc (352 mg, 3.59 mmol, 3.00 equiv.) were suspended in anhydrous and degassed 1,4-dioxane (6 mL). The mixture was stirred at 80 °C for 14 hours. The residue was allowed to cool to room temperature, diluted with CH_2Cl_2 and filtered. All volatiles were removed *in vacuo* and the residue was purified by recrystallisation (CH_2Cl_2/*n*-hexane) yielding *tert*-butyl-*N*-(*tert*-butoxycarbonyl)-(7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinazolin-2-yl)carbamate (**3.108-Bpin**, 212 mg, 0.450 mmol, 36%) as a colourless solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.41 (s, 1H), 8.49 (s, 1H), 8.01 (d, J = 8.0 Hz, 1H), 7.93 (d, J = 8.0 Hz, 1H), 1.42 (s, 18H), 1.38 (s, 12 H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ =162.1, 155.0, 150.9, 150.6, 135.8, 132.7, 125.9, 124.3, 84.6, 83.2, 27:9, 24.9; **^{11}B NMR** (128 MHz, $CDCl_3$): δ = 31.2; **HRMS** (ESI^+) for $C_{24}H_{35}BN_3O_6^+$ $[M+H]^+$ requires m/z = 472.2613,

found 472.2608; **IR** (ATR, neat) $\tilde{\nu}$ (cm^{-1}) = 2980, 1792, 1580, 1363, 1325, 1291, 1149, 1080, 963, 850, 783, 698, 663; **M.P.**: 165 °C.

7-Fluoroquinazolin-2-amine (3.180)

Prepared by Dr. Michael Schedler.



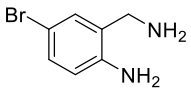
Applying a known procedure,[84] guanidine carbonate salt (2.34 g, 13.0 mmol, 1.30 equiv.) and DIPEA (4.42 mL, 26.0 mmol, 2.6 equiv.) were dissolved in NMP (20 mL) and the mixture was heated to 160 °C. A solution of 2,4-difluoro-benzaldehyde (1.10 mL, 10.0 mmol, 1.00 equiv.) in NMP (5 mL) was added slowly to the hot reaction mixture. After stirring the reaction at 160 °C for two hours, it was cooled below 100 °C and an ice-water mixture (100 mL) was added. The mixture was stirred at room temperature for 30 minutes. A golden precipitate formed, that was filtered off and washed with H_2O (20 mL) and EtOH (20 mL). The precipitate was then stirred with EtOH (20 mL) for one hour and filtered off again. After washing the solid with EtOH (20 ml), an EtOH/toluene mixture (20 mL, 1:1) and toluene (20 mL), the precipitate was dried *in vacuo*, yielding 7-fluoroquinazolin-2-amine (**3.180**, 96.8 mg, 0.594 mmol, 6%).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.09 (br s, 1H), 7.88 (t, J = 7.7 Hz, 1H), 7.12–7.00 (m, 4H); **^{13}C NMR** (101 MHz, DMSO-d_6): δ = 165.7 (d, J = 250.3 Hz), 162.1 (s), 161.3 (s), 153.6 (d, J = 14.6 Hz), 131.0 (d, J = 11.7 Hz), 116.9 (s), 111.7 (d, J = 25.2 Hz), 108.2 (d, J = 20.7 Hz); **^{19}F NMR** (376 MHz, DMSO-d_6): δ = –104.1 (ddd, J = 9.0, 9.0, 8.4 Hz); **HRMS** (ESI^+) for $C_8H_7FN_3^+$ $[M+H]^+$ requires m/z = 164.06185, found 164.06195; **IR**

(ATR, neat) $\tilde{\nu}$ (cm^{-1}) = 3315, 3135, 1624, 1491, 1430, 1215, 1170, 1110, 972, 855, 777,712, 636; **M.P.**: 221 °C (decomposition).

2-(Aminomethyl)-4-bromoaniline

Prepared by Dr. Michael Schedler.



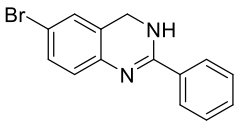
Following a known procedure,[85] 2-amino-5-bromo-benzonitrile (5.00 g, 25.4 mmol, 1.00 equiv.) was dissolved in anhydrous THF (25 mL) and the solution was cooled to 0 °C. A solution of BH_3.THF (1 M in THF, 33 mL, 33.0 mmol, 1.30 equiv.) was added and the reaction was stirred at room temperature for 40 hours. The mixture was then cooled to 0 °C and EtOH (20 mL) was added. The mixture was stirred at 0 °C for 30 minutes, after which a solution of HCl in 1,4-dioxane (4 M, 25 mL) was added. A voluminous precipitate formed that was filtered off and washed with *n*-pentane. The precipitate was dried *in vacuo* for several hours and then dissolved in aqueous NH_4OH solution (1 M, 200 mL). The solution was stirred until a precipitate formed again. This was filtered off and washed with 1 M NH_4OH solution. Drying of the precipitate yielded 2-(aminomethyl)-4-bromoaniline (2.61 g, 13.0 mmol, 51%) as a colourless solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.19 (d, J = 2.4 Hz, 1H), 7.04 (dd, J = 8.5, 2.5 Hz, 1H), 6.55 (d, J = 8.4 Hz, 1H), 5.22 (s, 2H), 3.31 (br s, 2H), 1.72 (br s, 2H); **^{13}C NMR** (101 MHz, DMSO-d_6): δ = 145.8, 129.9, 129.2, 129.2, 116.2, 106.6, 42.5; **HRMS** (ESI^+) for $C_7H_{10}BrN_2^+$ $[M+H]^+$ requires m/z = 201.0019, found 201.00195; **IR** (ATR, neat) $\tilde{\nu}$ (cm^{-1})

= 3397, 3367, 3187, 1647, 1483, 1429, 1365, 1281, 896, 851, 817, 778, 694, 627; **M.P.**: 91 °C.

6-Bromo-2-phenyl-3,4-dihydroquinazoline

Prepared by Dr. Michael Schedler.

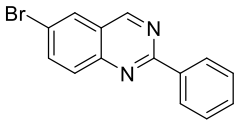


Following a known procedure,[85] 2-(aminomethyl)-4-bromoaniline (2.00 g, 9.95 mmol, 1.00 equiv.) and *p*-TSA.H_2O (283 mg, 1.49 mmol, 0.15 equiv.) were suspended in toluene. Trimethyl orthobenzoate (1.71 mL, 9.95 mmol, 1.00 equiv.) was added and the mixture was refluxed for 20 hours. The reaction was cooled to room temperature and diluted with EtOAc (30 mL). The organic solution was washed with saturated aqueous $NaHCO_3$ solution and H_2O. The organic phase was dried with $MgSO_4$, filtered and all volatiles were removed *in vacuo*. The residue was purified by flash column chromatography on silica (CH_2Cl_2/MeOH 95:5) yielding 6-bromo-2-phenyl-3,4-dihydroquinazoline (2.04 g, 7.11 mmol, 71%) as a colourless solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.81–7.78 (m, 2H), 7.50–7.42 (m, 3H), 7.30 (dd, J = 8.4, 2.3 Hz, 1H), 7.08–7.08 (m, 1H), 6.98 (d, J = 8.1 Hz, 1H), 4.76 (s, 2H); **^{13}C NMR** (126 MHz, $CDCl_3$): δ = 155.3, 141.3, 135.2, 131.1, 130.9, 128.7, 128.4, 126.6, 124.3, 122.5, 116.9, 44.0; **HRMS** (ESI$^+$) for $C_{14}H_{12}N_2Br^+$ $[M+H]^+$ requires m/z = 287.01784, found 278.01753; **IR** (ATR, neat) $\tilde{\nu}$ (cm^{-1}) = 3207, 1541, 1472, 1321, 1265, 1119, 1073, 866, 823, 774, 698; **M.P.**: 132 °C.

6-Bromo-2-phenylquinazoline

Prepared by Dr. Michael Schedler.

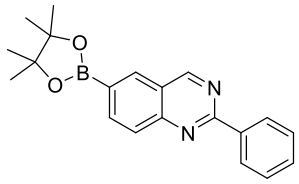


Adapting a known procedure,[86] 6-bromo-2-phenyl-3,4-dihydroquinazoline (1.98 g, 6.90 mmol, 1.00 equiv.) was dissolved in anhydrous THF (15 mL) and a solution of DDQ (1.57 g, 6.90 mmol, 1.00 equiv.) in anhydrous THF (15 mL) was added. The reaction was stirred at room temperature for 30 minutes. The reaction was then quenched by the addition of aqueous NaOH solution (3M, 1 mL). CH_2Cl_2 (15 mL) and H_2O (15 mL) were added to the reaction and the organic phase was separated. The aqueous phase was extracted with CH_2Cl_2 (2 x 15 mL) and the combined organic phases were dried with $MgSO_4$, filtered and all volatiles were removed *in vacuo*. The residue was purified by flash column chromatography on silica (*n*-pentane/EtOAc 99:1 to 90:10) yielding 6-bromo-2-phenylquinazoline (1.77 g, 6.21 mmol, 90%) as a yellowish solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.33 (s, 1H), 8.61–8.59 (m, 2H), 8.07 (t, J = 1.4 Hz, 2H), 7.95 (d, J = 1.4 Hz, 1H), 7.56–7.51 (m, 3H); **^{13}C NMR** (101 MHz, DMSO-d_6): δ = 161.5, 159.5, 149.6, 137.8, 137.7, 131.0, 130.6, 129.4, 128.8, 128.8, 124.6, 120.9; **MS** (ESI^+) for $C_{15}H_{14}BrN_2O^+$ $[M+MeOH+H]^+$ requires m/z = 317.0, found 317.0. The analytical data were in accordance with the literature.[87]

2-Phenyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinazoline (3.181-Bpin)

Prepared by Dr. Michael Schedler.

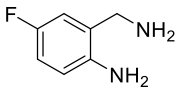


Modifying a known procedure,[37] 6-bromo-2-phenylquinazoline (500 mg, 1.75 mmol, 1.05 equiv.), B_2pin_2 (424 mg, 1.67 mmol, 1.00 equiv.), $Pd(dppf)Cl_2$ (36.7 mg, 0.0501 mmol, 0.030 equiv.) and KOAc (491 mg, 5.01 mmol, 3.00 equiv.) were suspended in anhydrous and degassed 1,4-dioxane (10 mL). The mixture was stirred at 80 °C for 14 hours. The mixture was allowed to cool to room temperature, diluted with CH_2Cl_2 and filtered through Celite. All volatiles were removed *in vacuo* and the residue was partially purified by flash column chromatography on silica (EtOAc). The partially purified product was further purified by recrystallisation from CH_2Cl_2/*n*-hexane, affording 2-phenyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinazoline (**3.181-Bpin**, 419 mg, 1.26 mmol, 72%) as a slightly brown solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.49 (s, 1H), 8.65–8.52 (m, 2H), 8.44 (s, 1H), 8.27 (dd, J = 8.4, 1.4 Hz, 1H), 8.05 (d, J = 8.5 Hz, 1H), 7.56–7.49 (m, 3H), 1.40 (s, 12H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 161.9, 161.2, 152.4, 139.0, 138.1, 135.5, 130.9, 128.8, 128.8, 127.7, 123.2, 84.6, 25.1; **^{11}B NMR** (128 MHz, $CDCl_3$): δ = 30.4; **HRMS** (ESI$^+$) for $C_{20}H_{22}BN_2O_2^+$ $[M+H]^+$ requires m/z = 333.17688, found 333.17684; **IR** (ATR, neat) $\tilde{\nu}$ (cm^{-1}) = 1619, 1553, 1423, 1367, 1303, 1267, 1140, 1077, 963, 849, 768, 714, 688, 665; **M.P.**: 131 °C.

2-(Aminomethyl)-4-fluoroaniline

Prepared by Dr. Michael Schedler.



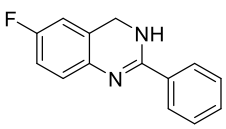
Adapting a known procedure,[85] 2-amino-5-fluoro-benzonitrile (2.00 g, 14.7 mmol, 1.00 equiv.) was dissolved in anhydrous THF (15 mL) and the solution was cooled to 0 °C. A solution of BH_3.THF (1 M in THF, 19 mL, 19.0 mmol, 1.30 equiv.) was added and the reaction was stirred at room temperature for 44 hours. The reaction was then quenched by addition of H_2O (50 mL) and the mixture was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic phases were dried with $MgSO_4$, filtered and all volatiles were removed *in vacuo*. The residue was dissolved in EtOH (10 mL) and HCl (4 M in 1,4-dioxane, 15 mL) was added. The mixture was stirred for 30 minutes at room temperature and the precipitate that formed was filtered off and washed with *n*-pentane. The precipitate was dried *in vacuo* and then dissolved in aqueous 1 M NH_4OH solution (100 mL). This aqueous solution was extracted with CH_2Cl_2 (3 x 50 mL) and the combined organic phases were dried over $MgSO_4$, filtered and all volatiles were removed *in vacuo*. Drying of the precipitate yielded 2-(aminomethyl)-4-fluoroaniline (1.09 g, 7.79 mmol, 53%) as a colourless solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.82–6.76 (m, 2H), 6.61–6.57 (m, 1H), 4.31 (br s, 2H), 3.85 (s, 2H), 1.34 (br s, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 156.0 (d, J = 235.4 Hz), 142.1 (d, J = 2.2 Hz), 127.6 (d, J = 6.4 Hz), 116.4 (d, J = 7.5 Hz), 115.4 (d, J = 22.4 Hz), 114.2 (d, J = 22.0 Hz), 44.7 (d, J = 1.5 Hz); **^{19}F NMR** (376 MHz, $CDCl_3$): δ = −127.5 (td, J = 8.8, 4.8 Hz); **HRMS** (ESI^+) for $C_7H_{10}FN_2^+$ $[M+H]^+$ requires m/z = 141.08225, found

141.08216; **IR** (ATR, neat) $\tilde{\nu}$ (cm^{-1}) = 3388, 3285, 3196, 1647, 1493, 1438, 1313, 1259, 1206, 1140, 966, 877, 852, 816, 792, 736, 701; **M.P.**: 53 °C.

6-Fluoro-2-phenyl-3,4-dihydroquinazoline

Prepared by Dr. Michael Schedler.



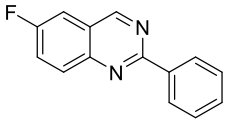
Adapting a known procedure,[85] 2-(aminomethyl)-4-fluoroaniline (1.06 g, 7.56 mmol, 1.00 equiv.) and *p*-TSA.H_2O (216 mg, 1.13 mmol, 0.15 equiv.) were suspended in toluene (20 mL). Trimethyl orthobenzoate (1.30 mL, 7.56 mmol, 1.00 equiv.) was added and the mixture was refluxed for 14 hours. The reaction was cooled to room temperature and diluted with EtOAc (20 mL). The organic solution was washed with saturated aqueous $NaHCO_3$ solution and H_2O. The organic phase was dried with $MgSO_4$, filtered and all volatiles were removed *in vacuo*. The residue was purified by flash column chromatography on silica (CH_2Cl_2/MeOH 95:5) yielding 6-fluoro-2-phenyl-3,4-dihydroquinazoline (880 mg, 3.89 mmol, 51%) as a colourless solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.78–7.75 (m, 2H), 7.47–7.38 (m, 3H), 7.06 (dd, *J* = 8.7, 5.2 Hz, 1H), 6.87 (td, *J* = 8.6, 2.9 Hz, 1H), 6.63 (dd, *J* = 8.5, 2.8 Hz, 1H), 5.06 (br s , 1H), 4.71 (s, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 160.1 (d, *J* = 243.0 Hz), 154.8 (s), 138.5 (br s), 135.5 (s), 130.7 (s), 128.7 (s), 126.5 (s), 124.5 (br s), 122.1 (d, *J* = 7.7 Hz), 114.8 (d, *J* = 22.1 Hz), 112.2 (d, *J* = 23.3 Hz), 44.2 (s); **^{19}F NMR** (376 MHz, $CDCl_3$): δ = −118.2 (br s); **HRMS** (ESI^+) for $C_{14}H_{12}N_2F^+$ $[M+H]^+$ requires m/z = 227.09790, found

227.09770; **IR** (ATR, neat) $\tilde{\nu}$ (cm^{-1}) = 3204, 1617, 1592, 1544, 1522, 1476, 1324, 1266, 1234, 1144, 1001, 953, 900, 860, 804, 776, 730, 706, 670, 638; **M.P.**: 124 °C.

6-Fluoro-2-phenylquinazoline (3.181)

Prepared by Dr. Michael Schedler.



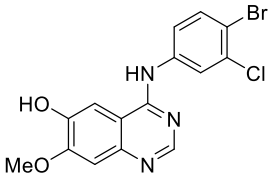
Adapting a known procedure,[86] 6-fluoro-2-phenyl-3,4-dihydroquinazoline (778 mg, 3.44 mmol, 1.00 equiv.) was dissolved in anhydrous THF (10 mL) and a solution of DDQ (227 mg, 3.44 mmol, 1.00 equiv.) in anhydrous THF (10 mL) was added. The reaction was stirred at room temperature for 30 minutes. The reaction was then quenched by the addition of aqueous NaOH solution (3M, 1 mL). CH_2Cl_2 (15 mL) and H_2O (15 mL) were added to the reaction and the organic phase was separated. The aqueous phase was extracted with CH_2Cl_2 (2 x 15 mL) and the combined organic phases were dried with $MgSO_4$, filtered and all volatiles were removed *in vacuo*. The residue was purified by flash column chromatography on silica (*n*-pentane/EtOAc 98:2 to 96:4) yielding 6-fluoro-2-phenylquinazoline (**3.181**, 653 mg, 2.92 mmol, 85%) as a colourless solid. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 9.40 (s, 1H), 8.59 (dd, *J* = 7.6, 2.1 Hz, 2 H), 8.08 (dd, *J* = 9.2, 5.0 Hz, 1H), 7.65 (td, *J* = 8.8, 2.8 Hz, 1H), 7.56–7.49 (m, 4H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 160.7 (d, *J* = 2.9 Hz), 160.4 (d, *J* = 251.0 Hz), 159.8 (d, *J* = 5.5 Hz), 147.9 (s), 137.7 (s), 131.4 (d, *J* = 8.4 Hz), 130.7 (s), 128.7 (s), 128.5 (s), 124.5 (d, *J* = 25.9 Hz), 123.9 (d, *J* = 9.2 Hz), 110.1 (d, *J* = 21.8); **^{19}F NMR** (376 MHz, $CDCl_3$): δ = −110.7

(td, J = 8.1, 5.0 Hz); **MS** (ESI$^+$) for $C_{15}H_{14}FN_2O^+$ [M+MeOH+H]$^+$ requires m/z = 257.1, found 257.1. The analytical data were in accordance with the literature.[88]

A.2.4 Gefitinib

4-((4-Bromo-3-chlorophenyl)amino)-7-methoxyquinazolin-6-ol

Prepared by Dr. Enrico Emer.



Adapting a known procedure,[89] a catalytic amount of DMF was added to a solution of 7-methoxy-4-oxo-3,4-dihydroquinazolin-6-yl acetate (5.00 g, 21.4 mmol, 1.00 equiv.) in $SOCl_2$ (70 mL) The solution was stirred at 83° C under N_2 for two hours, and then was cooled to room temperature. The $SOCl_2$ was removed *in vacuo* to afford 4-chloro-7-methoxyquinazolin-6-yl acetate hydrochloride, which was used in the next step without further purification.

4-Bromo-3-chloroaniline (4.50 g, 21.8 mmol, 1.02 equiv.) was added to a solution of 4-chloro-7-methoxyquinazolin-6-yl acetate hydrochloride (6.17 g, 21.4 mmol, 1 equiv.) in *i*-PrOH (170 mL). The reaction mixture was stirred at 85 °C under N_2 for two hours, and then was cooled to 0 °C. The resulting precipitate was collected by filtration and dried *in vacuo*. 4-((4-Bromo-3-chlorophenyl)amino)-7-methoxyquinazolin-6-yl acetate (**3.195**, 6.96 g, 15.15 mmol, 71%) was isolated as a cream solid and used in the next step without further purification.

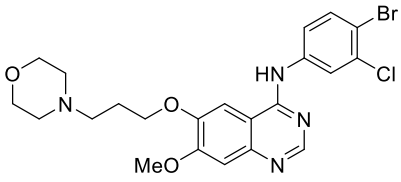
Adapting a known procedure,[114] ammonium hydroxide (35%, 7 mL) was added to a solution of 4-((4-bromo-3-chlorophenyl)amino)-7-methoxyquinazolin-6-yl acetate

(**3.195**, 3.63 g, 9.54 mmol, 1 equiv.) in MeOH (60 mL). The solution was stirred at room temperature for 24 hours, after which the solvent was removed *in vacuo*. 4-((4-Bromo-3-chlorophenyl)amino)-7-methoxyquinazolin-6-ol (3.57 g, 9.38 mmol, 98%) was precipitated from CH_2Cl_2 as a light brown solid.

^{1}H NMR (400 MHz; DMSO-d_6): δ = 9.75 (s, 1H), 9.55 (brs, 1H), 8.52 (s, 1H), 8.34 (d, J = 2.5 Hz, 1H), 7.85 (dd, J = 8.9, 2.5 Hz, 1H), 7.80 (s, 1H), 7.71 (d, J = 8.9 Hz, 1H), 7.23 (s, 1H), 3.98 (s, 3H); **^{13}C NMR** (100 MHz, DMSO-d_6): δ = 155.7, 154.0, 151.8, 146.9, 146.4, 140.8, 133.3, 132.6, 122.1, 121.3, 113.5, 109.8, 107.2, 105.3, 56.0; **HRMS** (ESI^+): for $C_{15}H_{12}BrClN_3O_2^+$ $[M+H]^+$ requires m/z = 379.97959; found 379.98020; **IR** (ATR, neat): $\tilde{\nu}$ (cm^{-1}) = 2990, 2910, 1571, 1504, 1430, 1398, 695; **M.P**.: 290-293 °C.

_N_-(4-Bromo-3-chlorophenyl)-7-methoxy-6-(3-morpholinopropoxy)quinazolin-4-amine (3.197)

Prepared by Dr. Enrico Emer.



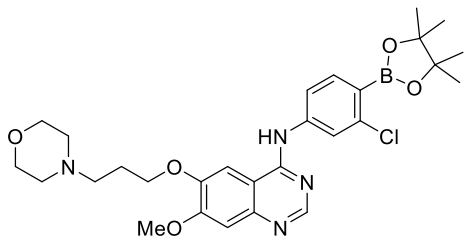
Adapting a known procedure,[89] K_2CO_3 (7.13 g, 51.6 mmol, 5.80 equiv.) was added to a solution of 4-((4-bromo-3-chlorophenyl)amino)-7-methoxyquinazolin-6-ol (3.38 g, 8.89 mmol, 1.00 equiv.) and 4-(3-chloropropyl)-morpholine (1.59 mL, 10.3 mmol, 1.16 equiv.) in DMF (70 mL). The solution was stirred at 80 °C under N_2 for two hours. The reaction mixture was then cooled to room temperature, diluted with H2O (70 mL) and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic extracts were washed with brine (20 mL), dried over

$MgSO_4$ and concentrated *in vacuo* to give crude product. Flash column chromatography (EtOAc/MeOH 85:15) afforded *N*-(4-bromo-3-chlorophenyl)-7-methoxy-6-(3-morpholinopropoxy)quinazolin-4-amine (**3.197**, 2.20 g, 4.32 mmol, 49%) as a white solid.

^{1}H NMR (400 MHz; DMSO-d_6): δ = 9.58 (s, 1H), 8.53 (s, 1H), 8.25 (d, J = 2.5 Hz, 1H), 7.82 (dd, J = 8.9, 2.5 Hz, 1H), 7.79 (s, 1H), 7.74 (d, J = 8.8 Hz, 1H), 7.20 (s, 1H), 4.17 (t, J = 6.4 Hz, 2H), 3.93 (s, 3H), 3.58 (t, J = 4.6 Hz, 4H), 3.34 (s, 1H), 2.47 (t, J = 7.5 Hz, 2H), 2.38 (bs, 4H), 1.99 (quintet, J = 6.7 Hz, 2H); **^{13}C NMR** (100 MHz, DMSO-d_6): δ = 155.7, 154.6, 152.4, 148.4, 147.1, 140.5, 133.4, 132.6, 122.6, 121.7, 113.9, 109.0, 107.3, 102.4, 67.1, 66.2, 55.9, 55.0, 53.4, 25.9; **HRMS** (ESI$^+$): for $C_{22}H_{25}BrClN_4O_3^+$ $[M+H]^+$ requires m/z = 507.07931; found 507.07977; **IR** (ATR, neat): $\tilde{\nu}$ (cm^{-1}) = 2988, 2909, 1504, 1470, 1426, 1394, 695, **M.P.**: 156-162 °C.

_N_-(3-Chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-7-methoxy-6-(3-morpholinopropoxy)quinazolin-4-amine (3.192)

Prepared by Dr. Enrico Emer.



$Pd(dppf)Cl_2$ (102 mg, 0.125 mmol, 0.05 equiv.) was added to a mixture of *N*-(4-bromo-3-chlorophenyl)-7-methoxy-6-(3-morpholinopropoxy)quinazolin-4-amine (**3.197**, 1.27 g, 2.50 mmol, 1.00 equiv.), KOAc (736 mg, 7.50 mmol, 3.00 equiv.) and B_2pin_2 (1.90 g, 7.49 mmol, 3.00 equiv.) in dry, degassed 1,4-dioxane (30 mL). The mixture was stirred at 80 °C under N_2 for 5

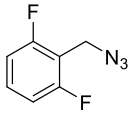
hours. The reaction mixture was cooled to room temperature and concentrated *in vacuo*. The residue was diluted with H2O (20 mL) and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic extracts were washed with brine (20 mL), dried over $MgSO_4$ and concentrated *in vacuo* to afford crude product. Flash column chromatography (EtOAc/MeOH 85:15) afforded *N*-(3-chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-7-methoxy-6-(3-morpholinopropoxy)quinazolin-4-amine (**3.192**, 721 mg, 1.30 mmol, 50%) as a light brown solid.

^{1}H NMR (400 MHz; DMSO-d_6): δ = 9.61 (s, 1H), 8.57 (s, 1H), 8.16 (d, *J* = 2.1 Hz, 1H), 7.85 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.85 (s, 1H), 7.68 (d, *J* = 8.3 Hz, 1H), 7.22 (s, 1H), 4.19 (t, *J* = 6.4 Hz, 2H), 3.94 (s, 3H), 3.58 (t, *J* = 4.7 Hz, 4H), 3.34 (s, 1H), 2.48 (t, *J* = 7.1 Hz, 2H), 2.39 (bs, 4H), 1.99 (quintet, *J* = 6.7 Hz, 2H), 1.31 (s, 2H); **^{13}C NMR** (100 MHz, DMSO-d_6): δ = 155.7, 154.6, 152.4, 148.4, 147.1, 143.5, 138.7, 136.9, 121.1, 118.7, 109.1, 107.3, 102.5, 83.6, 67.2, 66.1, 55.9, 54.9, 53.4, 25.8, 24.6; **^{11}B NMR** (128 MHz, DMSO-d_6): δ = 28.3 (br s) ; **HRMS** (ESI$^+$): for $C_{28}H_{37}BClN_4O_5^+$ $[M+H]^+$ requires m/z = 555.25400; found 555.25336; **IR** (ATR, neat): $\tilde{\nu}$ (cm^{-1}) = 2990, 2910, 1600, 1504, 1427, 1389, 1349, 1307, 1143, 1113, 696; **M.P.**: 93-96 °C (dec.).

A.2.5 Rufinamide

2-(Azidomethyl)-1,3-difluorobenzene

Prepared by Dr. Enrico Emer.



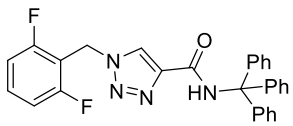
Adapting a known procedure,[90] 2-(chloromethyl)-1,3-difluorobenzene (1.0 g, 6.15 mmol, 1 equiv.) and NaN_3 (1.84 g, 28.2 mmol, 4.6 equiv.) were

dissolved in H_2O (15 mL) and stirred at 70 °C under N_2 overnight. The reaction mixture was cooled to room temperature, diluted with H_2O (15 mL) and extracted with EtOAc (3 x 30 mL). The organic extract was washed with brine (30 mL), dried over $MgSO_4$ and concentrated in vacuo to give the crude product. 2-(Azidomethyl)-1,3-difluorobenzene (976 g, 5.77 mmol, 94%) was obtained without further purification as light yellow oil.

^{1}H NMR (400 MHz; $CDCl_3$): δ = 7.38-7.30 (m, 1H), 6.97 (ddd, J = 16.5, 8.4, 1.5 Hz, 2H), 4.44 (s, 2H); **^{19}F NMR** (376 MHz; $CDCl_3$): δ = -114.7 (t, J = 6.6 Hz, 2F). The analytical data were in accordance with the literature.[91]

1-(2,6-Difluorobenzyl)-*N*-trityl-1*H*-1,2,3-triazole-4-carboxamide (3.220)

Prepared by Dr. Enrico Emer.



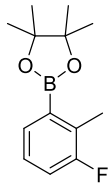
Adapting a known procedure,[92] 2-(azidomethyl)-1,3-difluorobenzene (500.0 mg, 2.64 mmol, 1 equiv.) and propiolic acid (195 ◎L, 3.17 mmol, 1.2 equiv.) were dissolved in *t*-BuOH/water (1:1, 5 mL). Then, $Cu(OAc)_2$ (48.0 mg, 0.26 mmol, 0.10 equiv) and L-ascorbic acid (91.6 mg, 0.52 mmol, 0.20 equiv) were added and the heterogeneous mixture was stirred vigorously for 15 minutes at room temperature and then sonicated for 30 seconds. The mixture was stirred for further 19 hours at room temperature then the solvent was removed under vacuum and the crude was used directly in the next step without any isolation.

Dry CH_2Cl_2 (18 mL) and dry DMF (4 drops) were added to the crude mixture under stirring and the suspension was cooled at 0 °C. After 10 minutes, oxalyl chloride (1.44 mL, 11.35 mmol, 4.30 equiv.) was added dropwise. The ice-bath was kept and the reaction was stirred for 7 hours, during which time it was allowed to reach room temperature. The solvent was then removed under a stream of nitrogen. The crude acyl chloride was then redissolved in dry CH_2Cl_2 (12 mL), before cooling at 0 °C. Triphenylmethanamine (1.88 g, 7.25 mmol, 2.75 equiv.) in DCM (10 mL) was then slowly added dropwise and the reaction stirred overnight at room temperature. The solvent was removed *in vacuo*. Flash column chromatography (CH_2Cl_2) followed by recrystallization from Et_2O afforded 1-(2,6-difluorobenzyl)-*N*-trityl-1*H*-1,2,3-triazole-4-carboxamide (**3.220**, 1.25 g, 2.49 mmol, 94%) as a white solid.

^{1}H NMR (400 MHz; $CDCl_3$): δ = 8.48 (s, 1H), 8.03 (s, 1H), 7.41 (tt, J = 8.5, 6.5 Hz, 1H), 7.33 (s, 4H), 7.32 (s, 7H), 7.31-7.26 (m, 4H), 7.03-6.97 (m, 2H), 5.66 (s, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 161.2 (dd, J = 251.9 Hz, 6.4 Hz), 159.0, 144.4, 131.8 (t, J = 10.3 Hz), 128.6, 128.0, 127.1, 125.5, 111.9 (dd, J = 19.3 Hz, 5.7 Hz), 110.1 (t, J = 19.1 Hz), 70.4, 41.7 (t, J = 3.8 Hz); **^{19}F NMR** (376 MHz; $CDCl_3$): δ = -114.04 (t, J = 6.8 Hz, 2F); **HRMS** (ESI^+): a satisfactory mass spectrum of this compound could not be obtained; **IR** (ATR, neat): $\tilde{\nu}$ (cm^{-1}) = 3407, 3145, 3058, 3026, 1684, 1628, 1594, 1562, 1492, 1473, 1449, 1358, 1235, 1201, 1045, 1031,796, 700; **M.P**.: 267-274 °C.

2-(3-Fluoro-2-methylphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.223)

Prepared by Dr. Enrico Emer.

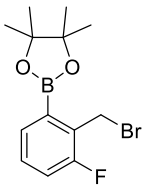


$Pd(dppf)Cl_2$ (539 mg, 0.66 mmol, 0.05 equiv.) was added to a mixture of 1-bromo-3-fluoro-2-methylbenzene (1.63 mL, 13.2 mmol, 1.00 equiv.), KOAc (3.89 g, 39.6 mmol, 3.00 equiv.) and B_2pin_2 (3.36 g, 13.2 mmol, 1.00 equiv.) in toluene (25 mL). The mixture was stirred at 85 °C under N_2 for 20 hours. The solution was diluted with H2O (30 mL) and extracted with CH_2Cl_2 (3 x 30 mL). The combined organic extracts were washed with brine (30 mL), dried over $MgSO_4$ and concentrated *in vacuo* to give the crude product. Flash column chromatography (*n*-hexane/EtOAc 90:10) afforded 2-(3-fluoro-2-methylphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**3.223**, 2.77 g, 11.8 mmol, 89%) as a light yellow oil.

^{1}H NMR (400 MHz; $CDCl_3$): δ = 7.54 (dd, J = 7.3, 1.3 Hz, 1H), 7.18-7.12 (m, 1H), 7.11-7.06 (m, 1H), 2.48 (d, J = 2.4 Hz, 3H), 1.36 (s, 12H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 161.3 (d, J = 243.3 Hz), 134.7, 131.2 (d, J = 3.4 Hz), 131.0 (d, J = 14.8 Hz), 126.3 (d, J = 7.9 Hz), 117.4 (d, J = 22.3 Hz), 83.7, 24.9, 13.3 (d, J = 4.8 Hz); **^{19}F NMR** (376 MHz; $CDCl_3$): δ = -117.5 (m); **^{11}B NMR** (128 MHz, $CDCl_3$): δ = 31 (br s); **HRMS** (ESI^+): a satisfactory mass spectrum of this compound could not be obtained; **IR** (ATR, neat): $\tilde{\nu}$ (cm^{-1}) = 2979, 2933, 1450, 1345, 1312, 1146, 1136, 1028, 721.

2-(2-(Bromomethyl)-3-fluorophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.224)

Prepared by Dr. Enrico Emer.

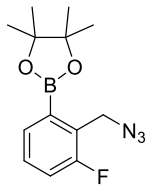


Adapting a known procedure,[93] 2-(3-fluoro-2-methylphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**3.223**, 2.71 g, 11.49 mmol, 1.00 equiv.), NBS (3.07 g, 17.2 mmol, 1.50 equiv.) and AIBN (19.0 mg, 0.11 mmol, 0.01 equiv.) were dissolved in MeCN (80 mL) and stirred at 80 °C under N_2 for two hours. The reaction mixture was cooled to room temperature and concentrated *in vacuo*. Flash column chromatography (*n*-hexane/EtOAc 90:10) afforded 2-(2-(bromomethyl)-3-fluorophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**3.224**, 3.29 g, 10.4 mmol, 91%) as a white solid.

^{1}H NMR (400 MHz; $CDCl_3$): δ = 7.61 (dd, J = 7.4, 1.2 Hz, 1H), 7.32-7.26 (m, 1H), 7.14 (ddd, J = 9.9, 8.4, 1.4 Hz, 1H), 4.98 (d, J = 1.7 Hz, 2H), 1.39 (s, 12H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 161.1 (d, J = 250.5 Hz), 131.9 (d, J = 4.2 Hz), 131.0 (d, J = 12.7 Hz), 129.5 (d, J = 8.4 Hz), 118.3 (d, J = 22.1 Hz), 84.1, 24.9, 24.8; **^{19}F NMR** (376 MHz; $CDCl_3$): δ = -117.3 (m); **^{11}B NMR** (128 MHz, $CDCl_3$): δ = 30.8 (br s); **HRMS** (ESI^+): a satisfactory mass spectrum of this compound could not be obtained; **IR** (ATR, neat): $\tilde{\nu}$ (cm^{-1}) = 3067, 2979, 2933, 1575, 1481, 1346, 1297, 1142, 1109, 968, 932, 678; **M.P.**: 62-70 °C.

2-(2-(Azidomethyl)-3-fluorophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.225)

Prepared by Dr. Enrico Emer.

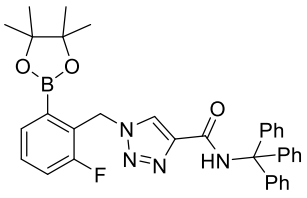


Adapting a known procedure,[93] 2-(2-(bromomethyl)-3-fluorophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**3.224**, 3.18 g, 10.1 mmol, 1.00 equiv.) and NaN_3 (1.64 g, 25.3 mmol, 2.50 equiv.) were dissolved in DMSO (30 mL) and stirred at 70 °C under N_2 for three hours. The reaction mixture was cooled to room temperature, diluted with EtOAc and washed with H2O (5 x 30 mL). The organic phase was washed with brine (30 mL), dried over $MgSO_4$ and concentrated *in vacuo* to give the crude product. 2-(2-(Azidomethyl)-3-fluorophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**3.225**, 2.75 g, 9.93 mmol, 98%) was obtained without further purification as a yellow oil.

^{1}H NMR (400 MHz; $CDCl_3$): δ = 7.67 (dd, *J* = 7.4, 1.2 Hz, 1H), 7.35 (ddd, *J* = 8.2, 7.4, 5.2 Hz, 1H), 7.20 (ddd, *J* = 9.8, 8.3, 1.4 Hz, 1H), 4.73 (d, *J* = 1.9 Hz, 2H), 1.37 (s, 12H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 161.4 (d, *J* = 247.9 Hz), 131.9 (d, *J* = 4.5 Hz), 129.6 (d, *J* = 8.1 Hz), 127.9 (d, *J* = 13.3 Hz), 118.3 (d, *J* = 23.1 Hz), 84.26, 46.0 (d, *J* = 4.7 Hz), 24.8; **^{19}F NMR** (376 MHz; $CDCl_3$): δ = -117.9 (m); **^{11}B NMR** (128 MHz, $CDCl_3$): δ = 30.8 (br s) ; **HRMS** (ESI^+): a satisfactory mass spectrum of this compound could not be obtained; **IR** (ATR, neat): $\tilde{\nu}$ (cm^{-1}) = 2980, 2935, 2095, 1480, 1447, 1346, 1321, 1145, 1133.

1-(2-Fluoro-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)-*N*-trityl-1*H*-1,2,3-triazole-4-carboxamide (3.221)

Prepared by Dr. Enrico Emer.



Adapting a known procedure,[92] 2-(2-(azidomethyl)-3-fluorophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**3.225**, 907 mg, 3.27 mmol, 1.00 equiv.) and propiolic acid (242 ◎L, 3.93 mmol, 1.20 equiv.) were dissolved in *t*-BuOH/water (1:1, 9 mL). $Cu(OAc)_2$ (60 mg, 0.33 mmol, 0.10 equiv.) and L-ascorbic acid (116 mg, 0.66 mmol, 0.20 equiv.) were then added and the corresponding heterogeneous mixture was stirred vigorously for 15 minutes at room temperature and then sonicated for 30 seconds. The mixture was stirred for a further 19 hours at room temperature, after which the solvent was removed *in vacuo*. The resulting crude material was used directly in the next step without any isolation.

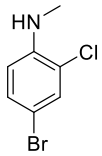
Dry CH_2Cl_2 (32 mL) and dry DMF (8 drops) were added to the crude mixture and the stirred suspension was cooled to 0 °C. After 10 minutes, oxalyl chloride (1.21 mL, 14.06 mmol, 4.30 equiv.) was added dropwise. The ice-bath was kept and the reaction was stirred for 7 hours, during which time it was allowed to reach room temperature. The solvent was then removed under a stream of nitrogen. The crude acyl chloride was then redissolved in dry CH_2Cl_2 (20 mL), before cooling to 0 °C. A solution of triphenylmethanamine (1.70 g, 6.54 mmol, 2.00 equiv.) in CH_2Cl_2 (16 mL) was then slowly added dropwise and the reaction stirred overnight at room

temperature. The solvent was removed *in vacuo*. Flash column chromatography (CH_2Cl_2) afforded impure title compound, which was recrystallised from Et_2O to afford 1-(2-fluoro-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)-*N*-trityl-1*H*-1,2,3-triazole-4-carboxamide (**3.221**, 566 mg, 0.96 mmol, 29%) as a white solid. **^{1}H NMR** (400 MHz; $CDCl_3$): δ = 8.45 (s, 1H), 7.93 (s, 1H), 7.69 (dd, *J* = 7.4, 1.3 Hz, 1H), 7.39 (ddd, *J* = 8.2, 7.5, 5.2 Hz, 1H), 7.31-7.29 (m, 5H), 7.29 (d, *J* = 2.2 Hz, 7H), 7.28-7.23 (m, 4H), 7.23-7.18 (m, 1H), 5.97 (d, *J* = 1.7 Hz, 2H), 1.34 (s, 12H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 161.43 (d, *J* = 249.6 Hz), 159.3, 144.5, 143.3, 132.4, 130.7 (d, *J* = 8.0 Hz), 128.7, 127.9, 127.0, 126.1 (d, *J* = 12.7 Hz), 125.6, 118.8 (d, *J* = 22.2 Hz), 84.5, 70.3, 46.4 (d, *J* = 4.7 Hz), 24.8; **^{19}F NMR** (376 MHz; $CDCl_3$): δ = -116.01 (m); **^{11}B NMR** (128 MHz, $CDCl_3$): δ = 31.0 (br s); **HRMS** (ESI^+): for $C_{35}H_{34}BFN_4O_3Na$ [M+Na] requires m/z = 611.26002; found 611.25977; **IR** (ATR, neat): $\tilde{\nu}$ (cm^{-1}) = 3340, 3158, 3059, 3026, 2979, 2933, 1687, 1562, 1491, 1447, 1348, 1144, 717, 700; **M.P**.: 214-226 °C.

A.2.6 Flutemetamol

4-Bromo-2-chloro-*N*-methylaniline (3.237)

Prepared by Dr. Sean Preshlock.



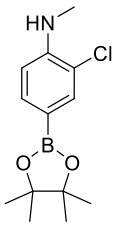
4-Bromo-2-chloroaniline (1.36 g, 6.7 mmol, 1.00 equiv.) and pyridine (1.9 mL, 23.5 mmol, 3.50 equiv.) were dissolved in dry 1,4-dioxane (45 mL) in an oven dried round bottom flask. $Cu(OAc)_2$ (3.0 g, 16.7 mmol, 2.50 equiv.) was added and the mixture was stirred at room temperature under an atmosphere of air for 15 minutes. Methylboronic acid (1.00 g, 16.7 mmol, 2.50 equiv.) was added and

the reaction vessel was equipped with a reflux condenser and heated to 90 °C under an atmosphere of air for three hours. The reaction was cooled to room temperature and the mixture was evaporated to dryness. Flash column chromatography (*n*-hexane/EtOAc 90:10) afforded 4-bromo-2-chloro-*N*-methylaniline (**3.237**, 1.00 g, 4.54 mmol, 72%) as a white solid.

^{1}H NMR (400 MHz; $CDCl_3$): δ = 7.27 (d, *J* = 2.3 Hz, 1H), 7.15 (dd, *J* = 8.7, 2.3 Hz, 1H), 6.40 (d, *J* = 8.7 Hz, 1H), 4.24 (br s, 1H), 2.77 (d, *J* = 3.7 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 144.0, 131.0, 130.5, 119.5, 111.6, 107.3, 30.3; **HRMS** (ESI$^+$): for $C_7H_8BrCl^+$ $[M+H]^+$ requires m/z = 219.95232; found 219.95247; **IR** (ATR, neat): $\tilde{\nu}$ (cm^{-1}) = 3429.7, 2911.2, 2831.5, 1593.6, 1504.7, 1319.5, 1273.2, 1169.3, 799.0; **M.P**.: 40-43°C.

2-Chloro-*N*-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (3.238)

Prepared by Dr. Sean Preshlock.

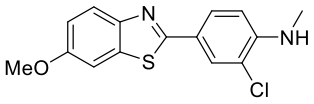


B_2pin_2 (1.10 g, 4.30 mmol, 1.00 equiv.), 4-bromo-2-chloro-*N*-methylaniline (**3.237**, 1.00 g, 4.80 mmol, 1.10 equiv.), $PdCl_2(dppf)\cdot CH_2Cl_2$ (195 mg, 0.24 mmol, 0.05 equiv.) and KOAc (1.40 g, 14.4 mmol, 3.30 equiv.) were weighed into an oven dried 50 mL Schlenk flask, which was then purged with N_2. 15 mL degassed toluene was added and the reaction was stirred at 90 °C. After 2.5 hours, the reaction was cooled to room temperature and the mixture was evaporated to dryness. Flash column chromatography (*n*-hexane/EtOAc 90:10) afforded 2-chloro-*N*-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (**3.238**, 283 mg, 1.06 mmol, 25%) as a white solid.

^{1}H NMR (400 MHz; $CDCl_3$): δ = 7.68 (d, J = 1.4 Hz, 1H), 7.59 (dd, J = 8.1, 1.4 Hz, 1H), 6.60 (d, J = 8.1 Hz, 1H), 4.60 (d, J = 2.9 Hz, 1H), 2.90 (d, J = 4.6 Hz, 3H), 1.31 (s, 12H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 147.2, 135.3, 134.8, 118.6, 109.7, 83.5, 30.1, 24.8; **^{11}B NMR** (128 MHz, $CDCl_3$): δ = 30.5 (br s); **HRMS** (EI): for $C_{13}H_{19}BClNO_2$ [M+] requires m/z = 266.1234; found 266.1227; **IR** (ATR, neat): $\tilde{\nu}$ (cm^{-1}) = 3424, 2979, 1601.9, 1353, 1312, 1144, 1124, 849, 670; **M.P**.: 96-100°C.

2-Chloro-4-(6-methoxybenzo[*d*]thiazol-2-yl)-*N*-methylaniline (3.240)

Prepared by Dr. Sean Preshlock.



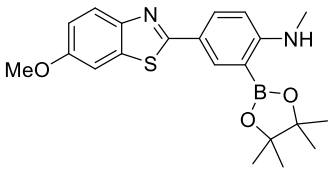
2-Bromo-6-methoxy-benzothiazole (347 mg, 1.40 mmol, 1.17 equiv.), 2-chloro-*N*-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (**3.238**, 316 mg, 1.20 mmol, 1.00 equiv.), $PdCl_2$(dppf)·CH_2Cl_2 (48 mg, 0.05 equiv.) and K_2CO_3 (828 mg, 6.00 mmol, 2.50 equiv.) were weighed into an oven dried 50 mL Schlenk flask, which was then purged with N_2. Degassed DMF (20 mL) and degassed H_2O (8 mL) were added and the reaction was stirred at 80 °C. After 5 hours, the mixture was allowed to cool to room temperature and all volatiles were removed *in vacuo*. Flash column chromatography (*n*-hexane/EtOAc 90:10) afforded 2-chloro-4-(6-methoxybenzo[*d*]thiazol-2-yl)-*N*-methylaniline (**3.240**, 228 mg, 0.75 mmol, 64%) as a light yellow solid.

^{1}H NMR (400 MHz; $CDCl_3$): δ = 8.00 (d, J = 2.1 Hz, 1H), 7.88 (d, J = 8.9 Hz, 1H), 7.82 (dd, J = 8.5, 2.0 Hz, 1H), 7.33 (d, J = 2.5 Hz, 1H), 7.06 (dd, J = 8.9, 2.6 Hz, 1H), 6.69 (d, J = 8.6 Hz, 1H), 4.72 (m, 1H), 3.90 (s, 3H), 2.98 (d, J = 5.2 Hz, 3H); **^{13}C NMR** (101 MHz,

$CDCl_3$): δ = 164.9, 157.4, 148.8, 146.7, 135.9, 127.7, 127.3, 123.0, 122.9, 119.2, 115.2, 110.1, 104.3, 55.8, 30.2; **HRMS** (EI): for $C_{15}H_{13}ClN_2OS$ [M+] requires m/z = 304.0437; found 304.0439; **IR** (ATR, neat): $\tilde{\nu}$ (cm^{-1}) = 3423, 2933, 1605, 1463, 1266, 1224, 1062, 833, 808; **M.P**.: 150-154°C.

4-(6-Methoxybenzo[*d*]thiazol-2-yl)-*N*-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (3.235)

Prepared by Dr. Sean Preshlock.



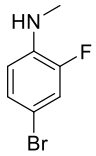
B_2pin_2 (289 mg, 1.10 mmol, 3.00 equiv.), 2-chloro-4-(6-methoxybenzo[*d*]thiazol-2-yl)-*N*-methylaniline (**3.240**, 116 mg, 0.38 mmol, 1.00 equiv.), XPhos-Pd-G2 (18 mg, 23 μmol, 0.06 equiv.), and KOAc (74 mg, 0.76 mmol, 2.00 equiv.) were weighed into an oven dried 25 mL Schlenk flask, which was then purged with N_2. Anhydrous 1,4-dioxane (15 mL) was added and the reaction was stirred at 90°C. After 20 hours, the reaction was cooled to room temperature and the mixture was evaporated to dryness. Semi-preparative HPLC afforded 4-(6-methoxybenzo[*d*]thiazol-2-yl)-*N*-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (**3.235**, 42 mg, 0.10 mmol, 28%) as a white solid.

^{1}H NMR (400 MHz; $CDCl_3$): δ = 8.28 (d, *J* = 2.3 Hz, 1H), 8.03 (dd, *J* = 8.7, 2.3 Hz, 1H), 7.87 (d, *J* = 8.9 Hz, 1H), 7.32 (d, *J* = 2.5 Hz, 1H), 7.04 (dd, *J* = 8.9, 2.6 Hz, 1H), 6.61 (d, *J* = 8.8 Hz, 1H), 6.20-6.18 (m, 1H), 3.89 (s, 3H), 2.93 (d, *J* = 5.0 Hz, 3H), 1.37 (s, 12H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 166.7, 157.1, 157.0, 149.0, 136.7, 135.9, 132.2, 122.7,

121.1, 114.7, 108.8, 104.4, 83.9, 55.8, 30.0, 24.9; **^{11}B NMR** (128 MHz, $CDCl_3$): δ = 30.8 (br s); **HRMS** (ESI^+): for $C_{21}H_{26}O_3N_2B_1S_1^+$ $[M+H]^+$ requires m/z = 397.17517; found 397.17530; **IR** (ATR, neat): $\tilde{\nu}$ (cm^{-1}) = 3418, 2978, 2933, 2831, 1604, 1462, 1404, 1261, 1142, 1063, 862; **M.P**.: 160-164 °C.

4-Bromo-2-fluoro-*N*-methylaniline

Prepared by Dr. Sean Preshlock.

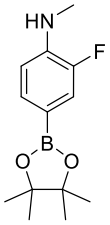


4-Bromo-2-fluoroaniline (1.27 g, 6.70 mmol, 1.00 equiv.) and pyridine (1.90 mL, 23.5 mmol, 3.50 equiv.) were dissolved in dry 1,4-dioxane (45 mL) in an oven dried round bottom flask. $Cu(OAc)_2$ (3.00 g, 16.7 mmol, 2.50 equiv.) was added and the mixture was stirred at room temperature under an atmosphere of air for 15 minutes. Methylboronic acid (1.00 g, 16.7 mmol, 2.50 equiv.) was added and the reaction vessel was equipped with a reflux condenser and heated to 90 °C under an atmosphere of air for three hours. The reaction was cooled to room temperature and the mixture was evaporated to dryness. Flash column chromatography (*n*-hexane/EtOAc 95:5) afforded 4-bromo-2-fluoro-*N*-methylaniline (642 mg, 3.15 mmol, 47%) as a white solid.

^{1}H NMR (400 MHz; $CDCl_3$): δ = 7.16-7.11 (m, 2H), 6.54 (t, J = 9.0 Hz, 1H), 3.96 (br s, 1H), 2.84 (d, J = 4.4 Hz, 3H); **^{13}C NMR** (101 MHz; $CDCl_3$): δ = 151.0 (d, J = 243.2 Hz), 136.9 (d, J = 12.2 Hz), 127.3 (d, J = 3.4 Hz), 117.4 (d, J = 21.5 Hz), 112.2 (d, J = 4.8 Hz), 106.5 (d, J = 9.6 Hz), 30.0; **^{19}F{^{1}H} NMR** (376 MHz; $CDCl_3$): δ = -134.4. The analytical data were in accordance with the literature.[94]

2-Fluoro-*N*-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline

Prepared by Dr. Sean Preshlock.

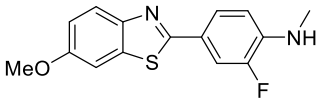


B_2pin_2 (876 mg, 3.45 mmol, 1.10 equiv.), 4-bromo-2-fluoro-*N*-methylaniline (642 mg, 3.15 mmol, 1.00 equiv.), $PdCl_2(dppf)\cdot CH_2Cl_2$ (122 mg, 0.15 mmol, 0.05 equiv.) and KOAc (926 mg, 9.45 mmol, 3.00 equiv.) were weighed into an oven dried 25 mL Schlenk flask, which was then purged with N_2. Degassed toluene (10 mL) was added and the reaction was stirred at 90 °C. After 7 hours, the reaction was cooled to room temperature and the mixture was evaporated to dryness. The product was extracted with Et_2O, loaded onto a short SiO_2 column and eluted with Et_2O. The filtrate was concentrated *in vacuo*. Flash column chromatography (*n*-hexane/EtOAc 90:10) afforded 2-fluoro-*N*-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (504 mg, 2.00 mmol, 32%) as a white solid.

^{1}H NMR (400 MHz; $CDCl_3$): δ = 7.50 (d, J = 7.8 Hz, 1H), 7.38 (d, J = 12.2 Hz, 1H), 6.66 (t, J = 8.3 Hz, 1H), 4.18 (br s, 1H), 2.91 (d, J = 4.8 Hz, 3H), 1.33 (s, 12H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 151.0 (d, J = 239 Hz), 140.4 (d, J = 11.7 Hz), 132.0, 119.6 (d, J = 16.1 Hz), 110.5, 83.5, 29.9, 24.8; **^{19}F NMR** (376 MHz; $CDCl_3$): δ = -139.2 (t, J = 10.9 Hz); **^{11}B NMR** (128 MHz, $CDCl_3$): δ = 30.9 (br s); **HRMS** (ESI^+): a satisfactory mass spectrum of this compound could not be obtained; **IR** (ATR, neat): $\tilde{\nu}$ (cm^{-1}) = 3440, 2917, 2887, 2821, 1616, 1512, 1333, 1282, 1194, 1164, 872, 858, 799; **M.P.**: 41-44 °C

2-Fluoro-4-(6-methoxybenzo[*d*]thiazol-2-yl)-*N*-methylaniline (3.234)

Prepared by Dr. Sean Preshlock.



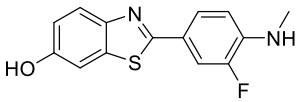
2-Bromo-6-methoxy-benzothiazole (488 mg, 2.00 mmol, 1.00 equiv.), 2-fluoro-*N*-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (504 mg, 2.00 mmol, 1.00 equiv.), $PdCl_2(dppf)\cdot CH_2Cl_2$ (82 mg, 0.10 mmol, 0.05 equiv.) and K_2CO_3 (1.66 g, 12.0 mmol, 6.00 equiv.) were weighed into an oven dried 50 mL Schlenk flask, which was then purged with N_2. Degassed DMF (25 mL) and degassed H_2O (10 mL) were added and the reaction was stirred at 80 °C. After 5 hours the reaction was cooled to room temperature and diluted with H_2O (60 mL), causing a dark brown solid to precipitate. The precipitate was collected by filtration and washed with Et_2O. Flash column chromatography (*n*-hexane/EtOAc 90:10) afforded 2-fluoro-4-(6-methoxybenzo[*d*]thiazol-2-yl)-*N*-methylaniline (**3.234**, 310 mg, 1.08 mmol, 54%) as a light yellow solid.

^{1}H NMR (400 MHz; $CDCl_3$): δ = 7.88 (d, J = 9.0 Hz, 1H), 7.73-7.68 (overlapping multiplet, 2H), 7.33 (d, J = 2.5 Hz, 1H), 7.06 (dd, J = 9.0, 2.6 Hz, 1H), 6.71 (t, J = 8.4 Hz, 1H), 4.29 (br s, 1H), 3.89 (s, 3H), 2.96 (d, J = 5.1 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 165.2, 157.3, 151.3 (d, J = 239.4 Hz), 148.7, 139.8 (d, J = 12.7 Hz), 135.9, 124.3 (d, J = 3.1 Hz), 123.0, 122.2 (d, J = 7.8 Hz), 115.1, 112.8 (d, J = 20.7 Hz), 110.7 (d, J = 3.1 Hz), 104.2, 55.8, 29.9; **^{19}F{^{1}H} NMR** (376 MHz; $CDCl_3$): δ = -137.2; **HRMS** (ESI^+): for $C_{15}H_{14}ON_2FS^+$ $[M+H]^+$ requires m/z = 289.08054; found 289.08069; **IR** (ATR, neat): $\tilde{\nu}$

(cm^{-1}) = 3433, 2936, 2830, 1621, 1543, 1462, 1434, 1292, 1265, 1224, 1060, 855, 806; **M.P.**: 131-134 °C.

2-(3-Fluoro-4-(methylamino)phenyl)benzo[*d*]thiazol-6-ol (3.187)

Prepared by Dr. Sean Preshlock.



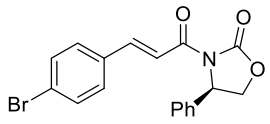
To a solution of 2-fluoro-4-(6-methoxybenzo[*d*]thiazol-2-yl)-*N*-methylaniline (29 mg, 0.1 mmol, 1.0 equiv.) in 1,2-dichloroethane (2 mL) was added BBr_3 (1.0 M in CH_2Cl_2, 250 ◎L, 0.25 mmol, 2.5 equiv.). The reaction was stirred at 80 °C for 30 minutes. The reaction was cooled to room temperature and quenched with saturated aqueous solution of $NaHCO_3$ (20 mL) and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic extracts were washed with brine (30 mL), dried over $MgSO_4$ and concentrated *in vacuo* to give the crude product. Flash column chromatography (*n*-hexane/EtOAc 75:25) afforded 2-(3-fluoro-4-(methylamino)phenyl)benzo[*d*]thiazol-6-ol (**3.187**, 21.6 mg, 0.08 mmol, 79%) as a light yellow solid.

^{1}H NMR (400 MHz; DMSO-d_6): δ = 9.77 (s, 1H), 7.73 (d, J = 8.8 Hz, 1H), 7.63 (t, J = 2.6 Hz, 1H), 7.61 (s, 1H), 7.34 (d, J = 2.4 Hz, 1H), 6.93 (dd, J = 8.8, 2.5 Hz, 1H), 6.74 (t, J = 8.7 Hz, 1H), 6.25 (dd, J = 4.8, 2.0 Hz, 1H), 2.79 (d, J = 4.8 Hz, 3H); **^{13}C NMR** (101 MHz, DMSO-d_6): δ = 163.2, 155.2, 150.5 (d, J = 239.7 Hz), 147.2, 140.2 (d, J = 12.7 Hz), 135.4, 124.4, 122.7, 120.2 (d, J = 6.4 Hz), 115.7, 112.0 (d, J = 20.1 Hz), 110.9 (d, J = 4.6 Hz), 106.8, 29.3; **^{19}F{^{1}H} NMR** (376 MHz; DMSO-d_6): δ = -135.0. The analytical data were in accordance with the literature.[95]

A.2.7 Paroxetine

(*R*)-3-(3-(4-Bromophenyl)acryloyl)-4-phenyloxazolidin-2-one (3.253)

Prepared by Dr. Enrico Emer.

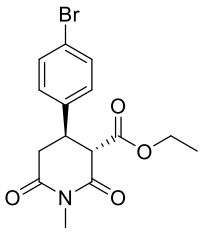


Adapting a known procedure,[96] to a solution of 4-bromocinnamic acid (37.5 g, 165 mmol, 1.00 equiv.) in CH_2Cl_2 (200 mL) was added Et_3N (55.0 mL, 396 mmol, 2.40 equiv.) and pivaloyl chloride (24.4 mL, 198 mmol, 1.20 equiv.) . The reaction mixture was stirred at room temperature for two hours. (*R*)-4-Phenyl-2-oxazolidinone (27.0 g, 165 mmol, 1.00 equiv.) and DMAP (202 mg, 0.01 equiv) were added to the reaction, which was then refluxed for 15 hours. The reaction mixture was then cooled to room temperature, diluted with water and extracted with CH_2Cl_2 (3 x 100 mL). The combined organic phases were dried with $MgSO_4$ and concentrated *in vacuo*. Flash column chromatography (*n*-hexane/EtOAc 70:30) afforded (*R*)-3-(3-(4-bromophenyl)acryloyl)-4-phenyloxazolidin-2-one (**3.253**, 45.0 g, 121 mmol, 73%) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.93 (d, *J* = 15.7 Hz, 1H), 7.70 (d, *J* = 15.7 Hz, 1H), 7.51 (d, *J* = 8.5 Hz, 2H), 7.44 (d, *J* = 8.5 Hz, 2H), 7.39 (dd, *J* = 6.7, 1.0 Hz, 2H), 7.36-7.34 (m, 3H), 5.55 (dd, *J* = 8.7, 3.9 Hz, 1H), 4.74 (t, *J* = 8.8 Hz, 1H), 4.32 (dd, *J* = 8.9, 3.9 Hz, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 164.4, 153.7, 145.1, 138.9, 133.3, 132.0, 129.9, 129.1, 128.7, 125.9, 124.9, 117.4, 70.0, 57.8; **HRMS** (ESI^+): for $C_{18}H_{14}O_3NBrNa$ [M+Na] requires m/z = 394.00493; found 394.00513; **IR** (ATR, neat): $\tilde{\nu}$ (cm^{-1}) = 3097, 3033, 2917, 1774, 1682, 1620, 1487, 1340, 1198, 1064, 817, 712; **M.P**.: 94-104 °C.

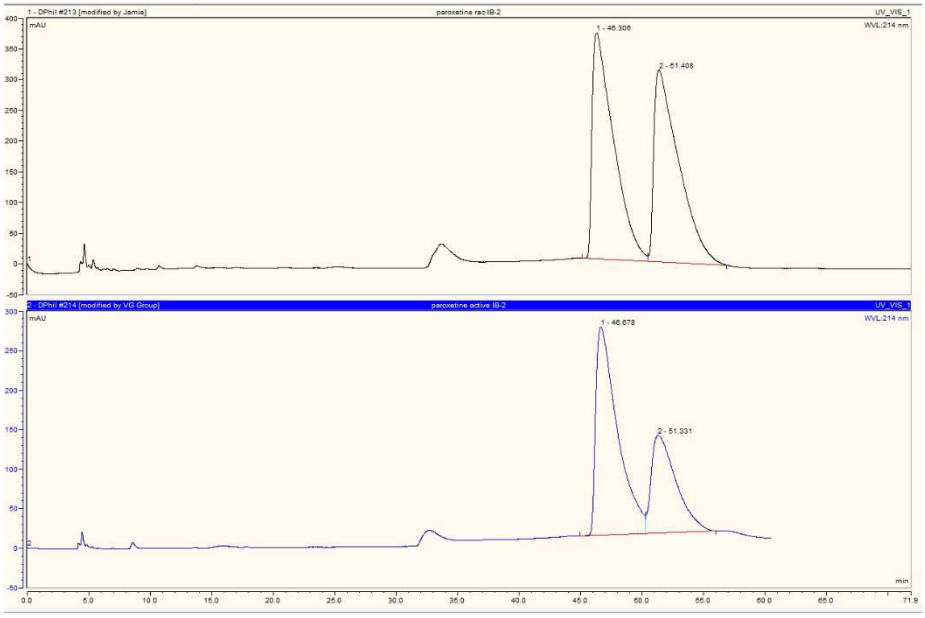
(3*S*,4*R*)-Ethyl 4-(4-bromophenyl)-1-methyl-2,6-dioxopiperidine-3-carboxylate (3.255)

Prepared by Dr. Enrico Emer.



Adapting a known procedure,[96] to a stirred solution of ethyl-*N*-methylmalonamide (14.5 g, 100 mmol, 1.00 equiv.) in DMSO (120 mL), was added NaH (60% in mineral oil, 5.60 g, 140 mmol, 1.40 equiv.) at 0° C under N_2. The reaction mixture was kept at 0 °C for 20 minutes, then (*R*)-3-(3-(4-bromophenyl)acryloyl)-4-phenyloxazolidin-2-one (37.2 g, 100 mmol, 1.00 equiv.) was added in one portion and the whole mixture was stirred at room temperature for 5 hours. The mixture was neutralised with AcOH (16 mL) and extracted with EtOAc (2 x 100 mL). The combined organic fractions were washed with water (4 x 100 mL) and brine, dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography (*n*-hexane/EtOAc 70:30) afforded (3*S*,4*R*)-ethyl 4-(4-bromophenyl)-1-methyl-2,6-dioxopiperidine-3-carboxylate (**3.255**, 27.0 g, 76.2 mmol, 77%) as a white solid.

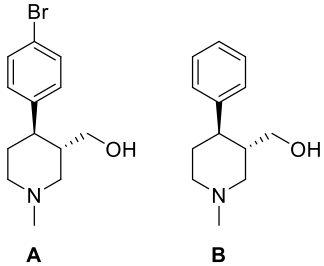
Enantiomeric excess of the product was determined to be 30% on a Chiralpak IB column (eluent *n*-hexane/*i*-PrOH 90:10, flow: 1.0 mL/min, ◎◎= 214 nm. T_{major} = 46 min, t_{minor} = 51 min).



^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.47 (d, J = 8.5 Hz, 2H), 7.10 (d, J = 8.3 Hz, 2H), 4.16-4.04 (m, 2H), 3.78 (d, J = 11.5 Hz, 1H), 3.65 (td, J = 11.8, 4.4 Hz, 1H), 3.20 (s, 3H), 2.99 (dd, J = 17.4, 4.5 Hz, 1H), 2.80 (dd, J = 17.4, 12.1 Hz, 1H), 1.11 (t, J = 7.1 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 170.1, 168.4, 167.4, 137.6, 132.2, 128.5, 121.9, 61.9, 55.9, 38.6, 37.8, 26.9, 13.9; **HRMS** (ESI^+): for $C_{15}H_{16}BrNNaO_4$ [M+Na] requires m/z = 376.01549; found 376.01556; **[α]**$_D^{25}$ = –12.5° (c = 1.0, EtOH); **IR** (ATR, neat): $\tilde{\nu}$ (cm^{-1}) = 2987, 2936, 1743, 1726, 1669, 1491, 1419, 1305, 1132, 1010, 822; **M.P.**: 109-114 °C.

((3*S*,4*R*)-4-(4-Bromophenyl)-1-methylpiperidin-3-yl)methanol (3.256)

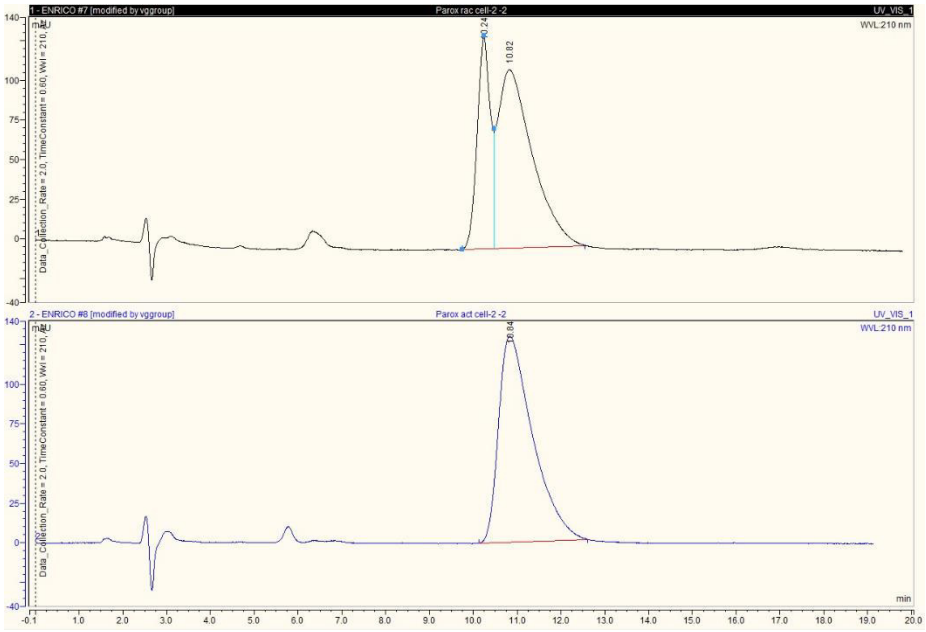
Prepared by Dr. Enrico Emer.



Adapting a known procedure,[97] to a stirred solution of $LiAlH_4$ (8.00 g, 213 mmol, 2.80 equiv.) in THF (70 mL) and toluene (24 mL) at 0 °C was slowly added a solution of (3*S*,4*R*)-ethyl 4-(4-bromophenyl)-1-methyl-2,6-dioxopiperidine-3-carboxylate (**3.255**, 27.0 g, 76.2 mmol, 1.00 equiv.) in THF (70 mL).

The resulting mixture was heated to 65 °C for 8 hours. The mixture was then cooled to 0 °C, quenched with water (8.0 mL) and basified with 15% NaOH (8.0 mL). A second aliquot of water (24 mL) was added to the reaction mixture, which was stirred for 15 minutes. $MgSO_4$ was added with stirring and the corresponding solid was filtered and washed with THF. The filtrate was concentrated *in vacuo*. Flash column chromatography (EtOAc/MeOH/Et_3N 80:10:10) afforded an inseparable mixture of ((3*S*,4*R*)-4-(4-bromophenyl)-1-methylpiperidin-3-yl)methanol (**A**) and ((3*S*,4*R*)-1-methyl-4-phenylpiperidin-3-yl)methanol (**B**) (**3.256 A:B** = 2.5 : 1, 16.4 g, 56.7 mmol, 77%).

The enantiopure mixture of **A** and **B** was isolated in 38% yield (8.18 g, 29.0 mmol) by diastereomeric resolution with (2*R*,3*R*)-di-*O*-*O*′-*p*-toluyl-D-tartaric acid ((-)DTTA).[98] Enantiomeric excess of the mixed products was determined to be > 99% on a LUX cellulose-2 column with 0.5% (20 mM) of NH_4HCO_3/DEA / 99.5% MeCN as eluent, flow: 0.5 mL/min, ◎◎= 210 nm. T_{minor} = 10.2 min, t_{major} = 10.8 min.

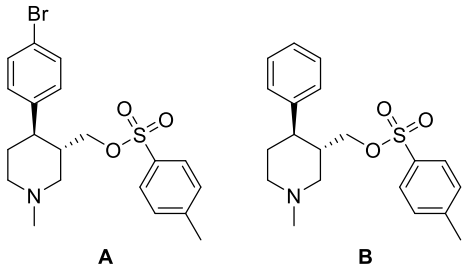


A ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35 (d, *J* = 8.4 Hz, 2H), 7.02 (d, *J* = 8.4 Hz, 2H), 4.07 (br s, 1H), 3.31-3.25 (m, 1H), 3.17 (m, 1H), 3.11-3.01 (m, 1H), 2.83 (br d, *J* =10.8 Hz, 1H), 2.22 (s, 3H), 2.22-2.11 (m, 1H), 2.01-1.86 (m, 2H), 1.82 (t, *J* = 11.0 Hz, 1H), 1.77-1.64 (m, 2H); **A ^{13}C NMR** (101 MHz, $CDCl_3$): δ = 143.2, 131.4, 129.1, 119.8, 62.9, 59.4 (d, *J* = 6.4 Hz), 55.9, 46.2 (m), 43.9 (d, *J* = 7.9 Hz), 43.7 (d, *J* = 4.8 Hz), 33.9 (d, *J* = 3.2 Hz); **A MS** (ESI^+): for $C_{13}H_{19}BrON^+$ $[M+H]^+$ requires m/z = 284.1, found 284.1.

B ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.26-7.21 (m, 3H), 7.18-7.11 (m, 2H), 4.07 (br s, 1H), 3.33-3.28 (m, 1H), 3.20 (m, 1H), 3.11-3.01 (m, 1H), 2.83 (br d, *J* =10.8 Hz, 1H), 2.22 (s, 3H), 2.22-2.11 (m, 1H), 2.01-1.86 (m, 2H), 1.81 (t, *J* = 11.1 Hz, 1H), 1.77-1.64 (m, 2H); **B ^{13}C NMR** (101 MHz, $CDCl_3$): δ = 144.1, 128.4, 127.3, 126.3, 63.2, 59.6 (d, *J* = 6.6 Hz), 56.1, 46.2 (m), 44.4 (d, *J* = 4.3 Hz), 44.1 (d, *J* = 7.9 Hz), 34.0 (d, *J* = 4.0 Hz); **B MS** (ESI^+): for $C_{13}H_{20}ON^+$ $[M+H]^+$ requires m/z = 206.2, found 206.2.

((3*S*,4*R*)-4-(4-Bromophenyl)-1-methylpiperidin-3-yl)methyl 4-methylbenzenesulfonate (3.257)

Prepared by Dr. Enrico Emer.



Adapting a known procedure,[97] a mixture of ((3*S*,4*R*)-4-(4-bromophenyl)-1-methylpiperidin-3-yl)methanol and ((3*S*,4*R*)-1-methyl-4-phenylpiperidin-3-yl)methanol (**3.256**, 8.18 g, 29.0 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (80 mL). Dimethylethylamine (4.70 mL, 43.4 mmol, 1.50 equiv.) was added and the resulting mixture was cooled to 0

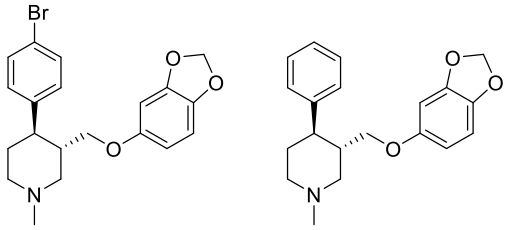
°C. A solution of *p*-toluenesulfonyl chloride (8.27 g, 43.4 mmol, 1.50 equiv.) in CH_2Cl_2 (40 mL) was slowly added to the reaction mixture, after which the reaction was stirred at 0 °C for one hour. A solution of aqueous NaOH (0.1 M, 50 mL) was added and the mixture was stirred for one hour. The organic layer was then separated, dried ($MgSO_4$), filtered and concentrated *in vacuo*. Flash column chromatography (EtOAc/MeOH/Et_3N 80:10:10) afforded an inseparable mixture of ((3*S*,4*R*)-4-(4-bromophenyl)-1-methylpiperidin-3-yl)methyl 4-methylbenzenesulfonate (**A**) and ((3*S*,4*R*)-1-methyl-4-phenylpiperidin-3-yl)methyl 4-methylbenzenesulfonate (**B**) (**3.257**, **A:B** = 2.5 : 1, 11.30 g, 25.8 mmol, 89%).

A ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.54 (d, *J* = 8.3 Hz, 2H), 7.23-7.16 (m, 4H), 6.81 (d, *J* = 8.4 Hz, 2H), 3.66 (dd, *J* = 9.9, 2.8 Hz, 1H), 3.48 (dd, *J* = 9.9, 6.3 Hz, 1H), 2.95-2.89 (m, 1H), 2.38 (s, 3H), 2.23 (s, 3H), 2.23-2.15 (m, 1H), 2.09-1.86 (m, 2H), 1.85 (t, *J* = 11.2 Hz, 1H), 1.75-1.60 (m, 2H); **A ^{13}C NMR** (101 MHz, $CDCl_3$): δ = 144.8, 141.8, 132.3, 131.6, 129.7, 128.9, 127.7, 120.2, 70.6, 58.4, 55.7, 46.3, 43.0, 41.2, 34.0, 21.6; **A MS** (ESI^+): for $C_{20}H_{25}BrNO_3S^+$ $[M+H]^+$ requires m/z = 438.1, found 438.0.

B ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.55 (d, *J* = 8.3 Hz, 2H), 7.18 (d, *J* = 7.8 Hz, 2H), 7.13-7.08 (m, 3H), 6.95 (dd, *J* = 7.6, 1.8 Hz, 2H), 3.69 (dd, *J* = 9.9, 2.9 Hz, 1H), 3.51 (dd, *J* = 9.9, 6.9 Hz, 1H), 2.98-2.90 (m, 1H), 2.36 (s, 3H), 2.23 (s, 3H), 2.23-2.15 (m, 1H), 2.09-1.86 (m, 2H), 1.82 (t, *J* = 11.2 Hz, 1H), 1.75-1.60 (m, 2H); **B ^{13}C NMR** (101 MHz, $CDCl_3$): δ = 144.5, 142.7, 132.5, 129.7, 128.6, 127.7, 127.2, 126.6, 71.0, 58.6, 55.9, 46.2, 43.6, 41.2, 34.1, 21.6; **B MS** (ESI^+): for $C_{20}H_{26}NO_3S^+$ $[M+H]^+$ requires m/z = 360.2, found 360.2.

(3*S*,4*R*)-3-((Benzo[*d*][1,3]dioxol-5-yloxy)methyl)-4-(4-bromophenyl)-1-methylpiperidine (3.259)

Prepared by Dr. Enrico Emer.



Adapting a known procedure,[99] to a stirred suspension of NaH (60% in mineral oil, 1.14 g, 28.4 mmol, 1.10 equiv.) in DMF (50 mL), was slowly added a solution of sesamol (4.27 g, 30.9 mmol, 1.20 equiv.) in DMF (50 mL). The reaction mixture was refluxed for three hours, then cooled to 0 °C. A solution of ((3*S*,4*R*)-4-(4-bromophenyl)-1-methylpiperidin-3-yl)methyl 4-methylbenzenesulfonate and ((3*S*,4*R*)-1-methyl-4-phenylpiperidin-3-yl)methyl 4-methylbenzenesulfonate (**3.257**, 11.3 g, 25.8 mmol, 1.0 equiv.) in DMF (50 mL) was then added and the corresponding mixture was heated under reflux for 4 hours. The mixture was quenched with H_2O and the solvent was removed *in vacuo*. Flash column chromatography (EtOAc/MeOH/Et_3N 80:10:10) afforded an inseparable mixture of (3*S*,4*R*)-3-((benzo[*d*][1,3]dioxol-5-yloxy)methyl)-4-(4-bromophenyl)-1-methylpiperidine (**A**) and (3*S*,4*R*)-3-((benzo[*d*][1,3]dioxol-5-yloxy)methyl)-1-methyl-4-phenylpiperidine (**B**) (**3.259**, **A:B** = 2.5 : 1, 7.29 g, 21.0 mmol, 81%).

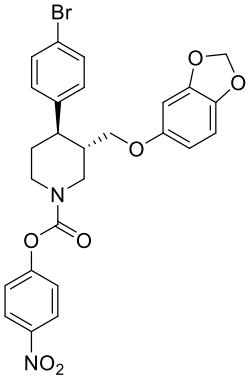
A ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40 (d, *J* = 8.4 Hz, 2H), 7.08 (d, *J* = 8.4 Hz, 2H), 6.62 (d, *J* = 8.5 Hz, 1H), 6.35 (d, *J* = 2.4 Hz, 1H), 6.13 (dd, *J* = 8.4, 2.5 Hz, 1H), 5.87 (s, 2H), 3.57 (dd, *J* = 9.4, 2.8 Hz, 1H), 3.21-3.15 (m, 1H), 3.01-2.92 (m, 1H), 2.48-2.38 (m, 1H), 2.36 (s, 3H), 2.27-2.17 (m, 1H), 2.10-1.96 (m, 2H), 1.95-1.77 (m, 2H); **A ^{13}C NMR**

(101 MHz, $CDCl_3$): δ = 154.2, 148.1, 143.0, 141.5, 131.6, 129.2, 120.1 107.8, 105.4, 101.0, 97.9, 69.4, 59.4, 56.0, 46.5, 43.7, 41.9, 34.1; **A MS** (ESI^+): for $C_{20}H_{23}BrNO_3^+$ $[M+H]^+$ requires m/z = 404.1, found 404.0.

B ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.31-7.27 (m, 3H), 7.21 (d, *J* = 7.2 Hz, 2H), 6.61 (d, *J* = 8.5 Hz, 1H), 6.34 (d, *J* = 2.4 Hz, 1H), 6.13 (dd, *J* = 8.4, 2.5 Hz, 1H), 5.86 (s, 2H), 3.59 (dd, *J* = 9.5, 2.9 Hz, 1H), 3.25-3.20 (m, 1H), 3.01-2.92 (m, 1H), 2.48-2.38 (m, 1H), 2.37 (s, 3H), 2.34-2.27 (m, 1H), 2.10-1.96 (m, 2H), 1.95-1.77 (m, 2H); **B ^{13}C NMR** (101 MHz, $CDCl_3$): δ = 154.3, 148.0, 143.9, 141.4, 128.6, 127.4, 126.5, 107.7, 105.5, 100.9, 97.9, 69.6, 59.6, 56.2, 46.4, 44.3, 41.8, 34.3; **B MS** (ESI^+): for $C_{20}H_{24}NO_3^+$ $[M+H]^+$ requires m/z = 326.2, found 326.2.

(3*S*,4*R*)-4-Nitrophenyl 3-((benzo[*d*][1,3]dioxol-5-yloxy)methyl)-4-(4-bromophenyl)piperidine-1-carboxylate (3.261)

Prepared by Dr. Enrico Emer.



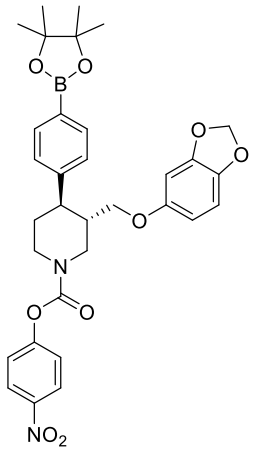
Adapting a known procedure,[100] to a stirred solution of (3*S*,4*R*)-3-((benzo[*d*][1,3]dioxol-5-yloxy)methyl)-4-(4-bromophenyl)-1-methylpiperidine and (3*S*,4*R*)-3-((benzo[*d*][1,3]dioxol-5-yloxy)methyl)-1-methyl-4-phenylpiperidine (**3.259**, 7.29 g, 21.0 mmol, 1.0 equiv.) in toluene (60 mL) at 110 °C, was slowly added a solution 4-nitrophenyl chloroformate (6.23 g, 30.9 mmol, 1.80 equiv.) in toluene (10 mL). The resulting mixture was stirred at 110 °C for 3 hours, then the solution was cooled to 60 °C and Et_3N (2.56 mL, 18.3 mmol,

1.03 equiv.) was added over about 15 minutes. The reaction mixture was stirred at 60 °C for one hour. Thereafter, the reaction mixture was cooled to room temperature and an aqueous NaOH solution (5% w/v, 80 mL) was added and the mixture stirred for 20 min. The organic phase was separated and the aqueous phase was extracted with toluene (3 x 60 mL). The combined organic phases were washed with brine, dried with $MgSO_4$, and concentrated *in vacuo* to give the crude product. Flash column chromatography (*n*-hexane/EtOAc 90:10 to 70:30) afforded (3*S*,4*R*)-4-nitrophenyl 3-((benzo[*d*][1,3]dioxol-5-yloxy)methyl)-4-(4-bromophenyl)piperidine-1-carboxylate (**3.261**, 5.25 g, 9.46 mmol, 45%) as a yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.28 (d, *J* = 9.2 Hz, 2H), 7.45 (d, *J* = 8.3 Hz, 2H), 7.35 (d, *J* = 8.5 Hz, 2H), 7.11 (d, *J* = 8.4 Hz, 2H), 6.65 (d, *J* = 8.4 Hz, 1H), 6.38 (s, 1H), 6.16 (d, *J* = 8.4 Hz, 1H), 5.90 (s, 2H), 4.60 (t, *J* = 15.6 Hz, 1H), 4.43 (t, *J* = 14.8 Hz, 1H), 3.67 (br s, 1H), 3.53 (br s, 1H), 3.15 (m, 1H), 3.02 (q, *J* = 11.8 Hz, 1H), 2.86-2.74 (m, 1H), 2.17 (br s, 1H), 1.95 (d, *J* = 12.4 Hz, 1H), 1.85 (qd, *J* = 12.7, 3.7 Hz, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$) (1:1 mixture of rotamers): δ = 156.2, (154.0, 153.9, rotamers **I** and **II**), 152.2, 148.2, 144.8, 141.7, 131.9, 129.1, 125.1, 122.3, 120.7, 107.9, 105.6, 101.2, 98.0, (68.5, 68.3, rotamers **I** and **II**), (48.0, 47.5, rotamers **I** and **II**), (45.2, 44.8, rotamers **I** and **II**), (44.0, 43.83, rotamers **I** and **II**), (41.9, 41.6, rotamers **I** and **II**), (33.7, 33.2, rotamers **I** and **II**); **HRMS** (CI^+): for $C_{26}H_{24}BrN_2O_7^+$ $[M+H]^+$ requires m/z = 555.0761, found 555.0751; **IR** (ATR, neat): $\tilde{\nu}$ (cm^{-1}) = 2930, 2866, 1722, 1521, 1488, 1345, 1201, 1186, 1037, 866, 817, 747; **M.P**.: 56-58 °C.

(3*S*,4*R*)-4-Nitrophenyl 3-((benzo[*d*][1,3]dioxol-5-yloxy)methyl)-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperidine-1-carboxylate (3.262)

Prepared by Dr. Enrico Emer.



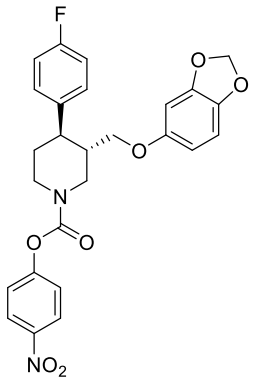
Adapting a known procedure,[101] $Pd(dppf)Cl_2$ (19.7 mg, 0.03 mmol, 0.03 equiv.) was added to a mixture of (3*S*,4*R*)-4-nitrophenyl 3-((benzo[*d*][1,3]dioxol-5-yloxy)methyl)-4-(4-bromophenyl)piperidine-1-carboxylate (**3.261**, 500 mg, 0.90 mmol, 1.00 equiv.), KOAc (265 mg, 2.70 mmol, 3.00 equiv.) and B_2pin_2 (252 mg, 0.99 mmol, 1.10 equiv.) in DMF (15 mL). The mixture was stirred at 80 °C under N_2 for 5 hours. The reaction mixture was cooled to room temperature, diluted with H_2O (50 mL) and extracted with Et_2O (3 x 50 mL). The combined organic phases were washed with brine (100 mL), dried over $MgSO_4$ and concentrated *in vacuo* to give the crude product. Flash column chromatography (*n*-hexane/EtOAc 90:10) afforded (3*S*,4*R*)-4-nitrophenyl 3-((benzo[*d*][1,3]dioxol-5-yloxy)methyl)-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperidine-1-carboxylate (**3.262**, 452 mg, 0.75 mmol, 83%) as a light yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.28 (d, *J* = 9.2 Hz, 2H), 7.78 (d, *J* = 7.8 Hz, 2H), 7.36-7.34 (m, 2H), 7.24 (d, *J* = 8.1 Hz, 2H), 6.63 (d, *J* = 8.4 Hz, 1H), 6.37 (d, *J* = 2.3 Hz, 1H), 6.15 (d, *J* = 8.4 Hz, 1H), 5.89 (s, 2H), 4.62 (t, *J* = 17.0 Hz, 1H), 4.43 (t, *J* = 14.8 Hz, 1H), 3.66 (m, 1H), 3.52 (m, 1H), 3.13 (q, *J* = 13.1 Hz, 1H), 3.01 (t, *J* = 12.5 Hz, 1H), 2.87-2.74 (m, 1H), 2.26-2.25 (m, 1H), 1.97-1.89 (m, 2H), 1.35 (s, 12H); **^{13}C NMR** (101 MHz, $CDCl_3$) (1:1 mixture of rotamers): δ = 156.3, (154.1, 153.9, rotamers **I** and **II**), 152.2,

148.1, 145.9, 144.8, 141.8 (d, J = 8.3 Hz), 135.3, 126.8, 125.1, 122.3, 107.8, 105.6, 101.1, 98.1, 83.8, (68.8, 68.5, rotamers **I** and **II**), (48.1, 47.6, rotamers **I** and **II**), (45.3, 44.9, rotamers **I** and **II**), (44.8, 44.6, rotamers **I** and **II**), (41.8, 41.4, rotamers **I** and **II**), (33.7, 33.2, rotamers **I** and **II**), 24.85; **^{11}B NMR** (128 MHz, $CDCl_3$): δ = 31.4 (br s); **HRMS** (CI^+): for $C_{32}H_{36}BN_2O_9^+$ $[M+H]^+$ requires m/z = 603.2508, found 603.2478; **IR** (ATR, neat): $\tilde{\nu}$ (cm^{-1}) = 2977, 1726, 1611, 1522, 1488, 1360, 1347, 1203, 1089; **M.P**.: 63-65 °C.

(3*S*,4*R*)-4-Nitrophenyl 3-((benzo[*d*][1,3]dioxol-5-yloxy)methyl)-4-(4-fluorophenyl)piperidine-1-carboxylate (3.263)

Prepared by Dr. Enrico Emer.



Adapting a known procedure,[101] to a stirred solution of (3*S*,4*R*)-3-[(2*H*-1,3-benzodioxol-5-yloxy)methyl]-4-(4-fluorophenyl)piperidine hydrochloride (400 mg, 1.09 mmol, 1.00 equiv.) in toluene (5 mL) at 60° C, was slowly added a solution 4-nitrophenyl chloroformate (397 mg, 1.97 mmol, 1.80 equiv.) in toluene (2 mL). The resulting mixture was stirred at 60° C for one hour, then Et_3N (456 ◎L, 3.27 mmol, 3.00 equiv.) was added over about 5 minutes. The corresponding solution was stirred at 60 °C for one hour. Thereafter, the reaction mixture was cooled to room temperature and an aqueous NaOH solution (5% w/v, 10 mL) was added and the mixture stirred for 20 min. The organic phase was separated and the aqueous phase was extracted with toluene (3 x 10 mL). The combined organic phases were washed with brine, dried with $MgSO_4$, and

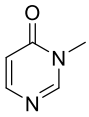
concentrated *in vacuo* to give the crude product. Flash column chromatography (*n*-hexane/EtOAc 90:10 to 70:30) afforded (3*S*,4*R*)-4-nitrophenyl 3-((benzo[*d*][1,3]dioxol-5-yloxy)methyl)-4-(4-fluorophenyl)piperidine-1-carboxylate (**3.263**, 503 mg, 1.02 mmol, 93%) as a yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.22 (d, *J* = 9.1 Hz, 2H), 7.34 (d, *J* = 8.5 Hz, 2H), 7.19 (dd, *J* = 8.6, 5.4 Hz, 2H), 7.00 (t, *J* = 8.6 Hz, 2H), 6.62 (dd, *J* = 7.9, 6.0 Hz, 1H), 6.38 (d, *J* = 7.6 Hz, 1H), 6.16 (t, *J* = 7.9 Hz, 1H), 5.85 (s, 2H), 4.61 (t, *J* = 15.6 Hz, 1H), 4.42 (t, *J* = 16.1 Hz, 1H), 3.66 (t, *J* = 9.8 Hz, 1H), 3.53 (t, *J* = 8.0 Hz, 1H), 3.23-3.07 (m, 1H), 3.07-2.93 (m, 1H), 2.80 (q, *J* = 11.3 Hz, 1H), 2.26-2.10 (m, 1H), 1.98-1.76 (m, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) (1:1 mixture of rotamers): δ = 161.29 (d, *J* = 244 Hz), 156.1, 153.8 (d, *J* = 9.6 Hz, 1C), 152.0, 147.9, 144.5, 141.5 (d, *J* = 8 Hz), 138.3 (d, *J* = 3 Hz), 128.5 (d, *J* = 8 Hz), 124.7, 122.0 (d, *J* = 4 Hz), 115.3 (d, *J* = 21 Hz), 107.6, 105.3 (d, *J* = 9 Hz), 107.6, 105.3, 100.9, 97.7, (68.3, 68.2, rotamers **I** and **II**), (47.7, 47.3, rotamers **I** and **II**), (45.0, 44.6, rotamers **I** and **II**), (43.4, 43.3, rotamers **I** and **II**), (41.8, 41.5, rotamers **I** and **II**), (33.7, 33.1, rotamers **I** and **II**); **^{19}F NMR** (376 MHz, $CDCl_3$): δ = -115.56 (t, *J* = 7.0 Hz); **HRMS** (CI^+): for $C_{26}H_{24}FN_2O_7^+$ $[M+H]^+$ requires m/z = 495.1562, found 495.1568; **IR** (ATR, neat): $\tilde{\nu}$ (cm^{-1}) = 2925, 2867, 1721, 1613, 1509, 1488, 1344, 1199, 1185, 1037, 832; **M.P.**: 50-52 °C.

A.2.8 Risperidone

3-Methylpyrimidin-4(3*H*)-one (3.288)

Prepared by Dr. Michael Schedler.

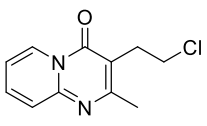


Following a known procedure,[102] pyrimidin-4(3H)-one (2.00 g, 20.8 mmol, 1.0 equiv.), K_2CO_3 (5.74 g, 41.6 mmol, 2.0 equiv.) and MeI (1.94 mL, 31.2 mmol, 1.5 equiv.) were suspended in anhydrous MeOH (40 mL) and the mixture was heated to reflux for 15 hours. The mixture was then cooled to room temperature and filtered. All volatiles of the filtrate were removed *in vacuo* and the residue was dissolved in water (200 mL). The aqueous solution was extracted with $CHCl_3$ (3 x 200 mL) and the combined organic phases were dried with $MgSO_4$, filtered and all volatiles were removed *in vacuo*. The resulting solid was purified by flash column chromatography on silica (CH_2Cl_2/MeOH 95:5) yielding 3-methylpyrimidin-4(3H)-one (**3.288**, 1.06 g, 9.63 mmol, 48%) as a colourless solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.09 (s, 1H), 7.86 (d, J = 6.6 Hz, 1H), 6.42 (dd, J = 6.6, 1.0 Hz, 1H), 3.50 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 161.5, 153.7, 151.5, 115.8, 34.5. Analytical data were in accordance with the literature.[102]

3-(2-Chloroethyl)-2-methyl-4*H*-pyrido[1,2-a]pyrimidin-4-one

Prepared by Dr. Michael Schedler.



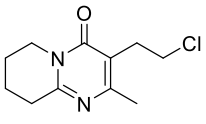
Following a known procedure,[103] 2-aminopyridine (12.1g, 128 mmol, 1.0 equiv.) and 2-acetylbutyrolactone (22.2 mL, 206 mmol, 1.6 equiv.) were dissolved in anhydrous toluene (300 mL) and $POCl_3$ (60 mL, 773

mmol, 6.0 equiv.) was added to the mixture over 60 min. The mixture was then refluxed for 5 h. After the reaction was cooled to room temperature, all volatiles were removed *in vacuo*. The residue was poured in a mixture of ice (200 mL) and aqueous NH_3 solution (1M, 500 mL). The aqueous mixture was extracted with CH_2Cl_2 (3 x 200 mL) and the combined organic phases were dried with $MgSO_4$, filtered and all volatiles were removed *in vacuo*. The residue was dissolved in *i*-PrOH (125 mL) and the suspension was heated to reflux in order to dissolve the solid. The solution was then slowly cooled to 0 °C. The formed precipitate was filtered off and dried *in vacuo* yielding 3-(2-chloroethyl)-2-methyl-4*H*-pyrido[1,2-a]pyrimidin-4-one (7.09 g, 31.8 mmol, 25%) as an off-white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.04 (dt, *J* = 7.1, 1.1 Hz, 1H), 8.31 (d, *J* = 8.9 Hz, 1H), 8.01 (td, *J* = 7.0, 3.5 Hz, 1H), 7.38 (t, *J* = 6.8 Hz, 1H), 3.80 (t, *J* = 6.6 Hz, 2H), 3.14 (t, *J* = 6.6 Hz, 2H), 2.70 (s, 3H); **MS** (ESI^+) for $C_{11}H_{12}ClN_2O^+$ $[M+H]^+$ requires m/z = 223.1, found 223.1. The analytical data were in accordance with the literature.[104]

3-(2-Chloroethyl)-2-methyl-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidin-4-one (3.297)

Prepared by Dr. Michael Schedler.



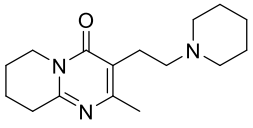
3-(2-Chloroethyl)-2-methyl-4*H*-pyrido[1,2-a]pyrimidin-4-one (6.00 g, 26.9 mmol, 1.0 equiv.) was dissolved in EtOH (100 mL) and Pd/C (100 mg) was added to the solution. The mixture was stirred under 1 atmosphere of H_2 gas for 20 h. The mixture was then filtered through Celite and all volatiles of the

filtrate were removed *in vacuo*. The resulting yellow oil was purified by flash column chromatography on silica (CH_2Cl_2/MeOH 98:2 to 97:3) yielding 3-(2-chloroethyl)-2-methyl-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidin-4-one (**3.297**, 2.88 g, 12.7 mmol, 47%) as an off-white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.89 (t, J = 6.22 Hz, 2H), 3.72 (t, J = 6.89 Hz, 2H), 2.97 (t, J = 6.9 Hz, 2H), 6.65 (t, J = 6.7 Hz, 2H), 2.30 (s, 3H), 1.97–1.83 (m, 4H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 162.4, 159.9, 156.7, 117.4, 42.9, 42.8, 31.6, 30.2, 22.0, 21.8, 19.3; **HRMS** (ESI$^+$) for $C_{11}H_{16}ON_2Cl^+$ $[M+H]^+$ requires m/z = 227.09457, found 227.09458; **IR** (ATR, neat) $\tilde{\nu}$ (cm^{-1}) = 2956, 2907, 1636, 1586, 1535, 1444, 1410, 1393, 1329, 1309, 1274, 1225, 1180, 1089, 1012, 955, 912, 885, 830, 811, 781, 702, 649; **M.P.**: 57 °C.

2-Methyl-3-(2-(piperidin-1-yl)ethyl)-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (3.289)

Prepared by Dr. Enrico Emer.



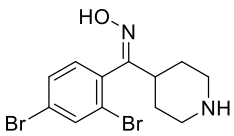
3-(2-Chloroethyl)-2-methyl-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**3.297**, 134 mg, 0.59 mmol, 1.0 equiv.) and piperidine (117 µL, 1.18 mmol, 2.0 equiv.) were dissolved in MeCN (10 mL). Then K_2CO_3 (163 mg, 1.18 mmol, 2.0 equiv.) and KI (98 mg, 0.59 mmol, 1.0 equiv.) were added and the corresponding mixture was stirred at 80 °C for 8 h. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. Flash column chromatography (EtOAc/MeOH/Et_3N 90:5:5) afforded 2-methyl-3-(2-

(piperidin-1-yl)ethyl)-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**3.289**, 148 mg, 0.54 mmol, 91%) as a white solid.

^{1}H NMR (400 MHz; $CDCl_3$): δ = 3.89 (t, *J* = 6.2 Hz, 2H), 2.83 (t, *J* = 6.7 Hz, 2H), 2.74-2.70 (m, 2H), 2.50 (br s, 4H), 2.44-2.40 (m, 2H), 2.26 (s, 3H), 1.96-1.90 (m, 2H), 1.87-1.81 (m, 2H), 1.60 (quintet, *J* = 5.6 Hz, 4H), 1.43 (q, *J* = 5.4 Hz, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 162.5, 158.4, 155.8, 119.3, 57.1, 54.3, 42.6, 31.4, 25.9, 24.3, 23.4, 22.0, 21.2, 19.2; **HRMS** (ESI^+): for $C_{16}H_{26}N_3O^+$ $[M+H]^+$ requires m/z = 276.20704; found 276.20683**; IR** (ATR, neat): $\tilde{\nu}$ (cm^{-1}) = 3471, 2933, 2799, 1655, 1535, 1415, 1191, 1121; **M.P**.: 76-79 °C.

(Z)-(2,4-Dibromophenyl)(piperidin-4-yl)methanone oxime (3.300)

Prepared by Dr. Michael Schedler.



N-Acetylisonipecotic acid (12.5 g, 73.0 mmol, 1.00 equiv.) was dissolved in $SOCl_2$ (75 mL) and stirred at room temperature for 19 hours. Petroleum ether (40°-60°C, 175 mL) was added to the mixture and the formed precipitate was filtered off and washed with petroleum ether. Drying of the precipitate yielded crude *N*-acetylisonipecotic acid chloride (16.1 g), that was used in the next step without further purification.

Following a known procedure,[105] the crude acid chloride and $AlCl_3$ (28.4 g, 213 mmol, 3.00 equiv.) were mixed in a round bottom flask and 1,3-dibromobenzene (42 ml, 236 mmol, 5.00 equiv.) was added. The mixture was stirred at 100 °C for 16 hours. The hot reaction mixture was then poured into a mixture of CH_2Cl_2 (500 mL)

and H_2O (500 mL). The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 500 mL). The combined organic phases were dried with $MgSO_4$, filtered and all volatiles were removed *in vacuo*. The resulting red oil was purified by flash column chromatography on silica (CH_2Cl_2/MeOH 97.5:2.5 to 95:5) yielding 1-(4-(2,4-dibromobenzoyl)piperidin-1-yl)ethan-1-one (**3.299**, 19.3 g) as a slightly red oil, that was used directly in the next step.

Following a known procedure,[105] 1-(4-(2,4-dibromobenzoyl)piperidin-1-yl)ethan-1-one (**3.299**, 19.3 g) was dissolved in aqueous HCl (6 M, 150 mL) and the solution was refluxed for 5 hours. The mixture was cooled to room temperature and the precipitate was filtered off and washed with H_2O. Drying the precipitate *in vacuo* yielded (2,4-dibromo-phenyl)(piperidin-4-yl)methanone (12.1 g) as a brown solid, that was used directly in the next step.

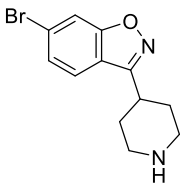
Following a known procedure,[105] (2,4-dibromo-phenyl)(piperidin-4-yl)methanone (12.1 g) and hydroxylamine hydrochloride (10.9 g, 157 mmol, 5.00 equiv.) were dissolved in pyridine and the mixture was stirred at 105 °C for 18 hours. The reaction was cooled to room temperature and aqueous Na_2CO_3 solution (1 M, 200 mL) was added to the reaction. All volatiles were removed *in vacuo* and the resulting solid was suspended in H_2O (350 mL). The suspension was stirred for one hour at room temperature and then the precipitate was filtered off and washed with H_2O. The precipitate was purified by flash column chromatography on silica (CH_2Cl_2/EtOH/.88 ammonia 90:10:1 to 80:20:2) yielded (Z)-(2,4-

dibromophenyl)(piperidin-4-yl)methanone oxime (**3.300**, 6.79 g, 18.8 mmol, 26% over 4 steps) as an off-white solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.76 (s, 1H), 7.90 (d, J = 1.9 Hz, 1H), 7.61 (dd, J = 8.2, 2.0 Hz, 1H), 7.08 (d, J = 8.2 Hz, 1H), 2.93 (br, 2H), 2.46–2.38 (m, 3H), 1.73–1.23 (m, 4H); **^{13}C NMR** (101 MHz, DMSO-d_6): δ = 158.0, 136.7, 134.6, 131.4, 130.8, 122.4, 121.9, 46.5, 42.3, 31.1, 30.7; **HRMS** (ESI$^+$) for $C_{12}H_{15}ON_2Br_2^+$ $[M+H]^+$ requires m/z =362.95252, found 362.95222; **IR** (ATR, neat) $\tilde{\nu}$ (cm^{-1}) = 3290, 2944, 2921, 2826, 1574, 1517, 1461, 1445, 1365, 1317, 1277, 1127, 1085, 1062, 1040, 1005, 964, 906, 869, 830, 811, 790, 749, 708, 653; **M.P.**: 189 °C.

6-Bromo-3-(piperidin-4-yl)benzo[d]isoxazole (3.301)

Prepared by Dr. Michael Schedler.



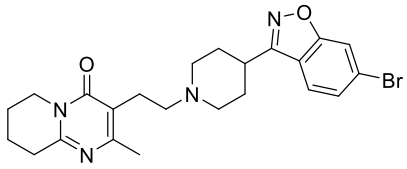
Following a known procedure,[105] (Z)-(2,4-dibromophenyl)(piperidin-4-yl)methanone oxime (**3.300**, 6.55 g, 18.1 mmol, 1.00 equiv.) and NaH (60% in mineral oil, 1.09 g, 27.1 mmol, 1.50 equiv.) were suspended in anhydrous DMF (100 mL) and the suspension was stirred at 100 °C for 30 minutes. The reaction was cooled to room temperature and all volatiles were removed *in vacuo*. The residue was dissolved in H_2O (250 mL) and the solution was acidified with 2 M aqueous HCl to pH = 1. The solution was then brought to pH = 8 by addition of saturated aqueous $NaHCO_3$ solution. The aqueous solution was extracted with CH_2Cl_2 (6 x 300 mL) and the combined organic phases were dried with $MgSO_4$, filtered and all volatiles were removed *in vacuo*. The

residue was purified by flash column chromatography on silica (CH_2Cl_2/EtOH/.88 ammonia 90:10:1) yielding 6-bromo-3-(piperidin-4-yl)benzo[d]isoxazole (**3.301**, 3.88 g, 13.8 mmol, 76%) as an off-white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.71 (d, J = 1.4 Hz, 1H), 7.58 (d, J = 8.4 Hz, 1H), 7.38 (dd, J = 8.4, 1.5 Hz, 1H), 3.21 (dt, J = 11.7, 3.0 Hz, 2H), 3.15 (dt, J =11.7, 3.9 Hz, 1H), 2.78 (td, J = 12.1, 2.7 Hz, 2H), 2.05–1.97 (bs, 2H), 1.93 (dd, J = 11.7, 4.0 Hz, 1H), 1.89–1.85 (m, 1H), 1.80 (bs, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 163.6, 161.4, 126.8, 14.2, 122.5, 119.9, 113.6, 46.5, 35.0, 31.6; **HRMS** (ESI^+) for $C_{12}H_{14}ON_2Br^+$ $[M+H]^+$ requires m/z = 281.02840, found 281.02817; **IR** (ATR, neat) $\tilde{\nu}$ (cm^{-1}) = 3287, 2922, 2860, 1600, 1512, 1454, 1401, 1351, 1136, 1006, 954, 912, 867, 834, 810, 786, 750; **M.P.**: 102 °C.

3-(2-(4-(6-Bromobenzo[d]isoxazol-3-yl)piperidin-1-yl)ethyl)-2-methyl-6,7,8,9-tetrahydro-4H-pyrido[1,2-*a*]pyrimidin-4-one (3.305)

Prepared by Dr. Michael Schedler.



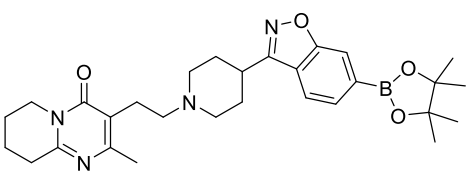
Following a known procedure,[106] 6-bromo-3-(piperidin-4-yl)benzo[d]isoxazole (**3.301**, 660 mg, 2.35 mmol, 1.00 equiv.), 3-(2-chloroethyl)-2-methyl-6,7,8,9-tetrahydro-4H-pyrido[1,2-*a*]pyrimidin-4-one (586 mg, 2.58 mmol, 1.10 equiv.) and Na_2CO_3 (498 mg, 4.70 mmol, 2.00 equiv.) were suspended in anhydrous MeOH (10 mL) and the reaction was stirred at 70 °C for 13 hours. The mixture was allowed to cool to room temperature and concentrated *in vacuo* to about half of the initial volume. H_2O (5 mL) was added to the reaction mixture. The suspension was cooled to 0 °C and the

precipitate was filtered off. The precipitate was then suspended in H_2O (5 mL) and this mixture was stirred at room temperature for one hour. The precipitate was then filtered off and washed with H_2O, yielding 3-(2-(4-(6-bromobenzo[d]isoxazol-3-yl)piperidin-1-yl)ethyl)-2-methyl-6,7,8,9-tetrahydro-4*H*-pyrido [1,2-*a*] pyrimidin-4-one (**3.305**, 858 mg, 1.82 mmol, 78%) as slightly yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.74 (d, *J* = 1.5 Hz, 1H), 7.61 (d, *J* = 8.4, 1H), 7.41 (dd, 8.4, 1.5 Hz, 1H), 3.93 (t, *J* = 6.2 Hz, 2H), 3.18 (dd, *J* = 7.9, 4.4 Hz, 2H), 3.08 (tq, *J* = 10.1, 5.5 Hz, 1H), 2.86 (t, *J* =6.6 Hz, 2H), 2.78–2.74 (m, 2H), 2.30 (s, 3H), 2.29–2.24 (m, 2H), 2.14–2.06 (m, 4H), 1.99–1.93 (m, 2H), 1.91–1.84 (m, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 163.8, 162.7, 161.4, 158.6, 156.0, 126.9, 124.3, 122.7, 120.1, 119.5, 113.7, 56.9, 53.5, 42.8, 34.8, 31.6, 30.7, 24.0, 22.2, 21.4, 19.4; **HRMS** (ESI$^+$) for $C_{23}H_{28}O_2N_4Br^+$ $[M+H]^+$ requires m/z = 471.13902, found 471.13802; **IR** (ATR, neat) $\tilde{\nu}$ (cm^{-1}) = 2943, 2798, 1646, 1594, 1530, 1444, 1396, 1353, 1192, 1145, 1127, 1095, 1046, 911, 865, 841, 795, 753, 712; **M.P.**: 146 °C.

2-Methyl-3-(2-(4-(6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[d]isoxazol-3-yl)piperidin-1-yl)ethyl)-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-a]pyrimidin-4-one (3.306)

Prepared by Dr. Michael Schedler.



Modifying a known procedure,[37] 3-(2-(4-(6-bromobenzo[d]isoxazol-3-yl)piperidin-1-yl)ethyl)-2-methyl-6,7,8,9-tetrahydro-4*H*-

pyrido[1,2-*a*]pyrimidin-4-one (**3.305**, 200 mg, 0.425 mmol, 1.05 equiv.), B_2pin_2 (102 mg, 0.402 mmol, 1.00 equiv.), $Pd(dppf)Cl_2$ (29.0 mg, 0.040 mmol, 0.10 equiv.) and KOAc (118 mg, 1.20 mmol, 3.00 equiv.) were suspended in anhydrous and degassed 1,4-dioxane (2 mL). The mixture was stirred at 80 °C for 16 hours. The reaction mixture was cooled to room temperature and all volatiles were removed *in vacuo.* The residue was suspended in toluene and all solids were filtered off. All volatiles of the filtrate were removed *in vacuo* and the residue was purified by recrystallization form toluene/*n*-hexane yielding 2-methyl-3-(2-(4-(6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[d]isoxazol-3-yl)piperidin-1-yl)ethyl)-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-a]pyrimidin-4-one (**3.306**, 133.0 mg, 0.256 mmol, 64%, 85% pure) as an off-white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.00 (s, 1H), 7.76 (dd, *J* = 7.9, 0.9 Hz, 1H), 7.69 (dd, *J* = 8.0, 0.7 Hz, 1H), 3.93 (t, *J* = 6.2 Hz, 2H), 3.20–3.17 (m, 2H), 3.14–3.08 (m, 1H), 2.86 (t, *J* = 6.7 Hz, 2H), 2.80–2.76 (m, 2H), 2.57–2.53 (m, 2H), 2.34–2.37 (m, 5H), 2.20–2.06 (m, 4H), 1.99–1.93 (m, 2H), 1.90–1.84 (m, 2H), 1.37 (s, 12H). Impurities at: 1.26 (s), 1.24 (s); **^{13}C NMR** (126 MHz, $CDCl_3$): δ = 163.1, 162.7, 161.3, 158.6, 156.1, 128.8, 123.0, 121.1, 119.4, 116.3, 88.4, 56.8, 53.5, 42.8, 34.8, 31.5, 30.4, 25.0, 23.7, 22.1, 21.3, 19.4. Impurities at: 82.7, 24.7; **^{11}B NMR** (128 MHz, $CDCl_3$): δ = 31.7. Impurities at: 22.6; **HRMS** (ESI^+) for $C_{29}H_{40}BN_4O_4^+$ $[M+H]^+$ requires m/z = 519.31371, found 519.31324; **IR** (ATR, neat) $\tilde{\nu}$ (cm^{-1}) = 2973, 1655, 1535, 1453, 1358, 1144, 855, 694; **M.P.**: 56 °C.

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