Organomediated Approaches to ^{18}F-Radiochemistry for PET

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Author's Declaration

The work presented in this thesis was conducted at the Chemistry Research Laboratory at the University of Oxford under the supervision of Prof. Véronique Gouverneur and at Turku PET Centre, Finland, in collaboration with Prof. Olof Solin, between Michaelmas Term 2011 and Trinity Term 2015. 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.

Faye Buckingham

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Abstract

This thesis has focussed on ^{18}F-fluorination reactions activated by an organomediator, with the aim of broadening the scope of metal-free reactions in ^{18}F-radiosynthesis.

Chapter 1 provides an introduction to positron emission tomography (PET) and ^{18}F-radiochemistry, including radioisotope production and modes of activation in ^{18}F-radiosynthesis.

In **Chapter 2**, the concept of chirality and its relevance in the context of radiotracer design is introduced. The previously disconnected fields of organomediated asymmetric fluorination and ^{18}F-radiosynthesis are merged for the first time via investigation of three distinct activation modes: chiral non-racemic secondary amine-mediated asymmetric α-^{18}F-fluorination of aldehydes employing [^{18}F]*N*-fluorobenzenesulfonimide; use of a phase transfer reagent for asymmetric ^{18}F-fluorocyclisation and application of a chiral non-racemic ^{18}F-fluorinating agent, chiral [^{18}F]Selectfluor bis-triflate. Application of the first of these approaches to the radiosynthesis of the PET tracer (2*S*,4*S*)-4-[^{18}F]fluoroglutamic acid with high d.r. is described.

Chapter 3 explores the use of hypervalent iodine reagents to mediate the oxidative fluorination of *N*-arylsulfonamides with nucleophilic fluoride via an umpolung approach. Preliminary studies on translation to radiosynthesis with [^{18}F]fluoride are also disclosed.

In **Chapter 4**, experimental data is provided for all compounds, as well as analytical and chiral HPLC traces for ^{18}F-reactions.

Acknowledgments

First and foremost, I would like to say a huge thank you to Véronique for her continuous support throughout my time in the group. I am very grateful she gave me the opportunity to complete this DPhil and it has been a privilege to work with such an inspiring supervisor who has truly pushed me to achieve my full potential.

The funding for this project was provided by the BBSRC and GE Healthcare, for which I am extremely thankful and I greatly appreciate all of the training I received in Amersham. I was very lucky to have enthusiastic industrial supervisors, and can't thank Matthias Glaser enough for his never ending patience during my placement, as well as Ian Newington for his continuous interest and advice and Sajinder Luthra for her support.

During the course of this thesis I was fortunate to work with some amazing collaborators. Much of the radiochemistry in this thesis was carried out at Turku PET Centre, Finland, and I would like to thank Olof Solin for welcoming me into his lab, and for providing so much help and interest during my time there. Thanks also to Sarita Forsback and Anna Kirjavainen for all of your help in the lab and for looking after me so well. Ania, Tom and Cheng- thank you so much, not only for your constant support in the lab (and all of the early mornings!) but for making me feel so at home during my visits. I hope we meet again soon!

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After 8 years in Oxford I have enjoyed being part of both Oriel and Lincoln colleges and made some wonderful friends- thanks for all of the support you all provided along the way. Thanks also to my amazing family, especially Mam, Dad and Gem, for all of your love and support (and the daily chats!) throughout my studies. I'm looking forward to finally living closer to home!

My final and biggest thank you must go to Jamie. I have so much to thank you for: teaching me everything I needed to know in the lab, never minding all of my chemistry questions over dinner and for being my rock of support when I needed you most. I couldn't have got through these last four years without you, and I can't wait to see what the future holds for us next.

Abbreviations and Acronyms

[^{18}F]FDG	2-[^{18}F]fluoro-2-deoxy-D-glucose
[^{18}F]FDHT	16β-[^{18}F]fluoro-5α-dihydrotestosterone
[^{18}F]FES	16α-[^{18}F]fluoroestradiol
[^{18}F]FLT	3'-deoxy-3'-[^{18}F]fluorothymidine
α	Alpha
$[\alpha]_D^{25}$	Specific rotation
δ	Chemical Shift
°C	Degrees Celsius
Ac	Acetyl
Am	Amyl
aq	Aqueous
Ar	Aryl
BHT	2,6-di-*tert*-Butyl-4-methylphenol
Bn	Benzyl
Boc	*t*-Butyloxycarbonyl
Bq	Becquerel (s^{-1})
br	Broad
Bu	Butyl
cat.	Catalytic
Cbz	Carboxybenzyl
CD	Cinchonidine
cm^{-1}	Wavenumber
CT	Computer tomography
d	Deuterated
d	Doublet
DABCO	Diazoniabicyclo[2.2.2]-octane
DCA	Dichloroacetic acid
DCE	1,2-Dichloroethane
DCM	1,2-Dichloromethane
DBN	1,5-Diazabicyclo[4.3.0]non-5-ene
DBSI	Dibenzenesulfonimide
DFT	Density functional theory
DHBQ	Dihydroquinine 4-chlorobenzoate
DHQDA	Dihydroquinidine acetate
$(DHQ)_2PHAL$	Hydroquinine 1,4-phthalazinediyl diether
$(DHQ)_2PYR$	Hydroquinine 2,5-diphenyl-4,6-pyrimidinediyl diether
DMF	*N*,*N*-Dimethylformamide
DMS	Dimethylsulfide
DMSO	Dimethyl sulfoxide
d.r.	Diastereomeric ratio
ee	Enantiomeric excess
eq.	Equivalents
ESI	Electrospray ionisation
Et	Ethyl
EWG	Electron withdrawing group
G	Giga
g	Gram
h	Hour(s)
HFIP	Hexafluoroisopropanol
HKR	Hydrolytic kinetic resolution
HOMO	Highest occupied molecular orbital
HPLC	High pressure liquid chromatography
HRMS	High resolution mass spectrometry
Hz	Hertz
IPA	Isopropanol
IR	Infrared (Spectroscopy)
J	Coupling constant
K_{222}	Kryptofix 2.2.2; 4,7,13,16,21,24-hexaoxa-1,10-diazabicyclo-[8.8.8]hexacosane
L	Litre
LG	Leaving group
LUMO	Lowest unoccupied molecular orbital
M	Meg
M	Moles per cubic decimetre
m	*Meta*
m	Multiplet
m-CPBA	3-chloroperoxybenzoic acid

Me	methyl
Mes	Mesitylene
min	Minute(s)
µ	Micro
m	Milli
mol	Mole(s)
MP	Melting point
Ms	Mesyl
m/z	Mass/charge ratio
MRI	Magnetic resonance imaging
MS	Mass spectroscopy
MS	Molecular sieves
n	Neutron
NFSI	*N*-Fluorobenzenesulfonimide
NHC	*N*-Heterocyclic carbene
NMR	Nuclear Magnetic Resonance Spectroscopy
Nu	Nucleophile
o	*Ortho*
OAc	Acetate
OTf	Triflate
OTs	Tosylate
p	*Para*
PET	Positron Emission Tomography
PG	Protecting group
Ph	Phenyl
PIDA	Diacetoxyiodobenzene
PIFA	Bis(trifluoroacetoxy)-iodobenzene
Piv	Pivaloyl
pK_a	Acid dissociation constant
ppm	Parts per million
Pr	Propyl
pyr	Pyridine
γ	Gamma
RCC	Radiochemical conversion
RCY	Radiochemical yield
Rf	Retention factor
rt	Room temperature
s	Singlet
S.A.	Specific activity
Selectfluor	1-Chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane
S_N2	Bimolecular nucleophilic substitution
S_NAr	Nucleophilic Aromatic Substitution
t	*Tert*
t	Triplet
TBAF	Tetra-*n*-butylammonium fluoride
TCA	Trichloroacetic acid
TEAF	Tetra-*n*-ethylammonium fluoride
Temp.	Temperature
THF	Tetrahydrofuran
TFA	Trifluoroacetic acid
Tmob	2,4,6-Trimethoxybenzyl
TMS	Trimethylsilyl
Tol	Tolyl
Ts	4-Toluenesulfonyl (Tosyl)
UV	Ultraviolet

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Chapter 1:

General Introduction

1. General Introduction

1.1 Positron Emission Tomography

Positron emission tomography (PET) is a non-invasive technique for *in vivo* molecular level imaging of physiological processes, normally carried out in combination with computed tomography (CT) or magnetic resonance imaging (MRI), which provide the corresponding anatomical data.[1] The radiotracers employed in PET imaging are synthesised by the incorporation of suitable positron emitting radioisotopes into biologically active molecules.[2] Radioisotopes used include ^{11}C, ^{18}F, ^{15}O, ^{13}N and ^{68} Ga. However, fluorine-18 is often the isotope of choice, due to its beneficially relatively long half life, of approximately 110 minutes, which allows for multistep radiosynthetic protocols and the distribution of radiotracers to satellite PET scan facilities.

The decay process of ^{18}F occurs with 97 % positron (β^+) emission. The PET scanner does not directly detect positrons, but rather the pairs of gamma (γ) photons that are released at a 180° trajectory to each other during the annihilation event that occurs when an emitted positron collides with an electron in the surrounding tissue. Advantageously, the emitted positron energy of ^{18}F is low, resulting in a short range in tissue and therefore better resolution scans than other common radioisotopes. The coincidence detection of these pairs of photons allows the site of the annihilation event, and consequently the approximate location of the radiotracer, to be traced.

PET is an incredibly sensitive technique, with only a very small amount of radioactive material sufficient to cause multiple annihilation events and provide enough data for an accurate image. This has the advantage that radiotracers can be employed for studies *in vivo* without perturbing the system under observation. Although fluorine occurs in very few naturally occurring biological molecules, it can often be substituted in *lieu* of a

hydrogen atom or hydroxyl group without significantly affecting the shape of a molecule. This is exemplified by the use of 2-[^{18}F]fluoro-2-deoxy-D-glucose ([^{18}F]FDG), a fluorinated analogue of glucose which plays a crucial role in cancer imaging (Figure 1.1).[3] The use of this tracer in diagnosis and disease mapping capitalises on the upregulation of aerobic glycolysis by cancer cells, which results in a high consumption of glucose.

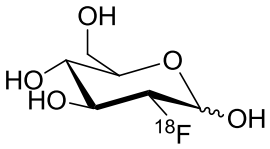


Figure 1.1: 2-[^{18}F]Fluoro-2-deoxy-D-glucose ([^{18}F]FDG)

Moreover, the incorporation of fluorine into drug molecules can often be advantageous, as modulation of both lipophilicity and p*K*a can occur as a result of its high electronegativity when compared to hydrogen or a hydroxyl group. A systematic fluorine scan is therefore now considered a rather routine process in drug development[4] and as such, currently around 25 % of pharmaceuticals now contain at least one fluorine atom.[5]

The vast utility of ^{18}F PET imaging therefore lies not only in clinical imaging but also in the potential facilitation of early drug development via radiolabelling of drug candidates.[6] The current drug discovery programme is long, costly and prone to failure, with clinical development and approval phases for a new drug lasting between 5 and 10 years[7] with an estimated total cost of up to $2.6 billion per drug.[8] The strength of PET imaging lies in its ability to provide early stage pharmacodynamic and pharmacokinetic data for a novel drug, thereby reducing attrition rates at later phases of clinical trials. It can also help to identify the most suitable location in a molecule for a fluorine atom, when a choice is available. Advantageously, as PET imaging requires administration of the potential drug in amounts below toxic levels, such studies can be carried out in

humans prior to Phase 1 clinical trials, thus eliminating poor drug candidates before this stage and streamlining the process in terms of both time and costs.[9] The use of small animal PET imaging also allows pre-clinical data to be obtained.[10]

PET imaging can be employed in drug development to evaluate both pharmacokinetics and pharmacodynamics.[11] It can also facilitate patient selection for a trial by determining if a particular molecular target is expressed or a physiological state, such as hypoxia, occurs. Directly radiolabelled drug molecules can be employed for biodistribution studies to determine if the concentration of a novel pharmaceutical in the target tissue is sufficient for pharmacological activity and also to monitor build-up in non-target tissue. This also allows assessment of blood brain barrier penetration. Occupancy studies can be employed to determine the displacement of a high affinity radioligand upon administration of a novel drug candidate, in order to guide dosing regimen. Alternatively, radiotracers can be utilised to determine response to therapy with a potential drug candidate, by monitoring cell proliferation, glucose uptake or receptor expression, for example.

However, use of this form of precision pharmacology relies upon the availability of a sufficient methodological toolkit for the incorporation of ^{18}F into molecules at the desired position. The current limitation of PET imaging lies in the methods available for synthesis of radiolabelled probes, with radiosynthesis controlled by strict time constraints and purification requirements.

1.2 Radioisotope Production

Radiosynthetic protocols should be as efficient as possible, with the radioisotope introduced late in the synthetic sequence in order to minimise decay. In fact, it is recommended that the time delay between production of the radionuclide in a cyclotron to

injection into a patient should not exceed 2 or 3 half-lives. However, this becomes increasingly more difficult as probes become more structurally complex or highly functionalised. Radioisotope production affords ^{18}F as one of two forms: nucleophilic [^{18}F]fluoride or electrophilic [^{18}F]F_2 (Table 1.1).[12]

Table 1.1: Summary of methods for production of [^{18}F]fluorine

Nuclear Reaction	Target	^{18}F-Labelled Precursor	S.A. (GBq/μmol)
$^{18}O(p,n)^{18}F$	$H_2{}^{18}O$	[^{18}F]F^-	5000
$^{20}Ne(d,\alpha)^{18}F$	$Ne + F_2$	[^{18}F]F_2	0.05-0.1
$^{18}O(p,n)^{18}F$	$^{18}O_2 + F_2$	[^{18}F]F_2	1.3
$^{18}O(p,n)^{18}F$	$H_2{}^{18}O$	Post-target produced [^{18}F]F_2	55

1.2.1 Nucleophilic Sources of ^{18}F

The proton bombardment of an ^{18}O enriched water target affords aqueous [^{18}F]fluoride with very high specific activity (S.A.), i.e. with a high amount of radioactivity per mole of compound. This is advantageous as it allows high quality PET images to be obtained by injection of just a small amount of the compound, therefore reducing patient dose and minimising perturbation of the system under investigation. This is especially important when considering radiotracers that may easily saturate receptor sites. Further advantages of [^{18}F]fluoride include the easier handling and higher selectivity of this reagent, as well as the possibility of distribution for radiosynthesis at satellite laboratories. As such, [^{18}F]fluoride is by far the most practical and widely available form of this isotope.

The high degree of solvation and resultant poor nucleophilicity of aqueous [^{18}F]fluoride[13] means that activation prior to use is normally required. This is achieved by use of an ion-exchange column to trap the [^{18}F]fluoride prior to elution with an appropriate countercation in acetonitrile/ water. Commonly employed countercations include tetraalkylammonium ions, or potassium ions in combination with a phase transfer

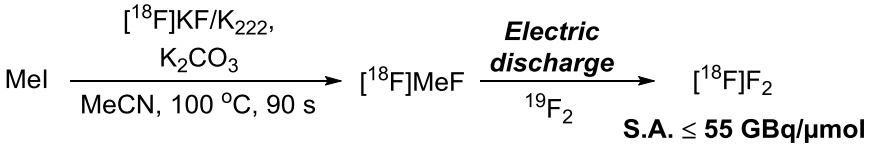
reagent, such as Kryptofix 2.2.2. (K_{222}), which is preferred clinically to 18-crown-6.[2] Following ion exchange, the solution is subjected to azeoptropic drying and is subsequently dissolved in an appropriate polar aprotic solvent for ^{18}F-labelling. This process can be carried out manually but is frequently automated in order to minimise radiation dose to the research worker.

1.2.2 Electrophilic Sources of ^{18}F

Two different nuclear reactions can be utilised for the cyclotron production of [^{18}F]F_2. The first employs deuterium bombardment of a nickel target loaded with ^{20}Ne and produces [^{18}F]F_2 with a very low S.A. (0.05-0.01 GBq/μmol) due to the high amount (40-60 μmol) of F_2 gas required as a carrier.[14] The alternative, and now more usual, route employs the more common proton beam to irradiate an [^{18}O]O_2 gaseous target, but also suffers from low S.A. (1.3 GBq/μmol).[15]

A report by Bergman and Solin in 1997 described the production of [^{18}F]F_2 with improved specific activity.[16] This method utilises the ^{18}O(p,n)^{18}F nuclear reaction with an enriched [^{18}O]H_2O target, to produce aqueous [^{18}F]fluoride in the usual way. This undergoes azeotopic drying in the presence of potassium carbonate and K_{222} and is subsequently reacted with methyl iodide in acetonitrile to produce [^{18}F]methyl fluoride, which is purified by gas chromatography. This is transferred to a discharge chamber with a small amount (0.15-1 μmol) of carrier $^{19}F_2$ in Ne. An electrical discharge causes atomisation, resulting in rearrangement and ^{18}F/^{19}F exchange to produce [^{18}F]F_2 (Scheme 1.1). The maximum specific activity that can be achieved with this method (55 Gbq/μmol) is significantly higher than previously described methods for the synthesis of [^{18}F]F_2, and whilst still two orders of magnitude lower than the specific activity of non-carrier added [^{18}F]fluoride, this method is in regular use at Turku PET Centre, Finland,

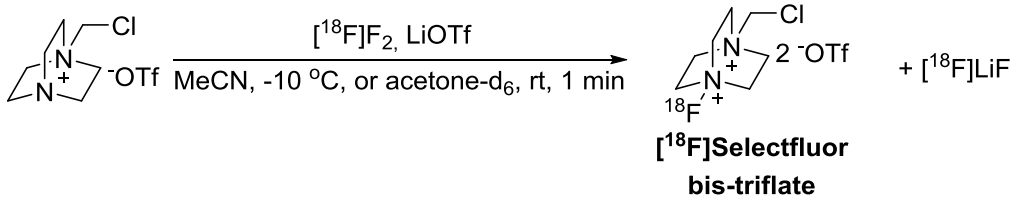
for the clinical production of radiopharmaceuticals. Advantageously, this system can be easily automated for safe and facile use.



Scheme 1.1: Synthesis of $[^{18}F]F_2$ from $[^{18}F]$fluoride

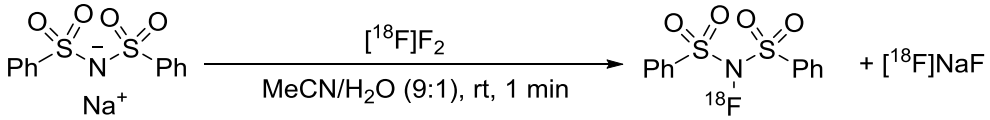
Whilst the labelling of electron rich substrates is more easily achieved with $[^{18}F]F_2$ compared to $[^{18}F]$fluoride, the high reactivity of fluorine gas can lead to poor selectivity and undesired side reactions. However, selectivity can be much improved by modulation of the reactivity of $[^{18}F]F_2$ gas by synthesis of more tempered fluorinating agents. Work in the Gouverneur group over recent years, in collaboration with GE Healthcare and Prof. Olof Solin at Turku PET Centre, has demonstrated the synthesis of the *N*-fluoro reagents $[^{18}F]$Selectfluor bis-triflate[17] and $[^{18}F]$NFSI[18] from $[^{18}F]F_2$.

The synthesis of $[^{18}F]$Selectfluor bis-triflate was achieved by bubbling $[^{18}F]F_2$ through a solution of the DABCO-derived precursor in acetonitrile at −10 °C or acetone at room temperature in the presence of lithium triflate (Scheme 1.2). The maximum theoretical RCY of $[^{18}F]$Selectfluor bis-triflate in this reaction is 50 %, due to the concomitant formation of one equivalent of $[^{18}F]$LiF. $[^{18}F]$Selectfluor bis-triflate is very difficult to identify by HPLC due to its lack of UV chromophore and because it polar nature causes co-elution with the $[^{18}F]$LiF side-product. Formation was therefore confirmed by mass spectral analysis of a decayed sample. The bis-triflate counterion was chosen to eliminate the isotopic exchange, which is possible with the tetrafluoroborate anion employed in the commercial reagent. This reagent has seen application to fluorination of silyl methyl ethers[17] and the synthesis of $[^{18}F]$FDOPA via destannylation or deborylation (see Scheme 1.7),[19] as well as fluorodecarboxylation.[20]



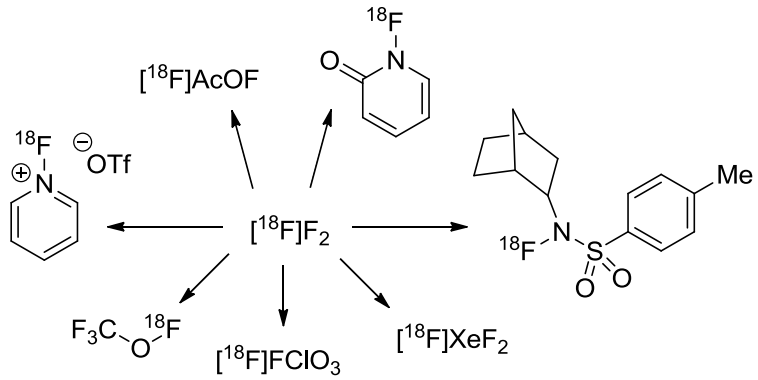
Scheme 1.2: Synthesis of [^{18}F]Selectfluor bis-triflate

[^{18}F]NFSI was similarly synthesised by bubbling [^{18}F]F_2 through a solution of the sodium salt precursor in acetontrile/ water (9:1) (Scheme 1.3). Again, the maximum theoretical RCY of this reagent is 50 %, with one equivalent of [^{18}F]NaF also formed in the reaction. However, advantageously, the synthesis of [^{18}F]NFSI can be analysed by radio-HPLC. Prior to use, the stock solution of this reagent was azeotropically dried and redissolved in the appropriate reaction solvent. This [^{18}F]N-F reagent has been employed in the fluorination of silyl methyl ethers.[18]



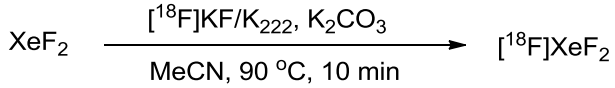
Scheme 1.3: Synthesis of [^{18}F]NFSI

Other [^{18}F]N-F reagents that have been reported include [^{18}F]*N*-fluoropyridinium triflate,[21] [^{18}F]1-fluoro-2-pyridone[22] and various *N*-fluoro-*N*-alkylsulfonamides (Scheme 1.4).[23] However, studies on the application of these reagents are currently limited.



Scheme 1.4: Electrophilic fluorinating reagent derived from [^{18}F]F_2

Other electrophilic fluorinating agents that can be derived from $[^{18}F]F_2$ include $[^{18}F]AcOF$,[24] $[^{18}F]CF_3OF$[25] and $[^{18}F]FClO_3$ (Scheme 1.4),[26] though the challenges associated with handling of these very reactive $[^{18}F]O$-F reagents has the result that they are not commonly employed in ^{18}F-radiosynthesis. The electrophilic fluorinating reagent $[^{18}F]XeF_2$ can be accessed directly by the reaction of Xe with $[^{18}F]F_2$ gas in a nickel reactor.[27] The synthesis of $[^{18}F]XeF_2$ via isotopic exchange with $[^{18}F]$fluoride has also been reported, by Pike and co-workers in 2001,[28] with a follow up report describing an adaptation to microfluidics in 2010.[29] Notably, this allows access to an ^{18}F-labelled electrophilic fluorinating reagent from a nucleophilic source, albeit in a carrier added approach (Scheme 1.5).

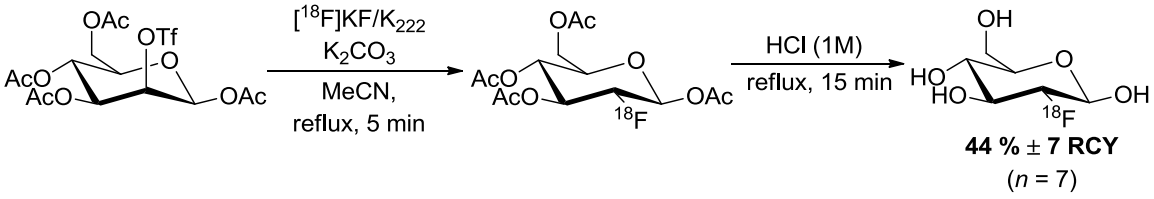


Scheme 1.5: Synthesis of $[^{18}F]XeF_2$ via isotopic exchange

1.3 Activation Modes in ^{18}F-Radiosynthesis

1.3.1 Substrate Activation

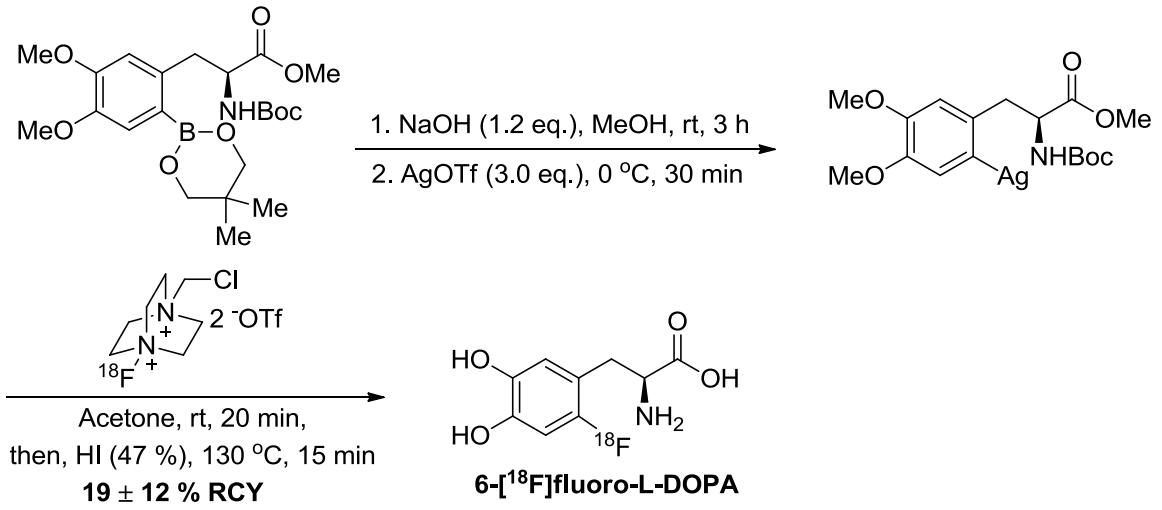
The most common method to introduce ^{18}F into a molecule is via S_N2 substitution with $[^{18}F]$fluoride on a molecule activated with a good leaving group, such as tosylate or triflate.[2] This method is highly efficient for the radiolabelling of a wide range of aliphatic molecules, including $[^{18}F]$FDG.[30]



Scheme 1.6: Synthesis of $[^{18}F]$FDG by Hamacher and co-workers

For ^{18}F-fluorination of arenes, direct fluorination employing $[^{18}F]F_2$ has had some success, but is often unselective and leads to the formation of multiple side products. As discussed above, to some extent the reactivity of $[^{18}F]F_2$ can be moderated by use of low

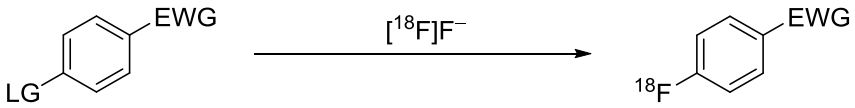
reaction temperatures and higher dilutions in neon,[31] or by employing milder derivatives such as [^{18}F]AcOF.[32] However, much higher selectivity can be obtained by pre-functionalisation of substrates as organo -metallic, -silicon or –boron derivatives. In particular, destannylation,[33] demercuration[34] and desilylation[35] reactions have facilitated the regiospecific radiosynthesis of PET radiotracers such as 6-[^{18}F]fluoro-L-DOPA and 2-[^{18}F]fluoro-L-tyrosine with [^{18}F]F_2. [^{18}F]Selectfluor bis-triflate has also been applied by the Gouverneur group to the labelling of 6-[^{18}F]fluoro-L-DOPA from an aryl stannane precursor,[19] with comparable RCYs to the corresponding synthesis with post-target produced [^{18}F]F_2[36] (RCYs = 12.1 % ± 3.7 % and 6.4 % ± 1.7 % respectively). A novel aryl boronic ester substrate was also found to be amenable to silver-mediated fluorination with [^{18}F]Selectfluor bis-triflate, thereby avoiding the toxicity issues associated with stannylated precursors (Scheme 1.7).[19]



Scheme 1.7: Synthesis of 6-[^{18}F]fluoro-L-DOPA by fluorodeborylation with [^{18}F]Selectfluor bis-triflate

However, the beneficial properties in terms of S.A. and wider availability means ^{18}F-fluorination of aromatics is preferable employing [^{18}F]fluoride. Early work on the ^{18}F-labelling of electron rich and neutral aromatics with [^{18}F]fluoride employed a Balz-Schiemann type fluorodediazonation reaction, but these reactions often suffer from low

S.A.[37] The most common method for introduction of [^{18}F]fluoride onto an aromatic ring is via an S_NAr reaction of substrates substituted with an appropriate leaving group, commonly nitro, halo, trimethylammonium or tosylate.[38] This method has the prerequisite that an electron withdrawing group, such as nitro, cyano or trifluoromethyl, is located *ortho* or *para* to the leaving group and commonly requires heating to high temperatures in polar aprotic solvents (Scheme 1.8).

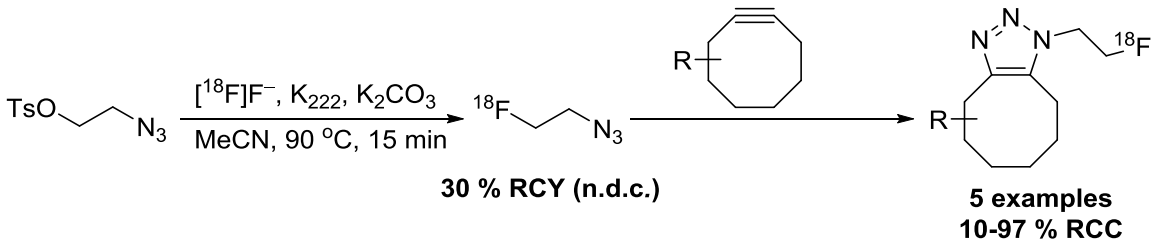


EWG = electron withdrawing group (NO_2, CN, CHO etc.)
LG = leaving group (NO_2, halo, triflate, tosylate, mesylate, tetraalkylammonium)

Scheme 1.8: S_NAr of electron poor aromatics with [^{18}F]fluoride

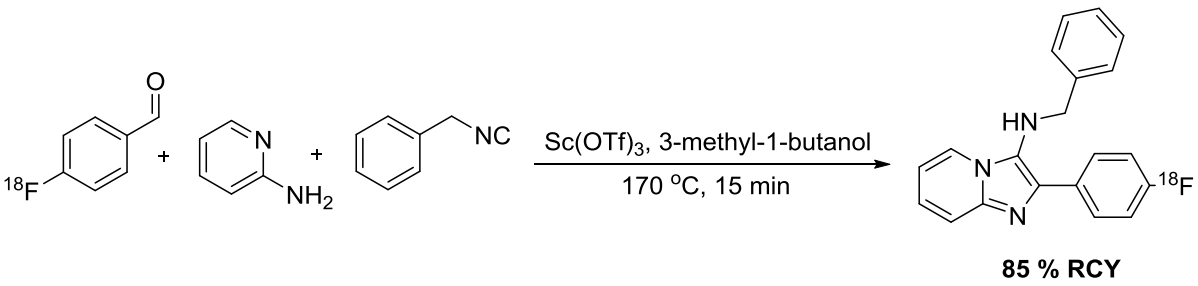
As such, direct late stage nucleophilic fluorination is therefore not achievable for some probes, as they are too complex, contain electron rich aromatic rings or, in the case of some biologically active molecules, are not compatible with the often harsh conditions required for nucleophilic ^{18}F-fluorination via S_NAr. The late-stage labelling of electron rich aromatics with [^{18}F]fluoride thus poses one of the main challenges in radiosynthesis today.[38]

One strategy to circumvent this problem employs molecules that are easy to label via a traditional S_N2 or S_NAr reaction as prosthetic groups.[39] Post-fluorination, these can then be coupled to the molecule of interest. For example, *N*-succinimidyl 4-[^{18}F]fluorobenzoate ([^{18}F]SFB) is one of the most common prosthetic groups and has been extensively employed in the synthesis of a range of ^{18}F-labelled proteins and peptides.[40] Another common strategy employs prosthetic group coupling via a copper, or more recently copper-free (Scheme 1.9),[41] azide-alkyne cycloaddition "click" reaction.[42]



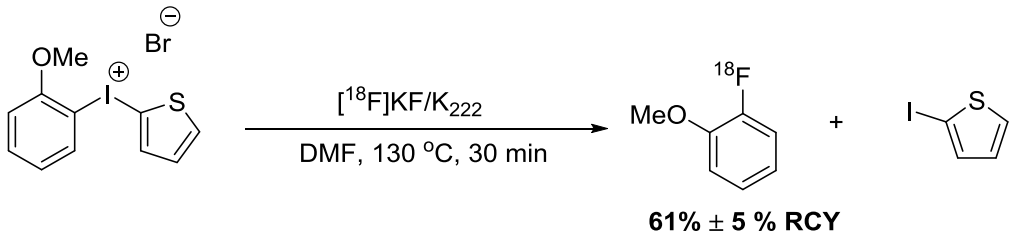
Scheme 1.9: Copper-free "click" reaction of 2-[^{18}F]fluoroethylazide by Carroll and co-workers

A report by the Gouverneur group in 2011 disclosed an alternative prosthetic group strategy, employing a convergent approach based on multicomponent reactions (MCRs).[43] MCRs are atom and step-economic reactions in which three or more starting compounds react to form a product in such a way that the majority of the atoms of the starting materials can be found in the product. It was proposed that introduction of an ^{18}F-label via a convergent rather than a linear strategy could allow for the construction of structurally diverse molecular scaffolds, which would otherwise be difficult to access by direct late stage nucleophilic fluorination, in a simple procedure which is ideally suited for radiosynthesis.[44] The use of substituted 4-[^{18}F]fluorobenzaldehydes as prosthetic groups was reported for the Biginelli, Ugi, Groebke-Bienaymé-Blackburn and Passerini reactions, with high RCY (Scheme 1.10). It was also demonstrated that further complexity of structure could be obtained by post reaction modifications, allowing the synthesis of a drug-type target via the Biginelli condensation. Whilst application of this methodology is limited to molecules constructed via a MCR, its potential utility lies in the possibility for direct translation to PET imaging of lead compounds highlighted via high throughput screening.



Scheme 1.10: Groebke-Bienaymé-Blackburn with 4-[^{18}F]fluorobenzaldehyde

The problem of late-stage ^{18}F-labelling of electron rich aromatics with [^{18}F]fluoride has also been overcome by the use of diaryliodonium salt precursors, as first reported by Pike and Aigbirhio in 1995.[45] This approach involves the activation of a substrate as a diaryliodonium salt, to promote reaction with [^{18}F]fluoride via an S_NAr type reaction and afford [^{18}F]fluoroarenes and iodoarenes, offering an advantage over traditional S_NAr reactions which are viable only for electron deficient aromatics. Since this first report, significant optimisation of the reaction in terms of yield and regioselectivity has taken place. Indeed, the use of unsymmetrical diaryliodonium salts[46] to promote fluorination of the desired ring is now common place. Nucleophilic substitution with [^{18}F]fluoride was found to take place on the most electron deficient aryl ring and as such the use of heteroaromatic iodonium salts containing an electron rich 2-thienyl ring to direct the fluorination has been disclosed by Coenen and co-workers (Scheme 1.11).[47]



Scheme 1.11: ^{18}F-Fluorination of heteroaromatic iodonium salts

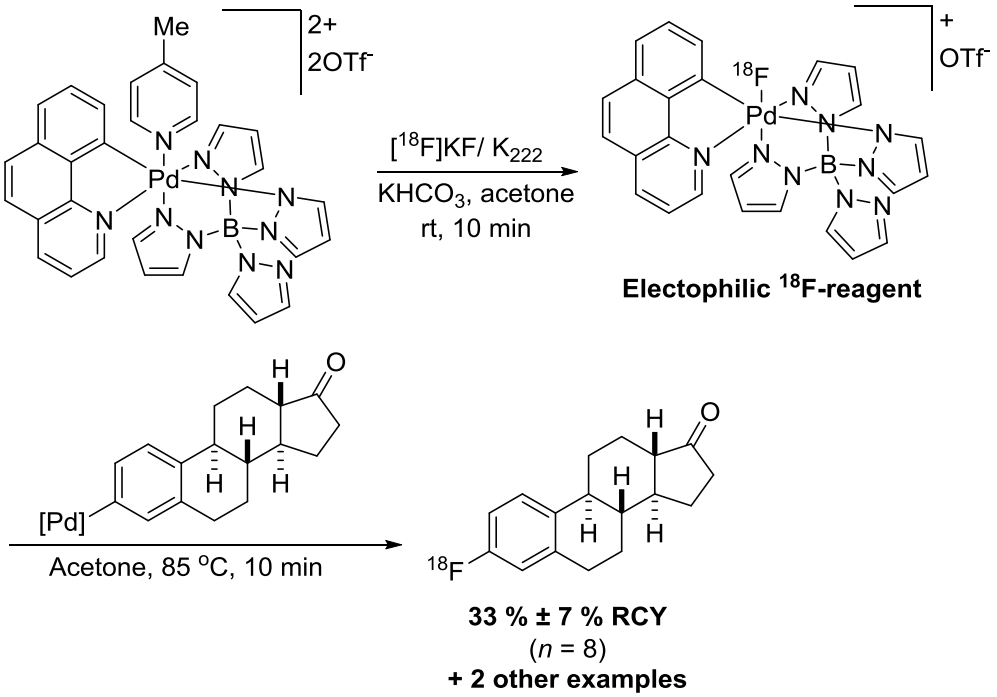
Nucleophilic ^{18}F-fluorinations of diaryliodonium salt precursors also show a marked so-called "*ortho* effect", in which the [^{18}F]fluoride nucleophile is directed to the ring

containing an *ortho* substituent.[48] The degree of regioselectivity was found to be affected by not only by electronics of the *ortho* substituent but also by steric bulk. This is proposed to be due to the steric influence of the *ortho* substituent on the conformation of the iodonium salt, which causes the *ortho* substituted aryl ring to lie in the equatorial plane of a trigonal bipyramidal structure in order to minimise steric repulsion, therefore facilitating access for attack by the [^{18}F]fluoride nucleoophile.

Unfortunately, like traditional S_NAr reactions, ^{18}F-fluorination of diaryliodonium salts often require significant thermal activation and as such are not suitable for reaction of temperature sensitive substrates. A further disadvantage of this methodology is the possibility of non-facile precursor synthesis for complex substrates, although numerous reports have been made expanding the scope of diaryliodonium precursors available for ^{18}F-fluorination.[49]

1.3.2 Reagent Activation

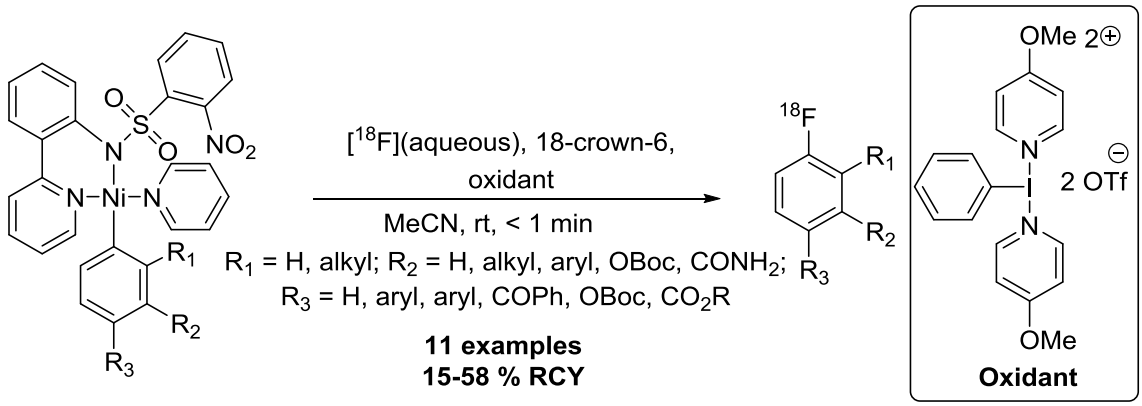
An alternative approach towards activation of a substrate to ^{18}F-fluorination is to employ an appropriate "catalyst" or reagent to promote the reaction. In breakthrough work in 2011, Ritter and co-workers reported the synthesis of a sophisticated palladium-based electrophilic fluorinating agent derived from [^{18}F]F^-, in a fluoride umpolung approach, and described its application for the late-stage fluorination of aromatics.[50] Nucleophilic fluorination of a palladium(IV) species with [^{18}F]KF/K_{222} afforded a palladium fluoride complex, which could act as a source of electrophilic fluorine to undergo oxidative fluorine transfer to a palladium(II) complex. The resultant high valency palladium(IV) aryl fluoride complex could then undergo carbon-fluorine reductive elimination to afford ^{18}F-labelled aryl fluorides (Scheme 1.12).



Scheme 1.12: Palladium-based electrophilic fluorinating agent from [^{18}F]fluoride by Ritter and co-workers

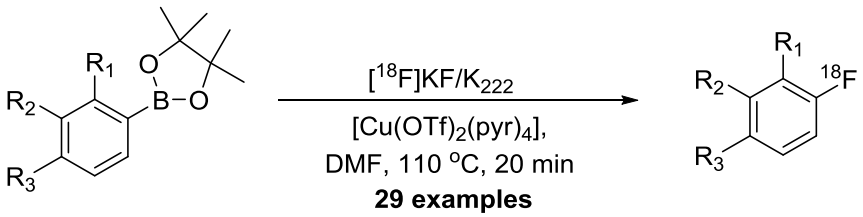
This work provided a novel solution to the synthesis of an ^{18}F-labelled electrophilic fluorinating reagent derived from [^{18}F]fluoride, without the low S.A. associated with traditional sources of electrophilic reagents derived from [^{18}F]F_2.

A later report by the same group disclosed the use of nickel aryl complexes for direct oxidative fluorination with [^{18}F]fluoride, in a one-step process mediated by a hypervalent iodine oxidant (Scheme 1.13).[51] This procedure has the further advantage that the [^{18}F]fluoride could be employed directly in aqueous form, therefore removing the usual time consuming azeotropic drying step. This method was applied to the synthesis of a range of ^{18}F-labelled fluoro-arenes, including those which are electron rich. However, in both cases, uptake of this methodology for clinical applications has been limited thus far due to the non-trivial preparation of the non-commercially available precursors.[52]



Scheme 1.13: Nickel-mediated ^{18}F-fluorination of aromatics by Ritter and co-workers

A further example of transition metal-mediated ^{18}F-fluorination of arenes was recently reported by the Gouverneur group.[53] Inspired by the work of Sanford and co-workers on the copper-mediated fluorination of aryltrifluoroborates,[54] this work described a [^{18}F]carbon-fluorine Chan-Lam cross-coupling reaction employing pinacol-derived boronic ester substrates to yield ^{18}F-labelled aryl fluorides from [^{18}F]KF/K_{222} in the presence of a commercially available $Cu(OTf)_2(pyr)_4$ complex (Scheme 1.14). The wide range of examples reported included aryl rings armed with electron donating groups, and this method could also be employed to produce a clinical dose of 6-[^{18}F]fluoro-L-DOPA. Scale-up and automation of this methodology was also demonstrated.

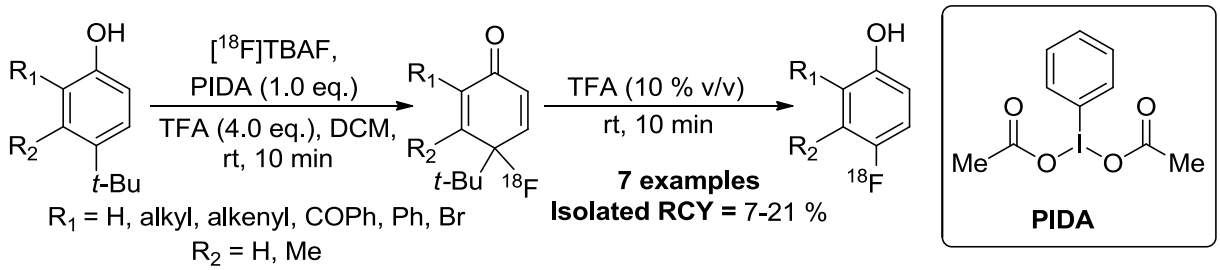


R_1 = H, CO_2Et, OMe, alkyl; R_2 = H, CHO, OR, Br, NR_2, alkyl, aryl; R_3 = H, CO_2R, COR, CHO, $CONR_2$, SO_2NR2, CN, NO_2, OH, OR, NHR, NR_2, allyl, vinyl, aryl.

Scheme 1.14: Copper-mediated nucleophilic ^{18}F-fluorination of arenes

Whilst the methods discussed thus far have all required activation by a transition metal complex, a complementary, metal-free approach employing a hypervalent iodine oxidant

was recently developed by the Gouverneur group.[55] As will be discussed in more detail in Chapter 3, hypervalent iodine reagents are capable of mediating a range of oxidative fluorination transformations.[49;56] Taking inspiration from the work of Langlois (see Chapter 3 for further discussion),[57] this reaction employed phenol substrates substituted with a *tert*-butyl group at the *para* position, which underwent oxidative fluorination with [^{18}F]fluoride, followed by acid promoted rearomatisation (Scheme 1.15).



Scheme 1.15: Hypervalent iodine-mediated oxidative fluorination of phenols with [^{18}F]fluoride by Gouverneur and co-workers

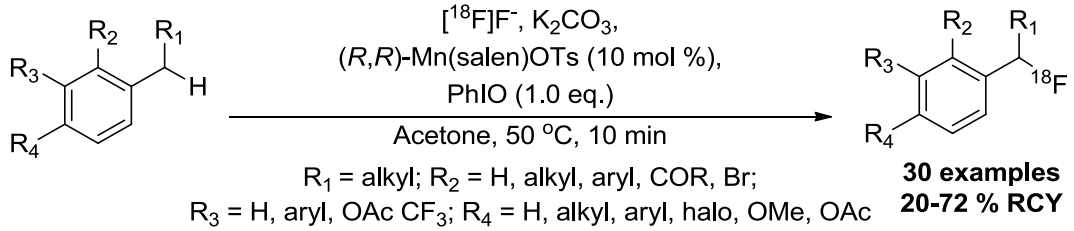
Hypervalent iodine-mediated oxidative fluorination of phenols generally employs HF as the nucleophilic source of fluorine. Since the ^{18}F-labelled variant of this reagent is not readily available with high specific activity,[58] an alternative fluorine source was required for the radiosynthetic reaction. Preliminary cold reactions indicated that whilst TBAF alone was not proficient for this oxidative fluorination, the reaction proceeded with a moderate yield when it was employed in combination with TFA. The reaction is therefore likely to occur via *in situ* formation of HF. Treatment of *p-tert*-butylphenol substrates with [^{18}F]TBAF and TFA, as well as diacetoxyiodobenzene (PIDA), in DCM for 10 minutes at room temperature, followed by addition of an extra portion of TFA to effect rearomatisation of the dienone intermediate with loss of the *tert*-butyl group, afforded *p*-[^{18}F]fluorophenol with good RCY.

Mechanistically, the reaction is proposed to proceed via initial two electron oxidation of the phenol substrate to generate an oxenium ion, which is attacked by nucleophilic

fluoride (see Chapter 3 for further discussion). These reaction conditions were shown to tolerate a range of functional groups at the *ortho* position, including a bromo subsituent, which allowed for post-fluorination funcationalisation via a Suzuki–Miyaura coupling. Notably, this methodology was complementary to that recently disclosed by Ritter (see Scheme 1.12),[50-51] as it constituted umpolung of the substrate, as opposed to the fluorine source.

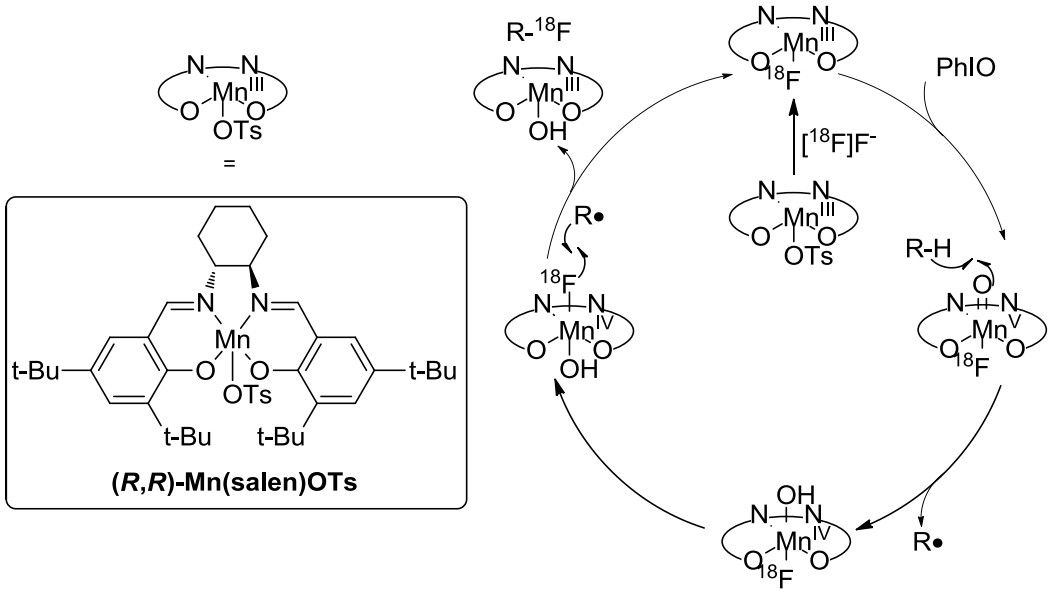
Whilst the reactions discussed above have been promoted by addition of a transition metal complex or hypervalent iodine oxidant, each has also required significant pre-functionalisation of the substrate, which can result in lengthy precursor synthesis. An ideal approach would involve the C-H activation of non-activated precursors.

A report by Groves and co-workers in 2014 set out to avoid this pre-functionalised approach to ^{18}F-labelling by development of a method which involved the direct replacement of a benzylic sp^3 hydrogen with fluorine.[59] In an extension of the ^{19}F-fluorination reactions reported by the same group,[60] this procedure facilitated the ^{18}F-fluorination of a wide range of precursors containing benzylic C-H bonds. The reaction was proposed to proceed via formation of a [^{18}F](salen)Mn fluorine complex, generated by reaction of Mn(salen)OTs with [^{18}F]fluoride from an ion-exchange cartridge, which undergoes oxidation in the presence of iodosobenzene. Reaction at 50 °C in acetone for 10 minutes afforded ^{18}F-labelled products with RCY reaching up to 72 %, with an array of functional groups tolerated under these conditions (Scheme 1.16).



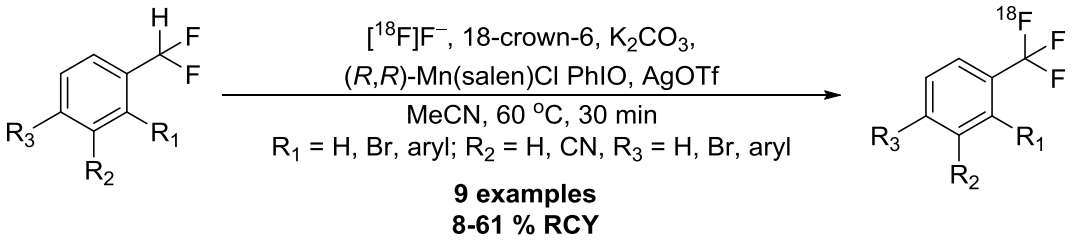
Scheme 1.16: Benzylic C-H activation with [^{18}F]F$^-$ by Groves and co-workers

Although for ^{19}F-fluorination reactions the authors proposed a mechanism that involved a *trans*-difluoromanganese(IV) complex as the reactive fluorine transfer intermediate, due to the substoichiometric amount of [^{18}F]fluoride it was proposed that a ^{18}F−Mn(IV)−OH intermediate was more likely in this case (Scheme 1.17). This theory was substantiated by DFT calculations, which indicated that the fluorine transfer from a F−Mn(IV)−OH complex to a benzyl radical is thermodynamically favoured with an activation energy of 9.6 kcal/mol and a calculated free energy change of −38.0 kcal/mol.



Scheme 1.17: Mechanism for manganese-mediated benzylic ^{18}F-fluorination proposed by Groves and co-workers

This work prompted a later report by Carroll and co-workers outlining extension of this methodology to aryl difluoro substrates, in order to afford access to ^{18}F-labelled trifluoromethyl arenes (Scheme 1.18).[61]



Scheme 1.18: Manganese-mediated synthesis of aryl [^{18}F]CF_3 compounds by Carroll and co-workers

Employing acetonitrile as solvent, this reaction was shown to be tolerant of a range of functional groups, although electron withdrawing substituents resulted in lower RCYs. A bromo substituted precursor also allowed for post-fluorination functionalisation via Suzuki coupling.

1.4 Thesis Outline

Many of the methods for ^{18}F-radiosynthesis discussed above require activation by a transition metal complex. The use of transition metals is often associated with drawbacks including the lengthy synthesis of non-commercial ligands and the requirement for anhydrous conditions, as well as the potential for trace metal contamination of resultant pharmaceuticals. On the contrary, metal-free reactions have many advantages in terms of operational simplicity; they are generally robust and occur under mild reaction conditions, without the need for strict exclusion of moisture, using reagents which are often commercially available and non-toxic.[62] As experimental simplicity is crucial in radiosynthesis, due to time constraints imposed by the short half life of isotopes and the benefits associated with automation, we recognised the value of an alternative, metal-free approach to ^{18}F-labelling. This thesis therefore aims to broaden the scope of organomediated ^{18}F-fluorination: Chapter 2 discloses the investigation of three organomediated approaches to asymmetric ^{18}F-fluorination, a field which is currently dominated by transition metal-mediated reactions. Chapter 3 reports the application of hypervalent iodine reagents in the umpolung reaction of *N*-arylsulfonamides with nucleophilic fluoride.

1.5 References

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Chapter 2:

Organomediated Enantioselective ^{18}F-Fluorination

2. Organomediated Enantioselective ^{18}F-Fluorination

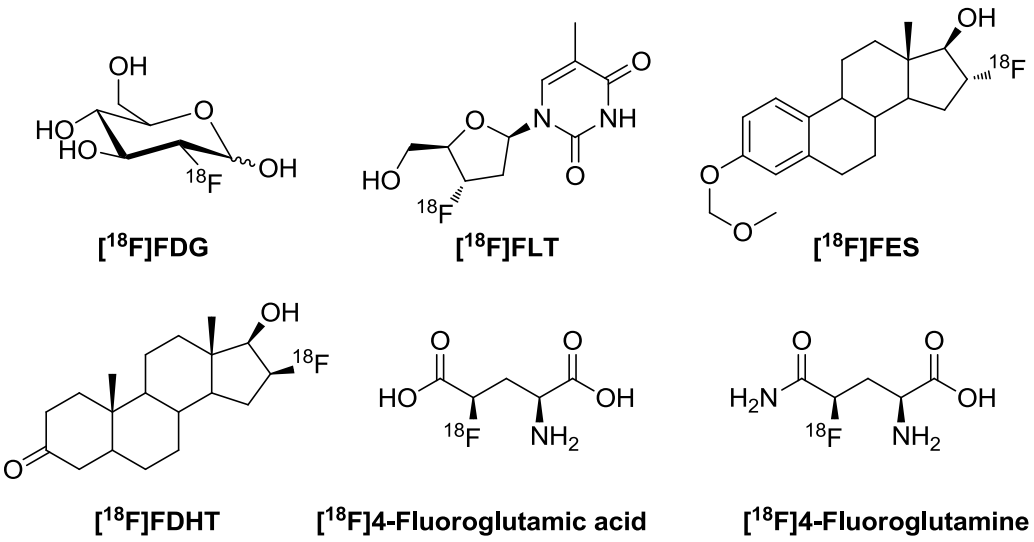
2.1 Introduction

The enantiomers of racemic drugs often display a significant difference in biological activity due to diverse interactions with chiral targets *in vivo*, such as receptors, enzymes and ion channels.[1] This chiral distinction of physiological processes plays a key role in drug development, as the use of enantiopure drugs is often advantageous, not only in order to reduce the total dose given to patients, but also to minimise possible toxicity of the "passive" enantiomer. The importance of chirality in the pharmaceutical industry is demonstrated by the fact that over half of all drugs in use today are employed as a single enantiomer.[2]

Chirality is equally important in the context of radiochemistry, both in terms of design of clinical radiotracers, and in terms of the significant potential of PET imaging as a tool in early stage drug development (see Section 1.1).[3] However, the utility of PET imaging in this way relies on the availability of comprehensive methodology for synthesis of appropriately labelled radiotracers. Indeed, the slow implementation of PET into the pharmaceutical industry perhaps highlights the current limitations in the synthetic methodologies available, and underscores the importance for continued research in this field. With the drive in industry to develop optically pure pharmaceuticals, the development of asymmetric methodology in radiochemistry is also crucial.

2.1.1 Synthesis of Radiotracers with ^{18}F-Containing Stereocentres

Today, several known radiotracers are employed in enantiopure form, including the ubiquitous [^{18}F]FDG (Scheme 2.1).[4]



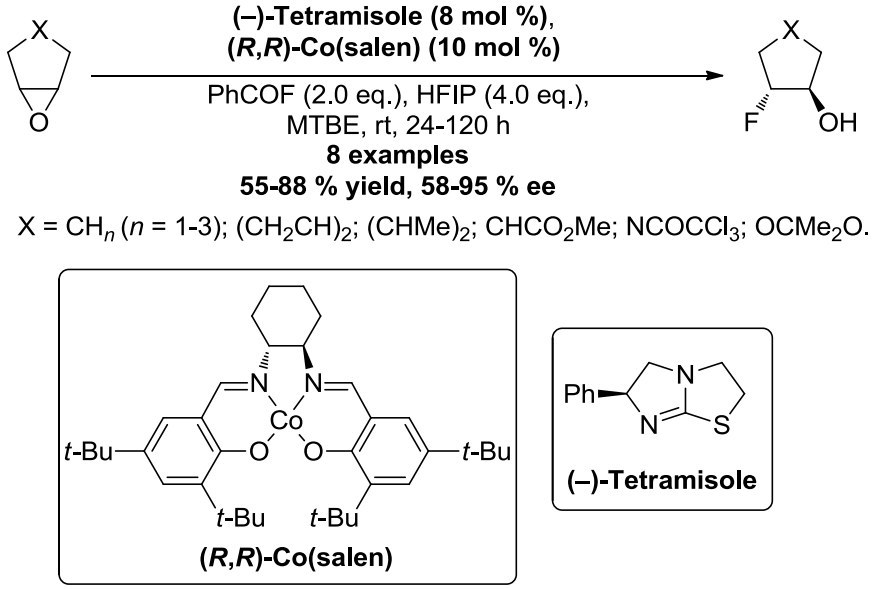
Scheme 2.1: Radiotracers containing ^{18}F-substituent on a stereogenic carbon

Most commonly, the stereogenic C-^{18}F bond is created via stereospecific S_N2 displacement by [^{18}F]fluoride on an enantioenriched starting material armed with a suitable leaving group at the stereocentre.[5] Whilst this method can be used very effectively to afford enantioenriched ^{18}F-labelled radiotracers with high SA, its utility is limited to substrates that tolerate the high temperatures required for ^{18}F-labelling, are not prone to elimination and can resist racemisation under the often harsh reaction conditions; this last criterion also stands true for the newly formed ^{18}F-substituted stereogenic carbon of the product. Other drawbacks include the propensity for incomplete inversion of the stereocentre[5f] and also the necessity for synthesis of a stereochemically pure precursor, which can be lengthy and far from facile. It is also possible to obtain an enantiomerically pure radiotracer by chiral HPLC resolution of the racemic compound, although this can be time consuming and the resultant loss of 50 % RCY in this case is far from ideal.

An alternative approach would involve setting the product stereochemistry during an asymmetric radiofluorination step, thereby avoiding many of these challenges. However, to date, asymmetric ^{18}F-fluorination reactions have met little success due to low enantiomeric excesses and lack of substrate scope.

2.1.2 Asymmetric ^{18}F-Fluorination

Inspired by seminal work of Bruns and Haufe in 2000,[6] a recent report by Doyle and co-workers described the enantioselective ring opening of terminal and *meso* epoxides by fluoride catalysed by *(R,R)*-Co(salen) and the chiral non-racemic amines DBN and (–)-tetramisole respectively.[7] The desymmetrisation of a range of *meso* epoxides, on five- to eight- membered rings, led to the formation of stereogenic carbon-fluorine centres, with ee values reaching up to 95 % (Scheme 2.2).

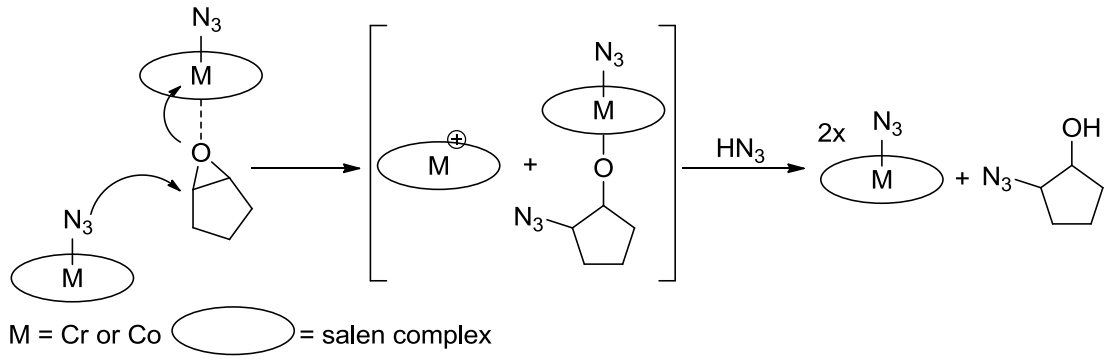


Scheme 2.2: Enantioselective opening of *meso* epoxides with fluoride by Doyle and co-workers. HFIP = hexafluoroisopropanol

Whilst previous work had identified that chiral Lewis acid-mediated epoxide ring-opening reactions that employed a HF·pyridine complex suffered from low enantioselectivity due to the racemic background reaction and catalyst degradation, Doyle and co-workers reported that a combination of benzoyl fluoride and hexafluoroisopropanol (HFIP) provided successfully mild conditions to afford fluorohydrin products with excellent enantiocontrol. The authors proposed that the reaction progressed via amine-catalysed slow *in situ* formation of HF, which in turn could generate a (salen)Co(III) fluorine complex. A significant mismatched effect on yield and

enantioselectivity was observed between the catalysts when (–)-tetramisole was employed in combination with *(S,S)*-Co(salen).

In a later report, the authors outlined more detailed mechanistic studies on this reaction.[8] Kinetic studies on the metal(salen)-catalysed desymmetrisation of *meso* epoxides by azides and the hydrolytic kinetic resolution (HKR) of terminal epoxides had previously been carried out by Jacobsen and co-workers.[9] These studies showed that both reactions were second order with respect to catalyst in the rate limiting step and that there was a nonlinear relationship between the ee value of the ring-opened product and the ee value of the catalyst, indicating that two molecules of catalyst were involved in the enantiodetermining epoxide opening step. Complexation of the catalyst with the azide nucleophile was also proposed and this complex could indeed be isolated and characterised by X-ray diffraction. As a result of these findings, Jacobsen proposed a mechanism in which one metal(salen) molecule activated the epoxide, whilst another molecule of catalyst delivered the nucleophile in a homobimetallic pathway (Scheme 2.3).



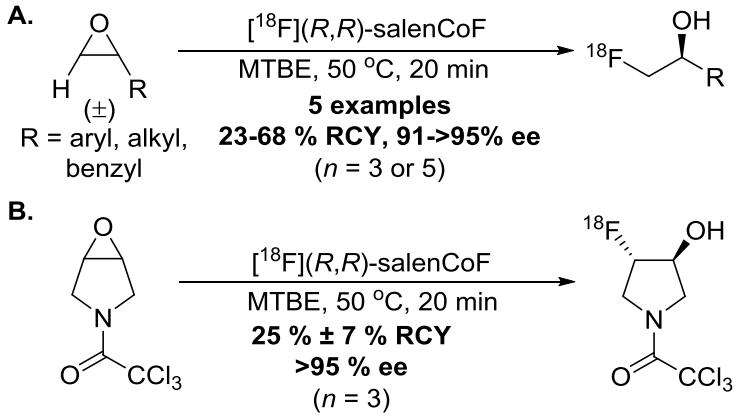
Scheme 2.3: Homobimetallic pathway proposed for ring opening of epoxides with azide nucleophile by Jacobsen and co-workers

Similar second order kinetics would also be expected for the ring opening of terminal epoxides with a fluoride nucleophile. However, preliminary kinetic studies by Doyle and co-workers indicated an observed first order dependence for both the Co(salen) complex

and the amidine co-catalyst. It was proposed that, in the presence of fluoride anion, the cobalt catalyst exists as a fluoride-bridged dimeric complex in its resting state. Dissociation of this catalyst dimer to an active monomer is rapid and reversible, and the amount of dissociated monomer at any time is low. In catalytic reactions, the presence of an inactive resting state dimer would be expected to result in half-order kinetics,[10] and so the involvement of two dimers of catalyst in the bimetallic rate limiting step has the result that first order kinetics are observed for this reaction. This apparent first order behaviour for a reaction that is otherwise determined to be bimolecular has similarly been observed for the reversible binding of hydrogen peroxide to cytochrome *c* oxidase.[11]

The rate enhancement provided by the amidine co-catalyst in this case was therefore at least partially attributed to the association of this Lewis base with the Co(salen) complex, which facilitates dissociation of the inactive oligomer and increases the concentration of active monomeric catalyst. As a result of these findings, the authors were able to develop an improved protocol for ring opening of both terminal and *meso* epoxides, which employed a dicarboxylate linked dimeric catalyst in low loading (0.25 mol %).

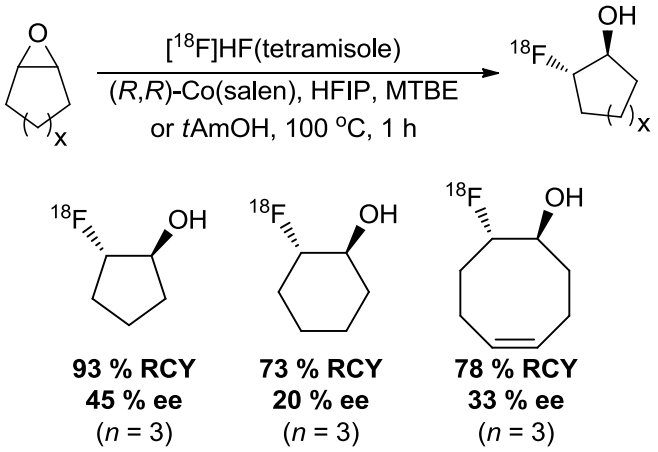
In 2014, a report from the same group, in collaboration with Kung, described extension of this methodology to radiofluorination with ^{18}F.[12] In this case, [^{18}F](salen)CoF was synthesised directly by reaction of (*R,R*)-(salen)CoOTs with [^{18}F]fluoride eluted from an ion-exchange cartridge, without the requirement for azeotropic drying, and was employed for reaction with terminal and *meso* epoxide precursors in methyl-*tert*-butylether (MTBE) to achieve hydrofluorination with high RCY and excellent ee values within 20 minutes (Scheme 2.4).



Scheme 2.4: Ring opening of A. terminal epoxides and B. *meso* epoxide with ^{18}F by Doyle and co-workers

Notably, as RCY is determined by amount of ^{18}F-labelled product relative to starting activity, in this case a RCY of greater than 50 % is possible for the kinetic resolution of terminal epoxides. An excellent level of enantiocontrol was demonstrated, despite increase of reaction temperature to 50 °C. The synthesis of a range of radiotracers was also well tolerated. However, in this report the majority of substrates were terminal epoxides and it contained just one example in which desymmetrisation of a *meso* epoxide led to a product with a stereogenic C-^{18}F centre.

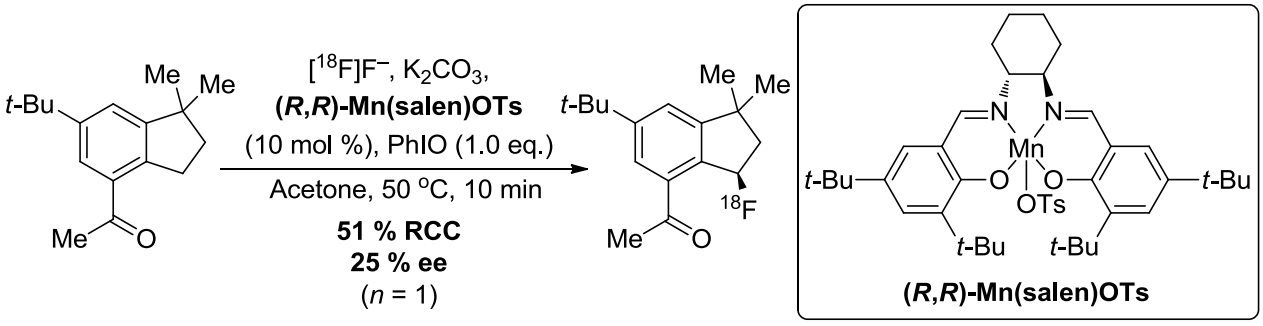
At the same time, a study by Revunov and Zhuravlev also took inspiration from the cobalt-mediated enantioselective epoxide opening with ^{19}F reported by Doyle and co-workers.[13] This work employed [^{18}F]fluoride treated with H_2SO_4, proposed by the authors to form [^{18}F]HF, which could be trapped by addition of (–)-tetramisole. The reaction took place by addition of the same *(R,R)*-Co(salen) complex employed by Doyle, as well as HFIP and the epoxide precursor in either MTBE or 2-methyl-2-butanol (*t*AmOH) (Scheme 2.5). The use of HFIP was found to be crucial to product formation. In this report the reaction was performed at 100 °C for 1 hour and afforded 3 examples of [^{18}F]fluorohydrin products from cyclic epoxides with good RCY but low ee values, which the authors hypothesised was due to the high reaction temperature.



Scheme 2.5: Hydrofluorination of *meso* epoxides with [^{18}F]HF(tetramisole) by Revunov and Zhuravlev.

In both of these reports, the use of [^{18}F]fluoride is advantageous as this form of the isotope is available with high S.A. and as such is the most commonly available source of ^{18}F at PET centres worldwide. However, the scope of this approach is currently very limited and precursors require significant pre-functionalisation as epoxides.

The manganese-mediated ^{18}F-fluorination of benzylic C-H bonds disclosed by Groves and co-workers was discussed in detail in Chapter 1.[14] Although this report focussed on racemic fluorination, an enantioselective reaction was employed as a tool to demonstrate the involvement of a manganese salen-bound ^{18}F-intermediate in the fluorine transfer step. In this singular example of the potential for synthesis of enantioenriched products employing this protocol, the Mn(salen)OTs mediated ^{18}F-fluorination of celestolide afforded the radiolabelled product with an ee of 25 % (Scheme 2.6).



Scheme 2.6: Asymmetric ^{18}F-fluorination of benzylic C-H bonds by Groves and co-workers

Although the optimisation of this reaction in terms of ee has yet to be reported, this preliminary example nevertheless highlights the potential opportunity for asymmetric ^{18}F-fluorination employing this methodology, which not only advantageously utilises nucleophilic [^{18}F]fluoride but also employs precursors that do not require pre-functionalisation with a leaving group.

The three enantioselective ^{18}F-fluorination reactions described thus far not only constitute the sum of the literature on this topic, but have also all required activation by a transition metal. That is to say, there are currently no examples of asymmetric ^{18}F-fluorination activated by an organomediator. In contrast, metal-free reactions to generate C-^{19}F stereocentres have been studied extensively.[15]

2.1.3 Organomediated Asymmetric Fluorination

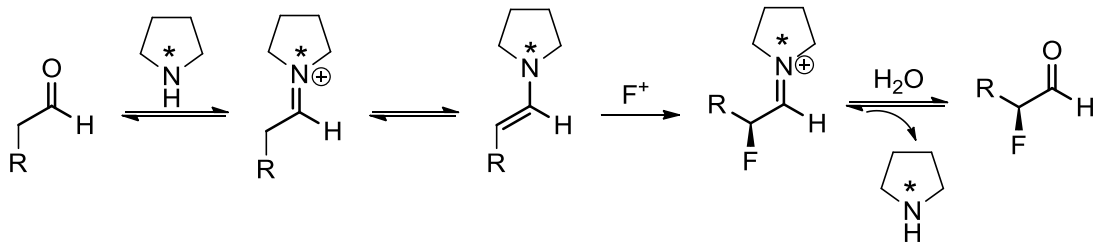
Over the past two decades, research in the field of enantioselective organocatalysis has increased exponentially,[16] with the result that it has now become a powerful tool in asymmetric synthesis.[17] There are several key activation modes in organocatalysed asymmetric fluorination, which will be reviewed below, including secondary amine, *N*-heterocyclic carbene and phase transfer catalysis. Although the concept of catalysis presents multiple advantages in cold chemistry,[18] especially when considering industrial scale up, the sub-stoichiometry of the ^{18}F source imposes that "catalysts" are actually

present in excess in the case of ^{18}F-radiosynthesis. For this reason we will also consider metal-free reactions which employ stoichiometric amounts of an organomediator.

2.1.3.1 Secondary Amine Catalysis

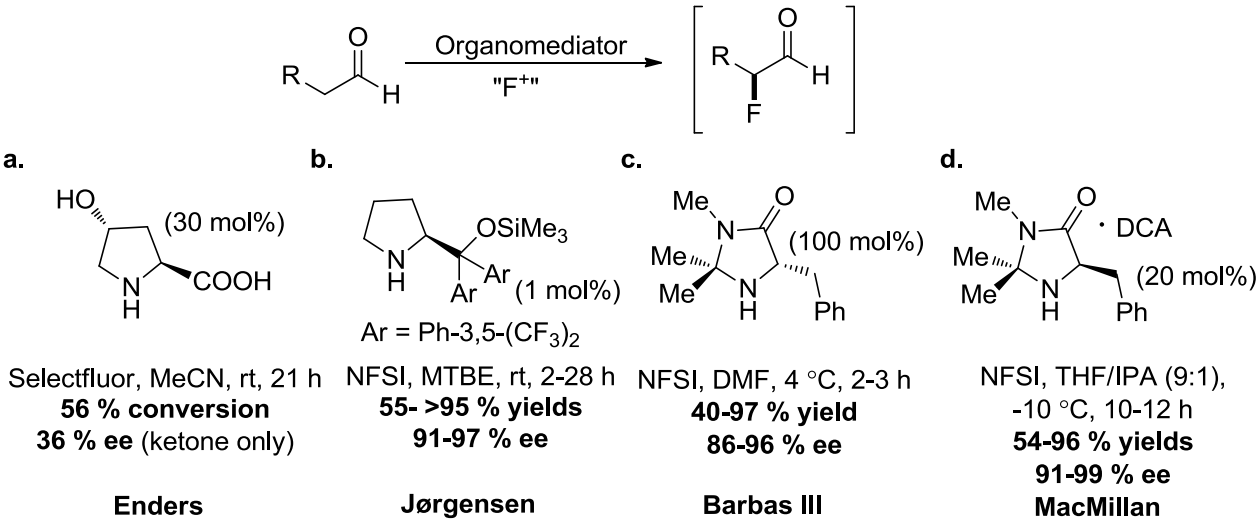
2.1.3.1.1 Enamine Catalysis of Aldehydes and Ketones

Enamine catalysis was pioneered in 1971 when a proline-catalysed intramolecular aldol reaction was reported independently by both Hajos and Parrish,[19] and Eder, Sauer, and Wiechert.[20] However, it was not until 2005 that the secondary amine-mediated enantioselective α-fluorination of carbonyls was reported independently by four research groups. Asymmetric enamine catalysis proceeds via the reversible condensation of a chiral non-racemic amine with a carbonyl substrate to afford an iminium ion.[21] Formation of this iminium ion lowers the LUMO energy of the system and therefore facilitates α-proton abstraction to afford an enamine species. This transformation raises the energy of the HOMO of the system, therefore promoting reaction of the chiral enamine with an achiral electrophilic species, in this case an electrophilic source of fluorine (Scheme 2.7).



Scheme 2.7: Mechanism of secondary amine-catalysed asymmetric fluorination

In the first of these reports by Enders, proline-based catalysts were employed for the α-fluorination of a range of aldehydes and ketones with Selectfluor as the electrophilic fluorinating agent (Scheme 2.8, a).[22]

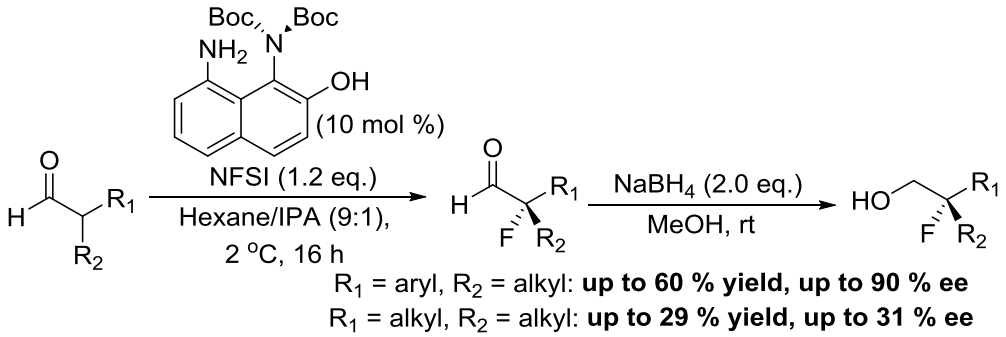


Scheme 2.8: Asymmetric fluorination of aldehydes via enamine catalysis
DCA = dichloroacetic acid

However, this met limited success, with enantiomeric excesses reaching only 36 % for the ketone substrates. Later the same year, Jørgensen[23] and Barbas[24] published consecutive papers also reporting the enantioselective α-fluorination of aldehydes via enamine catalysis and achieved much improved results by employing alternative catalysts and the less reactive NFSI as the achiral fluorine source (Scheme 2.8, b and c). Whilst Barbas employed stoichiometric amounts of an imidazolidinone-based chiral promoter at 4 °C in DMF to achieve excellent yields and enantiomeric excesses for the asymmetric fluorination of aliphatic aldehydes, Jørgensen was able to achieve similar results at room temperature, using catalytic amounts of a bulky silylated prolinol-derived amine in MTBE as solvent. However, in the latter case, an excess of aldehyde substrate and low catalyst loading was required to minimise formation of difluorinated side-product.

Both were also able to extend this methodology to the formation of quaternary centres, albeit with reduced enantioselectivity. The Jørgensen procedure was also later adapted by Shibatomi and Yamamoto for the asymmetric fluorination of racemic α-chloroaldehydes to afford α,α-chlorofluoro products with high enantioselectivity at room temperature.[25]

Later mechanistic studies led the authors to propose a mechanism that involved kinetic resolution of the α-chloroaldehyde substrate.[26] A report in 2006 from Jørgensen and co-workers sought to improve the α-fluorination of α-branched aldehydes using a chiral non-racemic 8-amino-2-naphthol-derived catalyst displaying non-biaryl atropisomeric functionality (Scheme 2.9).[27] In this case, good enantioselectivities were achieved when substrates bearing an aromatic substituent were employed.

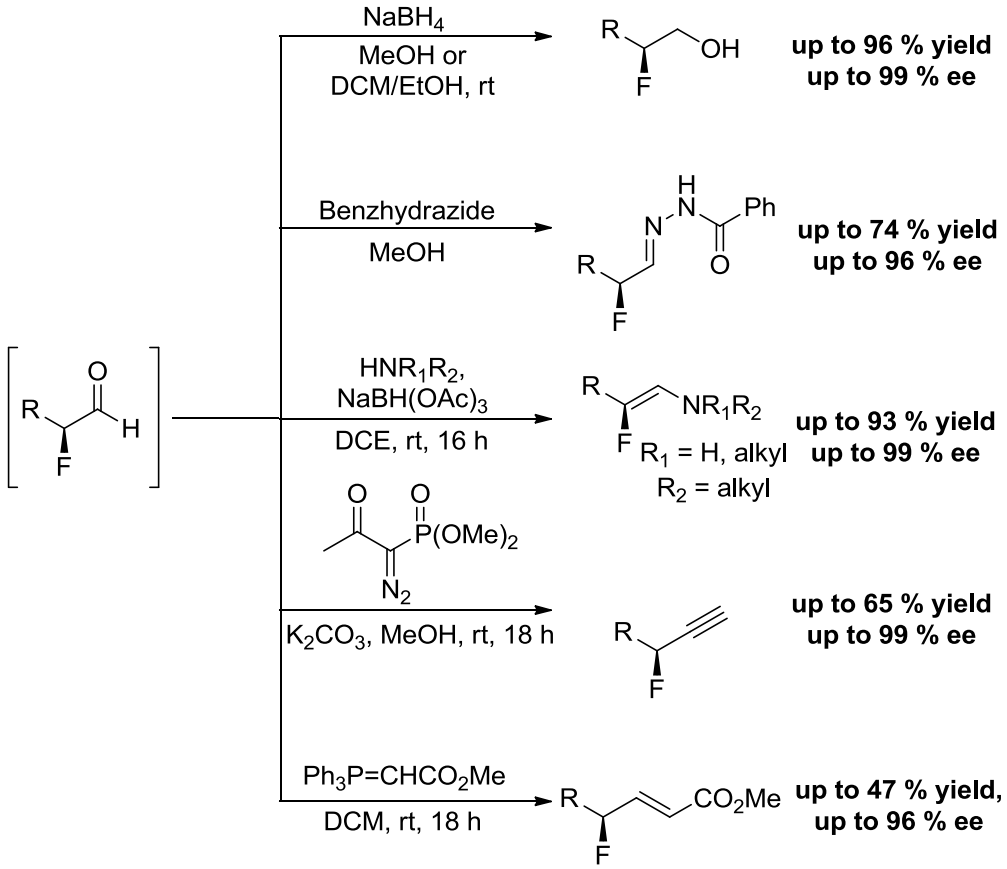


Scheme 2.9: α-Fluorination of α-branched aldehydes employing a non-biaryl atropisomeric catalyst by Jørgensen and co-workers

Finally, the α-fluorination of aldehydes was also reported by MacMillan and co-workers in 2005 (Scheme 2.8, d).[28] Excellent yields and enantiomeric excesses were achieved for the asymmetric α-fluorination of linear aldehydes by employing the commercially available dichloroacetate salt of the imidazolidinone catalyst utilised by Barbas, now often referred to as one of the "MacMillan organocatalysts". It was reported that addition of 10% IPA as a co-solvent greatly improved enantiocontrol of the reaction, as well as minimising formation of difluorinated side-product. This was proposed to be due to reaction of IPA with the fluoroaldehyde products to form a hemi-acetal, thereby preventing further reaction with catalyst, which could result in racemisation or reaction with a further molecule of NFSI.[29] Although no branched aldehydes were investigated in this case, a wide range of functional groups, including olefins, esters, amines, carbamates, and aryl rings were tolerated on the aldehydic substrate and one example leading to

formation of a product containing a benzylic fluorine was also described. Catalyst loadings as low as 2.5 % could be employed without loss of enantiocontrol. This methodology was later applied by O'Hagan and co-workers in the synthesis of cinacalcet anaologues developed for the treatment of hyperparathyroidism.[30]

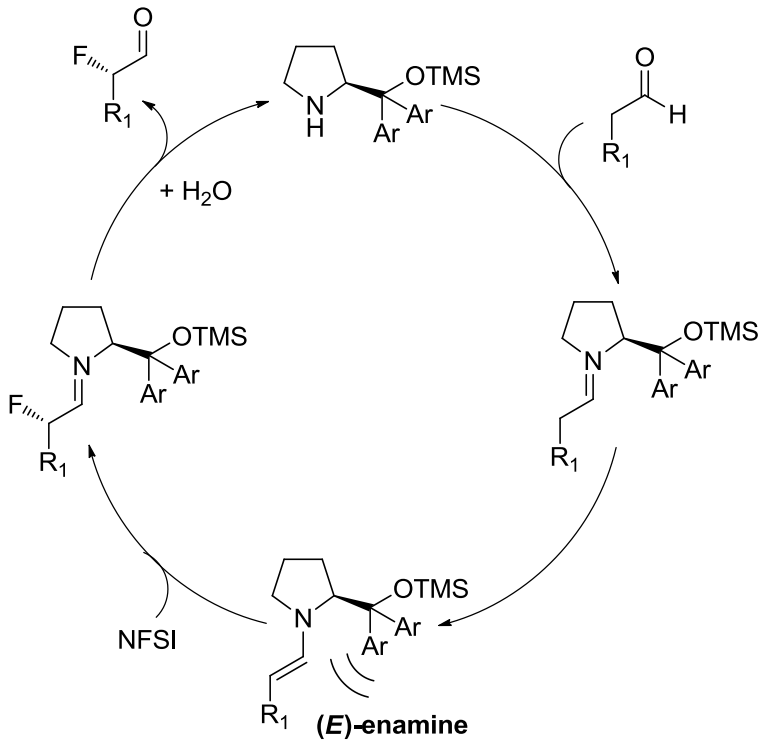
α-Fluoroaldehydes are notoriously unstable and susceptible to epimerisation and so in each of the above cases the enantioenriched fluorinated product was immediately derivatised for isolation and characterisation. This fortuitously provided a method to access to a range of optically enriched fluorinated motifs from a common intermediate (Scheme 2.10). The absolute stereochemistry of products could be determined by comparison of optical rotation values with those reported in the literature.



Scheme 2.10: Derivatisation of α-fluoroaldehydes for isolation and characterisation

Reported derivatisations for the above reactions include reduction with sodium borohydride to afford a β-fluorohydrin,[22;28;31] and reaction with benzhydrazide to afford the corresponding benzoylhydrazone.[24] Later reports included application of the same methodology to afford β-fluoroamines via a reductive amination reaction[32] and propargylic and allylic fluorides by reaction with the Ohira-Bestmann reagent or a Wittig reagent, respectively.[33] Crucially, it was necessary to employ conditions for the derivatisation which were mild enough to avoid racemisation of the newly formed stereocentre. MacMillan and co-workers reported that *in situ* reduction of the intermediate α-fluoroaldehydes with sodium borohydride was unsuccessful unless all NFSI and its acidic byproduct, dibenzenesulfonimide (DBSI) were first removed.[29] It was found that the remaining NFSI could be transformed to DBSI by reaction with dimethylsulfide (DMS), but that racemisation of the stereocentre occurred under these conditions when imidazolidinone catalyst was present. It was therefore first necessary to remove the imidazolidinone catalyst by filtration through Davisil silica gel at −78 °C, prior to addition of DMS. The resultant DBSI was then removed by aqueous work-up with saturated sodium bicarbonate prior to the derivatisation step. On the other hand, Barbas carried out isolation of the enantioenriched α-fluoroaldehyde intermediates by aqueous work up, whilst Jørgensen employed a filtration step prior to derivatisation.

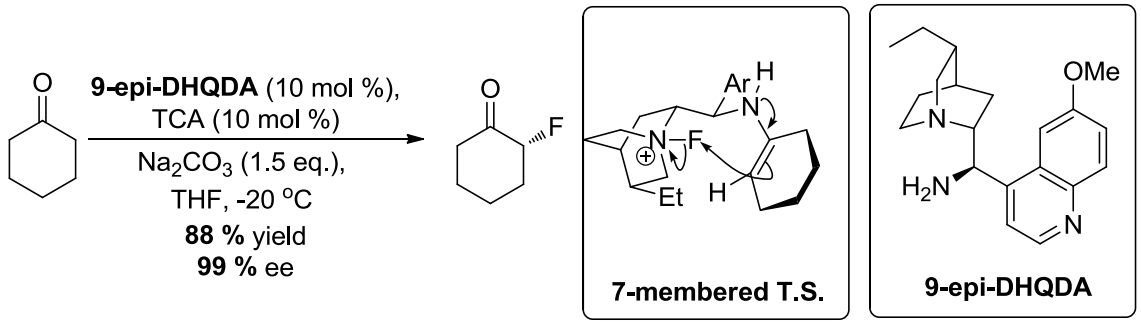
Jørgensen and co-workers proposed a stereochemical pathway for this asymmetric α-fluorination reaction, which was based on experimental findings and confirmed by DFT calculations (Scheme 2.11).[23;34]



Scheme 2.11: Proposed explanation for stereochemical outcome of secondary amine-catalysed asymmetric α-fluorination reaction by Jørgensen and co-workers

The preferential formation of the (*S*)-enantiomer in this case was rationalised by formation of the more stable *E*-configured enamine, in which the sterically demanding substituent of the pyrrolidine catalyst shields the *Re* face, therefore directing the electrophilic fluorination to the *Si* face of the enamine.

The more challenging asymmetric fluorination of ketone substrates, which condense only slowly with secondary amine catalysts, was not addressed until a further paper by MacMillan and co-workers in 2011.[35] High-throughput screening of 250 primary and secondary amines as catalysts for the α-fluorination of cyclohexanone allowed an optimum reaction protocol to be developed. It was found that use of 20 mol % of a dihydroquinidine-derived catalyst, in the presence of a trichloroacetic acid co-catalyst, could be employed to afford α-fluorinated ketones with excellent yields and enantiomeric excesses (Scheme 2.12).



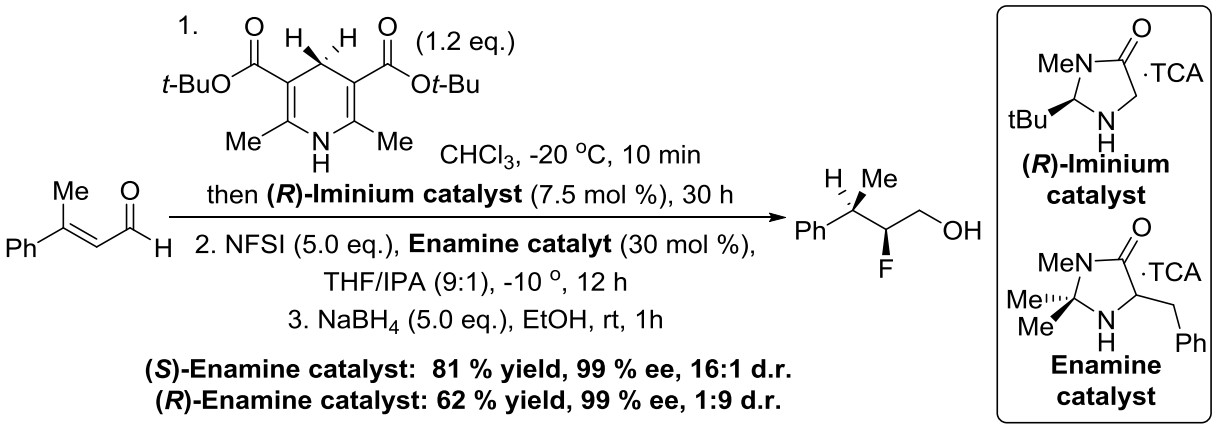
Scheme 2.12: Organocatalytic α-fluorination of ketones by MacMillan and co-workers

DHQDA = dihydroquinidine acetate; TCA = trichloroacetic acid

A computational study by Lam and Houk[36] determined that this reaction actually proceeded via fast fluorine transfer from NFSI to the cinchona alkaloid, resulting in intramolecular fluorine transfer to the enamine from the quinuclidine nitrogen-bound fluorine (see Section 2.1.3.4.2 for further discussion of cinchona alkaloids as chiral N-F reagents). Fluorine addition to the *Re* face is thus controlled via the favourable chair conformation of the 7 membered transition state (T.S.) and the preferred equatorial position of the bulky C9-quinoline of the catalyst.

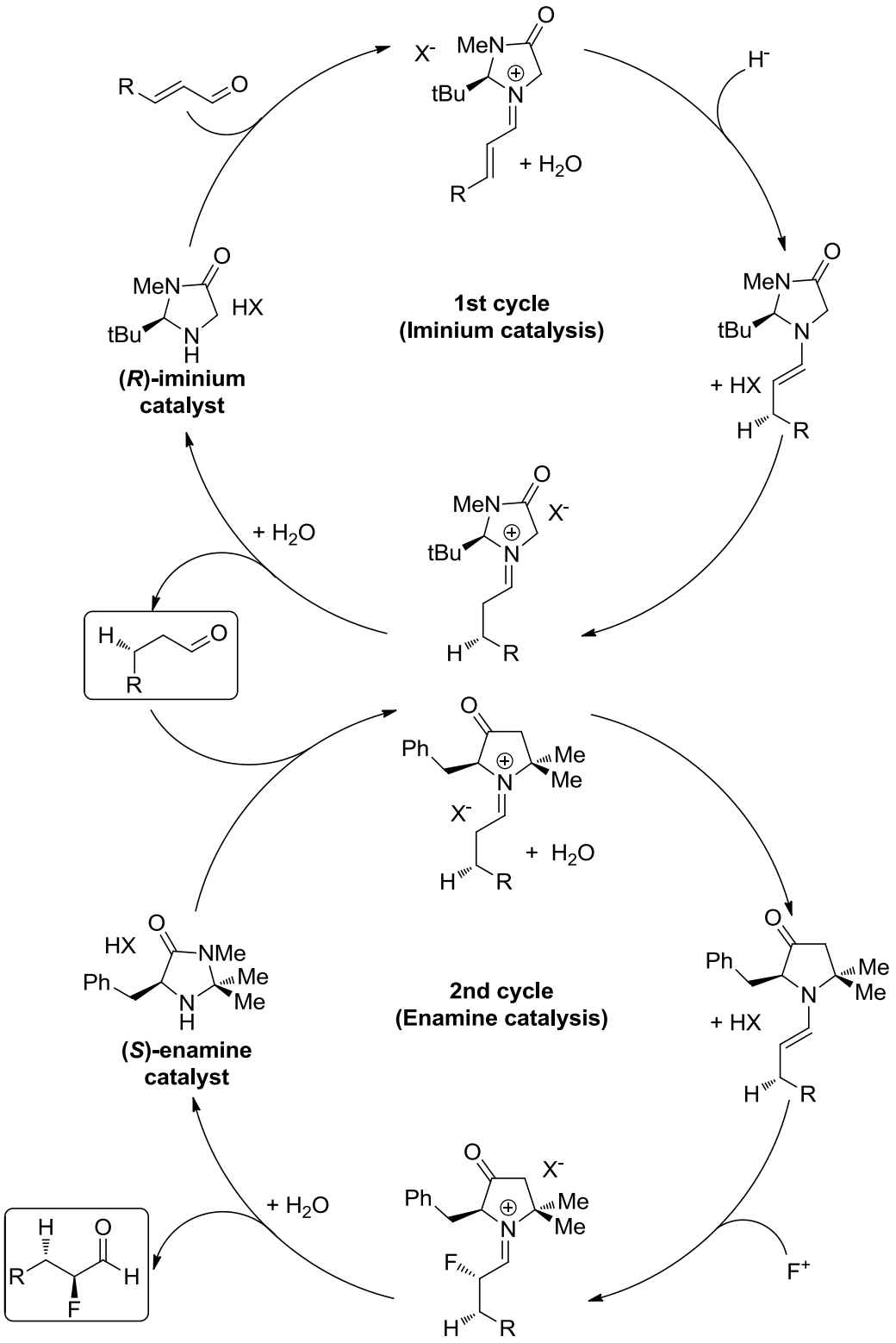
2.1.3.1.2 Cascade Reactions

A further report of the application of imidazolidinone catalysts to asymmetric fluorination was also made by the MacMillan group in 2005. In this work, iminium and enamine modes of activation were applied consecutively to an α,β-unsaturated aldehyde substrate, resulting in the formal *anti* addition of HF across the enal double bond with excellent diastero- and enantioselectivity (Scheme 2.13).[37] Optimum results actually required a different imidazolidinone catalyst for each of the modes of activation. Notably, the opposite enantiomer of the enamine catalyst could also be employed to achieve the opposite selectivity, therefore affording formal *syn* addition of HF across the double bond.



Scheme 2.13: Organocascade asymmetric fluorination pathway by MacMillan and co-workers

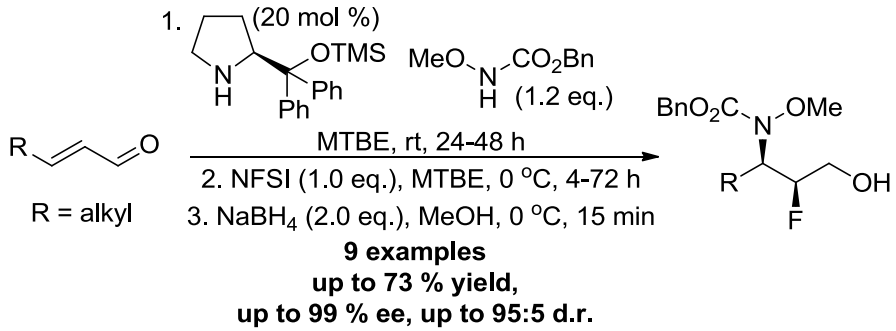
The reaction was proposed to proceed via a cascade pathway in which following an asymmetric hydride transfer from the Hantzsch ester to a (LUMO activated) chiral iminium species, the (HOMO activated) chiral enamine species generated reacted enantioselectively with NFSI (Scheme 2.14). This report not only demonstrated that iminium and enamine modes of activation could be combined in a cascade pathway but also that the selectivity of the reaction could be neatly modulated to provide the desired diastereo- and enantioselective outcome by choice of the appropriate amine catalysts.



Scheme 2.14: Catalytic cycle for iminium/ enamine cascade catalysis hydrofluorination pathway proposed by MacMillan and co-workers

Another example of asymmetric fluorination via cascade iminium/ enamine catalysis was reported by Brenner-Moyer and co-workers in 2010.[38] In this case, the same prolinol-

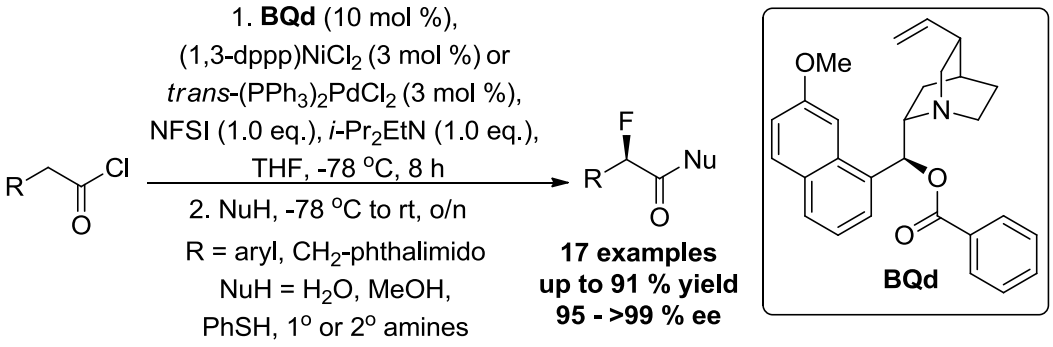
derived catalyst was employed for both steps of the reaction, in combination with a Cbz-protected amine nucleophile and NFSI as the electrophilic fluorine source (Scheme 2.15). This aminofluorination reaction proceeded with selectivity for formal *syn* addition across the double bond to afford β-fluoroamines with excellent enantio- and diastereo-selectivity.



Scheme 2.15: Enantioselective aminofluorination of enals by Brenner-Moyer and co-workers

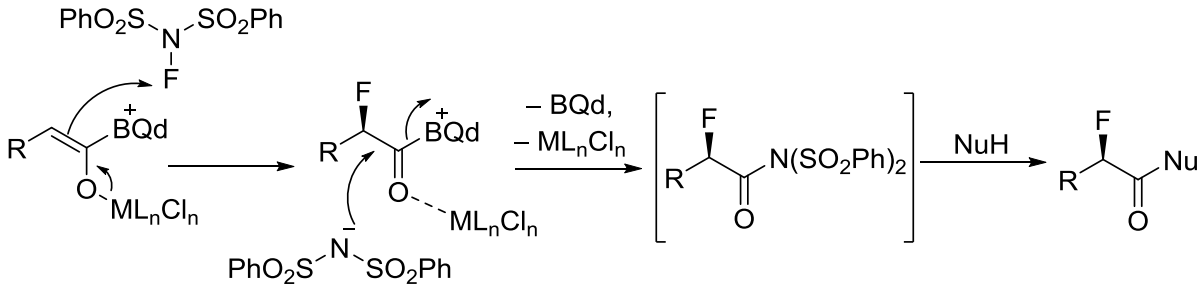
2.1.3.1.3 Dual-Activation Approach

A novel approach to asymmetric fluorination employing acid chloride substrates was reported by Lectka and co-workers in 2008.[39] This dual metal-ketene enolate approach employed the cinchona alkaloid derivative benzoyl quinidine as an asymmetric nucleophilic organocatalyst along with a nickel- or palladium-based Lewis acid co-catalyst and NFSI as the electrophilic fluorine source (Scheme 2.16).



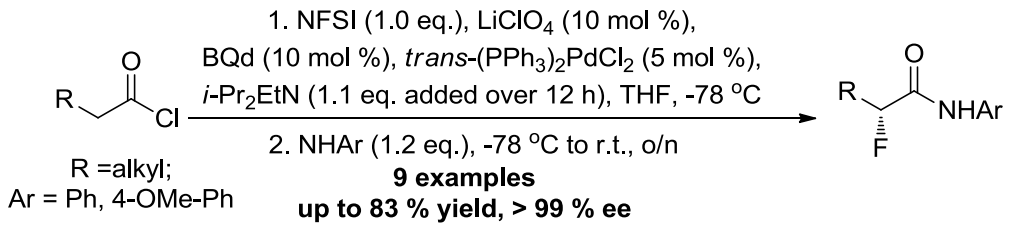
Scheme 2.16: Dual metal-ketene enolate approach by Lectka and co-workers
BQd = benzoyl quinidine

The reaction was proposed to proceed via a dually-activated enolate in which the metal co-catalyst significantly increases the reaction yield by co-ordination to the oxygen of the ketene enolate, which is formed by dehydrohalogenation, followed by nucleophilic attack by BQd (Scheme 2.17). Fluorination of the dually-activated species by NFSI results in an acyl ammonium salt, which is then rapidly attacked by the liberated dibenzenesulfonimide anion to regenerate the catalyst. The sulfonimide intermediate formed can then undergo a facile transacylation with a variety of nucleophiles during the reaction quench, facilitating the synthesis of a wide range of enantioenriched, α-fluorinated carboxylic acid derivatives, including esters, amides, thioesters and carboxylic acids. This mechanism was later supported by computational studies.[40]



Scheme 2.17: Mechanism of dual-activation approach proposed by Lectka and co-workers

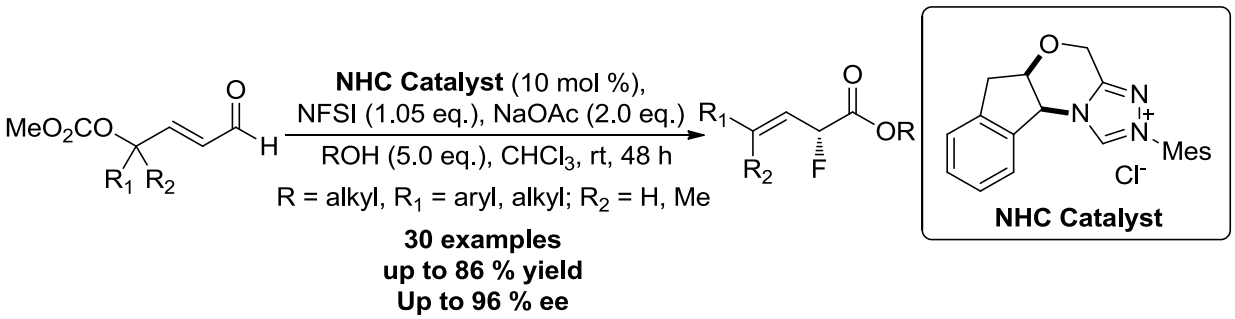
High enantiomeric excesses and yields were possible with a variety of aromatic and heteroaromatic substrates, however aliphatic substrates were found to work poorly, until a later report which included detailed optimisation of the procedure and kinetic data for the reaction.[40] These mechanistic investigations resulted in the evolution of the reaction to a trifunctional system, with $LiClO_4$ as a second Lewis acid catalyst, in order to provide excellent yields and enantiomeric excesses for a range of substrates, including aliphatic compounds (Scheme 2.18). It was proposed that $LiClO_4$ binds to NFSI and therefore enhances the electrophilicity of this fluorinating agent.



Scheme 2.18: Optimised conditions for trifunctional system by Lectka and co-workers

2.1.3.2 *N*-Heterocyclic Carbene Catalysis

A report by Lin, Sun and co-workers in 2012 outlined the first example of an *N*-heterocyclic carbene (NHC)-catalysed asymmetric fluorination reaction.[41] By employing enal substrates armed with a leaving group at the γ-position, the synthesis of enantioenriched β,γ-unsaturated α-fluoroesters was achieved using the combination of an appropriate pre-catalyst and base, with NFSI as the achiral fluorine source (Scheme 2.19).

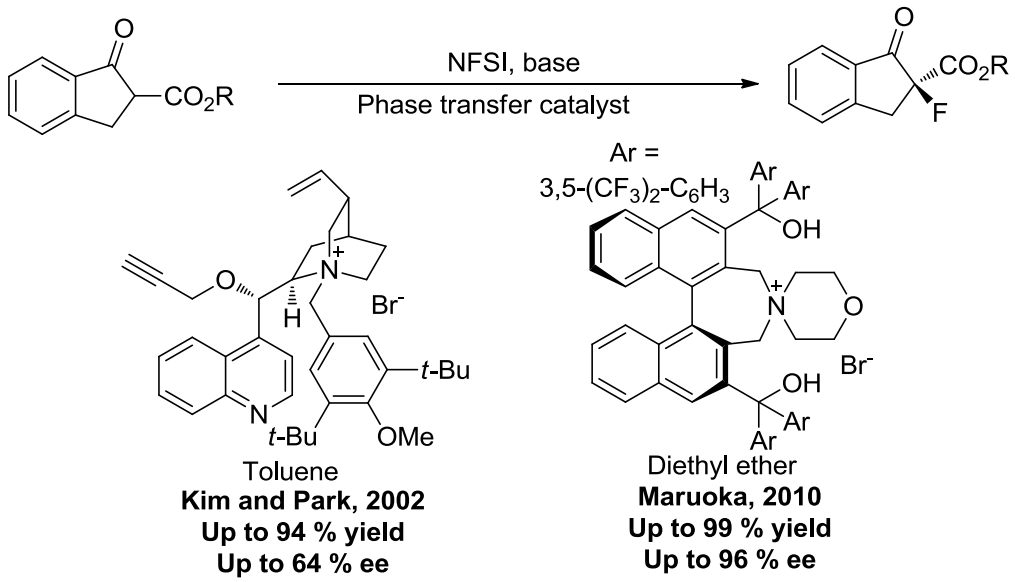


Scheme 2.19: *N*-Heterocyclic carbene-catalysed asymmetric fluorination by Lin, Sun and co-workers

The reaction was proposed to occur via addition of the NHC to the enal carbonyl group, followed by elimination and deprotonation of the resultant Breslow intermediate to afford a chiral NHC-bound dienolate species. DFT calculations suggested that the rotamer in which the bulk of the NHC blocks the *Re* face of this dienolate is 5.3 kcal/mol higher in energy than the alternative conformation in which the *Si* face is blocked. Fluorine addition from NFSI at the α-position therefore takes place selectively on the *Re* face of the enolate. This is followed by further acyl substitution by various alcohols to afford enantioenriched β,γ-unsaturated α-fluoroester products and regenerate the NHC catalyst.

2.1.3.3 Phase Transfer Catalysis

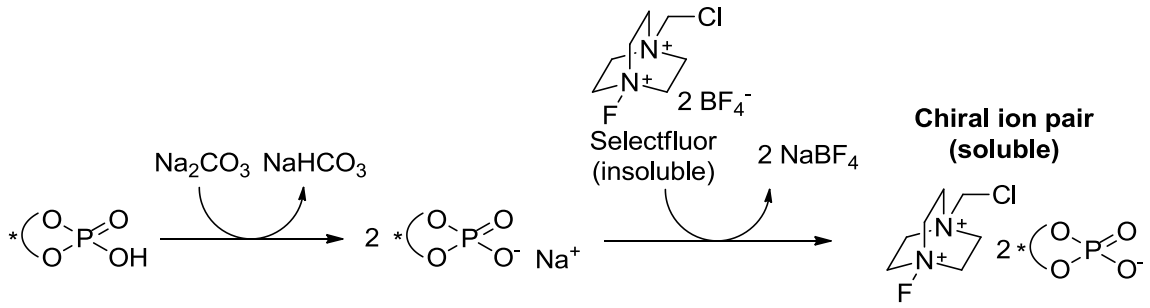
Phase transfer catalysis was first applied to asymmetric fluorination by Kim and Park in 2002. A cinchonine-derived quaternary ammonium salt was employed for the fluorination of cyclic β-ketoesters with excellent yields but only moderate enantioselectivity.[42] Some years later, a structurally rigid, C_2-selective spiro-ammonium salt derived from commercially available BINOL was employed as a cationic phase transfer catalyst in combination with NFSI for the enantioselective fluorination of β-ketoesters by Maruoka and co-workers.[43] Higher enantioselectivities were afforded with this catalyst, but substrates were still limited to those capable of two-point binding, thus allowing hydrogen bonding to the catalyst from both sites (Scheme 2.20).



Scheme 2.20: Cationic phase transfer catalysis applied to asymmetric fluorination

More recently, a new age of phase transfer catalysis was pioneered by the Toste research group.[44] Whilst previously phase transfer catalysis methods had employed a chiral cation to mediate the reaction between a substrate in solution and an insoluble or aqueous anionic reagent, the Toste group recognised the value of an analogous reaction in which chirality was provided by the anion.

This methodology employed catalytic BINOL-derived phosphates which were found to undergo anion exchange with the tetrafluoroborate anions of Selectfluor. Whilst Selectfluor is poorly soluble in non-polar solvents, association with lipophilic chiral phosphate anions was sufficient to bring the fluorinating agent into solution in hexane (Scheme 2.21). It was proposed that the phosphate can simultaneously form an anion pair with Selectfluor and co-ordinate with the substrate via H-bonding, therefore providing enantiocontrol for the fluorine transfer.[45]

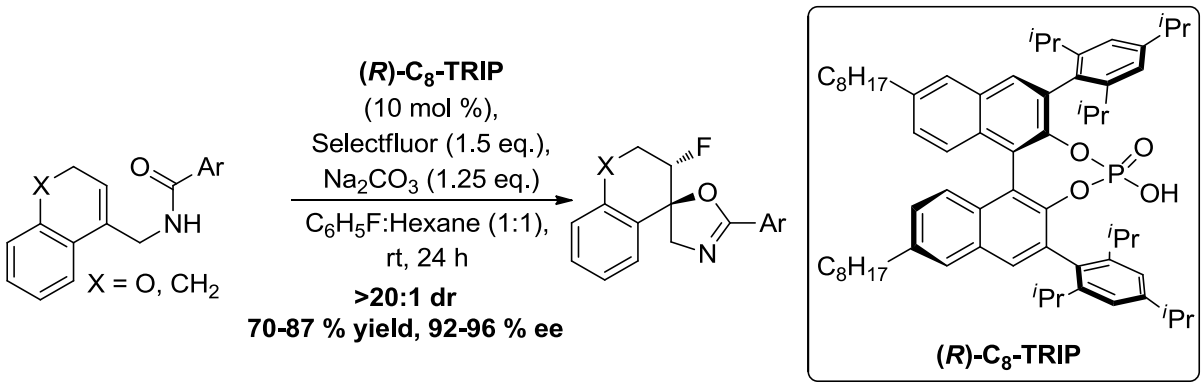


Scheme 2.21: Asymmetric Phase Transfer with Chiral Anion

Advantageously, upon fluorination the chiral phosphoric acid is regenerated and hence only a catalytic amount of the chiral reagent is required. At the same time, the racemic background reaction of highly reactive Selectfluor is suppressed due to the insolubility of the parent reagent in the non-polar reaction solvent.

This methodology was first applied to the fluorocyclisation of alkenes to afford access to fluoro-heterocycles with excellent enantio- and diastereo- selectivity (Scheme 2.22).[45] This reaction was proposed to proceed via fluorination of the double bond by the solubilised "chiral" Selectfluor, followed by intramolecular attack on the transient carbocation by the amide carbonyl to form a spiro-fused oxazoline. Notably, fluorination of alkenes is mechanistically distinct from the reaction of other halogens, proceeding via the irreversible generation of an acyclic cationic intermediate, in contrast to a bridged

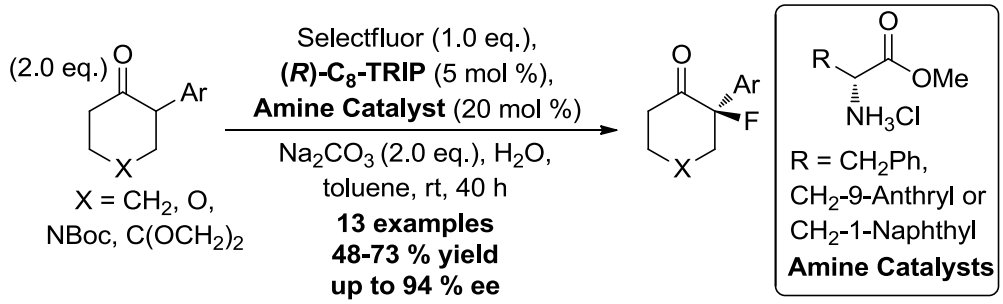
halonium ion.[46] This provides the caveat that for these reactions the enantio- and regio-selectivity of the fluorination must be set prior to the cyclisation event.



Scheme 2.22: Phase transfer-catalysed asymmetric fluorocyclisation by Toste and co-workers

This methodology has since been applied by the same research group to several key asymmetric fluorination reactions, including addition to conjugated dienes,[47] fluorination[48] and fluorohydration of enamides,[49] dearomatisation of phenols,[50] and fluorination of alkenes[51] and allylic alcohols[52] as well as by Alexakis and co-workers to the enantioselective fluorination-induced Wagner−Meerwein rearrangement of strained allylic alcohols,[53] therefore highlighting the significant utility of this procedure. However, it is currently limited to substrates that are capable are forming a hydrogen bond to the catalyst.

In a recent publication, the combination of phase transfer and enamine catalysis for application to the asymmetric fluorination of α-branched ketones was reported by the Toste group.[54] Whilst ketone substrates did not undergo fluorination under the previously developed phase transfer conditions, inclusion of a catalytic amount of an amino acid-derived primary amine was proposed to facilitate fluorine transfer from the soluble chiral Selectfluor bis-phosphate both by promoting enamine formation and through hydrogen-bond interaction with the chiral phosphate catalyst (Scheme 2.23).



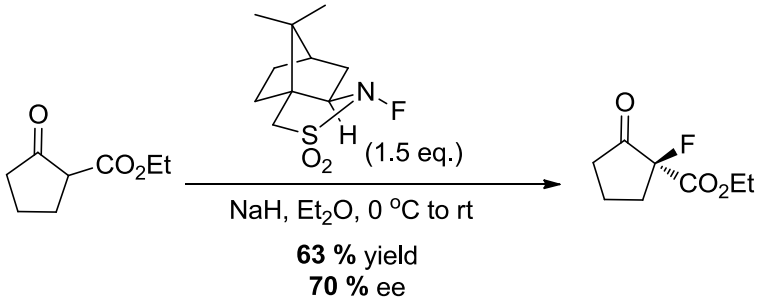
Scheme 2.23: Combination of enamine and phase transfer catalysis for asymmetric fluorination of α-branched ketones by Toste and co-workers

Under these conditions, α-aryl ketone substrates underwent successful electrophilic α-fluorination to afford quaternary stereocentres with high yield and enantioselectivity. Notably, this work represents a rare example of application of enamine catalysis to α-branched ketones, substrates which are commonly unreactive to this mode of catalysis.

2.1.3.4 Chiral Fluorinating Reagents

2.1.3.4.1 Early N-F Reagents

The first enantioselective fluorinating reagent was developed by Differding and Lang in 1988, by treatment of camphorsultam with elemental fluorine.[55] The *N*-fluorocamphorsultam reagent was successfully employed for the α-fluorination of the sodium enolate of ethyl 2-oxocyclopentanecarboxylate, to give a promising 70 % enantiomeric excess with a 63 % yield (Scheme 2.24). However, on extension to other substrates, substantially poorer results were obtained.

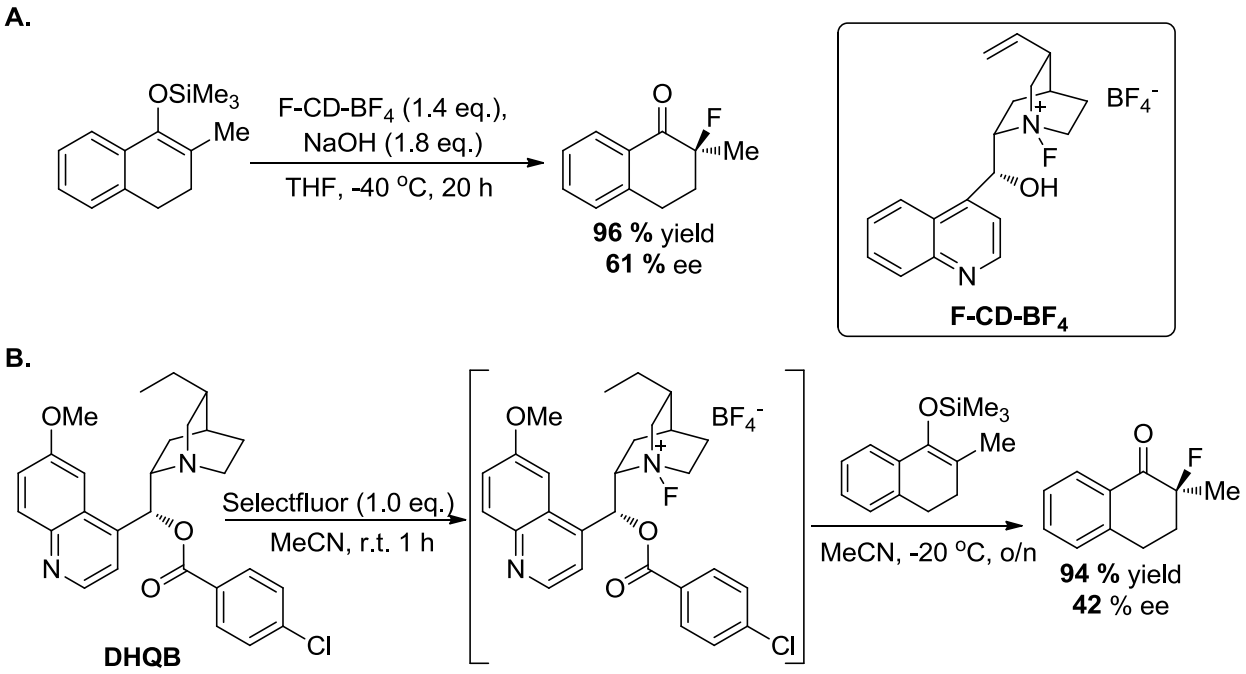


Scheme 2.24: Enantioselective fluorination using *N*-fluorocamphorsultam reagent by Differding and Lang

This work was further developed by Davis and co-workers to form the slightly modified *N*-fluoro-2,10-(3,3-dichlorocamphorsultam) reagent.[56] A small increase in enantioselectivity was observed relative to the non-substituted *N*-fluorocamphorsultam but again results were very substrate specific. In 1997, Takeuchi also reported the development of three new enantioselective fluorinating reagents based on chiral amines, but application of these reagents resulted in only low reactivity and enantioselectivity.[57]

2.1.3.4.2 Cinchona Alkaloids

The development of cinchona alkaloid-based chiral N-F reagents in 2000 provided a significant breakthrough in the field of chiral fluorinating agents.[58] Taking inspiration from Banks' initial findings in 1995 that fluorine transfer could take place from Selectfluor to quinuclidine to afford *N*-fluoroquinuclidinium salts,[59] reports by both Cahard[60] and Shibata[61] described the combination of cinchona alkaloids with Selectfluor, to afford chiral non-racemic N-F reagents without elemental fluorine (Scheme 2.25).



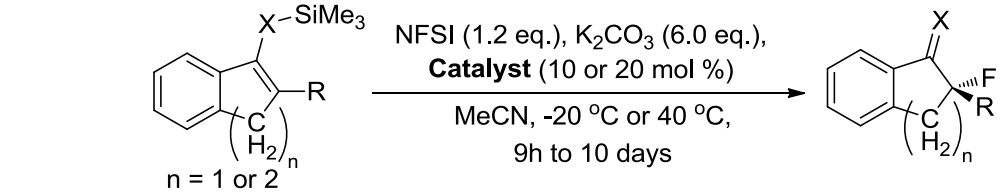
Scheme 2.25: A. Pre-formation and isolation of chiral N-F reagent by Cahard and co-workers. B. *In situ* formation of chiral N-F reagent by Shibata and co-workers
CD = cinchonidine, DHBQ = dihydroquinine 4-chlorobenzoate

Cahard and co-workers described the formation of an *N*-fluorocinchonidinium salt (F-CD-BF_4) by fluorine transfer from Selectfluor to the cinchona alkaloid cinchonidine. This enantioenriched N-F reagent was isolated and purified before being applied to the enantioselective fluorination of metal enolates and silyl enol ethers with high yields and good enantiomeric excesses. Shibata and co-workers, on the other hand, described the *in situ* formation of an enantioenriched N-F reagent by pre-mixing of equal amounts of DHQB and Selectfluor prior to addition of the substrate for fluorination in the same flask. This methodology was later extended by the Gouverneur group to include application to the enantioselective fluorodesilylation of allyl silanes[62] and to an asymmetric fluorocyclisation reaction.[63]

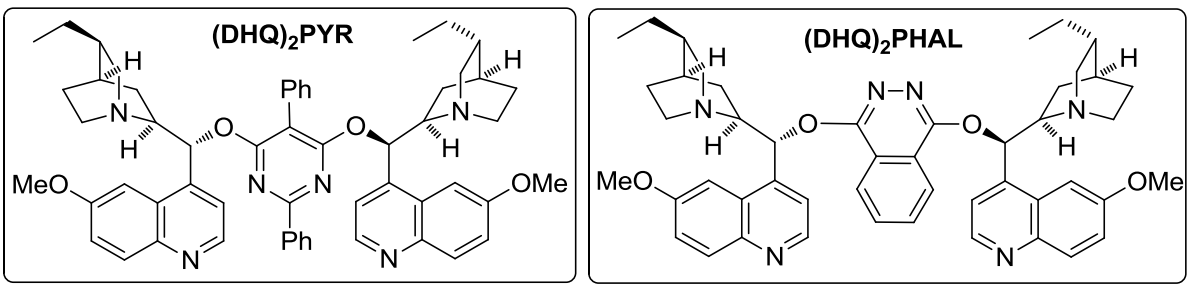
Later publications attempted to develop a catalytic variant of this cinchona alkaloid-mediated asymmetric fluorination reaction. Since the catalytic amount of the chiral N-F

reagent present at any one time is of similar or lower reactivity with respect to the parent achiral fluorinating agent, gaining high enantioselectivities presented an obvious challenge.

Work published by Shibata in 2006 employed silyl enol ether substrates for this catalytic reaction, but the enantioselectivity observed was negligible due to the rapidness of the racemic fluorination of silyl enol ethers by Selectfluor.[64] However, employing less reactive acyl enol ether substrates was successful at reducing the rate of the background reaction and therefore afforded the fluorinated products in good yields and with moderate enantiomeric excesses. A more successful reaction was published by the same group in 2008, in which the enantioselective fluorination of silyl enol ethers, allyl silanes and oxindoles was achieved with good to excellent yields and enantiomeric excesses, with only catalytic amounts of cinchona alkaloid (Scheme 2.26).[65] The fundamental difference between the two reports was the beneficial use of the less reactive NFSI as the achiral fluorine source, as opposed to Selectfluor.

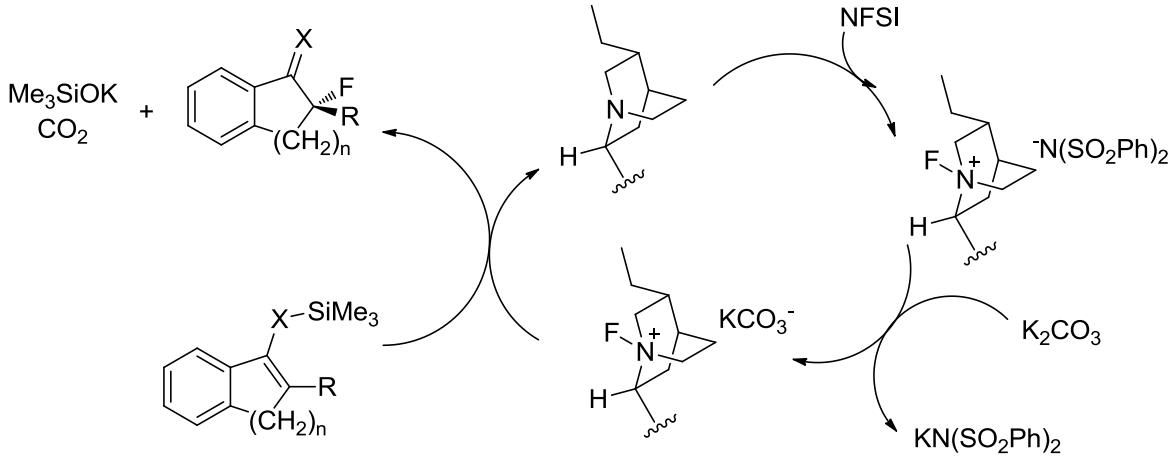


X = CH_2: Catalyst = $(DHQ)_2PYR$, 10 examples, yield up to 81 %, ee up to 95 %
X = O: Catalyst = $(DHQ)_2PHAL$, 6 examples, yield up to 95 %, ee up to 86 %



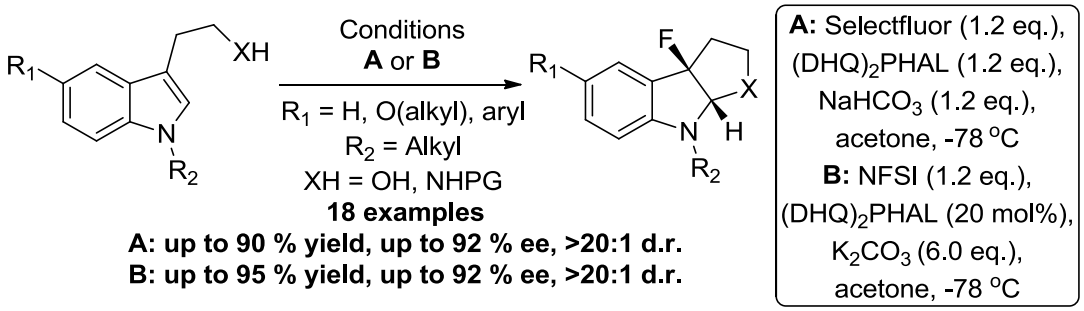
Scheme 2.26: Enantioselective fluorination using NFSI with catalytic cinchona alkaloid by Shibata and co-workers

Notably, it was found that both conversion and enantioselectivity for the catalytic reaction were poor in the absence of potassium carbonate as a base, with optimum conditions requiring a large excess. A mechanism was therefore proposed in which after the initial fluorine transfer to the cinchona alkaloid, an anion exchange occurs to form the more reactive *N*-fluoroammonium KCO_3^- salt. It was suggested that enantioselective fluorination of the substrate then occurs from this species, to regenerate the cinchona alkaloid catalyst (Scheme 2.27).



Scheme 2.27: Proposed mechanism for catalytic asymmetric electrophilic fluorination via an *N*-fluoroammonium species

This organocatalytic methodology was further exemplified by a report by the Gouverneur group in 2011, in which a cinchona alkaloid/ electrophilic fluorinating agent combination was employed for the asymmetric fluorocyclisation of prochiral indole systems under both stoichiometric and catalytic conditions (Scheme 2.28).[66] The beneficial effect of an α-nitrogen atom was exploited in order to activate the olefin towards fluorination, resulting in a transient iminium intermediate which could be captured by an internal nucleophile. Importantly, this provided the first example of a catalytic asymmetric fluorocyclisation procedure.



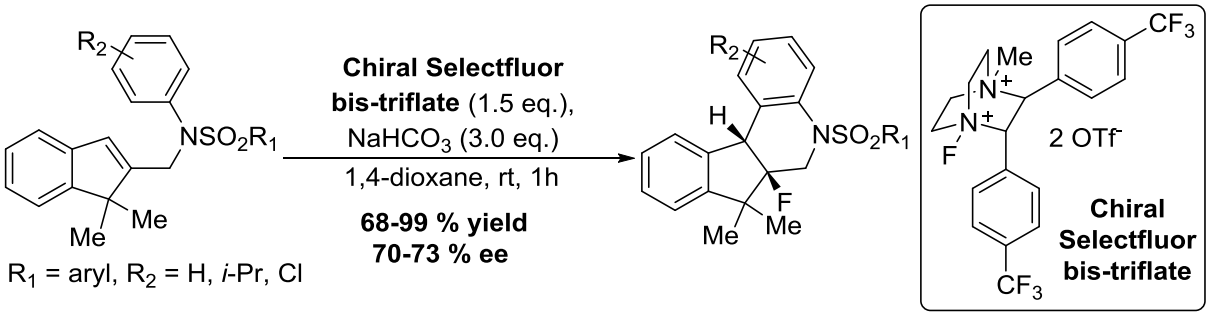
Scheme 2.28: Stoichiometric and catalytic asymmetric fluorocyclisation of indole systems by Gouverneur and co-workers

Interestingly, and in contrast to the literature precedent discussed (*vide supra*), several observations, including the very low temperature at which the reaction proceeded, led the authors to suggest that in this case the fluorine transfer to the substrate may occur directly from NFSI as opposed to from the fluorinated alkaloid. It was noted that a mechanism involving associative complexation of the alkaloid with the substrate could not be ruled out.

2.1.3.4.3 Chiral Selectfluor

A recent report from the Gouverneur group described the development of a novel class of chiral enantioenriched electrophilic fluorinating agents based on the structure of Selectfluor.[67] The synthesis of a range of 2,3-diaryl substituted DABCOs was achieved by re-optimisation of an original procedure reported by Sharpless over twenty years ago.[68] Chiral bis-cationic fluorinating reagents were then isolated via reaction of the mono-methylated enantiopure 1,2-disubstituted diazabicyclo[2.2.2]octane salts with fluorine gas or were formed *in situ* via fluorine transfer from the highly reactive *N*-fluoro-pentachloro-pyridinium triflate. These Selectfluor-based chiral fluorinating agents found application in a novel asymmetric fluoro-carbocyclisation reaction to afford fluorotetrahydro-5*H*-indeno-[2,1-*c*]quinolines with high yields and moderate enantioselectivity (Scheme 2.29). Whilst in this reaction the highest enantioselectivity was provided by a 2,3-(4-trifluoromethyl)phenyl substituted Selectfluor derivative, the

authors highlighted the potential to tailor the reactivity of this new class of chiral reagents by varying the steric and electronic properties of the substituents.



Scheme 2.29: Application of "Chiral Selectfluor" to fluoro-carbocyclisation reaction by Gouverneur and co-workers

The reaction was proposed to occur via electrophilic fluorination of the alkene to provide a benzylic stabilised carbocation which was captured by the pendent aromatic nucleophile. The absolute stereochemistry and *syn* configuration at the ring junction was determined by single crystal X-ray crystallography. Notably, these tetracyclic products contain a carbon-fluorine quaternary centre which would be very difficult to access via an alternative protocol. Indeed, application of the phase transfer methodology developed by Toste (Section 2.1.3.3)[45] was unsuccessful for these substrates, since they lack a hydrogen bonding site, and cinchona alkaloid-mediated fluorination was also unsuccessful due to insufficient reactivity. Therefore, whilst currently rather substrate dependent, these chiral Selectfluor reagents nevertheless represent an important step in the development of higher reactivity chiral N-F reagents.

2.1.4 Aims of Chapter

Given the wealth of activation modes known for organomediated enantioselective fluorination, it is perhaps surprising that this approach has not yet seen application to ^{18}F-radiosynthesis. This is perhaps an indication of the challenges associated with translation of this methodology to ^{18}F-fluorination, including avoidance of the long reaction times

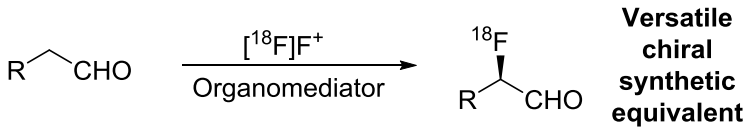
and low temperatures generally associated with organocatalysis, as well the effect of employing the ^{18}F source in sub-stoichiometric amounts relative to the organomediator.

Nevertheless, we envisaged that overcoming these challenges in order to merge the previously disconnected fields of organomediated enantioselective fluorination and radiochemistry could significantly broaden the scope of asymmetric ^{18}F-fluorination. Reaction design required a method that could provide access to valuable enantioenriched moieties using an experimentally simple procedure. Asymmetric fluorination of aldehydes via enamine catalysis was immediately attractive due to the widespread possibilities provided by the derivatisation step. Likewise, the potential range of reactivity provided by anionic phase transfer type catalysis was also appealing. Attracted by the facile synthetic procedure associated with chiral fluorinating agents, we also sought to investigate the application of ^{18}F-labelled chiral Selectfluor derivatives. As such, in this chapter we aimed to investigate in turn the application of each of these three modes of activation to ^{18}F-radiosynthesis.

2.2 Results and Discussion

2.2.1 Enamine Catalysis for Asymmetric α-[^{18}F]Fluorination of Aldehydes

The chiral amine-catalysed asymmetric fluorination of aldehydes has been reported by multiple groups (See Section 2.1.3.1.1). We envisaged that application of this methodology by use of an appropriate catalyst in combination with [^{18}F]NFSI could provide access to ^{18}F-labelled enantioenriched α-fluoroaldehydes; valuable versatile synthetic equivalents which could then undergo a variety of transformations (Scheme 2.30).



Scheme 2.30: Proposed asymmetric ^{18}F-fluorination reaction

However, the literature conditions for this asymmetric fluorination presented numerous challenges for consideration upon translation to a radiochemical reaction. As discussed above, the short half life of ^{18}F imposes that reactions are quick, and for experimental simplicity low temperatures are best avoided. For this reaction, the inherently low concentration of [^{18}F]NFSI with respect to the substrate and organomediator could promote undesired product racemisation. Also, the method of synthesis of [^{18}F]NFSI creates an equivalent amount of [^{18}F]NaF, which has the potential to act as a nucleophile causing either racemisation of the newly formed stereocentre, or decomposition of silyl-protected catalysts. Finally, to minimise time consuming purification steps, the asymmetric ^{18}F-fluorination and subsequent derivatisation step should be amenable to a one-pot process. The described literature methods generally require a work-up or purification procedure between the two steps to remove the catalyst and excess NFSI. These issues were initially examined in cold development reactions.

2.2.1.1 "Cold" Reaction Development

High yields and enantioselectivities for the chiral amine-catalysed asymmetric fluorination of aldehydes were achieved by both Jørgensen[31] and MacMillan[28] (Figure 2.1). The Jørgensen procedure has many advantages, such as room temperature conditions and a simple experimental procedure, with purification after the first step consisting of just a filtration. However, this reaction employs a TMS-protected prolinol catalyst, which may be desilylated in the presence of the [^{18}F]NaF, that is formed as a by-product in the production of [^{18}F]NFSI. The MacMillan procedure, on the other hand, employs a chiral non-racemic imidazolidinone catalyst which should be more stable under the ^{18}F-fluorination conditions. However, as discussed in Section 2.1.3.1.1, the experimental procedure is much more complex in this case and a reaction temperature of −10 °C is required. In both cases, reaction times were long. Initial reactions aimed to merge the two procedures, by investigation of the MacMillan imidazolidinone organocatalyst under the simple experimental conditions developed by Jørgensen.

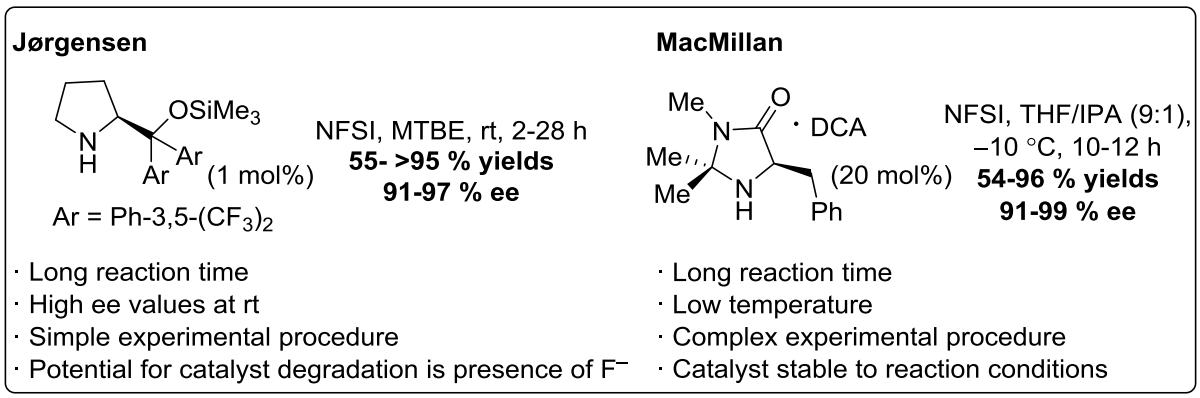
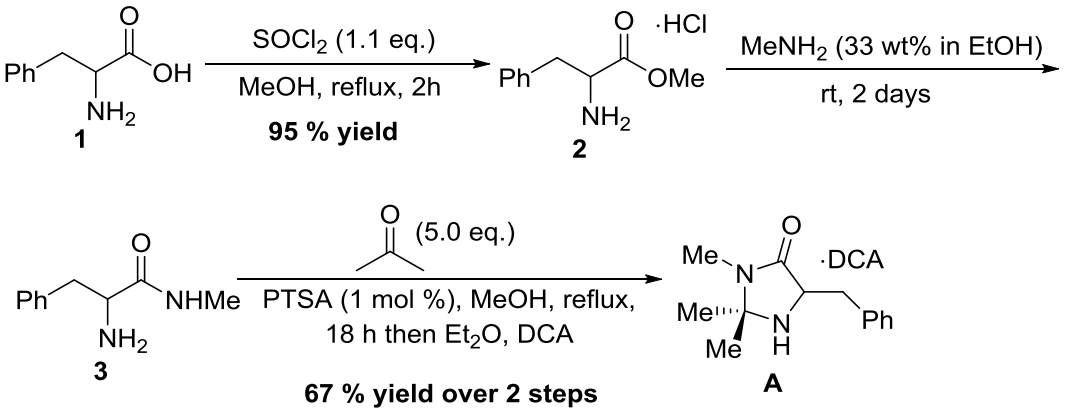


Figure 2.1: Comparison of reaction conditions developed by Jørgensen and MacMillan

This organocatalyst is commercially available as the (*S*) or (*R*) enantiomer but could also be synthesised on a multi-gram scale in three steps from phenylalanine, according to the literature procedure (Scheme 2.31).[69]

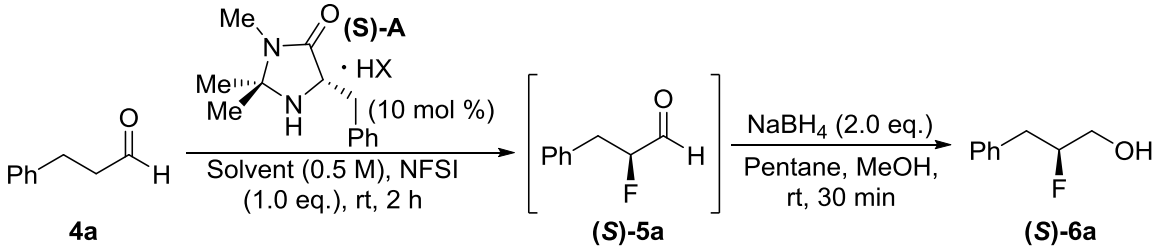


Scheme 2.31: MacMillan imidazolidinone synthesis
PTSA = *p*-toluenesulfonic acid, DCA = dichloroacetic acid

Methyl ester **2** was formed by reaction with thionyl chloride in methanol, with subsequent amide formation by addition of methyl amine at room temperature. The resulting amide **3** was used without purification in a double condensation reaction with acetone to afford the free amine of imidazolidinone **A**. This was dissolved in diethyl ether and treated with an excess of dichloracetic acid to precipitate the DCA salt of **A** as a white solid, with a 67 % yield over the 2 steps. Alternative salts could also be synthesised by addition of an alternative acid, such as HCl. This synthesis was performed with D-, L- and DL-phenylalanine to obtain the optically pure and racemic catalysts required.

Preliminary reactions, aimed at employing an imidazolidinone type catalyst in combination with the Jørgensen experimental procedure for α-fluorination of aldehydes, employed hydrocinnamaldehyde as the model substrate, which provided a UV chromophore for chiral HPLC analysis. In the first instance, following fluorination, the intermediate α-fluoroaldehyde was derivatised as the β-fluorohydrin, again following the procedure of Jørgensen and co-workers (Table 2.1).

Table 2.1: Preliminary screening reactions



Entry[a]	HX	Solvent	^{19}F NMR Yield (%)[b]	ee (%)
1	DCA	THF/IPA (9:1)	**0**	-
2	HCl	THF/IPA (9:1)	**0**	-
3	-	THF/IPA (9:1)	**0**	-
4	**DCA**	**MTBE**	**51**	**92**
5	HCl	MTBE	**10**	-
6	-	MTBE	**43**	92

[a] Reactions performed on a 0.5 mmol scale. [b] ^{19}F NMR yield determined by integration relative to 1-fluoro-3-nitrobenzene as an internal standard (D_1 = 10).

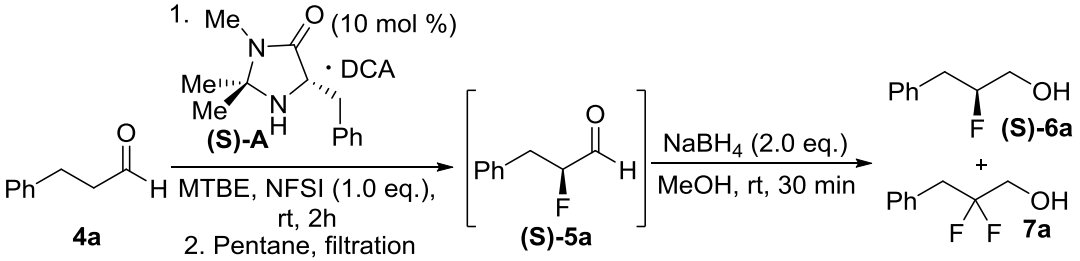
Hydrocinnamaldehyde, which was purified by silica gel chromatography prior to use, was treated with 10 mol % of imidazolidinone catalyst **(*S*)-A**, in combination with a range of acid co-catalysts, and stirred for 10 minutes before the addition of NFSI. After 2 hours, pentane was added to precipitate the catalyst as well as NFSI and DBSI, which were removed by filtration through a cotton wool plug. The filtrate was diluted with methanol and treated with an excess of sodium borohydride for 30 minutes. The ^{19}F NMR yield of product (^{19}F NMR, δ = −187.6 ppm, $CDCl_3$) was determined by integration against 1-fluoro-nitrobenzene (^{19}F NMR, δ = −109.7 ppm, $CDCl_3$) as an internal standard with relaxation time D_1 increased to 10 seconds to increase accuracy. The ee was determined by normal phase chiral HPLC of a small sample isolated by prep TLC. The corresponding racemic HPLC reference was obtained by employing racemic catalyst under the same conditions and absolute stereochemistry of the enantioenriched product was determined as *S* by comparison with the literature results. Whilst it is anticipated that higher conversion could be achieved by increasing reaction time, this short 2 hour reaction time

for the fluorination step proved convenient, sufficient for the aims of this screening reaction and should provide a better correlation to conditions for ^{18}F-radiosynthesis.

Initial screening showed that whilst the THF/ IPA mix employed by MacMillan did not yield any fluorinated product **6a** under these conditions, perhaps due to the poor effectiveness of the filtration step in this case (Table 2.1, entries 1-3), MTBE, which was employed in the Jørgensen procedure, is an appropriate alternative solvent, with an enantiomeric excess of 92 % achieved at room temperature (Entries 4 and 6). A brief screening of co-catalysts revealed that the dichloroacetate salt provided the highest yield of α-fluorinated product **(*S*)-6a**, at 51 % after just 2 hours (Entry 4). The hydrochloric acid salt of **(*S*)-A** and the free amine are less active (Entries 5 and 6). Preliminary results therefore suggest that MTBE is the most suitable solvent for a variation of this reaction employing a simplified procedure.

However, as well as providing the desired mono-fluorinated product, these conditions also provided a 23 % NMR yield of difluorinated side-product **7a** (^{19}F NMR, $\delta = -106.9$ ppm, $CDCl_3$) as a result of reaction of the α-fluoroaldehyde intermediate with a further molecule of NFSI. Whilst this is unlikely to be a problem that translates to the radiochemical reaction, due to the sub-stoichiometry of the [^{18}F]F^+ reagent, it does make isolation of cold reference compounds and determination of ee values more challenging. Therefore further optimisation was carried out in order to eradicate this side-product formation (Table 2.2).

Table 2.2: Optimisation to minimise difluorinated side-product formation



Entry[a]	Aldehyde (eq.)	Cat. (mol %)	Conc. (M)	6a (%)[b]	ee (%)	7a (%)[b]
1	1.0	1	0.5	**26**	**90**	23
2	1.0	1	0.2	**32**	**91**	7
3	1.5	1	0.5	**33**	**88**	20
4	1.5	1	0.2	**39**	**86**	19
5	1.0	10	0.5	**51**	**92**	23
6	1.0	10	0.2	**21**	**89**	6
7	1.5	10	0.5	**26**	**-**	20
8	**1.5**	**10**	**0.2**	**72**	**90**	**4**

[a] Reactions performed on a 0.5 mmol scale. [b] ^{19}F NMR yield determined by integration relative to 1-fluoro-3-nitrobenzene as an internal standard (D_1 = 10).

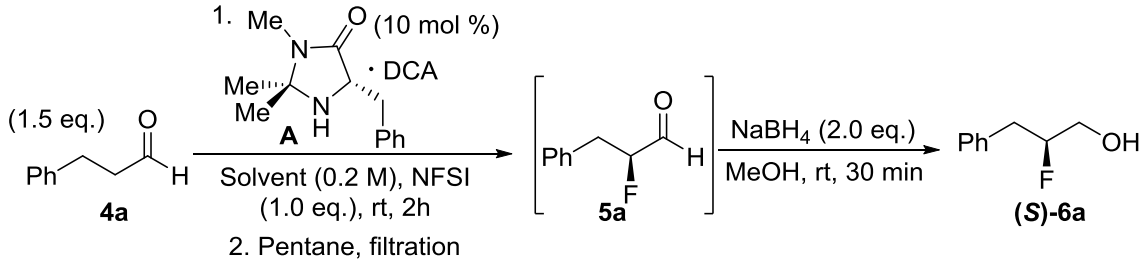
The reaction was carried out as previously, with yield of mono- and di-fluorinated alcohol product determined by ^{19}F NMR against an internal standard. Whilst lowering the catalyst loading to 1 mol % was not detrimental to the ee, it resulted in a slightly lower NMR yield of desired product **(*S*)-6a** and had very little effect on the yield of the difluorinated side-product **7a** (Table 2.2, entries 1-4). Dilution of the reaction from 0.5 M to 0.2 M was somewhat more successful, not only as it generally decreased the amount of the difluorinated alcohol formed, but also as it was visually observed that at this concentration the reaction stirring was much more effective, therefore leading to more consistent results (Entries 2, 4, 6 and 8).

Literature conditions for the asymmetric fluorination of aldehydes report circumvention of this side-product formation by employing an excess of the aldehyde in question relative to the fluorinating agent.[31] Reactions were therefore also performed employing 1.5 equivalents of hydrocinnamaldehyde **4a**. Generally, higher yields of mono-fluorinated product were obtained for those reactions employing an excess of the substrate and when

combined with the increased dilution conditions, this provided β-fluorohydrin **(*S*)-6a** with 72 % NMR yield and an ee value of 90 %, with difluorinated side-product formation almost entirely eliminated (Entry 8).

These optimisation reactions therefore demonstrated that the DCA salt of MacMillan imidazolidinone catalyst **A** may be suitable for use under conditions which are translatable to a radiochemical reaction; i.e. at room temperature and with a simple experimental procedure. Having demonstrated this and obtained sufficient conditions for isolation of the required racemic references, further optimisation of this cold reaction in terms of yield was unnecessary. A reaction time of 2 hours was therefore continued in future reactions. However, optimisation in terms of ee value was important and therefore a further temperature and solvent screen was carried out employing catalyst **(*S*)-A** (Table 2.3).

Table 2.3: Temperature and solvent screening reactions



Entry[a]	Solvent	^{19}F NMR Yield (%)[b]	ee (%)
1	**MTBE**	**72**	**90**
2	MTBE[c]	**19**	**86**
3	MTBE/IPA (9:1)	**42**	**90**
4	Acetone	**10**	**-*nd***
5	EtOAc	**11**	**-*nd***
6	*i*Pr$_2$O	**0**	**-*nd***
7	Et$_2$O	**10**	**-*nd***
8	MeCN	**27**	**20**
9	MeCN /IPA (9:1)	**36**	**82**

[a] Reactions performed on a 0.5 mmol scale. [b] ^{19}F NMR yield determined by integration relative to 1-fluoro-3-nitrobenzene as an internal standard (D_1 = 10). [c] Step 1 at 0 °C.

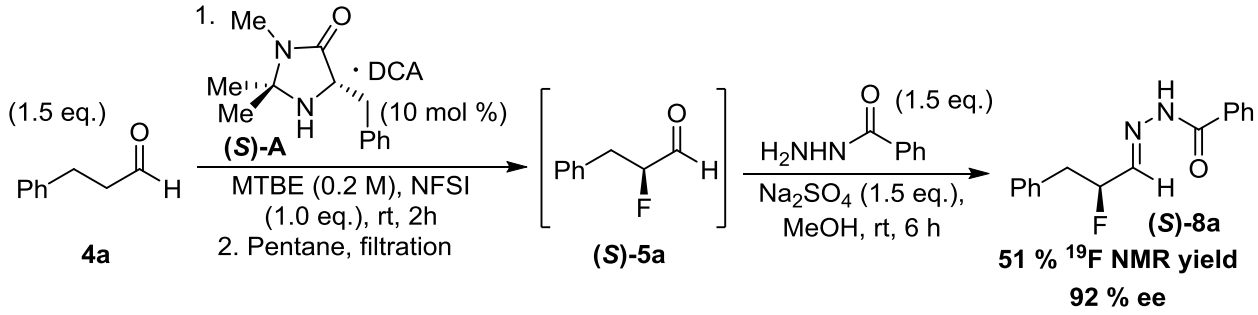
Lowering the temperature of the fluorination step to 0 °C was unsuccessful in terms of increasing the ee and afforded β-fluorohydrin **(*S*)-6a** with a lower NMR yield of 19 %

(Table 2.3, entry 2). A 9:1 solvent mixture of MTBE/IPA also had no effect on the enantioselectivity of the reaction with the ^{19}F NMR yield reduced slightly under these conditions (Entry 3). The various other common solvents employed afforded the fluorinated product in only very low yield (Entries 4-7), except for acetonitrile (Entry 8). In this case β-fluorohydrin **(*S*)-6a** was afforded with an NMR yield of 27 % but an ee of just 20 %. This could be improved to 82 % by employing an acetonitrile/IPA mixed solvent system (Entry 9) but was still inferior to MTBE as a solvent.

A further complication before preliminary radiochemical reactions could be carried out was consideration of chiral HPLC analysis of the radiolabelled product. Radiochemical laboratories are generally limited to the use of reverse phase HPLC systems running acetonitrile or methanol and water eluants, and therefore are incompatible with the normal phase HPLC systems (hexane/IPA) which are usually employed for chiral analysis of these fluorinated products. Unfortunately, extensive screening of reverse phase chiral HPLC columns was unsuccessful at providing separation of the two enantiomers of fluorohydrin **6a**, therefore chiral analysis of the corresponding ^{18}F-labelled product would not be possible.

2.2.1.2 Alternative Derivatisation for Chiral Analysis

It was envisaged that for proof of principle of this asymmetric ^{18}F-fluorination reaction, this problem could be evaded simply by employing an alternative derivatisation step which provided a fluorinated product which could be analysed by reverse phase HPLC. Barbas reported the derivatisation of α-fluoroaldehydes as hydrazone derivatives for characterisation by reverse phase chiral HPLC.[24] Therefore, following fluorination of hydrocinnamaldehyde under the previously optimised conditions, α-fluoroaldehyde **(*S*)-5a** was treated with benzhydrazide in methanol, in the presence of sodium sulfate as a dehydrating agent, according to the procedure of Barbas (Scheme 2.32).

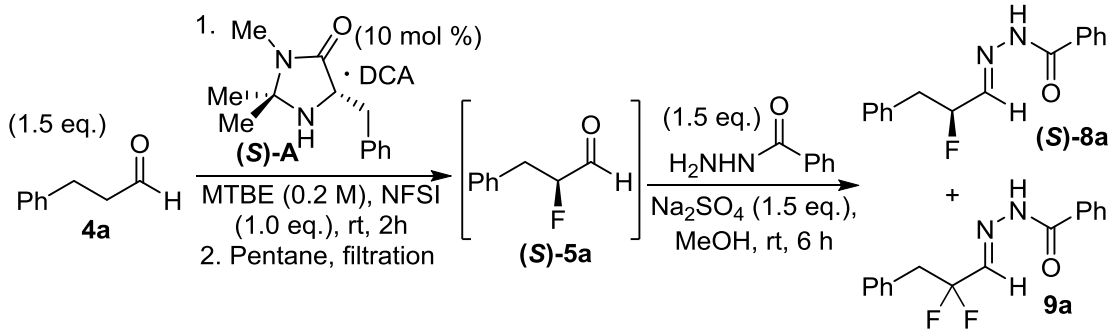


Scheme 2.32: Synthesis of α-fluorohydrazone derivative

This provided fluorinated benzoylhydrazone **(*S*)-8a** with a ^{19}F NMR yield of 51 % after 6 hours, which was assigned as the more stable *E*-isomer.[1] The corresponding racemic reference compound could be synthesised under the same conditions, employing racemic imidazolidinone catalyst, and pleasingly for this product, separation of enantiomers was possible by reverse phase chiral HPLC (see Figure 2.3 or Chapter 4.4 for HPLC spectra).

However, on repetition of this asymmetric fluorination reaction under identical conditions, a surprising drop in both yield and ee was observed (Table 2.4).

Table 2.4: Contrasting results from repetition of asymmetric fluorination reaction



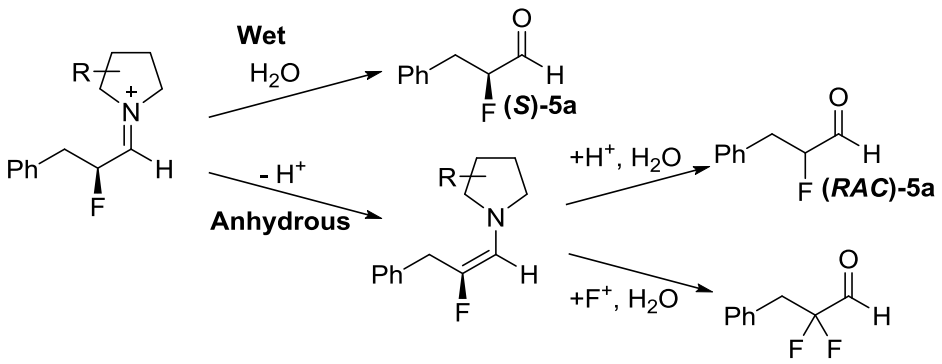
Entry[a]	(*S*)-8a (%)[b]	ee (%)	9a (%)[b]
Reaction 1	**51**	**92**	3
Reaction 2	**10**	**30**	29

[a] Reactions performed on a 0.5 mmol scale. [b] ^{19}F NMR yield determined by integration relative to 1-fluoro-3-nitrobenzene as an internal standard (D_1 = 10).

In addition, a significantly higher yield of difluorinated side product **9a** (29 % vs 3 %) was observed in reaction 2. The poor reproducibility of this reaction was obviously a

[1] Tentatively assigned based on literature precedent.

concern and so the difference between two reactions was investigated. It was concluded that the use of a new bottle of MTBE for reaction 2 was the only distinguishing condition. When ^{1}H NMR of the old and new solvents did not reveal any impurities, Karl-Fischer titrations were performed to investigate the water content of these two bottles of MTBE.[2] This revealed that the water content of the older bottle of MTBE was over 25 times that of bottle 2 (3243 and 132 ppm respectively). Although the requirement for use of "wet" solvent is not reported for secondary amine-catalysed asymmetric fluorination of aldehydes, these reactions commonly take place under air without measures to ensure the removal of water and often employ hygroscopic solvents such as DMF and IPA. Additionally, the beneficial effects of added water in enamine catalysis has previously been reported by Ohsawa and co-workers for a proline-catalysed Mannich reaction.[70] In the case of our fluorination reaction, it was envisaged that adventitious water could serve to release the transient α-fluoroimine more rapidly than under anhydrous conditions (Scheme 2.33).

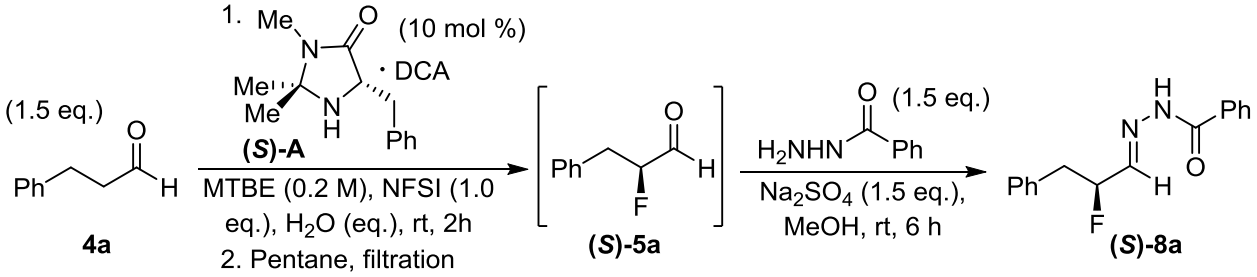


Scheme 2.33: Proposed effect of water on imine hydrolysis

It was anticipated that fast hydrolysis, as opposed to the alternative proton abstraction, would be multiply beneficial in order to reduce loss of stereochemical integrity, limit over-fluorination and increase rate of catalytic turnover. This theory was investigated by the addition of various quantities of water to the anhydrous bottle of MTBE (Table 2.5).

[2] Karl-Fischer titrations performed by Lydia Underdown.

Table 2.5: Effect of adventitious water on reaction



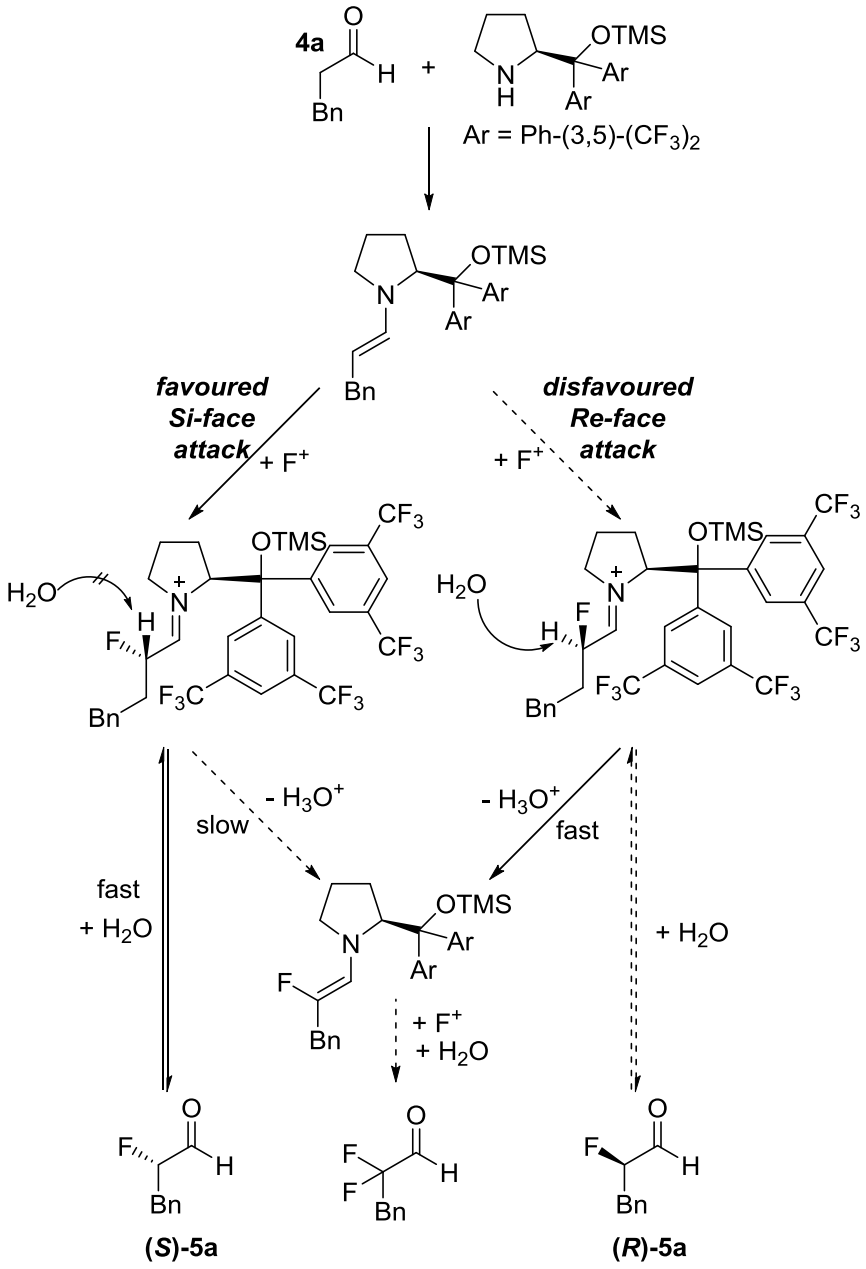
Entry[a]	H_2O (ppm)	^{19}F NMR Yield (%)[b]	ee (%)
1	**5,000**	**46**	**90**
2	25,000	**34**	**90**
3	250,000	**36**	**90**

[a] Reactions performed on a 0.5 mmol scale. [b] ^{19}F NMR yield determined by integration relative to 1-fluoro-3-nitrobenzene as an internal standard (D_1 = 10).

The addition of 5000 ppm of water (10 µL H_2O in 2.5 mL of solvent, 0.55 mmol, ~1.0 eq.) was successful at increasing both the ^{19}F NMR yield and enantioselectivity of the fluorination reaction to the values observed for reaction 1 (Table 2.5, entry 1). Greatly increasing the water content by addition of 5 or 50 equivalents did not further increase the NMR yield but was not significantly detrimental to the reaction either (Entries 2 and 3). Consistency in future experiments was therefore ensured by use of anhydrous solvent doped with 5000 ppm of water.

The importance for hydrolysis of the α-fluoroimine to occur faster than enamine formation is supported by the studies of Jørgensen and co-workers (Scheme 2.34).[31] The authors proposed that when attack on F^+ occurred on the less hindered *Si* face on the enamine, the observed high optical stability of α-fluorinated products was a result of hydrolysis of the α-fluoroimine occurring faster than deprotonation and formation of an enamine for the second time, due to steric shielding of the proton for abstraction. In contrast, if attack on F^+ occurred on the less favourable *Re* face, proton abstraction would be less hindered and therefore the second enamine formation could occur more quickly, thus leading to a higher yield of difluorinated product. This prediction was substantiated by a kinetic resolution experiment in which a racemic mixture of α-fluoroaldehyde **5a**

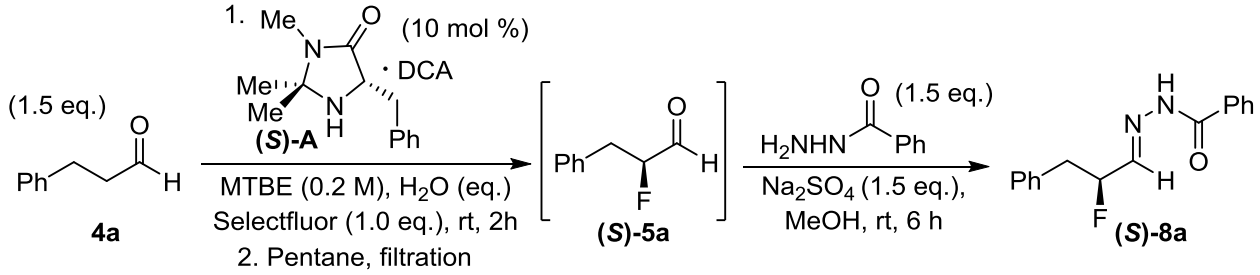
was treated with 0.5 equivalents of NFSI and 1 mol % of chiral non-racemic amine catalyst. After 4 hours an increase in ee of **(*S*)-5a** by 20 % indicated the faster consumption of **(*R*)-5a**. This corroborates with our findings on the effect of the relative rates of hydrolysis versus proton abstraction on ee and yield of difluorinated side-product.



Scheme 2.34: Proposed mechanism by Jørgensen and co-workers according to kinetic resolution studies

Finally, this reaction was also investigated employing Selectfluor as the electrophilic source of fluorine (Table 2.6). Although this fluorinating agent is generally more reactive than NFSI, it was envisaged that the racemic background reaction of hydrocinnamaldehyde would be sufficiently slow that this may not be problematic.

Table 2.6: Screening Selectfluor as electrophilic fluorine source



Entry[a]	H_2O (eq.)	^{19}F NMR Yield (%)[b]	ee (%)
1	0	**0**	**-**
2	**1.0**	**27**	**94**

[a] Reactions performed on a 0.5 mmol scale. [b] ^{19}F NMR yield determined by integration relative to 1-fluoro-3-nitrobenzene as an internal standard (D_1 = 10).

When commercially available Selectfluor was employed with imidazolidinone **(*S*)-A** in MTBE, no fluorinated product was observed (Table 2.6, entry 1). However, repetition of the reaction with MTBE doped with 5000 ppm water led to formation of the hydrazone **(*S*)-8a** with an NMR yield of 27 % and a high ee of 94 % (Entry 2). Whilst this increase in reactivity could be attributed to the beneficial properties properties of added water as discussed previously, it is likely that an increase in solubility of this notoriously insoluble reagent is also at least partially responsible for these differing results. These experiments demonstrated that [^{18}F]Selectfluor was also a potential suitable [^{18}F]F^+ source for this asymmetric fluorination reaction.

With various possible conditions found which afford high enantioselectivites in a simple experimental procedure, as well as the required racemic reference and conditions for chiral HPLC analysis now in hand, the reaction was next investigated employing ^{18}F.

2.2.1.3 Preliminary Investigations with High Specific Activity [^{18}F]F^+

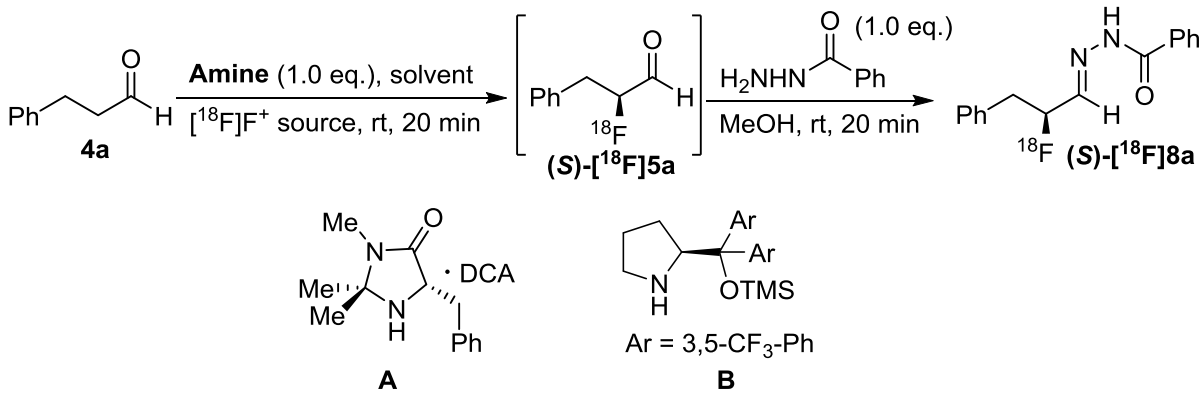
Reactions employing high specific activity [^{18}F]F_2 were carried out at Turku PET Centre, Finland, under the supervision of Prof. Olof Solin.

Initially, findings from cold work were supported by preliminary studies with various catalysts, solvents and electrophilic fluorinating reagents. [^{18}F]F_2 gas was prepared according to the literature procedure[71] and directly bubbled through an acetonitrile/water solution of sodium dibenzenesulfonimide to afford [^{18}F]NFSI[72] with the maximum theoretical yield of 50 %, along with 50 % of [^{18}F]NaF. The specific activity was determined, by comparison of the UV absorbance with a sample of known concentration, as 1.9 GBq/μmol (n = 3). This value was in line with the short irradiation time of 5 minutes applied to the cyclotron target in order to minimise exposure, but could theoretically be increased to the reported maximum specific activity of 55 GBq/μmol by increasing the irradiation time.[71] Following evaporation of solvent at 60 °C under a flow of helium gas, a further aliquot of acetonitrile was added and the drying step repeated once more. The azeotropically dried [^{18}F]NFSI was then redissolved in the reaction solvent using a lab dancer for agitation to improve dissolution.

Hydrocinnamaldehyde **4a** was treated with one equivalent of chiral non-racemic amine for 10 minutes, before addition of an aliquot of [^{18}F]NFSI (~ 200 MBq). It is worth noting that in this case the amine is not acting catalytically as it is in significant excess relative to the [^{18}F]F^+ source and will therefore be referred to as an organomediator. After stirring for 20 minutes, a solution of benzhydrazide in methanol was added directly to the reaction mixture without purification of the intermediate. An aliquot was taken for analytical radio-HPLC analysis after a further 20 minutes stirring and radiochemical conversion from the [^{18}F]F^+ reagent (RCC) was determined by integration of all organic peaks. It should be noted that RCCs are determined without integration of the HPLC

signal corresponding to [^{18}F]fluoride, due to poor reproducibility caused by the inadequate solubility of this species in the organic solvent systems employed. RCCs are therefore quoted with respect to the [^{18}F]F^{+} reagent without accounting for the loss of 50 % activity suffered due to [^{18}F]fluoride formation during production of [^{18}F]NFSI or [^{18}F]Selectfluor. The peak corresponding to product was collected and employed for chiral radio-HPLC analysis (Table 2.7).

Table 2.7: Optimisation of reaction conditions with [^{18}F]F^{+} sources



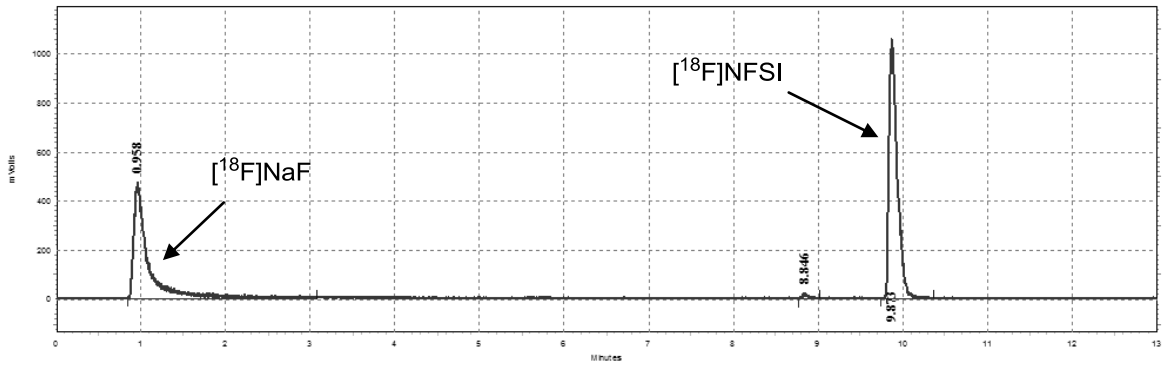
Entry	[^{18}F]F^{+} Source	Amine	Solvent	RCC (%)[a]	ee (%)[b]
1	**[^{18}F]NFSI**	**(*S*)-A**	**MTBE**	**62 ± 6** (*n* = 5)	**92 (*S*)**
2	[^{18}F]NFSI	**(*S*)-A**	THF/IPA (9:1)	**71** (*n* = 1)	**64 (*S*)**
3	[^{18}F]NFSI	**(*S*)-B**	MTBE	**45** (*n* = 1)	**92 (*S*)**
4	[^{18}F]Selectfluor	**(*S*)-A**	MTBE[c]	**0** (*n* = 2)	**-*nd***

[a] RCC determined by radio-HPLC relative to [^{18}F]F^{+} source. [b] Determined by chiral radio-HPLC of isolated product. [c] 5% H_2O.

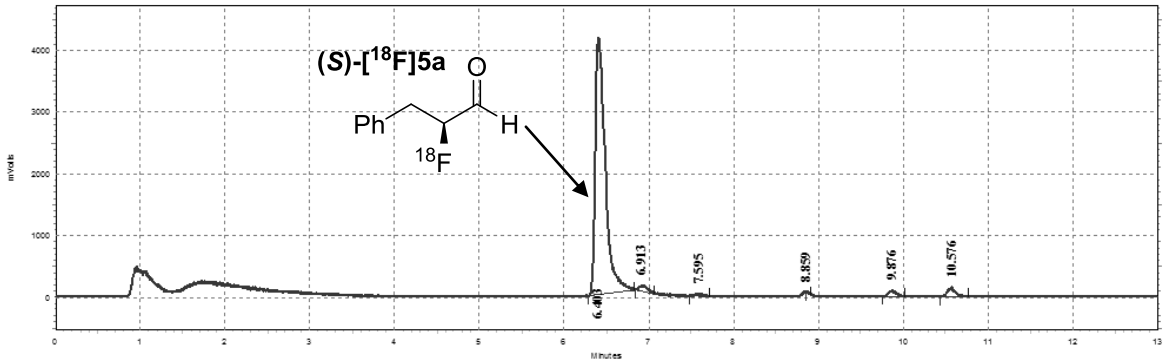
In the first instance, the reaction was performed using the optimum amine and solvent from "cold" optimisation reactions, imidazolidinone **A** and MTBE respectively (Table 2.7, entry 1). Under these conditions, we were very pleased to observe a RCC of 62 % ± 6 % (*n* = 5) over the two steps, without any need for purification of the intermediate **[^{18}F]5a**, probably due to the very low concentration of NFSI and DBSI present. This amenability to a one-pot procedure was very beneficial in terms of reducing the total synthesis time and simplifying the experimental procedure. Notably, unlike the cold reactions, there was also no requirement for additional water, perhaps because the need

for catalytic turnover had been removed. However, there was likely to be traces of water present regardless because even after extensive azeotropic drying of [^{18}F]NFSI it is unlikely to be completely anhydrous. It was possible to follow the reaction by taking aliquots of the crude reaction for radio-HPLC at each stage (Figure 2.2).

A. Radio-HPLC of [^{18}F]NFSI stock solution



B. Radio-HPLC of crude reaction mixture (20 min)



C. Radio-HPLC of crude reaction mixture (40 min)

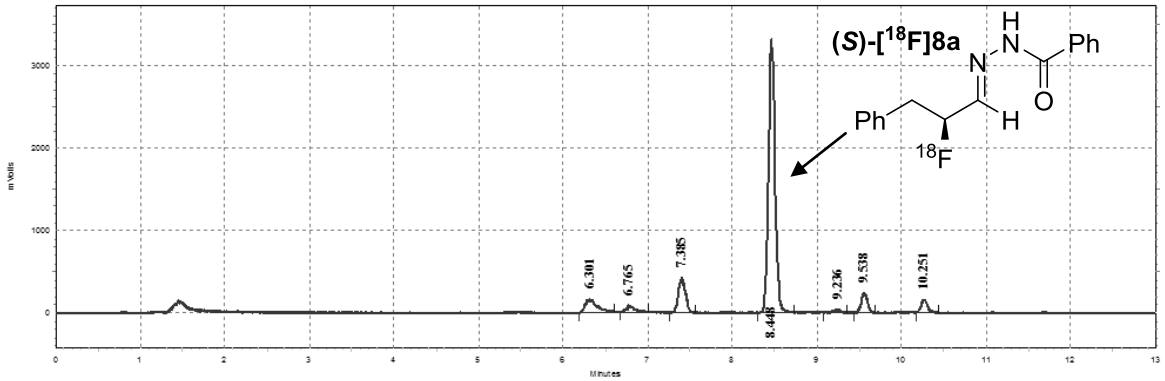
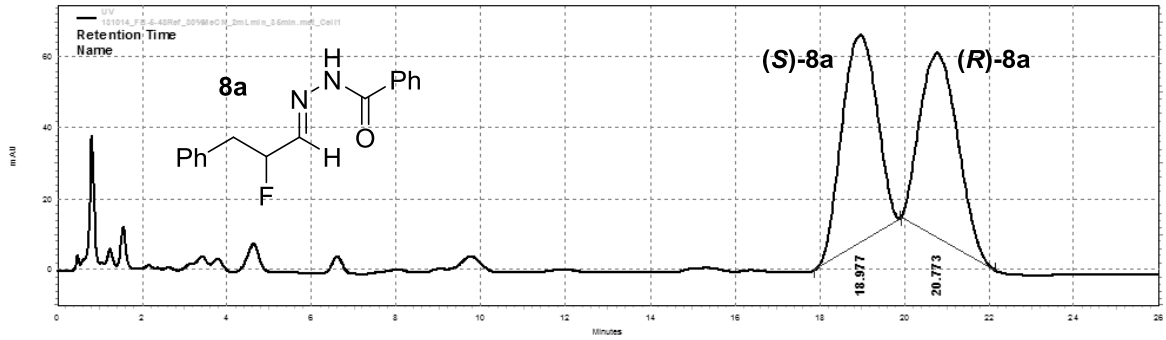


Figure 2.2: Monitoring of reaction by radio-HPLC

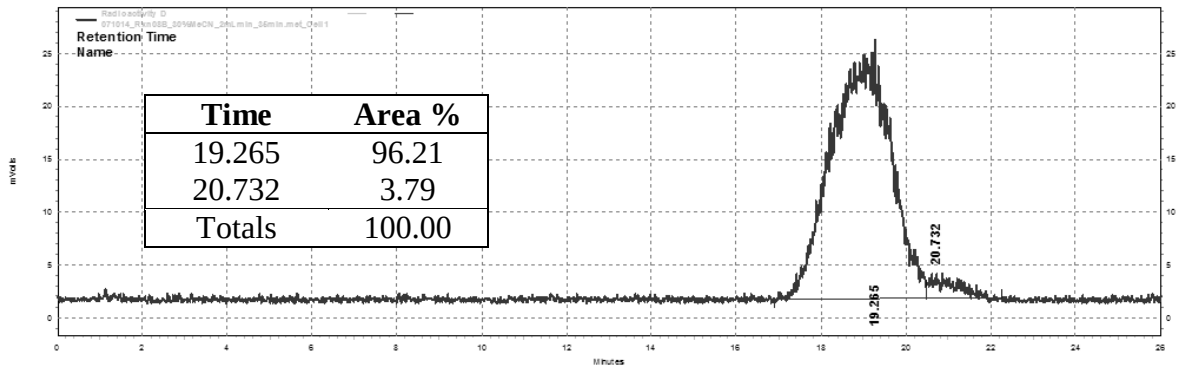
Waters Atlantis dc18 (5 µm, 3.9x150 mm), 1.5 mL/min, HPLC Conditions A, Sample: 1 mg/mL in MeCN/H_2O (4:1), UV = 254 nm, t_{prod} = 8.4 min.

This demonstrated that after 20 minutes all but a trace of [^{18}F]NFSI had been converted to intermediate α-fluoroaldehyde **(*S*)-[^{18}F]5a** (Figure 2.2, B). Following the direct addition of benzhydrazide in methanol, an aliquot taken after stirring for a further 20 minutes showed that the majority of this intermediate had reacted to provide ^{18}F-labelled benzoylhydrazone **(*S*)-[^{18}F]8a**, which was isolated and analysed by chiral radio-HPLC (Figure 2.3). It should be noted the UV detector is placed in series before the radiodetector and hence a short delay is observed between traces.

A. UV of racemic reference



B. Radio-HPLC of isolated product



Time	Area %
19.265	96.21
20.732	3.79
Totals	100.00

Figure 2.3: Reverse phase chiral HPLC analysis of hydrazone (*S*)-[^{18}F]8a
Phenomenex Lux Cellulose 1 (5 µm, 4.6x100 mm), 2.0 mL/min, 30 % MeCN isocratic, 200 µL injection, UV = 254 nm, t_1 = 19.0 min, t_2 = 20.8 min**.**

Since optimum results from cold screening do not necessarily translate directly to radiolabelling, a brief catalyst and solvent screen was also performed. Use of a THF/IPA solvent mixture, as initially reported by MacMillan,[28] resulted in a high RCC of 71 % over the 2 steps (Table 2.7, entry 2). However, very surprisingly, a significant

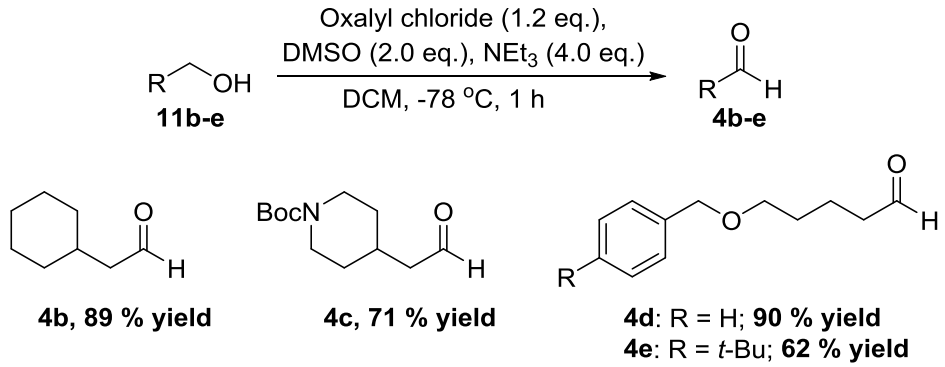
diminishment of enantioselectivity to 64 % was observed, perhaps indicating that purification of the intermediate prior to derivatisation would have been beneficial in this case. The trimethylsilyl ether-protected prolinol **B** employed in the original publication of Jørgensen was also investigated (Entry 3). Fears that this amine would decompose to its non-productive desilylated form in the presence of [^{18}F]NaF were unsubstantiated, with hydrazone **(*S*)-[^{18}F]8a** formed with an ee of 92 % when **(*S*)-B** was employed with MTBE as the solvent. Nonetheless, this organomediator proved to promote the reaction more slowly versus imidazolidinone **B**, with a RCC of just 45 % over the two steps.

[^{18}F]Selectfluor bis-triflate could also be synthesised directly from [^{18}F]F_2 according to the literature procedure.[73] Notably, this fluorinating agent contains a different counterion to the commercially available Selectfluor bis-tetrafluoroborate, in order to limit isotopic exchange with ^{18}F. Following the same azeotropic drying procedure employed previously, MTBE was then added to redissolve the [^{18}F]F^+ reagent. Unfortunately, measurement of an aliquot of this solution indicated that very little radioactivity was present, suggesting that solubility of [^{18}F]Selectfluor bis-triflate in this solvent was minimal. However, the addition of 5 % (v/v) water to the mixture was successful at increasing the solubility of this reagent so that it could be employed in the asymmetric fluorination reaction. Following the previously developed procedure with chiral non-racemic imidazolidinone **(*S*)-A**, no radiolabelled product was formed employing [^{18}F]Selectfluor bis-triflate (Entry 4). HPLC analysis confirmed that this was a result of a failure of the fluorination reaction in the first step. This may be attributed to the change of counterion to Selectfluor bis-triflate as opposed to Selectfluor bis-tetrafluoroborate, but is perhaps more likely to be caused by large amount of water required to increase the solubility of this reagent.

Notably, these initial optimisation reactions provided proof of principle for the first example of an organomediated asymmetric fluorination reaction with ^{18}F.

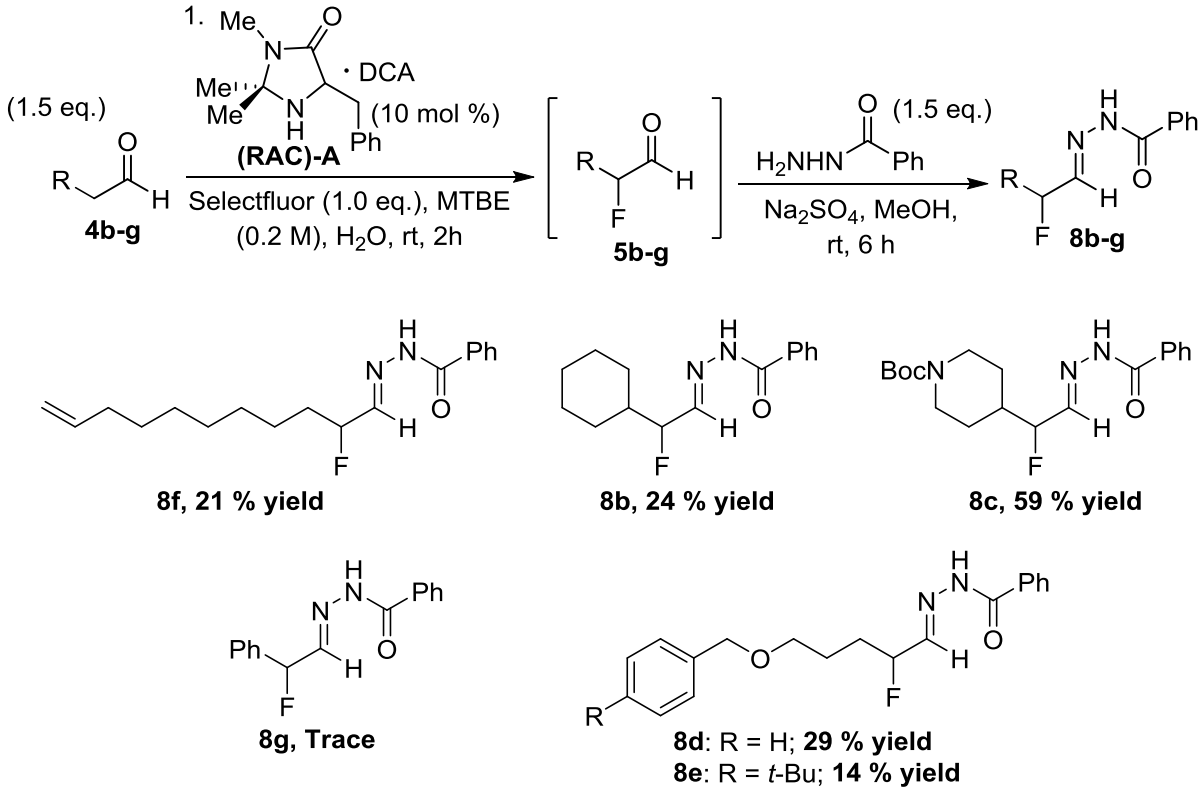
2.2.1.4 Substrate Scope

Having provided proof of principle for this novel asymmetric electrophilic ^{18}F-fluorination reaction, we were keen to investigate its application to alternative substrates. Aldehyde substrates which were commercially available were purified by distillation prior to use. Those which weren't commercially available were synthesised by Swern oxidation of the corresponding alcohols (Scheme 2.35).



Scheme 2.35: Preparation of aldehyde substrates by Swern oxidation

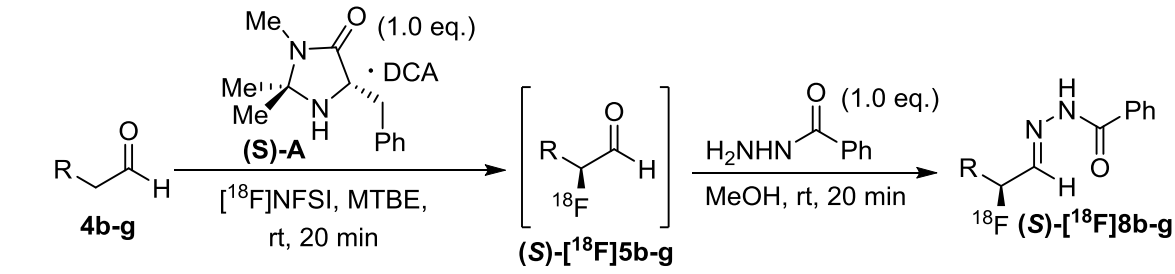
Racemic fluorinated references for chiral HPLC were prepared employing the previously optimised procedure for fluorination/ derivatisation with racemic imidazolidinone catalyst **(RAC)-A**. In the first instance, purification by column chromatography on silica gel to obtain clean isolated references was challenging, with many spots observed by TLC analysis of the crude reaction mixture. However, a change to employ Selectfluor as the electrophilic fluorine source as opposed to NFSI resulted in significantly cleaner crude reactions which could be purified by silica gel chromatography to afford the required fluorinated references (Scheme 2.36).

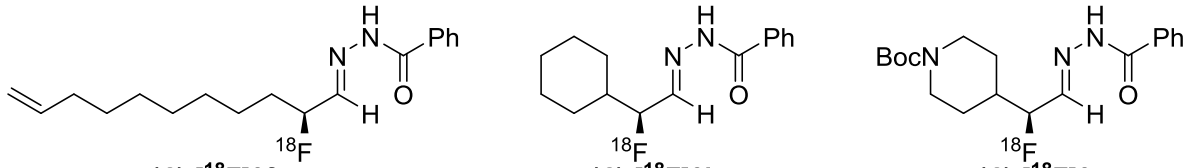


Scheme 2.36: Synthesis of racemic fluorinated references

As well as for the substrates prepared above, fluorination and derivatisation of commercially available undecanal and phenylacetaldehyde was also carried out. For undecanal, this yielded the desired racemic fluorinated hydrazone **8f** in a 21 % isolated yield. However, for phenylacetaldehyde, it was not possible to isolate more than a trace of fluorinated product **8g** by silica gel chromatography, despite a ^{19}F NMR yield of 81 %, likely due to further reaction following abstraction of the very acidic benzylic α-proton. Aldehyde **4d** was also submitted to the standard conditions for fluorination and afforded hydrazone **8d** with a 29 % isolated yield. Unfortunately, separation of enantiomers by reversed phase chiral HPLC was very poor for this fluorinated product. However, inclusion on a *tert*-butyl group at the *para* position of the benzyl was successful in improving the separation of enantiomers on a reverse phase HPLC column, so that this substrate could also be investigated with ^{18}F (see Chapter 4.4 for HPLC spectra).

With these fluorinated racemic references, as well as appropriate conditions for separation of their enantiomers by reverse phase HPLC, in hand, the previously optimised conditions for asymmetric fluorination with [^{18}F]NFSI were next applied to this library of substrates (Scheme 2.37).

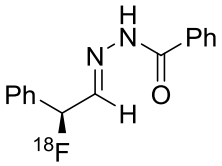




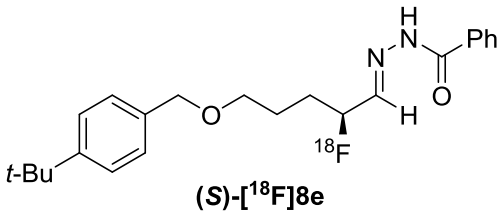
(*S*)-[^{18}F]8f
46 % ± 10 % RCC[a]
92 % ee[b]
(*n* = 3)

(*S*)-[^{18}F]8b
36 % ± 7 % RCC[a]
92 % ee[b]
(*n* = 3)

(*S*)-[^{18}F]8c
54 % ± 4 % RCC[a]
92 % ee[b]
(*n* = 3)



(*S*)-[^{18}F]8g
0 % RCC[a]
(*n* = 3)



(*S*)-[^{18}F]8e
0 % RCC[a]
(*n* = 2)

[a] RCC determined by radio-HPLC relative to [^{18}F]F^{+} source and reported with standard deviation of the mean.
[b] Determined by chiral radio-HPLC of isolated product

Scheme 2.37: Substrate scope for organomediated asymmetric fluorination with [^{18}F]NFSI

These substrates generally responded well to this fluorination/ derivatisation one-pot procedure with [^{18}F]NFSI, with ^{18}F-labelled benzoylhydrazones afforded with good RCCs and, as with the model substrate, a consistently high ee of 92 %. As anticipated, reaction of phenylacetaldehyde **4g** was also unsuccessful in hot mode and radio-HPLC analysis after step 1 and 2 indicated many overlapping signals around the retention time of this product. Analysis by mass spectrometry of collected samples after decay was

unsuccessful at identification of these side-products. The asymmetric fluorination of aldehyde **4e** appeared to proceed well initially, with almost complete conversion of [^{18}F]NFSI to the intermediate ^{18}F-labelled aldehyde.[3] However, we were surprised to find that derivatisation of this substrate was unsuccessful, with no reaction observed on addition of benzhydrazide in methanol.

These studies demonstrated that this reaction was suitable for substrates other than the model hydrocinnamaldehyde and that functional groups including carbamates, *t*-butyl esters and olefins could be tolerated under these conditions. Currently, extension to further substrates is limited by the necessity for analysis by reverse phase chiral HPLC, which appears to pose a significant challenge for this class of compounds.

2.2.1.5 Alternative Derivatisation of α-Fluoroaldehyde

Work so far has demonstrated the development of the organomediated asymmetric fluorination of aldehydes reaction with [^{18}F]NFSI to afford optically enriched α-[^{18}F]fluoroaldehydes. The instability and volatility of this species prompted further derivatisation, initially by reaction with benzhydrazide for convenience of analysis. However, the true value of this reaction lies with the extensive possibilities of reactivity modes for this valuable α-fluoroaldehyde synthetic equivalent. It was envisaged that access to a range of functional groups would be possible from one key intermediate, simply by altering the derivatisation step of this reaction.

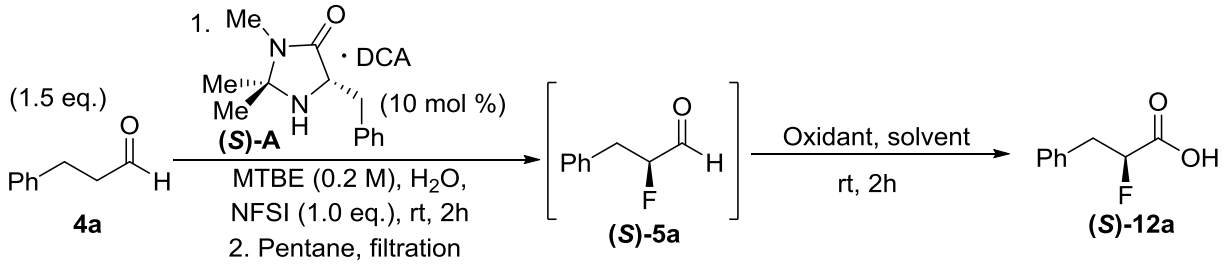
The development of alternative derivatisation steps posed a few challenges. Firstly, the reaction should be amenable to one-pot methodology to limit time-consuming purification of the intermediate. Secondly, the conditions should be mild so as not to cause racemisation of the newly formed stereocentre. Finally, reaction times must be short due to the limitations of the short half life of ^{18}F.

[3] Reaction performed by Ania Krzyczmonik and Tom Keller.

2.2.1.5.1 Oxidation

Oxidation of the intermediate α-fluoroaldehyde would provide an elegant route to optically enriched α-[^{18}F]fluorocarboxylic acids, a moiety which is generally difficult to access.[5e;5g] However, oxidations can often employ very basic or very acidic conditions which could cause racemisation of the stereocentre. It was therefore first necessary to find a mild method of oxidation which minimised loss of enantiopurity. Following fluorination of hydrocinnamaldehyde **4a** under the previously optimised conditions, oxidation was effected by addition of various oxidants in an appropriate solvent (Table 2.8). After stirring for 2 hours at room temperature, the resultant α-fluorocarboxylic acid **12a** was analysed by ^{19}F NMR and chiral stationary phase HPLC, with a reference compound obtained in 40 % isolated yield by employing racemic imiazolidinone catalyst **A** with Oxone as the oxidant. Chiral HPLC analysis of this racemic reference indicated good separation of enantiomers in reverse phase.

Table 2.8: Oxidant screening



Entry[a]	Oxidant (eq.)	Solvent	Additive (eq.)	^{19}F NMR Yield (%)[b]	ee (%)
1	Molecular O_2	DMSO	-	**0**	-[nd]
2	Oxone (2.0)	MeCN	-	**0**	-[nd]
3	Oxone (2.0)	DMF	-	**40**	**86**
4	Oxone (2.0)	DMF[c]	-	**26**	**70**
5	$KMnO_4$ (1.5)	MeOH/H_2O (1:1)	H_2SO_4 (1.5)	**0**	-
6	$KMnO_4$ (1.5)	MeOH/H_2O (1:1)	Na_2CO_3 (1.5)	**42**	**80**
7	$KMnO_4$ (1.5)	MeOH/H_2O (1:1)	Na_2HPO_4 (1.5)	**36**	**89**
8	$NaClO_2$ (10.0)	*t*-BuOH/H_2O (4:1)	NaH_2PO_4 (8.0 eq.), 2-methyl-2-butene (11.0 eq.)	**55**	**78**
9	$NaClO_2$ (10.0)	MeCN/H_2O (4:1)	NaH_2PO_4 (8.0 eq.), 2-methyl-2-butene (11.0 eq.)	**15**	**88**
10	$NaClO_2$ (10.0)	THF/H_2O (4:1)	NaH_2PO_4 (8.0 eq.), 2-methyl-2-butene (11.0 eq.)	**13**	**87**
11	$NaClO_2$ (10.0)	Toluene/H_2O (4:1)	NaH_2PO_4 (8.0 eq.), 2-methyl-2-butene (11.0 eq.)	**19**	**82**

[a] Reactions performed on a 0.5 mmol scale. [b] ^{19}F NMR yield determined by integration relative to 1-fluoro-3-nitrobenzene as an internal standard (D_1 = 10). [c] Fluorination reaction performed in DMF as solvent.

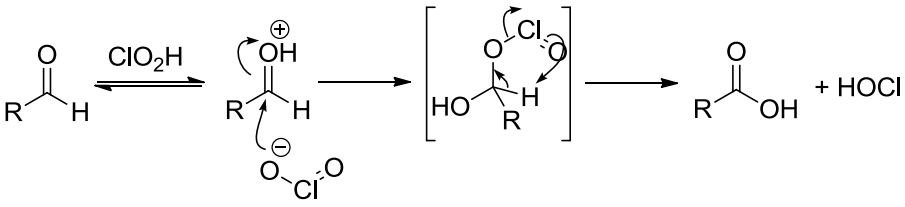
The oxidation of aldehydes in air has been known since a report by Liebig in 1835 describing the carboxylic acid impurities formed when an aldehyde had sat under air for some time and has been extensively researched since.[74] Molecular oxygen would therefore appear an ideal mild reagent to implement this oxidation reaction. Following α-fluoroaldehyde synthesis and filtration as carried out previously, the filtrate was diluted with DMSO and treated with a continuous flow of oxygen for 5 minutes, and then stirred under a balloon of oxygen for a further 2 hours at room temperature (Table 2.8, entry 1). However, under these conditions only aldehyde **5a** (^{19}F NMR, δ = −197.5 ppm, $CDCl_3$) could be observed by ^{19}F NMR analysis of the crude reaction mixture, with no trace of carboxylic acid **12a** (^{19}F NMR, δ = −189.6, $CDCl_3$).

Oxone is a relatively cheap, non-toxic reagent which has been shown to oxidise aliphatic and aromatic aldehydes to carboxylic acids.[75] This transformation is proposed to occur via a Baeyer-Villiger type process. Oxidation of α-fluoroaldehyde **(*S*)-5a** was attempted by dilution of the crude reaction mixture with an appropriate solvent following filtration, with subsequent addition of Oxone as a solid. When acetonitrile was employed as the solvent in combination with Oxone, no carboxylic acid product was observed by ^{19}F NMR (Entry 2). However, with DMF as the oxidation solvent, after 2 hours at room temperature the α-fluorocarboxylic acid **(*S*)-12a** was obtained in a 40 % ^{19}F NMR yield and with an ee value of 86 %, indicating that little or no racemisation occurs under these oxidation conditions (Entry 3). A further reaction, which employed DMF as a common solvent for both the asymmetric fluorination and oxidation steps, afforded α-fluorocarboxylic acid **(*S*)-12a** in a 26 % yield by ^{19}F NMR, but the with a lower ee of 70 % (Entry 4).

Potassium permanganate oxidation was also explored, since there is some literature precedent for the use of this reagent to mediate the formation of carboxylic acids from α-substituted aldehydes without racemisation under mild basic[76] or acidic conditions.[77] When the oxidation reaction was performed in the presence of sulfuric acid, no carboxylic acid product was observed by ^{19}F NMR (Entry 5). However, with sodium carbonate as the additive, the carboxylic acid product was formed in a ^{19}F NMR yield of 42 %, although the enantiomeric excess of **(*S*)-12a** was found to be 80 %, suggesting that some racemisation of the stereocentre had occurred under these basic conditions (Entry 6). The mild base disodium phosphate was recently employed by Ley and co-workers in a continuous flow process for the potassium permanganate-mediated oxidation of aldehydes.[78] When this base was employed along with potassium permanganate for the oxidation of α-fluoroaldehyde **(*S*)-5a**, pleasingly carboxylic acid **(*S*)-12a** was obtained in

an NMR yield of 36 % with the ee determined as 89 %, indicating that very little loss of enantiopurity had occurred under these reaction conditions (Entry 7).

There is some literature precedent for application of the Pinnick-Lindgren oxidation to optically enriched α-fluoroaldehydes without racemisation.[79] This reaction employs sodium chlorite, which forms the active oxidant chlorous acid in the presence of monosodium phosphate, as well as 2-methyl-but-2-ene as a scavenger to remove the hypochlorous acid formed as a side-product in the reaction (Scheme 2.38).[80]



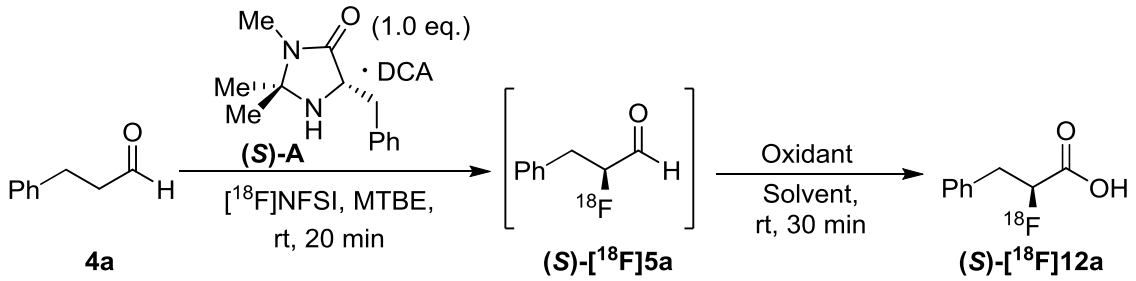
Scheme 2.38: Proposed mechanism of Pinnick-Lindgren oxidation

When *tert*-butanol was employed as the solvent for this reaction, whilst a high yield of carboxylic acid **(*S*)-12a** was obtained, an ee of 78 % indicated that some racemisation of the C-F stereocentre occurred under the reaction conditions (Entry 8). However, carrying out the reaction in acetonitrile, THF or toluene (Entries 9, 10 and 11, respectively) provided the α-fluorocarboxylic acid product with a lower NMR yield, but with greater retention of stereochemistry. Acetonitrile proved to be the most effective solvent, providing **(*S*)-12a** with an ee value of 89 %.

These studies demonstrated that there are three oxidants (Oxone, potassium permanaganate and sodium chlorite) which are able to promote the oxidation of α-fluoroaldehyde **(*S*)-5a** without causing racemisation of the stereocentre. Each of these oxidants was next investigated in turn for derivatisation of α-fluoroaldehyde **(*S*)-[^{18}F]12a**. The ^{18}F-fluorination reaction was performed under the previously optimised conditions on

hydrocinnamaldehyde **4a**. After stirring for 20 minutes at room temperature, the reaction was directly treated with the oxidant in the appropriate solvent (Table 2.9).

Table 2.9: Oxidant screening for reactions with [^{18}F]NFSI



4a **(*S*)-[^{18}F]5a** **(*S*)-[^{18}F]12a**

Entry	Oxidant (eq.)	Solvent	Additive (eq.)	RCC (%)[a]	ee (%)[b]
1	Oxone (2.0)	DMF	-	**0** (*n* = 1)	-[nd]
2[c]	Oxone (2.0)	DMF	-	**0** (*n* = 1)	-[nd]
3	$KMnO_4$ (1.0)	MeOH/H_2O (1:1)	-	**20** (*n* = 1)	-[nd]
4	$KMnO_4$ (1.0)	MeOH/H_2O (1:1)	Na_2HPO_4 (1.0)	**18** (*n* = 1)	-[nd]
5	$NaClO_2$ (2.5)	*t*BuOH	NaH_2PO_4 (4.0), 2-methyl-2-butene (5.0)	**81** (*n* = 1)	**50**
6	$NaClO_2$ (2.5)	MeCN	NaH_2PO_4 (4.0), 2-methyl-2-butene (5.0)	**75 ± 8** (*n* = 3)	**93**

[a] RCC determined by radio-HPLC relative to [^{18}F]F^+ source and reported with standard deviation of the mean. [b] Determined by chiral radio-HPLC of isolated product. [c] Change of order of addition.

In the first instance, the reaction was performed employing Oxone as the oxidant. However, as this is insoluble in DMF, it was not possible to add the reagent as a solution and adding such a small quantity as a solid was impractical. Therefore, following reaction of hydrocinnamaldehyde **4a** with [^{18}F]NFSI and imidazolidinone **(*S*)-A** for 20 minutes, the entire reaction mixture was transferred via syringe to a second reaction Eppendorf containing the oxidant and DMF (Table 2.9, entry 1). However, after stirring for 20 minutes at room temperature, no carboxylic acid **[^{18}F]12a** was observed by analytical radio-HPLC of an aliquot of the crude reaction. This was potentially due to the observation that the oxidant remained as a solid at the bottom of the reaction Eppendorf, without being dispersed through the reaction mixture. Therefore in a second reaction, the order of addition was changed so that the reaction mixture was transferred directly on to

the oxidant, prior to addition of DMF (Entry 2). However, the oxidation was similarly unsuccessful, with α-fluoroaldehyde **[^{18}F]5a** unreacted after 20 minutes.

The use of potassium permanganate was experimentally more simple due to the high solubility this oxidant in the methanol/water reaction solvent. Following α-fluorination of the model aldehyde substrate with [^{18}F]NFSI, a solution of the oxidant was added directly to the reaction mixture and stirring was continued at room temperature for a further 20 minutes (Entry 3). In this case carboxylic acid **[^{18}F]12a** was formed in a 20 % RCC over the two steps. Unfortunately, as a result of this low yield, the amount of radioactivity isolated was too low for chiral HPLC analysis. Despite having a positive influence on cold reactions, it was also found that the addition of disodium phosphate was not beneficial to this reaction employing [^{18}F]NFSI (Entry 4).

Finally, the Pinnick-Lindgren conditions for oxidation were considered. In the first instance, following the ^{18}F-labelling step, the reaction mixture was diluted with a solution of 2-methyl-but-2-ene in *tert*-butanol, followed directly by a solution of sodium chlorite and monosodium phosphate in water (Entry 5). Under these conditions, α-fluorocarboxylic acid **(*S*)-[^{18}F]12a** was provided with an excellent RCC of 81 %. As anticipated by cold results though, there was a significant loss of stereochemical integrity over the second step of the reaction, with the ee determined as just 50 %. However, pleasingly, use of acetonitrile as the solvent for this step proved much more successful and under these conditions carboxylic acid **(*S*)-[^{18}F]12a** was obtained with an excellent ee of 93 % and a RCC of 75 % ± 8 % (*n* = 3) (Entry 6) (see Chapter 4.4 for HPLC spectra).

These studies have therefore demonstrated that sodium chlorite is a suitable reagent to promote the oxidation of ^{18}F-labelled α-fluoroaldehyde **(*S*)-[^{18}F]5a** to the corresponding carboxylic acid with high RCC within 30 minutes. This was achieved in an

experimentally facile one-pot process. It was demonstrated that choice of solvent was critical for this oxidation reaction, with reaction in acetonitrile allowing the stereochemical integrity of the aldehyde intermediate to be maintained. This novel procedure provides access to a optically enriched α-[^{18}F]fluorocarboxylic acid from a racemic, non-prefunctionalised, commercially available starting material.

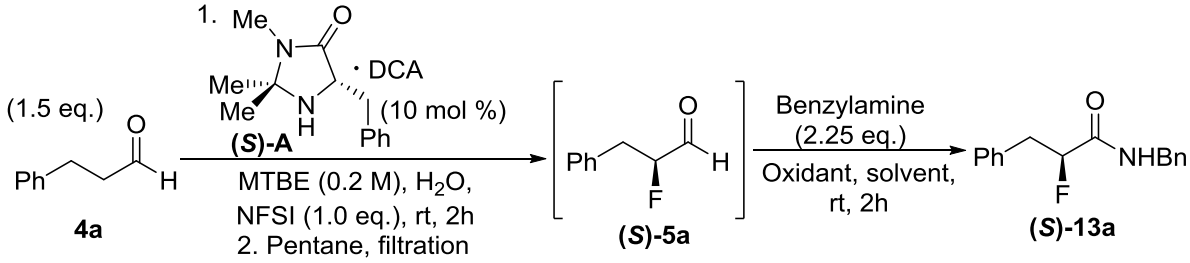
2.2.1.5.2 Amide Formation

Amide bond formation is one of the most common transformations in the synthesis of pharmaceuticals and polymers.[81] In fact, an analysis of medicinal chemistry databases revealed that more than 25% of drugs contain an amide linkage.[82] Development of a derivatisation method which affords access to optically enriched ^{18}F-labelled α-fluoroamides could therefore be a key tool for the synthesis of ^{18}F-labelled pharmaceuticals.

2.2.1.5.2.1 Secondary Amides

Synthesis of amides typically requires activation of a carboxylic acid derivative, or use of a coupling reagent, prior to reaction with an amine.[83] However, recent literature has reported the direct synthesis of amides from aldehydes via an oxidative amidation reaction. Therefore following fluorination of hydrocinnamaldehyde **4a** under the optimised conditions, oxidative amidation was performed to afford access secondary amide **(*S*)-13a** (Table 2.10). Benzylamine was employed either as the free base or as its HCl salt.

Table 2.10: Oxidative amidation condition screening



Entry[a]	Oxidant (eq.)	Solvent	Additive (eq.)	^{19}F NMR Yield (%)[b]	ee (%)
1[c]	TBHP (1.65)	MeCN	$CuSO_4$ (0.075), $CaCO_3$ (1.65)	**Trace**	-[nd]
2	$NaClO_2$ (3.75)	Toluene	NaH_2PO_4 (5.25 eq.), 2-methyl-2-butene (7.5 eq.)	**63**	**88**
3	$NaClO_2$ (3.75)	*t*BuOH/H_2O (4:1)	NaH_2PO_4 (5.25 eq.), 2-methyl-2-butene (7.5 eq.)	**36**	**66**

[a] Reactions performed on a 0.5 mmol scale. [b] ^{19}F NMR yield determined by integration relative to 1-fluoro-3-nitrobenzene as an internal standard (D_1 = 10). [c] Benzylamine·HCl used. TBHP = *tert*-butylhydroperoxide.

The copper-catalysed oxidative amidation of aldehydes to form primary, secondary and tertiary amides was reported by Chen et al. in 2012.[84] Although the vast majority of examples in this work related to aromatic aldehydes, extension to aliphatic aldehydes was also demonstrated, albeit with a slight reduction in yield. This work employed *tert*-butylhydroperoxide (TBHP) as an oxidant, calcium carbonate as a base and a copper sulfate catalyst in acetonitrile as solvent. The reaction was proposed to proceed via formation of a hemiaminal intermediate which undergoes oxidition to an amide via a free-radical pathway in the presence of TBHP and the copper(II) catalyst. The involvement of free-radicals was confirmed by inhibition of the reaction in the presence an equivalent of 2,6-di-tert-butyl-4-methylphenol (BHT).

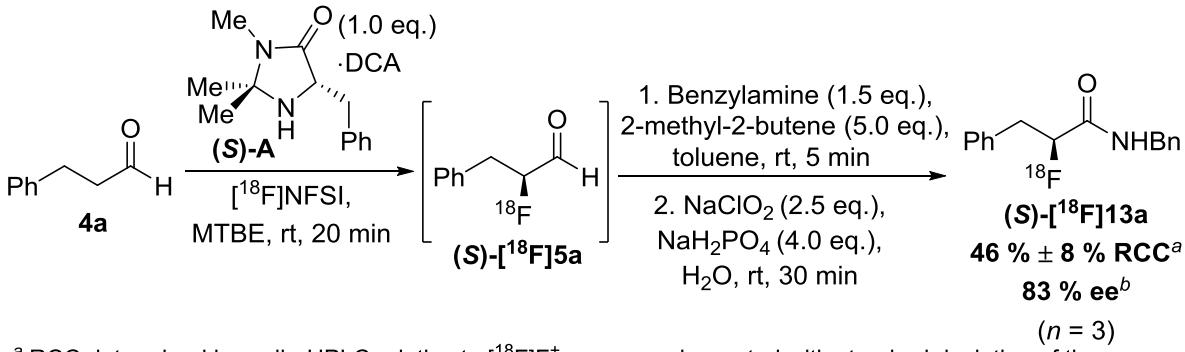
A preliminary reaction involved addition of TBHP, copper sulfate and calcium carbonate, along with benzylamine·HCl, to the crude reaction mixture following fluorination and filtration (Table 2.10, entry 1). However, only a trace of amide product **13a** was observed by NMR analysis (^{19}F NMR, δ = −189.1 ppm, $CDCl_3$) under these conditions, indicating

incompatibility of these oxidative amidation conditions with either this substrate or the pseudo one-pot procedure.

The previously investigated Pinnick-Lindgren oxidation has also been applied to the synthesis of secondary amides.[85] Addition of an amine to the aldehyde substrate affords a transient imine, which undergoes oxidation to a secondary amide on treatment with sodium chlorite. Again, monosodium phosphate is employed as a buffer, with 2-methyl-2-butene acting as a scavenger for hypochlorous acid. The crude reaction mixture of optically enriched α-fluoroaldehyde **(*S*)-5a** was therefore treated with benzylamine, 2-methyl-2-butene and toluene and stirred for 5 minutes at room temperature before the addition of sodium chlorite and monosodium phosphate as solids (Entry 2). Pleasingly, after reaction for 2 hours at room temperature, secondary amide **(*S*)-13a** was provided with an NMR yield of 63 %. The corresponding racemic reference could also be synthesised under the same conditions, with 35 % yield when racemic imidazolidinone **A** was employed, and HPLC analysis showed good separation of enantiomers in reverse phase. This allowed determination of the ee for entry 2 as 88 %, indicating that little or no racemisation of the stereocentre had taken place under these derivatisation conditions. Repetition of the reaction with the oxidant and buffer added as a solution in water (for convenience in hot mode) demonstrated no difference in either yield or ee under these conditions. The reaction was also attempted with *tert*-butanol as solvent for the oxidative amidation reaction, but, as also observed in oxidation to form carboxylic acids, the ee of amide **(*S*)-13a** was significantly lower in this case (Entry 3).

These conditions were translated directly to hot mode for reaction with [^{18}F]NFSI. Following formation of α-fluoroaldehyde **(*S*)-[^{18}F]5a**, the crude reaction mixture was treated with a solution of benzylamine and 2-methyl-2-butene in toluene. After stirring

for 5 minutes, $NaClO_2$ was added, along with monosodium phosphate, as a solution in water (Scheme 2.39).



[a] RCC determined by radio-HPLC relative to $[^{18}F]F^+$ source and reported with standard deviation of the mean.
[b] Determined by chiral radio-HPLC of isolated product

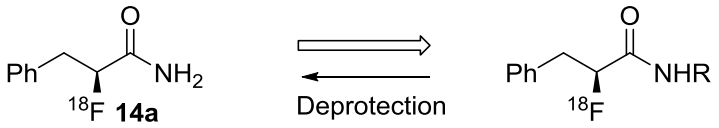
Scheme 2.39: Synthesis of enantioenriched ^{18}F-labelled secondary amide

Pleasingly, after stirring for 30 minutes at room temperature, α-fluoroamide **(*S*)-[^{18}F]13a** was afforded with a RCC of 46 % ± 8 % (*n* = 3). Again, no purification of the intermediate aldehyde was necessary, therefore allowing the two-step sequence to take place in one pot. Analysis by reverse phase chiral radio-HPLC indicated a slightly eroded ee of 83 % (see Chapter 4.4 for HPLC spectra).

In summary, this model reaction has demonstrated successful application of a Pinnick-like oxidative amidation reaction to an *in situ* generated ^{18}F-labelled optically enriched α-fluoroaldehyde in order to generate a secondary amide derivative, with high RCC and ee.

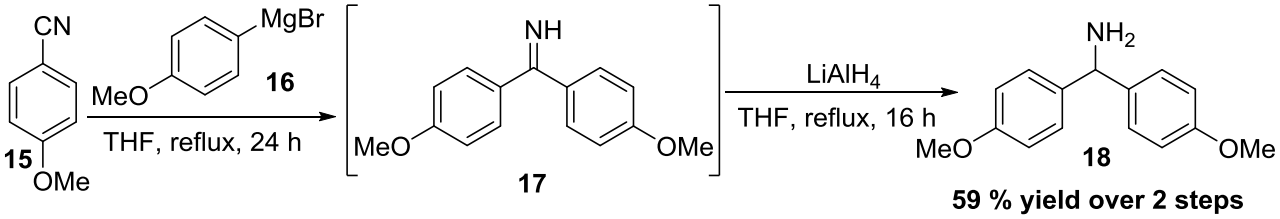
2.2.1.5.2.2 Primary Amides

Following the success of this oxidative amidation methodology to provide access to secondary amides, we were keen to extend this method to also include primary amides. Synthesis of primary amides directly from aldehydes poses a significant challenge and the Pinnick-like oxidative amidation reaction is not known for primary amides. An indirect synthesis of a primary α-fluoroaldehye via deprotection of a cleavable secondary amide was therefore proposed (Scheme 2.40).



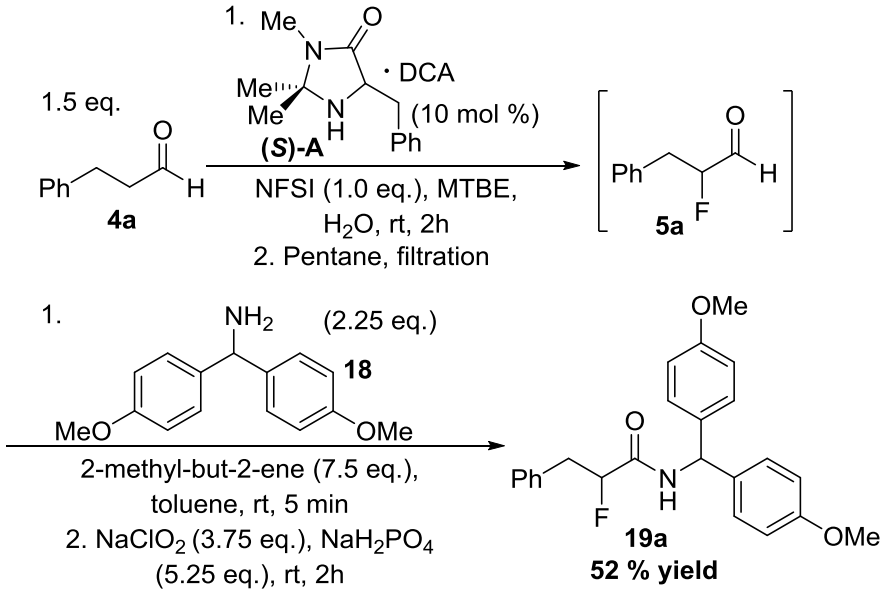
Scheme 2.40: Proposed synthesis of primary α-fluoroamide

A literature search revealed that the acid-mediated cleavage of bis(4-methoxyphenyl)methanamides to primary amides was reported by Henneuse in 1996.[86] Formation of an α-fluorinated variant of this secondary amide via an oxidative amidation reaction first required synthesis of the necessary amine **18** according to the literature procedure (Scheme 2.41).[87]



Scheme 2.41: Synthesis of bis(4-methoxyphenyl)methanamine

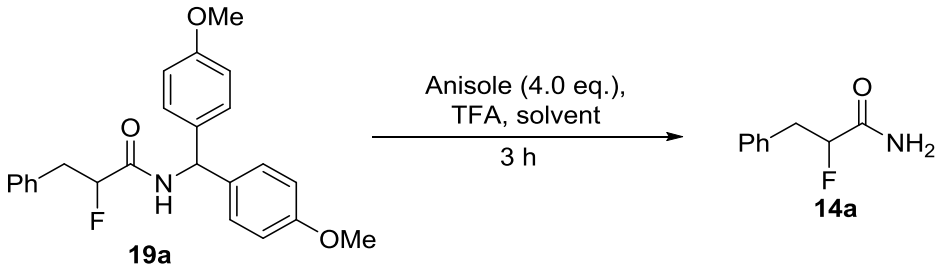
The required Grignard reagent was formed from *p*-methoxyphenylbromide and was reacted with *p*-methoxybenzonitrile to afford an imine, which could be reduced *in situ* with lithium aluminium hydride. With amine **18** in hand, the asymmetric fluorination/ oxidative amidation reaction was performed using this amine under the previously optimised conditions with racemic imidazolidinone **A** (Scheme 2.42).



Scheme 2.42: Oxidative amidation with bis(4-methoxyphenyl)methanamine

Pleasingly amide **19a** was formed with a yield of 52 % following isolation by silica gel chromatography. Next, this secondary amide was subjected to an investigation of acid-mediated cleavage conditions (Table 2.11).

Table 2.11: TFA mediated cleavage of secondary amide



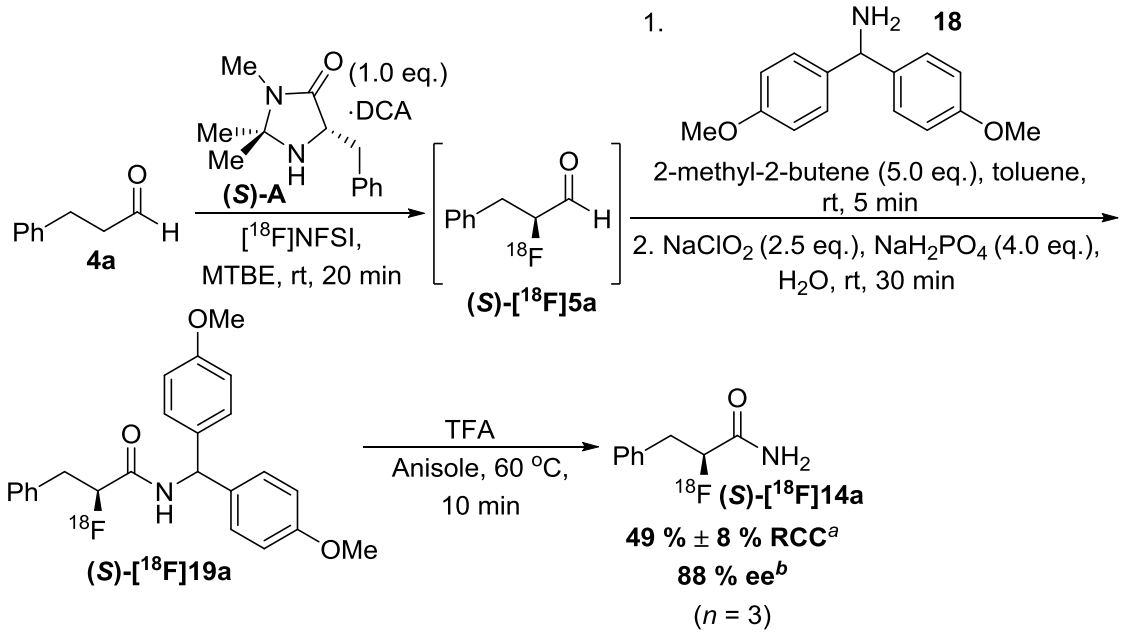
Entry[a]	Conditions	Temp. (°C)	^{19}F NMR Yield (%)[b]
1	10 % TFA in DCM	rt	**0**
2	Neat TFA	rt	**70**
3	**Neat TFA**	**60**	**100**

[a] Reactions performed on a 0.1 mmol scale. [b] ^{19}F NMR yield determined by integration relative to 1-fluoro-3-nitrobenzene as an internal standard (D_1 = 10).

When a solution of 10 % TFA in DCM was employed for this deprotection, along with anisole as a scavenger, only secondary amide **19a** was observed by NMR analysis of the crude reaction mixture (^{19}F NMR, δ = −189.1 ppm, $CDCl_3$) following removal of solvent (Table 2.11, entry 1). However, when TFA was instead used neat, a 70 % NMR yield of

the desired primary amide **14a** (^{19}F NMR, δ = −187.0 ppm, $CDCl_3$) was obtained after 3 hours (Entry 2). This could pleasingly be increased to 100 % NMR yield of primary amide by increasing the reaction temperature to 60 °C (Entry 3). 2-Fluoro-3-phenylpropanamide was isolated in a 60 % yield by silica gel chromatography and analysis by reverse phase chiral HPLC showed sufficient separation of the two enantiomers. Crucially, repetition of this sequence employing 10 mol % of **(*S*)-A** afforded (*S*)-*N*-(bis(4-methoxyphenyl)methyl)-2-fluoro-3-phenylpropanamide (***S*)-19a** with an ee of 81 %, which was maintained during TFA deprotection (see Chapter 4.4 for HPLC spectra).

For translation to reaction with ^{18}F, in the first instance this three step reaction was attempted in sequence in one-pot. Asymmetric fluorination with [^{18}F]NFSI on hydrocinnamaldehyde **4a** was performed as previously, followed by oxidative amidation with amine **18**. Cold investigations had highlighted the crucial effect of concentration on the TFA deprotection, and so prior to deprotection, the reaction volume was reduced by approximately half by heating to 60 °C under a stream of helium (Scheme 2.43).



[a] RCC determined by radio-HPLC relative to $[^{18}F]F^+$ source and reported with standard deviation of the mean.
[b] Determined by chiral radio-HPLC of isolated product

Scheme 2.43: Synthesis of ^{18}F-labelled enantioenriched primary amide (*S*)-[^{18}F]14a

Taking aliquots allowed the reaction to be monitored by analytical radio-HPLC after every step. As previously, condensation of the amine with α-fluoroaldehyde **(*S*)-[^{18}F]5a**, followed by oxidation with sodium chlorite, proceeded with high conversion. Deprotection in TFA at 60 °C for 10 minutes then afforded primary α-fluoroamide **(*S*)-[^{18}F]14a** with a RCC of 49 % ± 8 % (*n* = 3) and an ee value of 88 %, indicating good retention of stereochemistry.

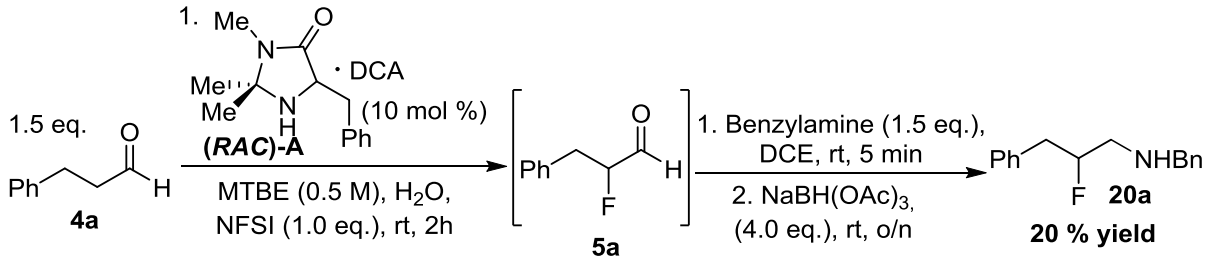
This reaction demonstrates extension of previously developed Pinnick-like amidation methodology to the synthesis of ^{18}F-labelled α-fluoro primary amides, with high radiochemical conversion and ee. Notably, there are few other methods currently known to acesss this chemotype.

2.2.1.5.3 Reductive Amination

The incorporation of β-fluoroamine motifs in drug molecules is common due to the beneficial effects of the fluorine substitution, which include reduced amine basicity and improved metabolic stability.[88] In 2009, Lindsley and co-workers reported an extension

of the asymmetric fluorination reaction described by MacMillan,[28] in which reductive amination of the fluorinated aldehydes afforded access to optically enriched β-fluoroamines (vide supra, Scheme 2.10).[32] This reaction employed sodium triacetoxyborohydride as the reducing agent, with dichloroethane (DCE) as solvent for the derivatisation step. We were keen to investigate this derivatisation in hot mode to provide a route to ^{18}F-labelled optically enriched β-fluoroamine moieties.

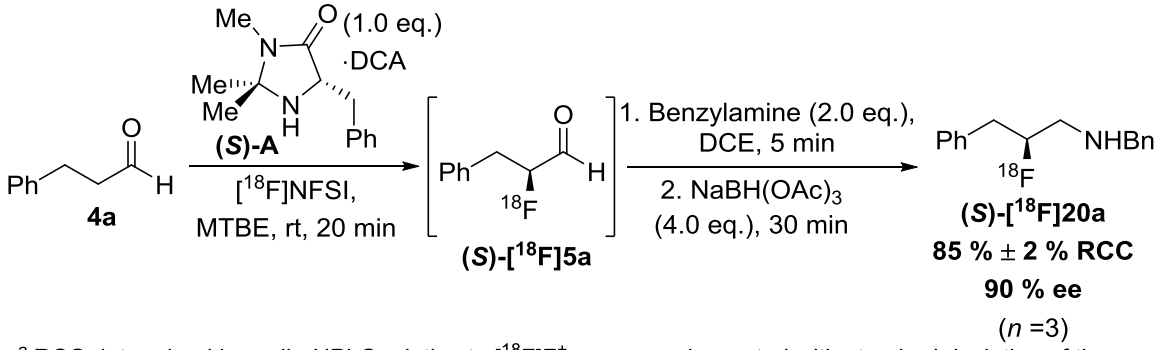
Firstly, the required racemic reference was synthesised by application of the previously optimised conditions for fluorination with catalytic racemic imidazolidinone **A**, followed by dilution of the filtrate with DCE and addition of benzylamine. After stirring for 5 minutes to invoke imine formation, sodium triacetoxyborohydride was added and stirring continued overnight (Scheme 2.44).



Scheme 2.44: Synthesis of β-fluoroamine racemic reference 20a

Under these conditions, β-fluoroamine **20a** was isolated in 20 % yield following silica gel chromatography, and analysed by reverse phase chiral HPLC to find conditions under which separation of enantiomers was observed.

With this reference in hand, these conditions were next investigated for reaction with [^{18}F]NFSI. α-Fluoroaldehyde **(*S*)-[^{18}F]5a** was synthesised under the usual conditions, prior to treatment with benzylamine, with subsequent addition of sodium triacetoxyborohydride, both as solutions in DCE (Scheme 2.45).



[a] RCC determined by radio-HPLC relative to $[^{18}F]F^+$ source and reported with standard deviation of the mean.
[b] Determined by chiral radio-HPLC of isolated product

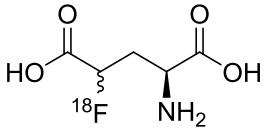
Scheme 2.45: Radiosynthesis of enantioenriched β-fluoroamine (*S*)-[^{18}F]20a

We were pleased to observe an excellent conversion of α-fluoroaldehyde **(*S*)-[^{18}F]5a** via this reductive amination reaction, to afford β-fluoroamine **(*S*)-[^{18}F]20a** with an 85 % ± 2 % RCC over the two steps (*n* = 3). The ee was determined as 90 %, demonstrating retention of stereochemistry during this derivatisation (see Chapter 4 for HPLC spectra).

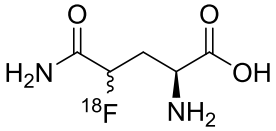
This reductive amination reaction adds further scope to the varied range of derivatisations developed for this α-[^{18}F]fluoroaldehyde synthetic equivalent, demonstrating the diverse utility of this divergent approach.

2.2.1.6 [^{18}F]4-Fluoroglutamic acid and [^{18}F]4-Fluoroglutamine

After establishing conditions for the synthesis and post-fluorination transformation of aldehyde **(*S*)-[^{18}F]5a**, we next focussed on application of this methodology to the synthesis of 4-[^{18}F]fluoroglutamic acid and 4-[^{18}F]fluoroglutamine, radiotracers that are difficult to access in diasteromerically pure form by known methods (Figure 2.4).



(2*S*)-[^{18}F]21
(2*S*)-4-[^{18}F]Fluoroglutamic acid



(2*S*)-[^{18}F]22
(2*S*)-4-[^{18}F]Fluoroglutamine

Figure 2.4: Structure of 4-fluoroglutamic acid and 4-fluoroglutamine

The increased uptake of glucose by malignant cells is exploited by the use of [^{18}F]FDG as the most commonly employed ^{18}F-radiotracer worldwide.[4] However, limitations of [^{18}F]FDG include uptake by inflamed tissue and high background in tissues displaying increased glucose metabolism, such as the brain and heart. Furthermore, [^{18}F]FDG does not accumulate in tumours with low glycolytic activity, such as prostate cancer. The development of novel tracers to target other pathways of tumour metabolism is therefore crucial.

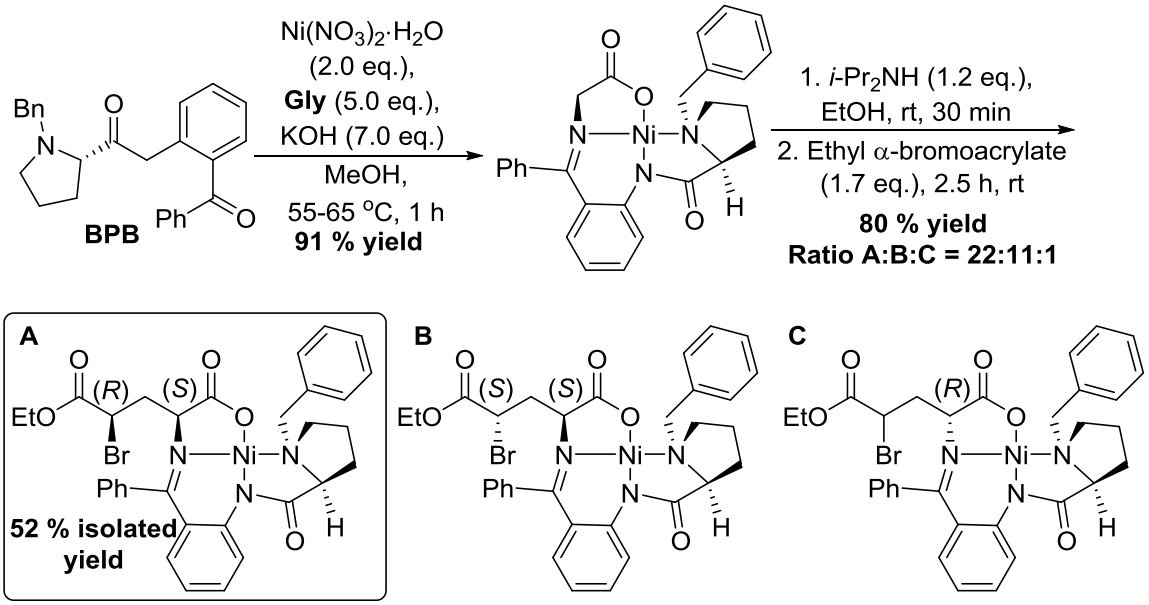
As well as increased glycolysis, tumour cells often show a higher consumption of glutamine than their non-malignant counterparts.[89] Glutamine is transported into cells mainly by the sodium ion-dependent systems A and ASC[90] and hydrolysed by the enzyme glutaminase to afford its deamidated catabolite glutamate. Both glutamine and glutamate can play key roles in energy formation, proliferation and signalling in cancer cells.[91] The increased uptake of these amino acids by some cancers not only highlights the potential of ^{18}F-labelled analogues as an alternative to [^{18}F]FDG in malignant tumour detection, but also the potential utility as a non-invasive method of determining likely response to glutamine and glutamate inhibitor therapy.

In vivo studies in mice have shown that (2*S*,4*R*)-4-[^{18}F]fluoroglutamine **(2*S*,4*R*)-[^{18}F]22** is taken up in tumours derived from highly glutaminolytic cells.[92] Furthermore, clinical trials have demonstrated a high ratio for tumour to background uptake of (2*S*,4*R*)-4-[^{18}F]fluoroglutamine in human glioma patients.[93] Despite the high amount of defluorination observed in animal models, (2*S*)-4-[^{18}F]Fluoroglutamic acid **(2*S*)-[^{18}F]21** was also recently highlighted as a potential PET tracer due to high uptake compared to background in breast and lung cancer cells *in vitro*, although in this case stereochemistry at the 4-position was not well controlled.[94] Given the known importance of chirality in

drugs, we envisaged a radiosynthesis in which the stereochemistry was controlled by application of our optimised asymmetric electrophilic ^{18}F-fluorination reaction.

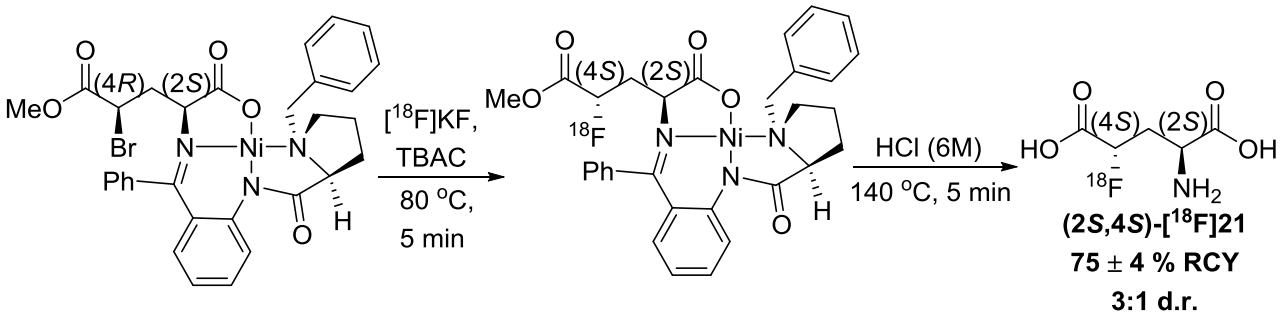
2.2.1.6.1 Literature Synthesis

The synthesis of 4-[^{18}F]fluoroglutamic acid by reaction of an diastereomerically pure Ni(II) precursor with [^{18}F]fluoride was recently described by Krasikova and co-workers.[5g] Synthesis of this Ni(II) precursor employed the procedure of Belokon and co-workers (Scheme 2.46),[95] although with a change from an ethyl to a methyl ester. In Belokon's procedure, a Ni(II) Schiff's base complex was derived from commercially available (*S*)-2-[*N*-(*N'*-benzylprolyl)amino]benzophenone (BPB) and glycine according to the literature procedure.[96] A Michael condensation with ethyl α-bromoacrylate afforded the corresponding 4-bromo-glutamic acid monoester as a mixture of diastereoisomers. Purification by prep-TLC on silica gel afforded the desired (2*S*,4*R*)-diastereomer as the major product in a 52 % isolated yield.



Scheme 2.46: Synthesis of Ni(II)-(*S*)-BPB-(2*S*,4*R*)-4-Br-Glu by Belokoand co-workers BPB = (*S*)-2-[*N*-(*N'*-benzylprolyl)amino]benzophenone, Gly = glycine

In the procedure of Krasikova, this diastereomerically pure precursor was treated with [^{18}F]KF and tetrabutylammonium carbonate (TBAC), followed by acidic deprotection in HCl to release the amino acid from the complex (Scheme 2.47).

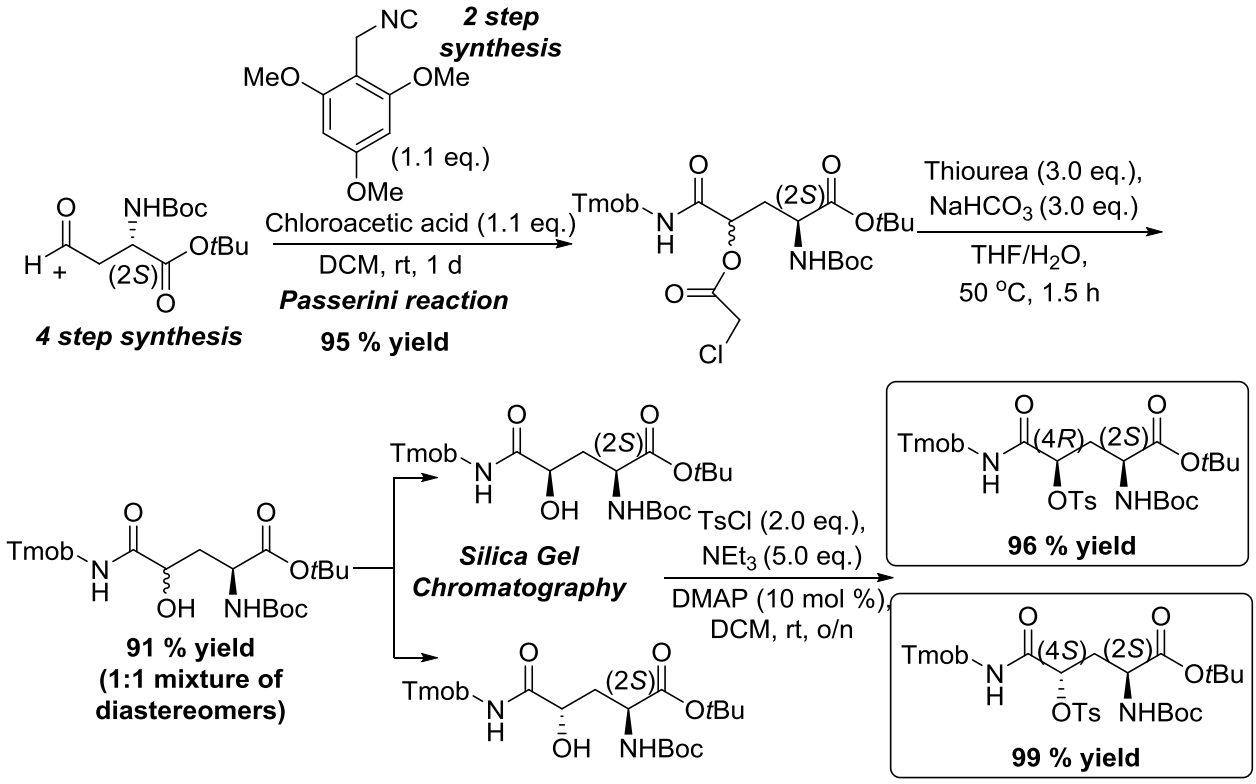


Scheme 2.47: 4-[^{18}F]Fluoroglutamic acid synthesis by Krasikova and co-workers
TBAC = tetrabutylammonium carbonate

Under these conditions, a 3:1 mixture of (2*S*,4*S*)- and (2*S*,4*R*)-4-[^{18}F]fluoroglutamic acid was formed due to incomplete inversion at the 4-position during S_N2 displacement with [^{18}F]fluoride. Isolation of the diastereomers for *in vitro* studies therefore still required time-consuming HPLC isolation, despite employing a diastereomerically pure precursor.

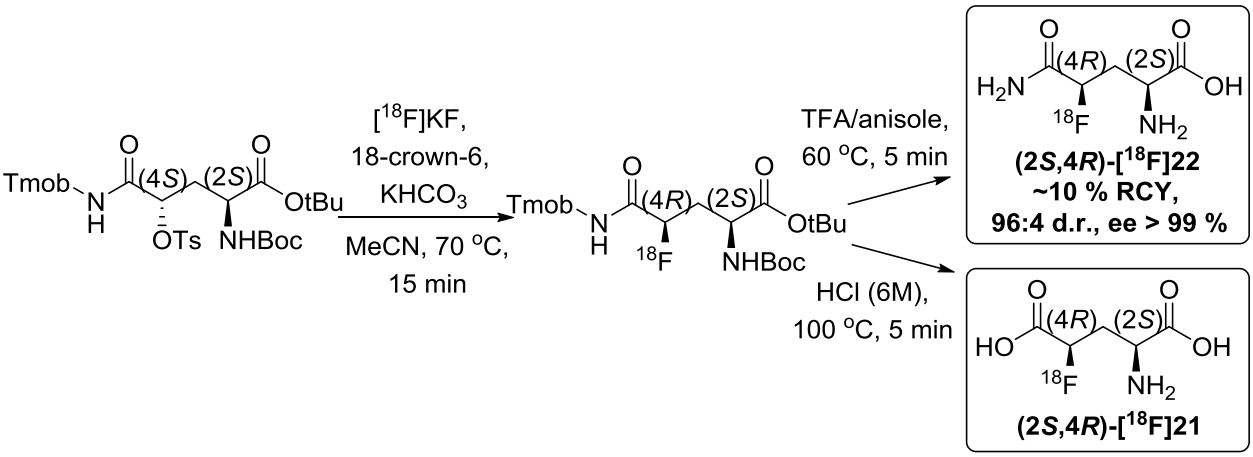
An alternative synthesis of 4-[^{18}F]fluoroglutamic acid and 4-[^{18}F]fluoroglutamine was recently described by Hank Kung and co-workers, in which all 4 diastereomers of a protected precursor was achieved by the S_N2 reaction of a diastereomerically pure tosylate substituted substrate with [^{18}F]fluoride.[5e;5f] Synthesis of this substrate required a multistep protocol including the two step synthesis of an isocyanide, which was subjected to a Passerini reaction with an aldehyde synthesised via reduction and subsequent Dess-Martin oxidation of protected L-aspartic acid. Following the Passerini reaction, the chloroacetyl protecting group was removed using thiourea, prior to silica gel chromatography to separate the *syn* and *anti* diastereomers of this compound. Each was then subjected to tosylate-protection to afford the desired precursors (Scheme 2.48). This synthesis could also be repeated employing the corresponding D-aspartic acid precursor. It

is notable that synthesis of this diastereomerically pure substrate in itself presents somewhat of a challenge, with a lengthy route including a difficult separation of diasteroisomers by silica gel chromatography.



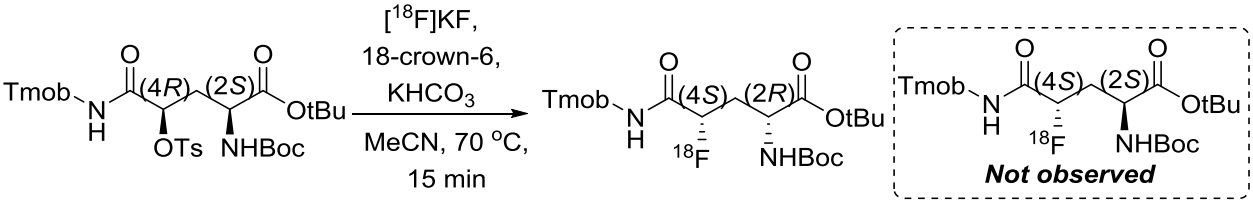
Scheme 2.48: 4-[^{18}F]Fluoroglutamic acid and 4-[^{18}F]fluoroglutamine precursor synthesis by Kung and co-workers Tmob = 2,4,6-trimethoxybenzyl

Treatment of the (2*S*,4*S*)-diastereomer of this substrate with [^{18}F]KF/18-crown-6 and potassium bicarbonate in acetonitrile at 70 °C for 15 minutes led to successful S_N2 displacement of the tosylate with full inversion at the 4 position (Scheme 2.49). The ^{18}F-labelled protected intermediate formed in this reaction was then treated with a TFA/anisole mixture to afford (2*S*,4*R*)-4-[^{18}F]fluoroglutamine with approximately 10 % isolated RCY and an excellent d.r. of 96:4. Alternatively, deprotection could be performed with aqueous HCl to afford access to (2*S*,4*R*)-4-[^{18}F]fluoroglutamic acid from the same intermediate.



Scheme 2.49: Synthesis of (2*S*,4*R*)-4-[^{18}F]fluoroglutamine and glutamic acid by Kung and co-workers

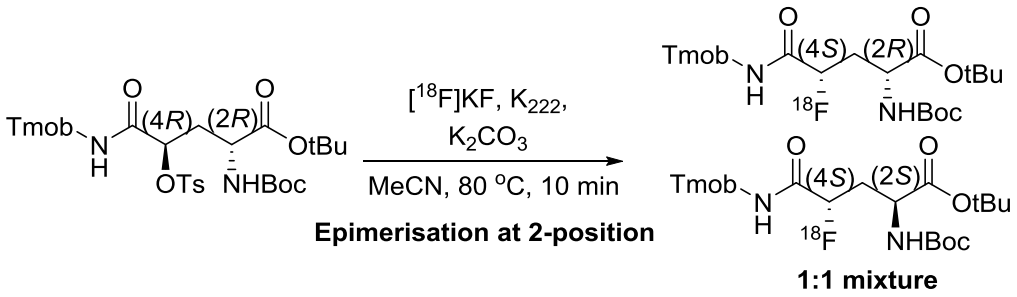
However, access to the *anti* diastereomer of this protected intermediate via this method proved significantly more challenging. It was reported that reaction of the (2*S*,4*R*)-substrate with [^{18}F]KF/18-crown-6 under the same conditions afforded the protected intermediate with not only the anticipated inversion at the 4 position, but also unexpected full inversion at the 2 position (Scheme 2.50). The authors proposed that this unexpected double inversion was due to slow reaction of the (2*S*,4*R*)-substrate under these ^{18}F-fluorination conditions. Base-induced epimerisation at the 2-position afforded the more reactive (2*S*,4*S*)-substrate, which underwent fast reaction with [^{18}F]fluoride to afford the (2*R*,4*S*)-diastereomer of product.



Scheme 2.50: Unexpected inversion at 2-position under ^{18}F-fluorination conditions

Instead, access to the (2*S*,4*S*)-enantiomer of 4-fluoroglutamine was somewhat circuitously provided by reaction of the (2*R*,4*R*)-precursor with [^{18}F]KF/K_{222}, which afforded the protected intermediate with not only the desired inversion at the 4 position,

but also epimerisation at the 2 position, to give a 1:1 mixture of the (2*S*,4*S*) and (2*R*,4*S*) protected intermediates (Scheme 2.51).



Scheme 2.51: Unexpected epimerisation at 2-position under ^{18}F-fluorination conditions

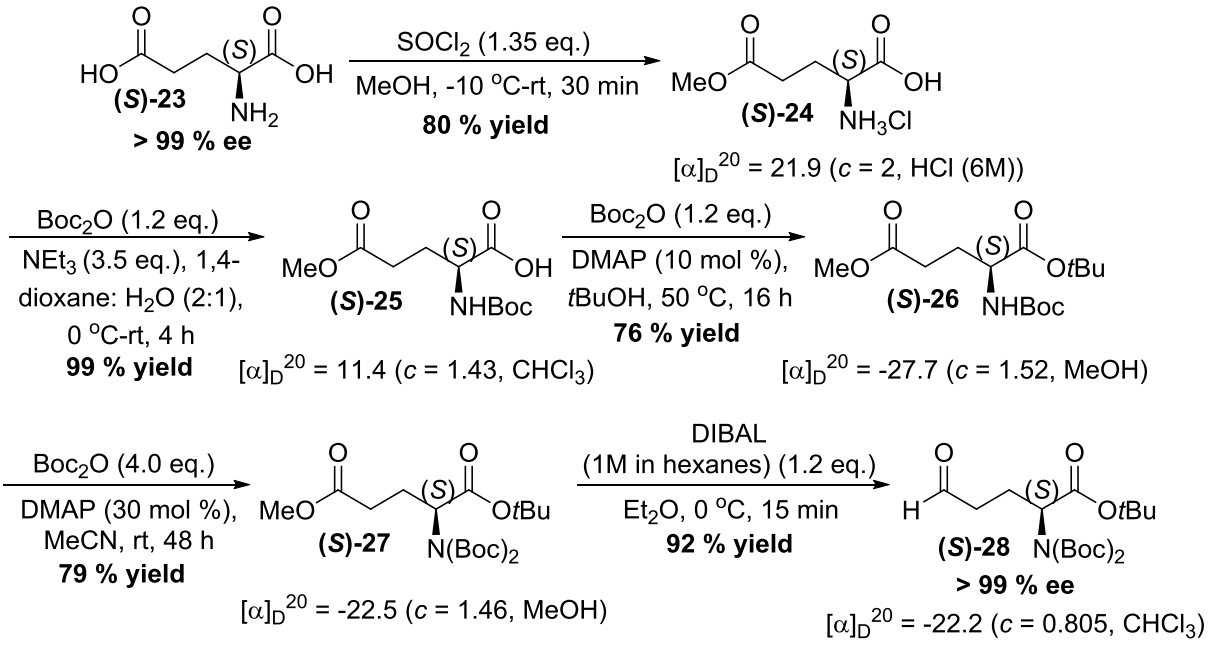
Separation and isolation of these intermediates was carried out using chiral prep-HPLC, prior to deprotection with TFA to give access to (2*S*,4*S*)-4-[^{18}F]fluoroglutamine.

Therefore, whilst methods exist for the synthesis of diastereomerically pure 4-[^{18}F]fluoroglutamic acid and 4-[^{18}F]fluoroglutamine, current limitations include lengthy synthesis of diastereomerically pure precursors and epimerisation at one or both of the stereocentres, especially for access to the *anti*-diastereomer. In order to circumvent this complex synthesis, and potentially limit defluorination *in vivo*, the radiosynthesis of glutamine and glutamic acid analogues bearing a 4-[^{18}F]fluoropropyl group have also been reported.[97]

2.2.1.6.2 Application of Organomediated Asymmetric Fluorination Reaction

We proposed an alternative radiosynthesis of the *anti*-diastereomers of 4-[^{18}F]fluoroglutamic acid and 4-[^{18}F]fluoroglutamine by applying our optimised conditions for asymmetric electrophilic ^{18}F-fluorination. We were encouraged by a report disclosed in 2013 by Brimble and co-workers describing the MacMillan imidazolidinone-catalysed asymmetric chlorination of a lysine analogue with excellent diastereoselectivity.[98] Advantageously, by employing our novel method, control of stereochemistry would be provided by the amine activator, therefore removing the challenges associated with

synthesis of a precursor which is diastereomerically pure. In fact, aldehyde **(*S*)-28** was synthesised from L-glutamic acid in just five facile steps (Scheme 2.52).[18] We chose to focus on the natural "L" isomer, as previous *in vitro* studies have described higher uptake of this species when compared to the "D" isomer.[5f]

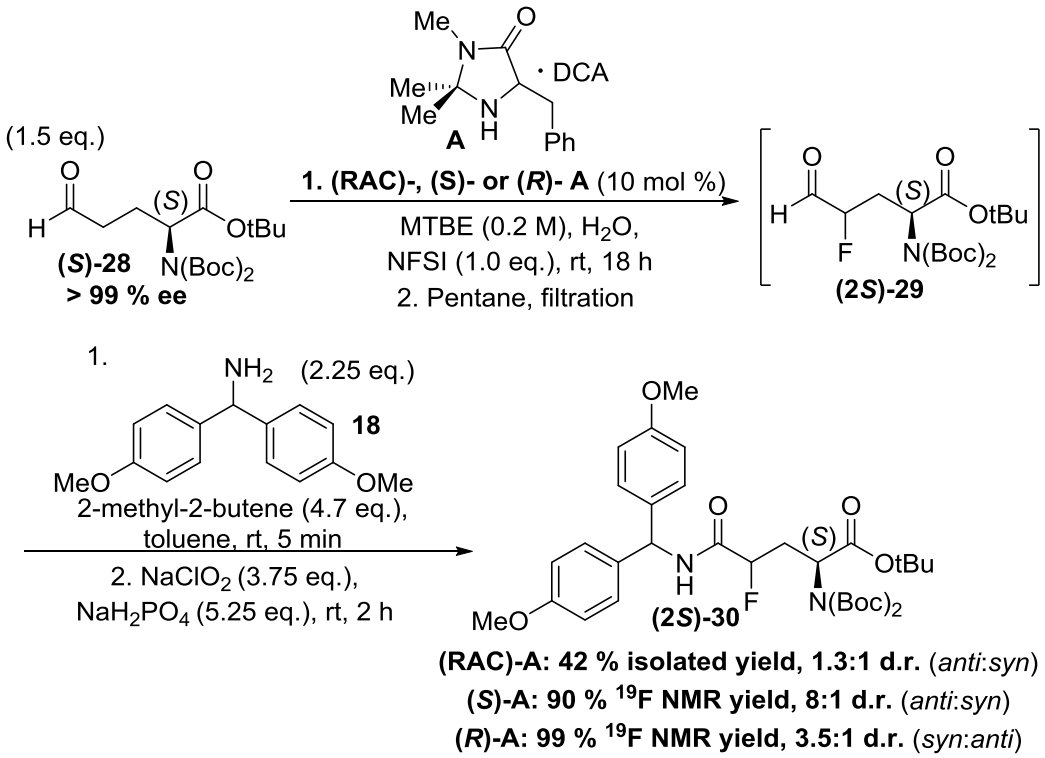


Scheme 2.52: Synthesis of aldehyde (*S*)-28

Firstly, selective esterification of the side-chain carboxylic acid was carried out employing thionyl chloride in methanol, to afford **(*S*)-24** as the hydrochloric acid salt with an 80 % yield. Three sequential steps then installed Boc and *tert*-butyl ester protecting groups on the α-amino and α-carboxylic acid groups respectively. Bis-Boc-protection was found to be necessary to prevent intramolecular cyclisation on aldehyde formation. Finally, DIBAL reduction proceeded quickly and selectively at 0 °C to afford aldehyde **(*S*)-28** with a 92 % yield after isolation by silica gel chromatography. Retention of stereochemistry throughout the sequence was ascertained by comparison of $[\alpha]_D$ values with those reported in the literature.

2.2.1.6.2.1 4-[^{18}F]Fluoroglutamine

Initially, derivatisation as an amide to afford access to 4-fluoroglutamine was investigated. When fluorination was performed under the previously optimised conditions employing 10 mol % of racemic imidazolidinone catalyst **A** for 2 hours, followed by oxidative amidation with amine **18**, just a trace of protected 4-fluoroglutamine **(2*S*)-30** was isolated. However, increasing the fluorination reaction time to 18 hours resulted in successful isolation of **30** in a 42 % yield (Scheme 2.53).



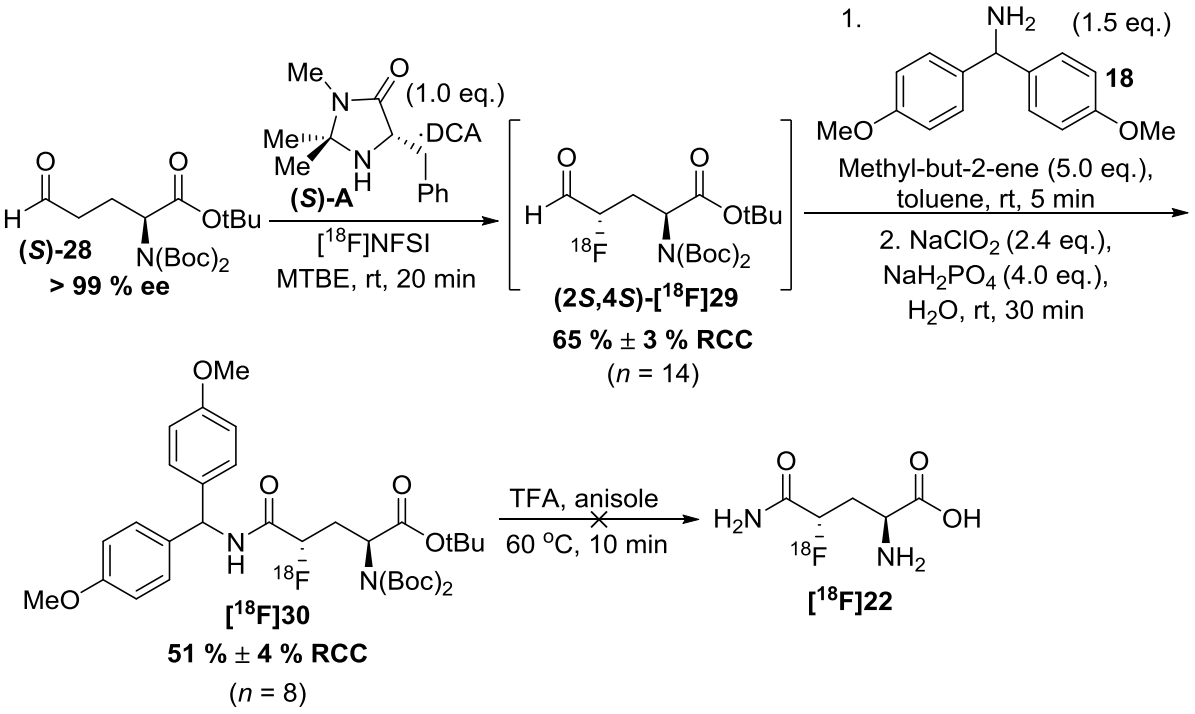
Scheme 2.53: Synthesis of protected 4-fluoroglutamine (2*S*)-30

Under these conditions with racemic catalyst, analysis of the crude reaction mixture by ^{19}F NMR indicated that amide **30** was afforded with a d.r. of 1.3:1 in favour of the *anti* (2*S*,4*S*) diastereomer (^{19}F NMR, *Anti*: δ = −189.7 ppm, $CDCl_3$; *Syn*: δ = −190.2 ppm, $CDCl_3$). This slight bias in diastereoselectivity can be attributed to the lower steric hindrance in formation of the *anti* diastereomer. When chiral non-racemic **(*S*)-A** was employed in the same reaction, pleasingly the d.r. increased to 8:1 in favour of the (2*S*,4*S*)-diastereomer. Crucially, this is the fluoroglutamine diastereomer that is difficult

to access via known methodology. However, use of the opposite enantiomer of catalyst displayed a mismatched effect with the substrate, with formation of the expected *syn* diastereomer achieved with just a 3.5:1 d.r., again attributed to the steric interaction of the large bis-Boc group with the incoming fluorine atom.

Global deprotection and amide cleavage of **30** could be carried out without loss of stereochemistry via treatment with neat TFA at 60 °C for 3 hours, in the presence of anisole as a scavenger. The corresponding compounds with the opposite stereochemistry at the 2-position were also required as HPLC references, in order to confirm that no epimerisation occurs at this position under conditions for radiofluorination, and could be similarly prepared starting from commercially available D-glutamic acid.

Synthesis of 4-[^{18}F]fluoroglutamine began by submission of aldehyde **(2*S*)-28** to the previously optimised conditions for fluorination with [^{18}F]NFSI and amine **(*S*)-A** (Scheme 2.54).

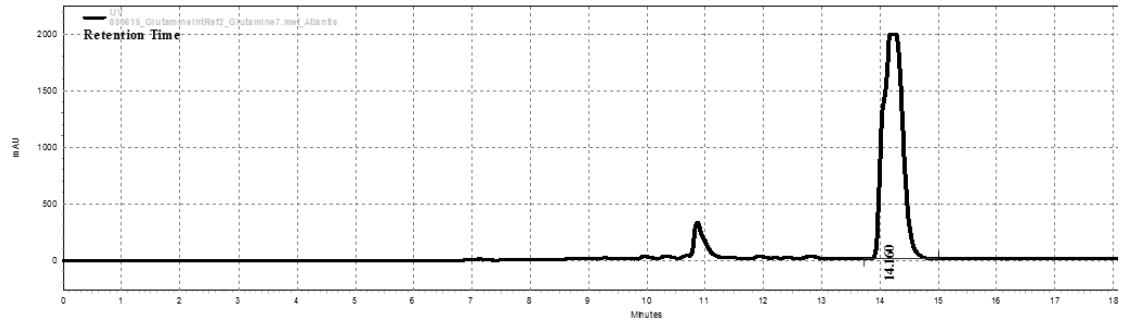


Scheme 2.54: Attempted synthesis of 4-[^{18}F]fluoroglutamine

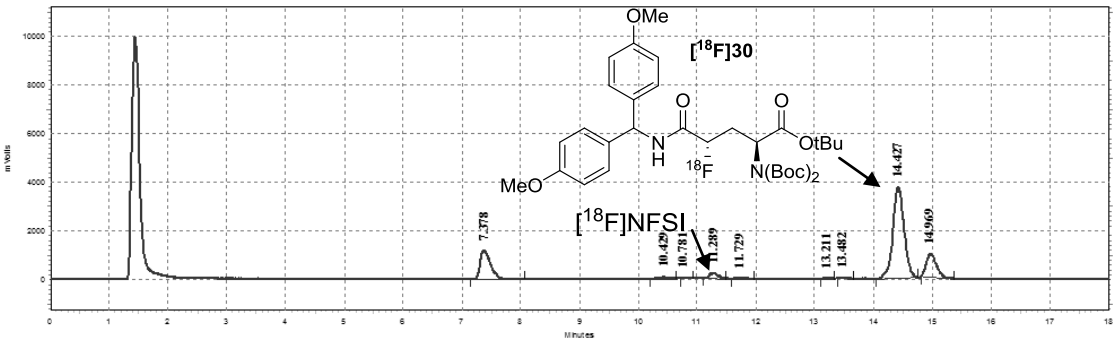
Under these conditions, pleasingly aldehyde **[^{18}F]29** was afforded with an excellent RCC of 65 % ± 3 %, which was shown to be very reproducible (n = 14). Oxidative amidation was carried out as previously, with imine formation brought about by addition of bis(4-methoxyphenyl)methanamine, prior to addition of sodium chlorite as oxidant. After stirring for 30 minutes at room temperature, analysis by analytical radio-HPLC indicated a 51 % ± 4 % RCC of amide **[^{18}F]30** (n = 8). However, following removal of solvent, direct deprotection of this species in TFA was somewhat unsuccessful. Although full consumption of amide **[^{18}F]30** was observed, analytical radio-HPLC indicated the formation of multiple ^{18}F-labelled compounds. The peak corresponding to the retention time of the 4-fluoroglutamine reference was collected for analysis by chiral radio-HPLC, but this again displayed multiple peaks, perhaps indicating an overlapping species. Analysis of these peaks by LRMS on a decayed sample was unsuccessful at identification of products.

It was envisaged that isolation of amide **[^{18}F]30** prior to deprotection could facilitate this process. Initially, this was attempted via Sep-Pak purification, but this was limited by the poor solubility of this compound in the loading solution, resulting in most of the radioactivity remaining on the surface of the loading syringe and only a trace amount of isolated product. However, isolation by prep-HPLC was more successful. The entire reaction mixture was diluted with an acetonitrile/water solution and transferred to a prep-HPLC column via a semi-automated device. The peak corresponding to the retention time of the reference compound was collected, with an 8 % isolated yield of amide **[^{18}F]30** relative to injection. The identity of this species was confirmed by analytical HPLC (Figure 2.5).

A. UV of reference compound



B. Radio-HPLC of crude reaction mixture (55 min)



C. Radio-HPLC after isolation by prep-HPLC

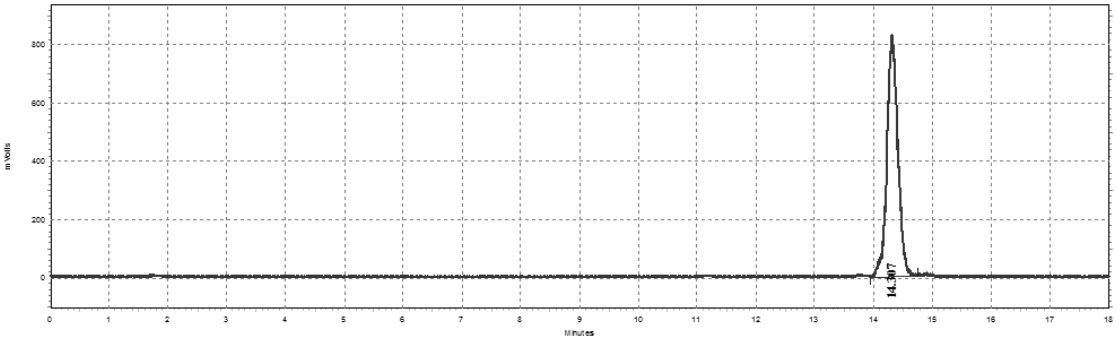
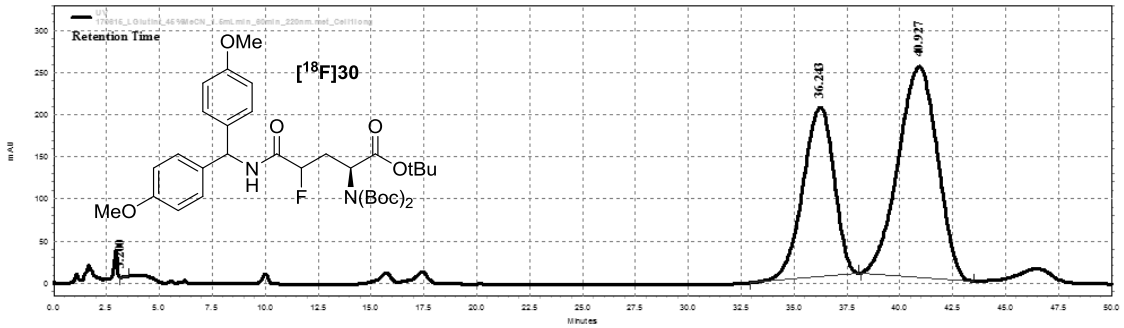


Figure 2.5: Analytical HPLC traces of amide [^{18}F]30

Waters Atlantis dc18 (5 µm, 3.9x150 mm), 1 mL/min, HPLC Conditions D, Sample: 1 mg/mL in MeCN, UV = 210 nm, t_{prod} = 14.2 min.

However, despite the success of this isolation procedure, analysis of protected amide **[^{18}F]30** by chiral radio-HPLC resulted in a very broad peak from which the d.r. of this intermediate could not be accurately determined (Figure 2.6).

A. UV of racemic reference



B. Radio-HPLC of isolated product

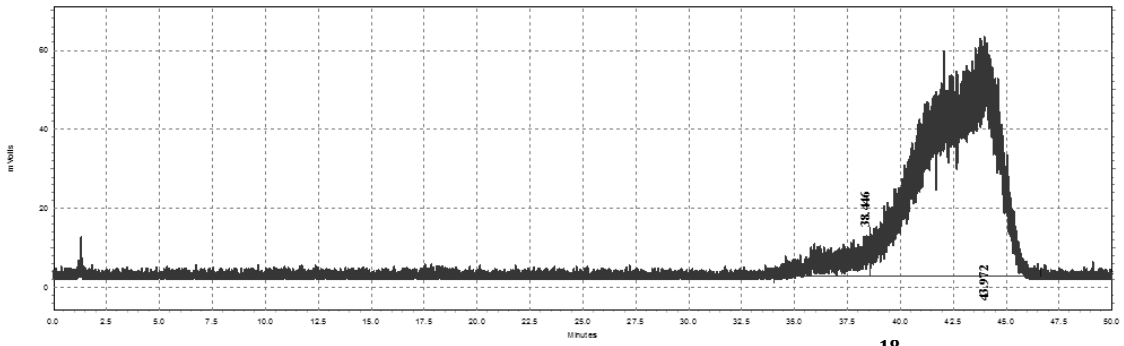
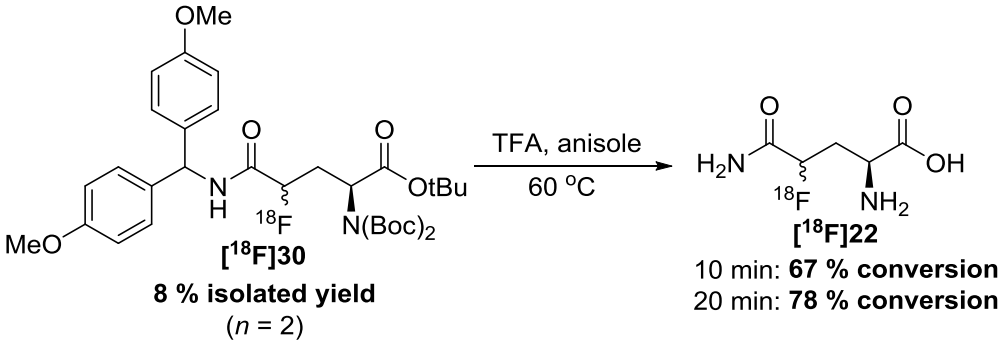


Figure 2.6: Chiral radio-HPLC of isolated amide [^{18}F]30

Phenomenex Lux Cellulose 1 (3 µm, 4.6x150 mm), 0.3 mL/min, 45 % MeCN isocratic, UV = 220 nm, t_1 = 36.2 min, t_2 = 40.9 min.

Following removal of the HPLC eluent at 60 °C under a flow of helium, deprotection of this isolated intermediate was performed in TFA at 60 °C. After heating for 10 minutes, analysis by radio-HPLC indicated complete consumption of amide **[^{18}F]30**, to afford a peak corresponding to deprotected 4-[^{18}F]fluoroglutamine **[^{18}F]22** with 67 % conversion, as well as one other ^{18}F-labelled species. A longer deprotection time of 20 minutes increased the conversion to 4-[^{18}F]fluoroglutamine to 78 %, suggesting that the side-product was the result of incomplete deprotection.

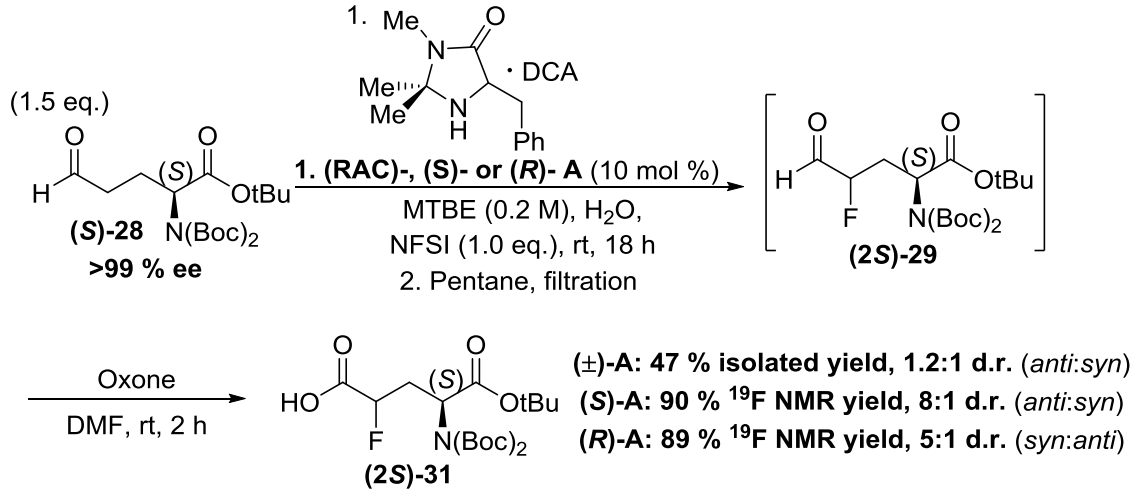


Scheme 2.55: TFA Deprotection of isolated amide [^{18}F]30

Unfortunately, although the deprotection of the isolated amide was notably cleaner when compared to the one-pot reaction, chiral HPLC of the peak corresponding to 4-[^{18}F]fluoroglutamine was equally ambiguous, and as such the d.r. of this species, and thus the utility of this asymmetric fluorination reaction, is yet to be determined.

2.2.1.6.2.2 4-[^{18}F]Fluoroglutamic acid

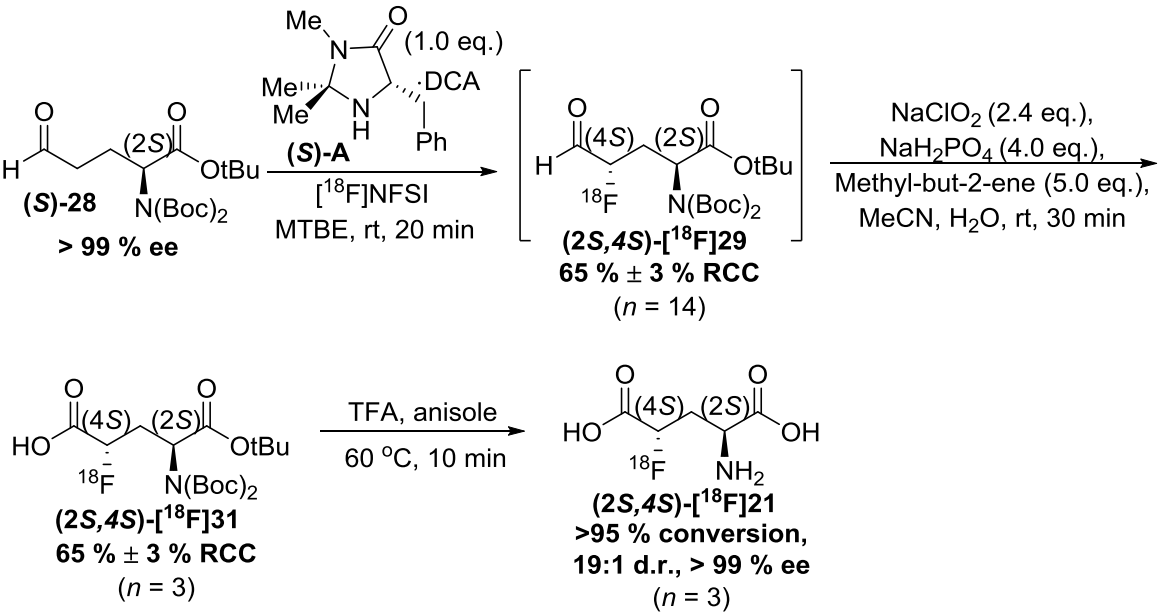
Finally, this methodology was then applied to the synthesis of 4-[^{18}F]fluoroglutamic acid. Once again employing aldehyde **(*S*)-28**, protected 4-fluoroglutamic acid **31** could be synthesised under the previously optimised conditions for fluorination, with reaction time increased to 18 hours, followed by oxidation with Oxone (Scheme 2.56).



Scheme 2.56: Synthesis of protected 4-fluoroglutamic acid (2*S*)-31

Under these conditions, protected 4-fluoroglutamic acid **(2*S*)-31** was afforded in a 47 % isolated yield, with a 1.2:1 d.r., determined by ^{19}F NMR of the crude reaction mixture, again demonstrating slight preferential formation of the *anti* diastereomer (^{19}F NMR, *Anti*: δ = −192.1 ppm, $CDCl_3$; *Syn*: δ = −193.7 ppm, $CDCl_3$). As demonstrated previously with the oxidative amidation derivatisation, this d.r. could be increased to 8:1 by employing **(*S*)-A** as catalyst, or to 1:5 by employing **(*R*)-A** as catalyst. Global deprotection could be performed in a mixture of TFA/anisole without loss of stereochemistry, to afford 4-fluoroglutamic acid which matched a commercial sample.

Formation of aldehyde **(2*S*,4*S*)-[^{18}F]29** was carried out as previously employing [^{18}F]NFSI and a stoichiometric amount of chiral non-racemic amine **(*S*)-A**. In this case, oxidation was then carried out employing the Pinnick-Lindgren conditions employed previously, with acetonitrile as the solvent. Pleasingly, this resulted in the formation of protected 4-fluoroglutamic acid **(2*S*,4*S*)-[^{18}F]31** with 65 % ± 3 % RCC (*n* = 3) (Scheme 2.57).

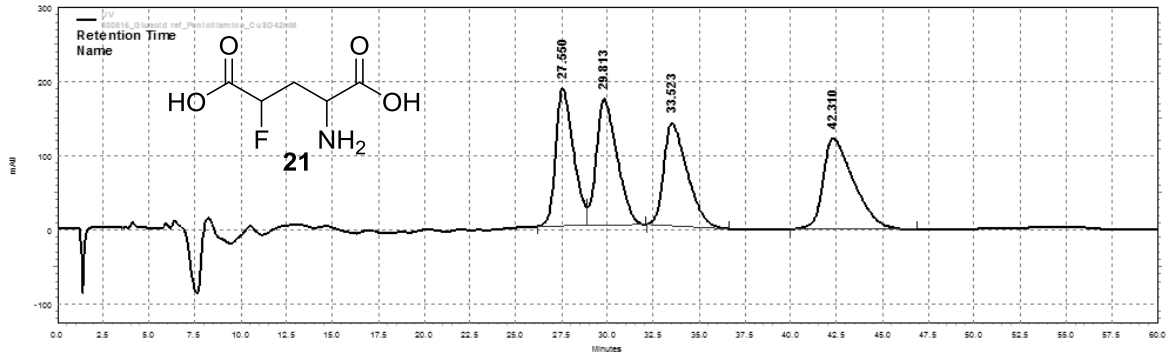


Scheme 2.57: Synthesis of 4-[^{18}F]fluoroglutamic acid

We were very pleased to observe that in this case, deprotection of the crude reaction mixture, following removal of solvent, proceeded with full conversion to afford (2*S*,4*S*)-4-[^{18}F]fluoroglutamic acid without any significant side product formation. The peak corresponding to product was collected for analysis by chiral HPLC. The use of a Phenomenex Penicilamine reverse phase column, in the presence of Cu^{2+} ions, provided separation of all 4 diastereomers of a commercial sample of 4-fluoroglutamic acid, with identity of the diastereomers determined by comparison with literature precedent (see Figure 2.7 or Chapter 4.4 for HPLC spectra). The d.r. of **(2*S*,4*S*)-[^{18}F]21** was determined as 19:1, demonstrating excellent control of stereochemistry by the amine catalyst (Figure

2.7). Unlike previous literature methods, the absence of other diastereomers indicated that no epimerisation was observed at the 2 position in this case and therefore an ee of >99 % was maintained throughout the sequence. This novel methodology therefore provides the first route to access (2*S*,4*S*)-4-[^{18}F]fluoroglutamic acid with a high d.r. and ee.

A. UV of racemic reference (all 4 diastereomers)



B. Radio-HPLC of isolated product

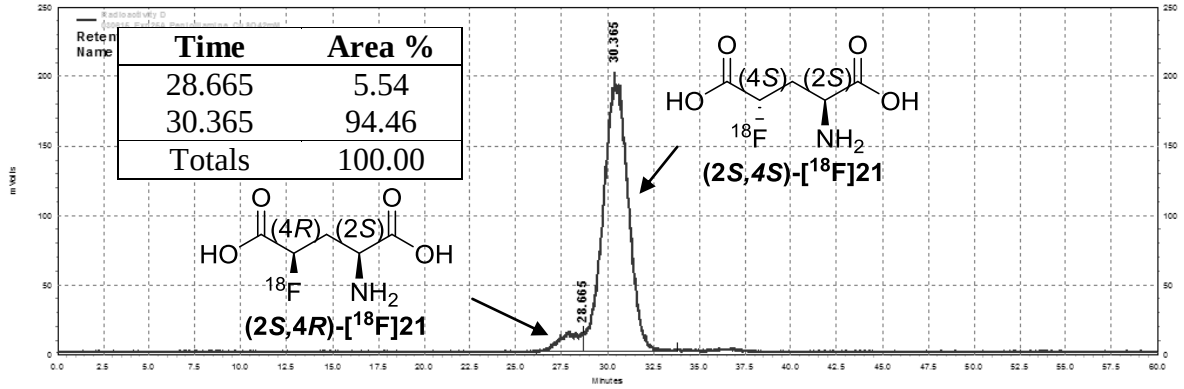


Figure 2.7: Chiral HPLC trace of (2*S*,4*S*)-4-[^{18}F]fluoroglutamic acid

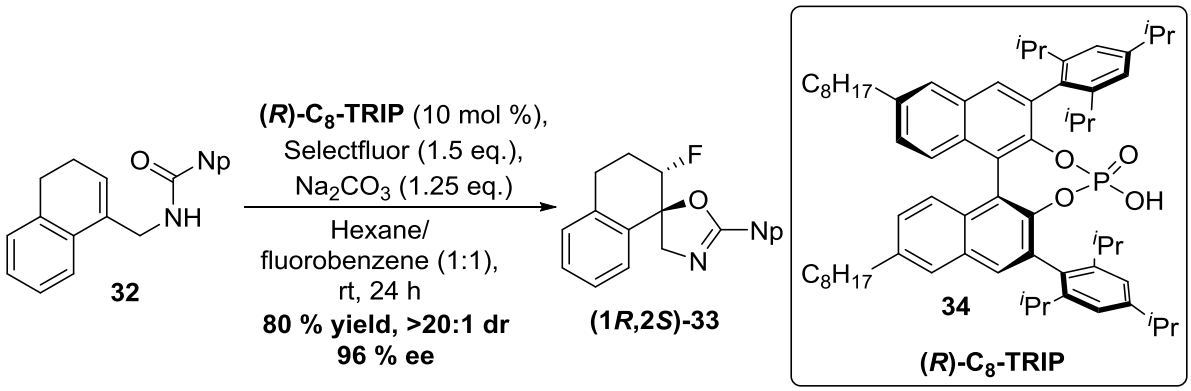
Phenomenex Chirex Penicillamine (5µ, 4.6x150mm), 1.0 mL/min, 100 % $CuSO_4$ (2 mM) isocratic, 200 µL injection, UV = 210 nm, t_1 = 27.6 min, t_2 = 29.8 min, t_3 = 33.5 min, t_4 = 42.3 min.

As anticipated from cold results, use of the alternative enantiomer of this catalyst, (*R*)-A, resulted in a mis-matched effect with this substrate, likely due to steric hindrance of the large bis-Boc groups. In this case, (2*S*,4*R*)-4-[^{18}F]fluoroglutamic acid was formed with a 47 % ± 5 % RCC (*n* = 1) and a d.r. of 7:3.

2.2.2 Phase Transfer Reagents for Asymmetric ^{18}F-Fluorination

As discussed in Section 2.1.3.3, the advent of chiral anion-mediated phase transfer-catalysed fluorination has had a considerable impact on the field of asymmetric

fluorination, and seen application to a wide range of processes.[44] Development of an ^{18}F-labelled variant of this methodology could therefore be of significant value. In order to validate this methodology with [^{18}F]F_2, a model reaction was selected from the literature for preliminary studies (Scheme 2.58).

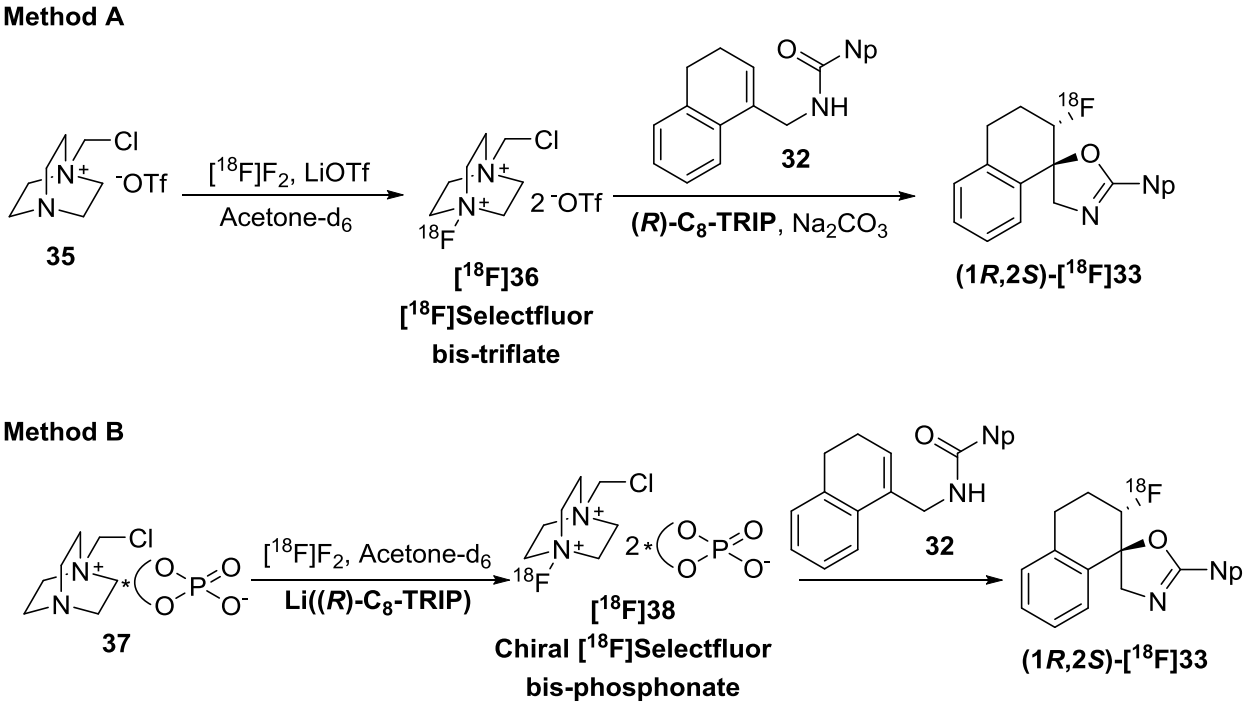


Scheme 2.58: Literature model reaction selected for preliminary studies with ^{18}F[45]

This fluorocyclisation reaction by Toste affords access to spiro-fused oxazoline product **(1*R*,2*S*)-33** with excellent yield, enantio- and diastereo-selectivity.[45] Advantageously for implementation with [^{18}F]Selectfluor bis-triflate, this model reaction takes place at room temperature, avoiding the low temperature reaction conditions often associated with organocatalysis. In hot mode, this reaction would require synthesis of [^{18}F]Selectfluor bis-triflate according to the literature procedure, prior to addition of the substrate, phosphate catalyst and base (Scheme 2.59, method A). However, the effect of the bis-triflate counter ions of [^{18}F]Selectfluor, rather than the tetrafluoroborate anions of the commercial cold reagent, should be considered.

Additionally, the short half life of ^{18}F requires that the long reaction should be reduced significantly. Notably, the change in stoichiometry for ^{18}F-radiosynthesis removes the requirement for a catalytic cycle, not only likely shortening reaction time, but also making feasible a procedure in which the [^{18}F]Selectfluor-chiral phosphate complex is isolated directly from [^{18}F]F_2 (Scheme 2.59, Method B). Isolation of this chiral non-

racemic fluorinating agent could also potentially allow the use of more polar reaction solvents whilst removing the possibility of a racemic background reaction.

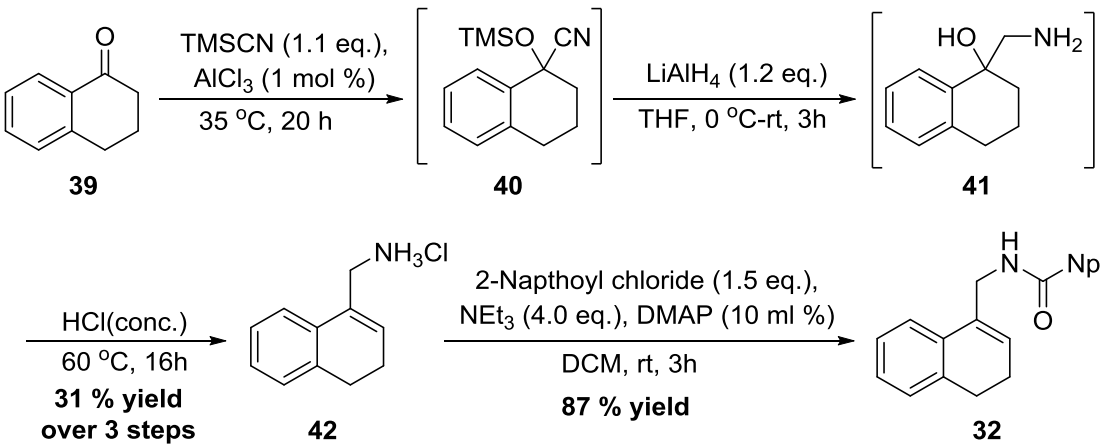


Scheme 2.59: Proposed radiosynthesis methods employing A. *in situ* formation or B. isolatation of chiral [^{18}F]Selectfluor bis-phosphate

The application of both the *in situ* methodology and isolation of the chiral fluorinating agent were therefore both investigated with ^{18}F.

2.2.2.1 Substrate and Reagent Synthesis

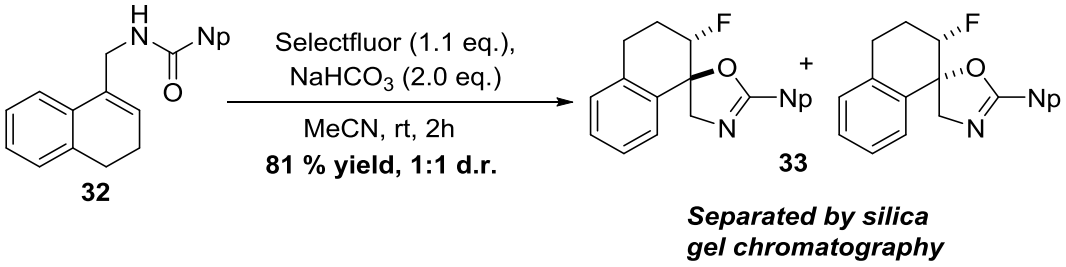
Firstly, the model dihydronaphthalene-derived substrate under investigation was prepared from α-tetralone according to the literature synthesis (Scheme 2.60).[45]



Scheme 2.60: Synthesis of dihydronaphthalene-based fluorocyclisation substrate

Trimethylsilyl cyanide was employed in the first step to form intermediate cyano-hydrin **40**, which was immediately reduced to the corresponding amine **41** using lithium aluminium hydride. Treatment with concentrated hydrochloric acid brought about dehydration to amine **42**, which was isolated as the hydrochloric acid salt. Acetylation with 2-naphthyl chloride in the presence of triethylamine and catalytic DMAP then afforded the required substrate **32**.

The substrate was then subjected to the reported conditions for racemic fluorocyclisation in order to synthesise the required HPLC reference (Scheme 2.61).[99]

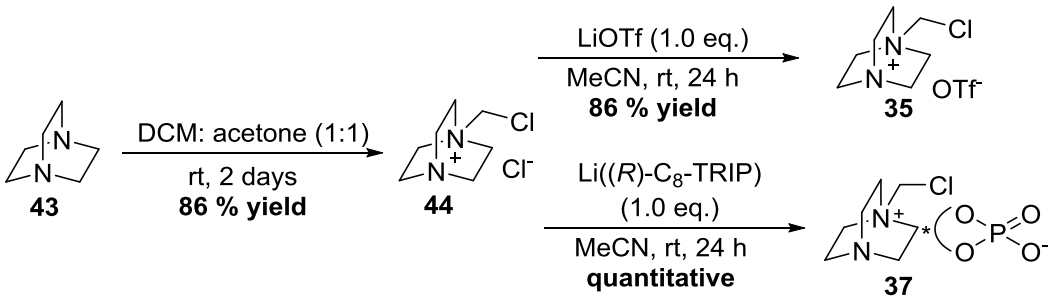


Scheme 2.61: Racemic reference synthesis

Interestingly, as had been reported previously,[99] this reaction in acetonitrile affords the fluorocyclised product as a one to one mixture of the *syn* and *anti* diastereomers, which can be separated by column chromatography. In contrast, when a chiral non-racemic phosphoric acid catalyst is employed, only the *anti* isomer is observed. This indicates that

not only is the catalyst controlling enantioselectivity, but also diastereoselectivity of this cyclisation reaction.

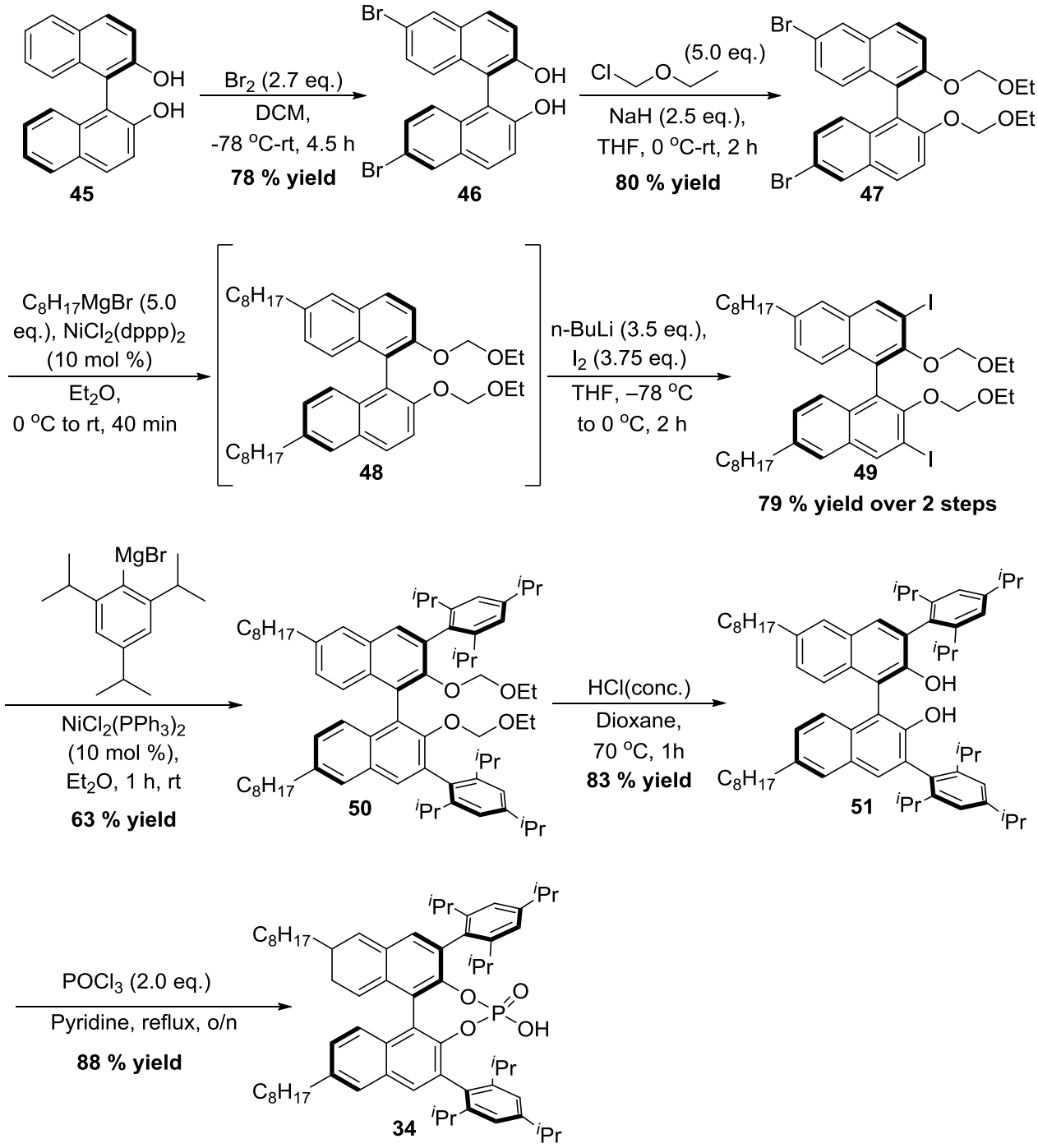
Next, the dabconium precursor to Selectfluor was synthesised according to the reported procedure by the chloromethylation of DABCO with DCM (Scheme 2.62).[100] The chloride salt **44** precipitated out of solution on formation and could be collected by filtration.



Scheme 2.62: Synthesis of Selectfluor precursors

Anion transfer was then performed by stirring with one equivalent of lithium triflate in acetonitrile. The lithium chloride formed in the reaction could be removed by filtration. The residue afforded after removal of solvent was washed with minimum ethyl acetate to remove remaining starting material and then dried under vacuum to afford [^{18}F]Selectfluor bis-triflate precursor **35**.

Anion transfer could similarly be performed with a chiral non-racemic lithium phosphate salt. The phosphoric acid catalyst employed, **(*R*)-C$_8$-TRIP**, is commercially available from Sigma Aldrich, but at the cost of over £3000 per mmol. Alternatively, it was synthesised in 7 steps from (*R*)-BINOL (~20p per mmol, Fluorochem) according to the literature procedure (Scheme 2.63).[45]



Scheme 2.63: Synthesis of (*R*)-C_8-TRIP

The bromination of non-protected BINOL took place selectively at the 6- and 6'-positions when the reaction was gradually warmed from −78 °C to room temperature over 4.5 hours, affording **46** with a yield of 78 %. A methylethyl ether protecting group was installed prior to a Kumada coupling to install the long alkyl chains. Directed *ortho*-

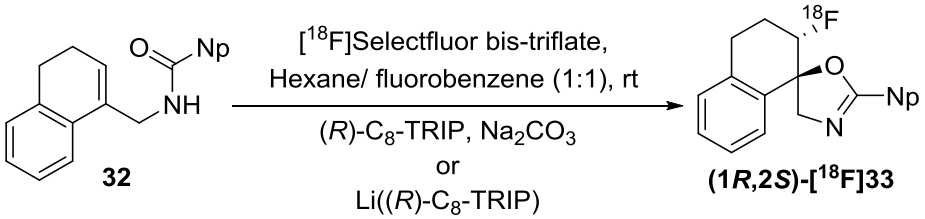
lithiation then facilitated iodination at the 2- and 2'- positions, at which point purification of compound **49** by column chromatography was necessary. A second Kumada coupling was employed to install the bulky tri-*iso*propyl phenyl groups with a yield of 63 %. Deprotection was achieved by heating in concentrated hydrochloric acid, followed by reaction with phosphorous oxychloride to afford **(*R*)-C_8-TRIP 34** in an overall yield of 23 % over 7 steps. Following purification by column chromatography, catalyst **34** was dissolved in ethyl acetate and washed with hydrochloric acid to ensure that all of the catalyst was present as the protonated acid, since contamination with metal salts has been shown to be detrimental to catalyst activity.[101] The corresponding lithium salt could be also formed by deprotonation with lithium hydroxide.

2.2.2.2 Investigations with ^{18}F

In the first instance, the literature synthesis of non-chiral [^{18}F]Selectfluor bis-triflate was repeated by bubbling [^{18}F]F_2 through a solution of the precursor in acetone and, since HPLC identification of Selectfluor is challenging due to its co-elution with the [^{18}F]LiF by-product, it was employed in the known fluoro-destannylation reaction of protected [^{18}F]FDOPA.[73a] The radiochemical conversion obtained was comparable to the reported value and therefore the correct conditions for the labelling of [^{18}F]Selectfluor bis-triflate were validated.

Next, an aliquot of [^{18}F]Selectfluor bis-triflate was transferred to a Wheaton v-vial containing **(*R*)-C_8-TRIP** and sodium carbonate and the solvent was removed under a flow of helium gas, prior to addition of the substrate as a solution in hexane/ fluorobenzene (1:1). The reaction was stirred at room temperature and aliquots for HPLC were taken after 20 and 60 minutes (Table 2.12, entry 1). RCC was determined by integration of all peaks in the HPLC trace, including [^{18}F]fluoride, with the consequence of a maximum RCC of 50 %.

Table 2.12: Investigations of asymmetric phase transfer catalysis with [^{18}F]Selectfluor bis-triflate



Entry	Catalyst (eq.)	Time (min)	RCC (%)[a]	ee (%)[b]
1[c]	(*R*)-C_8-TRIP (1.0)	20	**Trace**	**-**
		60	**Trace**	**-**
2[d]	Li((*R*)-C_8-TRIP) (1.0)	20	**3**	**74**
		60	**4**	**-**
3[e]	Li((*R*)-C_8-TRIP) (1.0)	20	**5**	**24**
		60	**17**	**10**
4[e]	Li((*R*)-C_8-TRIP) (4.0)	20	**Trace**	**-**
		60	**Trace**	**8**

[a] RCC determined by peak area according to radio-HPLC. [b] ee determined by radio-HPLC of isolated product. [c] [^{18}F]SF in acetone-d_6 added to rxn vial containing catalyst and base. Substrate added as a solution in hexane/ fluorobenzene following removal of solvent. [d] [^{18}F]SF in acetone-d_6 added to empty rxn vial and solvent removed. Substrate added as a solution in hexane/ fluorobenzene followed by addition of catalyst as a solid. [d] [^{18}F]SF in acetone-d_6 added to empty rxn vial and solvent removed. Catalyst added as a solution in hexane/ fluorobenzene followed by addition of substrate as a solution in hexane/ fluorobenzene.

Whilst a trace amount of product could be detected by radio-HPLC under these conditions, the radiochemical conversion was very low even after stirring for one hour. It was also observed that evaporation of the acetone solvent in the presence of catalyst and base had taken significantly longer than expected.

Addition of the [^{18}F]Selectfluor bis-triflate to an empty reaction vial resulted in the much quicker evaporation of solvent. The substrate was again added as a solution in hexane/ fluorobenzene (1:1) prior to addition of catalyst as a pre-formed lithium phosphate salt. In this case, the RCC by radio-HPLC was just 3 % after stirring for 20 minutes, with no significant increase after 60 minutes (Entry 2). Other unidentified side-products were also observed in trace amounts by radio-HPLC. The peak corresponding to product at 14.4 minutes was collected and the ee determined as 74 % by chiral radio-HPLC analysis. This was slightly lower than the ee which would be expected from the literature reaction, indicating perhaps that the racemic background reaction had not been eliminated, likely

due to the different solubility profile of Selectfluor bis-triflate versus the tetrafluoroborate analogue.

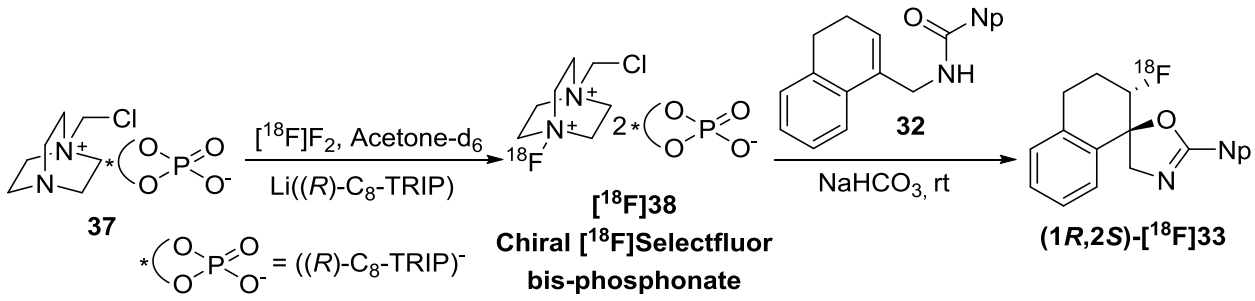
Change in the order of addition of reagents saw some success, with RCC increased to 17 % after 60 minutes (Entry 3). However, this was accompanied by a deterioration of ee throughout the reaction, indicating that in this case ^{18}F-transfer was occurring mainly from non-chiral [^{18}F]Selectfluor bis-triflate.

The suggested mechanism of the reaction requires initial anion transfer to afford a chiral non-racemic [^{18}F]Selectfluor bis-phosphate complex, prior to fluorine transfer. This lipophilic anion both solubilises the reagent in the non-polar solvent and imparts enantiocontrol on the fluorination step. The poor enantiomeric excesses achieved thus far suggested that this anion transfer was not occurring successfully. This was further evidenced by the low amount of radioactivity dissolved in the reaction mixture. In an attempt to promote this anion transfer, the next reaction was performed employing a large excess of the enantiopure lithium phosphate (Entry 4). However, this resulted in a significantly reduced radiochemical conversion and enantiomeric excess. It therefore appeared that this *in situ* method of formation of the chiral fluorinating species was challenging, likely due to problems with re-solubilising the reagent after solvent evaporation. Further studies of this reaction would perhaps require investigation of change in solvent for synthesis of [^{18}F]Selectfluor bis-triflate.

We therefore next turned our attention to the alternative approach proposed, involving isolation of the chiral non-racemic ^{18}F-fluorinating reagent by formation of [^{18}F]Selectfluor as the bis-phosphate directly from [^{18}F]F_2 in the presence of **Li((*R*)-C_8-TRIP)** (Table 2.13). Isolation of this chiral non-racemic reagent has not been previously reported, due to the advantages of a catalytic approach for cold chemistry. However, for

application to radiochemistry, isolation of the reagent may actually be beneficial in terms of solvent choice and simplification of procedure.

Table 2.13: Investigations of isolation of chiral [^{18}F]Selectfluor bis-phosphate

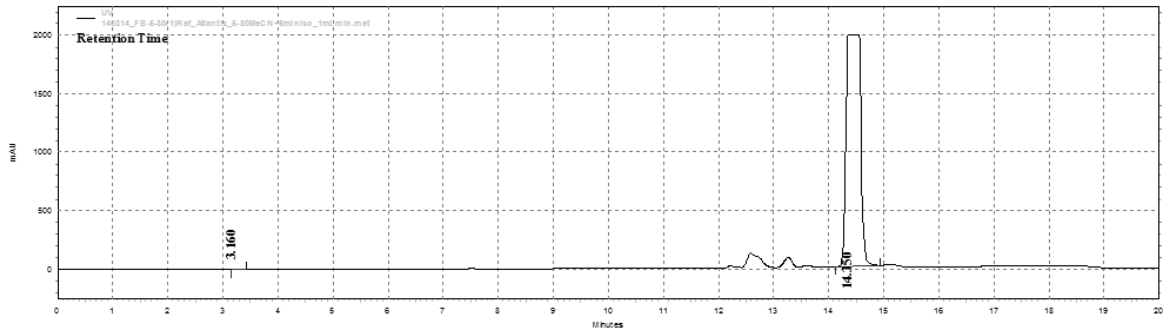


Entry	Solvent	Time (min)	RCC (%)[a]	ee (%)[b]
1 [c]	Acetone-d_6	30	**5**	**92**
		60	**6**	**92**
2 [d]	MeCN	30	**2**	**68**

[a] RCC determined by peak area according to radio-HPLC. [b] ee determined by radio-HPLC of isolated product. [c] [^{18}F]SF bis-phosphate in acetone-d_6 added to rxn vial containing substrate and base. [d] [^{18}F]SF bis-phosphate in acetone-d_6 added to rxn vial containing substrate and base. Solvent removed and MeCN added to residue.

In the first instance, an aliquot of chiral [^{18}F]Selectfluor bis-phosphate in acetone was added directly to a Wheaton v-vial containing dihydronaphthalene substrate **32** and sodium bicarbonate (Table 2.13, entry 1). The crude reaction mixture was analysed by HPLC after stirring at room temperature for 30 minutes (Figure 2.8).

A. UV of reference compound



B. Radio-HPLC of crude reaction mixture

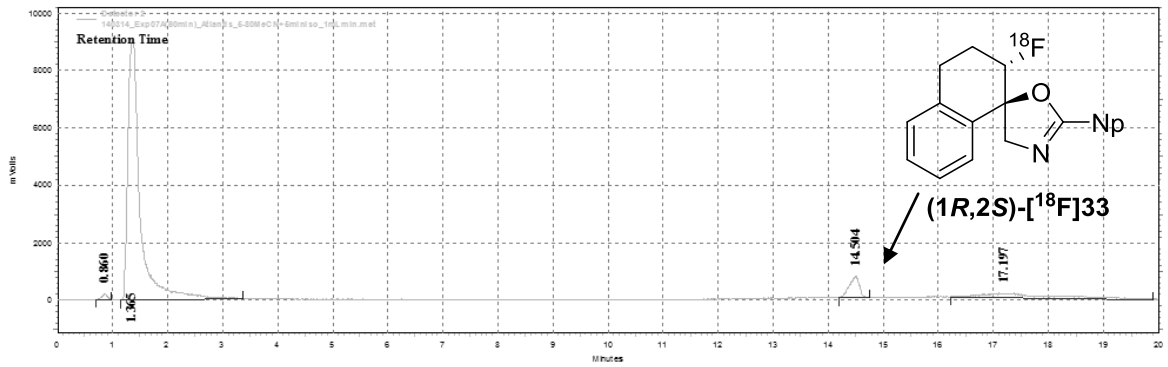
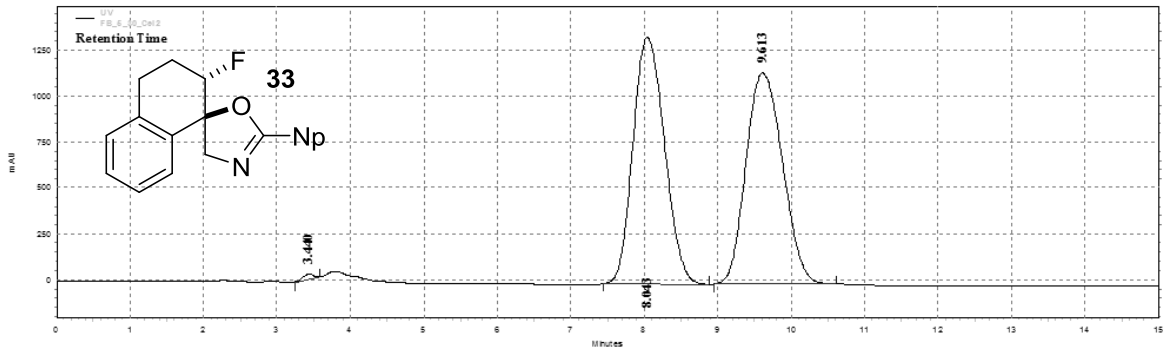


Figure 2.8: Analytical HPLC traces corresponding to Table 2.13, Entry 1

Water Atlantis dC18 (5µm, 3.9x150mm), 1.0 mL/min, UV = 240 nm, HPLC Conditions E, Sample: 1 mg/mL in MeCN, t_{prod} = 14.4 min.

Integration of the peak corresponding to product gave a RCC of 5 %, with very little increase after 60 minutes, though with very little side-product formation observed. In both cases the ee of **(1*R*,2*S*)-[^{18}F]33** was determined as 92 %, consistent with the literature value for the cold reaction and significantly higher than that achieved by attempts of *in situ* formation of the ^{18}F-labelled reagent, with no deterioration of enantioselectivity throughout the reaction (Figure 2.9). Whilst the radiochemical conversion was low, synthesis of the enantioenriched ^{18}F-labelled product provided noteworthy validation both for the isolation of this chiral fluorinating agent for the first time and for its application in fluorocyclisation.

A. UV of racemic reference



B. Radio-HPLC of isolate product

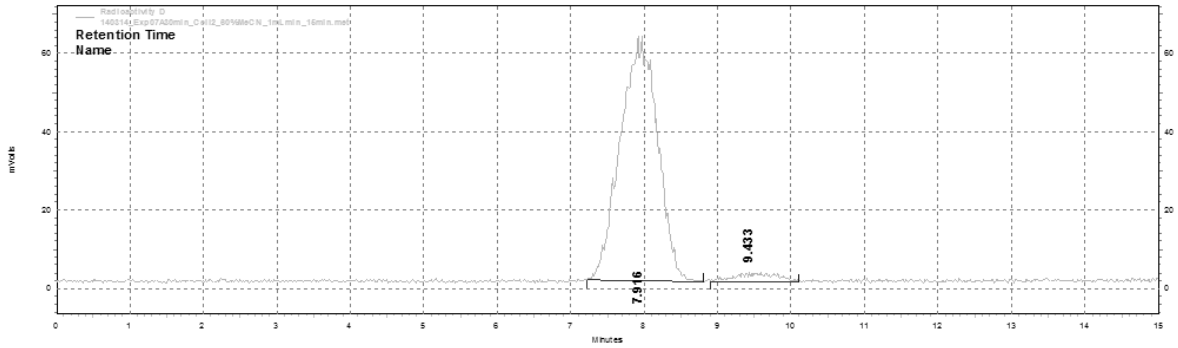


Figure 2.9: Chiral HPLC traces corresponding to Table 2.13, entry 1

Phenomenex Lux Cellulose 2 (5 µm, 4.6x100mm), 1.0 mL/min, UV = 240 nm, 60 % MeCN isocratic, t_1 = 8.0 min, t_2 = 9.6 min.

Acetonitrile is a solvent commonly utilised for reactions employing Selectfluor due to its favourable solubility profile. However, in this case, both the RCC and ee were lower when acetonitrile was employed as solvent (Entry 2).

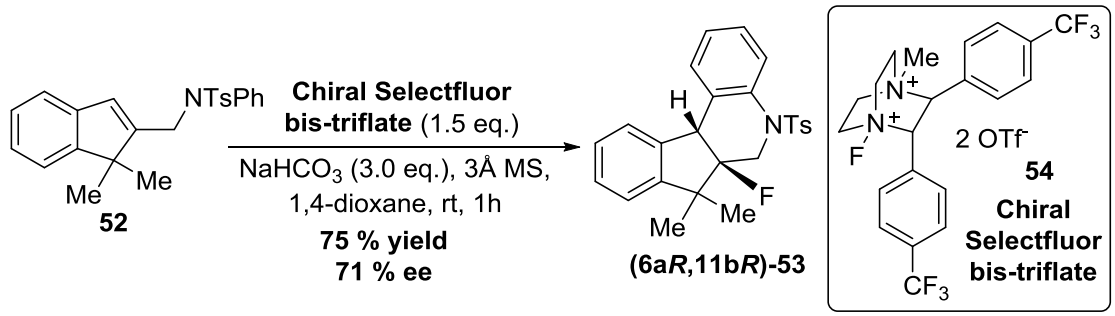
In summary, the application of BINOL-derived phase transfer catalysis to asymmetric fluorocyclisation with ^{18}F has been investigated both by *in situ* formation from [^{18}F]Selectfluor bis-triflate and by direct formation of the chiral fluorinating agent from [^{18}F]F_2. Initial screening of the *in situ* reaction highlighted reagent solubility related problems, including low enantiomeric excesses due to the unexpected racemic background reaction of [^{18}F]Selectfluor bis-triflate.

We have established that chiral [^{18}F]Selectfluor bis-phosphate can be synthesised directly under the same conditions as [^{18}F]Selectfluor bis-triflate, lending further weight to the phase transfer mechanism proposed by Toste. This allowed solubility problems to be

circumvented by use of a more polar solvent, leading to isolation of the ^{18}F-labelled fluorocyclised product with an excellent enantiomeric excess. Given the wide reactivity mode of this type of methodology in cold mode, this could have significant impact on the field of asymmetric ^{18}F-fluorination. However, currently RCCs of this reaction are very low, and extensive optimisation would be required to develop this method further.

2.2.3 Fluorocyclisation with Chiral [^{18}F]Selectfluor bis-triflate

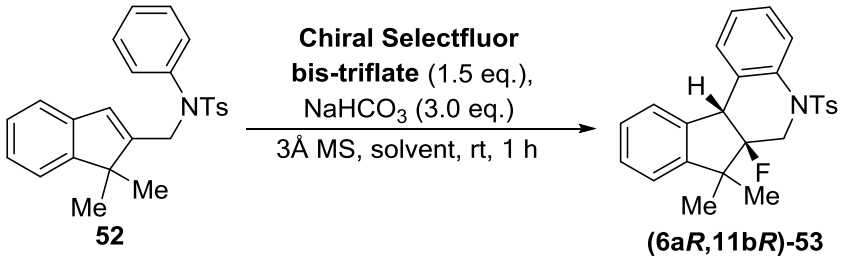
Selectfluor is a commonly employed fluorinating reagent and the utility of [^{18}F]Selectfluor bis-triflate has been previously demonstrated.[73] The synthesis of an ^{18}F-labelled variant of chiral non-racemic Selectfluor directly from [^{18}F]F_2 could therefore widen the field of asymmetric ^{18}F-fluorination. In the first instance, we aimed to synthesise chiral [^{18}F]Selectfluor bis-triflate and study its application on a model fluorocyclisation reaction from the literature (Scheme 2.64).[67]



Scheme 2.64: Model fluorocyclisation reaction by Gouverneur and co-workers

Whilst employing 1,4-dioxane as the reaction solvent provided the best compromise between yield and enantioselectivity, a solvent screen on this model substrate demonstrated that a similar degree of enantioselectivity was also possible in a range of other solvents (Table 2.14).

Table 2.14: Solvent screening reactions of carbo-fluorocyclisation with chiral Selectfluor bis-triflate by Gouverneur and co-workers[67]

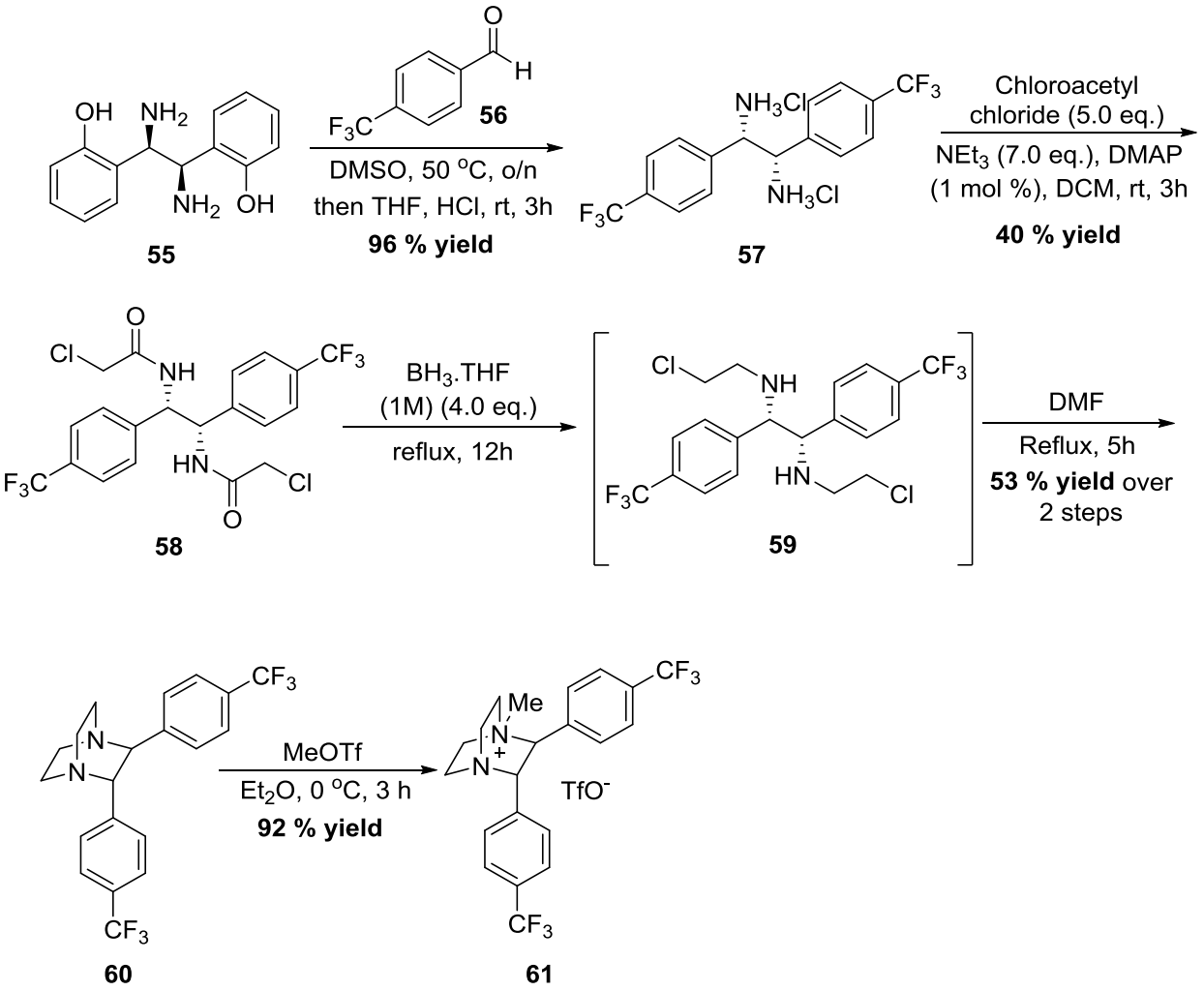


Entry	Solvent	Temp. (°C)	^{1}H NMR Yield (%)[a]	ee (%)
1	DCE	rt	59	74
2	DCM	rt	14	77
3	$MeNO_2$	rt	>95	60
4	THF	rt	22	81
5	MeCN	rt	37	52
6	Acetone	rt	14	72
7	1,4-Dioxane	rt	88	74
8	1,4-Dioxane	10	47	74

[a] ^{1}H NMR yield determined by integration relative to 1-fluoro-3-nitrobenzene as an internal standard.

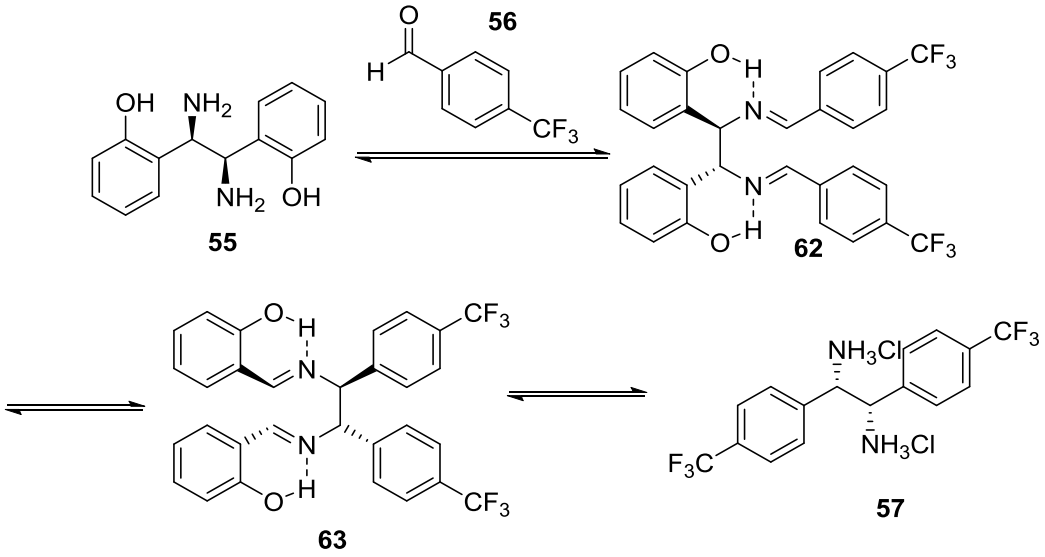
2.2.3.1 Substrate and Reagent Synthesis

In the recent report by the Gouverneur group, 2,3-(4-trifluoromethyl)phenyl substituted Selectfluor was the optimum chiral fluorinating agent in terms of yield and enantioselectivity for the model fluoro-carbocyclisation reaction.[67] Firstly, the precursor to this chiral fluorinating agent required for ^{18}F-labelling was synthesised by a slightly modified literature procedure (Scheme 2.65).



Scheme 2.65: Synthesis of chiral Selectfluor precursor

Chiral non-racemic diamine **57** was synthesised according to a procedure originally developed by Chin and co-workers.[102] The commercially available "mother" diamine was condensed with 4-trifluorophenyl benzaldehyde to form a diimine **62** which could undergo a stereospecific diaza-Cope rearrangement, via a chair-like transition state (Scheme 2.66). Acid hydrolysis afforded the required "daughter" diamine **57** quantitatively. The literature work-up procedure was adjusted to include an acid/base extraction followed by re-acidification to obtain diamine **57** as the HCl salt.

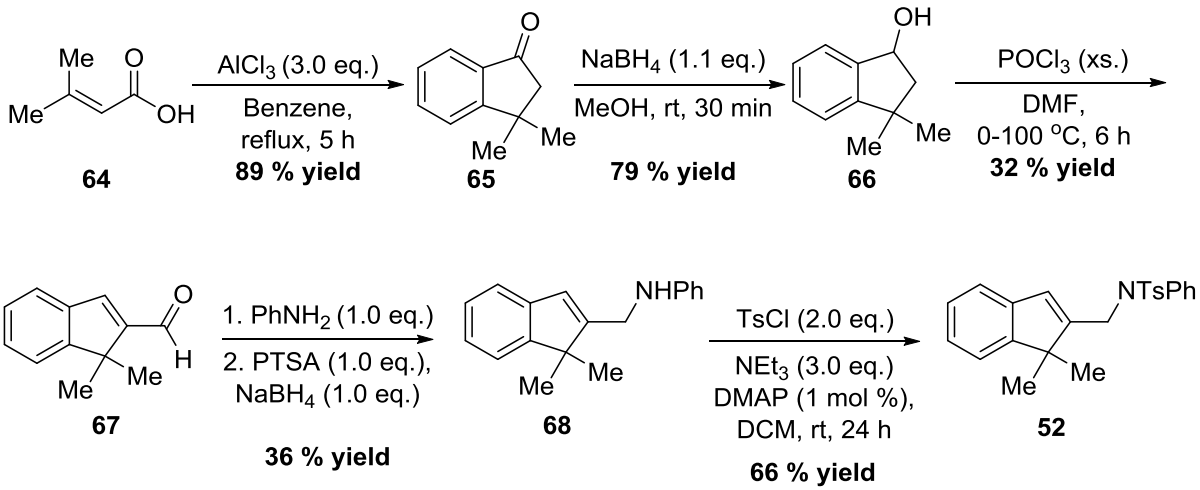


Scheme 2.66: Diaza-Cope rearrangement of Chin mother diamine

The following acetylation reaction was performed with chloroacetyl chloride in DCM over 3 hours. Initially, a low yield of 12 % was obtained under the literature conditions. It was found that this could be improved to 40 % by use of warm ethyl acetate as the extraction solvent, due to poor solubility of chloroacetylated product **58** in DCM. Reduction of the amide to a secondary amine was carried out employing borane tetrahydrofuran complex in refluxing THF, followed by direct dicyclisation in refluxing DMF to afford chiral DABCO **60** as a single stereoisomer. This could be purified by column chromatography to remove starting material and mono-cyclised product.

Mono-quaternisation of DABCOs with an alkyl group is essential in order to obtain a final reagent which is stable at room temperature.[103] Reaction with methyl triflate afforded mono-methylated chiral dabconium salt **61**. Over-reaction to afford bis-methylated product was avoided by a low reaction temperature and use of diethyl ether as solvent, which caused precipitation of the product as it formed.

Model substrate **52** was also synthesised according to the literature procedure in 5 steps from methylcrotonic acid (Scheme 2.67).[4]



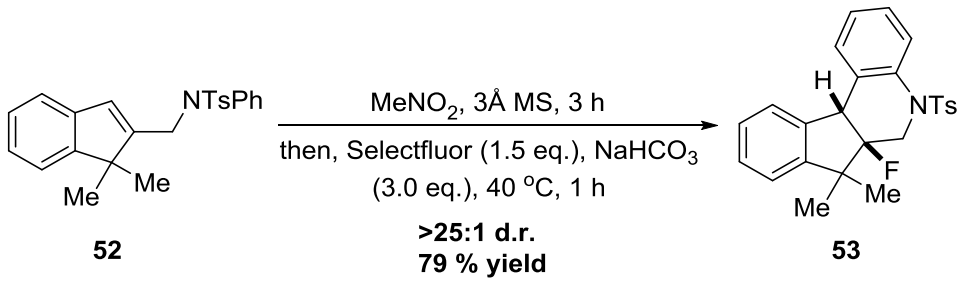
Scheme 2.67: Indene substrate synthesis

A tandem Friedel-Crafts acylation/ alkylation reaction of benzene with methylcrotonic acid afforded indanone **65** which was reduced with sodium borohydride. Dehydration with phosphorous oxychloride with a concomitant Vilsmeier-Haak reaction afforded aldehyde **67**. The subsequent reductive amination was performed under solvent free conditions in a pestle and mortar. Grinding aldehyde **67** with aniline for 15 minutes afforded an imine intermediate which could be reduced by simultaneous additions of sodium borohydride and *p*-toluenesulfonic acid. Amine **68** was then tosylated in the presence of excess triethylamine and catalytic DMAP.

Synthesis of the racemic fluorinated compound as a HPLC reference could be achieved according to the literature procedure by first pre-stirring substrate **52** in nitromethane for 3 hours in the presence of molecular sieves, to remove water from the reaction mixture and therefore prevent formation of the potential fluorohydrin side-product. After this time Selectfluor was added, and the reaction was heated to 40 °C for 1 hour to afford the fluoro-carbocyclised product **53** as a single diastereomer in a 79 % yield (Scheme 2.68).

[4] Synthesis of compounds 65, 66 and 67 performed by Jack Twilton.

Pleasingly, for this model product, the separation of enantiomers observed by reverse phase chiral HPLC was very good.



52 **53**

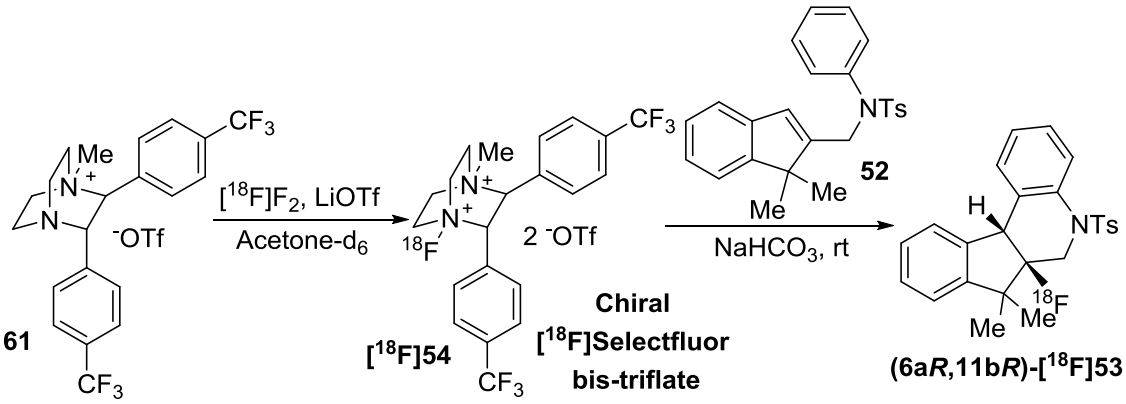
Scheme 2.68: Synthesis of racemic reference compound

With this chiral Selectfluor precursor, substrate and racemic reference in hand, studies with ^{18}F were next performed.

2.2.3.2 Investigations with ^{18}F

The synthesis of chiral [^{18}F]Selectfluor bis-triflate was performed according to the literature procedure for the racemic compound.[73a] The chiral dabconium precursor **61** and an excess of lithium triflate were dissolved in acetone and [^{18}F]F_2 was bubbled through the resultant solution for 30 seconds. Since efficiency of this synthesis could not be determined by radio-HPLC due to overlapping signals of [^{18}F]Selectfluor bis-triflate and the [^{18}F]LiF by-product, aliquots of this solution were then employed directly for the fluorocyclisation reaction of the model substrate (Table 2.15). It is worth noting that since 50 % of the activity eluted corresponds to [^{18}F]LiF, the maximum theoretical RCC of product in this case is 50 %.

Table 2.15: Investigation of chiral [^{18}F]Selectfluor bis-triflate in fluoro-carbocyclisation reaction

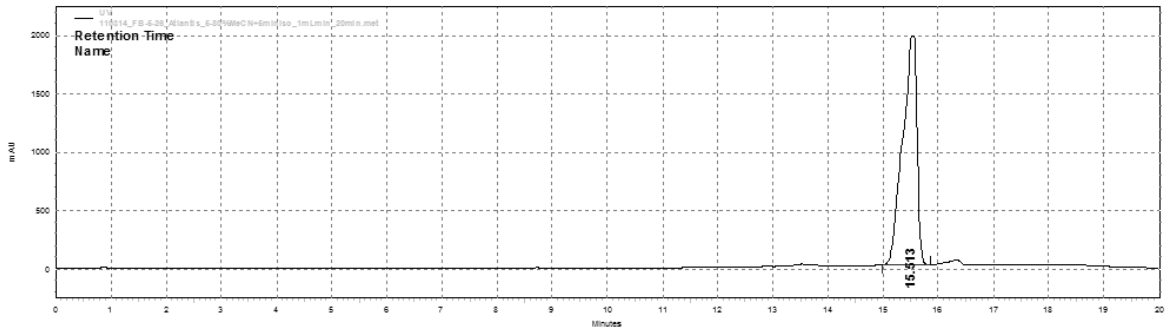


Entry	Solvent	Time (min)	RCC (%)[a]	ee (%)[b]
1 [c]	Acetone-d_6	30	**2**	-
		60	**3**	**61**
2 [d]	1,4-dioxane	30	**trace**	-
3 [e]	1,4-dioxane/ acetone-d_6 (4:1)	30	**2**	**60**
4 [e]	**DCE/ acetone-d_6 (4:1)**	**30**	**6**	**72**

[a] RCC determined by peak area according to radio-HPLC. [b] ee determined by radio-HPLC of isolated product. [c] Chiral [^{18}F]SF in acetone-d_6 added to rxn vial containing substrate and base. [d] Chiral [^{18}F]SF in acetone-d_6 added to empty rxn vial and solvent removed. Substrate and base added as a solution in 1,4-dioxane. [e] Chiral [^{18}F]SF in acetone-d_6 added to rxn vial containing base and solvent concentrated to ¼ volume. Substrate added as a solution in solvent.

In the first instance, a solution of chiral [^{18}F]Selectfluor bis-triflate **[^{18}F]54** in acetone was added directly to a Wheaton v-vial containing the indene precursor **52** and 3 equivalents of sodium bicarbonate. The reaction was stirred for 30 minutes before an aliquot was taken for analytical HPLC. The radio-detector trace showed a peak at 15.7 minutes, which corresponded to the UV retention time of the cold reference product, taking into account the small delay due to distance between detectors (Figure 2.10). A radiochemical conversion of 2 % was calculated by integration of the peak area (Table 2.15, entry 1). This value corresponded well with the yield calculated by comparison of radioactivity of the collected peak with the total injected activity, indicating that all of the activity had been eluted from the column.

A. UV of reference compound



B. Radio-HPLC of crude reaction mixture

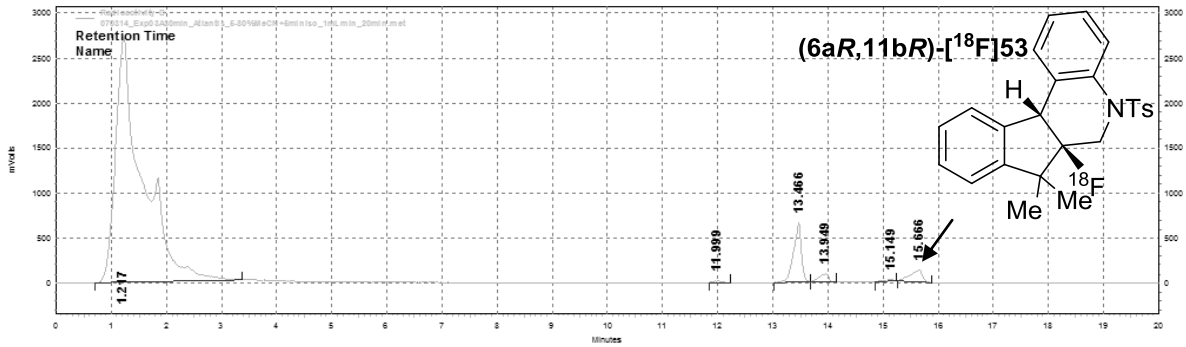
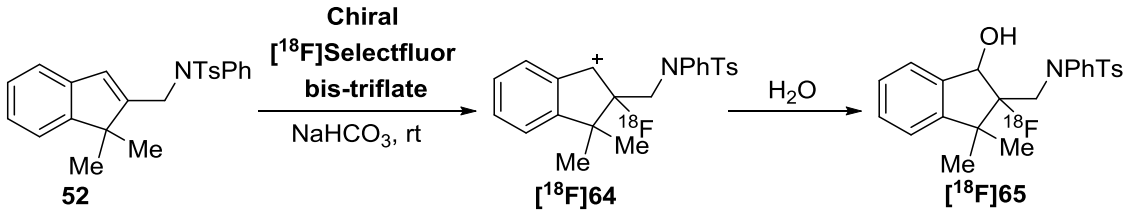


Figure 2.10: Analytical HPLC traces corresponding to Table 2.15, entry 1

Water Atlantis dC18 (5µm, 3.9x150mm), 1.0 mL/min, UV = 220 nm, HPLC Conditions E, Sample: 1 mg/mL in MeCN, t_{prod} = 15.5 min.

A major side product was observed at 13.5 minutes with a RCC of 7 %. This was postulated to be the fluorohydrin side-product **[^{18}F]65**, generated by capture of the benzylic carbocation formed in the fluorination step by a molecule of water (Scheme 2.69).

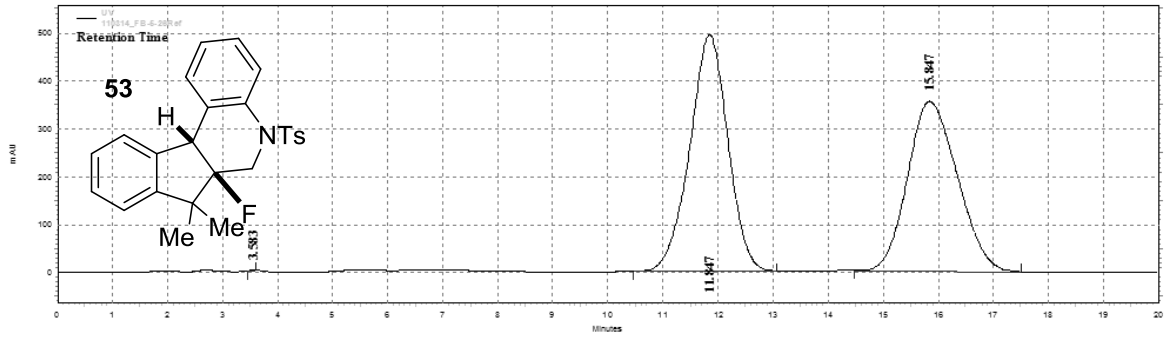


Scheme 2.69: Postulated formation of fluorohydrin by-product

After stirring for another 30 minutes, there was little effect on radiochemical conversion. The peak corresponding to the product was isolated and injected onto a reverse phase chiral HPLC column. The ee was determined as 61 %, demonstrating that enantioselectivity similar to that obtained with the cold reagent (ee = 72 % in acetone)[67]

could be achieved with the ^{18}F-labelled variant (Figure 2.11). However, it was not possible to determine whether the low RCC was a result of inefficient synthesis of chiral [^{18}F]Selectfluor bis-triflate, or low yield of the fluorocyclisation reaction.

A. UV of racemic reference



B: Radio-trace of isolated product

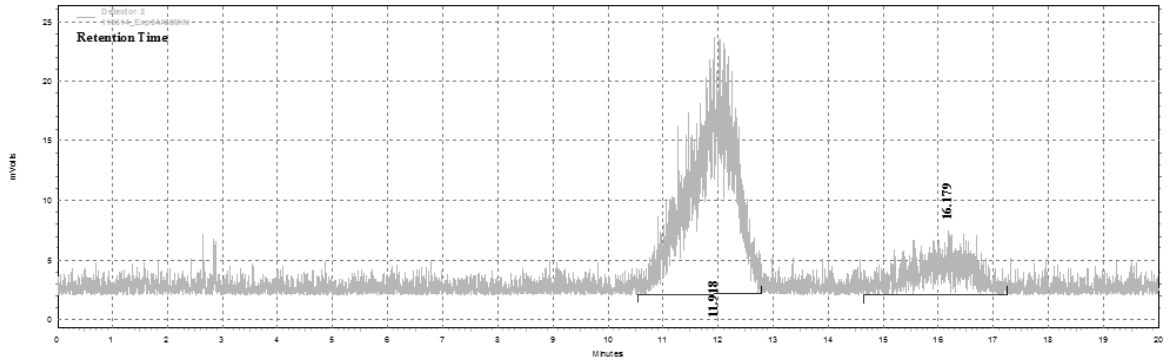


Figure 2.11: Chiral HPLC traces corresponding to Table 2.15, entry 1
Phenomenex Lux Cellulose 1 (5 µm, 4.6x100mm), 1.0 mL/min, UV = 220 nm, 60 % MeCN isocratic, t_1 = 11.8 min, t_2 = 15.8 min.

Use of 1,4-dioxane as solvent was most successful for the cold reaction (see Section 2.1.3.4.3). To perform this solvent switch, evaporation of solvent from an aliquot of chiral [^{18}F]Selectfluor bis-triflate in acetone took place under a flow of helium, prior to addition of a solution of substrate and $NaHCO_3$ in 1,4-dioxane. However, after stirring for 30 minutes just a trace of product was observed by analytical HPLC, along with a smaller amount of side-product (Table 2.15, entry 2). This was postulated to be due to chiral [^{18}F]Selectfluor bis-triflate sticking to the glass reaction vessel after solvent evaporation, resulting in poor re-solubility on addition of the reaction solvent.

In an effort to circumvent this problem, the next reaction was performed by concentration of the chiral [^{18}F]Selectfluor bis-triflate in acetone solution to approximately 1/4 volume, rather than dryness, prior to addition of the solution of substrate in 1,4-dioxane. Again the reaction was stirred for 30 minutes at room temperature before an aliquot was taken for HPLC (Entry 3). A RCC of 2 % was obtained with an enantiomeric excess of 60 %, indicating that this mixed solvent system was no more effective than pure acetone.

Finally, DCE was employed as the reaction solvent, in order to provide better solubility of the enantioenriched fluorinating agent. A slightly increased RCC of 6 % was achieved under these conditions, with an enantiomeric excess of 72 % (Entry 4). However, the RCC of the side-product at 13.5 minutes also increased to 8 % in this solvent system.

Whilst radiochemical conversions for this preliminary study were low, it provided important proof of principle of both the labelling of chiral [^{18}F]Selectfluor bis-triflate, and its application in this challenging fluoro-carbocyclisation reaction. In fact, these studies constitute the first example of ^{18}F-labelling of a enantioenriched fluorinating agent. The resultant tetracyclic product contained a quaternary ^{18}F-labelled stereogenic centre with ee values which corresponded to the values obtained in cold reactions. This enantioenriched ^{18}F-labelled product would be very difficult to synthesise by any previously reported method. However, further advancement of this methodology would require development of a method for analysis of the chiral [^{18}F]Selectfluor bis-triflate synthesis and significant optimisation of radiochemical conversion of the fluorocyclisation reaction, in terms of solvent, time, concentration and temperature.

2.3 Summary

In conclusion, this chapter has described the merging of the fields of organocatalysed enantioselective fluorination with ^{18}F-radiochemistry for the first time, allowing the

asymmetric ^{18}F-fluorination of aldehydes to proceed with high RCC and ee. This advance could open up considerable opportunities in PET radiotracer design and drug development. The advantages of this metal-free methodology include the use of non pre-functionalised, often commercially available starting materials, and facile control of stereochemistry by choice of enantiomer of catalyst employed. The utility of this method was further demonstrated by development of a range of diverse aldehyde derivatisation reactions, demonstrating that access to carboxylic acid, amide and amine functionalities could be provided from a single enantioenriched α-[^{18}F]fluoroaldehyde synthetic equivalent. Finally, application of this methodology allowed development of a novel method for the synthesis of (2*S*,4*S*)-4-[^{18}F]fluoroglutamic acid, a PET tracer which has been highlighted to have potential in breast and lung cancer imaging, but is currently difficult to access in diastereomerically pure form. Application to the synthesis of (2*S*,4*S*)-4-[^{18}F]fluoroglutamine was more challenging, and further work is required to finalise this route. These studies have resulted in the publication of this work in Angewandte Chemie/ Angewandte Chemie International Edition.[104] The current limitation of this methodology lies in the requirement for use of [^{18}F]NFSI, which is only available with low S.A. compared to [^{18}F]fluoride. The synthesis of this reagent with high S.A. would constitute a significant advancement in the field of ^{18}F-radiosynthesis.

Studies on two asymmetric ^{18}F-fluorocyclisation reactions employing phase transfer catalysis conditions and a chiral version of [^{18}F]Selectfluor bis-trfilate respectively provided preliminary results demonstrating the synthesis of products containing C-^{18}F stereocentres with moderate ee values. However, RCCs achieved employing these methods are currently low and significant optimisation would be required for further application.

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Chapter 3:

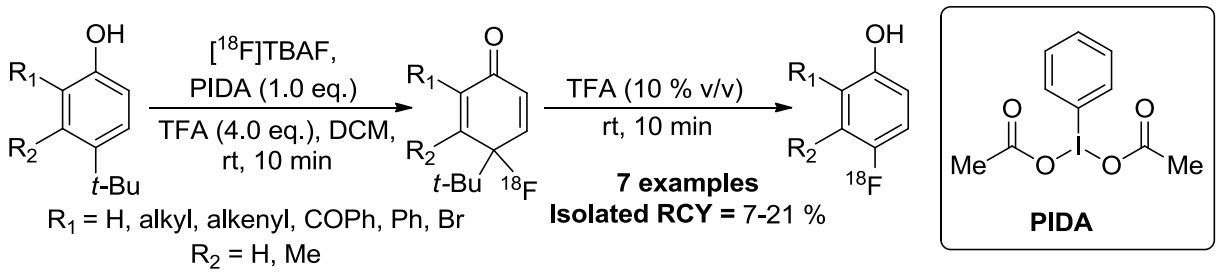
Hypervalent Iodine-Mediated Oxidative Fluorination of *N*-Arylsulfonamides

3. Hypervalent Iodine-Mediated Oxidative Fluorination of *N*-Arylsulfonamides

3.1 Introduction

Work in the previous chapter focussed on the ^{18}F-fluorination of compounds susceptible to electrophilic fluorination with [^{18}F]F_2-derived reagents. Whilst the methodology developed at the Turku PET Centre for the production of [^{18}F]F_2 gas with high SA is very valuable and allows clinical production of ^{18}F-labelled radiotracers which would be very difficult to synthesise under alternative methodology, it is currently somewhat geographically limited to this centre. Worldwide, the use of nucleophilic [^{18}F]fluoride is much more common in PET centres and thus use of this reagent is very advantageous. Much work is therefore currently ongoing to tackle the challenge posed by the ^{18}F-fluorination of nucleophilic substrates, particularly electron rich aromatics, with [^{18}F]fluoride.

As discussed in Chapter 1, many of the recent approaches to nucleophilic ^{18}F-fluorination of electron rich aromatics require activation by a transition metal.[1] A complementary, metal-free umpolung approach was developed by the Gouverneur group which employed a hypervalent iodine oxidant to impose a reversal of the reactivity profile of phenols, therefore rendering them amenable to fluorination with [^{18}F]fluoride .[2]



Scheme 3.1: Hypervalent iodine-mediated oxidative fluorination of phenols with [^{18}F]fluoride by Gouverneur and co-workers

Whilst iodine(III) reagents have received considerable attention as mild, non-toxic, metal-free reagents which can mediate a range of oxidative transformations,[3] this is currently

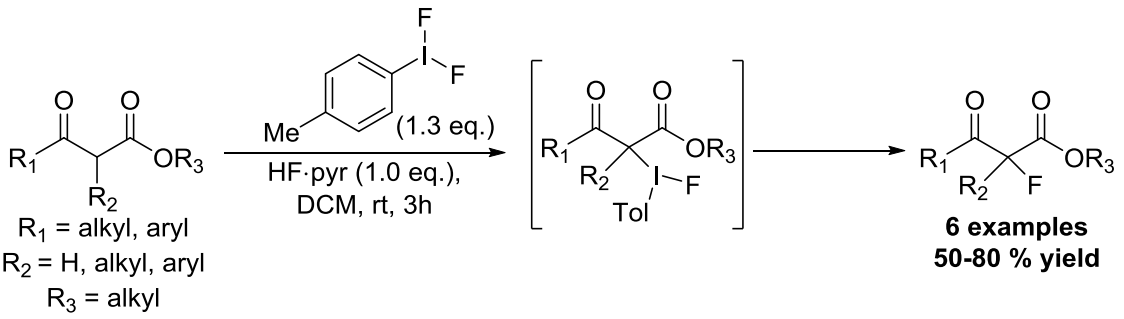
the only example of ^{18}F-fluorination mediated by a hypervalent iodine oxidant. This chapter aims to extend the scope of this metal-free umpolung methodology to widen its application in ^{18}F-radiosynthesis.

3.1.1 Hypervalent Iodine-Mediated Fluorination

Hypervalent iodine-mediated fluorination reactions commonly employ either I-F reagents, which act as both the oxidant and fluorinating agent, or a commercially available hypervalent iodine oxidant such as diacetoxyiodobenzene (PIDA) in combination with an external fluoride source.

3.1.1.1 Synthesis of Hypervalent Iodine-Based Fluorinating Reagents

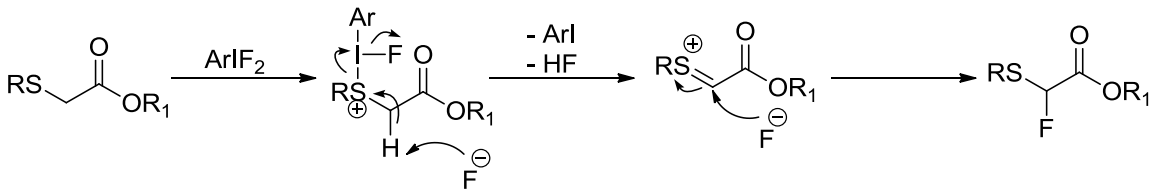
Difluoroiodoarenes are the most common class of hypervalent iodine-based fluorinating reagents. They have been shown to act as selective fluorinating agents for a range of substrate classes, including fluorination of alkenes and alkynes,[4] ring expansion[5] and contraction reactions[6] and fluorocyclisation reactions.[7] Following the first report on the fluorination of β-ketoesters by difluoroiodotoluene by Hara and co-workers in 1996 (Scheme 3.2),[8] they have also seen extensive application in the α-fluorination of carbonyls,[3e] including 1,3-diketones and β-ketoesters and amides,[7d;9] silyl enol ethers[10] and more recently, monocarbonyl compounds.[11]



Scheme 3.2: Fluorination of β-ketoesters with difluoroiodotoluene by Hara and co-workers

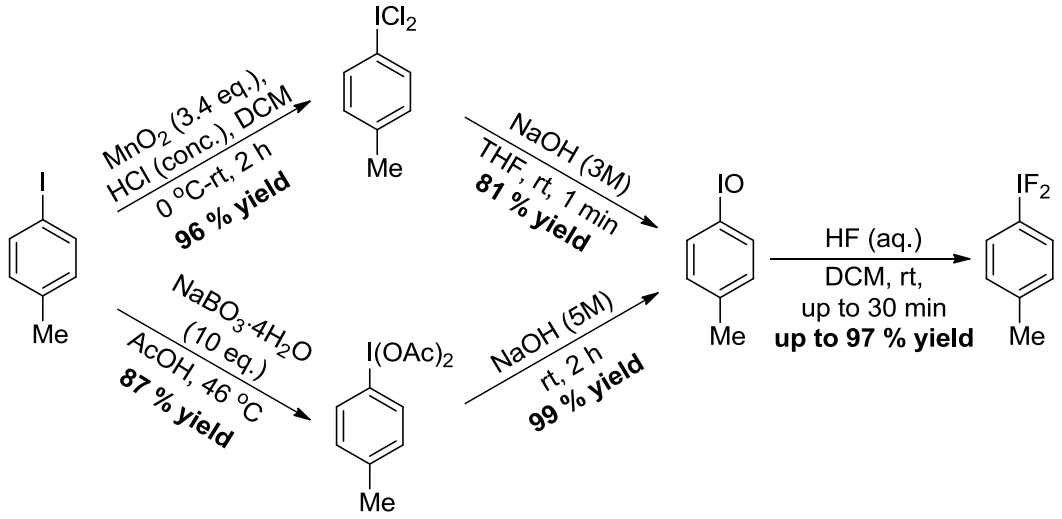
Despite corresponding to a formal electrophilic fluorination, this class of reactions is proposed to proceed via reaction of the enolised dicarbonyl with the difluoroiodoarene to

provide a hypervalent iodonium fluoride intermediate, followed by S_N2 displacement by nucleophilic fluoride (Scheme 3.2).[7d] The hypervalent iodine-mediated fluorination of α-phenylthioester[12] and amide substrates,[13] and α-selenoesters and amides[14] via a fluoro-Pummerer type mechanism has also been reported (Scheme 3.3).



Scheme 3.3: Fluoro-Pummerer type mechanism proposed for hypervalent iodine mediate fluorination of α-phenylthioester substrates

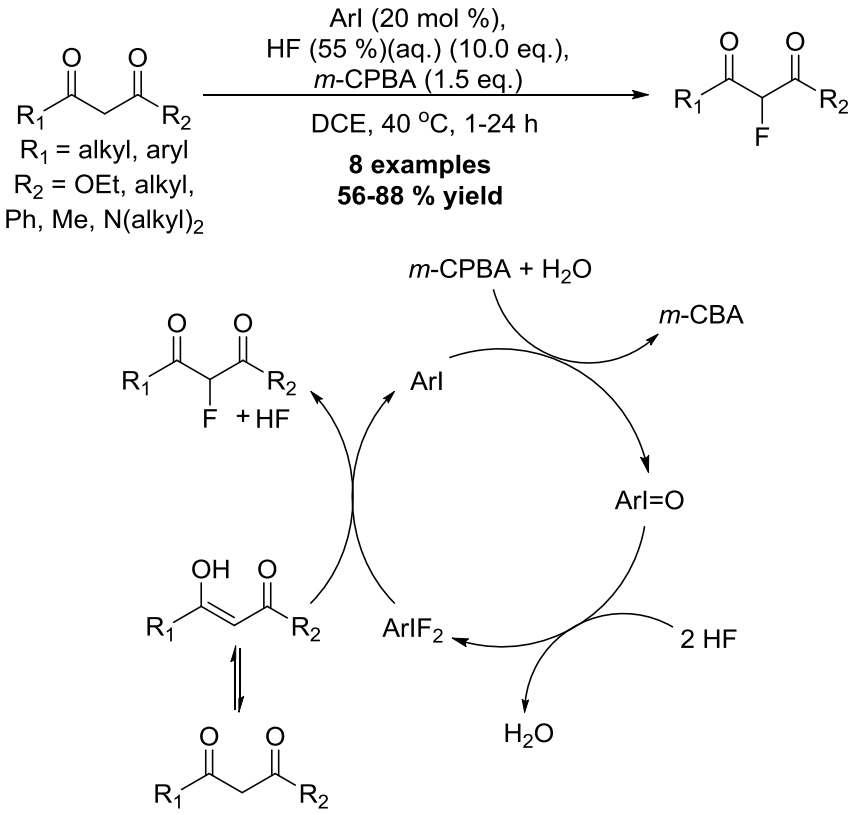
Several procedures for the synthesis and isolation of difluoroiodoarenes are known, including by the direct fluorination of iodoarenes with F_2 at very low temperature,[15] or with XeF_2 in the presence of anhydrous HF;[16] electrochemical reaction of iodoarenes in the presence of HF·triethylamine complexes[9b;17] or silver(I) fluorine in acetonitrile;[18] reaction of dichloroiodoarenes with aqueous HF in the presence of mercury oxide;[19] direct reaction of the corresponding arene with elemental iodine and Selectfluor;[20] reaction of di(trifluoroacetoxy)arenes with SF_4;[21] reaction of diacetoxyarenes with strictly anhydrous TBAF[22] or most commonly by the reaction of iodosoarenes with aqueous HF (Scheme 3.4).[14;23] This last reaction is generally the modern method of choice due to the capacity to prepare difluoroiodoarenes on a relatively large scale, whilst avoiding the use of difficult to handle or expensive starting materials. The iodosoarene precursors can be prepared by base hydrolysis of the corresponding dichloro[23a] or diacetoxy[14] compounds, with the latter being preferred due to its higher stability. These can in turn be prepared from the commercially available iodoarenes (Scheme 3.4).



Scheme 3.4: Literature synthesis of difluoroiodotoluene

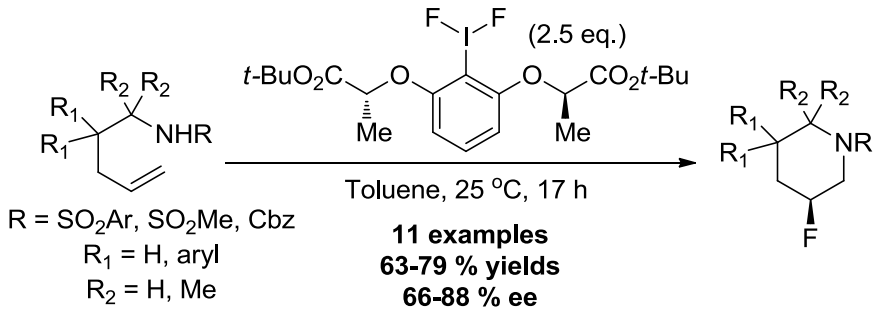
Although (diacetoxyiodo)benezene (PIDA) is commercially available, employing (diacetoxyiodo)toluene in this synthesis to afford difluoroiodotoluene[24] is more common due to the increased stability of this compound, as well as the corresponding iodosoarene, to storage for lengthy periods, when compared to the corresponding benzene compounds.

Due to their hygroscopicity, the *in situ* formation of difluoroiodoarenes during the course of a reaction is also common and, in 2013, Kitamura and co-workers reported a catalytic method for *in situ* formation of difluoroiodoarenes. This work employed *m*-CPBA as an oxidant to continually regenerate an iodosoarene catalyst which in turn afforded the corresponding difluoroiodoarene by reaction with aqueous HF (Scheme 3.5).[25] This method was successfully applied to the oxidative fluorination of 1,3-diketones, β-ketoesters and β-ketoamides.



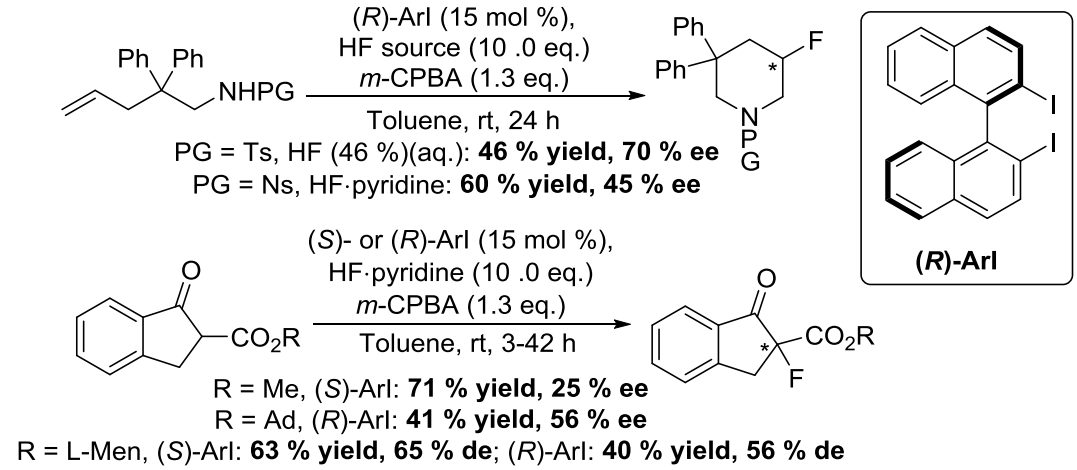
Scheme 3.5: Catalytic pathway for oxidative fluorination of 1,3-dicarbonyls
m-CPBA = 3-chloroperoxybenzoic acid

Synthesis and isolation of a chiral non-racemic difluoroiodoarene has also been reported recently been reported by Nevado and co-workers.[7c] This was synthesised by reaction of a chiral non-racemic iodoarene with Selectfluor in acetonitrile in the presence of $3HF{\cdot}NEt_3$ and was applied to an aminofluorination reaction to afford access to 2-fluoropiperidine and azepane products with moderate ee values, which could be improved by recrystallisation (Scheme 3.6). Unlike the majority of dilfluoroiodoarene-mediated reactions, which require a chlorinated solvent such as DCM, optimum results in terms of enantioselectivity were achieved employing toluene as solvent in this reaction.



Scheme 3.6: Aymmetric aminofluorination of alkenes by Nevado and co-workers

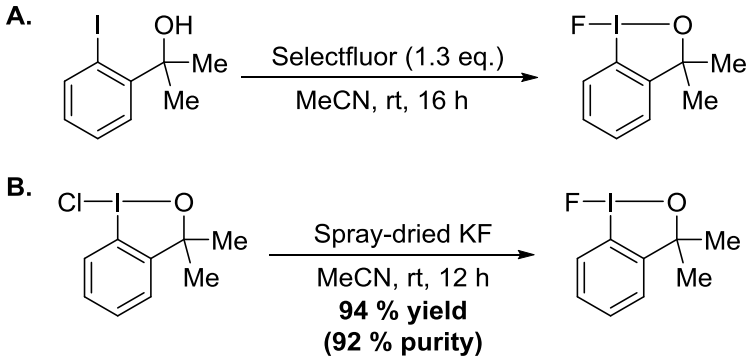
In 2014, Shibata, Kita and co-workers reported preliminary investigations into a catalytic, asymmetric variant of this reaction.[7d] A chiral non-racemic binaphthyldiiodide catalyst was employed in combination with *m*-CPBA as oxidant, to afford an aryliodoso compound which reacted with HF·pyridine to allow *in situ* formation of an enantioenriched difluoroiodoarene reagent. As well as the aminofluorination of alkenes, this methodology was also applied to the asymmetric fluorination of β-ketoesters (Scheme 3.7). In the latter case, highest enantioselectivity was achieved employing substrates bearing sterically demanding adamantly or menthyl esters.



Scheme 3.7: Catalytic asymmetric fluorination of β-ketoesters with HF by Shibata, Kita and co-workers

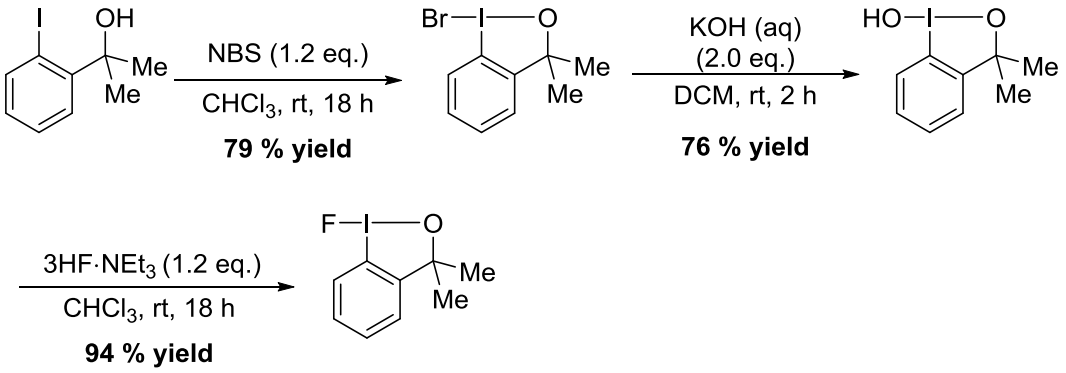
Although enantioselectivities were only moderate for these reactions, they are notable as the first examples of metal-free catalytic enantioselective fluorination reactions employing nucleophilic fluoride.

The preparation of 1-fluoro-3,3-dimethyl-1,2-benziodoxole, a hypervalent iodine reagent which is based on the structure of the Togni trifluoromethylating reagents, has also been recently described. Work by Legault and co-workers in 2012 reported its synthesis via oxidative fluorination of 2-(2-iodophenyl)propan-2-ol with an excess of Selectfluor, although a yield was not reported in this case (Scheme 3.8, A).[26] A later report by the Togni group employed halogen exchange of a chloroiodane precursor with spray dried potassium fluoride (Scheme 3.8, B).[27]



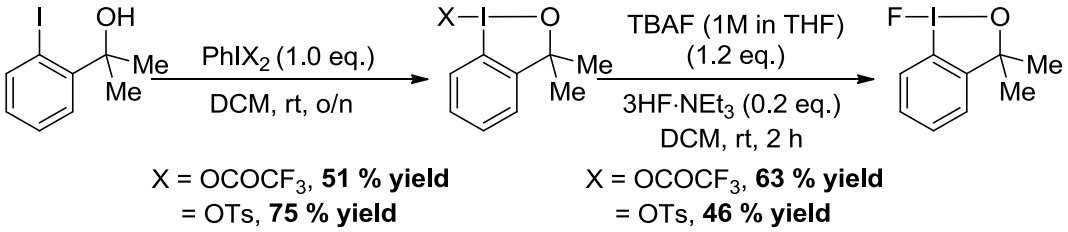
Scheme 3.8: Synthesis of 1-fluoro-3,3-dimethyl-1,2-benziodoxole by A. Legault and co-workers and B. Togni and co-workers

However, synthesis of this reagent on a multigram scale by these methods is restricted by, for the former, the expensive source of fluorine employed and for the latter the necessity for very dry reaction conditions. A report by the Stuart group in 2013 therefore sought to rectify this problem and demonstrated the synthesis of the same fluoroiodane reagent in 3 steps from relatively cheap starting materials, with $3HF{\cdot}NEt_3$ employed as the fluorine source in the final step (Scheme 3.9).[28]



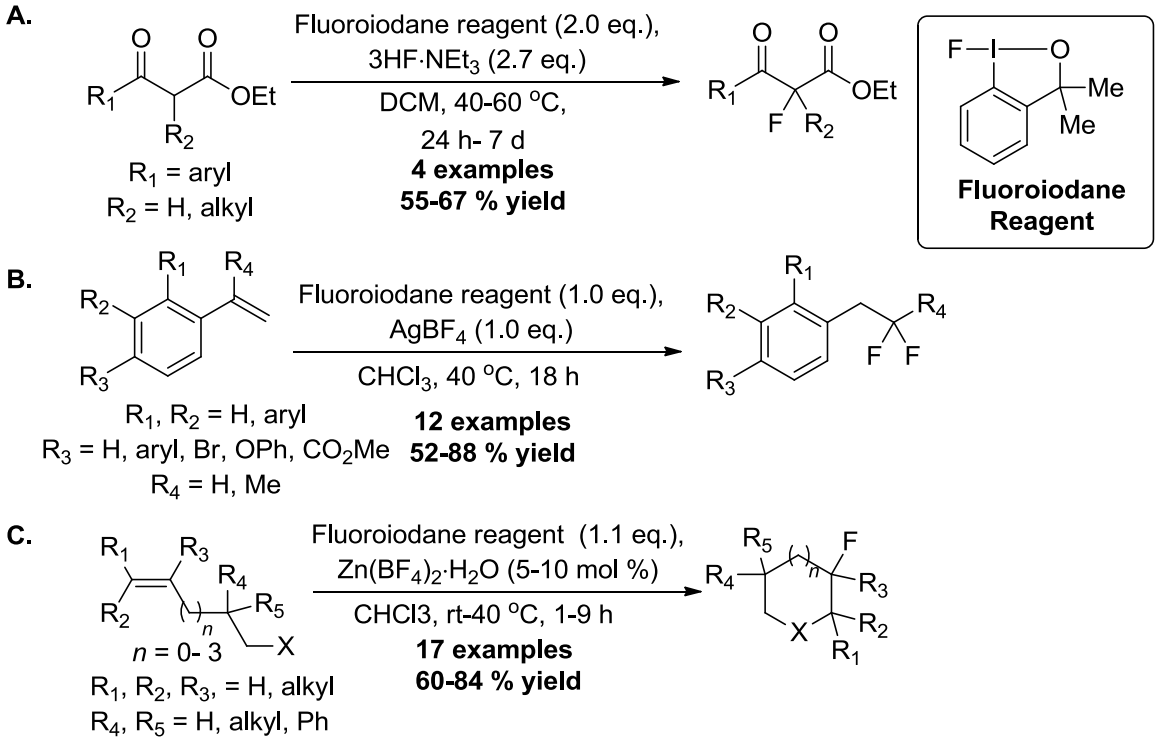
Scheme 3.9: Synthesis of 1-fluoro-3,3-dimethyl-1,2-benziodoxole from HF by Stuart and co-workers

This synthesis involved oxidative bromination of 2-(2-iodophenyl)propan-2-ol with NBS, prior to substitution at iodine by hydroxide, and then by fluoride. It was also reported that with an improved leaving group, such as triflate or tosylate, fluorine substitution could be performed employing TBAF with only catalytic HF (Scheme 3.10).



Scheme 3.10: Synthesis of fluoroiodane reagent 1-fluoro-3,3-dimethyl-1,2-benziodoxole from TBAF by Stuart and co-workers

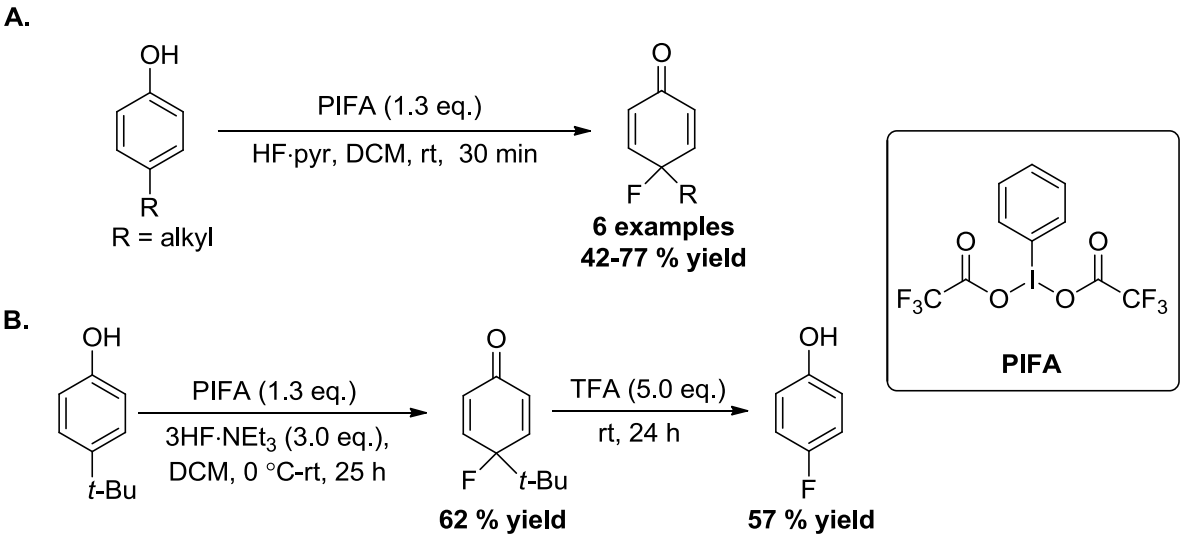
This is advantageous for radiolabelling applications, since [^{18}F]TBAF is much more commonly and easily available compared to [^{18}F]HF, although a non-carried added approach would require synthesis without catalytic HF. This reagent was applied by the Stuart group to the mono α-fluorination of β-ketoesters (Scheme 3.11, A) and to the difluorination of 1,3-diketones.[28-29] It since been applied to the silver-mediated geminal difluorination of styrenes (Scheme 3.11, B)[30] and to amino-, oxy-, and carbofluorocyclisation reactions (Scheme 3.11, C) by Szabó and co-workers.[31]



Scheme 3.11: Reported applications of fluoroiodane reagent

3.1.1.2 Hypervalent Iodine-Mediated Oxidative Fluorination of Aromatics

Following seminal work on the oxidative fluorination of aromatic compounds with a lead-based oxidant by Feiring in 1979,[32] the fluorination of phenols mediated by a hypervalent iodine oxidant was reported by Jouannetaud, Jacquesy and co-workers in 1994 (Scheme 3.12, A).[33] In this work, reaction of phenol with a slight excess of oxidant (bis(trifluoroacetoxy)iodo)benzene (PIFA) in combination with HF·pyridine (Olah's reagent) afforded 4-fluorocyclohexa-2,5-dienones. This methodology was later extended by Langlois and co-workers to the synthesis of 4-fluorophenol by incorporation of a *tert*-butyl leaving group at the *para* position, which facilitated acid-mediated rearomatisation of the isolated dienone in a second step (Scheme 3.12, B).[34]

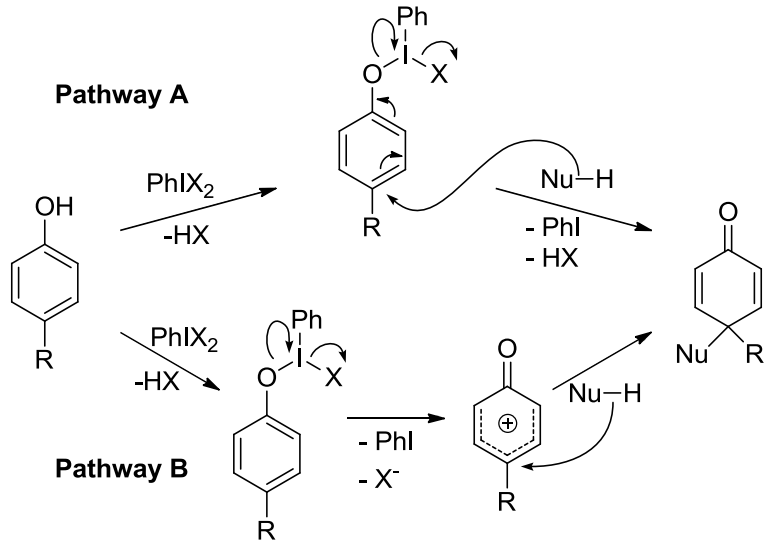


Scheme 3.12: Oxidative fluorination of phenol to afford A. 4-fluorocyclohexa-2,5-dienones and B. 4-fluorophenol

This reaction proceeded via oxidative fluorination of 4-*tert*-butylphenol with PIFA and $3HF{\cdot}NEt_3$ to afford 4-*tert*-butyl-4-fluorocyclohexa-2,5-dienone in a 62 % yield, which was then treated with TFA to promote rearomatisation with loss of isobutene. Notably, this two step synthesis corresponds to a formal electrophilic fluorination of phenol, with excellent regioselectivity for the *para* position.

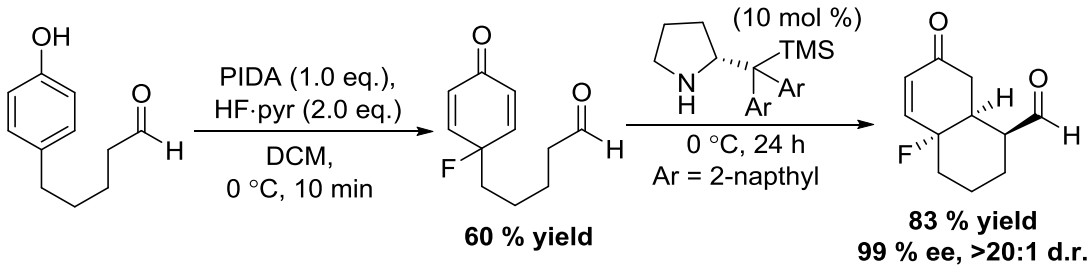
Mechanistically, two possible pathways have been suggested for the hypervalent iodine-mediated oxidative reaction of phenol with a nucleophile.[35] In the first, following ligand exchange between the phenol and hypervalent iodine reagent, nucleophilic attack, oxidation of the phenoxyl group and reduction of the iodine(III) centre then occur in a concerted process (Scheme 3.13, Pathway A). In the alternative pathway, following reaction of phenol with the oxidant, dissociation first occurs to afford a phenoxenium ion, which is then trapped by the nucleophile (Scheme 3.13, Pathway B). Whilst neither mechanism has been verified definitively, the presence of a phenoxenium ion has been supported by frontier molecular orbital analysis and by the observed strong degree of electronic control on regioselectivity.[36] An alternative mechanism, in which two

consecutive single electron transfers from the oxidant to the substrate occur to afford a radical cation and then a cation, has been discounted because use of other oxidiants known to oxidise phenols through a single electron transfer mechanism was unsuccessful.[34]



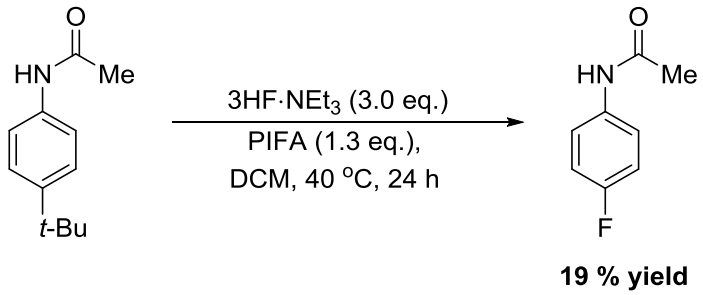
Scheme 3.13: Potential mechanisms for hypervalent iodine-mediated oxidation of phenols

The desymmetrisation of phenols employing a fluorination/cyclisation procedure is also known using hypervalent iodine-mediated oxidative fluorination methodology. Reports by Jouannetaud, Jacquesy and co-workers have described the fluorination of phenols containing a pendent amine nucleophile at the *para*-position, which was activated towards post-fluorination cyclisation by treatment with acid or base.[37] This was extended by a report from the Gaunt group in 2008 which involved merging the fields of organocatalysis and oxidative fluorination of aromatics.[38] This work demonstrated the oxidative dearomatization of substituted phenols mediated by PIDA, followed by a desymmetrising, chiral non-racemic amine-catalysed, asymmetric intramolecular Michael addition to afford complex polycyclic structures. One example employed HF·pyridine as the nucleophile, resulting in formation of a quaternary C-F bond with excellent diastero- and enantio-selectivity (Scheme 3.14).



Scheme 3.14: Enantioselective organocatalytic oxidative dearomatization of phenols by Gaunt and co-workers

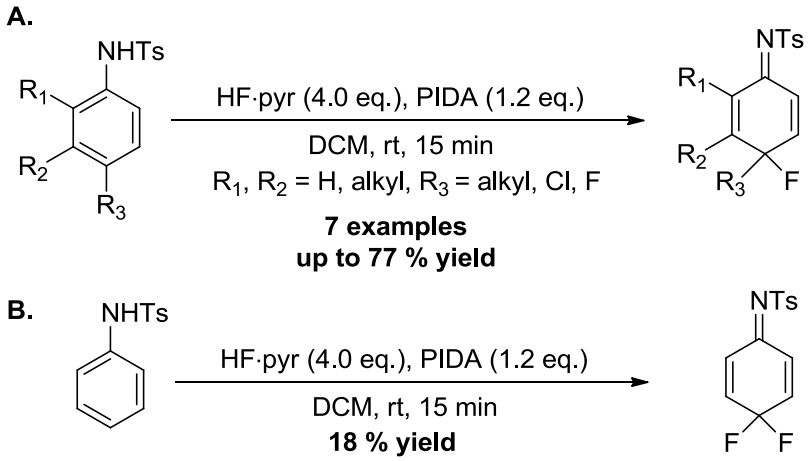
There is also some literature precedent for the oxidative fluorination of aniline derivatives. Although Langlois reported that no fluorinated product was obtained from the reaction of unprotected 4-*tert*-butylaniline with PIFA and $3HF{\cdot}NEt_3$, some success was found when an acetamide protecting group was employed (Scheme 3.15).[34] In this case, rearomatization was found to occur directly, without isolation of the expected 4-*tert*-butyl-4-fluorocyclohexa-2,5-dienimine intermediate.



Scheme 3.15: Hypervalent iodine-mediated oxidative fluorination of 4-*tert*-butylacetanilide by Langlois and co-workers

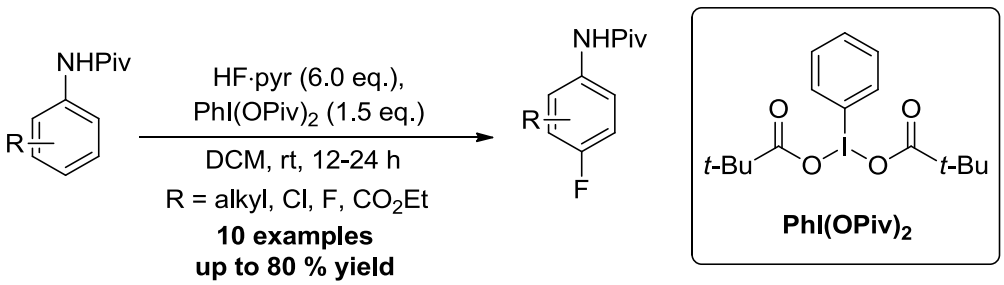
In 2008, Jouannetaud, Jacquesy and co-workers reported the successful oxidative fluorination of *N*-tosyl-protected anilines, employing HF·pyridine in combination with PIDA to afford 4-fluoro-4-substituted cyclohexa-2,5-dienimines, with yields of up to 77 % (Scheme 3.16, A).[39] The reaction was hindered by di-*ortho* methyl substitution due to steric effects and also by electron withdrawing groups at the *para* postion. In all cases, regioselectivity was high for the *para* position. However, when *N*-tosylaniline unsubstituted at the *para* position was employed as a precursor, only the 4,4-

difluorocyclohexa-2,5-dienimine product was observed as a result of over oxidation and reaction with a further molecule of HF (Scheme 3.16, B).



Scheme 3.16: Hypervalent iodine-mediated oxidative fluorination of *N*-tosyl derivatives by Jouannetaud, Jacquesy and co-workers

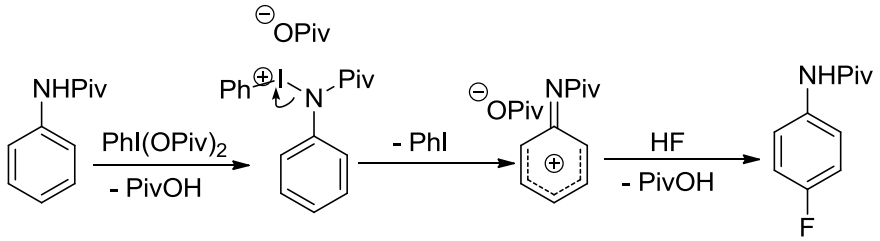
A further report of hypervalent iodine-mediated oxidative fluorination of protected aniline derivatives was made by Meng and Li in 2013 (Scheme 3.17).[40] Notably, this method provided access to rearomatised 4-fluoroaniline products directly without the need for a *tert*-butyl leaving group or addition of acid.



Scheme 3.17: Hypervalent iodine-mediated oxidative fluorination of *N*-pivaloyl derivatives by Meng, Li and co-workers

Although HF·pyridine was again employed as fluorine source, the use of commercially available *bis*(*tert*-butylcarbonyloxy)iodobenzene ($PhI(OPiv)_2$) as an oxidant was found to be more successful than PIDA or PIFA in this case. A protecting group screen revealed that the highest yields were achieved when the aniline was protected as an anilide, particularly with pivaloyl-protection. Advantageously, this protecting group could be

removed post-fluorination by refluxing in 6M HCl. However, in contrast to the work of Jacquesy and Jouannetaud, in this report, sulfonyl-protected aniline substrates were found to be unsuccessful under these conditions and led only to a complex mixture of products. The authors proposed a mechanism in which the anilide undergoes nucleophilic attack on the hypervalent iodine oxidant through reaction at the nitrogen atom, with the strong electronic effect on regioselectivity suggesting that the reaction proceeds via formation of a nitrenium ion intermediate (Scheme 3.18).



Scheme 3.18: Proposed mechanism for oxidative fluorination of anilides

3.1.2 Aims of Chapter

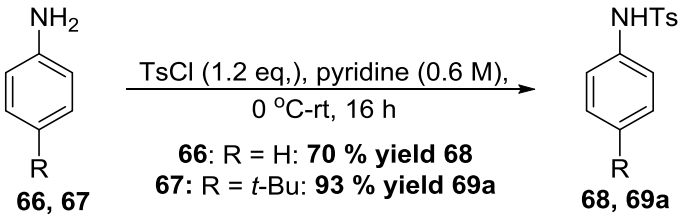
Previous work developed by the Gouverneur group employed hypervalent iodine-mediated oxidative fluorination to afford access to 4-[^{18}F]-fluorophenol derivatives from [^{18}F]fluoride.[2] Given the importance of the sulfonamide motif in pharmaceuticals,[41] we recognised the potential value of an analogous reaction which provides access to *N*-(4-fluorophenyl)sulfonamides and the corresponding ^{18}F-labelled compounds. Whilst the hypervalent iodine-mediated oxidative fluorination of sulfonyl-protected anilines to afford 4-fluoro-4-substituted cyclohexa-2,5-dieneimines is known,[39] the recent study of Meng and Li suggested that *N*-tosyl and *N*-mesylanilines are not suitable substrates for oxidative fluorination with subsequent rearomatisation.[40] Work in this chapter therefore aimed to find suitable conditions for this previously unknown transformation, and to develop a protocol for radiofluorination of *N*-arylsulfonamides.

3.2 Results and Discussion

Fluorination reactions for protecting group and substrate scope investigations and all ^{18}F-labelling reactions were carried out in conjunction with Samuel Calderwood (DPhil candidate, Gouverneur group, University of Oxford).

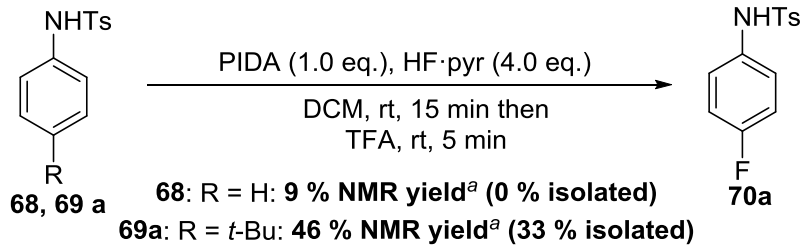
3.2.1 "Cold" Reaction Development

Preliminary reactions employed *N*-tosyl-protected aniline, both with and without *tert*-butyl substitution at the *para* position, which could be synthesised by reaction of the corresponding anilines with tosyl chloride in pyridine (Scheme 3.19). Use of catalytic DMAP in this reaction was found to promote bis-tosylation of the aniline and was therefore avoided.



Scheme 3.19: Model substrate synthesis

According to the optimised procedure for hypervalent iodine-mediated fluorination of phenols previously published by the Gouverneur group,[2] these model substrates were then subjected to reaction with PIDA (1.0 eq.) and HF·pyridine (4.0 eq.) with DCM as solvent (Scheme 3.20). After stirring for 15 minutes in a polypropylene Falcon tube, the reaction was treated directly with TFA for 5 minutes to promote rearomatisation in a one-pot procedure. Following neutralisation with saturated aqueous sodium bicarbonate and subsequent aqueous work-up and evaporation of solvent, ^{19}F NMR yields in $CDCl_3$ were determined by integration against 1-fluoro-3-nitrobenzene (^{19}F NMR, δ = −109.7 ppm, $CDCl_3$) as an internal standard with relaxation time D_1 increased to 10 seconds to increase accuracy.



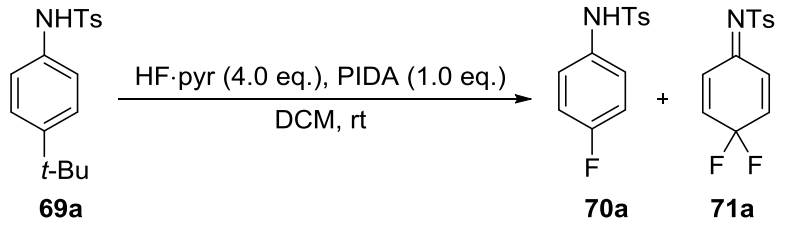
[a] Yields determined by ^{19}F NMR by integration relative to 1-fluoro-3-nitrobenzene as the internal standard (D_1 = 10).

Scheme 3.20: Preliminary study on oxidative fluorination of *N*-tosyl-protected anilines

When the non-substituted aniline **68** was employed, *N*-tosyl-4-fluoroaniline **70a** (^{19}F NMR, δ = −116.6 ppm, $CDCl_3$) was formed with just 9 % ^{19}F NMR yield. However, attempts to isolate this product by silica gel chromatography were unsuccessful due to co-elution with both the substrate and unidentified side-products. This is in agreement with the work of Meng and Li, who reported that oxidative fluorination of this substrate afforded a complex mixture of products.[40] However, when the aniline was armed with a *tert*-butyl group at the *para* position, pleasingly fluorinated product **70a** was formed with an increase in ^{19}F NMR yield to 46 %, via oxidative fluorination followed by acid promoted rearomatisation with loss of *iso*-butene. Given the known electronic dependence of this class of reactions,[36] it is likely that *tert*-butyl substitution not only facilitates rearomatisation, but also has a stabilising effect on a positively charged nitrenium intermediate via inductive donation of electrons and hyperconjugation.[40] Separation of the product from starting material was also more facile in this case, due to the larger difference in retention factor (Rf) between substrate and product.

As short reaction times are an essential criterion for ^{18}F-radiosynthesis, a short time study was next performed in order to monitor the progress of this reaction up to 15 minutes (Table 3.1).

Table 3.1: Time study of oxidative fluorination of *N*-tosyl-protected aniline

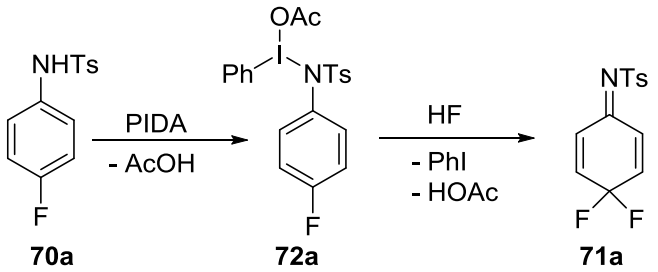


69a **70a** **71a**

Entry	Time (min)	^{19}F NMR Yield (%)[a]	
		5a	7a
1	1	**32**	**7**
2	5	**37**	**10**
3	**15**	**44**	**20**

[a]Yields determined by ^{19}F NMR by integration relative to 1-fluoro-3-nitrobenzene as the internal standard (D_1 = 10).

After reaction for 1 minute, *N*-(4-fluorophenyl)-4-methylbenzenesulfonamide **70a** was afforded in a 32 % NMR yield (Table 3.1, entry 1) which increased to 44 % after reaction for 15 minutes (Entry 3). However this increase in yield of product was concomitant with an increasing yield of difluorinated side-product **71a** (^{19}F NMR, δ = −96.6 ppm, $CDCl_3$), proposed to form as a result of oxidation of mono-fluorinated product **70a** with PIDA, followed by reaction with another molecule of HF (Scheme 3.21). In order to limit this product and oxidant consuming side-reaction, reaction time continued to be restricted to just 15 minutes in further studies.

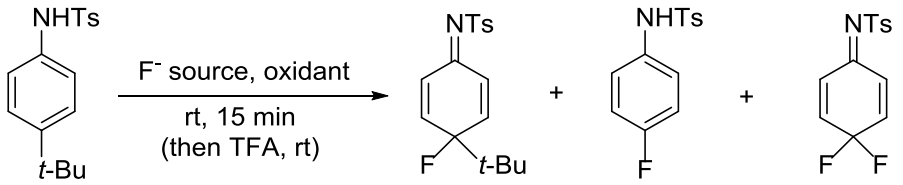


70a **72a** **71a**

Scheme 3.21: Proposed pathway for formation of difluorinated side-product 71a

Encouraged by these preliminary results, optimisation of this reaction in terms of fluoride source, oxidant and solvent was next performed employing the same model substrate (Table 3.2).

Table 3.2: Optimisation of oxidative fluorination of *N*-tosyl-protected aniline



69a **73a** **70a** **71a**

Entry	F^- (eq.)	Ox. (eq.)	Solvent	TFA[a] (min)	^{19}F NMR Yield (%)[b] 73a**, 70a,** 71a
1	HF·pyr (4.0)	PIDA (1.0)	DCM	-	0, **44**, 20
2	HF·pyr (4.0)	PIDA (1.0)	DCM	5	0, **46**, 6
3	HF·pyr (4.0)	$PhI(OPiv)_2$ (1.0)	DCM	5	0, **52**, 0
4	HF·pyr (4.0)	PIFA (1.0)	DCM	-	0, **34**, 6
5	HF·pyr (4.0)	PIDA (1.0)	DCE	-	0, **43**, 13
6	HF·pyr (4.0)	PIDA (1.0)	THF	-	0, **0**, 0
7	HF·pyr (4.0)	PIDA (1.0)	Et_2O	-	8, **0**, 0
8	$3HF{\cdot}NEt_3$ (4.0)	PIDA (1.0)	DCM	-	85, **0**, 0
9	$3HF{\cdot}NEt_3$ (4.0)	PIDA (1.0)	DCM	5	0, **42**, 9
10	$TBAF{\cdot}3H_2O$ (1.0)	PIDA (1.0)	DCM	5	0, **12**, 0
11	HF·pyr (1.0)	PIDA (1.0)	DCM	-	68,**19**, 6
12	**HF·pyr (1.0)**	**PIDA (1.0)**	**DCM**	**5**	**0, 94, 2**
13	HF·pyr (1.0)	$PhI(OPiv)_2$ (1.0)	DCM	5	0, **92**, 3
14	HF·pyr (1.0)	PIDA (2.0)	DCM	5	0, **0**, 43

[a] TFA added after 15 minutes. [b] Yields determined by ^{19}F NMR by integration relative to 1-fluoro-3-nitrobenzene as the internal standard (D_1 = 10).

Analysis of the crude reaction mixture indicated that as well as monofluorinated product **70a** and difluorinated side-product **71a**, in some cases the dearomatised *tert*-butylated fluoro-intermediate **73a** (^{19}F NMR, δ = −160.4 ppm, $CDCl_3$) was also observed. In the first instance, an excess of HF·pyridine (4.0 eq.) was employed, as in the previously reported work for oxidative fluorination of phenols.[2] A screen of commercial oxidants revealed that whilst yields were comparable when PIDA was replaced with $PhI(OPiv)_2$, use of PIFA resulted in a drop in NMR yield to 34 % (Table 3.2, entries 1–4). The cheaper and more commonly available PIDA was therefore employed in future reactions.

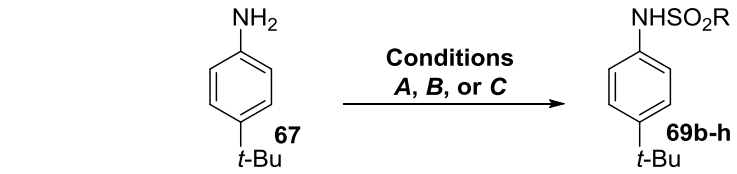
As anticipated, DCM and DCE emerged as the optimum solvents for this oxidative fluorination reaction, with no product observed in either THF or diethylether (Entries 5–7). A screen of nucleophilic fluorinating reagents revealed that only HF-based reagents

were suitable (Entry 10). Interestingly, whilst an excess of HF·pyridine was proficient at promoting the aromatisation of dienimine **73a** without addition of TFA (Entries 1 and 2), this was not the case for $3HF{\cdot}NEt_3$ (Entries 8 and 9). Contrary to expectation, reduction of the equivalents of HF·pyridine employed resulted in significantly increased yield of product **70a**, although under these conditions addition of TFA was required to facilitate the conversion of dienimine **73a** to **70a** (Entries 11-13). As might be expected, use of an excess of oxidant led mainly to the difluorinated dienimine **71a** resulting from further oxidative fluorination of **70a** (Entry 14). For this model substrate, the one-pot oxidative fluorination was therefore best performed with one equivalent of HF·pyridine and one equivalent of PIDA in DCM at room temperature, followed by treatment with TFA for 5 minutes before quenching with aqueous saturated sodium bicarbonate. Under these conditions, fluorinated product **70a** was formed in a 94 % NMR yield with just 2 % of difluorinated side-product **71a** (Entry 12). Purification by silica gel chromatography resulted in a 61 % isolated yield of **70a**, with the slight loss of yield attributed to the poor solubility of this sulfonamide in the eluant employed.

3.2.2 Protecting Group Study

Having established conditions for the oxidative fluorination of this *N*-tosyl-protected aniline model substrate, we next looked to investigate the tolerance of this reaction to other sulfonyl protecting groups. A range of sulfonyl-protected substrates were synthesised by reaction of 4-*tert*-butylaniline with commercially available aryl and alkyl sulfonyl chlorides in the presence of either pyridine or triethylamine as base (Table 3.3). Generally, the use of pyridine was found to be preferential in order to minimise formation of bis-tosylated side-product.

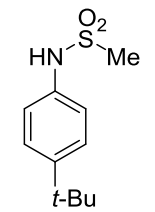
Table 3.3: Synthesis of sulfonyl-protected anilines



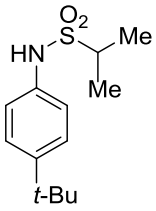
A: RSO_2Cl (1.2 eq,), pyridine (0.6 M), 0 ^oC-rt, 16 h

B: RSO_2Cl (1.2 eq,), NEt_3 (1.2 eq.), DCM (0.2 M), 0 ^oC-rt, 16 h

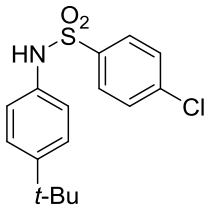
C: RSO_2Cl (1.0 eq,), pyridine (1.2 eq.), DCM (0.2 M), 0 ^oC-rt, 16 h



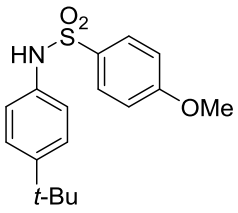
69b: *B*, 92 %



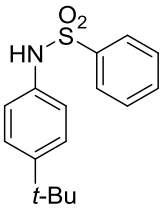
69c: *C*, 92 %



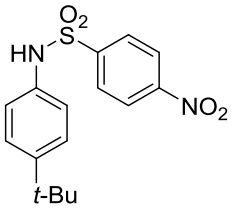
69d: *B*, 61 %



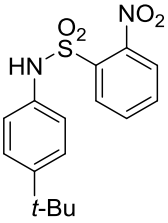
69e: *B*, 99 %



69f: *A*, 87 %



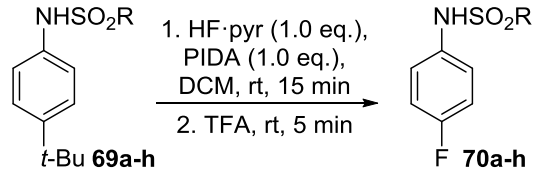
69g: *A*, 85 %

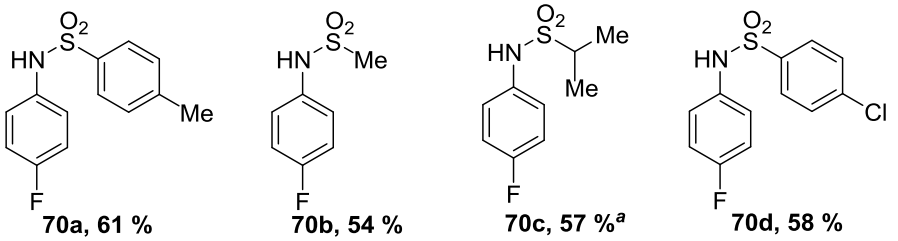


69h: *B*, 78 %

Under these conditions, sulfonyl-protected anilines **69b-h** were synthesised with yields between 78 and 92 % following purification by silica gel chromatography. These substrates were then subjected to the optimised conditions for this oxidative fluorination reaction (Table 3.4).

Table 3.4: Influence of sulfonyl group on oxidative fluorination reaction



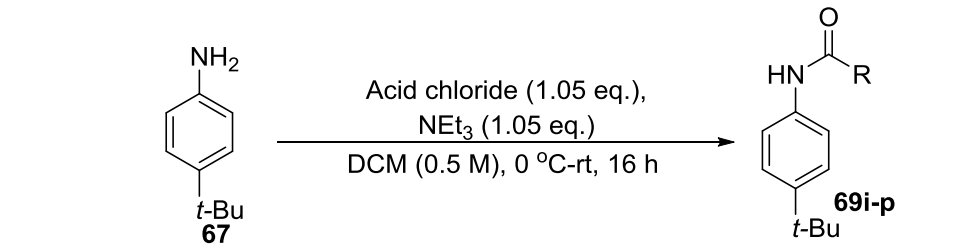


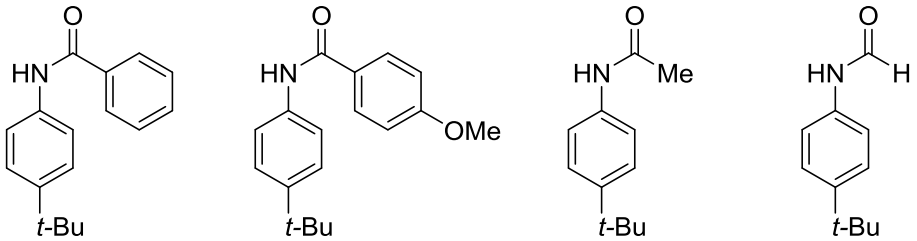
[a] Using HF·pyr (4.0 eq.)

The reaction was shown to be very generic with respect to sulfonyl groups and various aryl and alkyl sulfonamides underwent the oxidative fluorination reaction to afford *N*-(4-fluorophenyl)sulfonamides with isolated yields of 40 to 65 % following silica gel chromatography. Whilst aryl sulfonamides bearing a *para*-methoxy or *para*-chloro substituent afforded high yields of fluorinated product under the optimised conditions, for aryl sulfonamides with an electron withdrawing substituent such as an *ortho*- or *para*-nitro group, high yields were obtained only when an excess of HF·pyridine was employed. For these substrates, it is likely that inductive and mesomeric electron withdrawal causes reduced nucleophilicity of nitrogen during its initial attack on iodine. Although sulfonyl derivatives are often useful in their own right, for instances in which a primary aniline is required, the use of nosyl-protection may be advantageous due to the milder conditions for deprotection of this group, when compared to tosyl.[42]

The extension of this methodology to carbonyl-protected anilines was also considered. A series of anilide substrates was synthesised by reaction of 4-*tert*-butylaniline with commercially available acid chlorides in the presence of triethylamine as base, followed by purification by filtration or silica gel chromatography (Table 3.5). Ureas **69m** and **69n** could also be formed by reaction of the appropriate amines and isocyanates. Methylation of **69k** was carried out to afford bis-protected aniline **69p** in 71 % yield.

Table 3.5: Anilide substrate synthesis

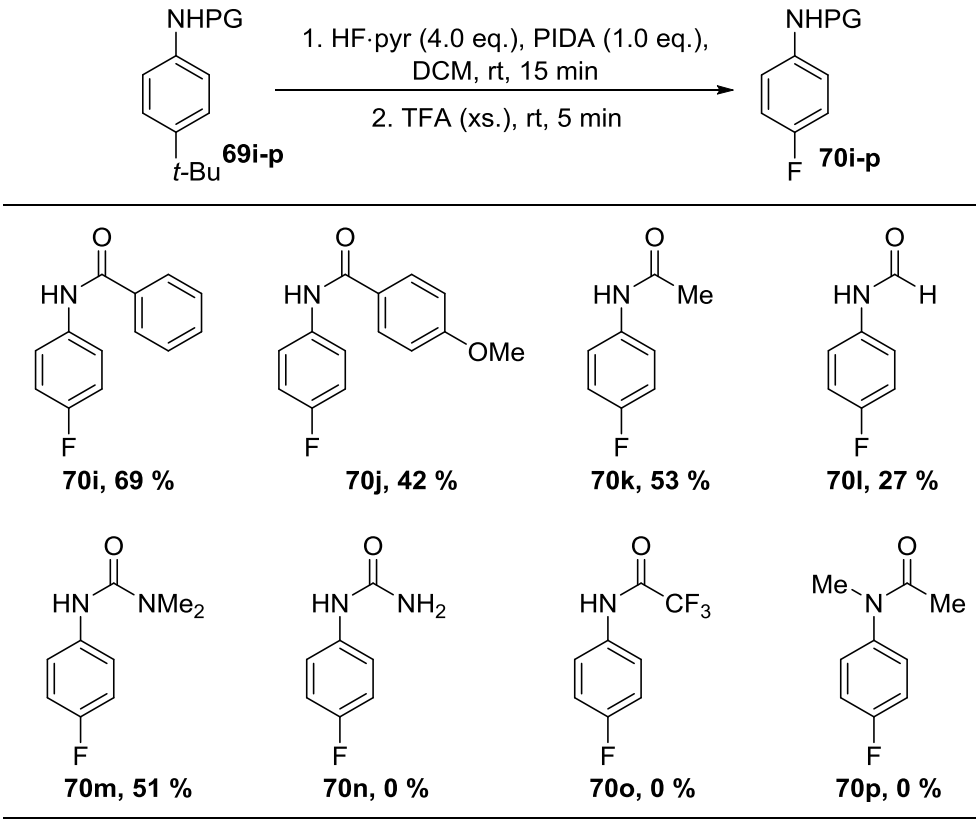




[a] 4-*tert*-Butylphenylisocyanate (1.0 eq.), $NHMe_2$·HCl (1.0 eq.), NEt_3 (1.2 eq.), DCM (0.2 M), 0 °C-rt, 16 h. [b] 4-*tert*-Butylaniline (1.0 eq.), HCl (2M), KCNO (1.2 eq.), 0 °C-rt, 4 h then 0 °C, 1 h. [c] **69k** (1.0 eq.), MeI (1.1 eq,), NaH (60 %) (1.5 eq.), rt, 14 h.

This range of anilide substrates was next subjected to the previously optimised conditions for oxidative fluorination (Table 3.6). However, for this class of substrates, highest isolated yields were obtained employing an excess of HF·pyridine, when compared to a stoichiometric amount.

Table 3.6: Extension of oxidative fluorination methodology to carbonyl protecting groups

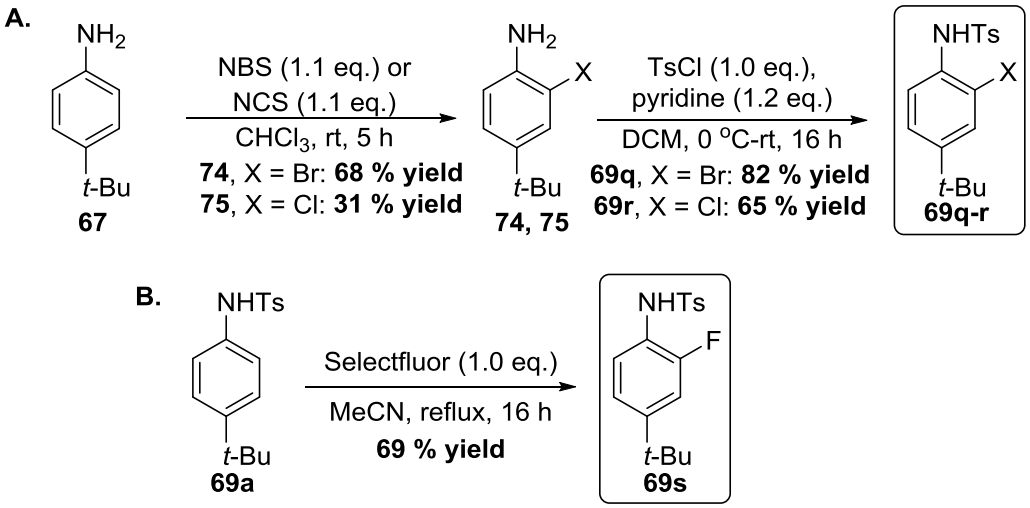


This reaction was shown to tolerate benzoyl groups as well as acetyl- and formyl-protection (Table 3.6, **70i to 70l**). When a urea protecting group was employed, bis-substitution of the primary amide group was crucial for the reaction to proceed (**70m** vs **70n**). An available lone pair on the nitrogen aniline is crucial and the reaction shut down completely when an inductively electron withdrawing trifluoroacetyl protecting group was employed (**70o**). As anticipated, bis-protected aniline **70p** was unresponsive to the oxidative fluorination reaction.

3.2.3 Substrate Scope

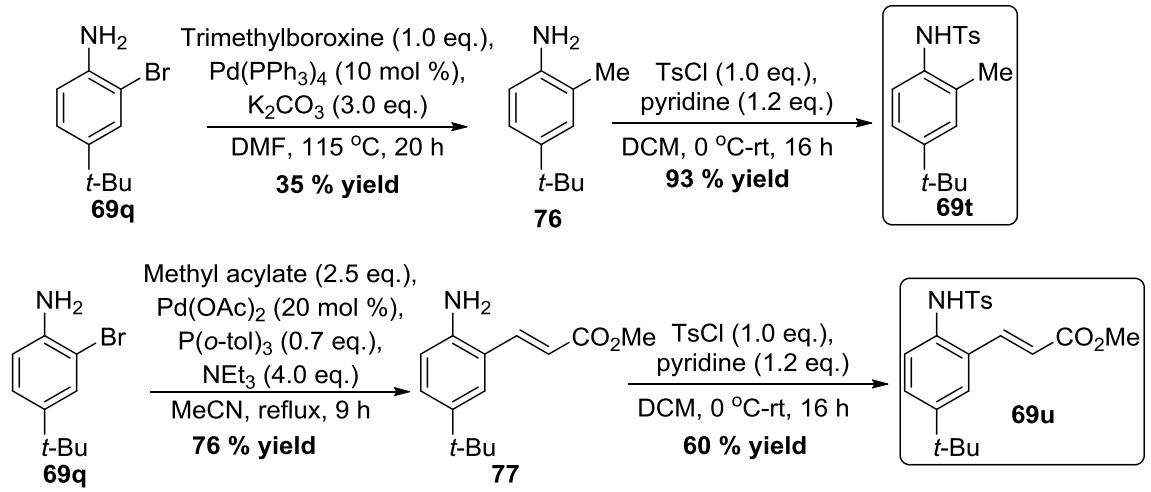
Next, to examine the influence of the *N*-aryl sub-motif on the oxidative fluorination reaction, a series of *N*-tosyl-protected anilines was employed. The synthesis of 2-bromo and 2-chloro substituted precursors **69q** and **69r** was achieved by reaction of 4-*tert*-butylaniline with *N*-bromosuccinimide (NBS) and *N*-chlorosuccinimide (NCS)

respectively, followed by tosyl-protection (Scheme 3.22, A). The 2-fluoro substituted aniline **69s** could also be obtained in a 69 % yield by reaction of *N*-(4-(*tert*-butyl)phenyl)-4-methylbenzenesulfonamide **69a** with Selectfluor in acetonitrile at reflux (Scheme 3.22, B).



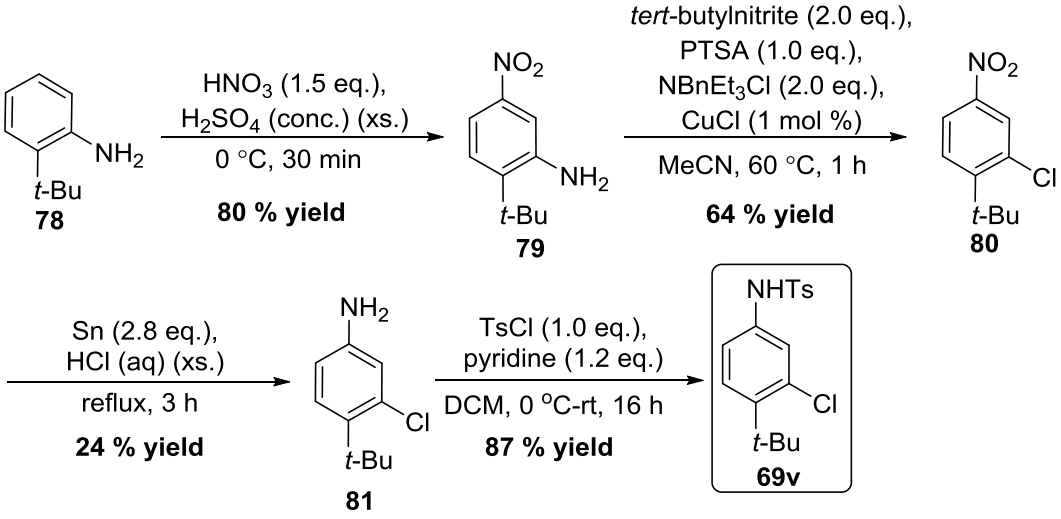
Scheme 3.22: Synthesis of 2-bromo, chloro and fluoro substituted *N*-arylsulfonamides

Access to two additional substrates was provided by further derivatisation of 2-bromo-4-*tert*-butylaniline **69q**. This aniline was subjected to a palladium-catalysed Suzuki-Miyaura coupling with trimethylboroxine to afford 2-methyl substituted aniline **76** (Scheme 3.23, A). Similarly, a Heck reaction of **69q** with methyl acrylate provided access to olefin substituted derivative **77** (Scheme 3.23, B). The double bond geometry of **69u** was confirmed as *trans* by a $^{3}J_{H\text{-}H}$ coupling constant of 15.8 Hz.



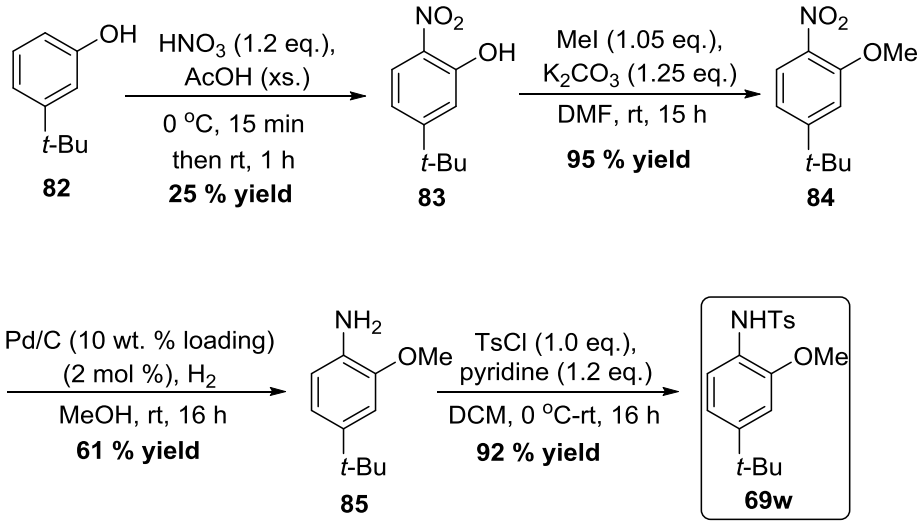
Scheme 3.23: Palladium-catalysed Suzuki-Miyaura and Heck couplings of 2-bromo substituted aniline 69q

The synthesis of 3-chloro substituted aniline **81** was somewhat more complicated and involved 3 steps from 2-*tert*-butylaniline (Scheme 3.24). When aniline **78** was treated with a mixture of nitric and sulfuric acid at 0 °C, regioselective nitration took place, due to protonation of the amine under the reaction conditions which rendered it *meta* directing. Diozatisation and chlorine substitution took place via a copper(I)-catalysed Sandmeyer reaction, followed by the low yielding reduction of the nitro group by a mixture of tin and hydrochloric acid.



Scheme 3.24: Synthesis of *N*-(4-(*tert*-butyl)-3-chlorophenyl)-4-methylbenzenesulfonamide 69v

Synthesis of 2-methoxy substituted aniline **85** could also be accomplished in 3 steps, from 2-*tert*-butylphenol **82** (Scheme 3.25). Nitration of this electron rich substrate was carried out in acetic acid, as opposed to sulfuric acid, in order to limit over nitration, with substitution *ortho* to the hydroxy substituent favoured over *para* substitution due to the steric effect of the 3-*tert*-butyl group. Only a low yield (25 %) of product was isolated in this reaction, but further optimisation was not deemed necessary for this substrate synthesis. Next, methylation with methyl iodide was performed to afford anisole derivative **84**, which was subjected to palladium-catalysed hydrogenation to provide aniline **85**.

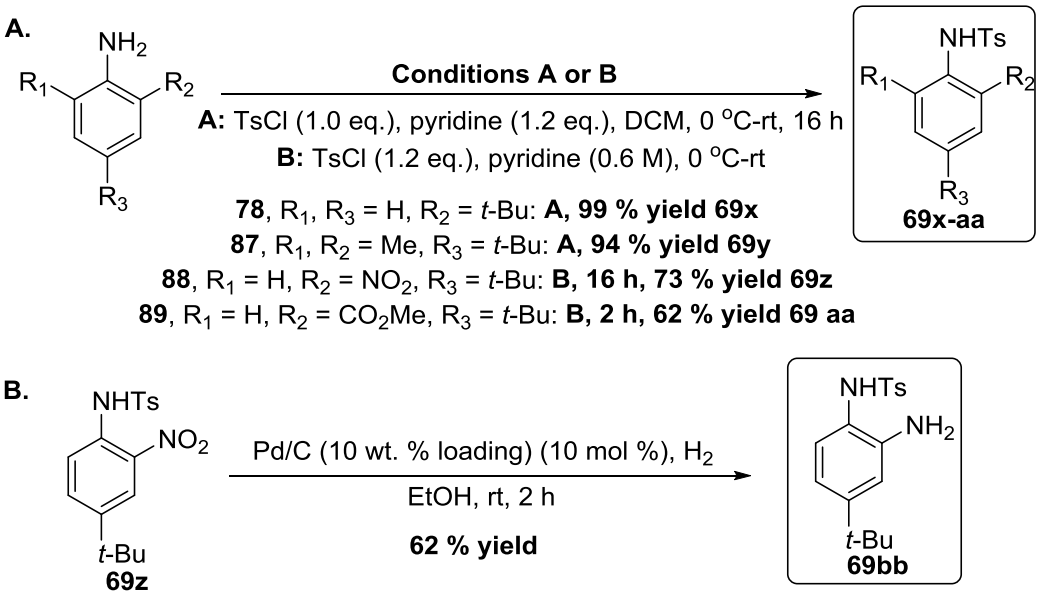


Scheme 3.25: Synthesis of *N*-(4-(*tert*-Butyl)-2-methoxyphenyl)-4-methylbenzenesulfonamide

These two lengthy precursor syntheses, imposed by the requirement for a *tert*-butyl leaving group, highlight a disadvantage of this methodology for complex substrates. In contrast, synthesis of substrates **69x-z** was performed by facile tosyl-protection of the corresponding commercially available anilines (Scheme 3.26, A). Tosylation of methyl 2-amino-5-*tert*-butyl benzoate ester[1] was also carried out to afford protected aniline **69aa** with a 62 % yield after just 2 hours. Furthermore, 2-amino derivative **69bb** could also be

[1] Methyl 2-amino-5-*tert*-butyl benzoate ester was synthesised by Dr Begoña Checa. See reference for experimental details.[43]

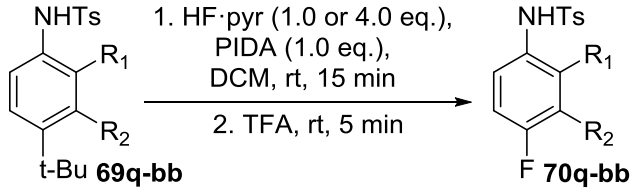
synthesised by palladium-catalysed hydrogenation of tosyl-protected aniline **69z** (Scheme 3.26, B).

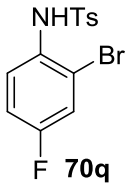
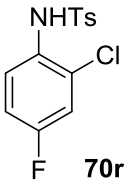
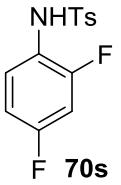
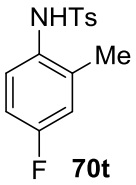
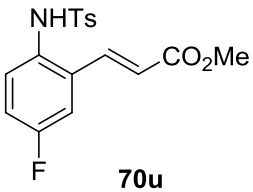
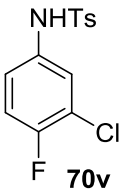
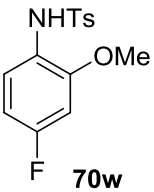
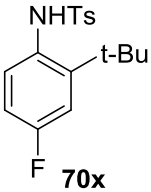
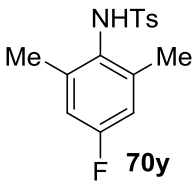
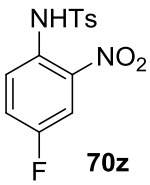
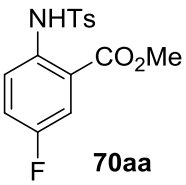
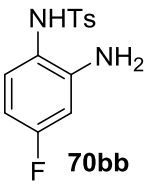


Scheme 3.26: Synthesis of *N*-arylsulfonamides 69x-bb

With this library of tosyl-protected anilines in hand, they were next subjected to the oxidative fluorination reaction, with the effect on yield determined when both stoichiometric and an excess of HF·pyridine was employed in each case (Table 3.7).

Table 3.7: Influence of *N*-aryl sub-motif on reactivity



	 **70q**	 **70r**	 **70s**	 **70t**
HF·pyr (4.0 eq.):	**52 %** (93 %)	**54 %** (71 %)	**45 %** (49 %)	**60 %** (68 %)
HF·pyr (1.0 eq.):	(44 %)	(47 %)	(28 %)	(45 %)
	 **70u**	 **70v**	 **70w**	 **70x**
HF·pyr (4.0 eq.):	**52%** (83 %)	**61 %** (67 %)	(22 %)	**39 %** (71 %)[a]
HF·pyr (1.0 eq.):	(46 %)	-	(24 %)	(51 %)
	 **70y**	 **70z**	 **70aa**	 **70bb**
HF·pyr (4.0 eq.):	(15 %)	(3%)	**21 %** (27 %)	(0 %)
HF·pyr (1.0 eq.):	(10 %)	(1 %)	(20 %)	-

Yields of isolated products; values under parenthesis refer to yields determined by ^{19}F NMR by integration relative to 1-fluoro-3-nitrobenzene as the internal standard (D_1 = 10). [a] Aniline **70x** was prepared from 2-*tert*-butyl-*N*-tosylaniline.

This study demonstrated that a range of *ortho* or *meta* substituents were tolerated, including alkyl, halogen and ester groups. However, in all cases, in contrast to the model substrate, best yields were obtained when an excess of HF·pyridine was employed. The low yield of ester substituted aniline **70aa** and nitro substituted aniline **70z** indicated that electron withdrawing groups have a detrimental effect on reactivity. However, distancing the ester functionality from the ring was beneficial to the yield, as demonstrated by the synthesis of fluorinated aniline **70u**. The low yield of aniline **70w** was likely due to the

non-productive side-reaction in which fluoride attack on the methoxy group occurs to form methyl fluoride.

We were surprised to observe that oxidative fluorination of 2-*tert*-butyl-*N*-tosylaniline was selective for the *para* position despite the presence of a *tert*-butyl leaving group at the *ortho* positon. The reaction afforded only aniline **70x** (^{19}F NMR, δ = −115.7 ppm, $CDCl_3$) with no trace of 2-fluoro-*N*-tosylaniline (^{19}F NMR, δ = −129.7 ppm, $CDCl_3$) or 2,4-difluoro-*N*-tosylaniline (^{19}F NMR, δ = −112.0 ppm and −123.4 pm, $CDCl_3$) detected in the crude reaction mixture. This preference for reaction at the *para* position was likely due to steric hindrance to fluorination at the *ortho* position of the nitrenium intermediate. Likewise, the low yield of aniline **70y** is perhaps due to the disfavoured attack on PIDA as a result of substitution at both *ortho* positions. In correspondence with literature precedent of oxidative fluorination of unprotected anilines,[34] free amine substituents were not tolerated under these reactions conditions.

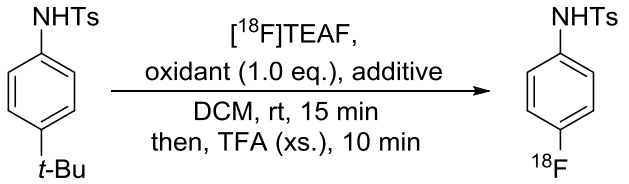
These studies have demonstrated for the first time that *N*-arylsulfonamides are suitable substrates for an oxidative fluorination/ rearomatisation procedure to afford *para*-fluoroaniline products. A range of sulfonyl protecting groups and aryl substituents are tolerated by the reaction, although some substrates required addition of an excess of HF·pyridine, in contrast to the model reaction.

3.2.4 Oxidative Fluorination of *N*-Arylsulfonamides with ^{18}F

Since the use of late-stage ^{18}F-fluorination is favourable for the synthesis of PET tracers, extension of this methodology to employ [^{18}F]fluoride was highly desirable. Whilst the short reaction time is beneficial for translation to radiofluorination, [^{18}F]HF-based reagents are available only with low specific activity and therefore are non-ideal.[44] Recent work by the Gouverneur group on the oxidative fluorination of phenols found that

[^{18}F]TBAF ([^{18}F]tetrabutylammonium fluoride) or [^{18}F]TEAF ([^{18}F]tetraethylammonium fluoride) in combination with TFA could be employed as a substitute for [^{18}F]HF reagents.[2] In the first instance, these literature conditions were applied to the oxidative fluorination of *N*-arylsulfonamides (Table 3.8).

Table 3.8: Oxidative fluorination of *N*-arylsulfonamide 69a with [^{18}F]TEAF



69a **[^{18}F]70a**

Entry[a]	Oxidant	Additive (eq.)	RCC (%)[b]
1	PIDA	TFA (4.0)	**2 ± 1** (*n* = 4)
2[c]	PIDA	TFA (4.0)	**0** (*n* = 2)
3	TolI=O	TFA (4.0)	**0** (*n* = 2)
4	PhI(OPiv)$_2$	TFA (4.0)	**0** (*n* = 2)
5	PIDA	AcOH (4.0)	**0** (*n* = 2)
6	PIDA	TCA (4.0)	**Trace** (*n* = 2)
7	PIDA	AgOTf (1.0)	**3 ± 1** (*n* = 2)
8	PIDA	AgOTf (4.0)	**0** (*n* = 2)
9	PIDA	AgOTf (1.0) + TFA (4.0)	**0** (*n* = 2)

[a] To substrate in vial with stirrer bar was added [^{18}F]TEAF in DCM followed by solution of oxidant and additive in DCM (total volume = 200 μL). Reaction was stirred for 15 minutes before addition of TFA. After a further 10 minutes aliquots were taken for radio-TLC and radio-HPLC. [b] RCC determined by product of radio-TLC yield and RCP by radio-HPLC and is listed with standard deviation of the mean. *n* = number of experiments. [c] MeCN as solvent ([^{18}F]TEAF dispensed in DCM). [^{18}F]TEAF = ([^{18}F]tetraethylammonium fluoride. TCA = trichloroacetic acid.

For these studies, [^{18}F]TEAF was employed, which displays similar reactivity to [^{18}F]TBAF but advantageously has a commercially available precursor, allowing the methodology to be more readily adapted for use by other sites or researchers. RCCs were determined by the product of the radio-TLC yield and the radiochemical purity (RCP) determined by radio-HPLC. When model substrate **69a** was treated with [^{18}F]TEAF in DCM in the presence of PIDA and TFA for 15 minutes, 4-[^{18}F]fluoro-*N*-tosylaniline **[^{18}F]70a** was formed with just a 2 % ± 1 % (*n* = 4) RCC following TFA promoted rearomatisation (Table 3.8, entry 1). This was surprising given the successful ^{18}F-

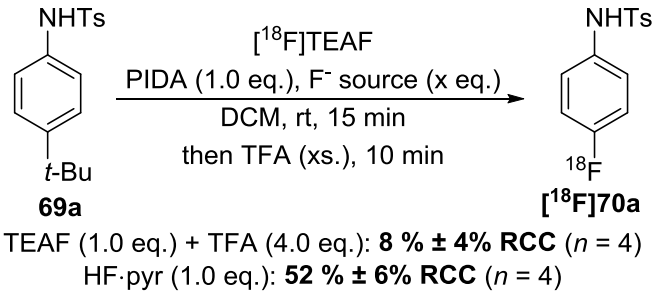
fluorination of phenols under these conditions but served to underscore the challenges posed by adaptation of methods to radiochemistry.

Change of solvent to acetonitrile, which is commonly employed for ^{18}F-fluorinations, was unsuccessful in this case (Entry 2). Similarly, no radiolabelled product was observed when iodosotoluene or *bis*(*tert*-butylcarbonyloxy)iodobenzene were employed as oxidant (Entries 3 and 4). There is a significant difference in pK_a between HF (pK_a = 3.2, H_2O) and TFA (pK_a = −0.3, H_2O).[2] However adjustment of pK_a by employing acetic acid (pK_a = 4.8, H_2O) or trichloroacetic acid (TCA) (pK_a = 0.7, H_2O) as alternatives was unsuccessful (Entries 5 and 6).

Work by Sanford and co-workers in 2012 reported that cesium fluoride could be employed for a hypervalent iodine-mediated C-H fluorination reaction, when used in conjunction with silver triflate.[45] Unfortunately, use of silver triflate as a promoter for our reaction resulted in a maximum RCC of 3 % ± 1 % (*n* = 2) (Entries 7-9).

However, it was found that the RCC of **[^{18}F]70a** increased significantly when a carrier-added approach was employed (Scheme 3.27). In the first instance, one equivalent of TEAF was utilised in combination with TFA, to afford **[^{18}F]70a** with 8 % ± 4 % RCC (*n* = 4). We were pleased to find that when HF·pyridine was employed as the carrier, this RCC increased to 52 % ± 6 % (*n* = 4) (Scheme 3.27).

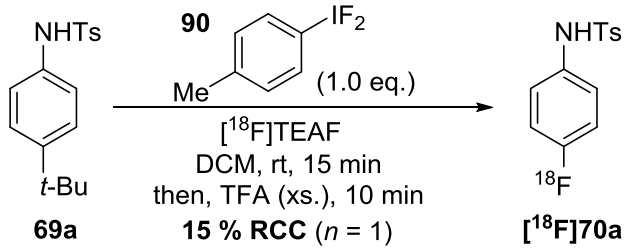
[2] Data from Evans pK_a table.



RCC determined by product of radio-TLC yield and RCP by radio-HPLC. *n* = number of experiments.

Scheme 3.27: Carrier added approach to oxidative fluorination of *N*-arylsulfonamide with [^{18}F]TEAF

Whilst currently unfavourable in terms of specific activity, this was a significant result highlighting that imposing a reactivity switch of *N*-arylsulfonamides to enable labelling with [^{18}F]fluoride was possible. We appreciated the possibility that the reaction may transit via formation of an IF_2 reagent and therefore the use of difluoroiodotoluene **90** as oxidant was also considered (Scheme 3.28).



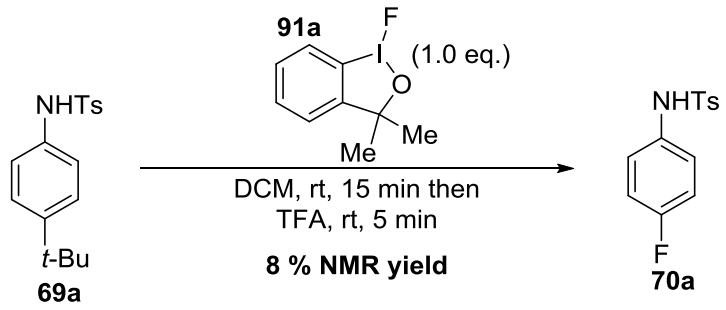
RCC determined by product of radio-TLC yield and RCP by radio-HPLC. *n* = number of experiments.

Scheme 3.28: Oxidative fluorination-mediated by difluoroiodotoluene

Under these conditions, **[^{18}F]70a** was formed with 15 % RCC. Although currently carrier-added, this underscores the potential for use of I-F reagents in this radiosynthesis. An ideal procedure would involve the *in situ* formation of an I-F reagent from [^{18}F]TEAF in order to obtain ^{18}F-labelled *N*-arylsulfonamides without dilution of specific activity.

With this in mind, the use of fluoroiodane **91a** was considered, since its synthesis from TBAF was recently reported by Stuart and co-workers.[28] A preliminary reaction in cold mode indicated that oxidative fluorination of model substrate **69a** could be achieved by

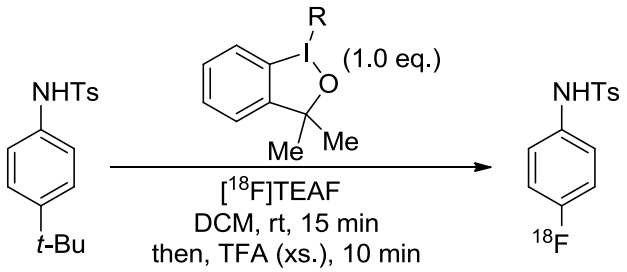
use of fluoroiodane **91a** to afford monofluorinated product **70a**, albeit in low yield (Scheme 3.29).



Scheme 3.29: Oxidative fluorination-mediated by fluoroiodane 91a

The next study therefore involved treatment of a series of fluoroiodane precursors with [^{18}F]TEAF to facilitate *in situ* formation of iodine reagent **[^{18}F]91a** prior to addition of the substrate (Table 3.9).

Table 3.9: Oxidative fluorination of *N*-arylsulfonamide with [^{18}F]TEAF mediated by *in situ* formation of I-F reagent



Entry[a]	R (91a-d)	Pre-stir (min)	RCC (%)[b]
1	CF_3CO_2 (**91b**)	-	**0** (*n* = 2)
2	CF_3CO_2 (**91b**)	10	**0** (*n* = 2)
3	OTs (**91c**)	-	**0** (*n* = 2)
4[c]	OTs (**91c**)	-	**0** (*n* = 2)
5	OTs (**91c**)	10	**0** (*n* = 2)
6	Cl (**91d**)	-	**0** (*n* = 2)
7	Br (**91d**)	-	**0** (*n* = 2)
8	F (**91a**)	-	**0** (*n* = 2)

[a] To oxidant in vial with stirrer bar was added [^{18}F]TEAF in DCM. The reaction was stirred for x min before addition of a solution of substrate in DCM (total volume = 300 μL). Reaction was stirred for 15 minutes before addition of TFA. After a further 10 minutes aliquots were taken for radio-TLC and radio-HPLC. [b] RCC determined by product of radio-TLC yield and RCP by radio-HPLC. *n* = number of experiments. [c] Addition of TFA (4.0 eq.).

Unfortunately, fluoroiodane **91a** cannot be observed by mass spectrometry and its poor stability in water prohibited radio-HPLC identification of this species, therefore the

reaction was monitored solely by formation of **[^{18}F]70a**. No product was formed when the triflate or tosylate precursors were employed (Table 3.9, entries 1 and 3) and pre-stirring the iodane precursors with [^{18}F]TEAF for 10 minutes prior to substrate addition was similarly unsuccessful (Entries 2 and 5). Addition of TFA had no effect on reaction yield (Entry 4) and chloro- and bromo- precursors were also inefficient at mediating the reaction (Entries 6 and 7). Surprisingly, even when fluoroiodane **91a** itself was employed in a carrier-added approach, no radiolabelled product was observed (Entry 8). This study therefore revealed that derivatives of fluoroiodane **91a** are currently not suitable for mediation of this oxidative ^{18}F-fluorination reaction and further progress of would benefit from development of an analytical method to determine yield of formation of this ^{18}F-labelled reagent.

3.3 Summary

This chapter has reported the hypervalent iodine-mediated one-pot oxidative fluorination and rearomatisation reaction of *N*-aryl sulfonamides, a class of substrates which until now were reported as incompatible with this transformation. We have demonstrated that the reaction tolerates a variety of protecting groups and aryl substituents and furthermore, that on a model substrate this umpolung methodology could be extended to the radiofluorination of *N*-arylsulfonamides using nucleophilic [^{18}F]fluoride. However, highest yields are obtained on addition of HF·pyridine carrier and therefore the labelled product currently suffers from diminished specific activity. These studies have resulted in publication of this work in the Journal of Fluorine Chemistry.[43]

3.4 References

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Chapter 4:

Experimental Data

4. Experimental Data

4.1 General Experimental

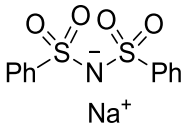
All NMR spectra were recorded on Bruker AVIII400 and AVII500 spectrometers. Proton and carbon-13 NMR spectra are reported as chemical shifts (δ) in parts per million (ppm) relative to the solvent peak using the Bruker internal referencing procedure (edlock). Fluorine-19 NMR spectra are referenced relative to $CFCl_3$ in $CDCl_3$. Coupling constants (*J*) are reported in units of hertz (Hz) to the nearest 0.1 Hz. The following abbreviations are used to describe multiplicities – s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), brs (broad singlet) brd (broad doublet). High resolution mass spectra (HRMS, *m/z*) were recorded on a Bruker MicroTOF spectrometer using positive/negative electrospray ionization (ESI). Infrared spectra were recorded either as the neat compound or as a solution using a Bruker Tensor 27 FT-IR spectrometer. Absorptions are reported in wavenumbers (cm^{-1}) and only peaks of interest are reported. Optical rotations were measured on a PerkinElmer Polarimeter model 341. Specific rotations are reported in 10^{-1} deg cm^2 g^{-1} and concentrations in g/100 mL. Melting points of solids were measured on a Griffin apparatus and are uncorrected. All reaction solvents were dried on a column of alumina prior to use. Unless performed in a glass vial or Teflon tube, all reactions were performed under argon. Chemicals were purchased from Acros, Alfa Aesar, Fisher Scientific, Fluorochem, TCI and Sigma-Aldrich and used as received, except for aldehydes which were purified by column chromatography on silica gel or distillation prior to use. Reactions were monitored by thin-layer chromatography (TLC) carried out on Merck Kiesegel 60 F254 plates. Silica gel chromatography was performed over Merck silica gel C60 (40-60 μm). Absolute stereochemistry of fluorinated products determined by comparison with literature reaction.

4.2 Chapter 2: Organomediated Enantioselective ^{18}F-Fluorination

4.2.1 Enamine Catalysis for Asymmetric α-[^{18}F]Fluorination of Aldehydes

4.2.1.1 Reagent Synthesis

Sodium dibenzenesulfonamide

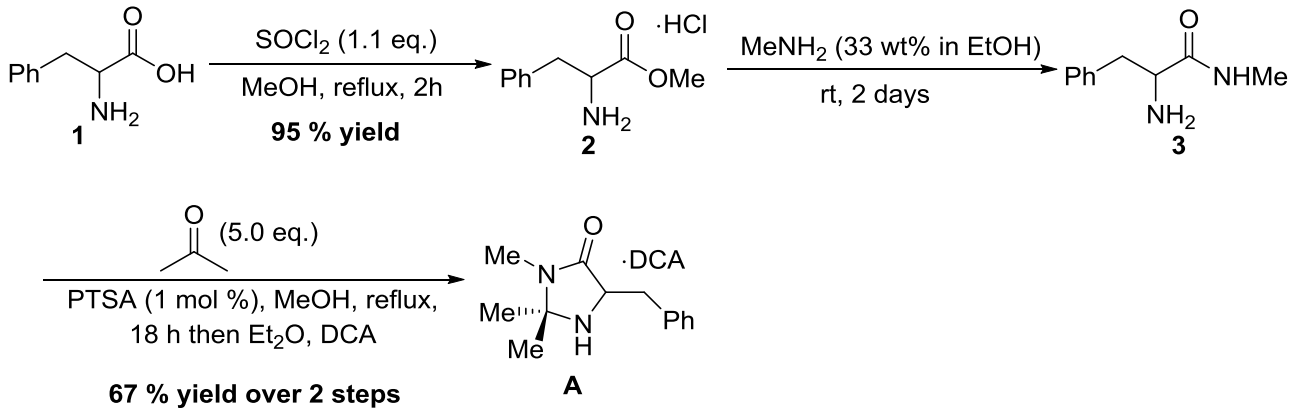


Dibenzenesulfonamide (1.00 g, 3.36 mmol, 1.0 eq) and sodium hydroxide (134 mg, 3.36 mmol, 1.0 eq.) in a solution of acetone/ water (1:1) (3.5 mL) were stirred for 15 hours at room temperature. The solvent was removed under reduced pressure to afford the title compound directly as a white solid (1.07 g, 3.35 mmol, quantitative).

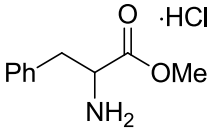
^{1}H NMR (400 MHz, D_2O): δ = 7.30-7.36 (m, 4H), 7.46 (tt, *J* = 7.3 Hz, *J* = 1.2 Hz, 2H), 7.52-7.56 (m, 4H); **^{13}C NMR (101 MHz, D_2O)** δ = 126.1, 128.9, 132.3, 140.9; **LRMS (ESI$^+$, m/z):** $[C_{12}H_{11}NNaO_4S_2]^+$ $(M+H)^+$ calc. 320.0, found 320.0.

2,2,3-Trimethyl-5-benzyl-4-imidazolidinone dichloroacetic acid (A)

Prepared according to literature procedure.[1]



Methyl 2-amino-3-phenylpropanoate hydrochloric acid (2)



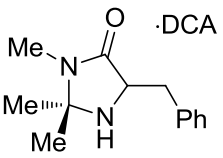
To DL-phenylalanine (5.00 g, 30.3 mmol. 1.0 eq.) in methanol (25 mL) at 0 °C was added thionyl chloride (2.42 mL, 33.3 mmol, 1.1 eq.). The

reaction was heated to reflux for 2 hours before the solvent was removed under reduced pressure to directly afford the title compound as a white solid (6.16 g, 28.6 mmol, 95 % yield).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.10 (dd, *J* = 13.7 Hz, *J* = 7.3 Hz, 1H), 3.24 (dd, *J* = 13.9 Hz, *J* = 5.4 Hz, 1H), 4.20 (dd, *J* = 7.3 Hz, *J* = 5.9 Hz, 1H), 7.20-7.35 (m, 5H), 8.86 (brs, 3H, NH_3^+); **^{13}C NMR (101 MHz, $CDCl_3$):** δ = 35.8, 52.5, 53.3, 127.3, 128.6, 129.4, 134.8, 169.3; **LRMS (ESI$^+$, m/z):** $[C_{10}H_{14}NO_2]^+$ $(M+H)^+$ calc. 180.1, found 180.1.

Data consistent with literature values.[2]

2,2,3-Trimethyl-5-benzyl-4-imidazolidinone (A) dichloroacetic acid



To a solution of methylamine (33 % in EtOH) (10 mL, 85.0 mmol, 3.0 eq.) was added methyl 2-amino-3-phenylpropanoate hydrochloric acid **2** (6.10 g, 28.3 mmol, 1.0 eq.). The reaction was stirred at room temperature for 48 hours before the solvent was removed under reduced pressure. Excess methylamine was removed by repeated addition of diethyl ether and removal under reduced pressure, until a white solid was obtained. This hydrochloric acid salt was treated with saturated aqueous $NaHCO_3$ and extracted into chloroform (x3), dried over sodium sulfate and the solvent removed under reduced pressure to yield the free amine **3**.

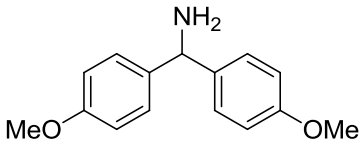
To the crude residue was added methanol (50 mL), acetone (10.4 mL) and *p*-toluenesulfonic acid (53 mg, 0.28 mmol, 1 mol %). The reaction was heated for reflux for 18 hours, then allowed to cool to room temperature before removal of the solvent under reduced pressure. The residue was dissolved in diethyl ether and dichloroacetic acid (2.33 mL, 28.3 mmol, 1.0 eq.) was added. The resultant precipitate was removed by filtration and dried under high vacuum to afford the title compound as a white solid (6.56 g, 18.8 mmol, 67 % yield).

^{1}H NMR (400 MHz, D_2O): δ = 1.51 (s, 3H), 1.59 (s, 3H), 2.82 (s, 3H), 3.04 (dd, *J* = 15.4 Hz, *J* = 9.6 Hz, 1H), 3.40 (dd, *J* = 15.2 Hz, *J* = 4.6 Hz, 1H), 4.58 (dd, *J* = 9.6 Hz, *J* = 4.4 Hz, 1H), 5.95 (s, 1H), 7.17-7.45 (m, 5H); **^{13}C NMR (101 MHz, D_2O):** δ = 21.6, 23.3, 25.2, 33.5, 58.4, 68.3, 78.4, 127.8, 129.0, 129.2, 134.5, 167.8, 170.7; **LRMS (ESI^+, m/z):** $[C_{13}H_{19}NO_2]^+$ $(M+H)^+$ calc. 219.1, found 219.2.

Data matched commercial sample.

Identical procedure was also performed employing D-phenylalanine and L-phenylalanine.

Bis(4-methoxyphenyl)methanamine (18)



Prepared according to literature procedure.[3]

A 2-neck flask equipped with a reflux condenser was charged with magnesium (700 mg, 44.0 mmol, 1.1 eq.) and heat dried under vacuum before the addition of THF (60 mL), 4-bromoanisole (5.50 mL, 44.0 mmol, 1.1 eq.) and a few crystals of iodine. The reaction was heated to reflux for 3 hours and then cooled to room temperature for the addition of 4-methoxybenzonitrile (5.32 g, 40.0 mmol, 1.0 eq.). The reaction was heated to reflux for a further 24 hours and then cooled to 0 °C. A solution of $LiAlH_4$ (1.52 g, 40.0 mmol, 1.0 eq.) in THF (40 mL) was transferred via cannula and the reaction was heated to reflux for a further 18 hours. Once cooled to room temperature, the reaction was quenched by the sequential addition of water (1.6 mL), NaOH (10 % aq.) (3.2 mL) and water (4.8 mL). The resultant suspension was filtered through Celite and washed with DCM. The filtrate was washed with brine, the organic phase was dried over $MgSO_4$ and the solvent was removed under reduced pressure. Purification by column chromatography on silica gel (SiO_2, petroleum ether 30-40: EtOAc 1:1-1:4 + 1% NEt_3) afforded the title compound as a white solid (6.85 g, 28.2 mmol, 71 % yield).

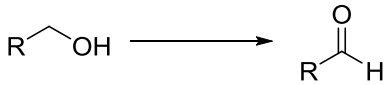
^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.78 (brs, 2H), 3.82 (s, 6H), 5.18 (s, 1H), 6.89 (d, *J* = 8.8 Hz, 4H), 7.32 (d, *J* = 8.8 Hz, 4H); **^{13}C NMR (101 MHz, $CDCl_3$):** δ = 55.2, 58.5, 113.8, 127.8, 138.2, 158.4; **LRMS (ESI$^+$, m/z):** $[C_{12}H_{18}NaO_2]^+$ $(M+Na)^+$ calc. 217.1, found 217.1.

Data consistent with literature values.[4]

4.2.1.2 Substrate Synthesis

General procedure for aldehyde synthesis via Swern oxidation

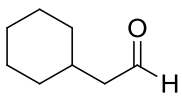
Carried out according to literature procedure.[5]



11b-e **4b-e**

To oxalyl chloride (1.2 eq.) in DCM (0.3 M) at −78 °C was added DMSO (2.0 eq.) in DCM (2.5 M). The reaction was stirred for 5 minutes before the addition of the alcohol substrate (1.0 eq.) in DCM (1.25 M) dropwise. After stirring for a further 15 minutes, NEt_3 (4.0 eq.) was added over a period of 5 minutes. The reaction was then warmed to 0 °C and stirred for 30 minutes. The reaction was quenched with saturated aqueous sodium bicarbonate, then organic phase was extracted with DCM, dried over $MgSO_4$ and the solvent removed under reduced pressure. Purification was performed by column chromatography on silica gel.

2-Cyclohexylacetaldehyde (4b)

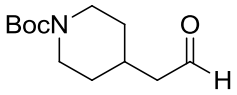


Prepared according to general procedure for Swern oxidation employing 2-cyclohexylethanol (1.26 mL, 9.00 mmol, 1.0 eq.). Purification by column chromatography on silica gel (SiO_2, petroleum ether 30-40: EtOAc 49:1) afforded the title compound as a colourless oil (1.03 g, 8.04 mmol, 89 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.90-1.07 (m, 2H), 1.07-1.21 (m, 1H), 1.21-1.36 (m, 2H), 1.59-1.77 (m, 5H), 1.80-1.95 (m, 1H), 2.28 (dd, *J* = 2.5 Hz, *J* = 6.9 Hz, 2H), 9.74 (t, *J* = 2.3 Hz, 1H); **^{13}C NMR (101 MHz, $CDCl_3$):** δ = 26.0, 26.0, 32.6, 33.2, 51.4, 202.9.

Data consistent with literature values.[6]

***tert*-Butyl 4-(2-oxoethyl)piperidine-1-carboxylate (4c)**

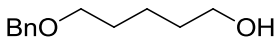


Prepared according to general procedure for Swern oxidation employing *N*-Boc-4-piperidineethanol (1.00g, 4.36 mmol, 1.0 eq.). Purification by column chromatography on silica gel (SiO_2, Pentane: Et_2O 17:3) afforded the title compound as a colourless oil (708 mg, 3.11 mmol, 71 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.14 (d, *J* = 4.2 Hz, 2H), 1.34-1.45 (m, 9H), 1.64 (d, *J* = 13.7 Hz, 2H), 1.93-2.07 (m, 1H), 2.34 (dd, *J* = 6.6 Hz, *J* = 1.7 Hz, 2H), 2.69 (t, *J* = 12.4 Hz, 2H), 4.03 (d, *J* = 9.5 Hz, 2H), 9.73 (t, *J* = 1.7 Hz, 1H) ; **^{13}C NMR (101 MHz, $CDCl_3$):** δ = 28.3, 30.5, 31.8, 43.6, 50.2, 79.2, 154.6, 201.4.

Data consistent with literature values.[7]

5-(Benzyloxy)pentan-1-ol (11d)



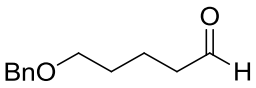
Prepared according to literature procedure.[5]

To a suspension of sodium hydride (60 %) (480 mg, 12.0 mmol, 1.2 eq.) in THF (40 mL) at room temperature, was added 1,5-pentanediol (7.40 mL, 70.0 mmol, 7.0 eq.) as a solution in THF (10 mL). Benzyl bromide (1.20 mL, 10.0 mmol, 1.0 eq.) was then added and the reaction was stirred for 5 hours. The resultant suspension was diluted with diethyl ether and quenched by addition of saturated aqueous ammonium chloride. The organic phase was extracted with ethyl acetate, dried over $MgSO_4$ and the solvent was removed under reduced pressure. Purification by column chromatography on silica gel (SiO_2, petroleum ether 30-40: EtOAc 19:1- 3:2) afforded the title compound as a colourless oil (1.76 g, 9.08 mmol, 91 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.41-1.51 (m, 2H), 1.55-1.62 (m, 2H), 1.62-1.70 (m, 2H), 3.49 (t, *J* = 6.5 Hz, 2H), 3.65 (t, *J* = 6.6 Hz, 2H), 4.51 (s, 2H), 7.27-7.37 (m, 5H); **^{13}C NMR (101 MHz, $CDCl_3$):** δ = 22.4, 29.4, 32.5, 62.8, 70.3, 72.9, 127.5, 127.6, 128.3, 138.5; **LRMS (ESI^+, m/z):** $[C_{12}H_{18}NaO_2]^+$ $(M+Na)^+$ calc. 217.1, found 217.1.

Data consistent with literature values.[8]

5-(Benzyloxy)pentanal (4d)

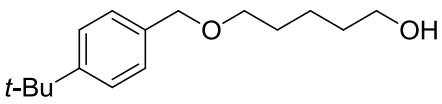


Prepared according to general procedure for Swern oxidation employing 5-(benzyloxy)pentan-1-ol **11d** (1.75 g, 9.00 mmol, 1.0 eq.). Purification by column chromatography on silica gel (SiO_2, petroleum ether 30-40: EtOAc 1:0-9:1) afforded the title compound as a colourless oil (1.57 g, 8.08 mmol, 90 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.62-1.71 (m, 2H), 1.71-1.80 (m, 2H), 2.46 (td, *J* = 7.2 Hz, *J* = 1.7, Hz, 2H), 3.50 (t, *J* = 6.1 Hz, 2H), 4.51 (s, 2H), 7.27-7.40 (m, 5H), 9.76 (t, *J* = 1.7 Hz, 1H); **^{13}C NMR (101 MHz, $CDCl_3$):** δ = 18.9, 29.1, 43.5, 69.7, 72.8, 127.5, 128.3, 138.4, 202.4; **LRMS (ESI^+, m/z):** $[C_{12}H_{16}NaO_2]^+$ $(M+Na)^+$ calc. 215.1, found 215.1.

Data consistent with literature values.[5]

5-((4-(*tert*-Butyl)benzyl)oxy)pentan-1-ol (11e)

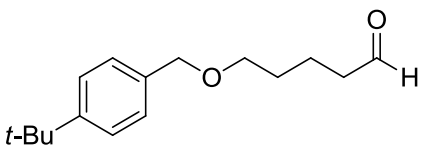


To a suspension of sodium hydride (60 %) (480 mg, 12.0 mmol, 1.2 eq.) in THF (40 mL) at room temperature, was added 1,5-pentanediol (7.40 mL, 70.0 mmol, 7.0 eq.) as a solution in THF (10 mL). 4-(*tert*-Butyl)benzyl bromide (1.84 mL, 10.0 mmol, 1.0 eq.) was then added and the reaction was stirred for 5 hours. The resultant suspension was diluted with diethyl ether and quenched by addition of saturated aqueous ammonium chloride. The organic phase was extracted with ethyl acetate, dried over $MgSO_4$ and the solvent was

removed under reduced pressure. Purification by column chromatography on silica gel (SiO_2, petroleum ether 30-40: EtOAc 19:1-4:1) afforded the title compound as a colourless oil (550 mg, 2.20 mmol, 22 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.35 (s, 9H), 1.43-1.53 (m, 2H), 1.56-1.72 (m, 4H), 1.87 (s, 1H), 3.52 (t, *J* = 6.5 Hz, 2H), 3.64 (t, *J* = 6.6 Hz, 2H), 4.51 (s, 2H), 7.31 (d, *J* = 8.3 Hz, 2H), 7.41 (d, *J* = 8.3 Hz, 2H); **^{13}C NMR (101 MHz, $CDCl_3$):** δ = 22.4, 29.4, 31.3, 32.4, 34.4, 62.6, 70.2, 72.7, 125.2, 127.5, 135.4, 150.4; **HRMS (ESI$^+$, m/z):** $[C_{16}H_{26}NaO_2]^+$ $(M+Na)^+$ calc. 273.1825, found 273.1824; **IR (ν, cm^{-1}):** 3454 (w, OH).

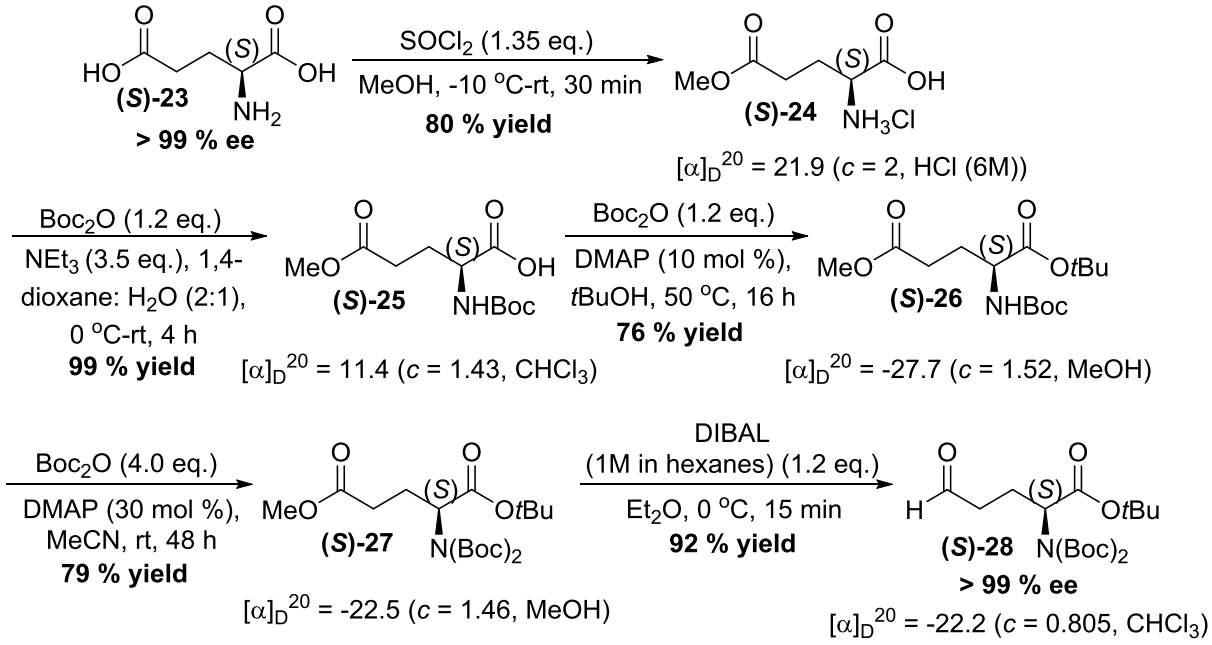
5-((4-(*tert*-Butyl)benzyl)oxy)pentanal (4e)



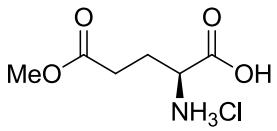
Prepared according to general procedure for Swern oxidation employing 5-((4-(*tert*-butyl)benzyl)oxy)pentan-1-ol **11e** (550 mg, 2.20 mmol, 1.0 eq.). Purification by column chromatography on silica gel (SiO_2, petroleum ether 30-40: EtOAc 19:1) afforded the title compound as a colourless oil (340 mg, 1.37 mmol, 62 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.24 (s, 9H), 1.53-1.61 (m, 2H), 1.62-1.71 (m, 2H), 2.37 (td, *J* = 7.3 Hz, *J* = 1.7 Hz, 2H), 3.41 (t, *J* = 6.1 Hz, 2H), 4.39 (s, 2H), 7.19 (d, *J* = 7.9 Hz, 2H), 7.29 (d, *J* = 8.2 Hz, 2H), 9.68 (t, *J* = 1.5 Hz, 1H); **^{13}C NMR (101 MHz, $CDCl_3$):** δ = 18.9, 29.1, 31.3, 34.5, 43.6, 69.7, 72.7, 125.3, 127.5, 135.4, 150.5, 202.5; **HRMS (ESI$^+$, m/z):** $[C_{16}H_{24}NaO_2]^+$ $(M+Na)^+$ calc. 271.1669, found 271.1669**, IR (ν, cm^{-1}):** 1725 (s, C=O).

(*S*)-1-*tert*-Butyl 2-[bis-(*tert*-butoxycarbonyl)amino]-5-oxopentanoate ((*S*)-28)



(*S*)-2-Amino-5-methoxy-5-oxopentanoic acid hydrochloride salt ((*S*)-24)



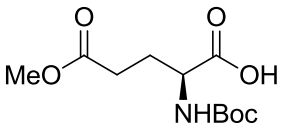
Prepared according to literature procedure.[9]

To methanol (50 mL) at −10 °C was added thionyl chloride (3.33 mL, 45.9 mmol, 1.35 eq.) followed by L-glutamic acid (5.00 g, 34.0 mmol, 1.0 eq.). The reaction was warmed to room temperature and stirred for 30 minutes before being poured onto diethyl ether (50 mL). The resultant precipitate was collected by filtration and dried under vacuum to afford the title compound as a white solid (5.35 g, 27.1 mmol, 80 % yield).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.98-2.15 (m, 2H), 2.42-2.68 (m, 2H), 3.61 (s, 3H), 3.91 (brs, 1H), 8.61 (brs, 3H); **^{13}C NMR (101 MHz, DMSO-d_6):** δ = 25.2, 29.1, 51.1, 51.6, 170.5, 172.2; **LRMS (ESI$^+$, m/z):** $[C_6H_{12}NO_4]^+$ $(M\text{-}Cl)^+$ calc. 162.1, found 162.1; **$[\alpha]_D^{20}$:** 21.9 (*c* = 2, 6M HCl) (Lit:[10] 29.2 (*c* = 2, 6M HCl)).

Data consistent with literature values.[9]

(*S*)-2-((*tert*-Butoxycarbonyl)amino)-5-methoxy-5-oxopentanoic acid ((*S*)-25)



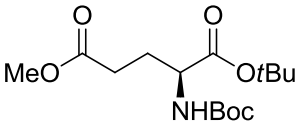
Prepared according to literature procedure.[11]

To a solution of (*S*)-2-amino-5-methoxy-5-oxopentanoic acid hydrochloride salt **(*S*)-24** (7.70 g, 39.0 mmol, 1.0 eq.) in dioxane (30 mL) and H_2O (15 mL) at 0 °C was added di-*tert*-butyl dicarbonate (10.2 g, 46.8 mmol, 1.2 eq.) and triethylamine (19.0 mL, 137 mmol, 3.5 eq.). The solution was stirred at room temperature for 4 hours before the dioxane was removed under reduced pressure. The reaction was washed with diethyl ether and the organics discarded. The aqueous phase was acidified with HCl (1M) to ~pH 4 and then extracted with ethyl acetate. The combined organic phases were dried over $MgSO_4$ and the solvent removed under reduced pressure to afford the title compound directly as a colourless oil which turned to a white solid on standing (10.1 g, 38.7 mmol, 99 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.45 (s, 9H), 1.94-2.13 (m, 1H), 2.17-2.33 (m, 1H), 2.36-2.58 (m, 2H), 3.69 (s, 3H), 4.18-4.43 (m, 1H), 5.22 (brs, 1H); **^{13}C NMR (101 MHz, $CDCl_3$):** δ = 27.4, 28.3, 30.2, 51.9, 52.9, 155.8, 173.6, 176.4; **LRMS (ESI^+, m/z):** $[C_{11}H_{19}NNaO_6]^+$ $(M+Na)^+$ calc. 284.1, found 284.1; **$[\alpha]_D^{20}$:** 11.4 (*c* = 1.43, $CHCl_3$) (Lit:[12] 7.32 (*c* = 1.43, $CHCl_3$)).

Data consistent with literature values.[12]

(*S*)-1-*tert*-Butyl 5-methyl 2-((*tert*-butoxycarbonyl)amino)pentanedioate ((*S*)-26)



Prepared according to literature procedure.[12]

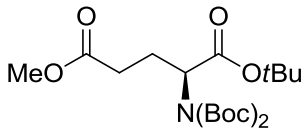
To a solution of (*S*)-2-((*tert*-butoxycarbonyl)amino)-5-methoxy-5-oxopentanoic acid **(*S*)-25** (9.20 g, 35.2 mmol, 1.0 eq.) in *tert*-butanol (100 mL) was added di-*tert*-butyl-dicarbonate (9.21 g, 42.2 mmol, 1.2 eq.) and DMAP (428 mg, 3.50 mmol, 10 mol %). The solution was stirred at 50 °C for 16 hours before the solvent was removed under reduced pressure. The residue was purified by column chromatography on

silica gel (SiO_2, petroleum ether 30-40: EtOAc 9:1) to afford the title compound as a colourless oil which turned to a white solid on standing (8.50g, 26.8 mmol, 76 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.44 (s, 9H), 1.47 (s, 9H), 1.92 (dtd, *J* = 14.2 Hz, *J* = 8.4 Hz, *J* = 6.2 Hz, 1H), 2.16 (td, *J* = 14.1 Hz, *J* = 6.0 Hz, 1H), 2.31-2.48 (m, 2H), 3.68 (s, 3H), 4.16-4.25 (m, 1H), 5.08 (brd, *J* = 7.8 Hz, 1H); **^{13}C NMR (101 MHz, $CDCl_3$):** δ = 28.0, 28.1, 28.3, 30.1, 51.7, 53.4, 79.7, 82.2, 155.3, 171.3, 173.3; **LRMS (ESI^+, m/z):** $[C_{15}H_{27}NNaO_6]^+$ $(M+Na)^+$ calc. 340.2, found 340.2; **$[\alpha]_D^{20}$:** −27.7 (*c* = 1.52, MeOH) (Lit:[13] −28.2 (*c* 1.52, MeOH)).

Data consistent with literature values.[12]

(*S*)-1-*tert*-Butyl 5-methyl 2-[bis-(*tert*-butoxycarbonyl)amino]pentanedioate ((*S*)-27)



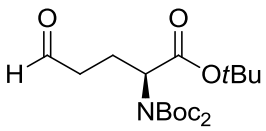
Prepared according to literature procedure.[13]

To a solution of (*S*)-1-*tert*-butyl 5-methyl 2-((*tert*-butoxycarbonyl)amino)pentanedioate **(*S*)-26** (3.00 g, 9.45 mmol, 1.0 eq.) in acetonitrile (50 mL) was added di-*tert*-butyl-dicarbonate (8.25 g, 37.8 mmol, 4.0 eq.) followed by DMAP (462 mg, 3.78 mmol, 40 mol %). The solution was stirred for 2 days at room temperature and then the solvent was removed under reduced pressure. Purification by column chromatography on silica gel (SiO_2, petroleum ether 30-40: EtOAc 4:1) afforded the title compound as a colourless oil which turned to a white solid on standing (3.10 g, 7.43 mmol, 79 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.45 (s, 9H), 1.50 (s, 18H), 2.12-2.21 (m, 1H), 2.23-2.43 (m, 3H), 3.67 (s, 3H), 4.75-4.81 (m, 1H); **^{13}C NMR (101 MHz, $CDCl_3$):** δ = 24.7, 27.9, 28.0, 30.9, 51.6, 58.1, 81.4, 82.9, 152.3, 169.2, 173.2; **LRMS (ESI^+, m/z):** $[C_{20}H_{35}NNaO_8]^+$ $(M+Na)^+$ calc. 440.2, found 440.2; **$[\alpha]_D^{20}$:** −22.5 (*c* = 1.46, MeOH) (Lit:[13] −24.5 (*c* = 1.46, MeOH)).

Data consistent with literature values.[13]

(*S*)-1-*tert*-Butyl 2-[bis-(*tert*-butoxycarbonyl)amino]-5-oxopentanoate ((*S*)-28)



Prepared according to literature procedure.[13]

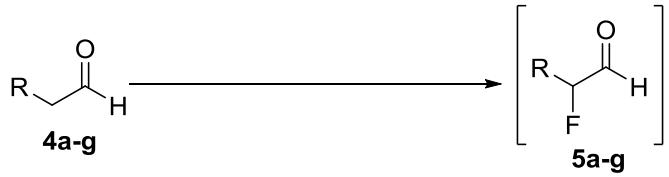
To a solution of (*S*)-1-*tert*-butyl 5-methyl 2-[bis-(*tert*-butoxycarbonyl)amino]pentanedioate **(*S*)-27** (1.56 g, 3.73 mmol, 1.0 eq.) in diethyl ether (50 mL) at −78 °C was added DIBAL (1M in hexane) (4.48 mL, 4.48 mmol, 1.2 eq.) dropwise over 3 minutes. The reaction was stirred at this temperature for 15 minutes and then quenched by the addition of water (1.1 mL) and allowed to warm to room temperature. The precipitate was removed by filtration through Celite and washed with diethyl ether. The solvent was removed under reduced pressure and residual water was removed by repeated co-evaporation with toluene. Purification by column chromatography on silica gel (SiO_2, petroleum ether 30-40: EtOAc, 17:3) afforded the title compound as a colourless oil which solidified on standing to give a white solid (1.33 g, 3.43 mmol, 92 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.45 (s, 9H), 1.51 (s, 18H), 2.09-2.21 (m, 1H), 2.39-2.65 (m, 3H), 4.74 (dd, *J* = 9.3 Hz, *J* = 5.1 Hz, 1H), 9.77 (t, *J* = 1.3 Hz, 1H); **^{13}C NMR (101 MHz, $CDCl_3$):** δ = 22.0, 27.9, 28.0, 40.7, 58.1, 81.5, 83.1, 152.4, 169.2, 201.2; **LRMS (ESI$^+$, m/z):** $[C_{19}H_{33}NKO_7]^+$ $(M+K)^+$ calc. 426.2, found 426.2; **$[\alpha]_D^{20}$:** −22.2 (*c* = 0.805, $CHCl_3$) (Lit:[13] −23.1 (*c* = 0.805, $CHCl_3$)).

Data consistent with literature values.[13]

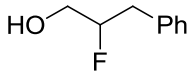
4.2.1.3 Racemic Fluorinated Reference Synthesis

General procedure for fluorination



To a solution of aldehyde (0.75 mmol, 1.5 eq.) in MTBE (2.5 mL) and H_2O (10 µL) in a 7 mL glass vial was added (±)2,2,3-trimethyl-5-benzyl-4-imidazolidinone dichloroacetic acid **A** (18 mg, 0.05 mmol, 10 mol %) and the reaction was stirred for 10 minutes before the addition of NFSI (158 mg, 0.50 mmol, 1.0 eq.) or Selectfluor (177 mg, 0.50 mmol, 1.0 eq.). The reaction was stirred for a further 2 hours at room temperature and then diluted with pentane (2 mL). The precipitate was removed by filtration through a cotton wool plug in a glass pipette.

2-Fluoro-3-phenylpropan-1-ol (6a)



Immediately following general procedure for fluorination with hydrocinnaladehyde **4a** (101 mg, 0.75 mmol, 1.5 eq.) and NFSI (158 mg, 0.50 mmol, 1.0 eq.), the filtrate was diluted with methanol (4 mL) before the addition of $NaBH_4$ (38 mg, 1.00 mmol, 2.0 eq.). The reaction was stirred for a further 30 minutes then quenched with $KHSO_4$ (1M) (3 mL), extracted into ethyl acetate and dried over $MgSO_4$. Purification by column chromatography (SiO_2, Pentane: Et_2O 9:1) afforded the title compound as a colourless oil (54 mg, 0.35 mmol, 70 % yield).

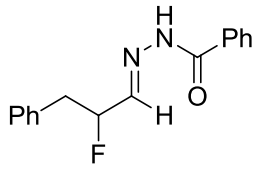
^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.10 (brs, 1H, O*H*), 3.06-3.29 (m, 2H), 3.79-4.03 (m, 2H), 4.97 (dm, *J* = 48.7 Hz, 1H), 7.37-7.58 (m, 5H); **^{13}C NMR (101 MHz, $CDCl_3$):** δ = 37.1 (d, *J* = 23.8 Hz), 63.8 (d, *J* = 20.7 Hz), 94.3 (d, *J* = 171.7 Hz), 126.4, 128.2, 129.0, 136.0 (d, *J* = 6.4 Hz); **^{19}F NMR (377 MHz, $CDCl_3$):** δ = −187.6; **LRMS (ESI$^+$, m/z):** $[C_9H_{11}FNaO]^+$ $(M+Na)^+$ calc. 177.1, found 177.0.

Data consistent with literature values.[14]

General procedure for hydrazone synthesis

Immediately following general procedure for fluorination, the filtrate was diluted with methanol (4.0 mL) before the addition of benzhydrazide (102 mg, 0.75 mmol, 1.5 eq.) and sodium sulfate (106 mg, 0.75 mmol, 1.5 eq.). The reaction was stirred for a further 6 hours at room temperature. The precipitate was removed by filtration and the solvent was then removed under reduced pressure. Purification was performed by column chromatography on silica gel.

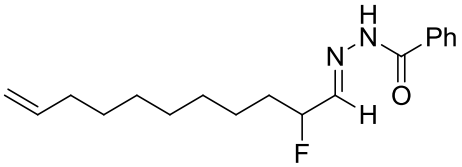
(±)-(*E*)-*N*'-(2-Fluoro-3-phenylpropylidene)benzohydrazide (8a)



Prepared according to general procedures for fluorination and hydrazone synthesis from hydrocinnamaldehyde **4a** (101 mg, 0.75 mmol, 1.5 eq.) and NFSI (158 mg, 0.50 mmol, 1.0 eq.). Purification by column chromatography on silica gel (SiO_2, DCM: EtOAc 98:2) afforded the title compound as a white solid (15 mg, 0.06 mmol, 11 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.91-3.18 (m, 2H), 5.22 (d, *J* = 46.2 Hz, 1H), 7.10-7.23 (m, 5H), 7.28-7.35 (m, 2H), 7.40-7.46 (m, 1H), 7.67 (brs, 1H), 7.75 (d, *J* = 6.4 Hz, 2H), 10.03 (brs, 1H); **^{13}C NMR (126 MHz, $CDCl_3$):** δ = 39.7 (d, *J* = 21.9 Hz), 91.6 (d, *J* = 169.8 Hz), 126.9, 127.5, 128.5, 128.7, 129.5, 132.3, 132.4, 135.3, 148.1 (d, *J* = 28.6 Hz), 164.8; **^{19}F NMR (377 MHz, $CDCl_3$):** δ = −182.3; **HRMS (ESI$^+$, m/z):** $[C_{16}H_{15}FNaN_2O]^+$ $(M+Na)^+$ calc. 293.1061, found 293.1057; **IR (ν, cm^{-1}):** 3227 (w, NH), 1652 (s, C=O); 1579 (m, C=N); **MP:** 96-98 °C.

(±)-(*E*)-*N*'-(2-Fluoroundec-10-en-1-ylidene)benzohydrazide (8f)

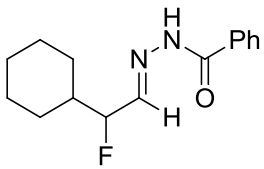


Prepared according to general procedures for fluorination and hydrazone synthesis from 10-

undecenal **4f** (126 mg, 0.75 mmol, 1.5 eq.) and Selectfluor (177 mg, 0.50 mmol, 1.0 eq.). Purification by column chromatography on silica gel (SiO_2, petroleum ether 30-40: EtOAc 4:1) afforded the title compound as a colourless oil (32 mg, 0.11 mmol, 21 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.22-1.52 (m, 10H), 1.59-1.91 (m, 2H), 1.97-2.10 (m, 2H), 4.90-5.03 (m, 2H), 5.09 (d, *J* = 49.2 Hz, 1H), 5.74-5.89 (m, 1H), 7.42 (t, *J* = 7.8 Hz, 2H), 7.53 (t, *J* = 7.3 Hz, 1H), 7.75 (brs, 1H), 7.84 (d, *J* = 7.3 Hz, 2H), 10.56 (brs, 1H); **^{13}C NMR (101 MHz, $CDCl_3$):** δ = 24.3 (d, *J* = 4.8 Hz), 28.8, 28.9, 29.2, 29.2, 33.3 (d, *J* = 20.7 Hz), 33.5, 91.9 (d, *J* = 165.3 Hz), 114.1, 127.5, 128.5, 132.2, 132.4, 139.0, 149.1 (d, *J* = 27.0 Hz), 164.9; **^{19}F NMR (377 MHz, $CDCl_3$):** δ = −183.6; **HRMS (ESI^+, m/z):** $[C_{18}H_{25}FNaN_2O]^+$ $(M+Na)^+$ calc. 327.1843, found 386.1839; **IR (ν, cm^{-1}):** 3241 (w, NH), 1655 (s, C=O); 1546 (m, C=N).

(±)-(*E*)-*N*'-(2-Cyclohexyl-2-fluoroethylidene)benzohydrazide (8b)

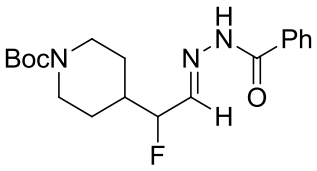


Prepared according to general procedures for fluorination and hydrazone synthesis from 2-cyclohexylacetaldehyde **4b** (95 mg, 0.75 mmol, 1.5 eq.) and Selectfluor (177 mg, 0.50 mmol, 1.0 eq.). Purification by column chromatography on silica gel (SiO_2, petroleum ether 30-40: EtOAc 3:1) afforded the title compound as a white solid (32 mg, 0.12 mmol, 24 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.98-1.29 (m, 5H), 1.53-1.79 (m, 5H), 1.84 (d, *J* = 11.7 Hz, 1H), 4.74 (dt, *J* = 48.2 Hz, *J* = 5.9 Hz, 1H), 7.39 (t, *J* = 7.1 Hz, 2H), 7.50 (t, *J* = 7.6 Hz, 1H), 7.78 (brs, 1H), 7.85 (d, *J* = 7.1 Hz, 1H), 10.50 (s, 1H); **^{13}C NMR (126 MHz, $CDCl_3$):** δ = 25.5, 25.6, 26.0, 27.4 (d, *J* = 4.8 Hz), 27.8 (d, *J* = 3.8 Hz), 41.3 (d, *J* = 21.0 Hz), 95.3 (d, *J* = 168.8 Hz), 127.4, 128.6, 132.2, 132.5, 148.5 (d, *J* = 30.5 Hz), 164.6; **^{19}F NMR (377 MHz, $CDCl_3$):** δ = −188.9; **HRMS (ESI^+, m/z):** $[C_{15}H_{19}FNaN_2O]^+$ $(M+Na)^+$

calc. 285.1374, found 293.1373; **IR (ν, cm^{-1}):** 3239 (w, NH), 1653 (s, C=O); 1547 (m, C=N); **MP:** 143-144 °C.

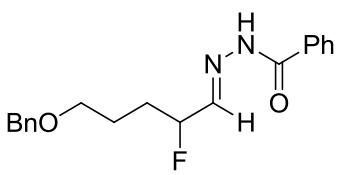
(±)-(*E*)-(*tert*-Butyl 4-(2-(2-benzoylhydrazono)-1-fluoroethyl)piperidine-1-carboxylate (8c)



Prepared according to general procedures for fluorination and hydrazone synthesis from *tert*-butyl 4-(2-oxoethyl)piperidine-1-carboxylate **4c** (171 mg, 0.75 mmol, 1.5 eq.) and Selectfluor (177 mg, 0.50 mmol, 1.0 eq.). Purification by column chromatography on silica gel (SiO_2, petroleum ether 30-40: EtOAc 4:1-7:3) afforded the title compound as a white solid (108 mg, 0.30 mmol, 59 % yield).

Line broadening/ splitting observed due to slow ring inversion. **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 1.18-1.32 (m, 2H), 1.43 (s, 9H), 1.54 (brd, *J* = 12.7 Hz, 1H), 1.74 (brd, *J* = 11.7 Hz, 1H), 1.87 (brd, *J* = 10.5 Hz, 1H), 2.61 (brs, 2H), 4.08 (brs, 2H), 4.81 (d, *J* = 47.4 Hz, 1H), 7.39 (t, *J* = 7.6 Hz, 2H), 7.51 (tt, *J* = 7.6 Hz, *J* = 1.2 Hz, 1H), 7.80 (brs, 1H), 7.85 (d, *J* = 7.6 Hz, 2H), 10.65 (brs, 1H); **^{13}C NMR (126 MHz, $CDCl_3$):** δ = 26.6 (brd, *J* = 47.7 Hz), 28.4, 39.7 (d, *J* = 21.9 Hz), 43.2 (brd, *J* = 72.5 Hz), 60.4, 65.8, 79.7, 94.3 (d, *J* = 168.8 Hz), 127.6, 128.6, 132.3, 132.4, 147.7 (d, *J* = 27.7 Hz), 154.7, 164.8; **^{19}F NMR (377 MHz, $CDCl_3$):** δ = −188.6, −191.5; **HRMS (ESI$^+$, m/z):** $[C_{19}H_{26}FNaN_3O_3]^+$ $(M+Na)^+$ calc. 386.1850, found 386.1847; **IR (ν, cm^{-1}):** 3241 (w, NH), 1694 (s, C=O); 1654 (s, C=O), 1546 (m, C=N); **MP:** 53-54 °C.

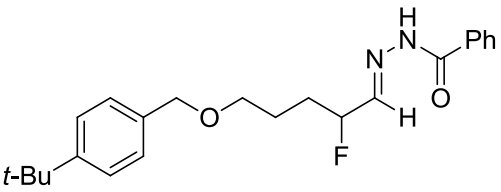
(±)-(*E*)-*N*'-(5-(Benzyloxy)-2-fluoropentylidene)benzohydrazide (8d)



Prepared according to general procedures for fluorination and hydrazone synthesis from 5-(benzyloxy)pentanal **4d** (144 mg, 0.75 mmol, 1.5 eq.) and Selectfluor (177 mg, 0.50 mmol, 1.0

eq.). Purification by column chromatography on silica gel (SiO_2, petroleum ether 30-40: EtOAc 3:1) afforded the title compound as a white solid (49 mg, 0.15 mmol, 30 % yield). **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 1.51-1.88 (m, 4H), 3.37 (t, *J* = 6.0 Hz, 2H), 4.37 (s, 2H), 4.96 (dd, *J* = 49.2 Hz, *J* = 5.6 Hz, 1H), 7.15-7.30 (m, 7H), 7.34-7.41 (m, 1H), 7.66 (brs, 1H), 7.74 (d, *J* = 7.1 Hz, 2H), 10.51 (brs, 1H); **^{13}C NMR (101 MHz, $CDCl_3$):** δ =24.6 (d, *J* = 3.2 Hz), 30.2 (d, *J* = 23.8 Hz), 69.4, 72.8, 91.6 (d, *J* = 165.3 Hz), 127.5, 127.5, 127.6, 128.3, 128.5, 132.1, 132.4, 138.3, 148.8 (d, *J* = 27.0 Hz), 164.9; **^{19}F NMR (377 MHz, $CDCl_3$):** δ = −183.5; **HRMS (ESI^+, m/z):** $[C_{19}H_{21}FN_2NaO_2]^+$ $(M+Na)^+$ calc. 351.1479, found 351.1477; **IR (ν, cm^{-1}):** 3227 (w, NH), 1652 (s, C=O); 1549 (m, C=N); **MP:** 70-70 °C.

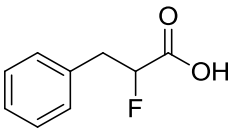
(±)-(*E*)-*N*'-(5-((4-(*tert*-Butyl)benzyl)oxy)-2-fluoropentylidene)benzohydrazide (8e)



Prepared according to general procedures for fluorination and hydrazone synthesis from 5-((4-(*tert*-butyl)benzyl)oxy)pentanal **4e** (182 mg, 0.75 mmol, 1.5 eq.) and Selectfluor (177 mg, 0.50 mmol, 1.0 eq.). Purification by column chromatography on silica gel (SiO_2, petroleum ether 30-40: EtOAc 13:7) afforded the title compound as a colourless oil (26 mg, 0.07 mmol, 14 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.23 (s, 9H), 1.57-1.91 (m, 4H), 3.41 (t, *J* = 6.0 Hz, 2H), 4.37 (s, 2H), 5.03 (d, *J* = 47.2 Hz, 1H), 7.17 (d, *J* = 8.1 Hz, 2H), 7.26-7.36 (m, 4H), 7.43 (tt, *J* = 7.3 Hz, *J* = 1.2 Hz, 1H), 7.62 (brs, 1H), 7.71-7.77 (m, 2H), 9.82 (brs, 1H); **^{13}C NMR (126 MHz, $CDCl_3$):** δ = 24.7 (d, *J* = 3.8 Hz), 30.3 (d, *J* = 22.9 Hz), 31.3, 34.5, 69.4, 72.7, 91.6 (d, *J* = 166.9 Hz), 125.3, 127.3, 127.5, 128.7, 132.3, 132.6, 135.3, 148.4 (d, *J* = 29.6 Hz), 150.6, 164.4; **^{19}F NMR (377 MHz, $CDCl_3$):** δ = −183.7; **HRMS (ESI^+, m/z):** $[C_{23}H_{29}FN_2NaO_2]^+$ $(M+Na)^+$ calc. 407.2105, found 407.2109; **IR (ν, cm^{-1}):** 3233 (w, NH), 1653 (s, C=O); 1545 (m, C=N).

(±)-2-Fluoro-3-phenylpropanoic acid (12a)

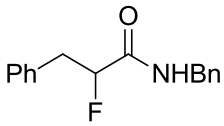


Immediately following general procedure for fluorination with hydrocinnaladehyde **4a** (101 mg, 0.75 mmol, 1.5 eq.), the filtrate was diluted with DMF (4 mL) prior to addition of Oxone (307 mg, 1.00 mmol, 2.0 eq.) and stirred for 2 hours at room temperature. The reaction mixture was then diluted with HCl (1M) and extracted into ethyl acetate. The combined organics were washed with water and brine, dried over $MgSO_4$ and the solvent removed under reduced pressure. Purification by column chromatography on silica gel (SiO_2, petroleum ether 30-40: EtOAc 4:1 + 0.1 % acetic acid) afforded the title compound as a white solid (34 mg, 0.20 mmol, 40 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.14-3.21 (m, 1H), 3.26-3.36 (m, 1H), 5.14 (ddd, *J* = 48.4 Hz, *J* = 7.9 Hz, *J* = 3.8 Hz, 1H), 7.23-7.35 (m, 5H), 8.41 (brs, 1H); **^{13}C NMR (101 MHz, $CDCl_3$):** δ = 38.4 (d, *J* = 20.7 Hz), 88.8 (d, *J* = 192.3 Hz), 127.4, 128.7, 129.4, 134.7, 174.2 (d, *J* = 25.4 Hz); **^{19}F NMR (377 MHz, $CDCl_3$):** δ = −190.6; **LRMS (ESI^+, m/z):** $[C_9H_9FO_2]^+$ $(M+H)^+$ calc. 191.0, found 191.0.

Data consistent with literature values.[15]

(±)-*N*-Benzyl-2-fluoro-3-phenylpropanamide (13a)

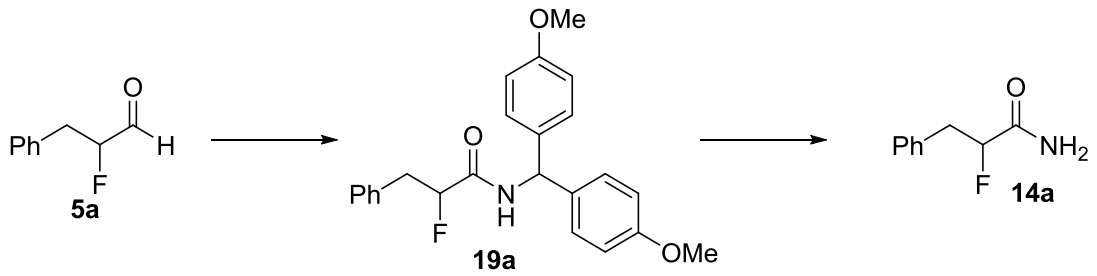


Immediately following general procedure for fluorination with hydrocinnaladehyde **4a** (101 mg, 0.75 mmol, 1.5 eq.), the filtrate was diluted with toluene (4 mL) before the addition of benzylamine (123 µL, 1.13 mmol, 2.25 eq.) and 2-methyl-2-butene (397 µL, 3.75 mmol, 7.5 eq.). The reaction was stirred for 5 minutes prior to the addition of sodium chlorite (80 %) (212 mg, 1.88 mmol, 3.75 eq.) and sodium dihydrogen phosphate (316 mg, 2.65 mmol, 5.25 eq.). The reaction was stirred for a further 2 hours at room temperature then diluted with H_2O and extracted with ethyl acetate. The combined organic phases were dried over $MgSO_4$

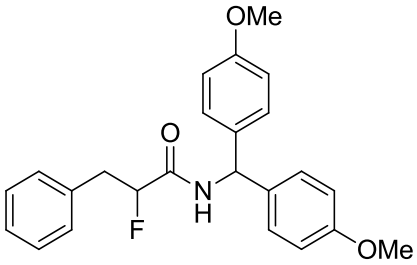
and the solvent removed under reduced pressure. Purification by column chromatography on silica gel (SiO_2, petroleum ether 30-40: EtOAc 9:1) provided the title compound as a white solid (45 mg, 0.17 mmol, 35 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.16 (ddd, *J* = 31.3 Hz, *J* = 14.7 Hz, *J* = 6.1 Hz, 1H), 3.33 (ddd, *J* = 27.1 Hz, *J* = 14.4 Hz, *J* = 3.7 Hz, 1H), 4.31 (dd, *J* = 14.7 Hz, *J* = 5.4 Hz, 1H), 4.47 (dd, *J* = 14.8 Hz, *J* = 6.2 Hz, 1H), 5.15 (ddd, *J* = 49.4 Hz, *J* = 6.6 Hz, *J* = 3.7 Hz, 1H), 6.46 (brs, 1H), 6.99-7.10 (m, 2H), 7.19-7.34 (m, 8H); **^{13}C NMR (101 MHz, $CDCl_3$):** δ = 38.3 (d, *J* = 20.7 Hz), 42.8, 91.9 (d, *J* = 189.1 Hz), 127.0, 127.5, 127.6, 128.4, 128.6, 129.7, 135.2, 137.3, 168.9 (d, *J* = 19.1 Hz); **^{19}F NMR (377 MHz, $CDCl_3$):** δ = −189.4; **LRMS (ESI$^+$, m/z):** $[C_{16}H_{16}FNNaO]^+$ $(M+Na)^+$ calc. 280.1, found 280.1. Data consistent with literature values.[15]

(±)-2-Fluoro-3-phenylpropanamide (14a)



(±)-*N*-(bis(4-Methoxyphenyl)methyl)-2-fluoro-3-phenylpropanamide (19a)



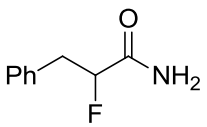
Immediately following general procedure for fluorination with hydrocinnaladehyde **4a** (101 mg, 0.75 mmol, 1.5 eq.), the filtrate was diluted with toluene (4 mL), before the addition of bis(4-methoxyphenyl)methanamine (275 mg, 1.13 mmol, 2.25 eq.) and 2-methyl-2-butene (397 µL, 3.75 mmol, 7.5 eq.). The reaction was stirred for 5 minutes prior to the addition of sodium chlorite (80 %) (212 mg, 1.88 mmol, 3.75 eq.) and sodium dihydrogen phosphate

(316 mg, 2.65 mmol, 5.25 eq.). The reaction was stirred for a further 2 hours at room temperature then diluted with H_2O and extracted with ethyl acetate. The combined organic phases were dried over $MgSO_4$ and the solvent removed under reduced pressure. Purification by column chromatography on silica gel (SiO_2, petroleum ether 30-40: EtOAc, 17:3) afforded the title compound as a white solid (102 mg, 0.26 mmol, 52 % yield).

Isolated as a mixture of rotamers (1:1 ratio at 25 °C):

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.12 (ddd, *J* = 33.7 Hz, *J* = 14.9 Hz, *J* = 5.9 Hz, 1H), 3.25 (ddd, *J* = 25.2 Hz, *J* = 14.9 Hz, *J* = 3.9 Hz, 1H), 3.70 (s, 3H), 3.70 (s, 3H), 5.10 (ddd, *J* = 49.4 Hz, *J* = 5.9 Hz, *J* = 3.9 Hz, 1H), 6.00 (s, 0.5H), 6.02 (s, 0.5H), 6.52-6.61 (m, 1H), 6.67 (s, 4H), 6.76 (d, *J* = 8.8 Hz, 2H), 7.01 (d, *J* = 8.6 Hz, 2H), 7.14-7.19 (m, 2H), 7.19-7.24 (m, 3H); **^{13}C NMR (101 MHz, $CDCl_3$):** δ = 38.2 (d, *J* = 19.1 Hz), 55.2, 55.3, 91.8 (d, *J* = 190.7 Hz), 113.8, 114.1, 127.0, 128.3, 128.5, 128.7, 129.9, 133.1, 133.4, 135.2, 158.8, 159.0, 167.9 (d, *J* = 19.1 Hz); **^{19}F NMR (377 MHz, $CDCl_3$):** δ = −189.2; **HRMS (ESI$^+$, m/z):** $[C_{24}H_{24}FNO_3Na]^+$ $(M+Na)^+$ calc. 416.16324, found 416.16342; **IR (ν, cm^{-1}):** 3324 (w, NH), 1652 (s, C=O), 1245 (s, C-F); **MP:** 154-155 °C.

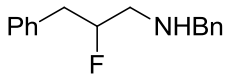
(±)-2-Fluoro-3-phenylpropanamide (14a)



To *N*-(bis(4-methoxyphenyl)methyl)-2-fluoro-3-phenylpropanamide **19a** (32 mg, 0.08 mmol, 1.0 eq.) was added anisole (35 µL, 0.32 mmol, 4.0 eq.) and TFA (400 µL) and the reaction was heated to 60 °C for 3 hours before the TFA was removed by evaporation under reduced pressure. The crude residue was dissolved in DCM and washed with saturated aqueous sodium bicarbonate. The organics were dried over $MgSO_4$ and the solvent removed under reduced pressure. Purification by column chromatography on silica gel (SiO_2, petroleum ether 30-40: EtOAc, 4:1) afforded the title compound as a white solid (8 mg, 0.048 mmol, 60 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.15 (ddd, *J* = 28.4 Hz, *J* = 14.9 Hz, *J* = 7.3 Hz, 1H), 3.34 (ddd, *J* = 29.8 Hz, *J* = 14.9 Hz, *J* = 3.4 Hz, 1H), 5.11 (ddd, *J* = 49.4 Hz, *J* = 7.3 Hz, *J* = 3.4 Hz, 1H), 5.95 (brs, 1H), 6.20 (brs, 1H), 7.25-7.30 (m, 3H), 7.31-7.37 (m, 2H); **^{13}C NMR (101 MHz, $CDCl_3$):** δ = 38.2 (d, *J* = 20.7 Hz), 91.7 (d, *J* = 189.1 Hz), 127.0, 128.4, 129.5, 135.2, 171.9 (d, *J* = 20.7 Hz); **^{19}F NMR (377 MHz, $CDCl_3$):** δ = −187.0; **HRMS (ESI$^+$, m/z):** $[C_9H_{10}FNaNO]^+$ $(M+Na)^+$ calc. 190.0639, found 190.0639; **IR (v, cm^{-1}):** 3393 (w, NH), 3199 (w, NH), 1662 (s, C=O).

(±)-*N*-Benzyl-2-fluoro-3-phenylpropan-1-amine (20a)

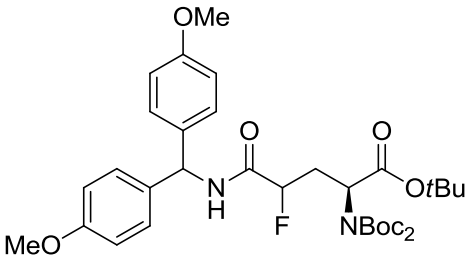


Immediately following general procedure for fluorination with hydrocinnaladehyde **4a** (101 mg, 0.75 mmol, 1.5 eq.), the filtrate was diluted with DCE (4 mL) and benzylamine (82 µL, 0.75 mmol, 1.5 eq.) was added and the reaction was stirred for 5 minutes prior to the addition of sodium triacetoxyborohydride (636 mg, 3.00 mmol, 4.0 eq.). The reaction was stirred at room temperature overnight before being quenched with water and extracted into ethyl acetate. The combined organics phases were dried over $MgSO_4$ and the solvent removed under reduced pressure. Purification by column chromatography on silica gel (SiO_2, petroleum ether 30-40: EtOAc, 4:1-7:3 + 0.1% NEt_3) afforded the title compound as a white solid (23 mg, 0.10 mmol, 20 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.94 (s, 1H), 2.74-2.97 (m, 4H), 3.79 (dd, *J* = 31.5 Hz, *J* = 13.0 Hz, 2H), 4.84 (dm, *J* = 49.4 Hz, 1H), 7.09-7.29 (m, 10 H); **^{13}C NMR (101 MHz, $CDCl_3$):** δ = 39.3 (d, *J* = 20.7 Hz), 51.5 (d, *J* = 20.7 Hz), 52.9, 93.0 (d, *J* = 171.7 Hz), 126.7, 127.6, 128.5, 128.5, 128.6, 129.3, 136.4 (d, *J* = 4.8 Hz), 137.9; **^{19}F NMR (377 MHz, $CDCl_3$):** δ = −184.2; **LRMS (ESI$^+$, m/z):** $[C_{16}H_{19}FN]^+$ $(M+H)^+$ calc. 244.1, found 244.1.

Data consistent with literature values.[16]

(2*S*)-1-*tert*-Butyl 5-((bis(4-methoxyphenyl)methyl)amino)-2-[bis-(*tert*-butoxycarbonyl)amino]-4-fluoro-5-oxopentanoate (30)



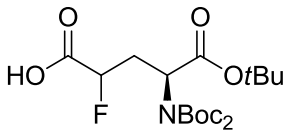
Immediately following general procedure for fluorination with (*S*)-1-*tert*-butyl 2-[bis-(*tert*-butoxycarbonyl)amino]-5-oxopentanoate **(*S*)-28** (580 mg, 1.50 mmol, 1.5 eq.) over 18 hours, the filtrate was diluted with toluene (8 mL), before the addition of bis(4-methoxyphenyl)methanamine (550 mg, 2.25 mmol, 2.25 eq.) and 2-methyl-2-butene (500 µL, 4.72 mmol, 4.72 eq.). The reaction was stirred for 5 minutes prior to the addition of sodium chlorite (80 %) (424 mg, 3.75 mmol, 3.75 eq.) and sodium dihydrogen phosphate (632 mg, 5.25 mmol, 5.25 eq.). The reaction was stirred for a further 2 hours at room temperature then diluted with H_2O and extracted with ethyl acetate. The combined organic phases were dried over $MgSO_4$ and the solvent removed under reduced pressure. Purification by column chromatography on silica gel (SiO_2, petroleum ether 30-40: EtOAc, 17:3) afforded the title compound as a white solid (273 mg, 0.42 mmol, 42 % yield). Isolated as a mixture of diastereoisomers (1.3:1 *anti*:*syn*).

***Anti*: ^{1}H NMR (400 MHz, $CDCl_3$):** δ = 1.46 (s, 9H), 1.51 (s, 18H), 2.48-2.76 (m, 2H), 3.80 (d, *J* = 2.2 Hz, 6H), 4.97-5.04 (m, 1H), 6.16 (d, *J* = 8.1 Hz, 1H), 6.87 (dd, *J* = 8.7 Hz, *J* = 1.3 Hz, 4H), 7.14 (ddd, *J* = 8.8 Hz, *J* = 2.2 Hz, *J* = 0.5 Hz, 4H); **^{19}F NMR (377 MHz, $CDCl_3$):** δ = −189.7.

***Syn*: ^{1}H NMR (400 MHz, $CDCl_3$):** δ = 1.46 (s, 9H), 1.50 (s, 18H), 2.25 (dddd, *J* = 7.3 Hz, *J* = 10.1 Hz, *J* = 15.4 Hz, *J* = 17.8 Hz, 1H), 2.97 (dddd, *J* = 2.9 Hz, *J* = 6.4 Hz, *J* = 15.4 Hz, *J* = 37.2 Hz, 1H), 3.80 (d, *J* = 1.2 Hz, 6H), 4.97-5.16 (m, 1H), 6.16 (d, *J* = 7.8 Hz, 1H), 6.84-6.88 (m, 4H), 7.11-7.17 (m, 4H); **^{19}F NMR (377 MHz, $CDCl_3$):** δ = −190.2.

HRMS (ESI$^+$, m/z): $[C_{34}H_{47}FN_2NaO_9]^+$ $(M+Na)^+$ calc. 669.3158, found 669.3155; **IR (ν, cm^{-1}):** 3331 (w, NH), 1736 (m, C=O), 1696 (m, C=O), 1610 (m, C=O).

(2*S*)-5-(*tert*-Butoxy)-4-(bis-*N*-(*tert*-butoxycarbonyl))-2-fluoro-5-oxopentanoic acid (31)



Immediately following general procedure for fluorination with (*S*)-1-*tert*-butyl 2-[bis-(*tert*-butoxycarbonyl)amino]-5-oxopentanoate **(*S*)-28** (78 mg, 0.20 mmol, 1.5 eq.) over 18 hours, the filtrate was diluted with DMF (1.6 mL) prior to addition of Oxone (80 mg, 0.26 mmol, 2.0 eq.) and stirred for 2 hours at room temperature. The reaction mixture was then diluted with H_2O and extracted into ethyl acetate. The combined organics were washed with water and brine, dried over $MgSO_4$ and the solvent removed under reduced pressure. Purification by column chromatography on silica gel (SiO_2, petroleum ether 30-40: EtOAc 7:3 + 0.1 % acetic acid) afforded the title compound as a white solid (26 mg, 0.06 mmol, 47 % yield). Isolated as a mixture of diastereomers (1.2:1 *anti*:*syn*)

***Anti*: ^{1}H NMR (400 MHz, $CDCl_3$):** δ = 1.46 (s, 9H), 1.51 (s, 9H), 2.36-2.62 (m, 2H), 4.84-4.99 (m, 2H), 9.45 (brs, 1H); **^{19}F NMR (377 MHz, $CDCl_3$):** δ = −192.1.

***Syn*: ^{1}H NMR (400 MHz, $CDCl_3$):** δ = 1.46 (s, 9H), 1.50 (s, 9H), 2.54-2.94 (m, 2H), 4.99-5.27 (m, 2H), 9.45 (brs, 1H); **^{19}F NMR (377 MHz, $CDCl_3$):** δ = −193.7.

HRMS (ESI$^-$, m/z): $[C_{19}H_{31}FNO_8]^-$ $(M-H)^-$ calc. 420.2039, found 420.2044; **IR (ν, cm^{-1}):** 2980 (w, OH), 1738 (s, C=O), 1700 (s, C=O).

4.2.1.4 Radiochemistry

HPLC Analysis

Analytical: Waters Atlantis dc18, 5 µm, 3.9x150 mm, 1.5 mL/min.

Chiral: Phenomenex Lux Cellulose 1, 5 µm, 4.6x100 mm; Phenomenex Lux Cellulose 1, 3 µm, 4.6x150 mm; Phenomenex Lux Cellulose 2, 5 µm, 4.6x100 mm; Phenomenex Chirex 3126 (D)-penicillamine 150x4.6 mm.

Conditions A		**Conditions B**	
0-1 min	5 % MeCN, 95 % H_2O	0-15 min	40 % MeCN, 60 % H_2O
1-9 min	5-80 % MeCN	15-18 min	40-80 % MeCN
9-10 min	80 % MeCN, 20 % H_2O	18-21 min	80 % MeCN, 20 % H_2O
10-12 min	80-5 % MeCN	21-23 min	80-40 % MeCN
12-13 min	5 % MeCN, 95 % H_2O		
Conditions C		**Conditions D**	
0-1 min	5 % MeCN, 95 % H_2O	0-2 min	5 % MeCN, 95 % H_2O
1-12 min	5-80% MeCN	2-9 min	5-80% MeCN
12-13 min	80 % MeCN, 20 % H_2O	9-16 min	80 % MeCN, 20 % H_2O
13-14 min	80-5% MeCN	16-17 min	80-5% MeCN
14-15 min	5 % MeCN	17-18 min	5 % MeCN

Preparation of [^{18}F]Fluoride

[^{18}F]Fluoride was produced through the nuclear reaction $^{18}O(p,n)^{18}F$ by irradiating ^{18}O-enriched water (^{18}O, > 98 atom%) with an 18 MeV proton beam produced with a CC-18/9 cyclotron (Efremov Scientific Research Institute of Electrophysical Apparatus, St Petersburg, Russia). A niobium target was filled with 2.1 mL ^{18}O-enriched water for irradiation. The target was typically irradiated for 5 minutes with 40 µA beam current. The irradiated water was transferred to the [^{18}F]F_2 synthesis device through PEEK tubing.

Preparation of High Specific Activity [^{18}F]F_2

[^{18}F]Fluoride in MeCN/H_2O (1:1) (2 mL) was transferred to a reaction vessel containing potassium carbonate (6-8 mg) and Kryptofix 2.2.2 (21-28 mg). The solution was evaporated to dryness under a stream of He with heating to 100 °C. After 4 minutes, MeCN (1 mL) was added and the evaporation step repeated twice. MeI-solution (10 % in MeCN) (1.0 ± 0.2 mL) was then added. The resulting solution was then heated to 100 °C

for 90 seconds. The radioactive gases and flushing gas (Ne, 40 mL) were then transferred to a syringe, from which the gas mixture was injected onto a GC column. The GC column was eluted with neon at room temperature and the [^{18}F]fluoromethane fraction was trapped in a steel loop lowered into liquid nitrogen. After the trapping of [^{18}F]fluoromethane, the steel loop was allowed to warm up for 70 seconds, after which [^{18}F]fluoromethane was transferred using neon to an electrical discharge chamber, containing a known amount of carrier fluorine (~ 1 μmol). An electrical discharge of approx. 30 kV was then initiated for 10 seconds, after which [^{18}F]F_2 was available for the labelling reaction.

Preparation of [^{18}F]NFSI

The [^{18}F]F_2 gas was bubbled into a vial containing sodium bis(phenylsulfonyl)amide (~7.5 mg, 23.5 μmol) in MeCN/H_2O (9:1) (1 mL) at room temperature for ~ 30 seconds. The activity of the crude stock solution ranged from 1.5-3.1 GBq depending on the cyclotron irradiation time. The specific activity of [^{18}F]NFSI following a 5 minute irradiation of the cyclotron was 1.90 GBq/μmol (n = 3) (calculated by comparison of UV absorbance with cold calibration curve). The contents of the reaction vial were transferred to an Eppendorf which was then heated to 60 °C under a stream of He gas until the solvent had evaporated. A further aliquot of MeCN (500 μL) was added and the drying step was repeated. MTBE (900 μL) was added to dissolve and the solution was agitated using a lab dancer. Aliquots (250 μl) were taken for reactions.

Analytical HPLC: HPLC Conditions A, t_{ret} = 9.5 minutes, UV = 254 nm.

General procedure for ^{18}F-fluorination of aldehydes

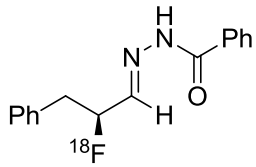
To an Eppendorf vial containing a stirrer bar and (*S*)-2,2,3-trimethyl-5-benzyl-4-imidazolidinone dichloroacetic acid **A** (1.7 mg, 5.0 μmol) was added a solution of aldehyde (5.0 μmol) in MTBE (50 μL) from stock solution. The reaction was stirred for

10 minutes prior to the addition of an aliquot of [^{18}F]NFSI in MTBE (250 µl). The reaction was stirred at room temperature, with an aliquot for HPLC (5 µL diluted in MeCN/H_2O (1:1) (20 µL), 10 µL injection) taken after 20 minutes.

General procedure for hydrazone synthesis

Immediately following general procedure for ^{18}F-fluorination, a solution of benzhydrazide (0.7 mg, 5.0 µmol) in MeOH (200 µL) (from stock solution) was added to the crude reaction mixture and the reaction was stirred for a further 20 minutes before an aliquot was taken for HPLC (10-20 µL, neat). The peak corresponding to the reference compound was collected and an aliquot injected for chiral HPLC analysis

(*S*,*E*)-[^{18}F]*N*'-(2-Fluoro-3-phenylpropylidene)benzohydrazide ((*S*)-[^{18}F]8a)

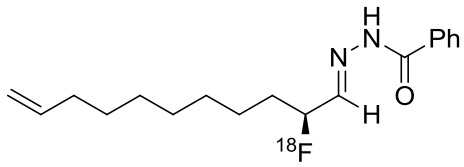


Prepared according to general procedure for hydrazone synthesis from hydrocinnamaldehyde **4a** (0.7 mg, 5.0 µmol) to afford the title compound (62 % RCC, 92 % ee, *n* = 5).

Analytical HPLC: HPLC Conditions A, Sample: 1 mg/mL in MeCN/H_2O (4:1), UV = 254 nm, t_{ret} = 8.4 min.

Chiral HPLC: Phenomenex Lux Cellulose 1 (5 µm, 4.6x100 mm), 2.0 mL/min, 30 % MeCN isocratic, 200 µL injection, UV = 254 nm, t_1 = 19.0 min, t_2 = 20.8 min.

(*S*,*E*)-[^{18}F]*N*'-(2-Fluoroundec-10-en-1-ylidene)benzohydrazide ((*S*)-[^{18}F]8f)

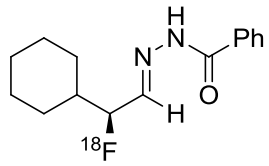


Prepared according to general procedure for hydrazone synthesis from 10-undecenal **4f** (0.8 mg, 5.0 µmol) to afford the title compound (46 % RCC, 92 % ee, *n* = 3).

Analytical HPLC: HPLC Conditions A, Sample: 1 mg/mL in MeCN/H_2O (1:1), UV = 254 nm, t_{ret} = 10.2 min.

Chiral HPLC: Phenomenex Lux Cellulose 1 (5 µm, 4.6x100 mm), 1.0 mL/min, 50 % MeCN isocratic, 200 µL injection, UV = 254 nm, t_1 = 13.8 min, t_2 = 16.7 min.

(*S*,*E*)-[^{18}F]*N*'-(2-Cyclohexyl-2-fluoroethylidene)benzohydrazide ((*S*)-[^{18}F]8b)

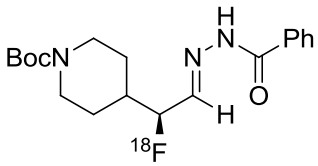


Prepared according to general procedure for hydrazone synthesis from 2-cyclohexylacetaldehyde **4b** (0.6 mg, 5.0 µmol) to afford the title compound (36 % RCC, 92 % ee, *n* = 3).

Analytical HPLC: HPLC Conditions A, Sample: 1 mg/mL in MeCN/H_2O (1:1), UV = 254 nm, t_{ret} = 8.8 min.

Chiral HPLC: Phenomenex Lux Cellulose 1 (5 µm, 4.6x100 mm), 1.0 mL/min, 40 % MeCN isocratic, 200 µL injection, UV = 254 nm, t_1 = 10.3 min, t_2 = 13.3 min.

(*S*,*E*)-[^{18}F]*tert*-Butyl 4-(2-(2-benzoylhydrazono)-1-fluoroethyl)piperidine-1-carboxylate ((*S*)-[^{18}F]8d)

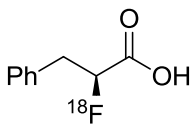


Prepared according to general procedure for hydrazone synthesis from *tert*-butyl 4-(2-oxoethyl)piperidine-1-carboxylate **4d** (1.1 mg, 5.0 µmol) to afford the title compound (54 % RCC, 92 % ee, *n* = 3).

Analytical HPLC: HPLC Conditions A, Sample: 1 mg/mL in MeCN/H_2O (1:1), UV = 254 nm, t_{ret} = 8.6 min.

Chiral HPLC: Phenomenex Lux Cellulose 1 (3 µm, 4.6x150 mm), 0.3 mL/min, 45 % MeCN isocratic, 20 µL injection, UV = 254 nm, t_1 = 30.4 min, t_2 = 32.7 min.

(*S*)-2-[^{18}F]Fluoro-3-phenylpropanoic acid ((*S*)-[^{18}F]12a)



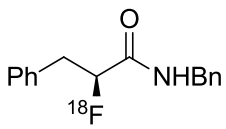
Immediately following general procedure with hydrocinnamaldehyde **4a** (0.7 mg, 5.0 µmol), solutions of 2-methyl-but-2-ene (1.8 mg, 25 µmol) in MeCN (200 µL) and $NaClO_2$ (80 %) (1.4 mg, 12 µmol) and NaH_2PO_4 (2.4 mg, 20 µmol) in H_2O (100 µL) were added to the crude reaction mixture. The reaction was

stirred for 30 minutes before an aliquot was taken for HPLC (Dilution: 10 µL in MeOH (20 µL), 20 µL injection). The peak corresponding to the reference compound was collected and an aliquot injected for chiral HPLC analysis (75 % RCC, 93 % ee, *n* = 3).

Analytical HPLC: HPLC Conditions A, 0.1 % TFA, Sample: 1 mg/mL in MeCN/H_2O (1:1), UV = 210 nm, t_{ret} = 7.4 min.

Chiral HPLC: Phenomenex Lux Cellulose 1 (5 µm, 4.6x100 mm), 0.3 mL/min, 25 % MeCN isocratic, 0.1 % TFA, 20 µL injection, UV = 210 nm, t_1 = 22.3 min, t_2 = 23.7 min.

(*S*)-[^{18}F]*N*-Benzyl-2-fluoro-3-phenylpropanamide ((*S*)-[^{18}F]13a)

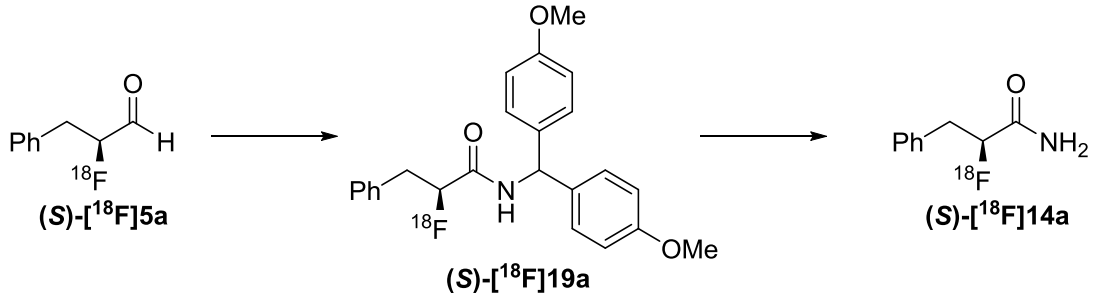


Immediately following general procedure with hydrocinnamaldehyde **4a** (0.7 mg, 5.0 µmol), a solution of benzylamine (1.1 mg, 10 µmol) and 2-methyl-but-2-ene (1.8 mg, 25 µmol) in toluene (200 µL) was added to the crude reaction mixture. After stirring for 5 minutes, a solution of $NaClO_2$ (80 %) (1.4 mg, 12 µmol) and NaH_2PO_4 (2.4 mg, 20 µmol) in H_2O (100 µL) was added and the reaction was stirred for 30 minutes before an aliquot was taken for HPLC (Dilution: 50 µL in MeOH (20 µL), 20 µL injection). The peak corresponding to the reference compound was collected and an aliquot injected for chiral HPLC analysis (46 % RCC, 83 % ee, *n* = 4).

Analytical HPLC: HPLC Conditions A, Sample: 1 mg/mL in MeCN/H_2O (4:1), UV = 210 nm, t_{ret} = 9.0 min.

Chiral HPLC: Phenomenex Lux Cellulose 1 (5 µm, 4.6x100 mm), 1.8 mL/min, 30 % MeCN isocratic, 200 µL injection, UV = 210 nm, t_1 = 28.7 min, t_2 = 30.9 min.

(*S*)-2-[^{18}F]Fluoro-3-phenylpropanamide ((*S*)-[^{18}F]14a)



Immediately following general procedure with hydrocinnamaldehyde **4a** (0.7 mg, 5.0 µmol), a solution of bis(4-methoxyphenyl)methanamine (1.8 mg, 7.5 µmol) and 2-methyl-but-2-ene (1.8 mg, 25 µmol) in toluene (200 µL) was added to the crude reaction mixture. After stirring for 5 minutes, a solution of $NaClO_2$ (80 %) (1.4 mg, 12 µmol) and NaH_2PO_4 (2.4 mg, 20 µmol) in H_2O (100 µL) was added and the reaction was stirred for 30 minutes. An aliquot was taken for HPLC analysis (5 µL neat).

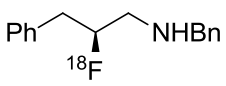
The solvent of the crude reaction mixture was reduced to approximately half the initial volume by heating to 60 °C under a flow of helium. A mixture of anisole (5 µL) and TFA (250 µL) was added and the solution was heated to 60 °C for a further 10 minutes before an aliquot was taken for HPLC (Dilution: 20 µL in MeCN/H_2O 1:1 (20 µL), 20 µL injection). The peak corresponding to the reference compound was collected and an aliquot injected for chiral HPLC analysis (49 % RCC, 88 % ee, *n* = 3).

Analytical HPLC (Int.): HPLC Conditions A, Sample: 1 mg/mL in MeCN/H_2O (4:1), UV = 210 nm, t_{ret} = 9.8 min.

Analytical HPLC (After deprotection): HPLC Conditions A, Sample: 1 mg/mL in MeCN/H_2O (4:1), UV = 210 nm, t_{ret} = 6.4 min.

Chiral HPLC (After deprotection): Phenomenex Lux Cellulose 2 (5 µm, 4.6x100 mm), 1.0 mL/min, 20 % MeCN isocratic, 200 µL injection, UV = 210 nm, t_1 = 7.2 min, t_2 = 8.4 min.

(*S*)-[^{18}F]*N*-benzyl-2-fluoro-3-phenylpropan-1-amine ((*S*)-[^{18}F]20a)

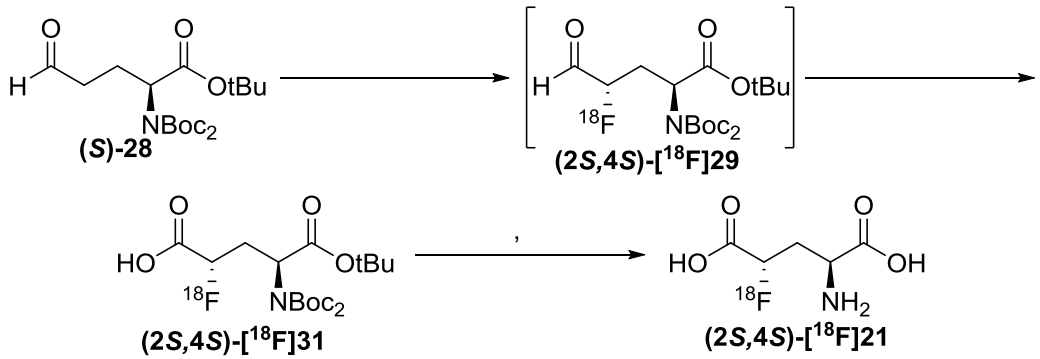


Immediately following general procedure with hydrocinnamaldehyde **4a** (0.7 mg, 5.0 µmol), a solution of benzylamine (1.1 mg, 10 µmol) in DCE (100 µL) was added to the crude reaction mixture. After stirring for 5 minutes, a solution of sodium triacetoxyborohydride (4.2 mg, 20 µmol) in DCE (150 µL) was added and the reaction was stirred for 30 minutes before an aliquot was taken for HPLC (Dilution: 50 µL in MeOH (20 µL), 20 µL injection). The peak corresponding to the reference compound was collected and an aliquot injected for chiral HPLC analysis (85 % RCC, 90 % ee, *n* = 3).

Analytical HPLC: HPLC Conditions B, $(NH_4)_2CO_3$ (20 mM) + 0.1 % DEA, Sample: 1 mg/mL in MeCN/H_2O (1:1), UV = 210 nm, t_{ret} = 14.3 min.

Chiral HPLC: Phenomenex Lux Cellulose 1 (5 µm, 4.6x100 mm), 1.5 mL/min, 40 % MeCN isocratic, $(NH_4)_2CO_3$ (20 mM) + 0.1 % DEA, 200 µL injection, UV = 210 nm, t_1 = 19.7 min, t_2 = 20.9 min.

(2*S*,4*S*)-4-[^{18}F]Fluoroglutamic acid ((2*S*,4*S*)-[^{18}F]21)



To an Eppendorf vial containing a stirrer bar and (*S*)-2,2,3-trimethyl-5-benzyl-4-imidazolidinone dichloroacetic acid (1.7 mg, 5.0 µmol) was added a solution of (*S*)-1-*tert*-butyl 2-[bis-(*tert*-butoxycarbonyl)amino]-5-oxopentanoate **(*S*)-28** (1.9 mg, 5.0 µmol) in MTBE (50 µL). The reaction was stirred for 10 minutes prior to the addition of an aliquot of [^{18}F]NFSI in MTBE (250 µl). The reaction was stirred at room temperature,

with an aliquot for HPLC (Dilution: 5 µL in MeOH (20 µl), 20 µL injection) taken after 20 minutes.

Solutions of 2-methyl-but-2-ene (1.8 mg, 25 µmol) in MeCN (200 µL) and $NaClO_2$ (80 %) (1.4 mg, 12 µmol) and NaH_2PO_4 (2.4 mg, 20 µmol) in H_2O (100 µL) were then added to the crude reaction mixture. The reaction was stirred for 30 minutes before an aliquot was taken for HPLC (Dilution: 5 µL in MeOH (20 µL), 20 µL injection).

The reaction mixture was then concentrated to dryness by heating to 60 °C under a flow of helium. A mixture of anisole (5 µL) and TFA (200 µL) was added and the solution was heated to 60 °C for a further 10 minutes before the reaction mixture was again concentrated to dryness under a flow of helium at this temperature. The crude residue was diluted with MeOH/H_2O (1:1) (100 µL) and an aliquot (20 µL) taken for HPLC analysis. The entire peak corresponding to the commercial reference compound was collected and an aliquot injected for chiral HPLC analysis.

Analytical HPLC (Int.): HPLC Conditions C, 0.1 % TFA, Sample: 1 mg/mL in MeCN/H_2O (1:1), UV = 210 nm, t_{ret} = 12.0 min.

Analytical HPLC (After deprotection): HPLC Conditions C, Sample: 1 mg/mL in H_2O, UV = 210 nm, t_{ret} = 1.5 min.

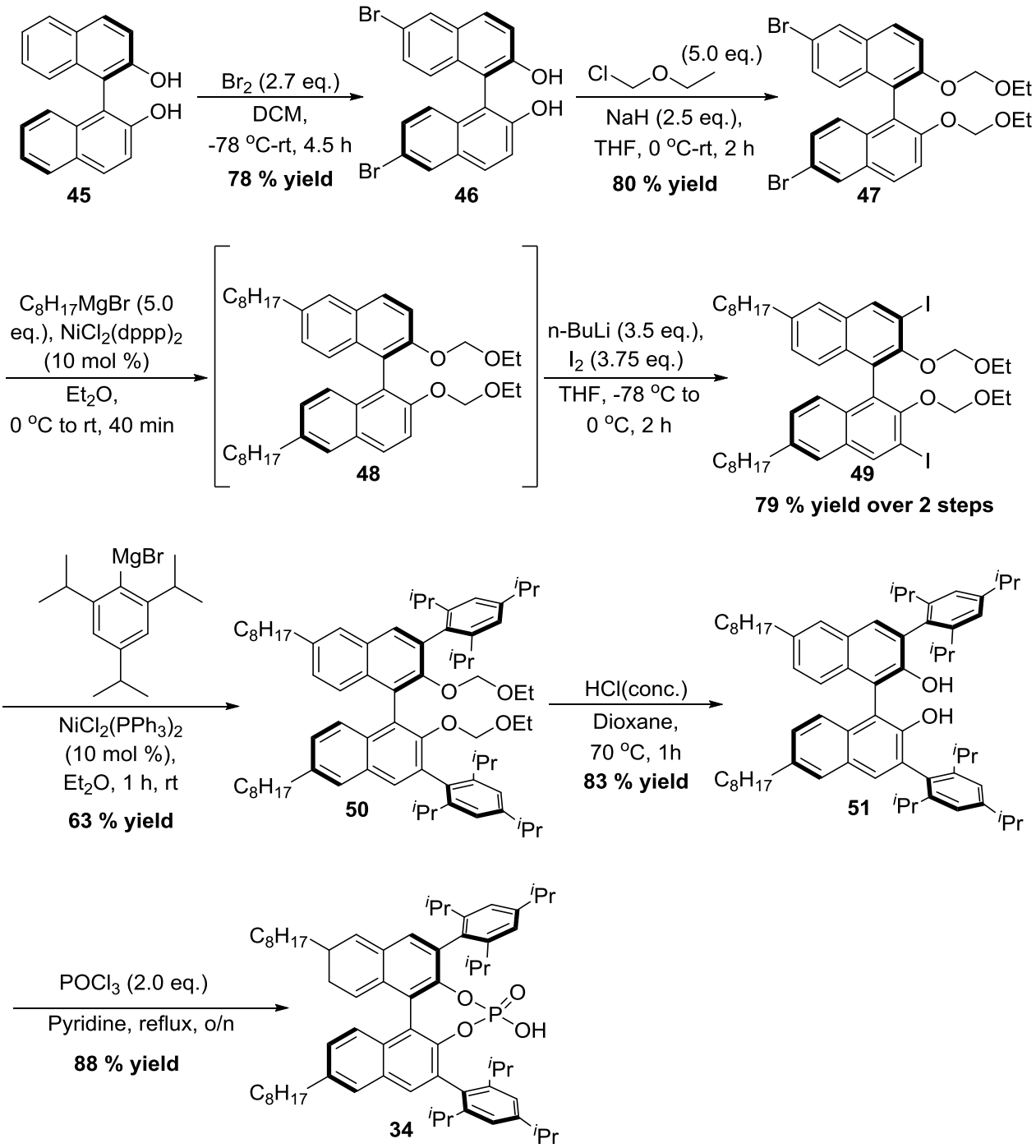
Chiral HPLC (After deprotection): Phenomenex Chirex Penicillamine (5µ, 4.6x150mm), 1.0 mL/min, 100 % $CuSO_4$ (2 mM) isocratic, 200 µL injection, UV = 210 nm, t_1 = 27.6 min, t_2 = 29.8 min, t_3 = 33.5 min, t_4 = 42.3 min.

4.2.2 Phase Transfer Reagents for Asymmetric [^{18}F]Fluorination

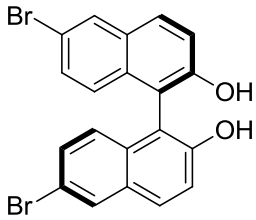
4.2.2.1 Reagent Synthesis

(*R*)-C_8-TRIP (34)

Prepared according to literature procedure.[17]



(*R*)-6,6'-dibromo-[1,1'-binaphthalene]-2,2'-diol ((*R*)-46)

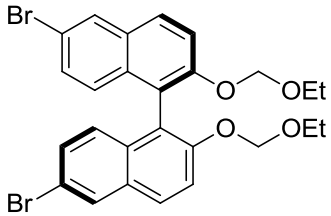


To a solution of (*R*)-BINOL (9.80 g, 34.2 mmol, 1.0 eq.) in DCM (200 mL) at −78 °C was added a solution of bromine (4.7 mL, 92.6 mmol, 2.7 eq.) in DCM (40 mL) dropwise over 30 minutes. The reaction was stirred for a further 2 hours at −78 °C before being allowed to warm to room temperature and stirred for a further 2 hours. The reaction was then quenched by slow addition of saturated aqueous sodium bisulfite. The organic phase was separated, washed with brine and dried over $MgSO_4$. The solvent was removed under reduced pressure to afford the title compound directly as a white solid (11.9 g, 26.7 mmol, 78 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.06 (brs, 2H), 6.97 (d, *J* = 9.0 Hz, 2H), 7.38 (dd, *J* = 8.9 Hz, *J* = 2.1 Hz, 2H), 7.39 (d, *J* = 8.8 Hz, 2H), 7.88 (d, *J* = 9.0 Hz, 2H), 8.05 (d, *J* = 1.7 Hz, 2H); **^{13}C NMR (101 MHz, $CDCl_3$):** δ = 110.6, 118.0, 118.9, 125.8, 130.4, 130.5, 130.6, 130.8, 131.8, 152.9; **LRMS (ESI^-, m/z):** $[C_{20}H_{11}Br_2O_2]^-$ $(M\text{-}H)^-$ calc. 442.9, found 442.6.

Data consistent with literature values.[18]

(*R*,*R*)-6,6'-dibromo-2,2'-bis(ethoxymethoxy)-1,1'-binaphthalene ((*R*,*R*)-47)



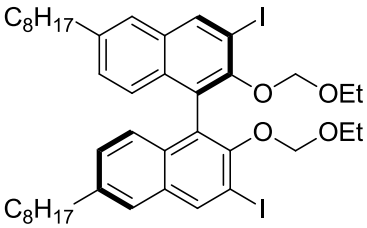
To a suspension of NaH (60 wt%) (2.25 g, 56.3 mmol. 2.5 eq.) in THF (130 mL) at 0 ºC was added a solution of (*R*)-6,6'-dibromo-[1,1'-binaphthalene]-2,2'-diol **(*R*)-46** (10.0 g, 22.5 mmol, 1.0 eq.) in THF (20 mL). The resulting solution was stirred for 1 h at 0 ºC before chloromethylethyl ether (6.33 mL, 67.5 mmol, 3.0 eq.) was added in one portion. The reaction was stirred for 1 h while gradually warming to room temperature. The reaction was quenched by careful addition of water and extracted with ethyl acetate. The organic phase was washed with brine, dried over $MgSO_4$ and the

solvent removed under reduced pressure. The crude residue was dissolved in minimal DCM and precipitated by addition of methanol. The precipitate was dried under high vacuum to afford the title compound as a white solid (10.14 g, 18.1 mmol, 86 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.04 (t, *J* = 7.1 Hz, 6H, 2 x CH_2CH_3), 3.39 (m, 4H, 2 x CH_2CH_3), 5.03 (d, *J* = 7.1 Hz, 2H), 5.14 (d, *J* = 7.1 Hz, 2H), 6.97 (d, *J* = 9.0 Hz, 2H), 7.29 (dd, *J* = 9.0 Hz, *J* = 2.0 Hz, 2H), 7.63 (d, *J* = 9.0 Hz, 2H), 7.87 (d, *J* = 9.0 Hz, 2H), 8.04 (d, *J* = 2.2 Hz, 2H); **^{13}C NMR (101 MHz, $CDCl_3$):** δ = 14.9, 64.1, 93.7, 117.9, 118.1, 120.6, 127.1, 128.6, 129.6, 129.8, 130.8, 132.4, 153.1; **LRMS (ESI^+, m/z):** $[C_{26}H_{24}Br_2NaO_4]^+$ $(M+Na)^+$ calc. 583.0, found 582.8.

Data consistent with literature values.[17]

(*R,R*)-2,2'-Bis(ethoxymethoxy)-3,3'-diiodo-6,6'-dioctyl-1,1'-binaphthalene ((*R,R*)-49)



To a three-neck round bottom flask equipped with a reflux condenser and dropping funnel, which was heat dried under vacuum, was added magnesium turnings (3.24 g, 133.5 mmol, 7.5 eq.), a single crystal of iodine and diethyl ether (10 mL). A solution of 1-bromooctane (15.3 mL, 89.0 mmol, 5.0 eq.) in diethyl ether (10 mL) was added via the dropping funnel over 10 minutes. The reaction was heated to reflux for 3 hours.

To another three-neck round bottom flask equipped with a reflux condenser, which was heat dried under vacuum, was added NiCl2(dppp) (965 mg, 1.78 mmol, 10 mol %), (*R*)-6,6'-dibromo-2,2'-bis(ethoxymethoxy)-1,1'-binaphthalene **(*R,R*)-47** (10.0 g, 17.8 mmol, 1.0 eq.) and diethyl ether (70 mL). The suspension was cooled to 0 °C before addition of the Grignard reagent prepared above via cannula. Following the addition, the reaction was stirred at room temperature for 30 minutes. The reaction mixture was carefully poured

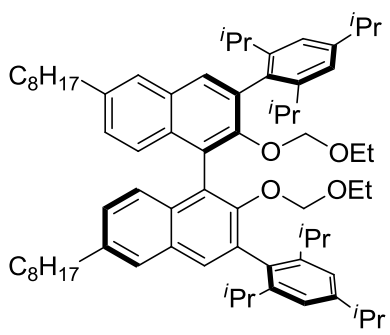
over cold HCl (1M) (100 mL) and extracted into diethyl ether. The combined organic phases were dried over $MgSO_4$ and filtered through a small pad of silica before removal of the solvent under reduced pressure.

To the crude residue was added THF (200 mL) and the solution was cooled to –78 ºC. After 10 minutes, *n*-BuLi (2.5 M in hexane) (25.0 mL, 62.3 mmol, 3.5 eq.) was added drop-wise over 10 minutes. The solution was kept at –78 ºC for 30 minutes and then warmed to 0 ºC and stirred for 1.5 hours. The reaction mixture was then cooled to –78 ºC and iodine (16.9 g, 66.8 mmol, 3.75 eq.) was added in one portion. The reaction mixture was stirred for 10 minutes at this temperature and then warmed to room temperature over 40 minutes. The reaction was quenched by the careful addition of saturated aqueous Na_2SO_3 and extracted into ethyl acetate. The combined organic phases were washed with water and brine, dried over $MgSO_4$ and the solvent was removed under reduced pressure. Purification by column chromatography on silica gel (SiO_2, petroleum ether 30-40: EtOAc 1:0-9:1) afforded the title compound as a white solid (11.7 g, 14.1 mmol, 79 % yield over 2 steps).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.65 (t, *J* = 7.0 Hz, 6H), 0.88 (t, *J* = 6.8 Hz, 6H), 1.25-1.39 (m, 20H), 1.65 (quin, *J* = 7.2 Hz, 4H), 2.62-2.69 (m, 2H), 2.71 (t, *J* = 7.6 Hz, 4H), 3.07 (dq, *J* = 9.3 Hz, *J* = 7.1 Hz, 2H), 4.70 (d, *J* = 5.6 Hz, 2H, 2 x OCH_2O), 4.86 (d, *J* = 5.6 Hz, 2H), 7.08 (d, *J* = 8.6 Hz, 2H), 7.14 (dd, *J* = 8.6 Hz, *J* = 1.7 Hz, 2H), 7.53 (s, 2H), 8.46 (s, 2H); **^{13}C NMR (101 MHz, $CDCl_3$):** δ = 13.8, 14.1, 22.3, 28.9, 29.0, 29.1, 30.8, 31.5, 35.5, 64.6, 92.1, 97.7, 124.8, 125.7, 126.0, 128.5, 131.8, 132.1, 139.0, 140.2, 151.1; **LRMS:** Peak not found.

Data consistent with literature values.[17]

(*R*,*R*)-2,2'-Bis(ethoxymethoxy)-6,6'-dioctyl-3,3'-bis(2,4,6-triisopropylphenyl)-1,1'-binaphthalene ((*R*,*R*)-50)



To a three-neck round bottom flask equipped with a reflux condenser and dropping funnel, which was heat dried under vacuum, was added magnesium turnings (554 mg, 22.8 mmol, 6.3 eq.), a single crystal of iodine and THF (1 mL). The mixture was heated until the colour of the iodine disappeared. To this activated magnesium was added 1,3,5-triisopropylbromobenzene (5.50 mL, 21.7 mmol, 6.0 eq.) in THF (25 mL) via the dropping funnel. The resulting mixture was heated at reflux for 3 hours and then cooled to room temperature.

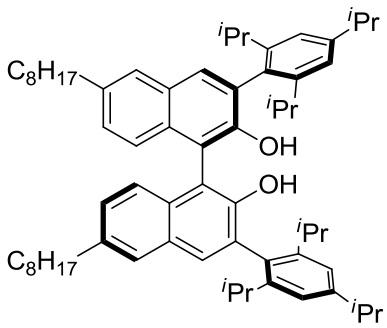
To another round bottom flask, which was heat dried under vacuum, was added (*R*)- 2,2'-bis(ethoxymethoxy)-3,3'-diiodo-6,6'-dioctyl-1,1'-binaphthalene **(*R*,*R*)-49** (3.00 g, 3.62 mmol, 1.0 eq) and $NiCl_2(PPh_3)_2$ (236 mg, 0.36 mmol, 10 mol %) and the mixture was suspended in diethyl ether (10 mL). To the solution at room temperature was added via cannula the Grignard prepared above. The reaction was stirred for 45 min and then carefully poured over ice-cold HCl (1M) and extracted with DCM. The combined organic phases were washed with brine, dried over $MgSO_4$, the solvent removed under reduced pressure. Purification by column chromatography on silica gel (SiO_2, hexane: DCM, 1:0-9:1) afforded the title compound as a colourless oil (2.34 g, 2.28 mmol, 63 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.48 (t, *J* = 7.1 Hz, 6H), 0.84-0.91 (m, 6H), 0.98 (d, *J* = 6.8 Hz, 6H), 1.20 (dd, *J* = 13.0 Hz, *J* = 6.8 Hz, 12H), 1.26-1.33 (m, 38H), 1.63-1.75 (m, 4H), 2.34-2.54 (m, 4H), 2.67-2.77 (m, 4H), 2.78-3.01 (m, 6H), 4.22 (d, *J* = 5.1 Hz, 2H), 4.24 (d, *J* = 5.1 Hz, 2H), 7.09 (dd, *J* = 13.4 Hz, *J* = 1.7 Hz, 4H), 7.16 (dd, *J* = 8.6 Hz, *J* = 1.7 Hz, 2H), 7.29 (d, *J* = 8.6 Hz, 2H), 7.59 (d, *J* = 1.2 Hz, 2H), 7.70 (s, 2H); **^{13}C NMR**

(101 MHz, $CDCl_3$): δ = 14.1, 14.4, 22.7, 23.2, 23.3, 24.2, 25.2, 26.0, 29.3, 29.5, 29.6, 30.8, 30.9, 31.4, 31.9, 34.3, 36.0, 63.4, 96.4, 120.4, 120.7, 121.3, 125.9, 126.1, 127.6, 130.3, 130.5, 132.1, 133.5, 134.1, 139.4, 146.7, 147.6, 148.1, 151.6; **LRMS:** Peak not found.

Data consistent with literature values.[17]

(*R*,*R*)-6,6'-Dioctyl-3,3'-bis(2,4,6-triisopropylphenyl)-[1,1'-binaphthalene]-2,2'-diol ((*R*,*R*)-51)

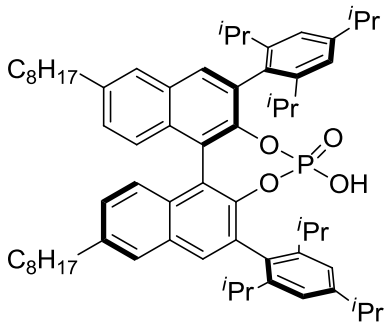


To a solution of (*R*,*R*)-2,2'-bis(ethoxymethoxy)-6,6'-dioctyl-3,3'-bis(2,4,6-triisopropylphenyl)-1,1'-binaphthalene **(*R*,*R*)-50** (2.30 g, 2.23 mmol, 1.0 eq.) in dixoane (50 mL) was added HCl (conc.) (5 mL). The reaction was heated to 70 °C for 1 hour before removal of the solvent under reduced pressure. The crude residue was dissolved in DCM and washed with aqueous saturated $NaHCO_3$, water and brine. The organic phase was dried over $MgSO_4$ and the solvent was removed under reduced pressure. Purification by column chromatography on silica gel (SiO_2, hexane: DCM 1:0-4:1) afforded the title compound as a white solid (1.69 g, 1.84 mmol, 83 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.84-0.93 (m, 6H), 0.99-1.23 (m, 22H), 1.23-1.45 (m, 34H), 1.64-1.75 (m, 4H), 2.66-2.78 (m, 6H), 2.81-2.91 (m, 2H), 2.97 (s, 2H), 4.87 (s, 2H, 2 x O*H*), 7.14 (d, *J* = 8.8 Hz, 4H), 7.17 (d, *J* = 8.8 Hz, 2H), 7.22 (d, *J* = 8.6 Hz, 2H), 7.63 (s, 2H), 7.69 (s, 2H); **^{13}C NMR (101 MHz, $CDCl_3$):** δ = 14.1, 22.7, 23.7, 23.9, 24.0, 24.1, 24.3, 24.3, 29.3, 29.5, 29.6, 30.8, 30.8, 31.5, 31.9, 34.3, 35.9, 112.9, 121.1, 124.5, 126.5, 128.2, 129.0, 129.1, 130.2, 130.7, 131.7, 138.4, 147.6, 147.7, 148.9, 150.0; **LRMS:** Peak not found.

Data consistent with literature values.[17]

(*R*,*R*)-4-Hydroxy-9,14-dioctyl-2,6-bis(2,4,6-triisopropylphenyl)dinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepine 4-oxide ((*R*,*R*)-34) ((*R*)-C_8-TRIP)



To (*R*,*R*)-6,6'-dioctyl-3,3'-bis(2,4,6-triisopropylphenyl)-[1,1'-binaphthalene]-2,2'-diol **(*R*,*R*)-51** (1.65 g, 1.80 mmol, 1.0 eq.) was added pyridine (5 mL) followed by phosphoryl chloride (335 µL, 3.60 mmol, 2.0 eq.). The reaction was heated to 95 °C for 16 hours before being cooled to room temperature. Water (6 mL) was added and the reaction was heated to 105 °C for a further 5 hours before being cooled to room temperature and diluted with DCM. The solution was washed with HCl (3M) (x3), the organic phase was dried over $MgSO_4$ and the solvent removed under reduced pressure. Purification was performed by column chromatography on silica gel (SiO_2, DCM: MeOH 1:0-19:1). The resulting residue was dissolved in DCM and washed with HCl (2M). The organic phase was dried over $MgSO_4$ and the solvent removed under reduced pressure to afford the title compound as a white solid (1.55 g, 1.58 mmol, 88 % yield).

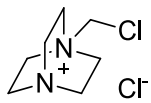
^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.74 (d, *J* = 6.4 Hz, 6H), 0.86-0.93 (m, 12H), 0.97 (d, *J* = 6.6 Hz, 6H), 1.06 (d, *J* = 6.6 Hz, 6H), 1.23 (dd, *J* = 6.2 Hz, *J* = 6.9 Hz, 12H), 1.26-1.49 (m, 20H), 1.65-1.82 (m, 4H), 2.49-2.63 (m, 4H), 2.78 (t, *J* = 7.7 Hz, 4H), 2.80-2.88 (m, 2H), 6.92 (d, *J* = 2.4 Hz, 4H), 7.15-7.22 (m, 2H), 7.22-7.27 (m, 2H), 7.63 (s, 2H), 7.72 (s, 2H); **^{13}C NMR (101 MHz, $CDCl_3$):** δ = 14.1, 22.7, 23.4, 24.0, 24.1, 25.0, 26.4, 29.3, 29.5, 29.6, 30.6, 30.9, 31.4, 31.9, 34.1, 35.9, 120.2, 121.0, 121.9, 126.3, 127.3, 127.6, 130.6, 131.1, 131.2, 132.0, 140.3, 147.2, 147.7, 148.1; **^{31}P NMR (162, DMSO-d_6):** δ = 1.62; **LRMS:** Peak not found; **IR:** 1019 (s, P=O), **$[\alpha]^{22}_D$:** −38.3 (c 0.30, MeOH) [No lit. ref.].

Data consistent with literature values.[19]

The corresponding lithium salt was formed by addition of LiOMe (1.0 eq.) in DCM/ MeOH (1:1). After stirring at room temperature for 30 minutes, the solvent was removed under reduced pressure to afford lithium salt as a while solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 0.81-0.88 (m, 12H), 1.06 (d, *J* = 6.8 Hz, 6H), 1.14 (dd, *J* = 6.6 Hz, *J* = 4.6 Hz, 12H), 1.22-1.28 (m, 24H), 1.31 (brs, 8H), 1.56-1.70 (m, 4H), 2.54-2.62 (m, 2H), 2.68 (t, *J* = 6.0 Hz, 4H), 2.85-3.00 (m, 4H), 6.96 (d, *J* = 8.8 Hz, 2H), 6.99 (d, *J* = 1.2 Hz, 2H), 7.09 (d, *J* = 1.5 Hz, 2H), 7.13 (dd, *J* = 8.8 Hz, *J* = 1.7 Hz, 2H), 7.64 (s, 2H), 7.71 (s, 2H); **^{31}P NMR (162, DMSO-d_6):** δ = 3.59; **IR (ν, cm^{-1}):** 1094 (s, P=O); **MP:** 170 °C (decomp.).

1-(Chloromethyl)-1,4-diazabicyclo[2.2.2]octan-1-ium chloride (44)



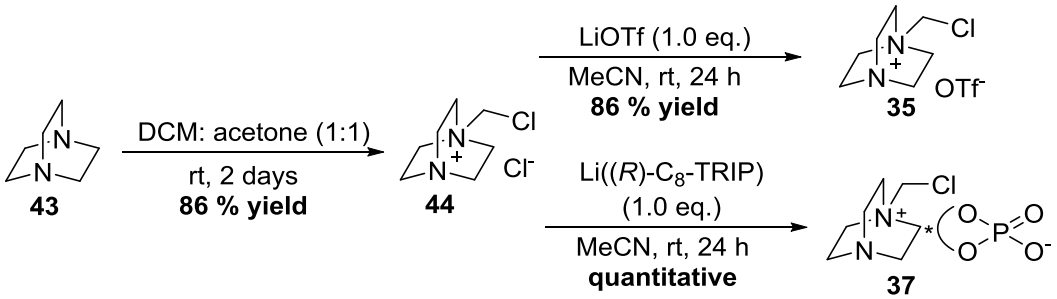
Prepared according to literature procedure.[20]

A solution of DABCO (5.00 g, 44.6 mmol, 1.0 eq.) in DCM/ acetone (1:1) (50 mL) was left to stand for 48 hours. The resultant white precipitate was removed by filtration, washed with acetone and dried under high vacuum to afford the title compound directly as a white solid (6.14 g, 38.2 mmol, 86 % yield).

^{1}H NMR (400 MHz, CD_3CN): δ = 3.15 (t, *J* = 7.8 Hz, 6H), 3.57 (t, *J* = 7.3 Hz, 6H), 5.50 (s, 2H); **^{13}C NMR (101 MHz, CD_3CN):** δ = 45.6, 52.1, 69.0.

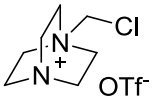
Data consistent with literature values.[21]

General procedure for anion transfer



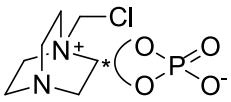
To a solution of dabconium salt (1.0 eq.) in acetonitrile (0.8 M), was added exactly one equivalent of lithium salt. The reaction was stirred for 24 hours then filtered to remove lithium chloride. The solvent was removed under reduced pressure.

1-(Chloromethyl)-1,4-diazabicyclo[2.2.2]octan-1-ium triflate (35)



Prepared according to general procedure employing 1-(chloromethyl)-1,4-diazabicyclo[2.2.2]octan-1-ium chloride **44** (5.91 g, 36.8 mmol, 1.0 eq.) and lithium triflate (5.74 g, 36.8 mmol, 1.0 eq.). Purification by trituration with ethyl acetate afforded title compound as a white solid (5.95 g, 36.8 mmol, quantitative). Purity was analysed by ^{19}F NMR by comparison with a known amount of a fluorinated reference compound.

1-(Chloromethyl)-1,4-diazabicyclo[2.2.2]octan-1-ium (*R*,*R*)-9,14-dioctyl-2,6-bis(2,4,6-triisopropylphenyl)dinaphtho[2,1-d:1',2'-f][1,3,2]dioxaphosphepin-4-olate 4-oxide (37)



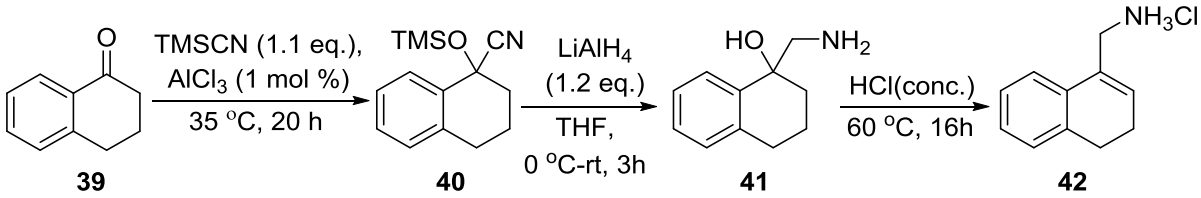
Prepared according to general procedure employing 1-(chloromethyl)-1,4-diazabicyclo[2.2.2]octan-1-ium chloride **44** (99 mg, 0.50 mmol, 1.0 eq.) and Li((*R*)-C_8-TRIP) (492 mg, 0.50 mmol, 1.0 eq.). Purification by trituration with ethyl acetate afforded the title compound as a white solid (570 mg, 0.50 mmol, quantitative).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 0.80-0.88 (m, 12H), 1.06 (d, *J* = 6.8 Hz, 6H), 1.14 (dd, *J* = 6.7 Hz, *J* = 3.3 Hz, 12H), 1.23 (brs, 8H), 1.26 (d, *J* = 7.1 Hz, 16H), 1.31 (brs, 8H), 1.63 (ddd, *J* = 27.9 Hz, *J* = 11.7 Hz, *J* = 5.9 Hz, 4H), 2.54-2.62 (m, 2H), 2.68 (t, *J* = 5.7 Hz, 4H), 2.86-2.98 (m, 4H), 3.04 (t, *J* = 6.8 Hz, 6H), 3.34-3.39 (m, 6H), 5.29 (d, *J* = 2.9 Hz, 2H), 6.96 (d, *J* = 8.8 Hz, 2H), 6.99 (d, *J* = 1.2 Hz, 2H), 7.09 (d, *J* = 1.5 Hz, 2H), 7.14 (dd, *J* = 1.7 Hz, *J* = 8.8 Hz, 2H), 7.65 (s, 2H), 7.71 (s, 2H); **^{31}P NMR (162, DMSO-d_6):** δ = 3.72; **IR (v, cm^{-1}):** 1098 (s, P=O).

4.2.2.2 Substrate Synthesis

(3,4-Dihydronaphthalen-1-yl)methanammonium chloride (42)

Prepared according to literature procedure.[17]

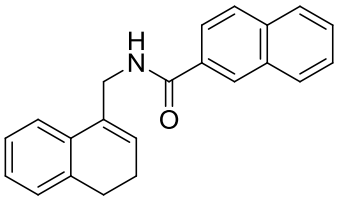


To α-tetralone (1.93 mL, 14.5 mmol, 1.0 eq.) and $AlCl_3$ (2 mg, 0.01 mmol, 1 mol %) was added TMSCN (2.0 mL, 16.0 mmol, 1.1 eq.). The reaction was warmed to 35 °C and stirred for 20 hours before the addition of THF (30 mL). It was then cooled to 0 °C for the addition of $LiAlH_4$ (662 mg, 17.4 mmol, 1.2 eq.) portionwise. The reaction was warmed to room temperature and stirred for 3 hours before being quenched by the addition of $NaSO_4 \cdot 10H_2O$ (1.00 g). The reaction mixture was then filtered and washed with diethyl ether. The solvent was removed under reduced pressure and the residue was redissolved in ethanol (100 mL). To the solution was added HCl (conc.) (10 mL) and the reaction was heated to 60 °C for 16 h. The solvent was then removed under reduced pressure and the resulting solid was washed with diethyl ether and DCM and dried under high vacuum to afford the title compound as a white solid (0.875 g, 4.47 mmol, 31 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.27-2.41 (m, 2H), 2.79 (t, *J* = 7.9 Hz, 2H), 3.99 (s, 2H), 6.25 (t, *J* = 4.5 Hz, 1H), 7.20-7.22 (m, 2H), 7.25-7.28 (m, 2H); **^{13}C NMR (101 MHz, $CDCl_3$):** δ = 24.1, 28.7, 41.8, 123.2, 128.1, 129.2, 129.3, 131.5, 131.6, 133.0, 137.9; **LRMS (ESI$^+$, m/z):** $[C_{11}H_{14}N]^+$ $(M\text{-}Cl)^+$ calc. 160.1, found 160.1.

Data consistent with literature values.[17]

_N_-((3,4-Dihydronaphthalen-1-yl)methyl)-2-naphthamide (32)



Prepared according to literature procedure.[17]

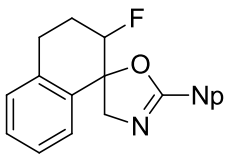
To a solution of (3,4-dihydronaphthalen-1-yl)methanammonium chloride **42** (280 mg, 1.43 mmol, 1.0 eq.) in DCM (15 mL) was added triethylamine (797 µL, 5.72 mmol, 4.0 eq.), 2-napthyl chloride (410 mg, 2.15 mmol, 1.5 eq.) and DMAP (17 mg, 0.40 mmol, 10 mol %). The reaction was stirred at room temperature for 3 hour before being quenched by the addition of saturated aqueous ammonium chloride (50 mL). The organics were extracted with DCM, the combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure. Purification by column chromatography on silica gel (SiO_2, petroleum ether 30-40: DCM: EtOAc 13:4:3) afforded the title compound as a white solid (390 mg, 1.25 mmol, 87 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.27-2.46 (m, 2H), 2.83 (t, *J* = 8.1 Hz, 2H), 4.52-4.62 (m, 2H), 6.18 (t, *J* = 4.5 Hz, 1H), 6.30 (brs, 1H), 7.21-7.26 (m, 1H), 7.36 (d, *J* = 7.1 Hz, 1H), 7.50-7.59 (m, 2H), 7.79-7.94 (m, 4H), 8.28 (s, 1H); **^{13}C NMR (101 MHz, $CDCl_3$):** δ = 23.1, 27.9, 42.6, 122.7, 123.6, 126.7, 126.8, 127.3, 127.6, 127.7, 127.8, 128.4, 128.5, 128.9, 131.6, 132.6, 133.0, 133.0, 134.7, 136.4, 167.4; **LRMS (ESI$^+$, m/z):** $[C_{22}H_{20}NO]^+$ $(M+H)^+$ calc. 314.2, found 314.2.

Data consistent with literature values.[17]

4.2.2.3 Racemic Fluorinated Reference Synthesis

2-Fluoro-2'-(naphthalen-2-yl)-3,4-dihydro-2*H*,4'*H*-spiro[naphthalene-1,5'-oxazole] (33)



Prepared according to literature procedure.[22]

To a solution of *N*-((3,4-dihydronaphthalen-1-yl)methyl)-2-naphthamide **32** (100 mg, 0.32 mmol, 1.0 eq.) in acetonitrile (5 mL), was added sodium bicarbonate (54 mg, 0.64 mmol, 2.0 eq.) and Selectfluor (125

mg, 0.35 mmol, 1.1 eq.). The reaction was stirred at room temperature for two hours before being diluted with DCM (25 mL) and washed with water followed by brine. The organic phase was dried over $MgSO_4$ and the solvent removed under reduced pressure. The crude product was analysed by ^{19}F NMR to determine diastereoselectivity. Purification by column chromatography on silica gel (SiO_2, petroleum ether 30-40: EtOAc 9:1-4:1) afforded the title compound as a 1:1 mixture of diastereoisomers.

***Anti* diastereoisomer**: White solid (40 mg, 0.12 mmol, 38 % yield)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.09-2.24 (m, 1H), 2.30-2.49 (m, 1H), 2.95-3.14 (m, 2H), 4.14 (dd, *J* = 15.2 Hz, *J* = 2.9 Hz, 1H), 4.64 (d, *J* = 15.4 Hz, 1H), 5.15 (ddd, *J* = 49.9 Hz, *J* = 10.8 Hz, *J* = 3.4 Hz, 1H), 7.15-7.20 (m, 1H), 7.26-7.31 (m, 2H), 7.37-7.42 (m, 1H), 7.51-7.61 (m, 2H), 7.86-7.95 (m, 3H), 8.15 (d, *J* = 8.6 Hz, *J* = 1.2 Hz, 1H), 8.55 (brs, 1H); **^{13}C NMR (101 MHz, $CDCl_3$):** δ = 26.2 (d, *J* = 19.1 Hz), 26.4 (d, *J* = 9.5 Hz), 64.2 (d, *J* = 6.4 Hz), 86.5 (d, *J* = 20.7 Hz), 92.1 (d, *J* = 181.2 Hz), 124.7, 124.8, 126.6, 127.4, 127.6, 127.8, 128.2, 128.3, 128.4, 128.9, 132.7, 134.8, 137.6 (d, *J* = 3.2 Hz), 163.7; **^{19}F NMR (377 MHz, $CDCl_3$)** δ = −193.2; **LRMS (ESI^+, m/z):** $[C_{22}H_{19}FNO]^+$ $(M+H)^+$ calc. 332.1, found 332.2.

***Syn* diastereomer**: White solid (42 mg, 0.13 mmol, 41 % yield)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.06-2.27 (m, 1H), 2.29-2.47 (m, 1H), 2.97-3.12 (m, 2H), 4.13 (dd, *J* = 15.2 Hz, *J* = 2.9 Hz, 1H), 4.63 (dd, *J* = 15.2 Hz, *J* = 0.5 Hz, 1H), 5.14 (ddd, *J* = 50.1 Hz, *J* = 10.8 Hz, *J* = 3.4 Hz, 1H), 7.15-7.19 (m, 1H), 7.26-7.31 (m, 1H), 7.38-7.43 (m, 1H), 7.50-7.60 (m, 2H), 7.86-7.94 (m, 3H), 8.13 (dd, *J* = 8.6 Hz, *J* = 1.7 Hz, 1H), 8.52 (brs, 1H); **^{13}C NMR (101 MHz, $CDCl_3$):** δ = 25.2 (d, *J* = 19.1 Hz), 25.3 (d, *J* = 6.4 Hz), 66.2 (d, *J* = 3.2 Hz), 84.9 (d, *J* = 17.5 Hz), 91.6 (d, *J* = 182.8 Hz), 124.6, 124.8, 126.6, 126.8, 127.3, 127.6, 127.8, 128.2, 128.5, 128.9, 129.1, 132.7, 134.8, 135.3,

163.9; **^{19}F NMR (377 MHz, $CDCl_3$)** δ = −193.2; **LRMS (ESI$^+$, m/z):** $[C_{22}H_{19}FNO]^+$ $(M+H)^+$ calc. 332.1, found 332.2.

Data consistent with literature values.[17]

4.2.2.4 Radiochemistry

HPLC Analysis

Analytical: Water Atlantis dC18, 5µm, 3.9x150mm, 1.0 mL/min, UV = 240 nm, Sample: 1 mg/mL in MeCN, t_{Prod} = 14.4 min.

HPLC Conditions E

0-1 min, 5 % MeCN, 95 % H_2O
1-11 min, 5-80 % MeCN
11-16 min, 80 % MeCN, 20 % H_2O
16-19 min, 80-5 % MeCN
19-20 min, 5 % MeCN, 95 % H_2O

Chiral: Phenomenex Lux Cellulose 2, 5 µm, 4.6x100mm, 1.0 mL/min, UV = 240 nm, 60 % MeCN isocratic, t_1 = 8.0 min, t_2 = 9.6 min.

Production of [^{18}F]fluoride and [^{18}F]F_2 was performed as described in Section 4.2.1.4.

Preparation of [^{18}F]Selectfluor bis-triflate ([^{18}F]36)

[^{18}F]F_2 gas was bubbled into a vial containing 1,4-diazabicyclo[2.2.2]octan-1-ium triflate **35** (1.1 mg, 3.5 µmol) and lithium triflate (0.9 mg, 6 µmol) in acetone-d_6 (0.75 mL) at room temperature for ~ 30 seconds. The activity of the crude stock solution in acetone-d_6 ranged from 2.0-3.5 GBq. Aliquots (0.25 mL) of this crude stock solution were employed directly in labelling reactions.

Preparation of chiral [^{18}F]Selectfluor bis-phosphonate([^{18}F]38)

[^{18}F]F_2 gas was bubbled into a vial containing 1,4-diazabicyclo[2.2.2]octan-1-ium phosphonate **37** (3.6 mg, 3.2 µmol) and Li((*R*)-C_8-TRIP) (3.2 mg, 3.3 µmol) in acetone-d_6 (0.75 mL) at room temperature for ~ 30 seconds. The activity of the crude stock solution

in acetone-d_6 was 3.1 GBq. Aliquots (0.25 mL) of this crude stock solution were employed directly in labelling reactions.

General procedure for asymmetric fluorocyclisation with [^{18}F]Selectfluor bis-triflate

To a Wheaton v-vial vial containing (*R*)-C_8-TRIP **34** (4.9 mg, 5.0 µmol) and sodium carbonate (1.0 mg, 10.0 µmol) was added an aliquot of [^{18}F]Selectfluor bis-triflate **[^{18}F]36** in acetone-d_6 (250 µl). The solvent was removed under a flow of helium gas and *N*-((3,4-dihydronaphthalen-1-yl)methyl)-2-naphthamide **32** (1.6 mg, 5.0 µmol) was added as a solution in hexane/ fluorobenzene (1:1) (500 µL). The reaction was stirred at room temperature, with aliquots for HPLC (50 µL crude reaction diluted in MeCN/H_2O (1:1) (100 µL)) taken after 20 and 60 minutes of stirring.

In subsequent reactions, an aliquot of [^{18}F]Selectfluor bis-triflate **[^{18}F]36** in acetone-d_6 (250 µl) was added to an empty reaction vial and the solvent evaporated under a flow of helium gas, before addition of the catalyst and substrate in hexane: fluorobenzene (1:1).

General procedure for phase transfer fluorination with chiral [^{18}F]Selectfluor bis-phosphonate

To a Wheaton v-vial vial containing *N*-((3,4-dihydronaphthalen-1-yl)methyl)-2-naphthamide **32** (1.6 mg, 5.0 µmol) and sodium bicarbonate (0.8 mg, 10.0 µmol) was added an aliquot of [^{18}F]Selectfluor bis-phosphonate **[^{18}F]38** in acetone-d_6 (250 µl). The reaction was stirred at room temperature, with aliquots for HPLC (10 µL crude reaction diluted in MeCN/H_2O (1:1) (100 µL)) taken after 30 and 60 minutes of stirring. The peak corresponding to the reference compound was collected and an aliquot injected for chiral HPLC analysis (200 µl neat).

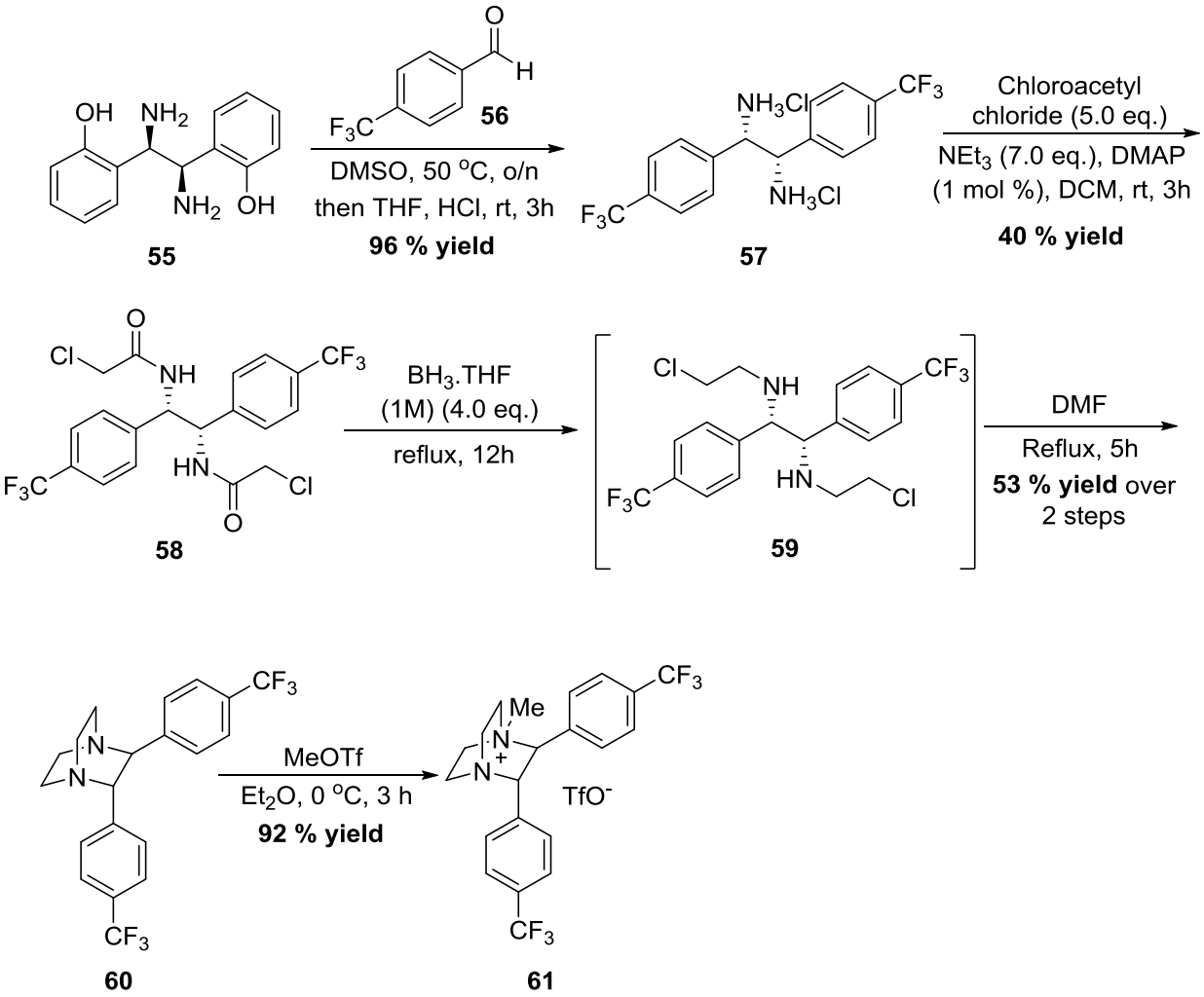
In a subsequent reaction, [^{18}F]Selectfluor bis-phosphonate **[^{18}F]38** in acetone-d_6 (250 µl) was added to a reaction vial containing substrate and base and the solvent was evaporated under a flow of helium gas, before addition of MeCN (250 µL).

4.2.3 Fluorocyclisation with Chiral [^{18}F]Selectfluor bis-triflate

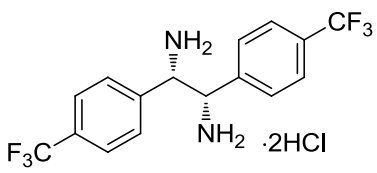
4.2.3.1 Reagent Synthesis

(2*S*,3*S*)-1-methyl-2,3-bis(4-(trifluoromethyl)phenyl)-1,4-diazabicyclo[2.2.2]octan-1-ium triflate ((2*S*,3*S*)-61)

Prepared according to literature procedure.[23]



(1*S*,2*S*)-1,2-Bis(4-(trifluoromethyl)phenyl)ethane-1,2-diamine hydrochloric acid salt ((1*S*,2*S*)-57)



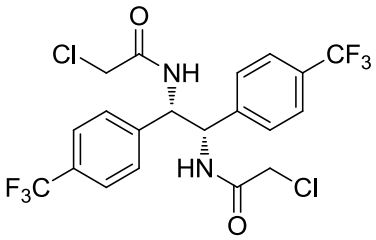
To a solution of (1*R*,2*R*)-1,2-bis(2-hydroxylphenyl)-1,2-diaminoethane **(1*R*,2*R*)-55** (1.90 g, 7.78 mmol, 1.0 eq.) in DMSO (40 mL) was added 4-trifluoromethyl benzaldehyde **56** (5.30 mL, 38.9 mmol, 5.0 eq.). The resulting mixture was stirred overnight at 50 °C before being poured onto water (120 mL). The aqueous layer was extracted with ether and the combined organic phases were washed with water, dried over $MgSO_4$ and evaporated under reduced pressure.

To the resultant diimine intermediate was added THF (80 mL) and HCl (conc.) (2.3 mL). The reaction was stirred for 3 hours at room temperature before removal of the solvent under reduced pressure. The crude residue was dissolved in HCl (1M) and washed with diethyl ether. The organic layer was extracted twice more with HCl (1M). The organic phase was then discarded (to remove aldehyde substrate) and the combined aqueous phases were basified using minium NaOH (1M). The resultant diamine was extracted into ethyl acetate and dried over $MgSO_4$. To this solution was added HCl (conc.) (2 mL) and the solvent was removed under reduced pressure to provide the title compound directly as a white solid (3.15 g, 7.48 mmol, 96 % yield).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 5.32 (s, 2H), 7.64 (d, *J* = 8.6 Hz, 4H), 7.69 (d, *J* = 8.3 Hz, 4H), 9.51 (brs, 6H, 2 x N*H*$_3$); **^{13}C NMR (101 MHz, DMSO-d_6):** δ = 56.4, 124.3 (q, *J* = 270), 125.9 (q, *J* = 3), 130.0 (q, *J* = 32), 130.3, 137.9; **^{19}F NMR (377 MHz, DMSO-d_6)** δ = −61.3; **LRMS (ESI$^+$, m/z):** $[C_{16}H_{15}F_6N_2]^+$ (Free amine+H)$^+$ calc. 349.1, found 349.1; **[α]$^{22}_D$** −52.9 (c 0.06, MeOH) [Lit = −34.5 (c 0.06, MeOH)].

Data consistent with literature values.[24]

_N_,_N_'-((1_S_,2_S_)-1,2-Bis(4-(trifluoromethyl)phenyl)ethane-1,2-diyl)bis(2-chloroacetamide) ((1_S_,2_S_)-58)

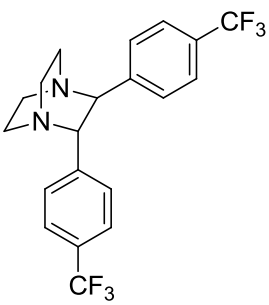


To a solution of diamine **(1_S_,2_S_)-57** (3.15 g, 7.48 mmol, 1.0 eq) in DCM (50 mL) at 0 °C was added triethylamine (7.31 mL, 52.4 mmol, 7.0 eq.), DMAP (1 mol %) and chloroacetyl chloride (3.00 mL, 37.5 mmol, 5.0 eq.) The reaction was stirred at room temperature for 3 hours before quenching with water (15 mL) and acidifying with HCl (1M). The aqueous phase was extracted with a large excess of warm ethyl acetate (x2) and the combined organic phases were dried over $MgSO_4$ and evaporated under reduced pressure. Purification by trituration with MeCN (2 mL) afforded the title compound as a white solid. A further batch of product was obtained by removal of solvent from the filtrate and recrystallisation of the residue from minimum hot ethyl acetate (Total = 1.52 g, 3.03 mmol, 40 % yield).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 4.05 (d, *J* = 13.0 Hz, 2H), 4.09 (d, *J* = 13.2 Hz, 2H), 5.33-5.41 (m, 2H), 7.45 (d, *J* = 8.1 Hz, 4H), 7.61 (d, *J* = 8.3 Hz, 4H), 9.03 (brd, *J* = 7.8 Hz, 2H, N*H*); **^{13}C NMR (100 MHz, DMSO-d_6):** δ = 42.5, 56.6, 124.2 (q, *J* = 271.6 Hz, CF3), 125.0 (q, *J* = 3.7 Hz), 127.9 (q, *J* = 31.6 Hz), 128.2, 144.0, 165.8; **^{19}F NMR (377 MHz, DMSO-d_6)** δ = −60.9; **LRMS (ESI$^+$, m/z):** $[C_{22}H_{16}Cl_2F_6N_2O_2Na]^+$ $(M+Na)^+$ calc. 523.0, found 522.8; **[α]$^{22}_D$** +16.7 (c 0.15, MeOH) [No lit. ref.].

Data consistent with literature values.[23]

(2_S_,3_S_)-2,3-Bis(4-(trifluoromethyl)phenyl)-1,4-diazabicyclo[2.2.2]octane ((2_S_,3_S_)-60)



To a solution of *N*,*N*'-((1*S*,2*S*)-1,2-bis(4-(trifluoromethyl)phenyl)ethane-1,2-diyl)bis(2-chloroacetamide) **(1_S_,2_S_)-58** (200 mg, 0.40 mmol, 1.0 eq) in THF (4 mL) at 0 °C was added BH_3·THF (1M solution in THF) (1.60 mL, 1.60 mmol,

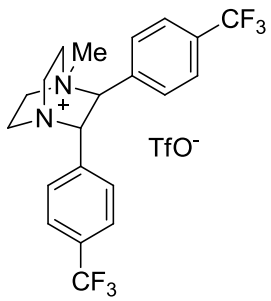
4.0 eq) and the reaction was heated at reflux for 12 hours before cooling to 0 °C and quenching by dropwise addition of methanol. The reaction was stirred for a further 2 hours at room temperature then washed with H_2O and extracted into DCM. The combined organic phases were dried over $MgSO_4$ and the solvent removed under reduced pressure to afford intermediate **59** as a white solid, which was used directly in the next step without further purification.

A solution of diamine **59** in DMF (2 mL) was heated at reflux for 5 hours before removal of the solvent under reduced pressure. The crude residue was dissolved in water and basified with NaOH (3M). The aqueous phase was extracted with DCM and the combined organic phases were washed with brine, dried over $MgSO_4$ and the solvent removed under reduced pressure. Purification by column chromatography on silica gel (SiO_2, DCM:MeOH 1:0-97:3) afforded the title compound as a pale yellow oil (85 mg, 0.21 mmol, 53 % yield over 2 steps).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.52-2.67 (m, 4H), 2.87-2.97 (m, 4H), 4.06 (s, 2H), 7.49 (d, *J* = 8.3 Hz, 4H), 7.55 (d, *J* = 8.3 Hz, 4H); **^{13}C NMR (101 MHz, DMSO-d_6):** δ = 41.2, 49.4, 62.1, 124.1 (q, *J* = 272.4 Hz, CF_3), 125.3 (q, *J* = 4.0 Hz), 128.0, 129.6 (q, *J* = 32.6 Hz), 145.0; **^{19}F NMR (377 MHz, DMSO-d_6)** δ = −62.5; **LRMS (ESI$^+$, m/z):** $[C_{20}H_{19}N_2F_6]^+$ $(M+H)^+$ calc. 401.1, found 401.1.

Data consistent with literature values.[23]

(2*S*,3*S*)-1-Methyl-2,3-bis(4-(trifluoromethyl)phenyl)-1,4-diazabicyclo[2.2.2]octan-1-ium triflate ((2*S*,3*S*)-61)



To a solution of (2*S*,3*S*)-2,3-bis(4-(trifluoromethyl)phenyl)-1,4-diazabicyclo[2.2.2]octane **(2*S*,3*S*)-60** (339 mg, 0.847 mmol, 1.0 eq) in Et_2O (40 mL) at 0 °C was added a solution of methyl triflate (139 mg, 0.847 mmol, 1.0 eq.) in Et_2O (5 mL) dropwise. The

reaction was stirred for 3 hours, after which the precipitate was removed by filtration. The resulting solid was washed with Et_2O to afford the title compound as a white solid (440 mg, 0.78 mmol, 92 % yield).

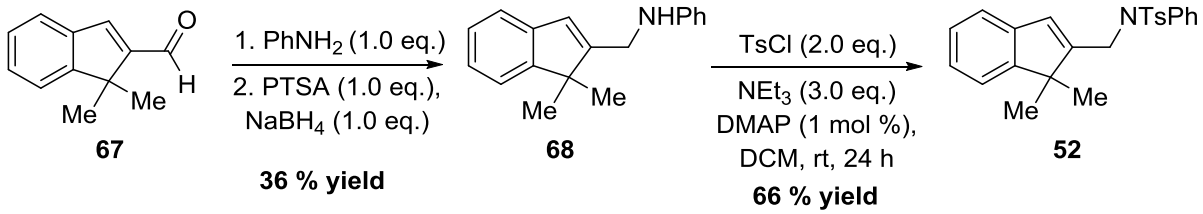
^{1}H NMR (400 MHz, CD_3CN): δ = 2.63 (s, 3H), 3.00-3.11 (m, 1H), 3.13-3.24 (m, 2H), 3.40-3.56 (m, 4H), 3.70-3.82 (m, 1H), 4.81 (d, *J* = 9.3 Hz, 1H), 4.90 (d, *J* = 9.8 Hz, 1H), 7.48 (d, *J* = 8.3 Hz, 2H), 7.66 (d, *J* = 8.3 Hz, 2H), 7.92 (d, *J* = 8.3 Hz, 2H), 7.99 (d, *J* = 8.3 Hz, 2H); **^{13}C NMR (101 MHz, CD_3CN):** δ = 40.8, 46.9, 50.0, 50.7, 58.4, 62.9, 71.2, 121.6 (q, *J* = 320.5 Hz, OTf), 124.7 (q, *J* = 270.2 Hz, CF_3), 125.0 (q, *J* = 271.1 Hz, CF_3), 126.4 (q, *J* = 3.9 Hz), 127.7 (q, *J* = 3.7 Hz), 128.8, 128.8, 130.5 (q, *J* = 32.1 Hz), 133.4 (q, *J* = 33.3 Hz), 135.4, 142.1; **^{19}F NMR (377 MHz, CD_3CN)** δ = −63.2 (CF_3), −63.5 (CF_3), −79.3 (TfO); **LRMS (ESI$^+$, m/z):** $[C_{21}H_{21F6}N_2]^+$ M^+ calc. 415.2, found 415.2; **$[\alpha]^{22}_D$** +53.9 (c 0.30, MeOH) [Lit = +43.0 (c 0.30, MeOH)].

Data consistent with literature values.[23]

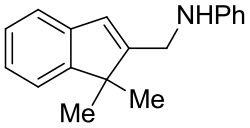
4.2.3.2 Substrate Synthesis

***N*-((1,1-Dimethyl-1*H*-inden-2-yl)methyl)-4-methyl-*N*-phenylbenzenesulfonamide (52)**

Prepared according to literature procedure.[23]



***N*-((1,1-Dimethyl-1*H*-inden-2-yl)methyl)aniline (68)**



To a pestle and mortar was added 1,1-dimethyl-1*H*-indene-2-carbaldehyde **67**[1] (1.49 g, 8.65 mmol, 1.0 eq.) **10** and aniline (788 μL, 8.65 mmol, 1.0 eq.) and the mixture was ground for 15 minutes to afford a sticky yellow oil. To the resulting imine was added $NaBH_4$ (327 mg, 8.65 mmol, 1.0 eq.) and

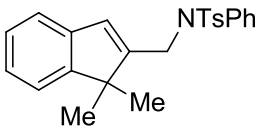
[1] Prepared by Jack Twilton according to literature procedure.[23]

PTSA (1.65 g, 8.65 mmol, 1.0 eq.) simultaneously. Grinding was continued for 5 minutes before the mixture was dissolved in DCM and washed with saturated aqueous sodium bicarbonate and brine. The organic phase was dried over $MgSO_4$ and the solvent removed under reduced pressure. Purification by column chromatography on silica gel (SiO_2, petroleum ether 30-40: EtOAc 19:1) afforded the title compound as a yellow solid (769 mg, 3.08mmol, 36 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.37 (s, 6H), 4.08 (brs, 1H, N*H*), 4.09 (d, *J* = 1.6 Hz, 2H), 6.59 (s, 1H), 6.69 (d, *J* = 7.9 Hz, 2H), 6.75 (t, *J* = 7.9 Hz, 1H), 7.17-7.28 (m, 5H), 7.35 (d, *J* = 6.9 Hz, 1H); **^{13}C NMR (101 MHz, $CDCl_3$):** δ = 24.4, 41.5, 49.7, 113.0, 117.6, 120.8, 121.0, 124.0, 124.6, 126.6, 129.3, 141.9, 148.2, 153.9, 155.5; **LRMS:** Peak not found.

Data consistent with literature values.[23]

_N_-((1,1-Dimethyl-1_H_-inden-2-yl)methyl)-4-methyl-_N_-phenylbenzenesulfonamide (52)



To a solution of *N*-((1,1-dimethyl-1*H*-inden-2-yl)methyl)aniline **68** (760 mg, 3.05 mmol, 1.0 eq.) **11** in DCM (30 mL) at room temperature was added NEt_3 (1.28 mL, 9.14 mmol, 3.0 eq.), DMAP (1 mol %) and tosyl chloride (1.16 g, 6.10 mmol 2.0 eq.). The reaction was stirred for 24 hours before the addition of H_2O. The reaction was stirred for a further 30 minutes before being washed with saturated aqueous ammonium chloride (x2), saturated aqueous sodium bicarbonate and brine. The organic phase was dried over $MgSO_4$ and the solvent removed under reduced pressure. Purification by column chromatography on silica gel (SiO_2, petroleum ether 30-40: EtOAc 9:1) afforded the title compound as a white solid (817 mg, 2.02 mmol, 66% yield).

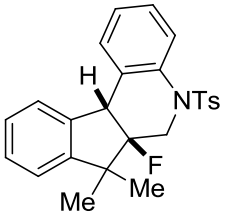
^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.29 (s, 6H), 2.45 (s, 3H), 4.51 (d, *J* = 1.2 Hz, 2H), 6.40 (s, 1H), 7.10-7.18 (m, 5H), 7.21-7.30 (m, 6H), 7.51 (d, *J* = 8.2 Hz, 2H); **^{13}C NMR**

(101 MHz, $CDCl_3$): δ = 21.6, 24.1, 47.8, 50.0, 121.0, 121.0, 125.0, 126.4, 127.6, 127.8, 128.3, 128.4, 128.7, 129.5, 134.9, 139.2, 141.3, 143.5, 150.8, 154.0; **LRMS (ESI^+, m/z):** $[C_{25}H_{25}NNaO_2S]^+$ $(M+Na)^+$ calc. 426.1, found 426.1.

Data consistent with literature values.[23]

4.2.3.3 Racemic Fluorinated Reference Synthesis

6a-Fluoro-7,7-dimethyl-5-tosyl-6,6a,7,11b-tetrahydro-5H-indeno[2,1-c]quinoline (53)



To a solution of *N*-((1,1-dimethyl-1*H*-inden-2-yl)methyl)-4-methyl-*N*-phenylbenzenesulfonamide **52** (50 mg, 0.12 mmol, 1.0 eq.) in nitromethane (5 mL) was added a few activated 3Å molecular sieves. The solution was left for 3 hours before addition of $NaHCO_3$ (31 mg, 0.36 mmol, 3.0 eq.) and the reaction was warmed to 40 °C. Once at 40 °C, Selectfluor (63 mg, 0.18 mmol, 1.5 eq.) was added in one portion and the reaction was stirred for 1 hour before being filtered through a pipette of Celite, eluted with ethyl acetate and the solvent removed under reduced pressure. Purification by column chromatography on silica gel (SiO_2, petroleum ether 30-40: EtOAc 9:1) afforded the title compound as a white solid (40 mg, 0.09 mmol, 79 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.35 (d, *J* = 3.2 Hz, 3H), 1.36 (s, 3H), 2.35 (s, 3H), 3.27 (dd, *J* = 37.4 Hz, *J* = 14.7 Hz, 1H), 4.29 (d, *J* = 15.7 Hz, 1H), 4.82 (ddd, *J* = 14.8 Hz, *J* = 12.3 Hz, *J* = 1.5 Hz, 1H), 7.13-7.20 (m, 6H), 7.20-7.26 (m, 2H), 7.36 (dd, *J* = 7.6 Hz, *J* = 1.5 Hz, 1H), 7.67 (d, *J* = 8.3 Hz, 2H), 7.87 (dd, *J* = 8.2 Hz, *J* = 1.3 Hz, 1H); **^{13}C NMR (101 MHz, $CDCl_3$):** δ = 21.0, 21.6, 24.4 (d, *J* = 9.5 Hz), 46.9 (d, *J* = 20.7 Hz), 47.6 (d, *J* = 22.3 Hz), 47.8 (d, *J* = 20.7 Hz), 101.2 (d, *J* = 200.3 Hz), 122.2, 122.4, 124.2, 124.4, 126.9, 127.3, 127.4, 127.9 (d, *J* = 3.2 Hz), 128.2, 129.2, 130.3, 135.5, 136.7, 139.3 (d, *J* = 8.0 Hz), 143.5, 147.7 (d, *J* = 3.2 Hz); **^{19}F NMR (377 MHz, $CDCl_3$)** δ = −169.4; **LRMS (ESI^+, m/z):** $[C_{25}H_{24}FNNaO_2S]^+$ $(M+Na)^+$ calc. 444.1, found 444.2.

Data consistent with literature values.[23]

4.2.3.4 Radiochemistry

HPLC Analysis

Analytical: Water Atlantis dC18, 5µm, 3.9x150mm, 1.0 mL/min, UV = 220 nm, Sample: 1 mg/mL in MeCN, t_{Prod} = 15.5 min.

HPLC Conditions E

0-1 min, 5 % MeCN, 95 % H_2O
1-11 min, 5-80 % MeCN
11-16 min, 80 % MeCN, 20 % H_2O
16-19 min, 80-5 % MeCN
19-20 min, 5 % MeCN, 95 % H_2O

Chiral: Phenomenex Lux Cellulose 1, 5 µm, 4.6x100mm, 1.0 mL/min, UV = 220 nm, MeCN 60 % isocratic, t_1 = 11.8 min, t_2 = 15.8 min.

Production of [^{18}F]fluoride and [^{18}F]F_2 was performed as described in Section 4.2.1.4.

Preparation of chiral [^{18}F]Selectfluor bis-triflate (2*S*,3*S*)-[^{18}F]54

[^{18}F]F_2 gas was bubbled into a vial containing (2*S*,3*S*)-1-methyl-2,3-bis(4-(trifluoromethyl)phenyl)-1,4-diazabicyclo[2.2.2]octan-1-ium triflate **(2*S*,3*S*)-61** (1.7 mg, 3 µmol) and lithium triflate (1.0 mg, 11 µmol) in acetone-d_6 (0.75 mL) at room temperature for ~ 30 seconds. The activity of the crude stock solution in acetone-d_6 ranged from 1.3-1.9 GB. Aliquots (0.25 mL) of this crude stock solution were employed directly in labelling reactions.

Fluorocyclisation with chiral [^{18}F]Selectfluor bis-triflate

To a Wheaton v-vial vial containing *N*-((1,1-dimethyl-1*H*-inden-2-yl)methyl)-4-methyl-*N*-phenylbenzenesulfonamide **52** (2.0 mg, 5.0 µmol), $NaHCO_3$ (1.3 mg, 15.0 µmol) and a stirrer bar was added an aliquot of chiral[^{18}F]Selectfluor bis-triflate **(2*S*,3*S*)-[^{18}F]54** in acetone-d_6 (250 µl). The reaction was stirred at room temperature, with aliquots for HPLC (5-50 µL crude reaction diluted in MeCN/H_2O (1:1) (100 µL)) taken after 30 and

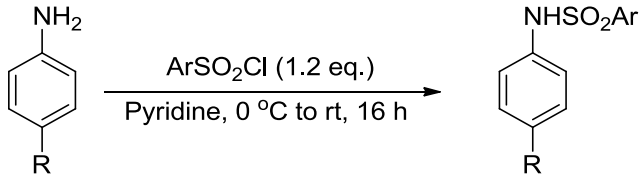
60 minutes of stirring. The peak corresponding to the reference compound was collected and an aliquot injected for chiral HPLC analysis (200 µl neat).

In subsequent reactions, an aliquot of chiral [^{18}F]Selectfluor bis-triflate **(2*S*,3*S*)[^{18}F]-54** in acetone-d_6 (250 µl) was added to an empty reaction vial and the solvent evaporated under a flow of helium gas, before addition of the substrate in an alternative solvent.

4.3 Chapter 3: Hypervalent Iodine-Mediated Oxidative Fluorination of *N*-Arylsulfonamides

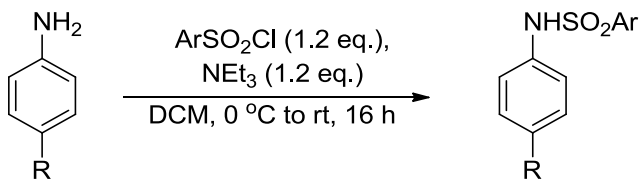
4.3.1 Substrate Synthesis

General procedure A: Sulfonyl-protection of aniline derivatives



To a solution of aniline (1.0 eq.) in pyridine (0.6 M) at 0 °C was added the sulfonyl chloride (1.2 eq.). The reaction was gradually warmed to room temperature and stirred for 16 hours before concentration under reduced pressure. The residue was dissolved in EtOAc and washed with HCl (1 M), NaOH (1 M) and brine. The organic phase was dried over $MgSO_4$ and the solvent removed under reduced pressure. Purification was performed by column chromatography on silica gel.

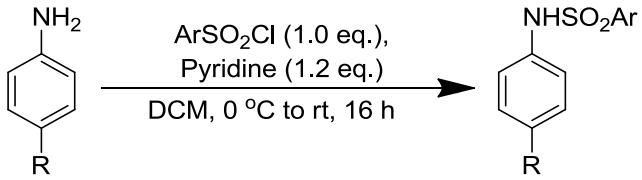
General procedure B: Sulfonyl-protection of aniline derivatives



To a solution of aniline (1.0 eq.) and triethylamine (1.2 eq.) in DCM (0.2 M) at 0 °C, was added the sulfonyl chloride (1.2 eq.). The reaction was gradually warmed to room temperature and stirred for 16 hours before quenching with water and stirring for a further

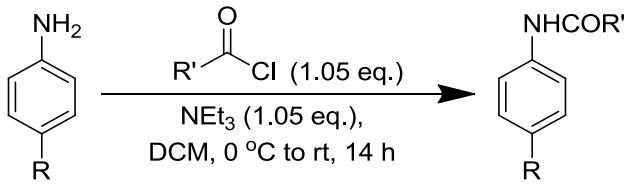
30 minutes. The reaction was then extracted into DCM, the organic phase was washed with HCl (1 M), saturated aqueous sodium bicarbonate and brine, dried over $MgSO_4$ and the solvent removed under reduced pressure. Purification was performed by column chromatography on silica gel.

General procedure C: Sulfonyl-protection of aniline derivatives



To a solution of aniline (1.0 eq.) and pyridine (1.2 eq.) in DCM (0.2 M) at 0 °C, was added the sulfonyl chloride (1.0 eq.). The reaction was gradually warmed to room temperature and stirred for 16 hours before quenching with water and stirring for a further 30 minutes. The reaction was then extracted into DCM and the organic phase was washed with HCl (1 M), saturated aqueous sodium bicarbonate and brine, dried over $MgSO_4$ and the solvent removed under reduced pressure. Purification was performed by column chromatography on silica gel.

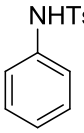
General procedure D: Acyl-protection of aniline derivatives



To a solution of aniline (1.0 eq.) and triethylamine (1.05 eq.) in DCM (0.5 M) at 0 °C, was added the acid chloride (1.05 eq.) dropwise. The reaction was allowed to warm to room temperature and stirred for 16 hours, then quenched with water and extracted into DCM. The organic phase was washed with HCl (1M), saturated aqueous sodium

bicarbonate and brine before being dried over $MgSO_4$ and the solvent removed under reduced pressure.

***N*-Phenyl-4-methylbenzenesulfonamide (68)**

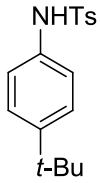


Prepared according to general procedure A from aniline **66** (1.00 mL, 11.0 mmol, 1.0 eq.) and *p*-toluenesulfonyl chloride (2.52 g, 13.2 mmol, 1.2 eq.). Purification by column chromatography on silica gel (SiO_2, petroleum ether 30-40: EtOAc 9:1-4:1) afforded the title compound as a white solid (1.90 g, 7.67 mmol, 70 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.38 (s, 3H), 6.80 (brs, 1H), 7.05-7.10 (m, 2H), 7.12 (dt, *J* = 7.5 Hz, *J* = 1.4 Hz, 1H), 7.21-7.27 (m, 4H), 7.67 (d, *J* = 8.3 Hz, 2H); **^{13}C NMR (101 MHz, $CDCl_3$):** δ = 21.6, 121.6, 125.4, 127.3, 129.4, 129.7, 136.0, 136.5, 143.9; **LRMS (ESI^-, *m/z*):** $[C_{13}H_{12}NO_2S]^-$ $(M-H)^-$ calc. 246.1, found 246.1.

Data consistent with literature values.[25]

***N*-(4-(*tert*-Butyl)phenyl)-4-methylbenzenesulfonamide (69a)**

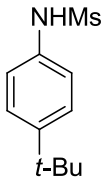


Prepared according to general procedure A from 4-*tert*-butylaniline **67** (800 µL, 5.00 mmol, 1.0 eq.) and *p*-toluenesulfonyl chloride (1.14 g, 6.00 mmol, 1.2 eq.). Purification by column chromatography on silica gel (SiO_2, petroleum ether 30-40: EtOAc 9:1-0:1) afforded the title compound as a white solid (1.41 g, 4.64 mmol, 93 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.27 (s, 9H), 2.39 (s, 3H), 6.67 (brs, 1H), 6.99 (d, *J* = 8.6 Hz, 2H), 7.21-7.28 (m, 4H), 7.67 (d, *J* = 8.1 Hz, 2H); **^{13}C NMR (101 MHz, $CDCl_3$):** δ = 21.6, 31.3, 34.4, 121.6, 126.2, 127.3, 129.6, 133.7, 136.4, 143.7, 148.5; **LRMS (ESI^-, *m/z*):** $[C_{17}H_{20}NO_2S]^-$ $(M-H)^-$ calc. 302.12, found 302.12.

Data consistent with literature values.[26]

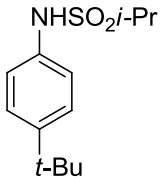
***N*-(4-(*tert*-Butyl)phenyl)methanesulfonamide (69b)**



Prepared according to general procedure B from 4-*tert*-butylaniline **67** (800 µL, 5.00 mmol, 1.0 eq.) and methanesulfonyl chloride (464 µL, 6.00 mmol, 1.2 eq.). Purification by column chromatography on silica gel (SiO_2, petroleum ether 30-40: EtOAc, 4:1) afforded the title compound as a white solid (1.04 g, 4.58 mmol, 92 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.33 (s, 9H), 3.02 (s, 3H), 6.60 (brs, 1H), 7.17 (dt, *J* = 8.8 Hz, *J* = 2.7 Hz, 2H), 7.38 (dt, *J* = 8.8 Hz, *J* = 2.7 Hz, 2H); **^{13}C NMR (101 MHz, $CDCl_3$):** δ = 31.3, 34.4, 39.2, 121.1, 126.6, 133.8, 148.8; **HRMS (ESI$^+$, *m/z*):** $[C_{11}H_{17}NNaO_2S]^+$ $(M+Na)^+$ calc. 250.0872, found 250.0867; **IR (ν, cm^{-1}):** 3258 (w, NH), 1465 (w, C=C_{Ar}), 1323 (m, S=O), 1147 (s, S=O); **MP:** 80-81 °C.

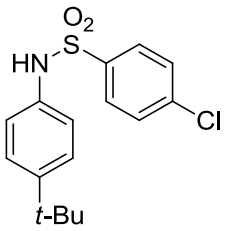
***N*-(4-(*tert*-Butyl)phenyl)propane-2-sulfonamide (69c)**



Prepared according to general procedure C from 4-*tert*-butylaniline **67** (0.49 mL, 2.50 mmol, 1.0 eq) and 2-propanesulfonyl chloride (0.31 mL, 2.75 mmol, 1.1 eq). Purification by column chromatography on silica gel (SiO_2, hexane: EtOAc 4:1) afforded the title compound as a yellow solid (594 mg, 2.33 mmol, 92 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.31 (s, 9H), 1.41 (d, *J* = 6.8 Hz, 6H), 3.30 (sept., *J* = 6.8 Hz, 1H), 6.73 (brs, 1H), 7.18 (d, *J* = 8.6 Hz, 2H), 7.34 (d, *J* = 8.6 Hz, 2H); **^{13}C NMR (101 MHz, $CDCl_3$):** δ = 16.7, 31.5, 34.6, 52.3, 120.7, 126.6, 134.5, 148.2; **HRMS (ESI$^+$, *m/z*):** $[C_{13}H_{21}NNaO_2S]^+$ $(M+Na)^+$ calc. 278.1185, found 278.1196; **IR (ν, cm^{-1}):** 3257 (w, NH), 1514 (m, C=C_{Ar}), 1327 (m, S=O), 1170 (s, S=O); **MP:** 74-76°C.

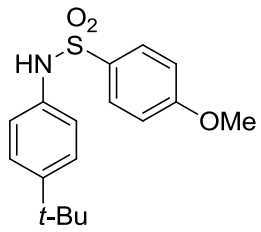
***N*-(4-(*tert*-Butyl)phenyl)-4-chlorobenzenesulfonamide (69d)**



Prepared according to general procedure B from 4-*tert*-butylaniline **67** (1.00 mL, 6.28 mmol, 1.0 eq.) and *p*-chlorobenzenesulfonyl chloride (1.59 g, 7.54 mmol, 1.2 eq.). Purification by column chromatography on silica gel (SiO_2, $CHCl_3$: MeOH 1:0-9:1) afforded the title compound as a white solid (1.25 g, 3.86 mmol, 61 % yield).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.19 (s, 9H), 6.99 (d, *J* = 8.8 Hz, 2H), 7.25 (d, *J* = 8.6 Hz, 2H), 7.63 (d, *J* = 8.6 Hz, 2H), 7.75 (d, *J* = 8.6 Hz, 2H), 10.27 (brs, 1H); **^{13}C NMR (101 MHz, DMSO-d_6):** δ = 31.9, 34.9, 121.1, 126.8, 129.4, 130.3, 135.5, 138.5, 139.5, 147.6; **HRMS (ESI$^+$, *m/z*):** $[C_{16}H_{18}ClNNaO_2S]^+$ $(M+Na)^+$ calc. 346.0639, found 346.0628; **IR (ν, cm^{-1}):** 3218 (br, NH), 1477 (w, C=C_{Ar}), 1328 (s, S=O), 1180 (s, S=O), 757 (s, C-Cl); **MP:** 182-183 °C.

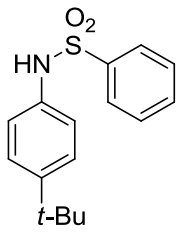
***N*-(4-(*tert*-Butyl)phenyl)-4-methoxybenzenesulfonamide (69e)**



Prepared according to general procedure B from 4-*tert*-butylaniline **67** (1.00 mL, 6.28 mmol, 1.0 eq.) and *p*-methoxybenzenesulfonyl chloride (1.56 g, 7.54 mmol, 1.2 eq.). Purification by column chromatography on silica gel (SiO_2, petroleum ether 30-40: EtOAc 4:1-0:1) afforded the title compound as a white solid (2.01 g, 6.21 mmol, 99 % yield).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.17 (s, 9H), 3.77 (s, 3H), 6.99 (d, *J* = 8.6 Hz, 2H), 7.04 (d, *J* = 8.8 Hz, 2H), 7.22 (d, *J* = 8.6 Hz, 2H), 7.69 (d, *J* = 8.8 Hz, 2H), 10.06 (brs, 1H); **^{13}C NMR (101 MHz, DMSO-d_6):** δ = 31.9, 34.8, 56.4, 115.2, 120.5, 126.7, 129.7, 132.3, 136.0, 147.0, 163.2; **HRMS (ESI$^+$, *m/z*):** $[C_{17}H_{21}NNaO_3S]^+$ $(M+Na)^+$ calc. 342.1134, found 342.1123; **IR (ν, cm^{-1}):** 3235 (m, NH), 1445 (w, C=C_{Ar}), 1326 (m, S=O), 1181 (s, S=O); **MP:** 163-164 °C.

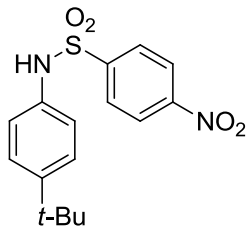
***N*-(4-(*tert*-Butyl)phenyl)benzenesulfonamide (69f)**



Prepared according to general procedure A from 4-*tert*-butylaniline **67** (1.00 mL, 6.28 mmol, 1.0 eq.) and benzenesulfonyl chloride (962 µL, 7.54 mmol, 1.2 eq.). Purification by column chromatography on silica gel (SiO_2, $CHCl_3$: MeOH 1:0-9:1) afforded the title compound as a white solid (1.59 g, 5.48 mmol, 87 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.26 (s, 9H), 6.76 (brs, 1H), 6.99 (d, *J* = 8.6 Hz, 2H), 7.25 (d, *J* = 8.8 Hz, 2H), 7.40-7.49 (m, 2H), 7.55 (m, 1H), 7.80 (d, *J* = 7.3 Hz, 2H); **^{13}C NMR (101 MHz, $CDCl_3$):** δ = 31.3, 34.4, 121.8, 126.2, 127.2, 129.0, 132.9, 133.5, 139.3, 148.7; **HRMS (ESI$^+$, *m/z*):** $[C_{16}H_{19}NNaO_2]^+$ $(M+Na)^+$ calc. 312.1029, found 312.1034; **IR (ν, cm^{-1}):** 3204 (m, NH), 1513 (m, C=C_{Ar}), 1363 (m, S=O), 1157 (s, S=O); **MP:** 154-155 °C.

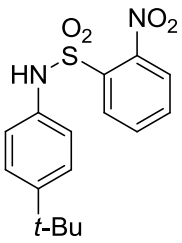
***N*-(4-(*tert*-Butyl)phenyl)-4-nitrobenzenesulfonamide (69g)**



Prepared according to general procedure A from 4-*tert*-butylaniline **67** (1.00 mL, 6.28 mmol, 1.0 eq.) and *p*-nitrobenzenesulfonyl chloride (1.67 g, 7.54 mmol, 1.2 eq.). Purification by column chromatography on silica gel (SiO_2, $CHCl_3$) afforded the title compound as a yellow solid (1.79 g, 5.36 mmol, 85 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.27 (s, 9H), 6.91 (s, 1H), 7.01 (d, *J* = 8.6 Hz, 2H), 7.29 (d, *J* = 8.6 Hz, 2H), 7.95 (d, *J* = 8.8 Hz, 2H), 8.29 (d, *J* = 8.8 Hz, 2H); **^{13}C NMR (101 MHz, $CDCl_3$):** δ = 31.2, 34.5, 122.4, 124.2, 126.5, 128.5, 132.4, 144.8, 149.7, 150.2; **HRMS (ESI$^+$, *m/z*):** $[C_{16}H_{18}N_2NaO_4S]^+$ $(M+Na)^+$ calc. 357.0879, found 357.0874; **IR (ν, cm^{-1}):** 3248 (m, NH), 1530 (s, N=O), 1466 (w, C=C_{Ar}), 1349 (m, S=O), 1308 (m, N=O), 1166 (s, S=O); **MP:** 143-144 °C.

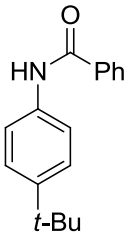
***N*-(4-(*tert*-Butyl)phenyl)-2-nitrobenzenesulfonamide (69h)**



Prepared according to general procedure B from 4-*tert*-butylaniline **67** (749 µL, 4.70 mmol, 1.0 eq.) and *o*-nitrobenzenesulfonyl chloride (1.25 g, 5.64 mmol, 1.2 eq.) Purification by column chromatography on silica gel (SiO_2, petroleum ether 30-40: EtOAc 17:3-4:1) afforded the title compound as a pale yellow solid (1.22 g, 3.65 mmol, 78 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): 1.27 (s, 9H), 7.11 (d, *J* = 8.5 Hz, 2H), 7.19 (brs, 1H), 7.28 (d, *J* = 8.9 Hz, 2H), 7.59 (td, *J* = 7.6 Hz, *J* = 1.0 Hz, 1H), 7.70 (td, *J* = 7.8 Hz, *J* = 1.3 Hz, 1H), 7.86 (m, 2H); **^{13}C NMR (101 MHz, $CDCl_3$):** δ = 31.2, 34.4, 123.0, 125.2, 126.3, 131.8, 132.4, 132.5, 132.6, 133.8, 148.2, 149.7; **HRMS (ESI$^+$, *m/z*):** $[C_{16}H_{18}N_2NaO_4S]^+$ $(M+Na)^+$ calc. 357.0879, found 357.0872; **IR (ν, cm^{-1}):** 3290 (w, NH), 1537 (m, N=O), 1458 (w, $C=C_{Ar}$), 1343 (m, S=O), 1307 (m, N=O), 1164 (s, S=O)**; MP:** 146-148 °C.

***N*-(4-(*tert*-Butyl)phenyl)benzamide (67i)**

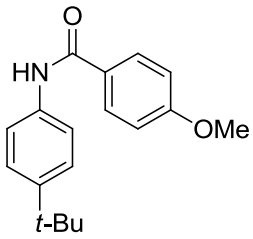


Prepared according to general procedure D from 4-*tert*-butylaniline **67** (800 µL, 5.00 mmol) and benzoyl chloride (610 µL, 5.25 mmol, 1.05 eq.). The crude residue was washed with hexane and filtered to afford the title compound as a white solid (1.12 g, 4.42 mmol, 88 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): 1.34 (s, 9H), 7.40 (d, *J* = 8.8 Hz, 2H), 7.49 (tt, *J* = 6.8 Hz, *J* = 1.5 Hz, 2H), 7.53-7.60 (m, 3H), 7.81 (brs, 1H, N*H*), 7.85-7.90 (m, 2H); **^{13}C NMR (101 MHz, $CDCl_3$):** δ = 31.4, 34.5, 120.0, 126.0, 127.0, 128.8, 131.8, 135.1, 135.3, 147.6, 165.7; **LRMS (ESI$^-$, m/z):** $[C_{17}H_{18}NO]^-$ $(M-H)^-$ calc. 252.1, found 252.1.

Data consistent with literature values.[27]

***N*-(4-(*tert*-Butyl)phenyl)-4-methoxybenzamide (69j)**

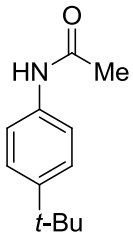


Prepared according to general procedure D from 4-*tert*-butylaniline **67** (800 µL, 5.00 mmol, 1.0 eq.) and 4-methoxybenzoyl chloride (711 µL, 5.25 mmol, 1.05 eq). The crude residue was purified by column chromatography on silica gel (SiO_2, petroleum ether 30-40 30-40: EtOAc 4:1-0:1) to afford the title compound as a white solid (1.34 g, 4.73 mmol, 95 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.28-1.44 (m, 9H), 3.88 (s, 3H), 6.97 (d, *J* = 9.0 Hz, 2H), 7.39 (d, *J* = 8.8 Hz, 2H), 7.56 (d, *J* = 8.6 Hz, 2H), 7.76 (brs, 1H, N*H*), 7.84 (d, *J* = 9.0 Hz, 2H); **^{13}C NMR (101 MHz, $CDCl_3$):** δ = 31.4, 34.4, 55.4, 113.9, 119.9, 125.9, 127.3, 128.8, 135.4, 147.3, 162.4, 165.1; **LRMS (ESI$^+$, m/z):** $[C_{18}H_{22}NO_2]^+$ $(M+H)^+$ calc. 284.2, found 284.2.

Data consistent with literature values.[27]

***N*-(4-(*tert*-Butyl)phenyl)acetamide (69k)**

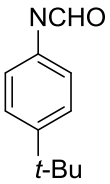


To a solution of 4-*tert*-butylaniline **67** (1.60 mL, 10.0 mmol, 1.0 eq.) in DCM (20 mL) at 0 °C, was added acetic anhydride (1.20 mL, 11.1 mmol, 1.1 eq.) dropwise. The reaction was stirred for 30 minutes at 0 °C before concentration under reduced pressure. The crude residue was washed with hexane and filtered to afford the title compound as a white solid (1.70 g, 8.86 mmol, 89 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.33 (s, 9H), 2.19 (s, 3H), 7.23 (brs, 1H, N*H*), 7.32-7.40 (m, 2H), 7.40-7.48 (m, 2H); **^{13}C NMR (101 MHz, $CDCl_3$):** δ = 24.6, 31.4, 34.4, 119.8, 125.8, 135.2, 147.4, 168.2; **LRMS (ESI$^+$, m/z):** $[C_{12}H_{18}NO]^+$ $(M+H)^+$ calc. 192.1, found 192.1.

Data consistent with literature values.[27]

***N*-(4-(*tert*-Butyl)phenyl)formamide (69l)**



A flask containing 4-*tert*-butylaniline **67** (1.00 mL, 6.28 mmol, 1.0 eq.) in ethyl formate (5 mL) was fitted with a reflux condenser and heated to 70 °C for 16 hours before concentration under reduced pressure. Purification by column chromatography on silica gel (SiO_2, petroleum ether 30-40: EtOAc 19:1-3:1) afforded the title compound as a pale yellow solid (974 mg, 5.50 mmol, 88 % yield). Formed as a mixture of rotamers (1:1).

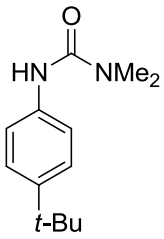
Trans isomer: **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 1.32 (s, 9H), 7.35-7.43 (m, 2H), 7.43-7.51 (m, 2H), 8.04 (brd, *J* = 9.6 Hz, 1H, N*H*), 8.66 (d, *J* = 11.6 Hz, 1H, C*H*O); **^{13}C NMR (101 MHz, $CDCl_3$):** δ = 31.3, 34.4, 118.8, 126.6, 134.1, 148.5, 162.8.

Cis isomer: **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 1.31 (s, 9H), 6.99-7.08 (m, 2H), 7.33-7.39 (m, 3H, H_{Ar} + N*H*), 8.36 (d, *J* = 1.7 Hz, 1H, C*H*O); **^{13}C NMR (101 MHz, $CDCl_3$):** δ = 31.3, 34.4, 119.9, 125.9, 134.3, 147.8, 159.1.

LRMS (ESI^+, m/z): $[C_{11}H_{15}NNaO]^+$ $(M+Na)^+$ calc. 200.10, found 200.10; **IR (ν, cm^{-1}):** 3268 (w, NH), 1683 (s, C=O), 1521 (m, $C=C_{Ar}$).

Data consistent with literature values.[28]

3-(4-(*tert*-Butyl)phenyl)-1,1-dimethylurea (69m)



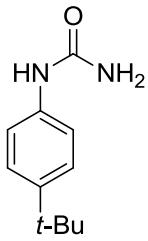
Prepared according to modified literature procedure.[29]

To a solution of dimethylamine hydrochloride (294 mg, 3.00 mmol, 1.0 eq.) in DCM (15 mL) at 0 °C was added triethylamine (495µL, 3.60 mmol, 1.2 eq.). After stirring for 10 minutes, 4-*tert*-butylphenyl isocyanate (530 µL, 3.00 mmol, 1.0 eq.) was added before the reaction was gradually warmed to room temperature and stirred for 16 hours. The solution was washed with HCl (2M) and extracted into DCM. The organic phase was dried over Na_2SO_4 and the solvent

removed under reduced pressure to afford the title compound directly as a white solid (657 mg, 2.98 mmol, 99% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.28 (s, 9H), 2.88 (s, 6H), 7.04 (brs, 1H), 7.22 (d, *J* = 8.8 Hz, 2H), 7.30 (d, *J* = 8.8 Hz, 2H); **^{13}C NMR (101 MHz, $CDCl_3$):** δ = 31.3, 34.0, 36.2, 120.2, 125.2, 136.8, 145.3, 156.3; **HRMS (ESI^+, m/z):** $[C_{13}H_{20}N_2NaO]^+$ $(M+Na)^+$ calc. 243.1468, found: 243.1474; **IR (ν, cm^{-1}):** 3306 (w, NH), 1685 (s, C=O), 1538 (s, $C=C_{Ar}$); **MP:** 98-99 °C.

1-(4-(*tert*-Butyl)phenyl)urea (69n)

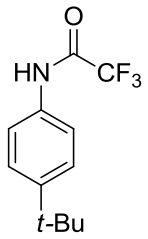


To 4-*tert*-butylaniline **67** (895 mg, 6.00 mmol, 1.0 eq.) in HCl (2M) (3 mL) at 0 °C was added potassium cyanate (585 mg, 7.20 mmol, 1.2 eq.) portionwise over 30 minutes. The reaction was stirred for 4 hours at room temperature and then left to stand, without stirring, at 0 °C for 1 hour. The resultant precipitate was removed by filtration, washed with ice cold water and dried under vacuum. Purification by column chromatography on silica gel (SiO_2, hexane: EtOAc 1:1-0:1) afforded the title compound as a white solid (554 mg, 2.88 mmol, 48 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.21 (s, 9H), 4.93 (brs, 2H), 7.13 (d, *J* = 8.6 Hz, 3H), 7.23 (d, *J* = 8.6 Hz, 2H); **^{13}C NMR (101 MHz, $CDCl_3$):** δ = 31.4, 34.4, 121.7, 126.2, 135.6, 147.5, 157.4; **LRMS (ESI^+, m/z):** $[C_{11}H_{16}N_2NaO]^+$ $(M+Na)^+$ calc. 215.1, found 215.1.

Data consistent with literature values.[30]

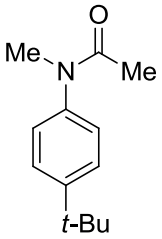
***N*-(4-(*tert*-Butyl)phenyl)-2,2,2-trifluoroacetamide (69o)**



To a solution of 4-*tert*-butylaniline **67** (3.00 g, 20.0 mmol, 1.0 eq.) and pyridine (3.20 mL, 40.0 mmol, 2.0 eq.) in DCM (50 mL) at 0 °C was added trifluoroacetic anhydride (2.80 mL, 20 mmol, 1.0 eq.). The reaction was stirred for 3 hour at 0 °C, then quenched with saturated aqueous sodium bicarbonate and extracted into DCM. The organic phase was dried over $MgSO_4$ and the solvent removed under reduced pressure. Purification by column chromatography on silica gel (SiO_2, petroleum ether 30-40: EtOAc 4:1) afforded the title compound a pale yellow solid (4.36 g, 17.8 mmol, 89 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.33 (s, 9H), 7.41 (d, *J* = 9.2 Hz, 2H), 7.50 (d, *J* = 9.2 Hz, 2H), 7.91 (brs, 1H); **^{13}C NMR (101 MHz, $CDCl_3$):** δ = 31.3, 34.6, 114.4, 120.3, 126.2, 132.4, 149.6; **^{19}F NMR (377 MHz, $CDCl_3$)** δ = −75.7; **HRMS (ESI$^+$, m/z):** $[C_{12}H_{14}F_3NNaO]^+$ $(M+Na)^+$ calc. 268.0920, found 268.0921; **IR (ν, cm^{-1}):** 3300 (w, NH), 1705 (s, C=O), 1518 (m, C=C_{Ar}), 1161 (s, C-F); **MP:** 49-50 °C.

***N*-(4-(*tert*-Butyl)phenyl)-*N*-methylacetamide (69p)**

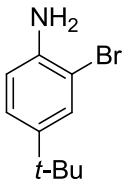


To a solution of *N*-(4-(*tert*-butyl)phenyl)acetamide **69k** (1.00 g, 5.23 mmol, 1.0 eq.) in THF (25 mL), was added methyl iodide (358 µL, 5.75 mmol, 1.1 eq.) and sodium hydride (60 % in mineral oil) (314 mg, 7.85 mmol, 1.5 eq.). After stirring at room temperature for 14 hours, the reaction was poured onto water and extracted into DCM. The organic phase was dried over $MgSO_4$ and the solvent removed under reduced pressure. Purification by column chromatography on silica gel (SiO_2, petroleum ether 30-40: EtOAc 4:1) afforded the title compound as a white solid (725 mg, 3.53 mmol, 71 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.34 (s, 9H), 1.88 (s, 3H), 3.25 (s, 3H), 7.10 (d, *J* = 8.3 Hz, 2H), 7.42 (d, *J* = 8.6 Hz, 2H); **^{13}C NMR (101 MHz, $CDCl_3$):** δ = 22.4, 31.3, 34.6,

37.1, 126.5, 126.5, 141.9, 150.7, 170.8; **HRMS (ESI$^+$, m/z):** $[C_{13}H_{19}NNaO]^+$ $(M+Na)^+$ calc. 228.1359, found 228.1365; **IR (ν, cm^{-1}):** 1663 (s, C=O), 1511 (m, C=C_{Ar}); **MP:** 55-57 °C.

2-Bromo-4-(*tert*-butyl)aniline (74)

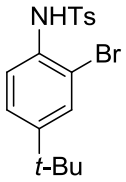


Prepared according to literature procedure.[31]

To a solution of 4-*tert*-butylaniline **67** (5.50 mL, 34.5 mmol, 1.0 eq.) in chloroform (200 mL) at 0 °C was added *N*-bromosuccinimide (6.76 g, 37.9 mmol, 1.1 eq.). The reaction was warmed to room temperature and stirred for 5 hours, then washed with water and extracted into chloroform. The organic phase was dried over Na_2SO_4 and the solvent removed under reduced pressure. Purification by column chromatography on silica gel (SiO_2, hexane) afforded the title compound as a brown oil (5.35 g, 23.5 mmol, 68 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.30 (s, 9H), 3.95 (brs, 2H), 6.47 (d, *J* = 8.3 Hz, 1H), 7.16 (dd, *J* = 8.3 Hz, *J* = 2.2 Hz, 1H), 7.45 (d, *J* = 1.7 Hz, 1H); **^{13}C NMR (101 MHz, $CDCl_3$):** δ = 31.3, 33.9, 109.2, 115.5, 125.3, 129.2, 142.7, 141.4; **HRMS (ESI$^+$, *m/z*):** $[C_{10}H_{15}BrN]^+$ $(M+H)^+$ calc. 228.0382, found 228.0386; **IR (ν, cm^{-1}):** 3469 (w, NH), 3379 (w, NH), 1541 (m, C=C_{Ar}).

***N*-(2-Bromo-4-*tert*-butylphenyl)-4-methylbenzenesulfonamide (69q)**

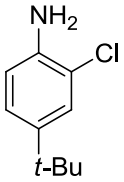


Prepared according to general procedure C from 2-bromo-4-(*tert*-butyl)aniline **74** (684 mg, 3.00 mmol, 1.0 eq.) and *p*-toluenesulfonyl chloride (572 mg, 3.00 mmol, 1.0 eq.). Purification by column chromatography on silica gel (SiO_2, petroleum ether 30-40: EtOAc 9:1) afforded the title compound as a white solid (945 mg, 2.47 mmol, 82 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.26 (s, 9H), 2.39 (s, 3H), 6.87 (brs, 1H), 7.23 (d, *J* = 8.3 Hz, 2H), 7.28 (dd, *J* = 8.6 Hz, *J* = 2.2 Hz, 1H), 7.40 (d, *J* = 2.2 Hz, 1H), 7.56 (d, *J* =

8.6 Hz, 1H), 7.66 (d, *J* = 8.3 Hz, 2H); **^{13}C NMR (101 MHz, $CDCl_3$):** δ = 21.6, 31.1, 34.5, 115.6, 122.3, 125.7, 127.3, 129.4, 129.6, 132.1, 136.2, 144.0, 149.9; **HRMS (ESI^+, *m/z*):** $[C_{17}H_{20}BrNNaO_2S]^+$ $(M+Na)^+$ calc. 404.0290, found 404.0282; **IR (ν, cm^{-1}):** 3268 (w, NH), 1499 (m, $C=C_{Ar}$), 1336 (m, S=O), 1164 (s, S=O), 611 (m, C-Br); **MP:** 92-93 °C.

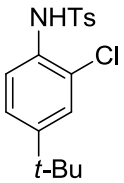
4-(*tert*-Butyl)-2-chloroaniline (75)



To a solution of 4-*tert*-butylaniline **67** (5.00 mL, 31.4 mmol, 1.0 eq.) in chloroform (200 mL) at 0 °C was added *N*-chlorosuccinimide (4.61 g, 34.5 mmol, 1.1 eq.). The reaction was warmed to room temperature and stirred for 5 hours, then washed with water and extracted into chloroform. The organic phase was dried over $MgSO_4$ and the solvent removed under reduced pressure. Purification by column chromatography on silica gel (SiO_2, petroleum ether 30-40: EtOAc 9:1) afforded the title compound as a brown oil (1.43 g, 9.82 mmol, 31 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.19 (s, 9H), 3.83 (brs, 2H), 6.63 (d, *J* = 8.3 Hz, 1H), 7.01 (dd, *J* = 8.3 Hz, *J* = 2.2 Hz, 1H), 7.17 (d, *J* = 2.2 Hz, 1H); **^{13}C NMR (101 MHz, $CDCl_3$):** δ = 31.4, 34.1, 115.7, 119.1, 124.7, 126.3, 140.3, 142.5; **HRMS (ESI^+, *m/z*):** $[C_{10}H_{15}ClN]^+$ $(M+H)^+$ calc. 184.0888, found 184.0883; **IR (ν, cm^{-1}):** 3384 (w, NH), 1622 (m, NH), 1508 (s, $C=C_{Ar}$), 1273 (w, C-N), 725 (m, C-Cl).

***N*-(4-(*tert*-Butyl)-2-chlorophenyl)-4-methylbenzenesulfonamide (69r)**

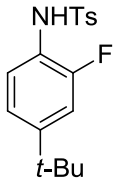


Prepared according to general procedure C from 2-chloro-4-(*tert*-butyl)aniline **75** (735 mg, 4.00 mmol, 1.0 eq.) and *p*-toluenesulfonyl chloride (763 mg, 4.00 mmol, 1.0 eq.). Purification by column chromatography on silica gel (SiO_2, hexane: EtOAc 9:1) afforded the title compound as a purple solid (879 mg, 2.60 mmol, 65 % yield.)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.26 (s, 9H), 2.39 (s, 3H), 6.90 (brs, 1H), 7.21-7.26 (m, 4H), 7.55 (d, *J* = 9.3 Hz, 1H), 7.66 (d, *J* = 8.3 Hz, 2H); **^{13}C NMR (101 MHz, $CDCl_3$):** δ

= 21.8, 31.3, 34.7, 122.3, 125.0, 125.1, 126.5, 127.4, 129.8, 130.9, 136.4, 144.2, 149.7; **HRMS (ESI$^+$, *m/z*):** $[C_{17}H_{20}ClNNaO_2S]^+$ $(M+Na)^+$ calc. 360.0795, found 360.0786; **IR (ν, cm^{-1}):** 3266 (w, NH), 1493 (m, C=C_{Ar}), 1337 (m, S=O), 1163 (s, S=O), 664 (m, C-Cl); **MP:** 105-106 °C.

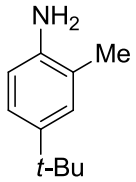
***N*-(4-(*tert*-Butyl)-2-fluorophenyl)-4-methylbenzenesulfonamide (69s)**



To a solution of *N*-(4-(*tert*-butyl)phenyl)-4-methylbenzenesulfonamide **69a** (1.21 g, 4.00 mmol, 1.0 eq.) in acetonitrile (40 mL) was added Selectfluor (1.42 g, 4.00 mmol, 1.0 eq.). The reaction was heated to reflux for 16 hours, then cooled to room temperature and concentrated under reduced pressure. The crude residue was dissolved in DCM and washed with water, saturated aqueous sodium bicarbonate and brine. The organic phase was dried over Na_2SO_4 and the solvent removed under reduced pressure. Purification by column chromatography on silica gel (SiO_2, hexane: EtOAc 9:1) afforded the title compound as a red solid (887 mg, 2.76 mmol, 69 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.25 (s, 9H), 2.39 (s, 3H), 6.71 (brs, 1H), 6.97 (dd, *J* = 12.5 Hz, *J* = 2.0 Hz, 1H), 7.10 (dd, *J* = 8.4 Hz, *J* = 1.6 Hz, 1H), 7.23 (d, *J* = 7.8 Hz, 2H), 7.47 (t, *J* = 8.6 Hz, 1H), 7.67 (d, *J* = 8.3 Hz, 2H); **^{13}C NMR (101 MHz, $CDCl_3$):** δ = 21.7, 31.3, 34.7, 112.7 (d, *J* = 19.9 Hz), 121.7 (d, *J* = 3.2 Hz), 121.8, 123.3, 127.4, 129.8, 136.3, 144.2, 150.6 (d, *J* = 5.6 Hz), 155.1 (d, *J* = 243.2 Hz); **^{19}F NMR (377 MHz, $CDCl_3$):** δ = −129.6; **HRMS (ESI$^+$, *m/z*):** $[C_{17}H_{20}FNNaO_2S]^+$ $(M+Na)^+$ calc. 344.1091, found 344.1091; **IR (ν, cm^{-1}):** 3258 (w, NH), 1506 (m, C=C_{Ar}), 1338 (m, S=O), 1166 (s, S=O), 1092 (m, C-F); **MP:** 114-115 °C.

4-(*tert*-Butyl)-2-methylaniline (76)



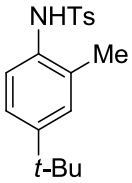
Prepared according to a modified literature procedure.[32]

To a solution of 2-bromo-4-(*tert*-butyl)aniline **74** (1.00g, 4.38 mmol, 1.0 eq.) in DMF (10 mL) was added potassium carbonate (1.81 g, 13.1 mmol, 3.0 eq.), tetrakis(triphenylphosphine)palladium(0) (508 mg, 0.44 mmol, 0.1 eq.) and trimethylboroxine (612 µL, 4.38 mmol, 1.0 eq.). The reaction was heated to 115 °C for 20 hours before being cooled to room temperature and filtered through Celite (Et_2O). The organic phase was washed several times with brine, dried over $MgSO_4$ and the solvent removed under reduced pressure. Purification by column chromatography on silica gel (SiO_2, petroleum ether 30-40: EtOAc 9:1) afforded the title compound as a bright pink oil (249 mg, 1.52 mmol, 35 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.31 (s, 9H), 2.21 (s, 3H), 3.52 (brs, 2H), 6.66 (d, *J* = 8.1 Hz, 1H), 7.07-7.14 (m, 2H); **^{13}C NMR (101 MHz, $CDCl_3$):** δ = 17.7, 31.6, 33.9, 114.8, 122.0, 123.7, 127.4, 141.5, 142.1; **IR (v, cm^{-1}):** 3430 (w, NH), 3372 (w, NH), 1509 (s, C=C_{Ar}); **LRMS (ESI$^+$, *m/z*):** $[C_{11}H_{17}NNa]^+$ $(M+Na)^+$ calc. 186.1, found 186.3.

Data consistent with literature values.[33]

***N*-(4-(*tert*-Butyl)-2-methylphenyl)-4-methylbenzenesulfonamide (69t)**

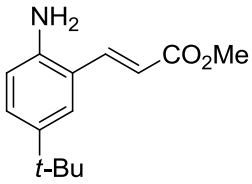


Prepared according to general procedure C from 4-(*tert*-butyl)-2-methylaniline **76** (230 mg, 1.41 mmol, 1.0 eq.) and *p*-toluenesulfonyl chloride (269 mg, 1.41 mmol, 1.0 eq.). Purification by column chromatography on silica gel (SiO_2, petroleum ether 30-40: EtOAc 9:1-4:1) afforded the title compound as an off-white solid (418 mg, 1.32 mmol, 93 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.27 (s, 9H), 2.02 (s, 3H), 2.41 (s, 3H), 6.19 (brs, 1H), 7.07-7.19 (m, 3H), 7.24 (d, *J* = 8.2 Hz, 2H), 7.63 (d, *J* = 8.2 Hz, 2H); **^{13}C NMR (101 MHz, $CDCl_3$):** δ = 17.9, 21.5, 31.3, 34.3, 123.9, 124.3, 127.2, 127.7, 129.6, 131.1, 137.0,

137.1, 143.6, 149.4; **HRMS (ESI$^+$, *m/z*):** $[C_{18}H_{23}NNaO_2S]^+$ $(M+Na)^+$ calc. 340.1342, found 340.1352; **IR (ν, cm^{-1}):** 3274 (w, NH), 1506 (m, C=C_{Ar}), 1363 (m, S=O), 1161 (s, S=O); **MP:** 132-133 °C.

(*E*)-Methyl 3-(2-amino-5-(*tert*-butyl)phenyl)acrylate (77)

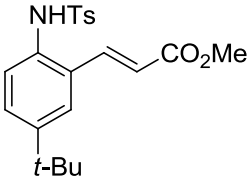


Prepared according to a modified literature procedure.[34]

To a solution of 2-bromo-4-(*tert*-butyl)aniline **74** (684 mg, 3.00 mmol, 1.0 eq.) in acetonitrile (6 mL) at room temperature, was added methyl acrylate (675 µL, 7.50 mmol, 2.5 eq.), palladium acetate (135 mg, 0.6 mmol, 20 mol %), tri-*o*-tolyl phosphine (640 mg, 2.10 mmol, 0.7 eq.) and triethylamine (1.67 mL, 12.0 mmol, 4.0 eq.). The reaction was heated to reflux for 9 hours, cooled to room temperature and concentrated under reduced pressure. The crude residue was dissolved in ethyl acetate, washed with water and the aqueous phase extracted with ethyl acetate. The combined organic phases were dried over $MgSO_4$ and the solvent removed under reduced pressure. Purification by column chromatography on silica gel (SiO_2, petroleum ether 30-40: EtOAc 9:1-4:1) afforded the title compound as a yellow solid (531 mg, 2.28 mmol, 76 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.29 (s, 9H), 3.82 (s, 3H), 3.88 (brs, 2H), 6.38 (d, *J* = 15.8 Hz, 1H), 6.68 (d, *J* = 8.4 Hz, 1H), 7.24 (dd, *J* = 8.4 Hz, *J* = 2.3 Hz, 1H), 7.39 (d, *J* = 2.3 Hz, 1H), 7.86 (d, *J* = 15.8 Hz, 1H); **^{13}C NMR (101 MHz, $CDCl_3$):** δ = 31.4, 34.0, 51.7, 116.8, 117.3, 119.4, 124.6, 128.8, 141.0, 141.8, 143.2, 167.8; **HRMS (ESI$^+$, *m/z*):** $[C_{14}H_{19}NNaO_2]^+$ $(M+Na)^+$ calc. 256.1308, found 256.1302; **IR (ν, cm^{-1}):** 3371 (w, NH), 3243 (w, NH), 1699 (s, C=O), 1618 (s, C=C), 1460 (w, C=C_{Ar}); **MP:** 77-78 °C.

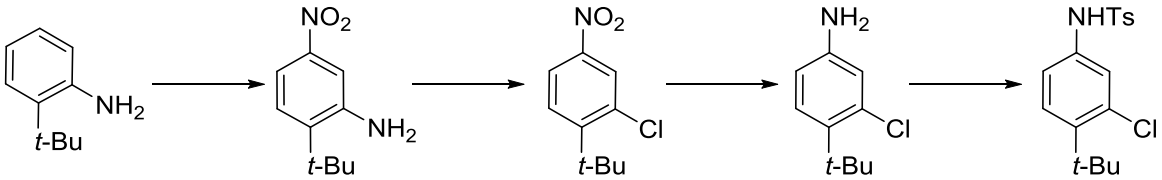
(*E*)-Methyl 3-(5-(*tert*-butyl)-2-(4-methylphenylsulfonamido)phenyl)acrylate (69u)



Prepared according to general procedure C from (*E*)-methyl 3-(2-amino-5-(*tert*-butyl)phenyl)acrylate **77** (512 mg, 2.19 mmol, 1.0 eq.) and *p*-toluenesulfonyl chloride (418 mg, 2.19 mmol, 1.0 eq.). Purification by column chromatography on silica gel (SiO_2, petroleum ether 30-40: EtOAc 4:1) afforded the title compound as a yellow solid (513 mg, 1.32 mmol, 60 % yield).

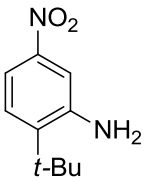
^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.30 (s, 9H), 2.39 (s, 3H), 3.80 (s, 3H), 6.18 (d, *J* = 15.8 Hz, 1H), 6.52 (brs, 1H), 7.22 (d, *J* = 8.3 Hz, 2H), 7.27 (d, *J* = 8.6 Hz, 1H), 7.38 (dd, *J* = 8.6 Hz, *J* = 2.2 Hz, 1H), 7.46 (d, *J* = 2.2 Hz, 1H), 7.53 (d, *J* = 15.8 Hz, 1H), 7.59 (d, *J* = 8.3 Hz, 2H); **^{13}C NMR (101 MHz, $CDCl_3$):** δ = 21.5, 31.2, 34.7, 51.8, 120.0, 123.9, 127.1, 127.3, 128.4, 129.7, 130.0, 131.9, 136.1, 139.5, 144.0, 150.5, 166.7; **HRMS (ESI$^+$, *m/z*):** $[C_{21}H_{25}NNaO_4S]^+$ $(M+Na)^+$ calc. 410.1397, found 410.1381; **IR (ν, cm^{-1}):** 3244 (NH, w), 1698 (m, C=O), 1634 (m, C=C), 1494 ($C=C_{Ar}$), 1324 (m, S=O); **MP:** 118-119 °C.

***N*-(4-(*tert*-Butyl)-3-chlorophenyl)-4-methylbenzenesulfonamide (69v)**



78 **79** **80** **81** **69v**

2-(*tert*-Butyl)-5-nitroaniline (79)



Prepared according to a modified literature procedure.[35]

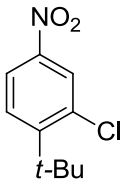
To a solution of 2-*tert*butylaniline **78** (2.00 mL, 12.8 mmol, 1.0 eq.) in conc. sulfuric acid (6.5 mL) at 0 °C was added nitric acid (846 µL, 19.2 mmol, 1.5 eq.) dropwise, whilst ensuring that the reaction temperature remained below 5 °C. The

reaction was stirred for a further 30 minutes at room temperature before being poured onto ice water, neutralised with NaOH (10M) and the resultant precipitate removed by filtration. Purification by column chromatography on silica gel (SiO_2, petroleum ether 30-40: EtOAc 9:1-4:1) afforded the title compound as a yellow solid (1.98 g, 10.2 mmol, 80 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.45 (s, 9H), 4.17 (brs, 2H), 7.35 (d, *J* = 8.8 Hz, 1H), 7.47 (d, *J* = 2.4 Hz, 1H), 7.54 (dd, *J* = 8.7 Hz, *J* = 2.3 Hz, 1H); **^{13}C NMR (101 MHz, $CDCl_3$):** δ = 29.2, 34.8, 111.4, 113.1, 127.4, 140.5, 145.5, 147.0; **LRMS (ESI^+, *m/z*):** $[C_{10}H_{15}N_2O_2]^+$ $(M+H)^+$ calc. 195.1, found 195.2.

Data consistent with literature values.[36]

1-(*tert*-Butyl)-2-chloro-4-nitrobenzene (80)

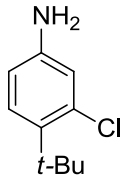


Prepared according to a modified literature procedure.[37]

To a solution of 2-(*tert*-butyl)-5-nitroaniline **79** (194 mg, 1.00 mmol, 1.0 eq.) in acetonitrile (5 mL) was added *p*-toluenesulfonic acid (228 mg 1.20 mmol, 1.0 eq.), *tert*-butyl nitrite (238 µL, 2.00 mmol, 2.0 eq.), benzyltriethyl ammonium chloride (456 mg, 2.00 mmol, 2.0 eq.) and copper(I) chloride (2 mg, 0.01 mmol, 1 mol %). The reaction was heated to 60 °C for 1 hour and cooled to room temperature before concentration under reduced pressure. Purification of the crude residue by column chromatography on silica gel (SiO_2, petroleum ether 30-40: EtOAc 19:1-9:1) afforded the title compound as a yellow solid (134 mg, 0.63 mmol, 64 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.43 (s, 9H), 7.61 (d, *J* = 8.9 Hz, 1H), 8.02 (dd, *J* = 8.9 Hz, *J* = 2.5 Hz, 1H), 8.19 (d, *J* = 2.5 Hz, 1H); **^{13}C NMR (101 MHz, $CDCl_3$):** δ = 29.2, 36.8, 121.5, 126.8, 128.5, 134.6, 146.3, 154.1; **HRMS (FI^+, *m/z*):** $[C_{10}H_{12}NO_2Cl]^+$ $(M)^+$ calc. 195.0895, found 195.0893; **IR (ν, cm^{-1}):** 1524 (s, N=O), 1467 (w, C=C_{Ar}), 1343 (s, N=O); **MP:** 66-67 °C.

4-(*tert*-Butyl)-3-chloroaniline (81)

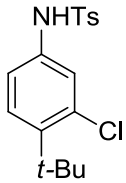


To 1-(*tert*-butyl)-2-chloro-4-nitrobenzene **80** (560 mg, 2.62 mmol, 1.0 eq.) and tin (872 mg, 7.54 mmol, 2.8 eq.) in water (8 mL) was added conc. HCl (3 mL). The reaction was heated to reflux for 3 hours and cooled to room temperature before neutralisation with NaOH (10 M). The resultant precipitate was removed by filtration and washed with cold water. The solid was then dissolved in EtOAc and filtered before the organic phase was washed with brine, dried over $MgSO_4$ and the solvent removed under reduced pressure. Purification by column chromatography on silica gel (SiO_2, petroleum ether 30-40: EtOAc 9:1) afforded the title compound as a colourless oil (117 mg, 0.64 mmol, 24 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.44 (s, 9H), 3.65 (brs, 2H), 6.53 (dd, *J* = 8.6 Hz, *J* = 2.7 Hz, 1H), 6.73 (d, *J* = 2.7 Hz, 1H), 7.19 (d, *J* = 8.6 Hz, 1H); **^{13}C NMR (101 MHz, $CDCl_3$):** δ = 30.0, 35.3, 113.4, 118.4, 128.3, 134.1, 136.5, 144.9; **LRMS (ESI$^+$, *m/z*):** $[C_{10}H_{15}ClN]^+$ $(M+H)^+$ calc. 184.1, found 184.1.

Data consistent with literature values.[38]

***N*-(4-(*tert*-Butyl)-3-chlorophenyl)-4-methylbenzenesulfonamide (69v)**

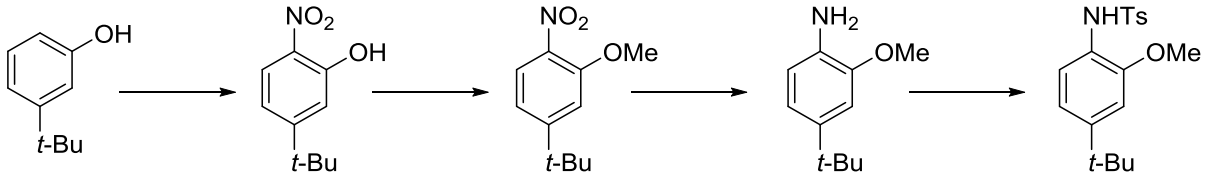


Prepared according to general procedure C from 4-(*tert*-butyl)-3-chloroaniline (**15**) (114 mg, 0.62 mmol, 1.0 eq.) and *p*-toluenesulfonyl chloride (118 mg, 0.62 mmol, 1.0 eq.). Purification by column chromatography on silica gel (SiO_2, petroleum ether 30-40: EtOAc 7:3) afforded the title compound as a white solid (183 mg, 0.54 mmol, 87 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.41 (s, 9H), 2.40 (s, 3H), 6.94 (dd, *J* = 8.7 Hz, *J* = 2.6 Hz, 1H), 7.00 (brs, 1H), 7.08 (d, *J* = 2.4 Hz, 1H), 7.24-7.29 (m, 1H), 7.27 (d, *J* = 8.3 Hz, 2H), 7.72 (d, *J* = 8.3 Hz, 2H); **^{13}C NMR (101 MHz, $CDCl_3$):** δ = 21.6, 29.5, 35.7, 118.9, 124.0, 127.3, 128.4, 129.8, 134.1, 135.2, 136.1, 143.3, 144.1; **HRMS (ESI$^+$, *m/z*):**

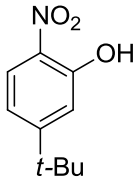
$[C_{17}H_{20}ClNNaO_2S]^+$ $(M+Na)^+$ calc. 360.0795, found 360.0788; **IR (ν, cm^{-1}):** 3254 (w, NH), 1490 (m, C=C_{Ar}), 1321 (m, S=O), 1158 (s, S=O); **MP:** 136-138 °C.

N-(4-(*tert*-Butyl)-2-methoxyphenyl)-4-methylbenzenesulfonamide (69w)[39]



82 **83** **84** **85** **86**

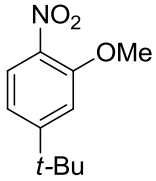
5-(*tert*-Butyl)-2-nitrophenol (83)



To 2-*tert*-butylphenol **82** (3.00 g, 20.0 mmol, 1.0 eq.) in glacial acetic acid (5 mL) at 0 °C was added nitric acid (1.07 mL, 24.0 mmol, 1.2 eq.) in glacial acetic acid (5 mL). The reaction was stirred at 0 °C for 15 minutes and then for a further hour at room temperature. The reaction was then poured onto ice water and extracted into diethyl ether. The combined organic phases were washed with brine, dried over $MgSO_4$ and the solvent removed under reduced pressure. Purification by column chromatography on silica gel (SiO_2, petroleum ether 30-40: EtOAc 9:1) afforded the title compound as a yellow oil (964 mg, 4.94 mmol, 25 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.33 (s, 9H), 7.02 (dd, *J* = 9.0 Hz, *J* = 2.2 Hz, 1H), 7.14 (d, *J* = 2.2 Hz, 1H), 8.03 (d, *J* = 9.0 Hz, 1H), 10.63 (s, 1H); **^{13}C NMR (101 MHz, $CDCl_3$):** δ = 30.7, 35.6, 116.4, 118.2, 124.7, 128.1, 155.0, 162.7; **HRMS (FI$^+$, *m/z*):** $[C_{10}H_{13}NO_2]^+$ $(M)^+$ calc. 195.0895, found 195.0893**; IR (ν, cm^{-1}):** 1621 (m, N=O), 1529 (w, C=C_{Ar}), 1322 (s, N=O).

4-(*tert*-Butyl)-2-methoxy-1-nitrobenzene (84)

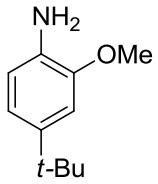


A slurry of 5-(*tert*-butyl)-2-nitrophenol **83** (900 mg, 4.61 mmol, 1.0 eq.) and potassium carbonate (796 mg, 5.76 mmol, 1.25 eq.) in DMF (25 mL) was stirred for 15 minutes before the addition of iodomethane (301 µL,

4.84 mmol, 1.05 eq.). The reaction was stirred for a further 14 hours then quenched with water and extracted in ethyl acetate. The combined organic phases were washed with brine, dried over $MgSO_4$ and the solvent removed under reduced pressure to afford the title compound directly as a brown solid (919 mg, 4.39 mmol, 95 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ =1.35 (s, 9H), 3.98 (s, 3H), 7.05 (dd, *J* = 8.5 Hz, *J* = 1.8 Hz, 1H), 7.07 (d, *J* = 1.8 Hz, 1H), 7.84 (d, *J* = 8.5 Hz, 1H); **^{13}C NMR (101 MHz, $CDCl_3$):** δ = 31.0, 35.6, 56.4, 110.6, 117.6, 125.7, 137.2, 153.0, 159.0; **HRMS (ESI^+, *m/z*):** $[C_{11}H_{15}NNaO_3]^+$ $(M+Na)^+$ calc. 232.0944, found 232.0943; **IR (ν, cm^{-1}):** 1603 (m, N=O), 1518 (s, C=C_{Ar}), 1363 (m, N=O); **MP:** 41-42 °C.

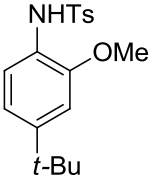
4-(*tert*-Butyl)-2-methoxyaniline (85)



To a solution of 4-(*tert*-butyl)-2-methoxy-1-nitrobenzene **83** (850 mg, 4.06 mmol, 1.0 eq.) in MeOH (25 mL) was added palladium on carbon (10 wt. % loading) (100 mg, 0.1 mmol, 2 mol %). The reaction was stirred under an atmosphere of hydrogen for 16 hours before filtration through a pad of Celite (MeOH). The solvent was removed under reduced pressure to afford the title compound directly as a dark purple solid (444 mg, 2.47 mmol, 61 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.31 (s, 9H), 3.70 (brs, 2H), 3.88 (s, 3H), 6.68 (d, *J* = 8.1 Hz, 1H), 6.83 (dd, *J* = 8.1 Hz, *J* = 2.0 Hz, 1H), 6.86 (d, *J* = 2.0 Hz, 1H); **^{13}C NMR (101 MHz, $CDCl_3$):** δ = 31.6, 34.3, 55.5, 108.2, 114.7, 117.6, 133.6, 141.9, 147.0; **HRMS (ESI^+, *m/z*):** $[C_{11}H_{18}NO]^+$ $(M+H)^+$ calc. 180.1383, found 180.1375; **IR (ν, cm^{-1}):** 3430 (w, NH), 3342 (m, NH), 1519 (s, C=C_{Ar}); **MP:** 40-41 °C.

***N*-(4-(*tert*-Butyl)-2-methoxyphenyl)-4-methylbenzenesulfonamide (69w)**

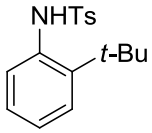


Prepared according to general procedure C from 4-(*tert*-butyl)-2-methoxyaniline **85** (430 mg, 2.40 mmol, 1.0 eq.) and *p*-toluenesulfonyl

chloride (458 mg, 2.40 mmol, 1.0 eq.). Purification by column chromatography on silica gel (SiO_2; hexane: EtOAc 4:1) afforded the title compound as a light brown solid (738 mg, 2.21 mmol, 92 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ =1.27 (s, 9H), 2.37 (s, 3H), 3.65 (s, 3H), 6.75 (d, *J* = 2.0 Hz, 1H), 6.91 (dd, *J* = 8.3, *J* = 2.0 Hz, 2H), 7.20 (d, *J* = 8.3 Hz, 2H), 7.40 (d, *J* = 8.4 Hz, 1H), 7.66 (d, *J* = 8.3, 2H); **^{13}C NMR (101 MHz, $CDCl_3$):** δ = 21.7, 31.5, 34.9, 55.7, 108.1, 118.0, 120.7, 123.6, 127.4, 129.5, 136.8, 143.6, 148.9, 149.3; **HRMS (ESI^+, *m/z*):** $[C_{18}H_{24}NO_3S]^+$ $(M+Na)^+$ calc. 334.1471, found 334.1461; **IR (ν, cm^{-1}):** 3266 (w, NH), 1517 (w, $C=C_{Ar}$), 1339 (m, S=O), 1163 (s, S=O), 1130 (m, C-O); **MP:** 94-95 °C.

***N*-(2-(*tert*-Butyl)phenyl)-4-methylbenzenesulfonamide (69x)**

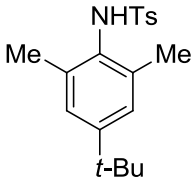


Prepared according to general procedure C from 2-*tert*-butylaniline **78** (1.00 mL, 7.00 mmol, 1.0 eq.) and *p*-toluenesulfonyl chloride (1.33 g, 7.00 mmol, 1.0 eq.). Purification by column chromatography on silica gel (SiO_2, petroleum ether 30-40: EtOAc 4:1) afforded the title compound as a white solid (2.11 g, 6.95 mmol, 99 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.36 (s, 9H), 2.41 (s, 3H), 6.73 (s, 1H), 7.08 (td, *J* = 7.7 Hz, *J* = 1.6 Hz, 1H), 7.15 (td, *J* = 7.6 Hz, *J* = 1.6 Hz, 1H), 7.27 (d, *J* = 8.1 Hz, 2H), 7.34 (dd, *J* = 7.8 Hz, *J* = 1.7 Hz, 1H), 7.45 (dd, *J* = 7.8 Hz, *J* = 1.5 Hz, 1H), 7.76 (d, *J* = 8.6 Hz, 2H); **^{13}C NMR (101 MHz, $CDCl_3$):** δ = 21.5, 30.9, 34.2, 122.4, 125.1, 126.9, 127.0, 127.3, 129.5, 135.0, 137.1, 140.2, 143.8; **LRMS (ESI^+, *m/z*):** $[C_{17}H_{22}NO_2S]^+$ $(M+H)^+$ calc. 304.1, found 304.2.

Data consistent with literature values.[40]

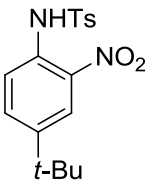
***N*-(4-(*tert*-Butyl)-2,6-dimethylphenyl)-4-methylbenzenesulfonamide (69y)**



Prepared according to general procedure C from 4-(*tert*-butyl)-2,6-dimethylaniline **87** (710 mg, 4.00 mmol, 1.0 eq.) and *p*-toluenesulfonyl chloride (763 mg, 4.00 mmol, 1.0 eq.). Purification by column chromatography on silica gel (SiO_2, petroleum ether 30-40: EtOAc 9:1-3:2) afforded the title compound as a white solid (1.25 g, 3.76 mmol, 94 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.28 (s, 9H), 2.04 (s, 6H), 2.44 (s, 3H), 5.83 (brs, 1H), 7.02 (s, 2H), 7.26 (m, *J* = 8.3 Hz, 2H), 7.63 (d, *J* = 8.3 Hz, 2H); **^{13}C NMR (101 MHz, $CDCl_3$):** δ = δ 19.0, 21.6, 31.3, 34.3, 125.8, 127.2, 129.6, 130.0, 137.1, 138.1, 143.5, 150.7**, HRMS (ESI$^+$, m/z):** $[C_{19}H_{25}NNaO_2S]^+$ $(M+Na)^+$ calc. 354.1498, found 354.1488; **IR (ν, cm^{-1}):** 3259 (m, NH), 1484 (w, C=C_{Ar}), 1327 (m, S=O), 1158 (s, S=O); **MP:** 123-124 °C.

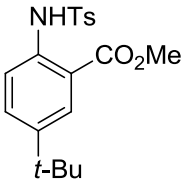
***N*-(4-(*tert*-Butyl)-2-nitrophenyl)-4-methylbenzenesulfonamide (69z)**



Prepared according to general procedure A from 4-(*tert*-butyl)-2-nitroaniline **88** (1.00 g, 5.14 mmol, 1.0 eq.) and *p*-toluenesulfonyl chloride (1.18 g, 6.17 mmol, 1.2 eq.). Purification by column chromatography on silica gel (SiO_2, petroleum ether 30-40: EtOAc 19:1-9:1) afforded the title compound as a yellow solid (1.30 g, 3.73 mmol, 73 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.30 (s, 9H), 2.40 (s, 3H), 7.27 (d, *J* = 8.2 Hz, 2H), 7.61 (dd, *J* = 8.8 Hz, *J* = 2.2 Hz, 1H), 7.74 (d, *J* = 8.2 Hz, 2H), 7.75 (d, *J* = 8.8 Hz, 1H), 8.08 (d, *J* = 2.2 Hz, 1H), 9.74 (s, 1H); **^{13}C NMR (101 MHz, $CDCl_3$):** δ = 21.6, 30.9, 34.6, 120.9, 122.5, 127.2, 130.0, 131.4, 133.4, 136.0, 136.9, 144.7, 147.6; **HRMS (ESI$^+$, m/z):** $[C_{17}H_{20}N_2NaOS]^+$ $(M+Na)^+$ calc. 371.1036, found 371.1036; **IR (ν, cm^{-1}):** 3294 (w, NH), 1530 (s, N=O), 1464 (w, C=C_{Ar}), 1347 (m, S=O), 1278 (m, N=O), 1159 (s, S=O); **MP:** 88-90 °C.

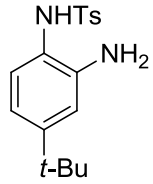
Methyl 5-(*tert*-butyl)-2-(4-methylphenylsulfonamido)benzoate (69aa)



Prepared according to general procedure A from methyl 2-amino-5-*tert*-butyl benzoate ester [2] **89** (544 mg, 2.60 mmol, 1.0 eq.) and *p*-toluenesulfonyl chloride (595 mg, 3.12 mmol, 1.2 eq.), with the reaction time reduced to 2 hours. Purification by column chromatography on silica gel (SiO_2, hexane: DCM 9:1-0:1) afforded the title compound as a yellow solid (585 mg, 1.61 mmol, 62 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.27 (s, 9H), 2.37 (s, 3H), 3.88 (s, 3H), 7.22 (d, *J* = 8.3 Hz, 2H), 7.48 (dd, *J* = 8.6 Hz, *J* = 2.2 Hz, 1H), 7.59 (d, *J* = 8.8 Hz, 1H), 7.74 (d, *J* = 8.3 Hz, 2H), 7.91 (d, *J* = 2.2 Hz, 1H), 10.52 (brs, 1H); **^{13}C NMR (101 MHz, $CDCl_3$):** δ = 21.5, 31.1, 34.2, 52.3, 115.4, 118.8, 127.2, 127.5, 129.6, 131.8, 136.7, 137.9, 143.7, 145.7, 168.4; **HRMS (ESI$^+$, *m/z*):** $[C_{19}H_{23}NNaO_4S]^+$ $(M+Na)^+$ calc. 384.1240, found 384.1234; **IR (ν, cm^{-1}):** 2960 (w, NH), 1686 (s, C=O), 1249 (m, S=O) ,1167 (s, S=O); **MP:** 110-113 °C.

***N*-(2-Amino-4-(*tert*-butyl)phenyl)-4-methylbenzenesulfonamide (69 bb)**



To a solution of *N*-(4-(*tert*-butyl)-2-nitrophenyl)-4-methylbenzenesulfonamide **69z** (1.25 g, 3.59 mmol, 1.0 eq.) in EtOH (25 mL) was added palladium on carbon (10 wt. % loading) (383 mg, 0.36 mmol, 10 mol %). The reaction was stirred under a balloon of H_2 for 2 hours before filtration through a pad of Celite (EtOH). The solvent was removed under reduced pressure to afford the title compound directly as a pink solid (706 mg, 2.21 mmol, 62 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.24 (s, 9H), 2.44 (s, 3H), 3.28 (brs, 2H), 6.01 (brs, 1H), 6.40 (d, *J* = 8.3 Hz, 1H), 6.56 (dd, *J* = 8.3 Hz, *J* = 2.2 Hz, 1H), 6.77 (d, *J* = 2.2 Hz,

[2] Methyl 2-amino-5-*tert*-butyl benzoate ester prepared by Dr. B. Checa.[41]

1H), 7.27 (d, *J* = 8.2 Hz, 2H), 7.66 (d, *J* = 8.2 Hz, 2H); **^{13}C NMR (101 MHz, $CDCl_3$):** δ = 21.6, 31.2, 34.5, 114.4, 116.1, 118.6, 127.6, 128.2, 129.6, 136.3, 143.8, 143.9, 152.5; **HRMS (ESI$^+$, m/z):** $[C_{17}H_{22}N_2NaO_2S]^+$ $(M+Na)^+$ calc. 341.1294, found 341.1294; **IR (ν, cm^{-1}):** 3385 (w, NH), 3257 (w, NH), 1509 (w, C=C_{Ar}), 1320 (m, S=O), 1159 (s, S=O); **MP:** 160-161 °C.

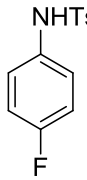
4.3.2 Fluorinated Product Synthesis

General procedure for oxidative fluorination

To a solution of *N*-protected aniline (1.0 eq.) in DCM (0.5 M) in a Falcon tube was added HF·pyridine (70 %) (1.0/4.0 eq.) followed by PIDA (1.0 eq.). The reaction was stirred at room temperature for 15 minutes before the addition of TFA (1.0 mL). After stirring for a further 5 minutes the reaction was quenched with saturated aqueous sodium bicarbonate and extracted into DCM. The combined organic phases were washed with brine, dried over $MgSO_4$ and the solvent removed under reduced pressure. Purification was performed by column chromatography on silica gel.

To obtain ^{19}F NMR yields, the reaction was performed on a 0.50 mmol scale. The crude residue was fully dissolved in $CDCl_3$ before the addition of 1-fluoro-3-nitrobenzene (53 µL, 0.50 mmol, 1.0 eq.) as an internal standard. An aliquot of the resulting solution was taken for NMR analysis.

***N*-(4-Fluorophenyl)-4-methylbenzenesulfonamide (70a)**

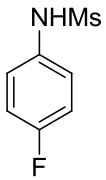


Prepared according to general procedure from *N*-(4-(*tert*-butyl)phenyl)-4-methylbenzenesulfonamide **69a** (303 mg, 1.00 mmol, 1.0 eq.) and HF·pyridine (70 %) (26 µL, 1.00 mmol, 1.0 eq.). Purification by column chromatography on silica gel (SiO_2, petroleum ether 30-40: EtOAc 9:1-4:1) afforded the title compound as a yellow solid (162 mg, 0.61 mmol, 61 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.36 (s, 3H), 6.90 (t, *J* = 6.9 Hz, 2H), 7.05-7.13 (m, 2H), 7.21 (d, *J* = 8.1 Hz, 2H), 7.64 (brs, 1H, N*H*), 7.68 (d, *J* = 8.1 Hz, 2H); **^{13}C NMR (101 MHz, $CDCl_3$):** δ = 21.5, 116.0 (d, *J* = 22.4 Hz), 124.3 (d, *J* = 8.0 Hz), 127.3, 129.7, 132.5 (d, *J* = 3.2 Hz), 135.5, 144.1, 160.5 (d, *J* = 244.5 Hz); **^{19}F NMR (377 MHz, $CDCl_3$)** δ = −116.6; **LRMS (ESI$^-$, m/z):** $[C_{13}H_{11}FNO_2S]^-$ $(M-H)^-$ calc. 264.05, found 264.05.

Data consistent with literature values.[42]

***N*-(4-Fluorophenyl)methanesulfonamide (70b)**

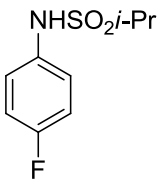


Prepared according to general procedure from *N*-(4-(*tert*-butyl)phenyl)methanesulfonamide **69b** (227 mg, 1.00 mmol, 1.0 eq.) and HF·pyridine (70 %) (26 µL, 1.00 mmol, 1.0 eq.). Purification by column chromatography on silica gel (SiO_2, petroleum ether 30-40: EtOAc 4:1) afforded the title compound as an off-white solid (102 mg, 0.54 mmol, 54 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.92 (s, 3H), 6.90 (brs, 1H, N*H*), 6.95-7.03 (m, 2H), 7.15-7.21 (m, 2H); **^{13}C NMR (101 MHz, $CDCl_3$):** δ = 39.1, 116.5 (d, *J* = 23.8 Hz), 123.9 (d, *J* = 7.9 Hz), 132.5 (d, *J* = 3.2 Hz), 160.7 (d, *J* = 244.8 Hz); **^{19}F NMR (377 MHz, $CDCl_3$)** δ = −116.2; **LRMS (ESI$^-$, m/z):** $[C_7H_7FNO_2S]^-$ $(M-H)^-$ calc. 188.0, found 188.0.

Data consistent with literature values.[43]

***N*-(4-Fluorophenyl)propane-2-sulfonamide (70c)**

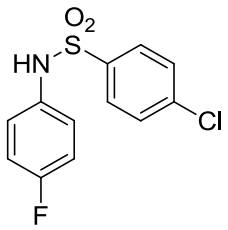


Prepared according to general procedure from *N*-(4-(*tert*-butyl)phenyl)propane-2-sulfonamide **69c** (255 mg, 1.00 mmol, 1.0 eq.) and HF·pyridine (70 %) (104 µL, 4.00 mmol, 4.0 eq.). Purification by column chromatography on silica gel (SiO_2, petroleum ether 30-40: EtOAc 17:3) afforded the title compound as a pale orange solid (125 mg, 0.57 mmol, 57 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.40 (d, *J* = 6.8 Hz, 6H), 3.27 (sept., *J* = 6.9 Hz, 1H),

6.60 (brs, 1H), 7.00-7.08 (m, 2H), 7.21-7.27 (m, 2H); **^{13}C NMR (101 MHz, $CDCl_3$):** δ = 16.5, 52.5, 116.4 (d, *J* = 22.3 Hz), 123.1 (d, *J* = 9.5 Hz), 132.8 (d, *J* = 3.2 Hz), 160.3 (d, *J* = 244.8 Hz); **^{19}F NMR (377 MHz, $CDCl_3$)** δ = −117.1; **HRMS (ESI^+, m/z):** $[C_9H_{12}FNNaO_2S]^+$ $(M+Na)^+$ calc. 240.0465, found 240.0474; **IR (ν, cm^{-1}):** 3257 (w, NH), 1506 (s, C=C_{Ar}), 1322 (m, S=O), 1140 (s, S=O), 1099 (w, CF); **MP:** 74-76 °C.

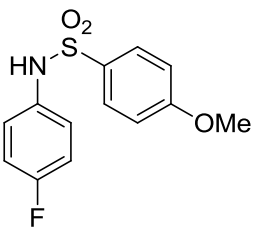
4-Chloro-*N*-(4-fluorophenyl)benzenesulfonamide (70d)



Prepared according to general procedure from *N*-(4-(*tert*-butyl)phenyl)-4-chlorobenzenesulfonamide **69d** (323 mg, 1.00 mmol, 1.0 eq.) and HF·pyridine (70 %) (26 µL, 1.00 mmol, 1.0 eq.). Purification by column chromatography (SiO_2, petroleum ether 30-40: EtOAc 9:1-7:3) afforded the title compound as an off-white solid (166 mg, 0.58 mmol, 58 % yield).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.04-7.15 (m, 4H), 7.61-7.66 (m, 2H), 7.67-7.74 (m, 2H), 10.32 (brs, 1H, N*H*); **^{13}C NMR (126 MHz, DMSO-d_6):** δ = 116.0 (d, *J* = 21.9 Hz), 123.2 (d, *J* = 8.6 Hz), 128.6, 129.4, 133.5 (d, *J* = 2.9 Hz), 137.8, 138.0, 159.3 (d, *J* = 242.2 Hz); **^{19}F NMR (471 MHz, DMSO-d_6)** δ = −115.5; **HRMS (ESI^+, m/z):** $[C_{12}H_9ClFNNaO_2S]^+$ $(M+Na)^+$ calc. 307.9199, found 307.9906; **IR (ν, cm^{-1}):** 3261 (w, NH), 1507 (s, C=C_{Ar}), 1332 (m, S=O), 1163 (s, S=O), 1094 (m, C-F), 755 (s, C-Cl); **MP:** 106-108 °C.

***N*-(4-Fluorophenyl)-4-methoxybenzenesulfonamide (70e)**

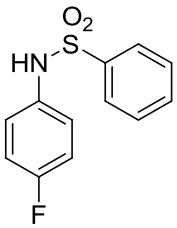


Prepared according to general procedure from *N*-(4-(*tert*-butyl)phenyl)-4-methoxybenzenesulfonamide **69e** (319 mg, 1.00 mmol, 1.0 eq.) and HF·pyridine (70 %) (26 µL, 1.00 mmol, 1.0 eq.). Purification by column chromatography (SiO_2, petroleum ether 30-

40: EtOAc 17:3-7:3) afforded the title compound as a white solid (176 mg, 0.59 mmol, 59 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.84 (s, 3H), 6.58 (brs, 1H, N*H*), 6.90 (d, *J* = 8.8 Hz, 2H), 6.92-6.97 (m, 2H), 7.01-7.06 (m, 2H), 7.66 (d, *J* = 8.8 Hz, 1H); **^{13}C NMR (101 MHz, $CDCl_3$):** δ = 51.2, 109.9, 111.7 (d, *J* = 24.0 Hz), 120.1 (d, *J* = 9.6 Hz), 125.1, 125.7, 128.1 (d, *J* = 3.2 Hz), 156.2 (d, *J* = 244.5 Hz), 158.8; **^{19}F NMR (471 MHz, $CDCl_3$)** δ = −116.4; **HRMS (ESI$^+$, m/z):** $[C_{13}H_{12}FNNaO_3S]^+$ $(M+Na)^+$ calc. 304.0414, found 304.0403; **IR (ν, cm^{-1}):** 3246 (m, N-H), 1449 (w, C=C_{Ar}), 1333 (m, S=O), 1149 (s, S=O), 1090 (m, C-F); **MP:** 72-74 °C.

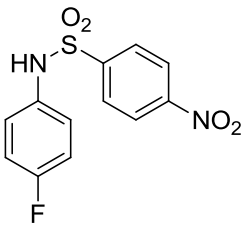
***N*-(4-Fluorophenyl)benzenesulfonamide (70f)**



Prepared according to general procedure from *N*-(4-(*tert*-butyl)phenyl)benzenesulfonamide **69f** (289 mg, 1.00 mmol, 1.0 eq.) and HF·pyridine (70 %) (26 µL, 1.00 mmol, 1.0 eq.). Purification by column chromatography (SiO_2, petroleum ether 30-40: EtOAc 9:1) afforded the title compound as a white solid (151 mg, 0.60 mmol, 60 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.87-6.99 (m, 2H), 7.03-7.11 (m, 2H), 7.19 (brs, 1H), 7.40-7.51 (m, 2H), 7.52-7.60 (m, 1H), 7.75-7.79 (m, 2H); **^{13}C NMR (101 MHz, $CDCl_3$):** δ = 116.1 (d, *J* = 22.3 Hz), 124.7 (d, *J* = 9.5 Hz), 127.3, 129.1, 132.1 (d, *J* = 3.2 Hz), 133.2, 138.6, 160.7 (d, *J* = 246.4 Hz); **^{19}F NMR (471 MHz, $CDCl_3$)** δ = −116.1; **HRMS (ESI$^+$, m/z):** $[C_{12}H_{10}FNNaO_2S]^+$ $(M+Na)^+$ calc. 274.0308, found 274.0302; **IR (ν, cm^{-1}):** 3259 (w, NH), 1507 (s, C=CAr), 1328 (m, S=O), 1157 (s, S=O), 1091 (m, C-F); **MP:** 106-108 °C.

***N*-(4-Fluorophenyl)-4-nitrobenzenesulfonamide (70g)**

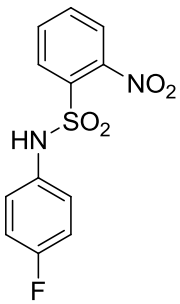


Prepared according to general procedure from *N*-(4-(*tert*-butyl)phenyl)-4-nitrobenzenesulfonamide **69g** (334 mg, 1.00 mmol, 1.0 eq.) and HF·pyridine (70 %) (104 µL, 4.00 mmol, 1.0 eq.). Purification by column chromatography (SiO_2, petroleum ether 30-40: EtOAc 17:3-7:3) afforded the title compound as a yellow solid (193 mg, 0.65 mmol, 65 % yield).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.09 (brs, 2H), 7.10 (d, *J* = 1.3 Hz, 2H), 7.94 (d, *J* = 8.8 Hz, 2H), 8.36 (d, *J* = 8.8 Hz, 2H); 10.56 (brs, 1H); **^{13}C NMR (101 MHz, DMSO-d_6):** δ = 117.0 (d, *J* = 22.4 Hz), 124.5 (d, *J* = 8.0 Hz), 125.5, 129.2, 133.9, 145.4, 150.7, 160.4 (d, *J* = 241.3 Hz); **^{19}F NMR (471 MHz, $CDCl_3$)** δ = −114.2; **LRMS (ESI$^+$, m/z):** $[C_{12}H_9FN_2NaO_4S]^+$ $(M+Na)^+$ calc. 319.0, found 319.0.

Data consistent with literature values.[44]

***N*-(4-Fluorophenyl)-2-nitrobenzenesulfonamide (70h)**



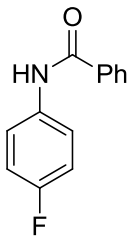
Prepared according to general procedure from *N*-(4-(*tert*-butyl)phenyl)-2-nitrobenzenesulfonamide **69h** (334 mg, 1.00 mmol, 1.0 eq.) and HF·pyridine (70 %) (104 µL, 4.00 mmol, 1.0 eq.). Purification by column chromatography (SiO_2, petroleum ether 30-40: EtOAc 17:3-7:3) afforded the title compound as a yellow solid (118 mg, 0.40 mmol, 40 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.92-7.01 (m, 2H), 7.17 (dd, *J* = 8.8 Hz, *J* = 4.8 Hz, 2H), 7.26 (s, 1H, N*H*), 7.60 (dd, *J* = 7.8 Hz, *J* = 1.3 Hz, 1H), 7.72 (td, *J* = 7.8 Hz, *J* = 1.4 Hz, 1H), 7.77 (dd, *J* = 7.8 Hz, *J* = 1.5 Hz, 1H), 7.87 (dd, *J* = 8.0 Hz, *J* = 1.1 Hz, 1H); **^{13}C NMR (101 MHz, $CDCl_3$):** δ = 116.3 (d, *J* = 22.4 Hz), 125.3, 126.0 (d, *J* = 9.6 Hz), 131.3 (d, *J* = 3.2 Hz), 131.8, 131.9, 132.7, 134.1, 148.2, 161.3 (d, *J* = 247.7 Hz); **^{19}F NMR (471**

MHz, $CDCl_3$): δ = −114.3; **LRMS (ESI$^+$, m/z):** $[C_{12}H_9FN_2NaO_4S]^+$ $(M+Na)^+$ calc. 319.0, found 319.0.

Data consistent with literature values.[45]

_N_-(4-Fluorophenyl)benzamide (70i)

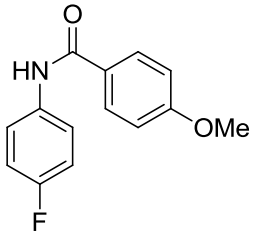


Prepared according to general procedure from *N*-(4-(tert-butyl)phenyl)benzamide **69i** (253 mg, 1.00 mmol, 1.0 eq.) and HF·pyridine (70 %) (104 µL, 4.00 mmol, 4.0 eq.). Purification by column chromatography on silica gel (SiO_2, petroleum ether 30-40: EtOAc 19:1-9:1) afforded the title compound as a white solid (148 mg, 0.69 mmol, 69 % yield).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.16-7.26 (m, 2H), 7.51-7.58 (m, 2H), 7.58-7.65 (m, 1H), 7.76-7.84 (m, 2H), 7.93-7.99 (m, 2H), 10.32 (brs, 1H); **^{13}C NMR (101 MHz, DMSO-d_6):** δ = 115.7 (d, *J* = 22.3 Hz), 122.6 (d, *J* = 7.9 Hz), 128.1, 128.9, 132.1, 135.3, 136.0, 158.8 (d, *J* = 240.0 Hz), 165.9; **^{19}F** (**377 MHz, DMSO-d_6)** δ = −118.9; **LRMS (ESI$^-$, m/z):** $[C_{13}H_9FNO]^-$ $(M-H)^-$ calc. 214.1, found 214.1.

Data consistent with literature values.[46]

_N_-(4-Fluorophenyl)-4-methoxybenzamide (70j)



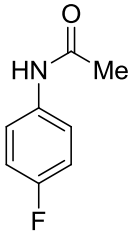
Prepared according to general procedure, from *N*-(4-(*tert*-butyl)phenyl)-4-methoxybenzamide **69j** (283 mg, 1.00 mmol, 1.0 eq.) and HF·pyridine (70 %) (104 µL, 4.00 mmol, 4.0 eq.). Purification by column chromatography on silica gel (SiO_2, petroleum ether 30-40: EtOAc 4:1-3:2) afforded the title compound as a white solid (104 mg, 0.42 mmol, 42 % yield).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.85 (s, 3H), 7.07 (d, *J* = 8.8 Hz, 2H), 7.19 (t, *J* = 8.8 Hz, 2H), 7.76-7.82 (m, 2H), 7.96 (d, *J* = 9.0 Hz, 2H), 10.16 (s, 1H, N*H*); **^{13}C NMR (101 MHz, DMSO-d_6):** δ = 55.9, 114.1, 115.6 (d, *J* = 22.3 Hz), 122.6 (d, *J* = 7.9 Hz),

127.3, 130.0, 136.2 (d, *J* = 3.2 Hz), 158.6 (d, *J* = 240.0 Hz), 162.4, 165.3; **^{19}F NMR (377 MHz, DMSO-d$_6$)** δ = −119.3; **LRMS (ESI$^+$, m/z):** $[C_{14}H_{13}FNO_2]^+$ $(M+H)^+$ calc. 246.1, found 246.1.

Data consistent with literature values.[46]

_N_-(4-(Fluoro)phenyl)acetamide (70k)

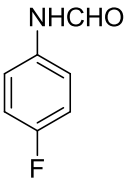


Prepared according to general procedure, from *N*-(4-(*tert*-butyl)phenyl)acetamide **69k** (191 mg, 1.00 mmol, 1.0 eq.) and HF·pyridine (70 %) (104 µL, 4.00 mmol, 4.0 eq.). Purification by column chromatography on silica gel (SiO_2, petroleum ether 30-40: EtOAc 7:3-3:2) afforded the title compound as a white solid (81 mg, 0.53 mmol, 53 % yield).

^{1}H NMR (400 MHz, DMSO-d$_6$): δ = 2.03 (s, 3H), 7.08-7.17 (m, 2H), 7.55-7.63 (m, 2H), 10.00 (brs, 1H, N*H*); **^{13}C NMR (101 MHz, DMSO-d$_6$):** δ = 24.3, 115.7 (d, *J* = 22.3 Hz), 121.1 (d, *J* = 7.9 Hz), 136.2, 158.3 (d, *J* = 235.2 Hz), 168.6; **^{19}F NMR (377 MHz, DMSO-d$_6$)** δ = −119.8; **LRMS (ESI$^+$, m/z):** $[C_8H_8FNNaO]^+$ $(M+Na)^+$ calc. 176.1, found 176.1.

Data consistent with literature values.[47]

_N_-(4-Fluorophenyl)formamide (70l)



Prepared according to general procedure, from *N*-(4-(*tert*-butyl)phenyl)formamide **69l** (177 mg, 1.00 mmol, 1.0 eq.) and HF·pyridine (70 %) (104 µL, 4.00 mmol, 4.0 eq.), with reaction time increased to 30 minutes. Purification by column chromatography on silica gel (SiO_2, petroleum ether 30-40: EtOAc 9:1) afforded the title compound as a white solid (38 mg, 0.27 mmol, 27 % yield). Formed as a mixture of rotamers (1:1 ratio).

Trans isomer: **^{1}H NMR (400 MHz, DMSO-d$_6$):** δ = 7.11-7.24 (m, 4H), 8.68 (d, *J* = 11.0 Hz, 1H, C*H*O), 10.13 (d, *J* = 11.0 Hz, 1H, N*H*); **^{13}C NMR (101 MHz, DMSO-d$_6$):** δ =

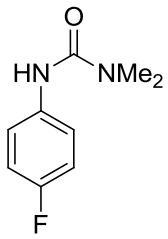
116.9 (d, *J* = 22.4 Hz), 120.4 (d, *J* = 8.0 Hz), 135.6 (d, *J* = 3.2 Hz), 159.0 (d, *J* = 239.7 Hz), 163.6; **^{19}F NMR (377 MHz, DMSO-d_6)** δ = −119.7.

Cis isomer: **^{1}H NMR (400 MHz, DMSO-d_6):** δ = 7.11-7.24 (m, 2H), 7.57-7.63 (m, 2H), 8.25 (d, *J* = 2.0 Hz, 1H, C*H*O), 10.23 (brs, 1H, N*H*); **^{13}C NMR (101 MHz, DMSO-d_6):** δ = 116.3 (d, *J* = 22.4 Hz), 121.8 (d, *J* = 8.0 Hz), 135.5 (d, *J* = 3.2 Hz), 159.0 (d, *J* = 239.7 Hz), 160.4; **^{19}F NMR (377 MHz, DMSO-d_6)** δ = −118.8.

LRMS (ESI$^+$, m/z): $[C_7H_6FNONa]^+$ $(M+Na)^+$ calc. 162.03, found 162.03.

Data consistent with literature values.[48]

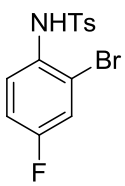
3-(4-Fluorophenyl)-1,1-dimethylurea (70m)



Prepared according to general procedure, from 3-(4-(*tert*-butyl)phenyl)-1,1-dimethylurea **69m** (205 mg, 1.00 mmol, 1.0 eq.) and HF·pyridine (70 %) (104 µL, 4.00 mmol, 4.0 eq.). Purification by column chromatography on silica gel (SiO_2, hexane: EtOAc 3:1) afforded the title compound as a white solid (93 mg, 0.51 mmol, 51 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.00 (s, 6H), 6.40 (brs, 1H), 6.92-6.99 (m, 2H), 7.28-7.34 (m, 2H); **^{13}C NMR (101 MHz, $CDCl_3$):** δ = 36.6, 115.5 (d, *J* = 22.3 Hz), 122.1 (d, *J* = 8.0 Hz), 135.3 (d, *J* = 2.4 Hz), 156.0, 160.0 (d, *J* = 241.6 Hz); **^{19}F NMR (377 MHz, $CDCl_3$):** δ = −120.4; **HRMS (ESI$^+$, m/z):** $[C_9H_{11}FN_2NaO]^+$ $(M+Na)^+$ calc. 205.0748, found 205.0748; **IR (ν, cm^{-1}):** 3293 (m, NH), 1641 (s, C=O), 1511 (s, C=C_{Ar}), 1098 (w, CF); **MP:** 117-118 °C.

***N*-(2-Bromo-4-fluorophenyl)-4-methylbenzenesulfonamide (70q)**

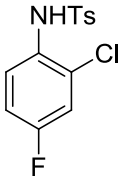


Prepared according to general procedure from *N*-(2-bromo-4-*tert*-butylphenyl)-4-methylbenzenesulfonamide **69q** (382 mg, 1.00 mmol, 1.0 eq.) and HF·pyridine (70 %) (104 µL, 4.00 mmol, 4.0 eq.). Purification by column

chromatography on silica gel (SiO_2, petroleum ether 30-40: EtOAc 19:1-9:1) afforded the title compound as a pale orange solid (179 mg, 0.52 mmol, 52 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.39 (s, 3H), 6.80 (brs, 1H), 7.03 (ddd, *J* = 8.9 Hz, *J* = 7.9 Hz, *J* = 2.9 Hz, 1H), 7.16 (dd, *J* = 7.7 Hz, *J* = 2.8 Hz, 1H), 7.22 (d, *J* = 8.3 Hz, 2H), 7.60 (d, *J* = 8.3 Hz, 2H), 7.68 (dd, *J* = 9.0 Hz, *J* = 5.4 Hz, 1H); **^{13}C NMR (101 MHz, $CDCl_3$):** δ = 21.8, 115.9 (d, *J* = 22.3 Hz), 117.1 (d, *J* = 9.5 Hz), 119.8 (d, *J* = 25.4 Hz), 125.2 (d, *J* = 8.7 Hz), 127.5, 129.9, 131.3 (d, *J* = 3.2 Hz), 135.8, 144.5, 160.0 (d, *J* = 249.5 Hz); **^{19}F NMR (377 MHz, $CDCl_3$)** δ = −114.2; **HRMS (ESI^+, m/z):** $[C_{13}H_{11}{}^{79}BrFNNaO_2S]^+$ $(M+Na)^+$ calc. 365.9570, found 365.9570; **IR (ν, cm^{-1}):** 3260 (w, NH), 1486 (s, $C=C_{Ar}$), 1334 (m, S=O), 1161 (s, S=O), 1090 (m, C-F); **MP:** 92-93°C.

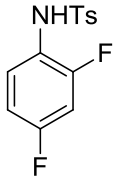
***N*-(2-Chloro-4-fluorophenyl)-4-methylbenzenesulfonamide (70r)**



Prepared according to general procedure from *N*-(2-chloro-4-*tert*-butylphenyl)-4-methylbenzenesulfonamide **69r** (338 mg, 1.00 mmol, 1.0 eq.) and HF·pyridine (70 %) (104 µL, 4.00 mmol, 4.0 eq.). Purification by column chromatography on silica gel (SiO_2, hexane: EtOAc 9:1-4:1) afforded the title compound as an pale orange solid (162 mg, 0.54 mmol, 54 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.38 (s, 3H), 6.89 (brs, 1H), 6.95-7.02 (m, 1H), 7.22 (d, *J* = 8.1 Hz, 1H), 7.14 (d, *J* = 8.0 Hz, 2H), 7.61 (d, *J* = 8.4 Hz, 2H), 7.66 (dd, *J* = 9.1 Hz, *J* = 5.4 Hz, 1H); **^{13}C NMR (101 MHz, $CDCl_3$):** δ = 21.7, 115.2 (d, *J* = 22.3 Hz), 116.7 (d, *J* = 26.2 Hz), 125.2 (d, *J* = 8.7 Hz), 127.0 (d, *J* = 10.3 Hz), 127.4, 129.7, 129.9 (d, *J* = 3.2 Hz), 135.8, 144.5, 159.7 (d, *J* = 249.5 Hz); **^{19}F NMR (377 MHz, $CDCl_3$):** δ = −114.2; **HRMS (ESI^+, m/z):** $[C_{13}H_{11}ClFNNaO_2S]^+$ $(M+Na)^+$ calc. 322.0075, found 322.0075; **IR (ν, cm^{-1}):** 3250 (m, NH), 1490 (s, $C=C_{Ar}$), 1339 (m, S=O), 1165 (s, S=O), 1091 (m, C-F), 729 (s, C-Cl); **MP:** 102-103 °C.

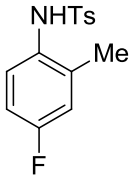
***N*-(2,4-Difluorophenyl)-4-methylbenzenesulfonamide (70s)**



Prepared according to general procedure from *N*-(2-fluoro-4-*tert*-butylphenyl)-4-methylbenzenesulfonamide **69s** (193 mg, 0.60 mmol, 1.0 eq.) and HF·pyridine (70 %) (62 µL, 2.40 mmol, 4.0 eq.). Purification by column chromatography on silica gel (SiO_2, hexane: EtOAc 9:1) afforded the title compound as an orange solid (77 mg, 0.27 mmol, 45 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.39 (s, 3H), 6.71 (ddd, *J* = 10.2 Hz, *J* = 8.3 Hz, *J* = 2.8 Hz, 1H), 6.81-6.88 (m, 2H), 7.23 (d, *J* = 8.1 Hz, 2H), 7.56 (td, *J* = 9.0 Hz, *J* = 5.8 Hz, 1H), 7.63 (d, *J* = 8.3 Hz, 2H); **^{13}C NMR (101 MHz, $CDCl_3$):** δ = 21.7, 104.2 (dd, *J* = 27.0 Hz, *J* = 23.8 Hz), 111.9 (dd, *J* = 22.3 Hz, *J* = 4.8 Hz), 120.8 (dd, *J* = 12.7 Hz, *J* = 4.0 Hz), 126.1 (dd, *J* = 9.5 Hz, *J* = 1.6 Hz), 127.3, 129.9, 135.8, 144.4, 155.0 (dd, *J* = 248.8 Hz, *J* = 11.9 Hz), 160.2 (dd, *J* = 248.8 Hz, *J* = 11.1 Hz); **^{19}F NMR (377 MHz, $CDCl_3$):** δ = −123.4 (d, *J* = 5.7 Hz, 1F), −112.0 (d, *J* = 5.7 Hz, 1F); **HRMS (ESI^+, m/z):** $[C_{13}H_{11}F_2NNaO_2S]^+$ $(M+Na)^+$ calc. 306.0371, found 306.0368; **IR (v, cm^{-1}):** 3250 (w, N-H), 1506 (s, C=C_{Ar}), 1335 (m, S=O), 1160 (s, S=O), 1092 (m, C-F); **MP:** 102-103 °C.

***N*-(4-Fluoro-2-methylphenyl)-4-methylbenzenesulfonamide (70t)**

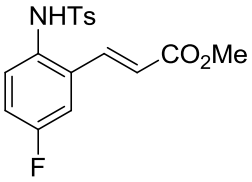


Prepared according to general procedure from *N*-(2-bromo-4-*tert*-butylphenyl)-4-methylbenzenesulfonamide **69t** (190 mg, 0.60 mmol, 1.0 eq.) and HF·pyridine (70 %) (62 µL, 2.40 mmol, 4.0 eq.). Purification by column chromatography on silica gel (SiO_2, petroleum ether 30-40: EtOAc 17:3) afforded the title compound as a pink solid (100 mg, 0.36 mmol, 60 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.99 (s, 3H), 2.41 (s, 3H), 6.65 (brs, 1H), 6.81 (d, *J* = 8.8 Hz, 1H), 6.82-6.85 (m, 1H), 7.18-7.23 (m, 1H), 7.24 (d, *J* = 8.2 Hz, 2H), 7.60 (d, *J* = 8.2 Hz, 2H); **^{13}C NMR (101 MHz, $CDCl_3$):** δ = 17.8, 21.6, 113.5 (d, *J* = 22.3 Hz), 117.3 (d, *J* = 22.3 Hz), 127.2, 127.7 (d, *J* = 9.5 Hz), 129.7, 130.2 (d, *J* = 3.2 Hz), 135.6 (d, *J* =

7.9 Hz), 136.5, 143.9, 161.0 (d, *J* = 246.4 Hz); **^{19}F NMR (377 MHz, $CDCl_3$)** δ = −115.5; **HRMS (ESI$^+$, m/z):** $[C_{14}H_{14}FNNaO_2S]^+$ $(M+Na)^+$ calc. 302.0621, found 302.0620; **IR (ν, cm^{-1}):** 3270 (w, NH), 1497 (m, C=$C_{Ar)}$, 1329 (m, S=O), 1161 (s, S=O), 1092 (w, C-F); **MP:** 95-96 °C.

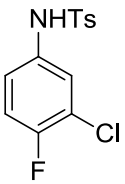
(*E*)-Methyl 3-(5-fluoro-2-(4-methylphenylsulfonamido)phenyl)acrylate (70u)



Prepared according to general procedure from methyl 5-(*tert*-butyl)-2-(4-methylphenylsulfonamido)benzoate **69u** (170 mg, 0.44 mmol, 1.0 eq.) and HF·pyridine (70 %) (46 µL, 1.76 mmol, 4.0 eq.). Purification by column chromatography on silica gel (SiO_2, petroleum ether 30-40: EtOAc 17:3) afforded the title compound as a white solid (80 mg, 0.23 mmol, 52 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.37 (s, 3H), 3.79 (s, 3H), 6.08 (d, *J* = 15.9 Hz, 1H), 7.03 (brs, 1H), 7.04-7.10 (m, 1H), 7.15 (dd, *J* = 9.0 Hz, *J* = 2.9 Hz, 1H), 7.20 (d, *J* = 8.2 Hz, 2H), 7.36 (dd, *J* = 9.0 Hz, *J* = 5.1 Hz, 1H), 7.48-7.55 (m, 1H), 7.53 (d, *J* = 8.2 Hz, 2H); **^{13}C NMR (101 MHz, $CDCl_3$):** δ = 21.5, 52.0, 113.3 (d, *J* = 23.8 Hz), 117.9 (d, *J* = 22.3 Hz), 121.1, 127.4, 129.7, 130.6 (d, *J* = 3.2 Hz), 130.7 (d, *J* = 9.5 Hz), 133.4 (d, *J* = 7.9 Hz), 135.5, 138.3, 144.2, 161.5 (d, *J* = 246.4 Hz), 166.6; **^{19}F NMR (377 MHz, $CDCl_3$):** δ = −113.1; **HRMS (ESI$^+$, m/z):** $[C_{17}H_{16}FNNaO_4S]^+$ $(M+Na)^+$ calc. 372.0676, found 372.0663; **IR (ν, cm^{-1}):** 3244 (w, NH), 1700 (m, C=O), 1632 (w, C=C), 1490 (m, C=C_{Ar}), 1328 (m, S=O), 1161 (s, S=O), 1092 (w, C-F); **MP:** 152-155 °C.

***N*-(3-Chloro-4-fluorophenyl)-4-methylbenzenesulfonamide (70v)**

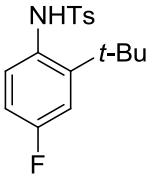


Prepared according to general procedure from *N*-(4-(*tert*-butyl)-3-chlorophenyl)-4-methylbenzenesulfonamide **69v** (169 mg, 0.50 mmol, 1.0 eq.) and HF·pyridine (70 %) (52 µL, 2.00 mmol, 4.0 eq.). Purification by column

chromatography on silica gel (SiO_2, hexane: EtOAc 9:1-4:1) afforded the title compound as an off white solid (91 mg, 0.30 mmol, 61 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.41 (s, 3H), 6.94-7.03 (m, 2H), 7.15 (brs, 1H), 7.19 (dd, *J* = 6.3 Hz, *J* = 2.5 Hz, 1H), 7.27 (d, *J* = 8.1 Hz, 2H), 7.67 (d, *J* = 8.3 Hz, 2H); **^{13}C NMR (101 MHz, $CDCl_3$):** δ = 21.6, 117.0 (d, *J* = 22.3 Hz), 121.6 (d, 19.1 Hz), 121.9 (d, *J* = 7.2 Hz), 124.3, 127.3, 129.2, 133.1 (d, *J* = 3.4 Hz), 135.4, 144.4, 156.0 (d, *J* = 247.8 Hz); **^{19}F NMR (377 MHz, $CDCl_3$):** δ = −118.9; **HRMS (ESI$^+$, m/z):** $[C_{13}H_{11}ClFNNaO_2S]^+$ $(M+Na)^+$ calc. 322.0075, found 322.0075; **IR (v, cm^{-1}):** 3251 (m, NH), 1499 (s, C=C_{Ar}), 1326 (m, S=O), 1161 (s, S=O), 1091 (m, C-F), 669 (m, C-Cl); **MP:** 110-112 °C.

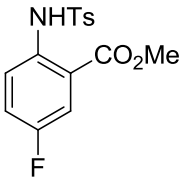
***N*-(2-(*tert*-Butyl)-4-fluorophenyl)-4-methylbenzenesulfonamide (70x)**



Prepared according to general procedure from *N*-(2-(*tert*-butyl)phenyl)-4-methylbenzenesulfonamide **69x** (303 mg, 1.00 mmol, 1.0 eq.) and HF·pyridine (70 %) (104 µL, 4.00 mmol, 4.0 eq.). Purification by column chromatography on silica gel (SiO_2, hexane: EtOAc 9:1) afforded the title compound as a purple solid (125 mg, 0.39 mmol, 39 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.28 (s, 9H), 2.38 (s, 3H), 6.54 (brs, 1H), 6.77 (ddd, *J* = 8.8 Hz, *J* = 7.1 Hz, *J* = 2.9 Hz, 1H), 7.01 (dd, *J* = 11.5 Hz, *J* = 2.9 Hz, 1H), 7.22-7.26 (m, 3H), 7.68 (d, *J* = 8.3 Hz, 2H); **^{13}C NMR (101 MHz, $CDCl_3$):** δ = 21.7, 30.9, 34.9, 113.4 (d, *J* = 22.3 Hz), 114.6 (d, *J* = 23.8 Hz), 126.0 (d, *J* = 8.7 Hz), 127.5, 129.8, 130.9 (d, *J* = 2.4 Hz), 137.4, 144.1, 145.2 (d, *J* = 7.2 Hz), 160.5 (d, *J* = 244.0 Hz); **^{19}F NMR (377 MHz, $CDCl_3$):** δ = −115.7; **HRMS (ESI$^+$, m/z):** $[C_{17}H_{20}FNNaO_2S]^+$ $(M+Na)^+$ calc. 344.1091, found 344.1086; **IR (v, cm^{-1}):** 3281 (w, NH), 1481 (m, C=C_{Ar}), 1326 (m, S=O), 1186 (s, S=O), 1093 (m, C-F); **MP:** 82-84 °C.

Methyl 5-fluoro-2-(4-methylphenylsulfonamido)benzoate (70aa)



Prepared according to general procedure from methyl 5-(*tert*-butyl)-2-(4-methylphenylsulfonamido)benzoate **69aa** (285 mg, 0.78 mmol, 1.0 eq.) and HF·pyridine (70 %) (81 µL, 3.12 mmol, 4.0 eq.). Purification by column chromatography on silica gel (SiO_2, hexane: EtOAc 9:1-4:1) afforded the title compound as a white solid (52 mg, 0.16 mmol, 21 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.37 (s, 3H), 3.87 (s, 3H), 7.16-7.22 (m, 1H), 7.22 (d, *J* = 8.1 Hz, 2H), 7.58 (dd, *J* = 9.0 Hz, *J* = 3.2 Hz, 1H), 7.68 (d, *J* = 8.3 Hz, 2H), 7.72 (dd, *J* = 9.2 Hz, *J* = 4.8 Hz, 1H), 10.28 (brs, 1H); **^{13}C NMR (101 MHz, $CDCl_3$):** δ =21.5, 52.7, 117.2 (d, *J* = 25.4 Hz), 117.7 (d, *J* = 6.4 Hz), 121.7 (d, *J* = 22.3 Hz), 121.9 (d, *J* = 4.8 Hz), 127.3, 129.6, 136.1, 136.6 (d, *J* = 3.2 Hz), 144.0, 158.0 (d, *J* = 246.4 Hz), 167.2 (d, *J* = 3.2 Hz); **^{19}F NMR (377 MHz, $CDCl_3$):** δ = −118.3; **HRMS (ESI$^+$, m/z):** $[C_{15}H_{14}FNNaO_4S]^+$ $(M+Na)^+$ calc. 346.0520, found 346.0513; **IR (ν, cm^{-1}):** 3184 (w, NH), 1691 (m, C=O), 1494 (m, $C=C_{Ar}$), 1342 (m, S=O), 1229 (m, C-O), 1162 (s, S=O), 1121 (m, C-O), 1090 (w, C-F); **MP:** 65-67 °C.

4.3.3 Radiochemistry

Azeoptropic drying of [^{18}F]fluoride

[^{18}F]Fluoride was produced by Erigal Ltd (Keele, UK) via the $^{18}O(p,n)^{18}F$ reaction and delivered as [^{18}F]fluoride in [^{18}O]water. Radiosynthesis and azeotropic drying was performed on a NanoTek® automated microfluidic device (Advion). [^{18}F]Fluoride was separated from ^{18}O-enriched-water using anion exchange cartridges (Chromafix, Macherey-Nagel, Düren, Germany) and subsequently released with 600 µL of a solution of NEt_4HCO_3 (7 mg) in MeCN/H_2O (4:1) (1 mL). The solution was dried with five cycles of azeotropic drying with acetonitrile (300 µL) and redissolved in anhydrous DCM (1000 µL) to form a stock solution of [^{18}F]NEt_4F.

Analysis

For all reactions, an aliquot was removed for analysis by radio-TLC and radio-HPLC.

TLC Analysis: Merck Kiesegel 60 F254 plates in hexane:EtOAc: (1:1).

HPLC Analysis: Waters Nova-Pak C18 Column, 4 μm, 3.9x150 mm, 1 mL/min, UV = 254 nm, Sample: 1 mg/mL in MeCN, t_{Prod} = 9.0 min.

HPLC Conditions F

0-1 min, 5 % MeCN, 95 % H_2O
1-10 min, 5 % to 95 % MeCN
10-14 min, 95 % MeCN, 5 % H_2O
14- 15 min, 95 % to 5 % MeCN
15- 17 min, 5 % MeCN, 95 % H_2O

Reported radiochemical yields are decay corrected and calculated by radio-TLC taking into account the radiochemical purity as determined by radio-HPLC.

Radiofluorination Procedure

[^{18}F]NEt_4F (15-30 MBq) was dispensed from the stock solution into a Wheaton v-vial containing a stirrer bar and *N*-(4-(*tert*-butyl)phenyl)-4-methylbenzenesulfonamide (**69a**, 12 mg, 40 μmol, 1.0 eq.). PIDA (13 mg, 40 μmol, 1.0 eq.) in DCM (150 μL) was added, followed by HF·pyridine (1 μL, 40 μmol, 1.0 eq.) in DCM (50 μL). The reaction mixture was stirred for 15 minutes before TFA (22 μL) was added and stirred for a further 10 minutes prior to radioHPLC and radioTLC analysis.

Alternatively, TFA (12 μL, 160 μmol, 4.0 eq.) was used in the place of HF·pyridine.

4.4 HPLC Spectra

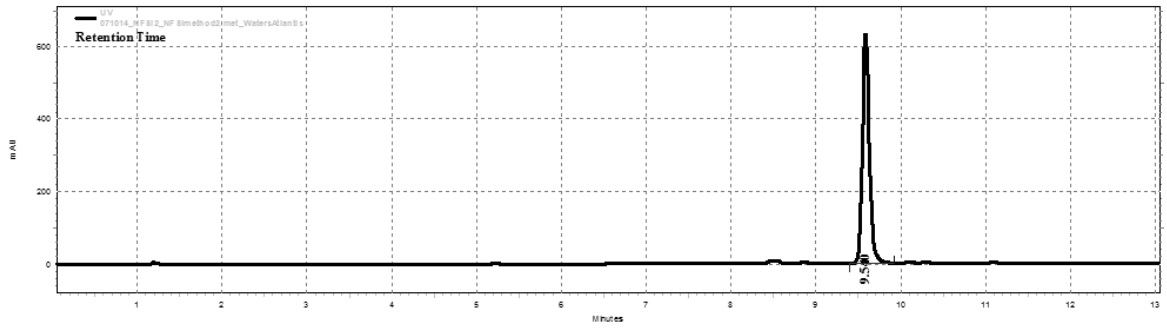
4.4.1 Chapter 2: Organomediated Enantioselective ^{18}F-Fluorination

4.4.1.1 Enamine Catalysis for Asymmetric α-[^{18}F]Fluorination of Aldehydes

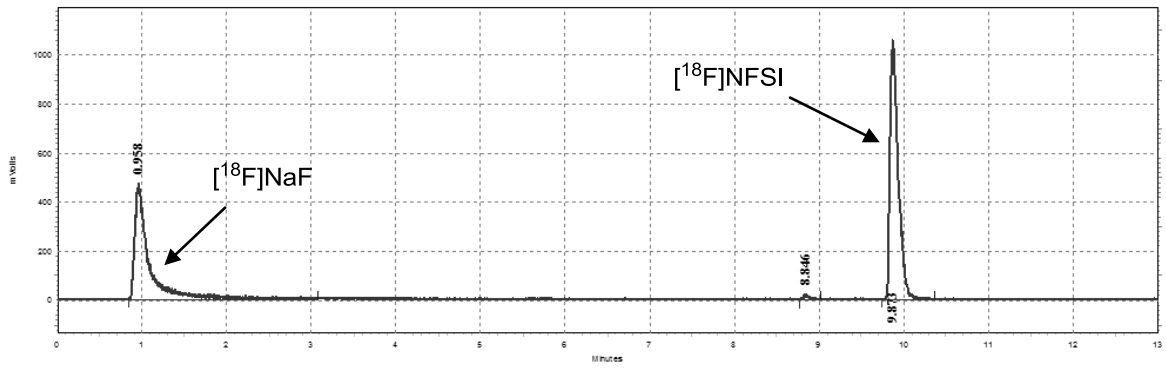
[^{18}F]NFSI

Analytical

UV of reference compound

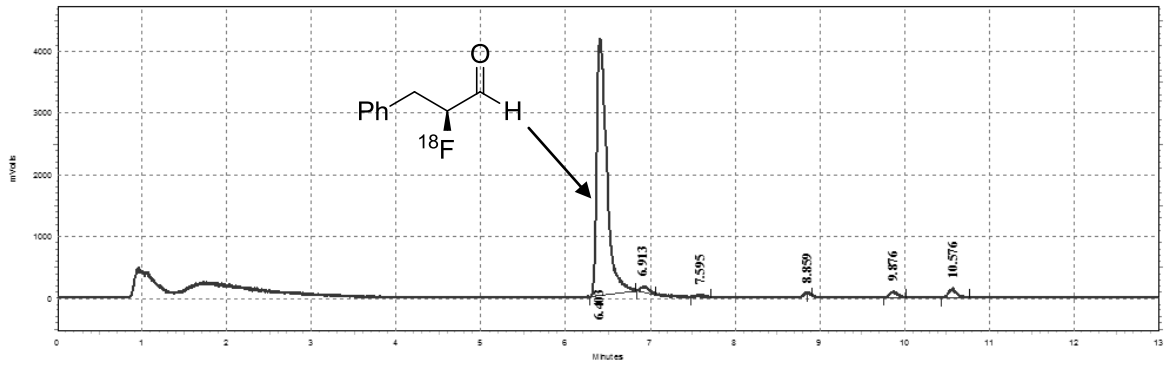


Radio-HPLC



(*S*)-2-[^{18}F]Fluorohydrocinnamaldehyde (*S*)-[^{18}F]5a

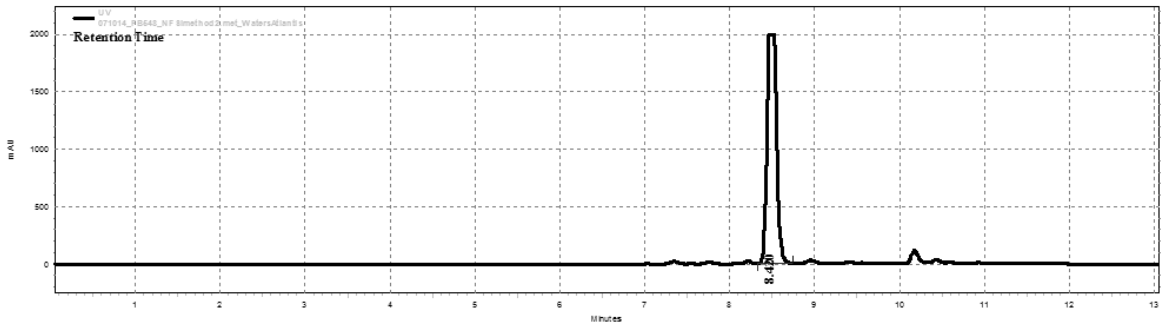
Radio-HPLC



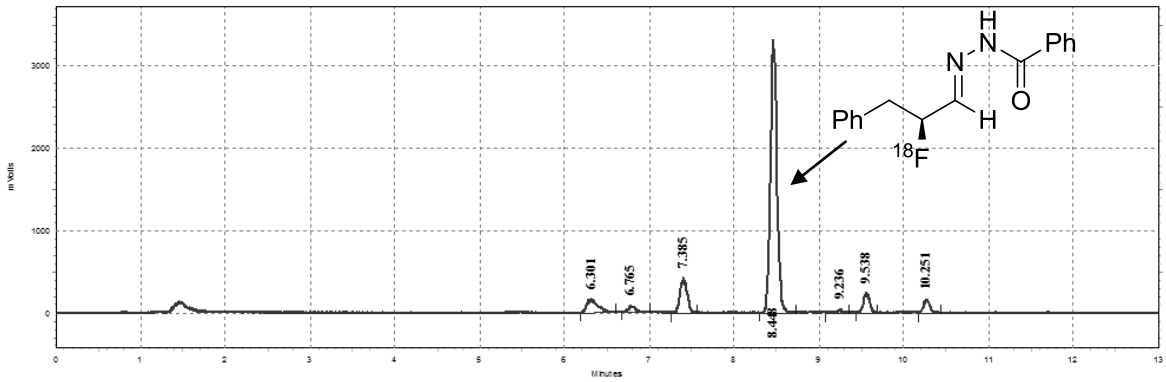
(*E*,*S*)-[^{18}F]*N*'-(2-Fluoro-3-phenylpropylidene)benzohydrazide (*S*)-[^{18}F]8a

Analytical

UV of reference compound

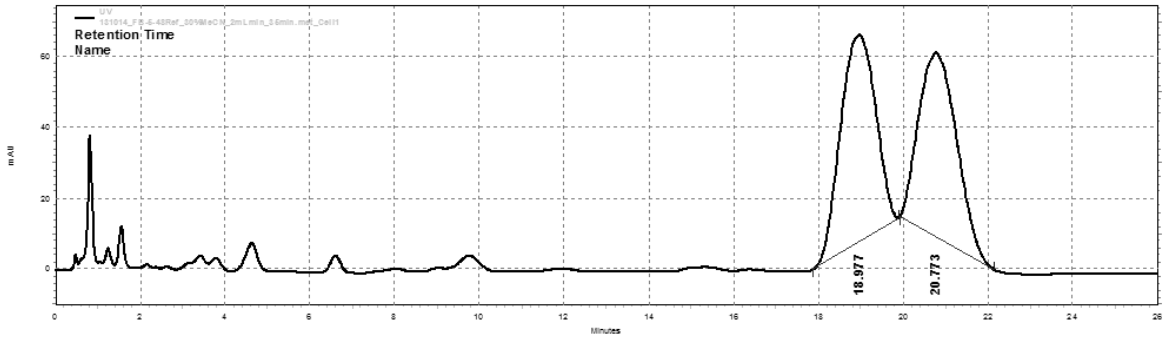


Radio-HPLC (Crude reaction)

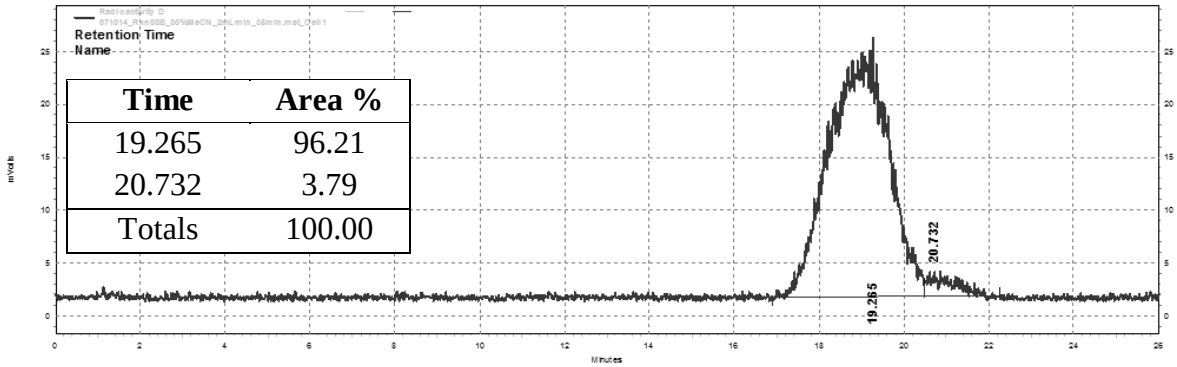


Chiral

UV of reference compound



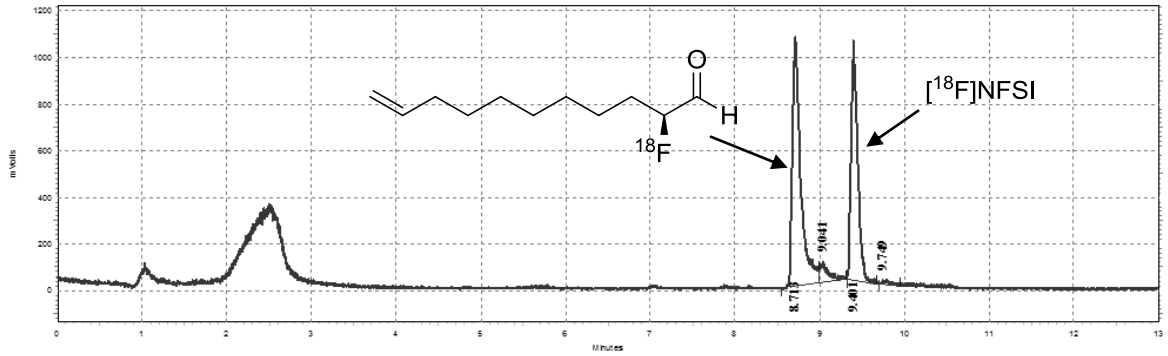
Radio-HPLC



Time	Area %
19.265	96.21
20.732	3.79
Totals	100.00

(*S*)-2-[^{18}F]Fluoroundec-10-enal (*S*)-[^{18}F]5f

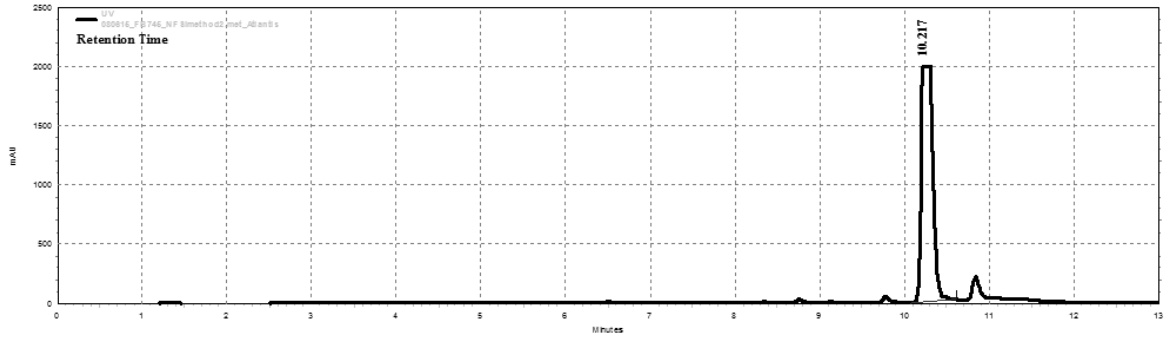
Radio-HPLC



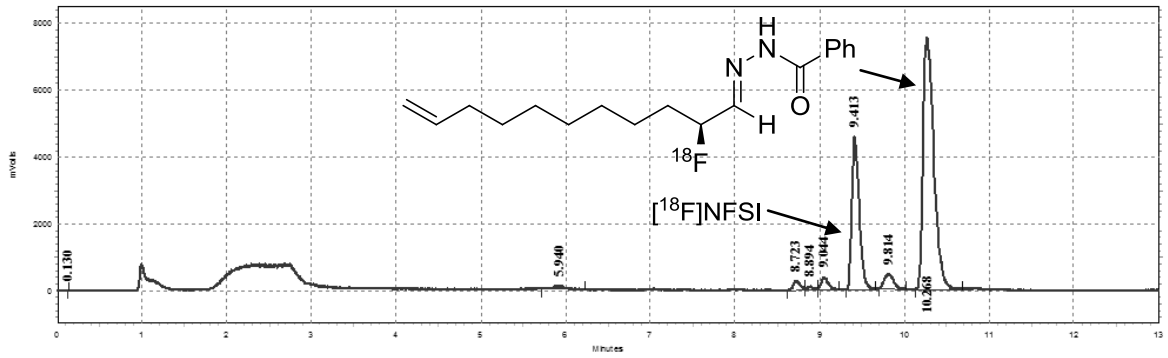
(*E*,*S*)-[^{18}F]*N*'-(2-Fluoroundec-10-en-1-ylidene)benzohydrazide (*S*)-[^{18}F]8f

Analytical

UV of reference compound

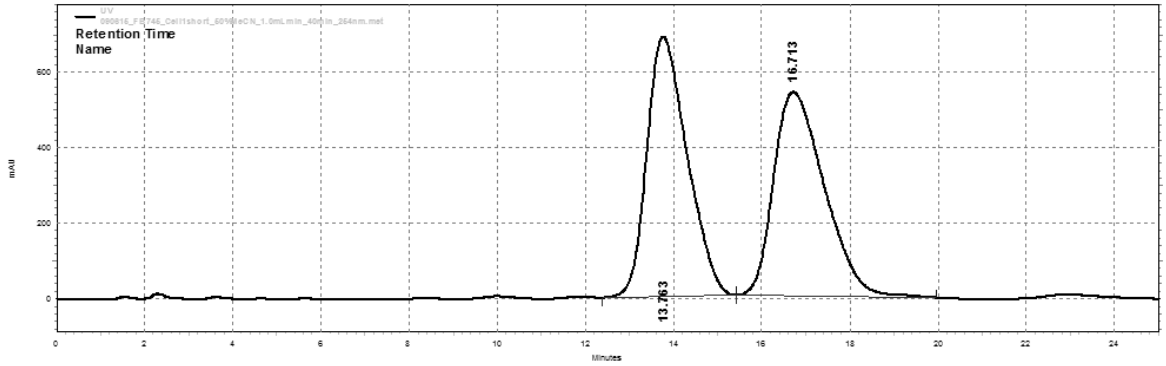


Radio-HPLC (Crude reaction)

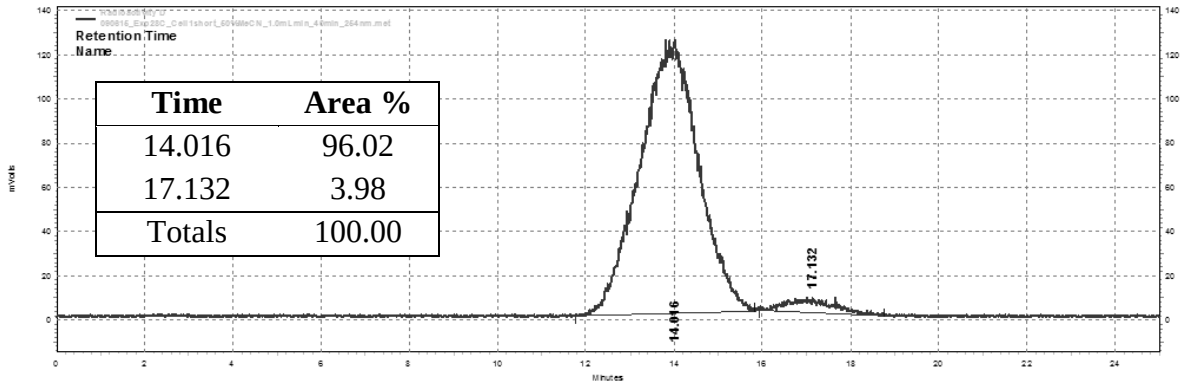


(*E*,*S*)-[^{18}F]*N*'-(2-Fluoroundec-10-en-1-ylidene)benzohydrazide (*S*)-[^{18}F]8f (cont.)
Chiral

UV of reference compound



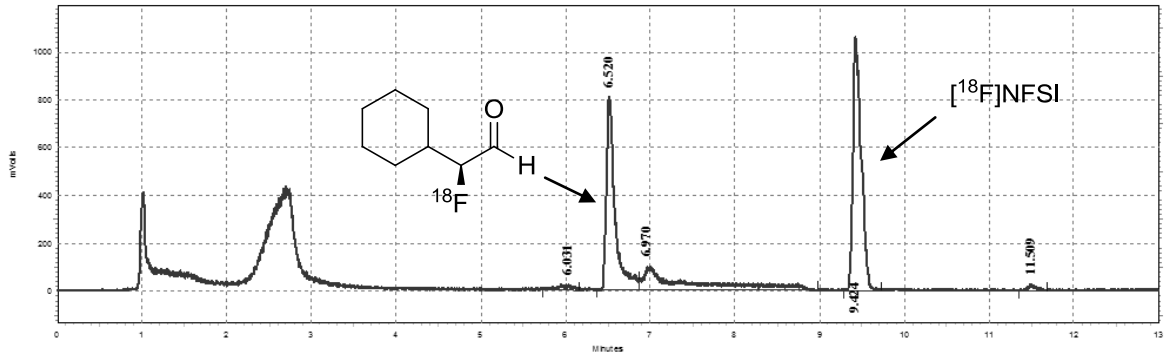
Radio-HPLC



Time	Area %
14.016	96.02
17.132	3.98
Totals	100.00

(*S*)-2-[^{18}F]Cyclohexyl-2-fluoroacetaldehyde (*S*)-[^{18}F]5b

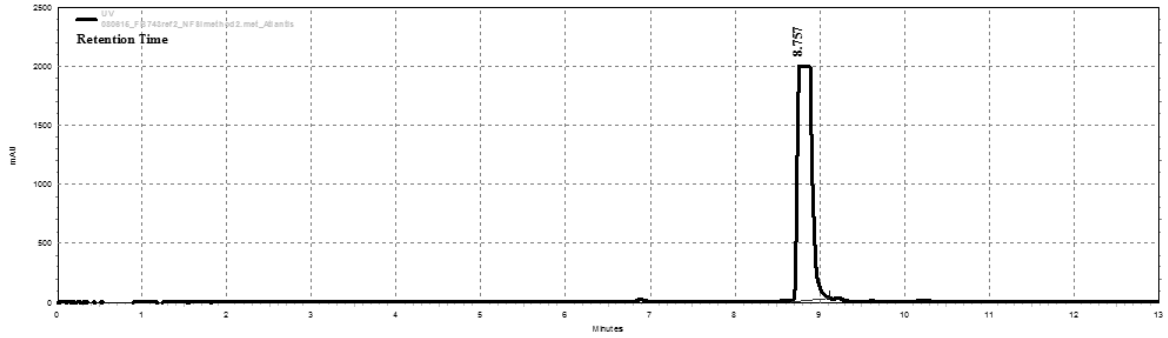
Radio-HPLC



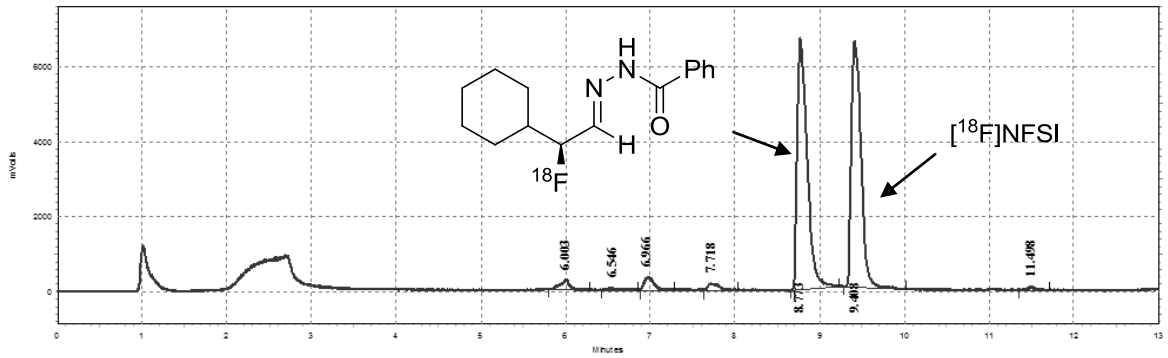
(*E*,*S*)-[^{18}F]*N*'-(2-Cyclohexyl-2-fluoroethylidene)benzohydrazide (*S*)-[^{18}F]8b

Analytical

UV of reference compound

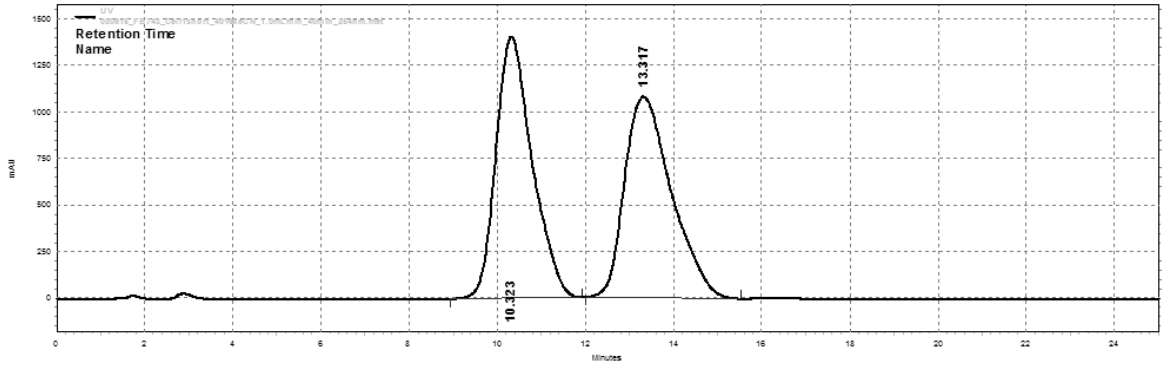


Radio-HPLC (Crude reaction)

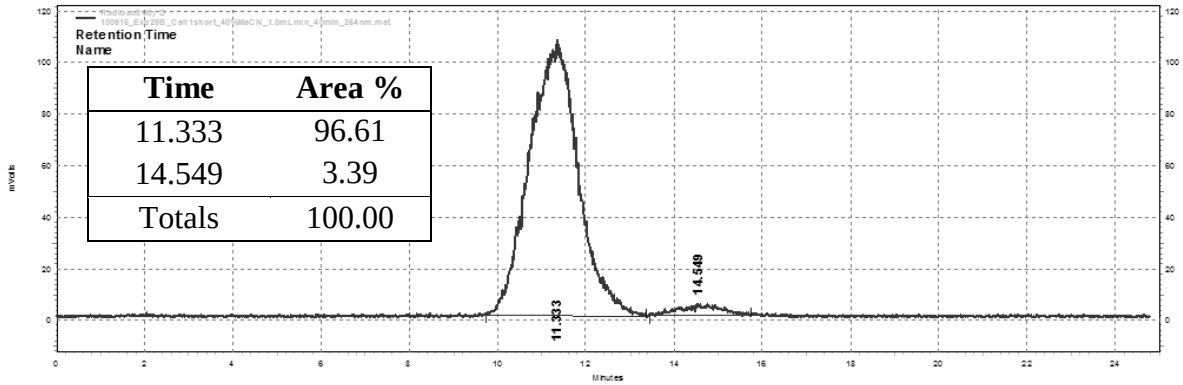


(*E*,*S*)-[^{18}F]*N*'-(2-Cyclohexyl-2-fluoroethylidene)benzohydrazide (*S*)-[^{18}F]8b (cont.)
Chiral

UV of reference compound



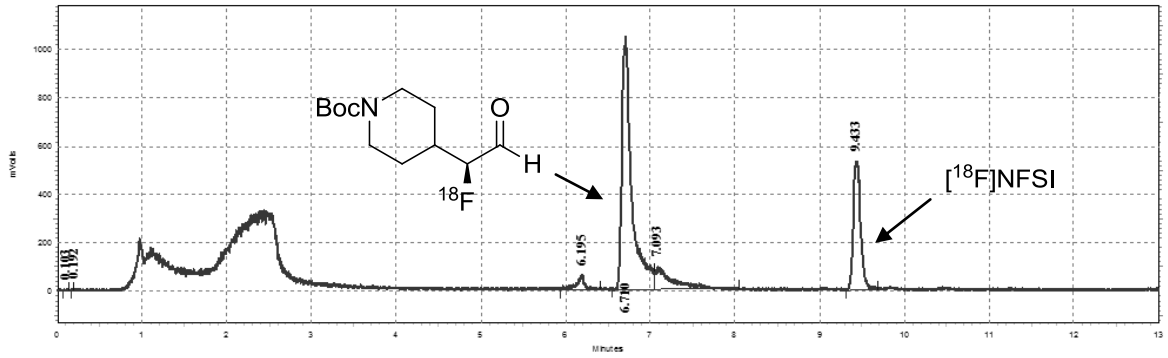
Radio-HPLC



Time	Area %
11.333	96.61
14.549	3.39
Totals	100.00

(S)-[^{18}F]*tert*-Butyl 4-(1-fluoro-2-oxoethyl)piperidine-1-carboxylate (*S*)-[^{18}F]5c

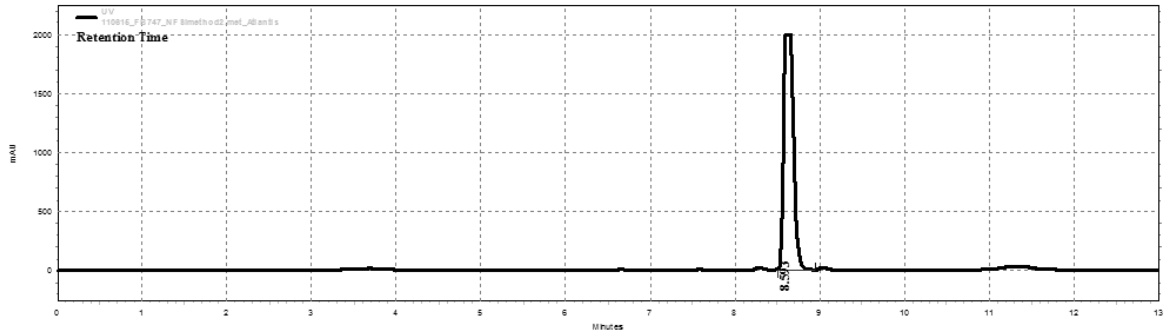
Radio-HPLC



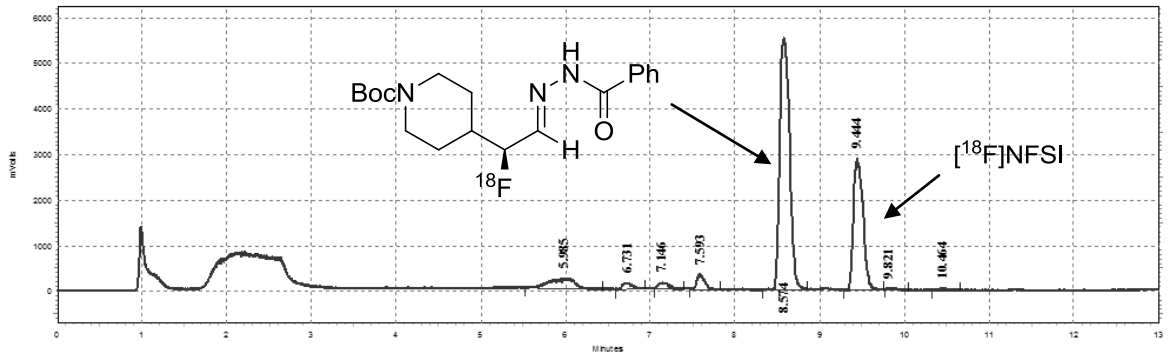
(*E*,*S*)-[^{18}F]*tert*-Butyl 4-(2-(2-benzoylhydrazono)-1-fluoroethyl)piperidine-1-carboxylate (*S*)-[^{18}F]8c

Analytical

UV of reference compound



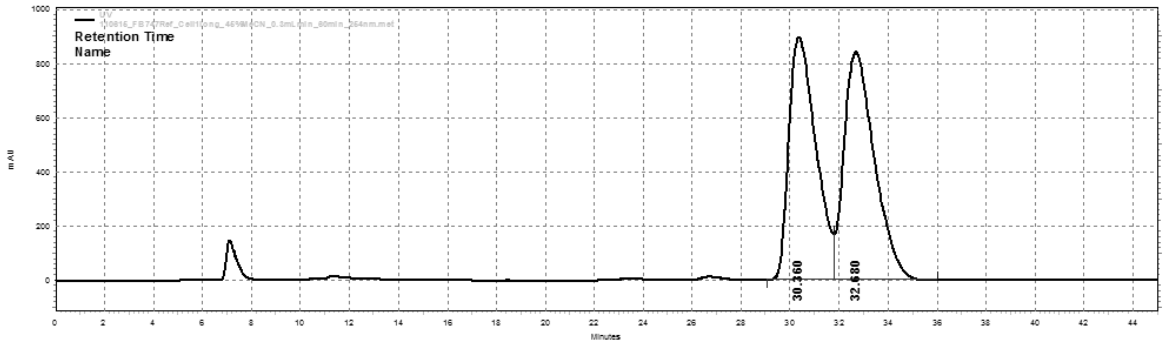
Radio-HPLC (Crude reaction)



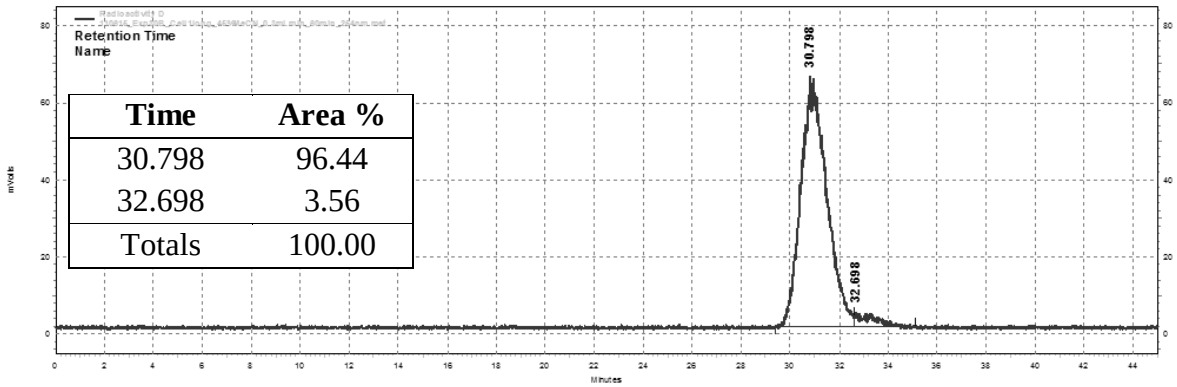
(*E*,*S*)-[^{18}F]*tert*-Butyl 4-(2-(2-benzoylhydrazono)-1-fluoroethyl)piperidine-1-carboxylate (*S*)-[^{18}F]8c (cont.)

Chiral

UV of reference compound

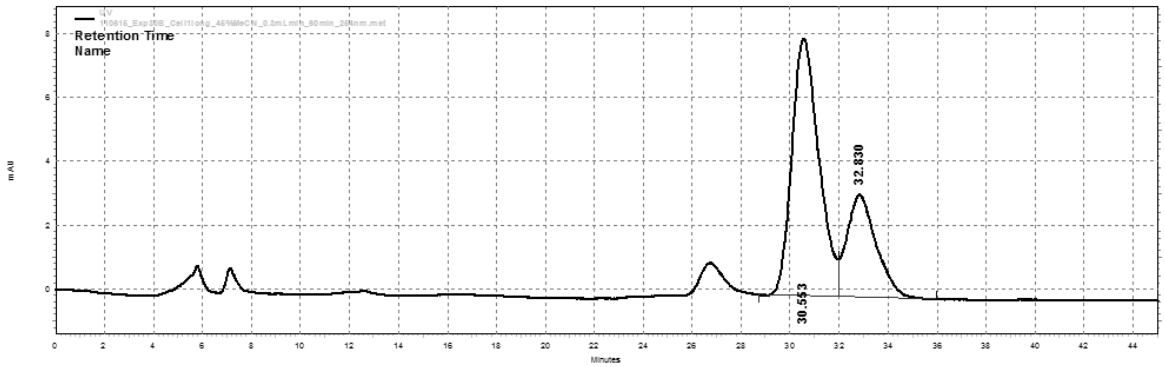


Radio-HPLC



Time	Area %
30.798	96.44
32.698	3.56
Totals	100.00

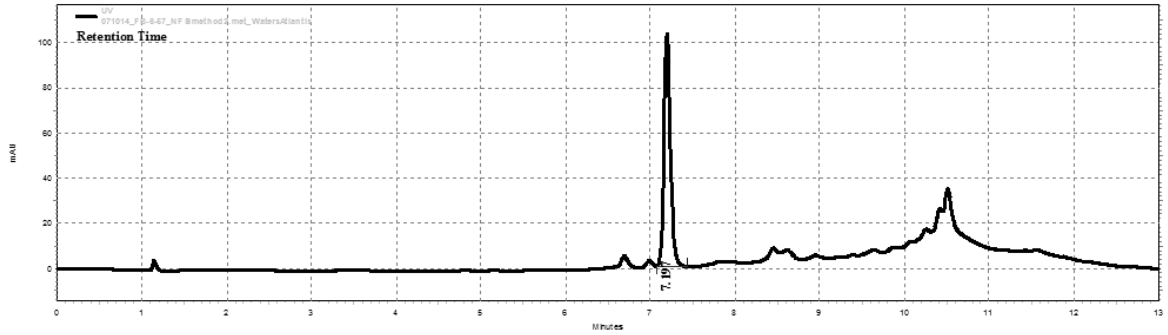
UV (spiked with racemic reference)



(*S*)-2-[^{18}F]Fluoro-3-phenylpropanoic acid (*S*)-[^{18}F]12a

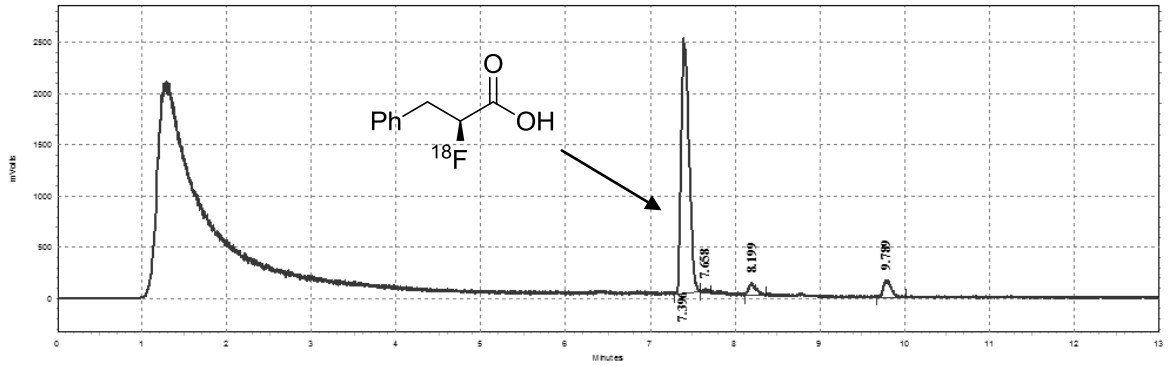
Analytical

UV of reference compound



Radio-HPLC

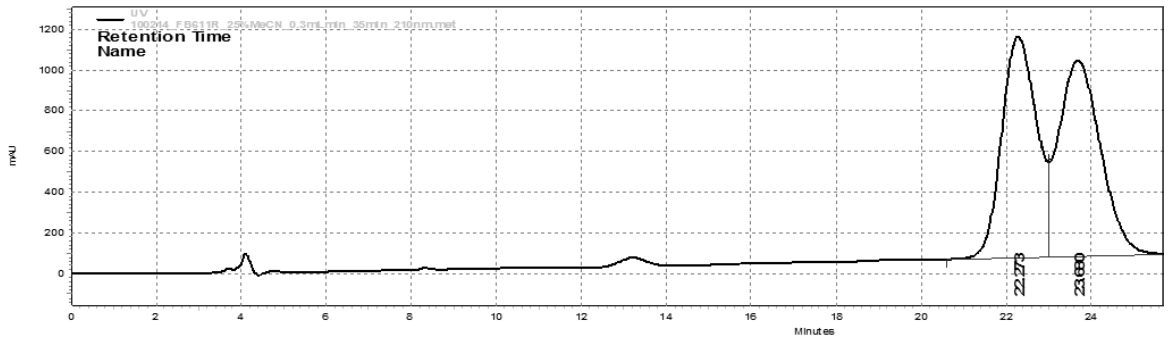
(Crude reaction)



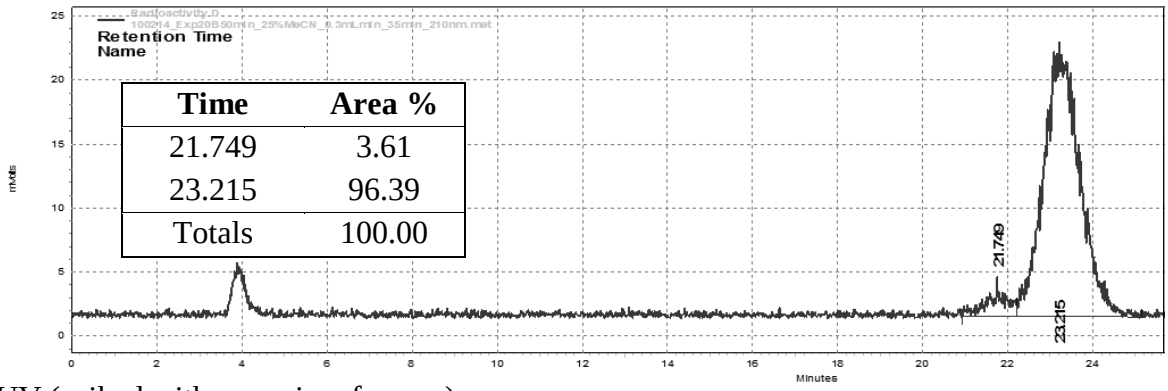
(*S*)-2-[^{18}F]Fluoro-3-phenylpropanoic acid (*S*)-[^{18}F]12a (cont.)

Chiral

UV of reference compound

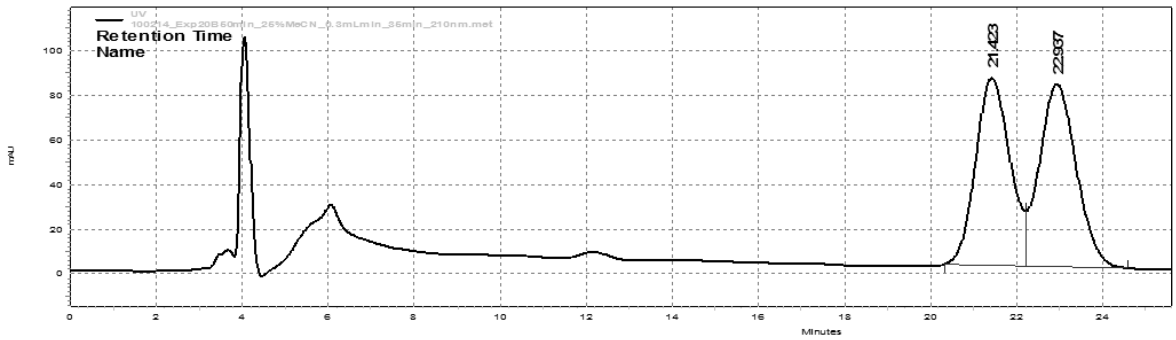


Radio-HPLC



Time	Area %
21.749	3.61
23.215	96.39
Totals	100.00

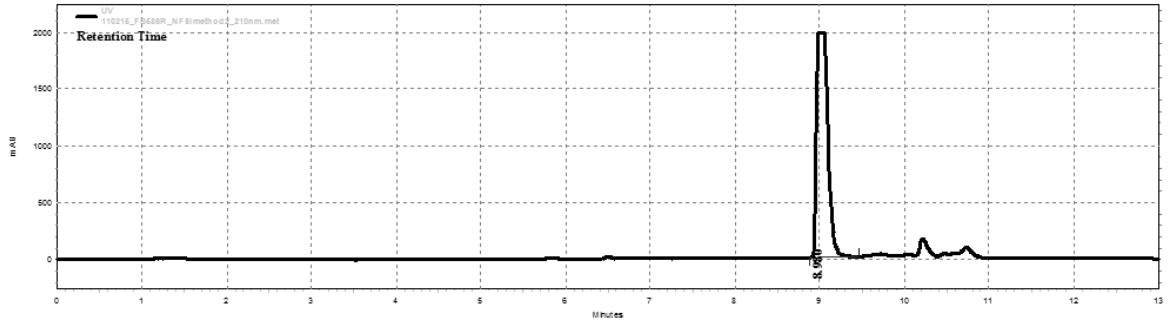
UV (spiked with racemic reference)



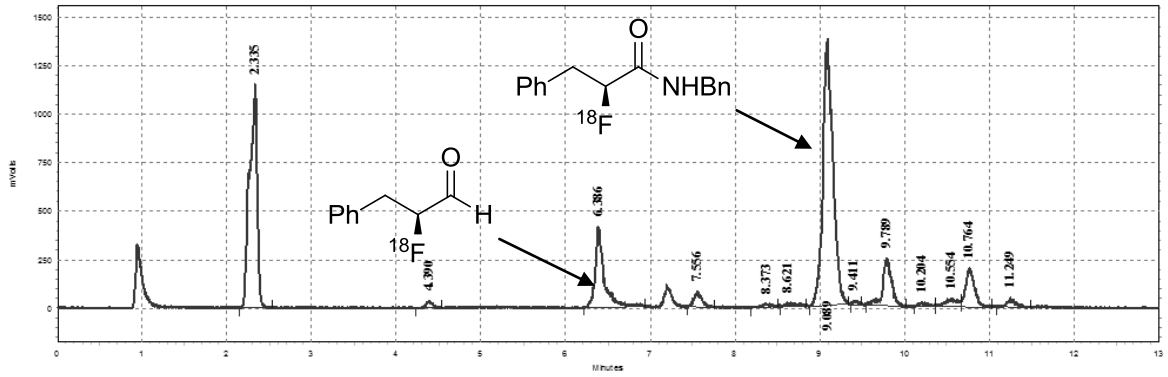
(*S*)-[^{18}F]*N*-Benzyl-2-fluoro-3-phenylpropanamide (*S*)-[^{18}F]13a

Analytical

UV of reference compound



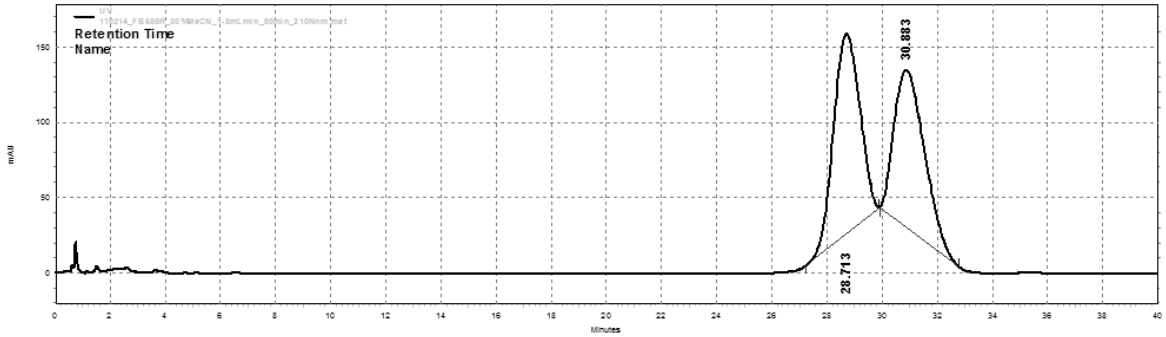
Radio-HPLC (Crude reaction)



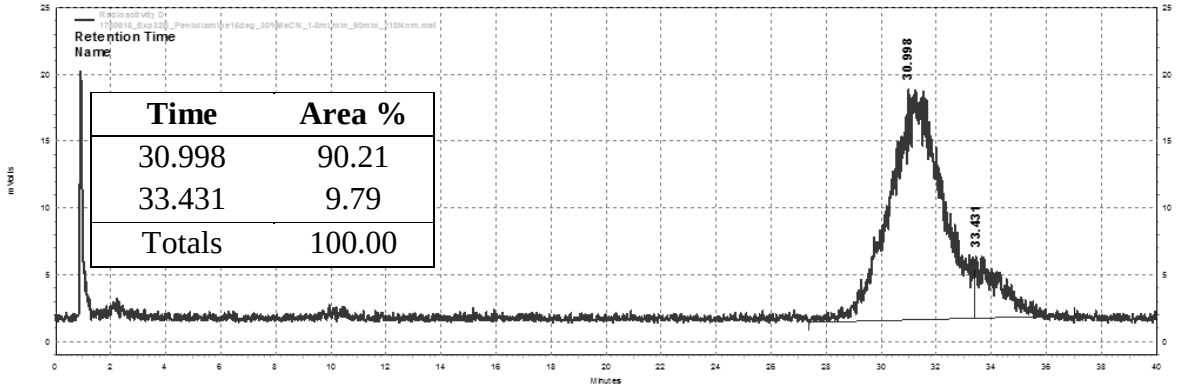
(*S*)-[^{18}F]*N*-Benzyl-2-fluoro-3-phenylpropanamide (*S*)-[^{18}F]13a (cont.)

Chiral

UV of reference compound

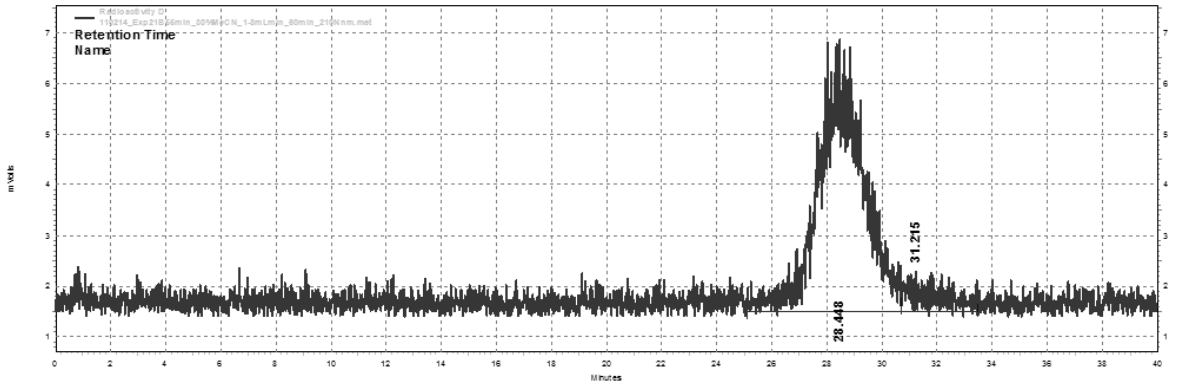


Reaction 1 Radio-HPLC



Time	Area %
30.998	90.21
33.431	9.79
Totals	100.00

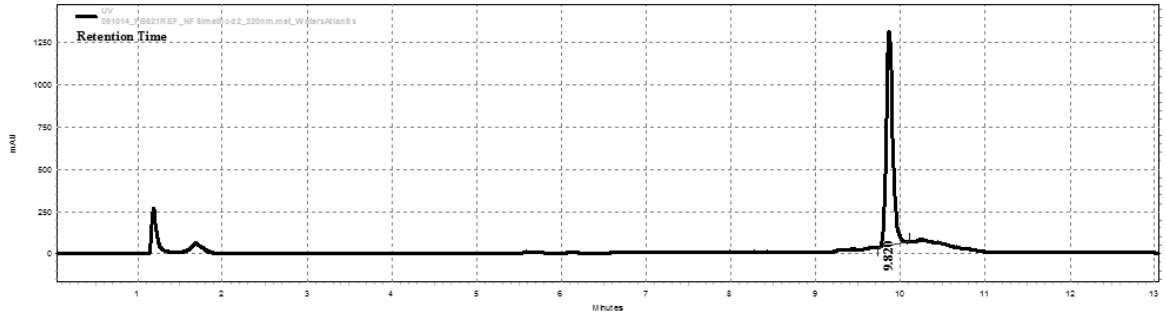
Reaction 2 Radio-HPLC



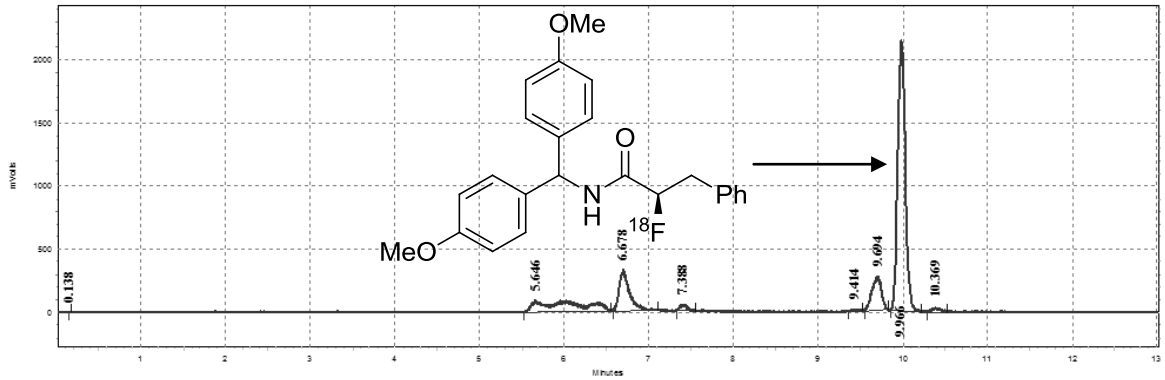
(*S*)-[^{18}F]*N*-(bis(4-Methoxyphenyl)methyl)-2-fluoro-3-phenylpropanamide (*S*)-[^{18}F]19a

Analytical

UV of reference compound



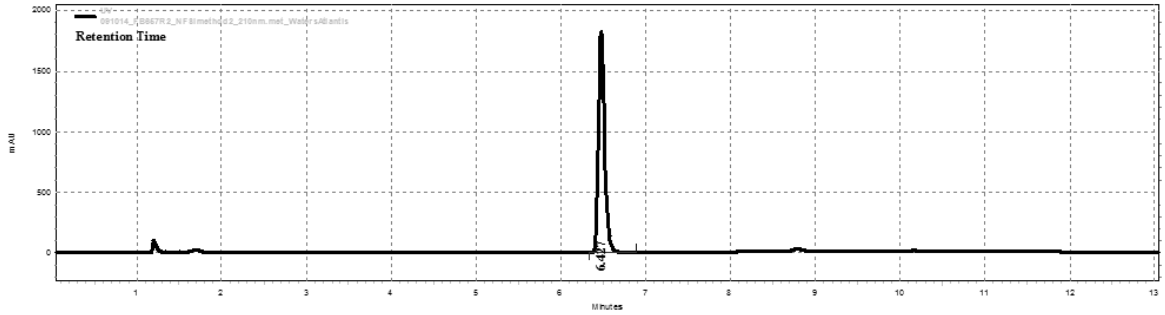
Radio-HPLC (Crude reaction)



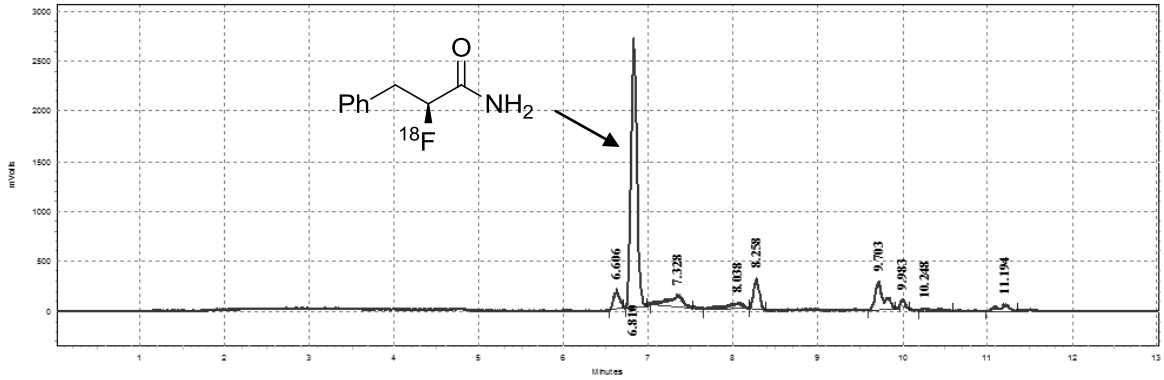
(*S*)-2-[^{18}F]Fluoro-3-phenylpropanamide (*S*)-[^{18}F]14a

Analytical

UV of reference compound

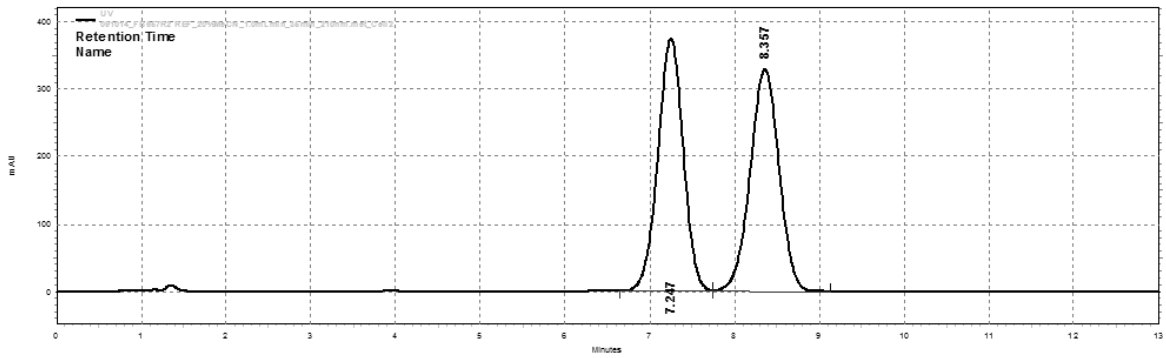


Radio-HPLC (Crude reaction mixture)

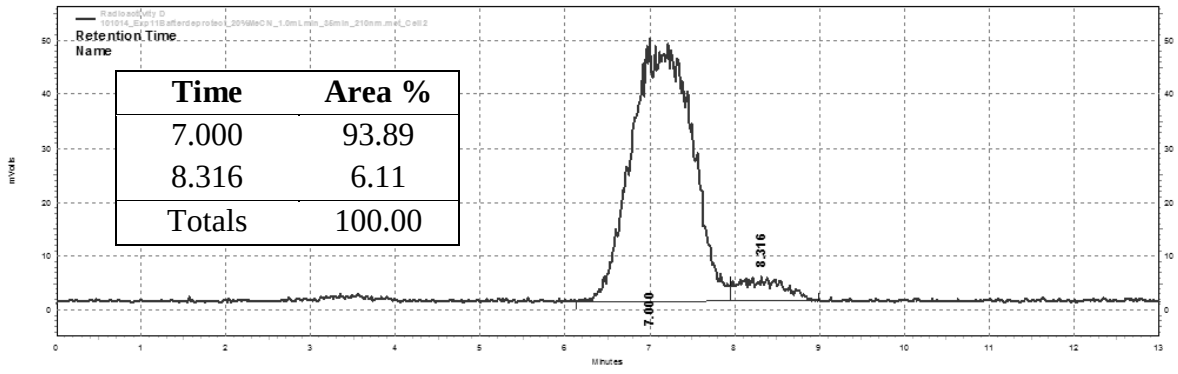


Chiral

UV of reference compound



Radio-HPLC

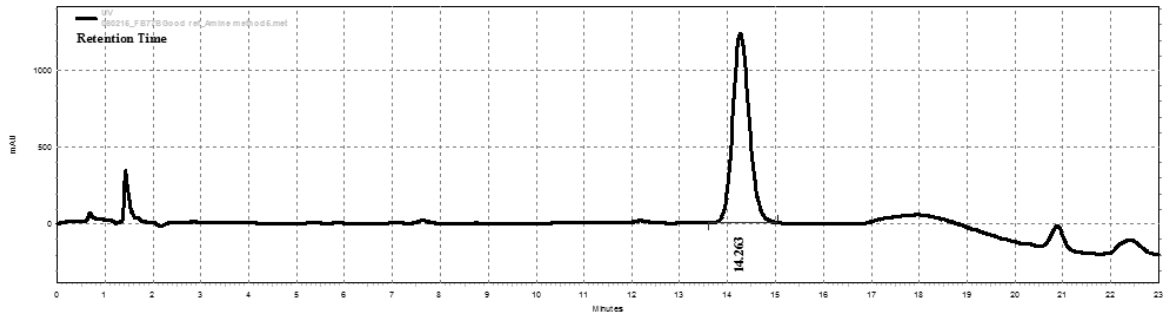


Time	Area %
7.000	93.89
8.316	6.11
Totals	100.00

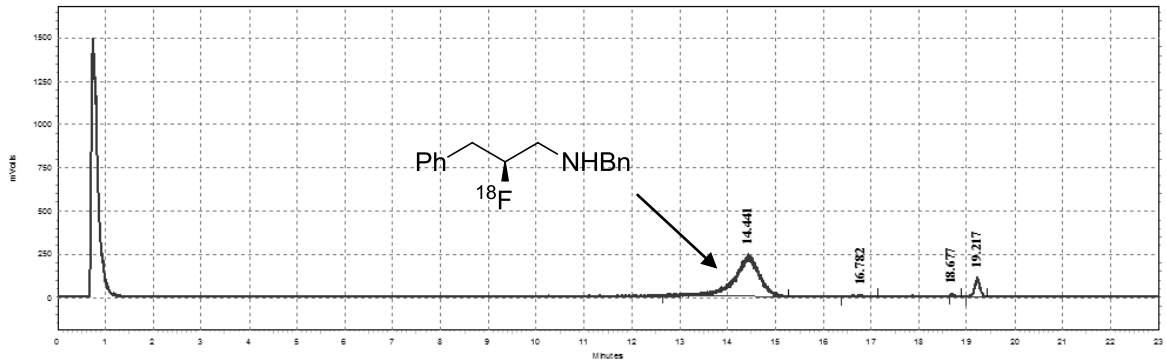
(*S*)-[^{18}F]*N*-benzyl-2-fluoro-3-phenylpropan-1-amine (*S*)-[^{18}F]20a

Analytical

UV of reference compound

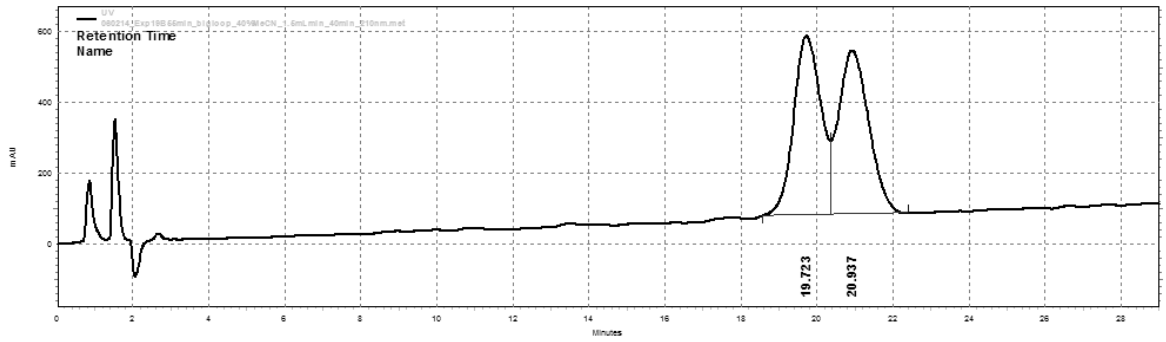


Radio-HPLC (Crude reaction)

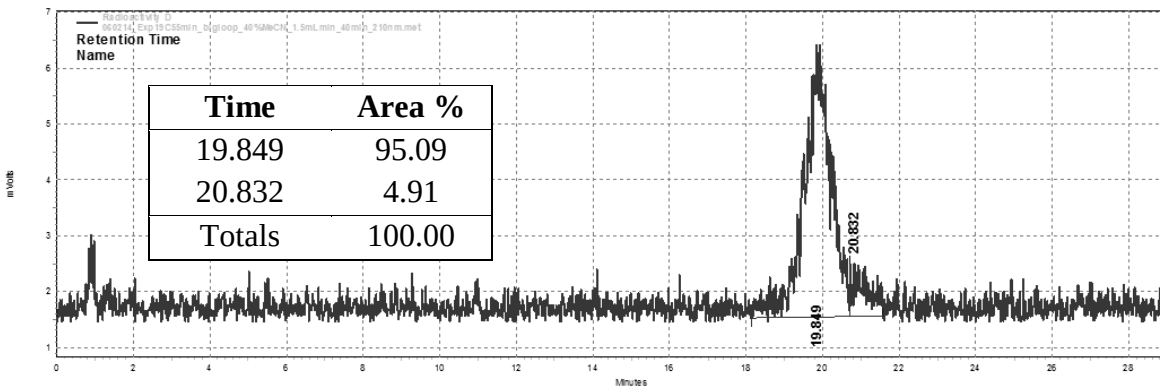


Chiral

UV of reference compound



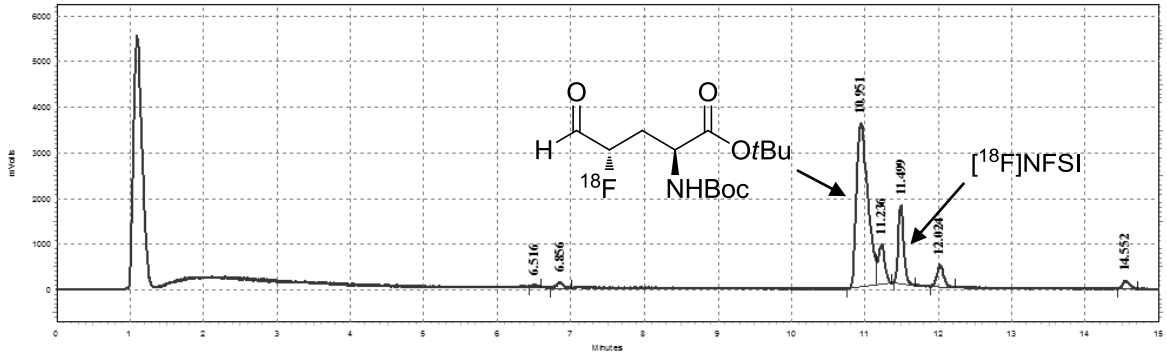
Radio-HPLC



Time	Area %
19.849	95.09
20.832	4.91
Totals	100.00

(2*S*,4*S*)-[^{18}F]*tert*-Butyl 2-(bis-*N*-(tert-butoxycarbonyl))-4-fluoro-5-oxopentanoate (2*S*,4*S*)-[^{18}F]29

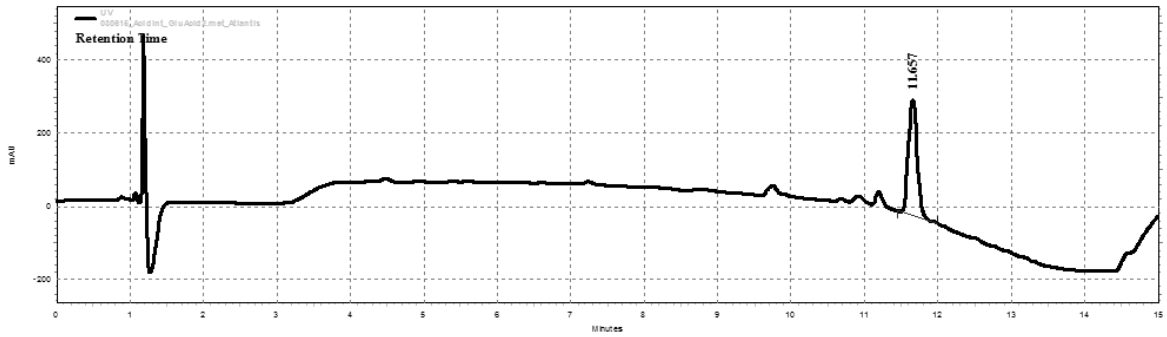
Analytical



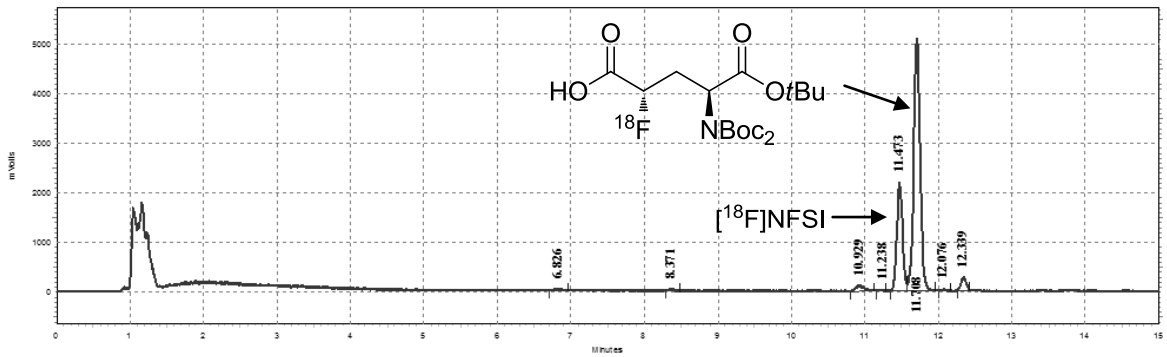
(2*S*,4*S*)-[^{18}F]5-(*tert*-Butoxy)-4-(bis-*N*-(*tert*-butoxycarbonyl))-2-fluoro-5-oxopentanoic acid (2*S*,4*S*)-[^{18}F]31

Analytical

UV of reference compound



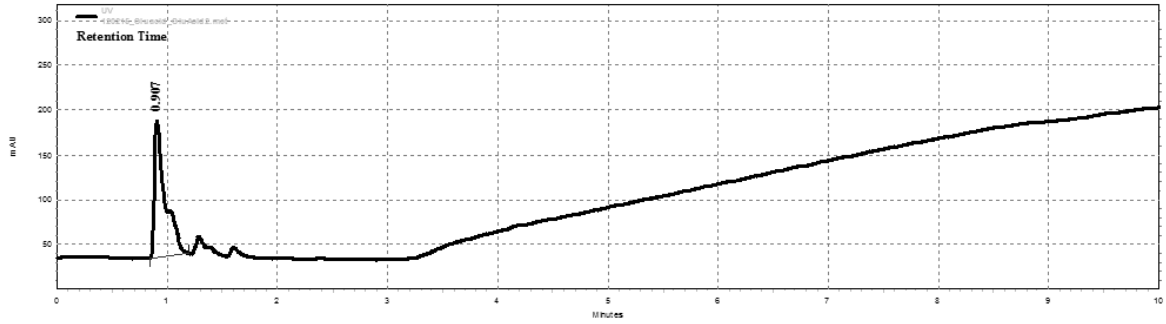
Radio-HPLC (Crude reaction)



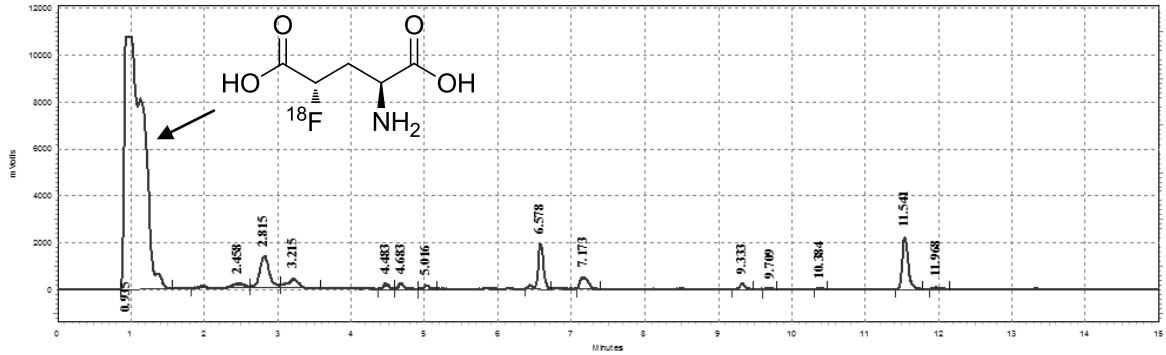
(2*S*,4*S*)-4-[^{18}F]Fluoroglutamic acid (2*S*,4*S*)-[^{18}F]21

Analytical

UV of reference compound

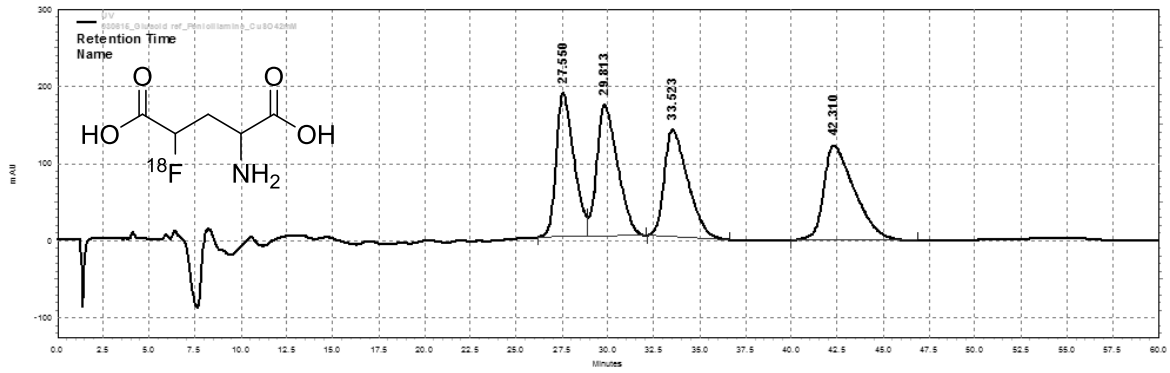


Radio-HPLC (Crude reaction)

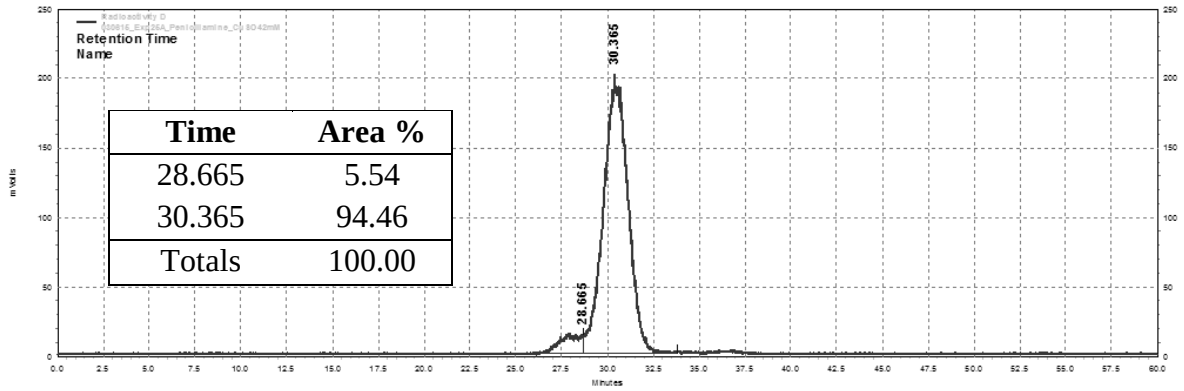


Chiral

UV of reference compound (all 4 diastereomers)



Radio-HPLC



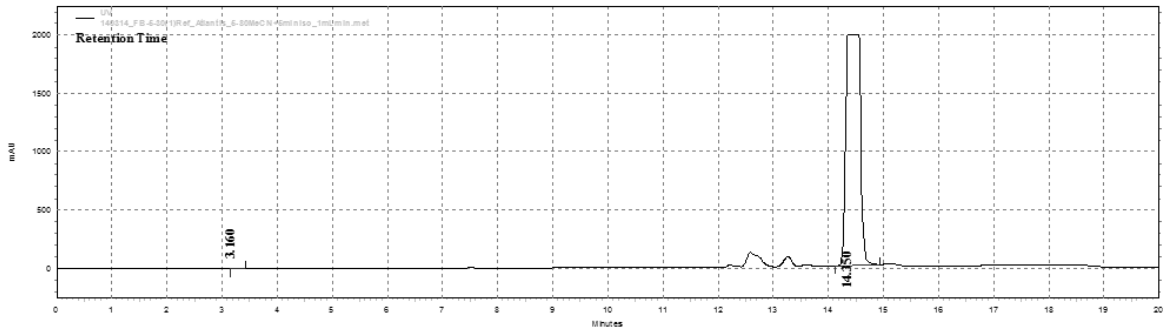
Time	Area %
28.665	5.54
30.365	94.46
Totals	100.00

4.4.1.2 Phase Transfer Reagents for Asymmetric [^{18}F]Fluorination

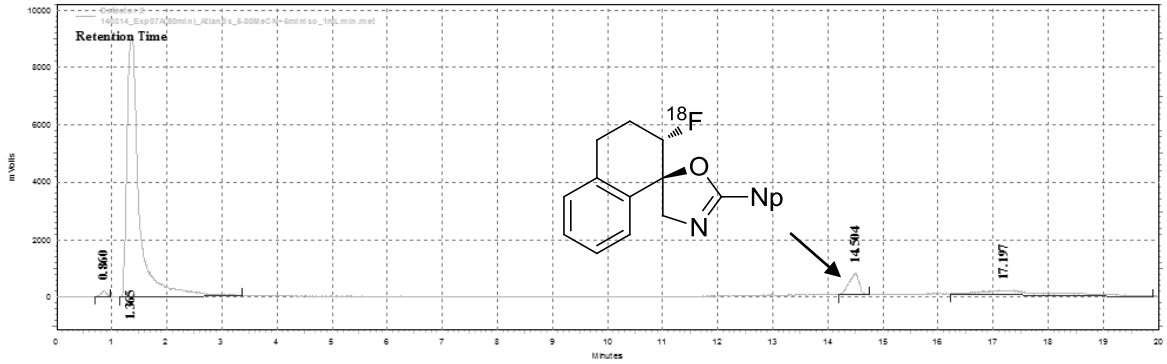
(1*R*,2*S*)-2-[^{18}F]Fluoro-2'-(naphthalen-2-yl)-3,4-dihydro-2*H*,4'*H*-spiro[naphthalene-1,5'-oxazole] (1*R*,2*S*)-[^{18}F]33

Analytical

UV of reference compound

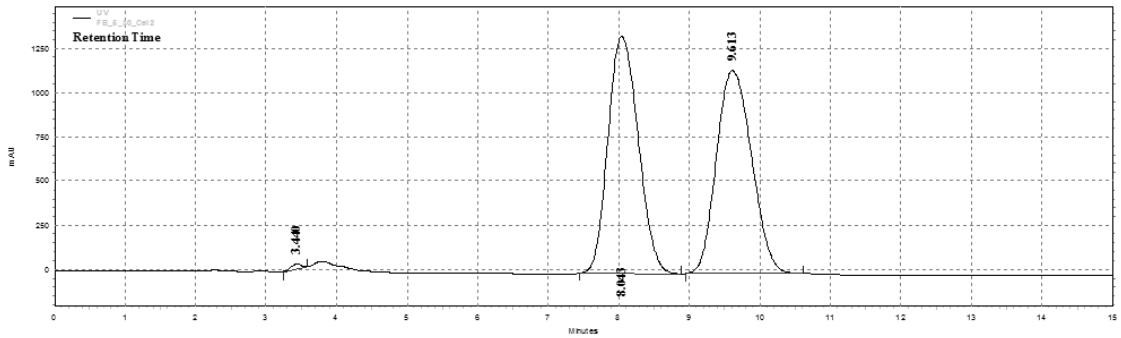


Radio-HPLC (Crude reaction mixture)

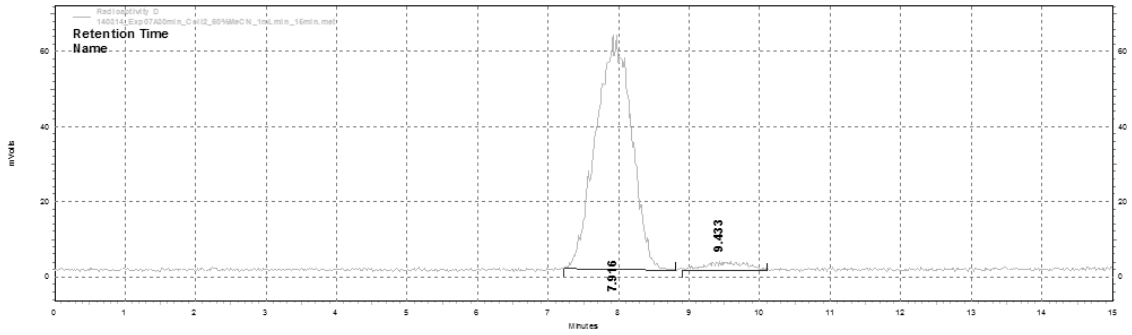


Chiral

UV of reference compound



Radio-HPLC

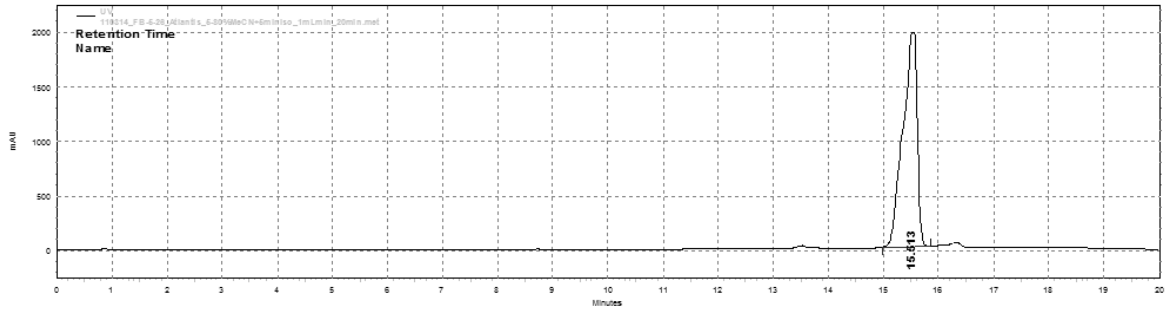


4.4.1.3 Fluorocyclisation with Chiral [^{18}F]Selectfluor bis-triflate

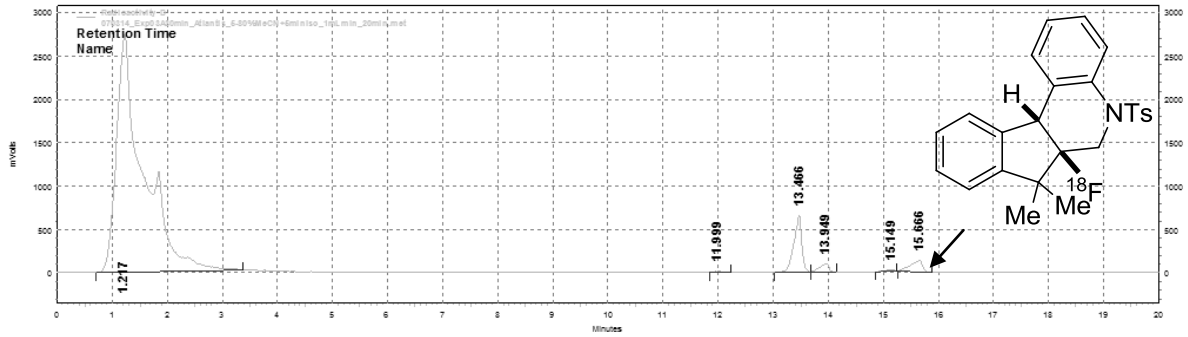
(6a*R*,11b*R*)-6a-[^{18}F]Fluoro-7,7-dimethyl-5-tosyl-6,6a,7,11b-tetrahydro-5H-indeno[2,1-c]quinoline (6a*R*,11b*R*)-[^{18}F]53

Analytical

UV of reference compound

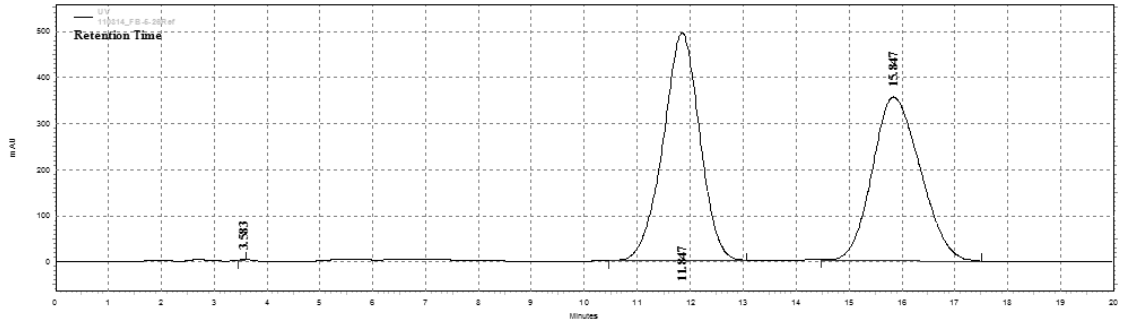


Radio-HPLC (Crude reaction)

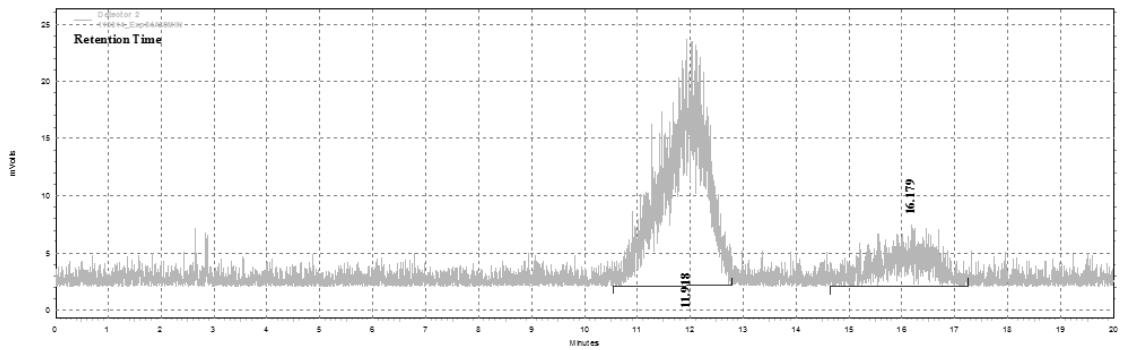


Chiral

UV of reference compound



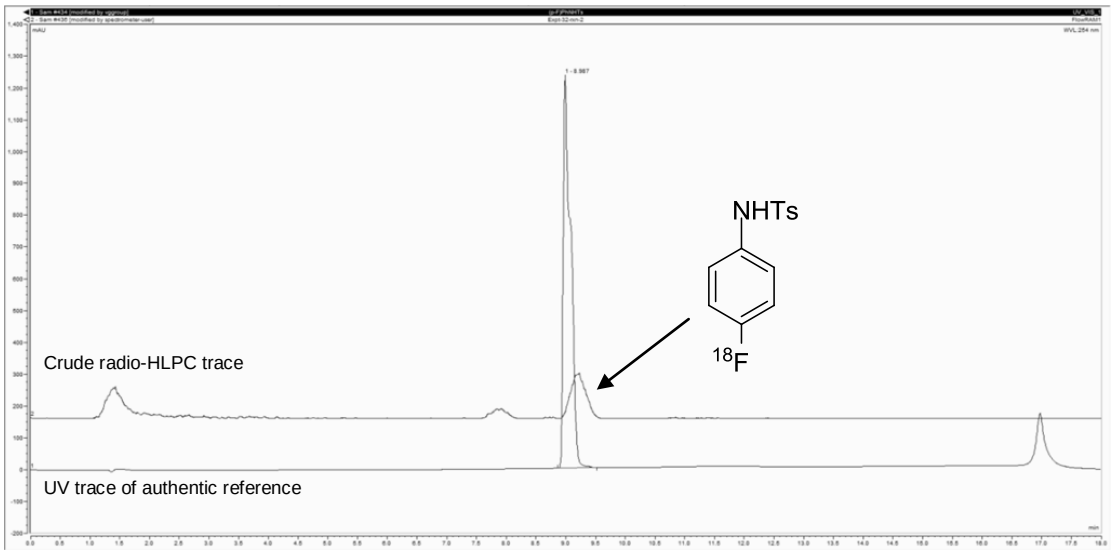
Radio-HPLC



4.4.2 Chapter 3: Hypervalent Iodine-Mediated Oxidative Fluorination of *N*-Arylsulfonamides

_N_-(4-[^{18}F]Fluorophenyl)-4-methylbenzenesulfonamide [^{18}F]70a

Analytical



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