^{18}F-Labelling of New Chemotypes for Drug Discovery

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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. All the work is my own, except where otherwise stated, and has not been submitted for any other degree at this or any other university.

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I am indebted to the Royal Thai Government and SCI for providing me with the financial support to undertake my D.Phil.

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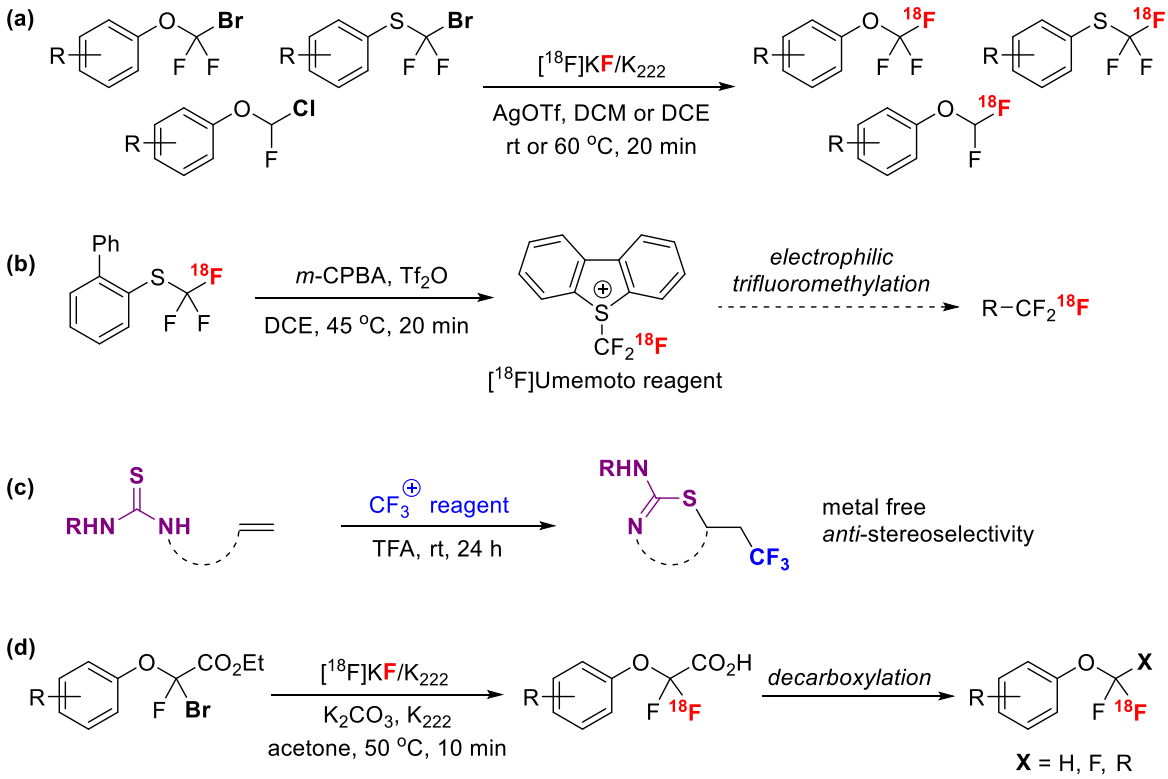
Summary: ^{18}F-Labelling of New Chemotypes for Drug Discovery

In this thesis, the ^{18}F-labelling of new "chemotypes" will be described with the aim of application in pharmaceutically interesting targets. In **Chapter 1**, a general introduction to the effect of fluorine substituents on molecular properties and reactivity is provided. This includes the application of organofluorine in both medicinal chemistry and positron emission tomography. **Chapter 2** describes a novel silver-mediated ^{18}F-labelling of Ar-SCF_3, Ar-OCF_3 and Ar-OCF_2H, including [^{18}F]Riluzole, the ^{18}F-labelled version of a drug for treatment of amyotrophic lateral sclerosis (ALS). This work demonstrates that AgOTf can induce halogen exchange nucleophilic ^{18}F-fluorination under mild reaction conditions with a wide range of substrates (Scheme Aa).[i] In addition, the ^{18}F-labelled Ar-SCF_3 substrate is further transformed into the [^{18}F]Umemoto reagent in a single step (Scheme Ab).



Scheme A (a) Silver-mediated ^{18}F-labelling of Ar-SCF_3, Ar-OCF_3 and Ar-OCF_2H; (b) Synthesis of [^{18}F]Umemoto reagent; (c) Trifluoromethylation-thiocyclisation of alkenes with electrophilic CF_3 reagents; (d) ^{18}F-Radiosynthesis of α-fluorinated aryl ethers.

The Umemoto reagent has been extensively used for electrophilic trifluoromethylation of various functional groups. Therefore the labelling of this reagent could potentially expand the radiochemical space available for PET applications. To augment the utility of this reagent, we developed a late-stage stereoselective trifluoromethylation-thiocyclisation of alkenes using electrophilic trifluoromethylating reagents such as Umemoto reagent or Togni reagent (Scheme Ac), which will be discussed in **Chapter 3**.[ii] In this process, thiourea acts as both S-nucleophile and CF_3 radical initiator; therefore no metal or photoredox catalyst is required. The reaction affords novel trifluoromethylated 2-amino-thiazolines and 2-amino-thiazines, important scaffolds in the development of aspartate beta-secretase enzyme (BACE–1) inhibitors, a therapeutic target for Alzheimer's disease.

Chapter 4 investigates the ^{18}F-labelling of α,α-difluoro-α-aryloxyacetic acid, a class of substrate that can serve as a versatile intermediate which can undergo various decarboxylative functionalisation reactions to afford a wide range of novel ^{18}F-labelled α-fluorinated aryl ethers (Scheme Ad).[iii] Finally, **Chapter 5** gives full experimental procedures and characterisation data for all compounds.

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Abbreviations and Acronyms

18-crown-6	1,4,7,10,13,16-hexaoxacyclo-octadecane
δ	chemical shift (ppm); partial charge
Δ	heat
Λ	wavelength
π	hydrophobicity constant
ν	wavenumbers (cm^{-1})
χ_P	Pauling electronegativity
Å	Angström (10^{-10} m)
aq.	aqueous
Ar	aryl
Asp	aspartic acid
Boc	*tert*-butyloxycarbonyl
bpy	2,2'-bipyridine
Bq	Becquerel
br	broad
BrettPhos	2-(dicyclohexyl-phosphino)-3,6-dimethoxy-2′,4′,6′-triisopropyl-1,1′biphenyl
°C	degrees Celcius
cal	calories
cat.	catalytic/catalyst
CHD	cyclohexadiene
CI	chemical ionisation
COD	1,5-cyclooctadiene
Cy	cyclohexyl
conc.	concentrated
"cold"	non-radioactive
DABCO	1,4-diazabicyclo[2.2.2]octane
DAST	diethylaminosulfur trifluoride
dba	dibenzylideneacetone
DBH	1,3-dibromo-5,5-dimethylhydantoin
DBN	1,5-diazabicyclo[4.3.0]non-5-ene
DBU	1,8-diazabicycloundec-7-ene
dc	decay corrected
DCC	*N*,*N*'-dicyclohexylcarbodiimide
DCE	1,2-dichloroethane
DCM	dichloromethane
DIPEA	*N*,*N*-diisopropylethylamine
DFT	density functional theory
DMA	*N*,*N*-dimethylacetamide
DMAP	4-dimethylaminopyridine
DMF	*N*,*N*-dimethylformamide

DMI	1,3-dimethyl-2-imidazolidinone
DMSO	dimethylsulfoxide
DMTMM	4-(4,6-dimethoxy[1,3,5] triazin-2-yl)-4-methylmorpholinium chloride
DNB	dinitrobenzene
dppf	1,1′-bis(diphenylphosphino)ferrocene
DPTU	diphenylthiourea
d.r.	diastereomeric ratio
ED_{50}	median effective dose
ee	enantiomeric excess
EI	electrospray ionization
E_{pa}	peak potential for the anodic sweep
EPR	electron paramagnetic resonance
eq.	equivalents
er	enantiomeric ratio
ESI	electrospray ionisation
Et	ethyl
eV	electron Volt
eyosin Y	2-(2,4,5,7-tetrabromo-6-oxido-3-oxo-3H-xanthen-9-yl)benzoate
F	bioavailability
FDG	2-deoxy-2-fluoro-D-glucose
FI	field ionisation
FMISO	fluoromisonidazole
g	gram(s)
gem-	germinal
h	hour(s)
halex	halogen exchange
HATU	*O*-(7-azabenzotriazol-1-yl)-1,1,3,3-tetra-methyluronium hexafluorophosphate
HBTU	*O*-(benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
Het	heterocycle
HMDS	hexamethyldisilazane
HMPA	hexamethylphosphoramide
HOMO	highest occupied molecular orbital
“hot”	radioactive
HPLC	high performance liquid chromatography
HRMS	high-resolution mass spectroscopy
Hz	Hertz
hν	light energy
i-Pr	*iso*-propyl
IC_{50}	half maximal inhibitory concentration
IR	infrared spectroscopy
J	scalar coupling constant
K_{222}	Kryptofix 2.2.2; 4,7,13,16,21,24-hexaoxa-1,10-diaza-bicyclo[8.8.8]-hexacosane

L	ligand; litre(s)
LA	Lewis acid
LDA	lithium diisopropylamide
LG	leaving group
LHMDS	lithium bis(trimethylsilyl)amide
Log D	distribution coefficient
LUMO	lowest unoccupied molecular orbital
M	moles per cubic decimetre ($moldm^{-3}$)
MB	methylene blue; 3,7-bis(dimethylamino)phenazathionium chloride
m-CPBA	*meta*-chloroperoxy-benzoic acid
Me	methyl
MeCN	acetonitrile (CH_3CN)
Mes	mesityl; 2,4,6-trimethylphenyl
Min	minute(s)
Mol	mole(s)
Mp	melting point
n	number of runs
NBS	*N*-bromosuccinimide
n-Bu	*normal*-butyl
NCS	*N*-chlorosuccinimide
nd	not determined
ndc	non-decay corrected
NFSI	*N*-fluorobenzenesulfonimide
NHC	*N*-heterocyclic carbine
NMM	*N*-methylmorpholine
NMP	*N*-methyl-2-pyrrolidone
NMR	nuclear magnetic resonance
NOE	nuclear overhauser effect
Ns	Nosyl; 4-nitrobenzenesulfonyl
Nu	nucleophile
[O]	oxidant; oxidation
OAc	acetate
OTf	triflate, trifluoromethanesulfonate
P	partition coefficient
PET	positron emission tomography; petroleum ether
Ph	phenyl
phen	1,10-phenanthroline
pico	picolinate
PIDA	(diacetoxyiodo)benzene
pin	pinacol ester
pK_a	acid dissociation constant
ppm	parts per million
py	pyridine

quant.	Quantitative
R	alkyl group
RCC	radiochemical conversion
RCP	radiochemical purity
RCY	radiochemical yield
RDS	rate-determining step
R_f	retention value
rose bengal	4,5,6,7-tetrachloro-2',4',5',7'-tetraiodofluorescein
rt	room temperature
salen	*N*,*N*'-ethylenebis(salicylimine)
SA	specific activity
sat.	saturated
SCE	saturated calomel electrode
Selectfluor	1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate)
SET	single electron transfer
SM	starting material
S_N1	unimolecular nucleophilic substitution
S_N2	bimolecular nucleophilic substitution
TAS	tris(dimethylamino)sulfonium
TBAF	tetrabutylammonium fluoride
TBAT	tetrabutylammonium difluorotriphenylsilicate
t-Bu	*tert*-butyl
TC	thiophene-2-carboxylate
TEAF	tetraethylammonium fluoride
temp.	temperature
TEMPO	2,2,6,6-tetramethylpiperidine 1-oxyl
tert	tertiary
Tf_2O	trifluoromethanesulfonic anhydride
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMEDA	*N*,*N*,*N*',*N*'-tetramethyl-1,2-ethylenediamine
TMP	2,2,6,6-tetramethylpiperidine
TMS	tetramethylsilyl
Togni I	3,3-dimethyl-1-(trifluoromethyl)-1,2-benziodoxole
Togni II	1-trifluoromethyl-1,2-benziodoxol-3(1H)-one
TRPV1	transient receptor potential cation channel subfamily V member 1
Umemoto	5-dibenzothiophenium trifluoromethanesulfonate
UV	ultraviolet
V	Volt
W	Watt
X	halogen

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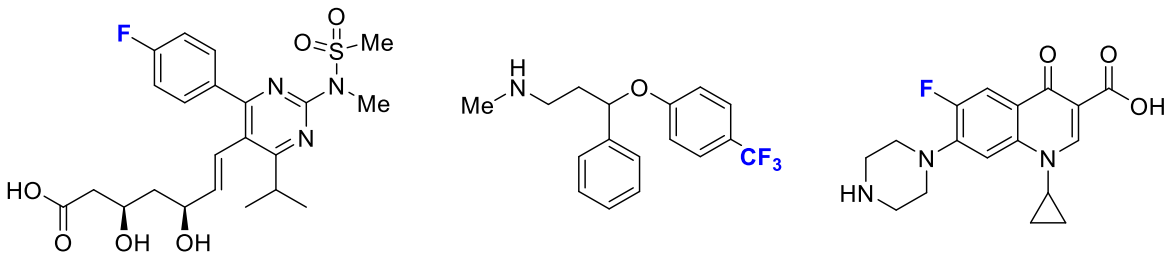
Chapter 1: Introduction

1.1 Organofluorine Chemistry for Drug Discovery

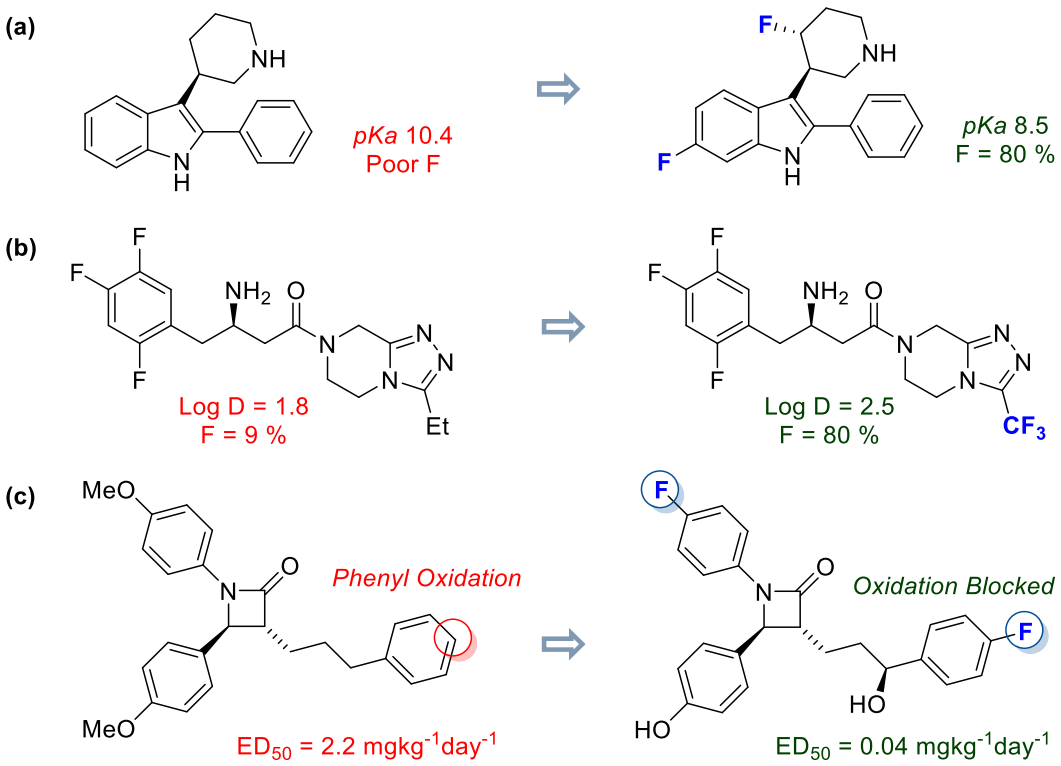
Organofluorine compounds have a wide range of applications in pharmaceutical,[1] agrochemical[2] and material sciences.[3] Approximately 30 % of agrochemicals and 20 % of pharmaceuticals contain fluorine, including a range of top-selling drugs such as the cholesterol-lowering drug rosuvastatin (Crestor),[4] the antidepressant fluoxetine (Prozac)[5] and the antibacterial ciprofloxacin (Ciprobay)[6] (Scheme 1.1). Despite the relatively high abundance of fluoride in the Earth's crust,[7] organic molecules containing C–F bond are extremely rare in nature.[8] Therefore, development of efficient and versatile synthetic methods for fluorination and perfluoroalkylation is highly in demand.



Scheme 1.1 Examples of fluorine-containing top-selling drugs.

The introduction of a fluorine substituent in a key position of biologically active molecules can lead to profound physicochemical and biological effects. Due to the small size of the fluorine atom (van der Waals radius = 1.47 Å), it has been demonstrated that replacing hydrogen with fluorine atom exerts only a minor steric demand at receptor sites.[9] Fluorine possesses the highest electronegativity of all elements (χ_P = 4);[10] consequently, the pK_a of its neighbouring ionisable functional groups can be dramatically altered,[11] which can greatly affect the pharmacokinetic properties and binding affinities of drug molecules.[12] This effect was exemplified in the development of 3-piperidinylindole antipsychotic drugs

(Scheme 1.2a). It was demonstrated that the amine group in the fluorinated analogue has lower basicity which in turn improved the bioavailability of the molecule and reduced undesirable side-effects, such as delusions and hallucinations.[13]



Scheme 1.2 Examples of fluorine substituents in drug discovery.
(F = bioavailability, Log D = distribution coefficient, ED_{50} = median effective dose)

Another recurring challenge in drug development is to achieve the optimum lipophilicity of drug molecules to effectively pass through a cell membrane without being trapped in it or becoming too insoluble in aqueous media.[14] Fluorine substitutions can modulate lipophilicity of drug molecules, for instance, fluorination or trifluoromethylation of saturated alkyl groups typically decreases lipophilicity, whereas aromatic fluorination or perfluoroalkylation increases lipophilicity due to the non-polarisability of the C–F bond.[15] In the development of sitagliptin (Junavia), a drug for treatment of type II diabetes mellitus, it was illustrated that replacement of an ethyl moiety with trifluoromethyl group led to an increase in distribution coefficient (log D) and a substantial improvement in bioavailability (Scheme 1.2b).[16]

Another common problem in drug development is the low metabolic stability of drug molecules due to oxidative metabolism which is typically mediated by a liver enzyme (P450 cytochrome monooxygenase).[17] This process can be circumvented by substitution of fluorine at the metabolically labile sites. The exceptionally high C–F bond strength (homolytic bond dissociation enthalpy = 441 kJ/mol)[18] prevents such metabolic process, thereby enhancing the half-life of a drug *in vivo* and allowing for the administration of smaller doses. This strategy was utilised in the development of various pharmaceuticals including the cholesterol inhibitor ezetimibe (Scheme 1.2c).[19] Moreover, fluorine substitution can alter molecular conformations as a result of stereoelectronic effects[20] and can also contribute to binding affinity in enzyme's active site *via* hydrogen bonding and dipole interactions.[21] These examples demonstrate the utility of organofluorine compounds in medicinal chemistry and drug development.

1.2 Positron Emission Tomography (PET)

Positron Emission Tomography (PET) is a non-invasive molecular imaging technique which can selectively probe *in vivo* metabolic processes at a functional level.[22] PET imaging requires the introduction of radioactive tracers, molecules containing radioactive isotopes, into the body. These isotopes then undergo β^+ decay with the emission of a positron, which is annihilated *in vivo* with a proximal electron, emitting two gamma rays (photons) of 511 keV energy at 180^o to each other. The exact location where the annihilation event was taken place can be determined by detecting the pair of coincident photons which move in opposite directions by a ring of highly sensitive photon detectors which are placed around the subject. When a large number of data is obtained, a 2D or 3D image which shows the distribution of the radiotracer throughout the tissue can be generated using mathematical modelling.[23]

The major clinical application of PET imaging is the *in vivo* diagnosis of cancer.[24] The most widely used radiotracer for clinical oncology is [^{18}F]fluorodeoxyglucose ([^{18}F]FDG), an analogue of glucose which can be rapidly taken up and trapped by cancer cells.[25] Combining with macroscopic structural imaging techniques such as nuclear magnetic resonance imaging (MRI) or computed tomography (CT), PET imaging can precisely identify the location of tumours and their environment (hypoxia, neo-angiogenesis), hence allowing clinicians to select the most suitable treatment for an individual patient.[26] In neurology, PET has been used for detection of early stage neurological disorders (such as Alzheimer's and Parkinson's disease) and the evaluation of psychiatric disorders.[27] In addition, the diagnosis of some cardiovascular diseases; in particular, coronary artery disease (CAD) can benefit from this technology.[28]

PET imaging technology has also been used to facilitate drug discovery process.[29] Absolute concentrations of radiolabelled compounds can be precisely and non-invasively measured on living subjects, providing valuable data on pharmacokinetics and pharmacodynamics of drug candidates, as well as information on safety, efficacy and potential drug-drug interactions. The availability of such information during the preclinical stage can help researchers eliminate drug candidates with unfavourable properties early in the drug discovery pipeline. This process can save time and prevent unnecessary cost when those candidates enter into more expensive phase I/II clinical trials.

1.3 Fluorine-18 for PET Imaging

^{18}F is one of the most commonly employed radionuclides due to several advantages over alternative non-metallic radioisotopes such as ^{11}C, ^{13}N and ^{15}O (Table 1.1).[30] ^{18}F undergoes a clean decay process consisting of 97 % positron emission and only 3 % electron capture, yielding stable ^{18}O. The positron emitted from the decay of ^{18}F has moderately low energy

with the maximum of 0.63 MeV, which corresponds to the maximum positron linear range in tissue of 2.4 mm, resulting in the highest resolution in PET imaging.[31] In addition, the relatively long half-life of ^{18}F (109.8 minutes) allows for multi-step synthetic approaches and also the transport to satellite PET units that do not have on-site cyclotron facility.

Radioisotope	**Half Life (min)**	**Decay Product**	**Maximum β^+ Energy (keV)**
^{11}C	20.4	^{11}B	960
^{13}N	10.0	^{13}C	1190
^{15}O	2.0	^{15}N	1720
^{18}F	109.8	^{18}O	635

Table 1.1 Properties of commonly used PET radioisotopes.

In order to access ^{18}F-labelled radiotracers, the ^{18}F-radioisotope must be initially generated by a cyclotron. Proton irradiation of [^{18}O]H_2O (85 - 99 % enriched) in a metal target can generate [^{18}F]F^- *via* the $^{18}O(p,n)^{18}F$ nuclear reaction.[32] Alternatively, gaseous [^{18}F]F_2 is generated by proton irradiation of [^{18}O]O_2 in a nickel or aluminium target,[33] or by deuteron bombardment of neon-20 in a nickel target *via* the $^{20}Ne(d,\alpha)^{18}F$ nuclear reaction.[34] The newly generated fluorine-18 is then flushed from the target using carrier $^{19}F_2$ gas, followed by second irradiation to stimulate isotope exchange to form [^{18}F]F_2.

The use of $^{19}F_2$ carrier gas is one of the major drawbacks in the production of [^{18}F]F_2 causing low specific activity (SA = 0.1 - 0.6 GBq/μmol)[35] compared to the "carrier-free" production of [^{18}F]F^- (SA = 1 - 5 TBq/μmol).[36] Specific activity (SA) is defined as the ratio of radioactivity per unit mass, which is a measure of the contamination of ^{18}F-labelled ("hot") compounds with its non-radioactive isotopic ("cold") compound.[37] The low specific activity of radiotracer would mean that higher injection dose is required, which potentially causes undesired pharmacological side effects. It could also lead to low uptake of ^{18}F-labelled

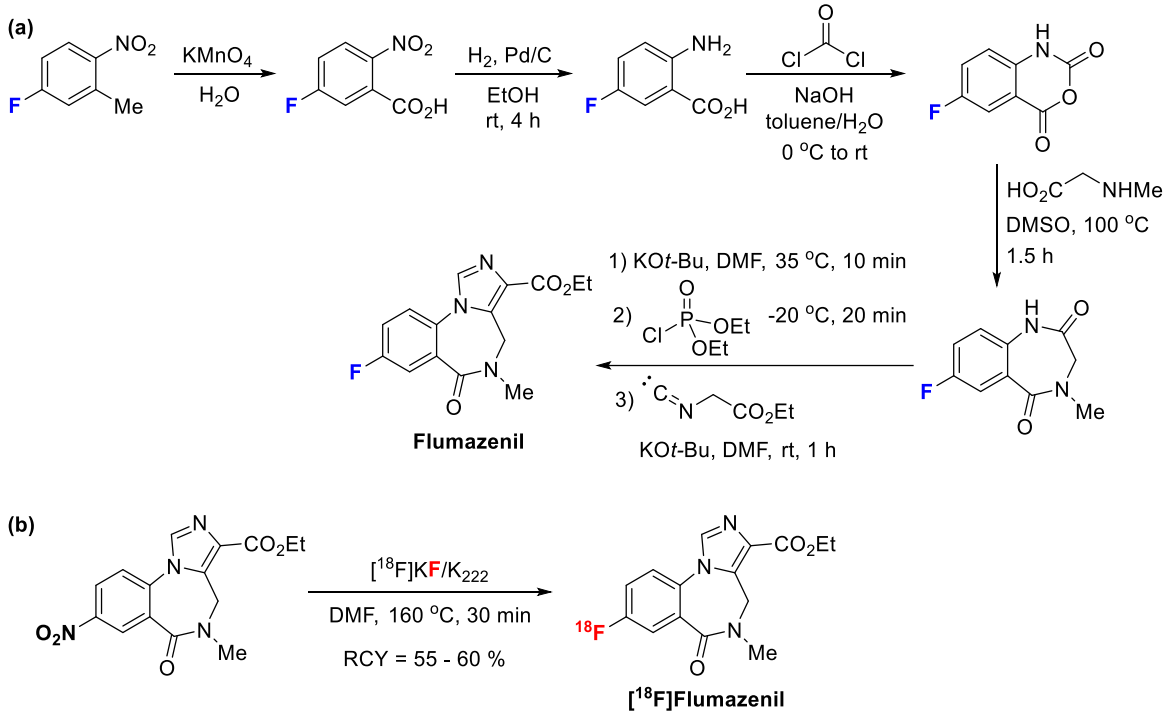
radiotracer caused by receptor saturation, which results in poor image quality due to low signal-to-noise ratio.[38] Another drawback of $[^{18}F]F_2$ lies in the fact that it is toxic and difficult to handle. The high reactivity of F_2 usually results in unselective reactions, yielding a mixture of ^{18}F-labelled products.

In contrast to the highly reactive fluorine gas, nucleophilic fluorination suffers from the low reactivity of $[^{18}F]F^-$. The $[^{18}F]F^-$ that is generated from the cyclotron is typically in a solution of $H_2{}^{18}O$ which leads to the reduction in the nucleophilicity due to solvation by water molecules[39] (solvation free energy = 439 kJ/mol).[40] The removal of $H_2{}^{18}O$ and metal impurities is performed by trapping the $[^{18}F]F^-$ on an ion-exchange cartridge, followed by eluting with a solution of a base such as potassium carbonate (K_2CO_3) and a chelator such as Kryptofix-2.2.2 (K_{222}) in a mixture of CH_3CN/H_2O. The eluted solution is then subjected to multiple cycles of azeotropic drying using anhydrous CH_3CN to remove residual traces of water, resulting in activated $[^{18}F]KF/K_{222}$ complex ready to be used for radiolabelling.

1.4 Late-Stage Functionalisation

Synthesis of radiolabelled compounds for PET imaging is a great challenge for synthetic chemists since the time delay between generation of a radionuclide in a cyclotron to administration to a patient is recommended to be within 2 or 3 half-lives in order to minimise decay.[22] Therefore, radioisotopes are often incorporated into the target molecules at a later stage in the synthetic sequence, preferably in the last step. Although many conventional fluorination reactions are well-established, these reactions usually require harsh reaction conditions which are not suitable for the application on complex molecules. As a result, the strategy implemented to synthesise fluorinated pharmaceuticals and agrochemicals on an industrial scale typically involves incorporation of fluorine substituents on simple substrates, which will then be used as building blocks for constructing more complex

molecules. For instance, the industrial production of Flumazenil, a selective benzodiazepine receptor antagonist used for the treatment of benzodiazepine overdose, described by F. Hoffmann-La Roche AG involves multi-step synthesis starting from 2-nitro-5-fluorotoluene as a fluorine-containing building block (Scheme 1.3a).[41]



Scheme 1.3 (a) Industrial production of Flumazenil; (b) Production of [^{18}F]Flumazenil.

In 1993, Pike *et al.* demonstrated that [^{11}C]Flumazenil can serve as a potent radioligand for PET studies of central benzodiazepine receptor (cBZR).[42] The modification of the conventional synthetic route was necessary in order to introduce the fluorine-18 in the last step. One of the methods for the production of [^{18}F]Flumazenil is *via* aromatic substitution reaction (S_NAr) from the corresponding nitro-precursor. Upon treating with [^{18}F]KF/K_{222} at 160 °C, the ^{18}F-labelled product was obtained in the range of 55 - 60 % radiochemical yields (RCY) (Scheme 1.3b).[43] However, the application on more complex radiotracers was not viable due to the use of high reaction temperature; as a result, a milder and more selective ^{18}F-labelling reaction is in great demand.

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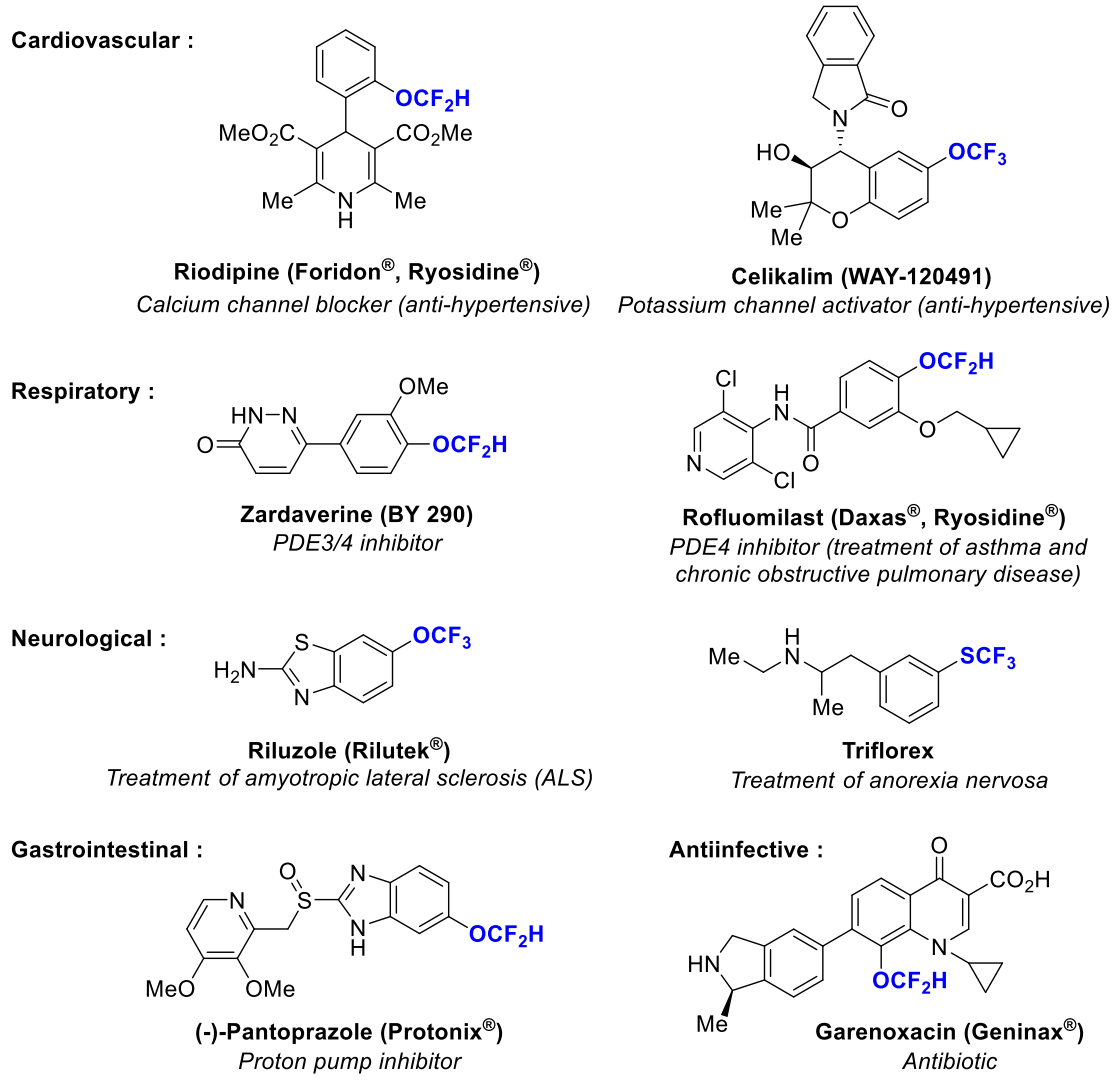
Chapter 2: ^{18}F-Labelling of Ar-SCF$_3$, -OCF$_3$ and -OCF$_2$H

The radiochemical reactions described in this chapter were carried out in collaboration with S. Verhoog (two people are required for operation of the radiochemical laboratory).[1]

2.1 Properties and Applications of Ar-SCF$_3$, -OCF$_3$ and -OCF$_2$H

The presence of fluorine in pharmaceuticals and agrochemicals is usually in the form of aromatic compounds containing fluorine atoms or trifluoromethyl groups. However, α-fluorinated ethers and thioethers have recently increased in popularity in these fields. Currently, Ar-SCF$_3$, -OCF$_3$ and -OCF$_2$H functionalities can be found in several marketed pharmaceuticals (Scheme 2.1).[2]



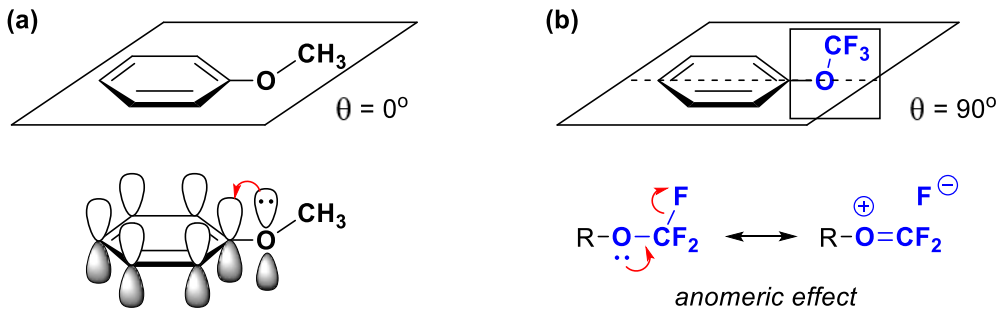
Scheme 2.1 Examples of drugs containing Ar-SCF$_3$, -OCF$_3$ and -OCF$_2$H functionalities.

As mentioned in Chapter 1, lipophilicity is an important parameter that governs the absorption and transport of drug molecules inside the body, hence directly affecting the bioavailability. Unlike a fluorine substituent that can either increase or decrease lipophilicity depending on its position on the molecule, the introduction of an *α*-fluorinated ether or thioether substituent invariably results in an increase of the lipophilicity.[3] This parameter can be measured as a partition coefficient (*P*), which is a ratio of concentrations of a compound in a mixture of two immiscible phases (most commonly *n*-octanol/water).[4] The effect of substituents on lipophilicity can be quantified as a hydrophobicity constant (π), which is a measure of a substituent's hydrophobicity relative to hydrogen [$\pi_x = \log(P_x/P_H)$];[5] (Table 2.1).[6] In comparison with the OCH_3 substituent, which has a minor effect on lipophilicity ($\pi = -0.02$), the OCF_3 group is much more lipophilic with $\pi = 1.04$. This value lies between CF_3 group ($\pi = 0.88$) and SCF_3 group ($\pi = 1.44$), therefore allowing researchers to fine-tune the structure to achieve the optimum lipophilicity of a drug molecule.

Substituent	**OCH_3**	**H**	**F**	**SCH_3**	**CF_3**	**OCF_3**	**SCF_3**	***i*-Pr**
π	–0.02	0.00	0.14	0.61	0.88	1.04	1.44	1.55

Table 2.1 Hydrophobicity parameters of various substituents on benzene.

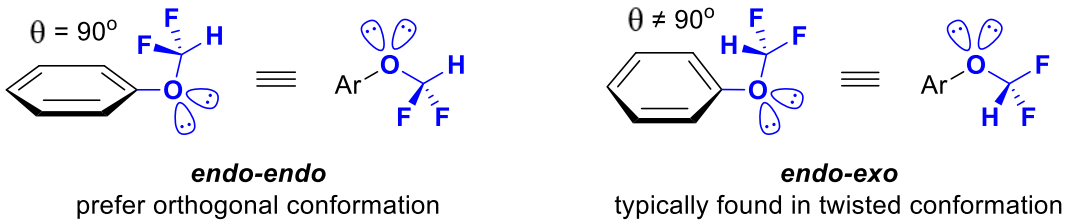
Furthermore, the introduction of *α*-fluorinated ethers and thioethers can induce unique conformational changes.[7] Aromatic compounds substituted with an anisotropic group such as OCH_3 or OCF_3 can adopt many different conformations upon rotation along the C–OR bond. The most stable conformer of Ar-OCH_3 is when the OCH_3 group lies in the plane of the aromatic ring, due to the conjugation between the p orbital of the sp^2-hybridised oxygen with the aromatic π system (Scheme 2.2a).[8] On the other hand, the OCF_3 group tends to lie out of the plane of the aromatic ring. The majority of the crystal structures of Ar-OCF_3 compounds reported in the Cambridge Structural Database adopt an orientation orthogonal to the aromatic plane, with the dihedral angle C=C–OCF_3 (θ) of around 90° (Scheme 2.2b).[9]



Scheme 2.2 Conformational preferences of the Ar-OCH$_3$ and -OCF$_3$.

In the case of Ar-OCF$_3$ compounds, the non-bonding electrons of the sp^3-hybridised oxygen atom can overlap with the antibonding orbitals of the C–F bonds leading to anomeric n_O - $\sigma^*_{C\text{-}F}$ conjugation with concomitant lengthening of the C–F bond and shortening of the C–O bond.[10] This effect also leads to a decrease in the electron density of the oxygen, hence disrupting the conjugation with the π system of the aromatic ring. As a result, the rotational barrier is significantly reduced allowing the OCF$_3$ group to rotate freely to adopt the conformation with minimised steric and electronic repulsion.[11] Such conformational flexibility can potentially result in higher binding efficiency of drug molecules in active sites. For example, the dihedral angle of the Ar-OCF$_3$ fragment of an inhibitor bound to serine protease trypsin is 81°.[12] Likewise, the SCF$_3$ group found in one crystal structure of Ar-SCF$_3$ also aligns perpendicularly to the aromatic ring (θ = 90°).[13]

Crystal structures of several Ar-OCF$_2$H compounds show no orientational preference with the dihedral angle ranging from 1° to 90°.[14] Rotation along O–CF$_2$H bond results in two additional conformers: *endo-endo* and *endo-exo* (scheme 2.3). In the *endo-endo* conformer, both C–F bonds are antiperiplanar to the oxygen lone pairs, leading to two anomeric effects resembling the OCF$_3$ group, which makes the orthogonal conformation more favourable. On the other hand, the *endo-exo* conformer has only one C–F bond in an anomeric position and typically adopted twisted conformation. This observation is confirmed by computational calculations revealing two equal energy minima at θ = 33° and 90°.



endo-endo
prefer orthogonal conformation

endo-exo
typically found in twisted conformation

Scheme 2.3 Conformational preferences of the Ar-OCF$_2$H (θ = dihedral angle of C=C–OCF$_2$H).

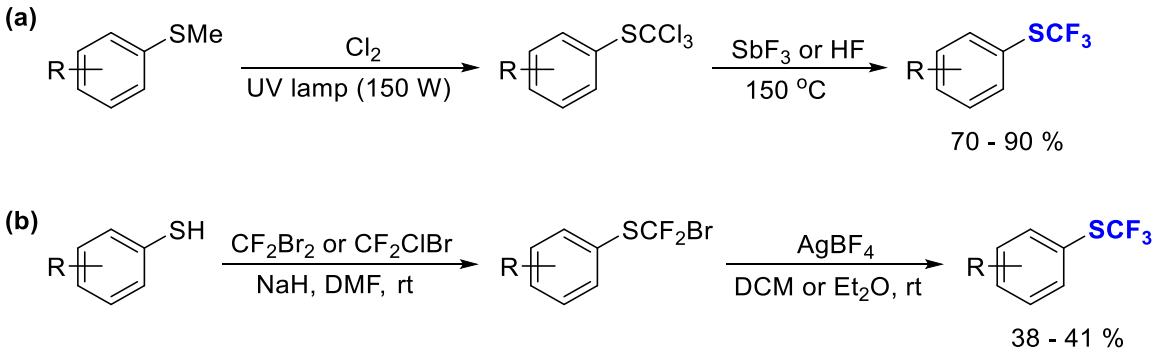
These two conformers affect orientational preferences and cause profound effects on the lipophilicity of the molecule. By using bond vector analysis, the *endo-endo* conformer is predicted be slightly more lipophilic than the OCF$_3$ group (ΔlogP ~ +0.1), whereas *endo-exo* conformer is predicted to be significantly more polar (ΔlogP ~ –0.8).[15] The ability of the OCF$_2$H group to adopt two easily interconverting conformations with considerable difference in lipophilicity is a unique characteristic for application in drug design, allowing drug molecules to be adaptable in different molecular environments. The utilisation of this effect is best illustrated by the development of a phosphodiesterase inhibitor for the treatment of respiratory diseases.[16] It was found that the -OCF$_2$H analogue (roflumilast) showed a superior binding affinity compared to the -OCH$_3$ analogue. This is due to the flexibility of the -OCF$_2$H group, allowing efficient hydrophobic interaction within the Q$_1$ pocket of the enzyme. In addition, the X-ray crystal structure of the roflumilast-enzyme complex also reveals an evidence of a multipolar C–F···C=O interaction between the OCF$_2$H group and the amide backbone.[14]

Despite these interesting properties, approved bioactive compounds bearing SCF$_3$, OCF$_3$ and OCF$_2$H moieties are relatively rare. This may be due to the lack of mild, reliable, and broadly applicable methods for the synthesis of these motifs.

2.2 Methods for the Synthesis Ar-SCF$_3$, -OCF$_3$ and -OCF$_2$H

2.2.1 Methods for the Synthesis of Ar-SCF$_3$

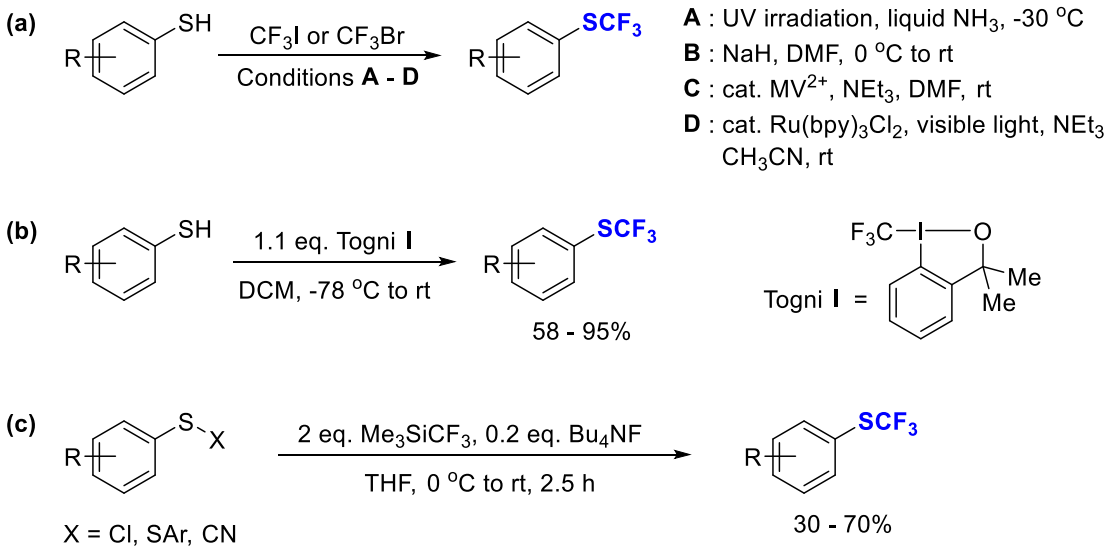
The strategy for the preparation of Ar-SCF$_3$ compounds relied for many years on halogen exchange of the corresponding Ar-SCCl$_3$ compounds. The reaction is typically performed by mixing at high temperature the substrate with an excess amount of SbF$_3$ in the absence of solvent (Scheme 2.4a).[17] Currently, this process is still commercially significant for the industrial scale production of SCF$_3$-containing building blocks using anhydrous HF as a fluoride source.[18] However, this method is not suitable for late-stage functionalisation of complex molecules due to the harsh reaction conditions applied. A milder approach was reported by Suda and Hino in 1981 utilising AgBF$_4$ to mediate the halogen exchange of the Ar-SCF$_2$Br precursors, leading to the formation of Ar-SCF$_3$ compounds in moderate yields at room temperature (Scheme 2.4b).[19]



Scheme 2.4 Synthesis of Ar-SCF$_3$ by halogen exchange approach.

Another route for the synthesis of Ar-SCF$_3$ is the construction of S–CF$_3$ bond *via* either radical or nucleophilic trifluoromethylation reactions. The radical approach was first reported by Boiko and co-workers in 1977 by the reaction of thiophenols with CF$_3$I or CF$_3$Br under UV light irradiation in liquid ammonia (Scheme 2.5a, conditions **A**).[20] However, this method suffers from the limited substrate scope, prolonged reaction times and harsh reaction conditions. Later on, milder reaction conditions were reported employing bases such as

NaH,[21] radical generators such as methyl viologen (MV^{2+})[22] or visible-light photoredox catalysis (Scheme 2.5a, conditions **B** - **D**).[23] Additionally, thiophenols can be trifluoromethylated using shelf-stable CF_3-electrophilic reagents such as the Umemoto reagent[24] and Togni reagents[25] under mild reaction conditions, allowing good reaction chemoselectivity (Scheme 2.5b).

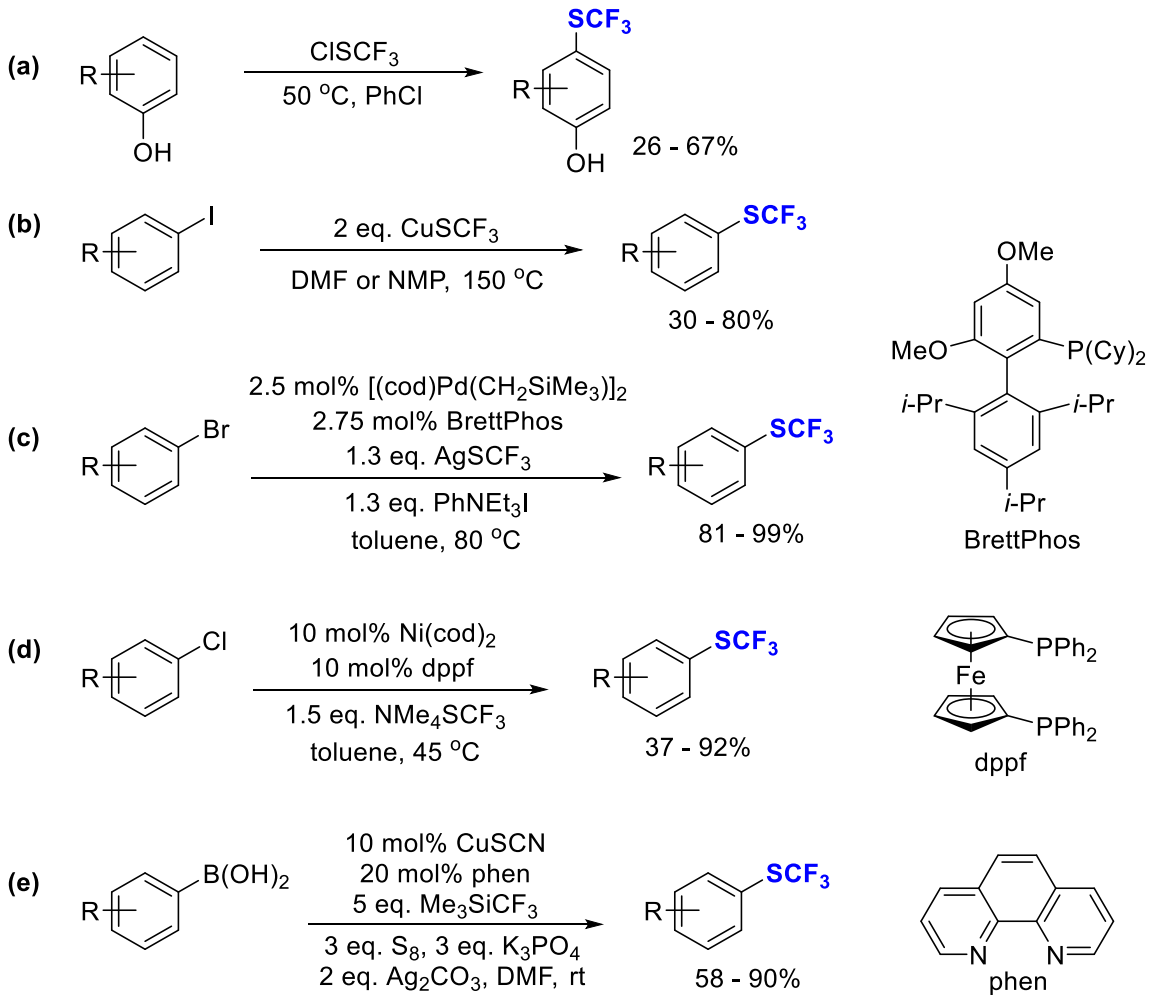


Scheme 2.5 Synthesis of Ar-SCF$_3$ *via* S–CF$_3$ bond construction.

The nucleophilic trifluoromethylation approach was first reported by Yagupolskii and co-workers starting from of aryl sulfenyl chlorides using trifluoromethyl trimethylsilane (Me_3SiCF_3) as a source of CF_3.[26] The procedure was further improved by Langlois and co-workers allowing the use of more accessible aryl disulfides and aryl sulfenyl cyanides as starting materials (Scheme 2.5c).[27] Other sources of CF_3 anion such as HCF_3,[28] CF_3CO_2K[29] or $PhSO_2CF_3$[30] were also reported as reagents for the production of Ar-SCF$_3$.

The final approach for the synthesis of Ar-SCF$_3$ is the formation of C–SCF$_3$ bond through direct trifluoromethylthiolation.[31] This transformation can be achieved by the reaction of electrophilic SCF_3 reagents such as CF_3SCl with electron-rich (hetero)aromatic compounds (Scheme 2.6a).[32] Alternatively, the SCF_3 group can be introduced nucleophilically using transition metal-mediated reactions. In 1975, Yagupolskii and co-workers reported direct

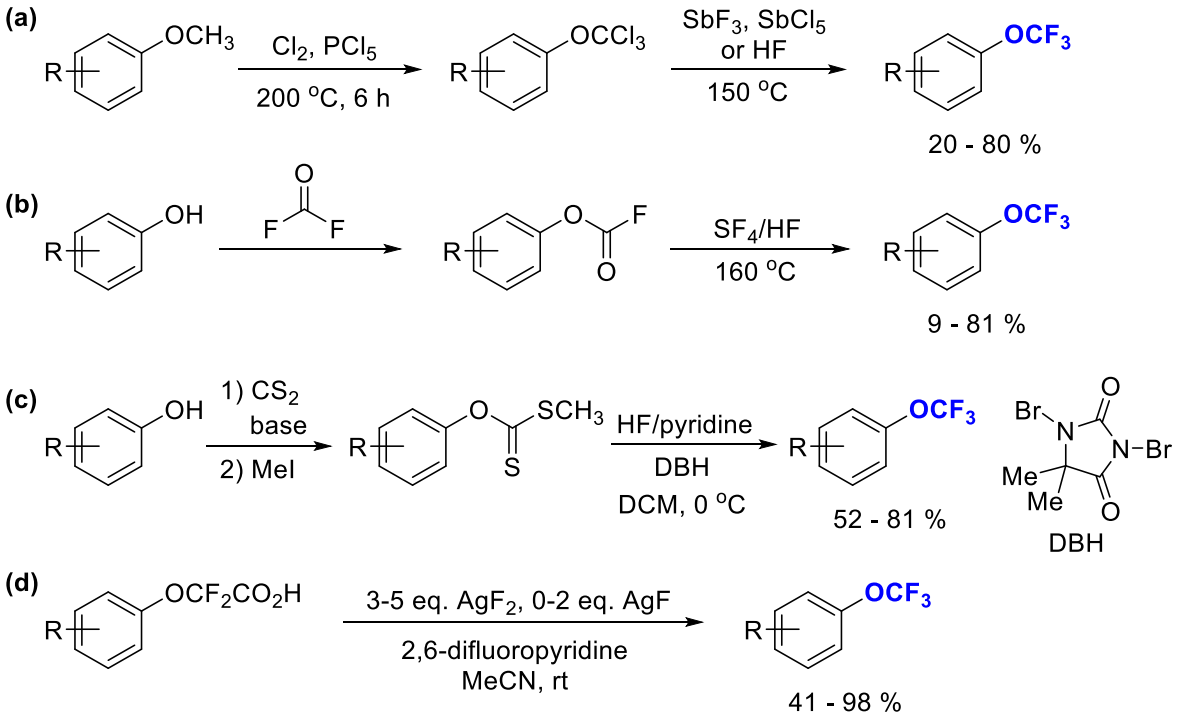
trifluoromethylthiolation using a stoichiometric amount of $CuSCF_3$ with aryl iodides at high temperature (Scheme 2.6b).[33] More recently, Huang and co-workers demonstrated that an air stable [(bpy)$CuSCF_3$] complex (derived from Me_3SiCF_3) could react smoothly with aryl iodides at lower temperatures.[34] Buchwald and co-workers developed Pd-catalysed trifluoromethylthiolation of aryl bromides using $AgSCF_3$ (prepared from AgF and CS_2) as the source of SCF_3 (Scheme 2.6c).[35] The scope of substrates was expanded to aryl chlorides using a nickel catalyst with Me_4NSCF_3 as the SCF_3 source (Scheme 2.6d).[36] In addition, aryl boronic acids can be used as starting materials for the production of Ar-SCF_3 in the presence of an oxidant. For example, Qing and co-workers reported the Cu-catalysed oxidative trifluoromethylthiolation using a combination of Me_3SiCF_3, S_8 and Ag_2CO_3 (Scheme 2.6e).[37]



Scheme 2.6 Synthesis of Ar-SCF_3 *via* C–SCF_3 bond construction.

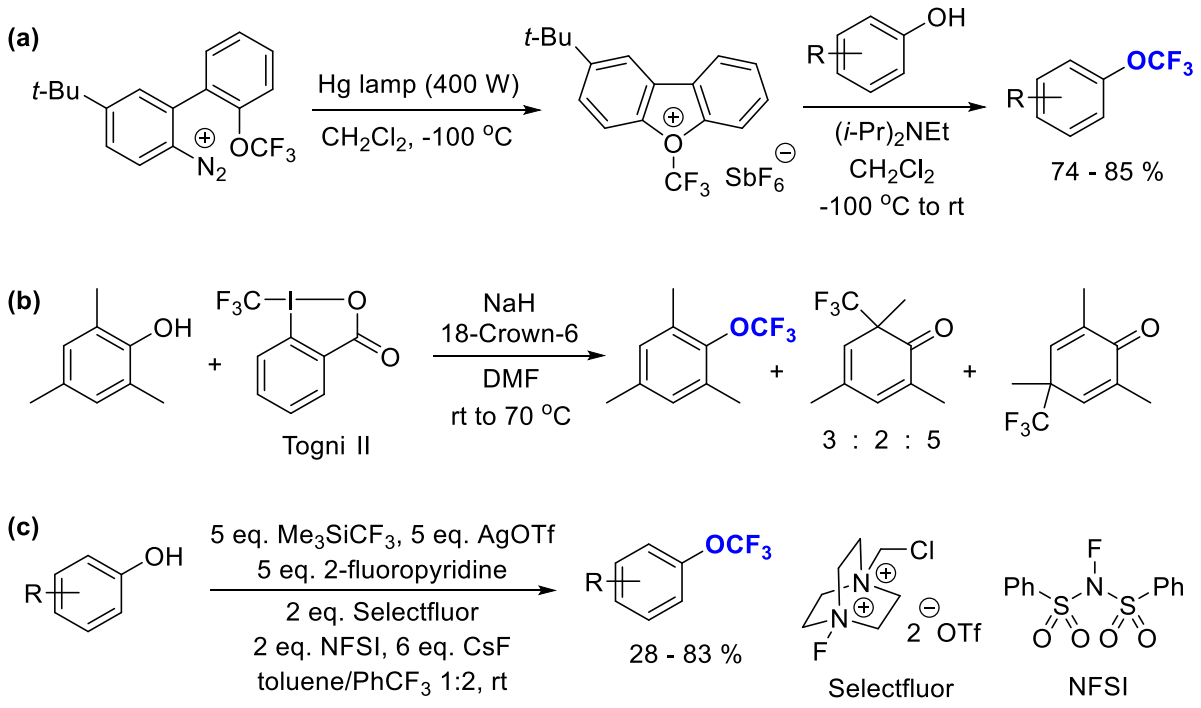
2.2.2 Methods for the Synthesis of Ar-OCF$_3$

In 1955, Yagupolskii and co-workers reported the first method for the preparation of trifluoromethyl ethers, which relied on the displacement of chlorine in Ar-OCCl$_3$ by fluorine using anhydrous HF or SbF$_3$ (Swart's reagent) in the presence of SbCl$_5$ (Scheme 2.7a).[38] The precursors can be prepared by reaction of corresponding anisoles with Cl$_2$ and PCl$_5$.[39,40] This chlorination/exchange sequence is routinely used for the industrial scale production of Ar-OCF$_3$ building blocks. Aryl chlorothionoformates[41] or fluoroformates[42] can also be used as precursors for nucleophilic fluorination (Scheme 2.7b), although the high toxicity of these compounds discourages the use of these methods. In 2000, Hiyama and co-workers disclosed the synthesis of Ar-OCF$_3$ *via* oxidative desulfurisation-fluorination of aryl methylxanthates using 1,3-dibromo-5,5-dimethylhydantoin (DBH) as an oxidant in the presence of a large excess of HF/pyridine (Olah reagent) (Scheme 2.7c).[43] Very recently, Hartwig and co-workers reported the synthesis of Ar-OCF$_3$ *via* fluorodecarboxylation of the corresponding *α*,*α*-difluorocarboxylic acids (Scheme 2.7d).[44]



Scheme 2.7 Synthesis of Ar-OCF$_3$ *via* C–F bond construction.

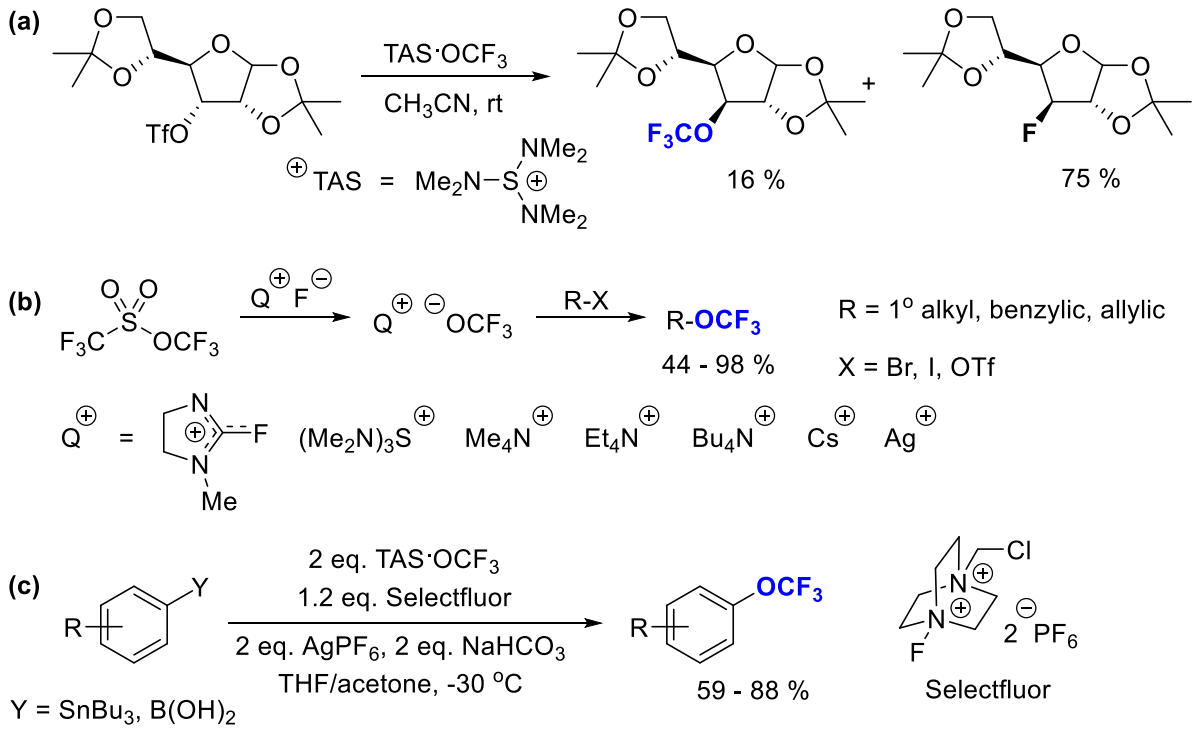
The O–CF_3 bond construction approach was not explored until 2007 when Umemoto and co-workers described the direct O-trifluoromethylation of phenols under mild conditions using O-trifluoromethyldibenzofuranium salts as electrophilic CF_3 sources (Scheme 2.8a).[45] However, the reagent is highly unstable and has to be prepared *in situ* at –100 °C. More recently, Togni has shown that reaction of the Togni reagent II with phenols results in a mixture of the desired O-trifluoromethylated compound and by-products resulting from C-trifluoromethylation (Scheme 2.8b).[46] In 2015, Qing and co-workers described silver-mediated oxidative trifluoromethylation of phenols using Me_3SiCF_3 as a source of CF_3 and a combination of Selectfluor and NFSI as oxidants (Scheme 2.8c).[47]



Scheme 2.8 Synthesis of Ar-OCF_3 *via* O–CF_3 bond construction.

Direct introduction of the OCF_3 group would be an ideal method for late stage synthesis of Ar-OCF_3 compounds; however, the OCF_3 anion is highly unstable due to the rapid equilibrium with volatile difluorophosgene and fluoride anion. In 1985, Trainor reported the use of tris(dimethylamino)sulfonium (TAS) as a bulky counter cation to stabilise the OCF_3

anion and demonstrated nucleophilic trifluoromethoxylation of carbohydrates at room temperature (Scheme 2.9a).[48] Kolomeitsev and co-workers subsequently reported that trifluoromethyl triflate could be used as a liquid reservoir of difluorophosgene. By treatment with fluoride sources, several trifluoromethoxide salts can be generated which can be used as nucleophilic OCF_3 reagents (Scheme 2.9b).[49] In 2011, Ritter and co-workers reported the first method for preparation of Ar-OCF_3 *via* direct trifluoromethoxylation. In this work, aryl stannanes and aryl boronic acids were reacted with TAS·OCF_3 using $AgPF_6$ to mediate the cross-coupling reaction (Scheme 2.9c).[50]

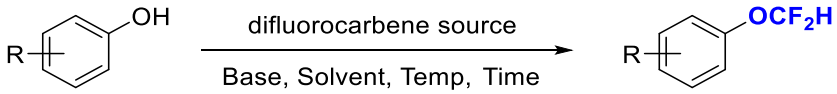


Scheme 2.9 Synthesis of R-OCF_3 *via* C–OCF_3 bond construction.

2.2.3 Methods for the Synthesis of Ar-OCF_2H

Syntheses of difluoromethyl ethers typically involve the reaction of the corresponding phenols with various difluorocarbene sources under basic conditions. One of the most commonly employed methods was reported by Miller and Thanassi in 1960, using ozone-depleting chlorodifluoromethane gas (HCF_2Cl) as the difluorocarbene precursor (Table 2.2,

entry 1).[51] Many alternative non-ozone-depleting difluorocarbene sources have been developed; for examples, diethyl bromodifluoromethylphosphonate ($(EtO)_2POCF_2Br$),[52] chlorodifluoroacetophenone ($PhCOCF_2Cl$),[53] chlorodifluoromethyl phenyl sulfone ($PhSO_2CF_2Cl$),[54] fluorosulfonyldifluoroacetic acid ($FSO_2CF_2CO_2H$),[55] difluoromethyl triflate (HCF_2OTf),[56] triethyl(bromodifluoromethyl)silane ($TESCF_2Br$)[57] and fluoroform (HCF_3)[58] (Table 2.2, entries 2 - 6). The mechanism of these reactions involves the formation of CF_2X^- (X = halogen), which undergoes facile α-elimination to generate difluorocarbene reactive species, which are subsequently trapped by the phenoxide anion.



Entry	:CF_2 source	Base	Conditions	Yields
1	1.5 eq. HCF_2Cl	5 eq. NaOH	dioxane/H_2O, 70 ^oC	10 - 66 %
2	2 eq. $(EtO)_2POCF_2Br$	20 eq. KOH	CH_3CN/H_2O, -78 ^oC to rt	60 - 98 %
3	5 eq. $PhCOCF_2Cl$	21 eq. KOH	CH_3CN/H_2O, 80 ^oC	51 - 79 %
4	2.3 eq. $PhSO_2CF_2Cl$	11 eq. KOH	CH_3CN/H_2O, 50 ^oC	65 - 96 %
5	3 eq. HCF_2OTf	12 eq. KOH	CH_3CN/H_2O, rt	51 - 92 %
6	8 eq. HCF_3	10 eq. KOH	dioxane/H_2O, 50 ^oC	40 - 93 %

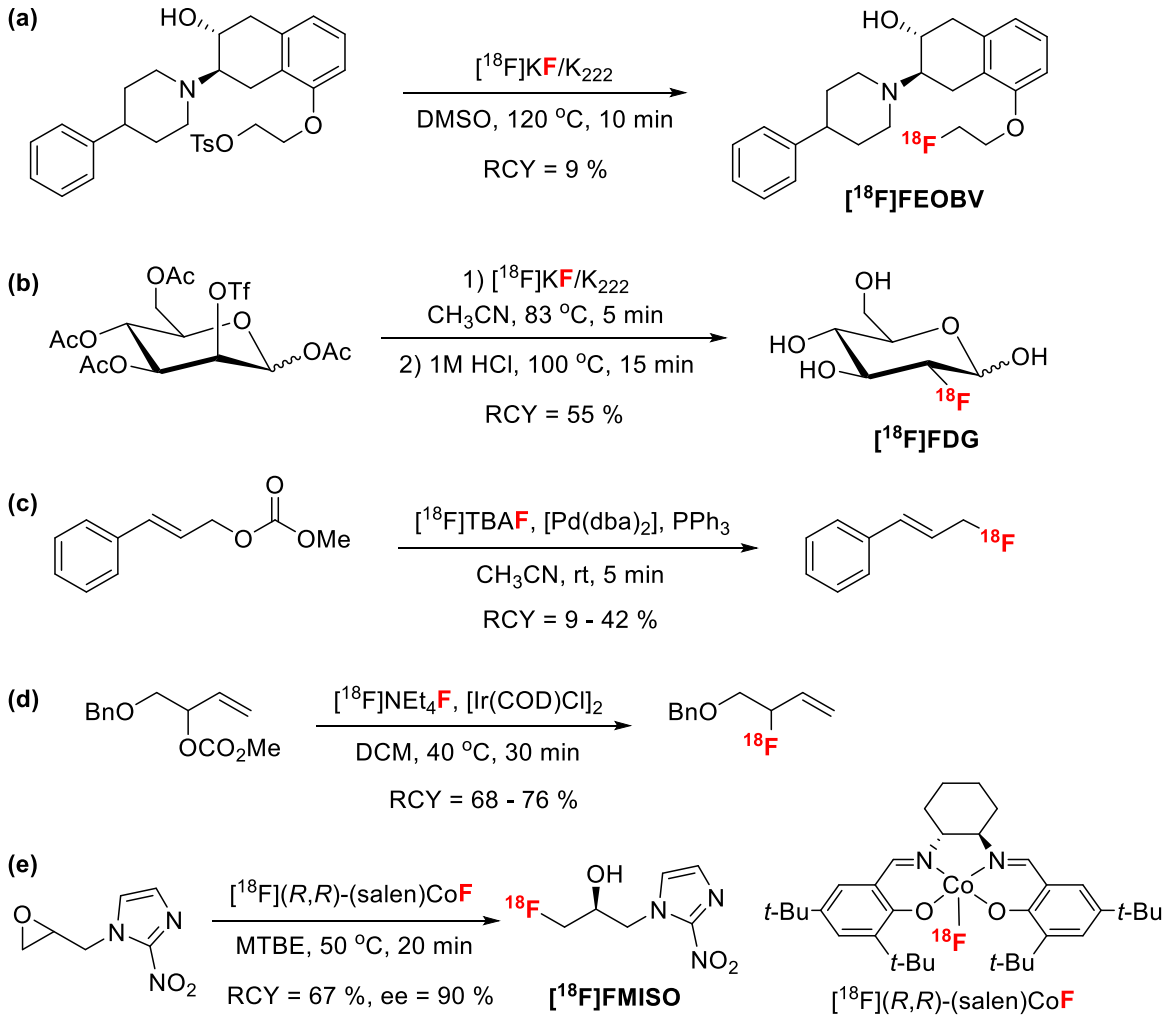
Table 2.2 Examples of difluoromethylation of phenols.

2.3 ^{18}F-Labelling Methods Using [^{18}F]Fluoride

Historically, many important radiopharmaceuticals were prepared using electrophilic fluorination methods. However, due to major drawbacks associated with [^{18}F]F_2 as described in Chapter 1.3, most of these have been replaced by nucleophilic fluorination methods using [^{18}F]fluoride. Moreover, the radiolabelling facility in Oxford is not equipped for the handling of [^{18}F]F_2 gas. For these reasons, we will only consider nucleophilic fluorination methods for the development of the ^{18}F-radiolabelling of Ar-SCF$_3$, -OCF$_3$ and -OCF$_2$H groups.

2.3.1 Methods for the Synthesis of [^{18}F]Alk-F using [^{18}F]Fluoride

Classical methods for radiolabelling with [^{18}F]fluoride usually involve displacement of leaving groups in aliphatic positions to form Csp^3–^{18}F bonds *via* standard nucleophilic substitution reactions. For instance, the radiolabelling of [^{18}F]fluoroethoxybenzovesamicol ([^{18}F]FEOBV), a radiotracer for the vesicular acetylcholine transporter, was performed by mixing the corresponding tosylate precursor with [^{18}F]KF/K$_{222}$ in DMSO at 120 °C (Scheme 2.10a).[59] This procedure is utilised in the production of the most widely used radiopharmaceutical, 2-deoxy-2-[^{18}F]fluoro-D-glucose ([^{18}F]FDG). The reaction of protected triflate precursor with [^{18}F]KF/K$_{222}$ in CH$_3$CN at 83 °C followed by deprotection with 1 M HCl at 100 °C provides [^{18}F]FDG in 55 % RCY (Scheme 2.10b).[60]



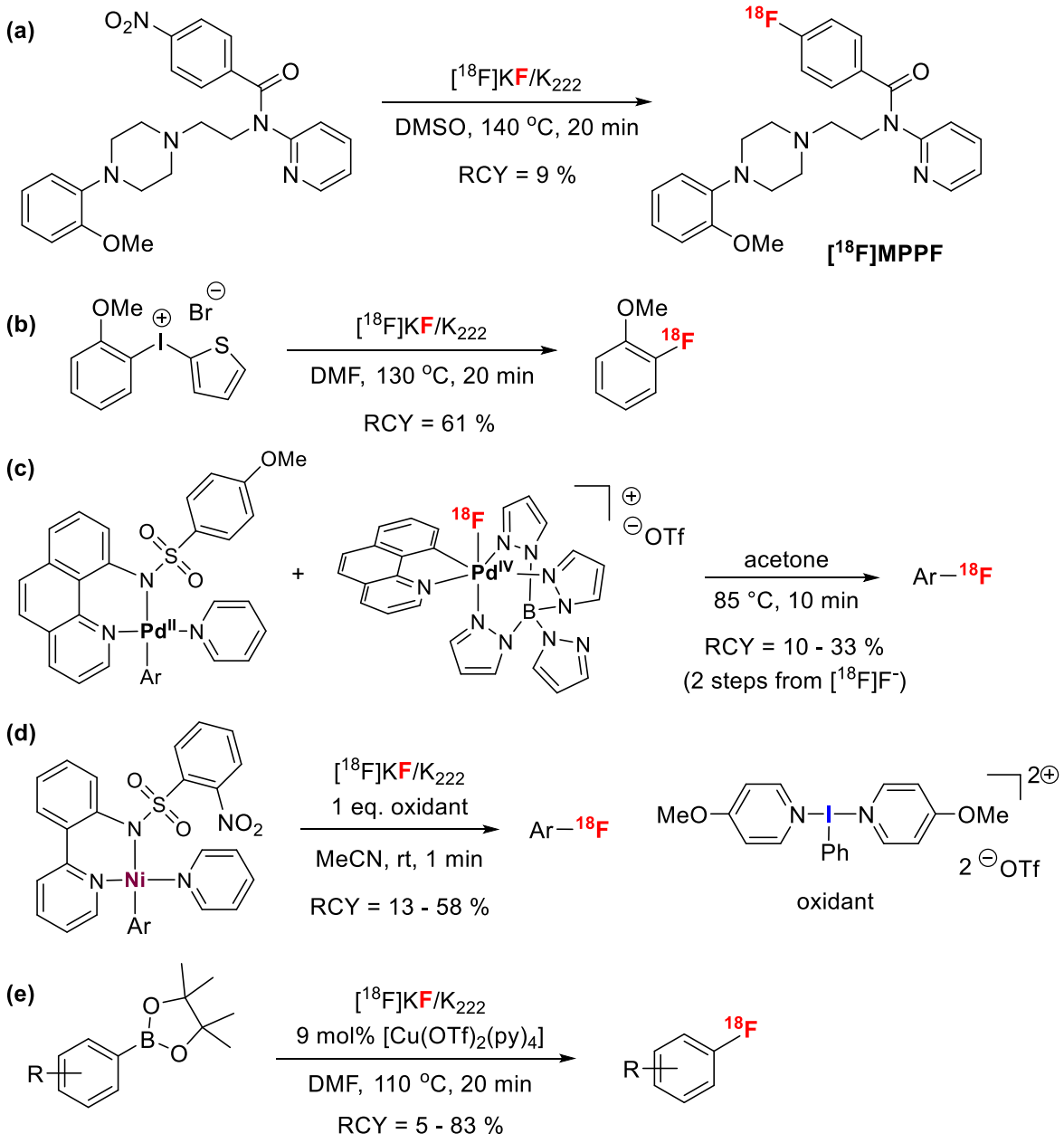
Scheme 2.10 Methods for preparation of [^{18}F]Alkyl-F using [^{18}F]fluoride.

Most of these classical methods require thermal activation to overcome the low reactivity of the fluoride; therefore, the scope of reaction is limited due to substrate decomposition at high temperature. Many research groups attempted to integrate the new technologies in modern synthetic organic chemistry such as transition metal catalysis to achieve ^{18}F-labelling at milder reaction conditions. In 2011, Gouverneur and co-workers developed a palladium-catalysed allylic ^{18}F-fluorination at room temperature using [Pd(dba)$_2$] as a catalyst and tetrabutylammonium [^{18}F]fluoride as a source of [^{18}F]fluoride (Scheme 2.10c).[61] Under the optimised conditions, cinnamyl methyl carbonate was successfully transformed into the ^{18}F-labelled cinnamyl fluoride in 9 - 42 % RCYs. The substrate scope was further expanded by the use of [Ir(COD)Cl]$_2$ as a catalyst, allowing access to the ^{18}F-labelling of both branched, linear (*E*)- and (*Z*)-allyl fluorides with high regioselectivity (Scheme 2.10d).[62] Nguyen and co-workers also reported iridium-catalysed allylic fluorination of trichloroacetimidate derivatives using [Ir(COD)OMe]$_2$ as a catalyst. The reaction operates at room temperature, affording desired ^{18}F-labelled products at 48 - 67 % RCYs.[63] More recently, Doyle and co-workers reported enantioselective radiosynthesis of [^{18}F]fluorohydrins by ring opening of epoxides using a chiral cobalt complex as a Lewis acid catalyst (Scheme 2.10e).[64] By using this methodology, [^{18}F]fluoromisonidazole ([^{18}F]FMISO) and [^{18}F]fluoroerythronitro-imidazole ([^{18}F]FETNIM) were successfully labelled in high RCYs and enantioselectivities.

2.3.2 Methods for the Synthesis of [^{18}F]Ar-F using [^{18}F]Fluoride

Nucleophilic aromatic substitution (S_NAr) of electron-deficient arenes with [^{18}F]fluoride is the most commonly used method for production of PET radiotracers bearing an ^{18}F-substituent on the arene.[65] The reaction typically requires a substrate with strong electron withdrawing groups such as -NO$_2$, -CF$_3$ or -CN positioned *ortho* or *para* to the leaving group.[66] The most widely employed leaving groups are -NO$_2$ and -NMe$_3^+$. For instance,

radiosynthesis of 4-(2′-methoxyphenyl)-1-[2′-(*N*-2″-pyridinyl)-*p*-[^{18}F]fluorobenzamido] ethylpiperazine ([^{18}F]MPPF), a radiotracer for serotonin-1A receptors, has been achieved using direct nucleophilic substitution of the nitro precursor at 140 °C (Scheme 2.11a).[67] The requirement of an electron-deficient precursor and a high reaction temperature are the major drawbacks of these procedures. One of the solutions is to enhance leaving group ability; for example, diaryliodonium salts[68] and triarylsulfonium salts[69] have been successfully employed as precursors for ^{18}F-fluorination of electron-rich arenes (Scheme 2.11b).



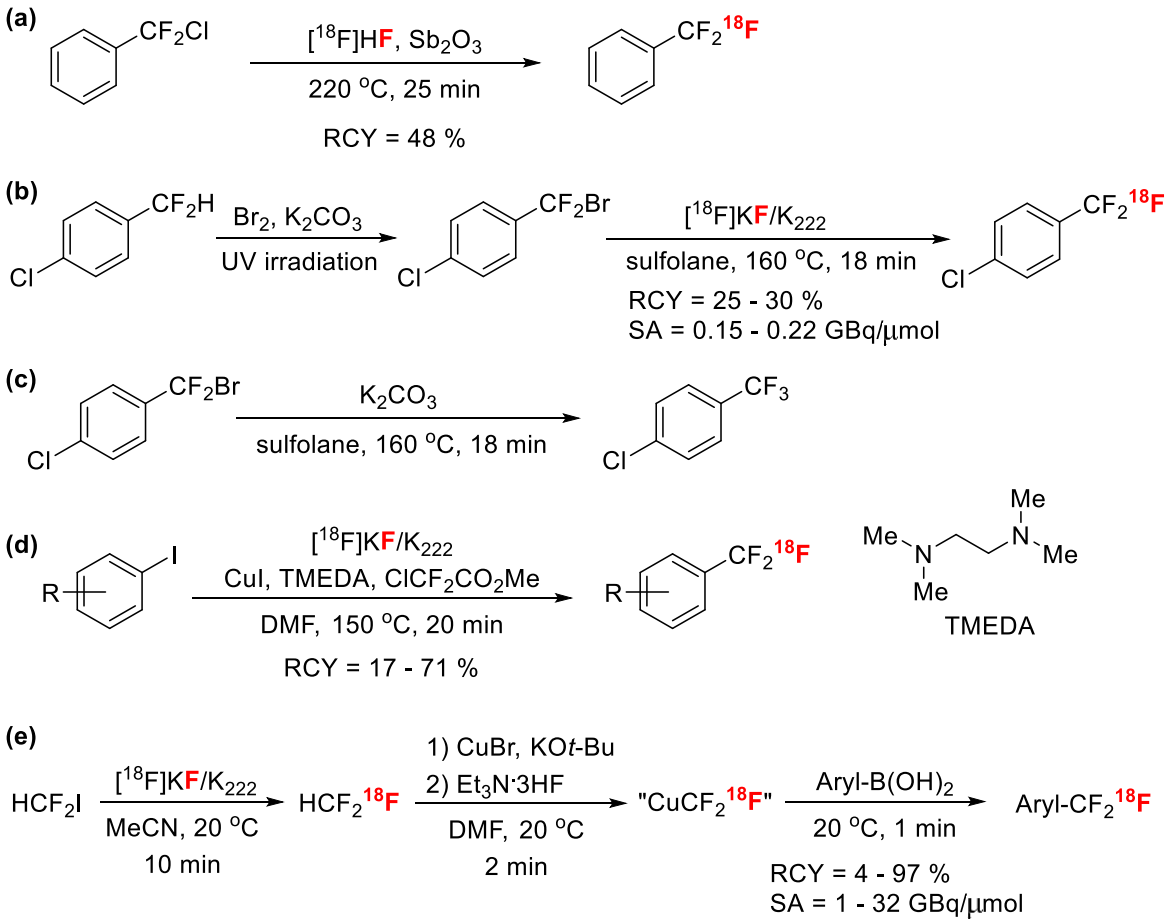
Scheme 2.11 Methods for preparation of [^{18}F]Ar-F using [^{18}F]fluoride.

An alternative strategy is the use of transition metal catalyst to mediate Csp^2–^{18}F bond formation. In 2011, Ritter and co-workers developed ^{18}F-fluorination of pre-formed Pd(II) aryl complexes using Pd(IV) fluoride complex derived from [^{18}F]fluoride (Scheme 2.11c).[70] In 2012, the same group also demonstrated that preformed Ni(II) aryl complexes can undergo ^{18}F-fluorination using [^{18}F]fluoride and an oxidant to afford the labelled product in high RCYs at room temperature (Scheme 2.11d).[71] In 2014, Gouverneur and co-workers reported a broadly applicable method for production of ^{18}F-labelled arenes from aryl boronic esters using [Cu(OTf)$_2$(py)$_4$] as a catalyst. This method tolerates a broad range of functional groups as well as both electron-rich and electron-deficient arenes (Scheme 2.11e).[72]

2.3.3 Methods for the Synthesis of [^{18}F]Ar-CF$_3$ using [^{18}F]Fluoride

It is well-documented that fluorine substituents on a carbon centre have detrimental effects on the rate of nucleophilic substitution reactions.[73] This phenomenon is mainly derived from the electrostatic interaction of fluorine lone pairs that repels the incoming nucleophile. As a result, the ^{18}F-labelling of [^{18}F]Ar-CF$_3$ usually requires high temperature and forcing reaction conditions. In 1979, Ido and co-workers reported the first synthesis of [^{18}F]trifluoromethyl arenes using a halogen exchange strategy starting from α-chloro-α,α-difluorotoluene as a precursor. Treating the substrate with a combination of carrier-added [^{18}F]HF and Sb$_2$O$_3$ at 220 ^{o}C results in the formation of ^{18}F-labelled product in 48 % RCY (Scheme 2.12a). Due to the use of the carrier-added procedure, the specific activity of this method is intrinsically low. Halogen exchange of Ar-CF$_2$Br can be achieved at significantly milder reaction conditions compared to those that use chloride as leaving groups. These precursors can be synthesised by radical bromination of the corresponding Ar-CF$_2$H substrates. Hammadi and Crouzel demonstrated that non-carrier-added [^{18}F]KF/K$_{222}$ can induce ^{18}F-fluorination of α-bromo-4-chloro-α,α-difluorotoluene in 25 - 30 % RCYs at 160 ^{o}C, although the specific activity is very low (Scheme 2.12b).[74] It was found that when

the same reaction was performed in the absence of fluoride source, the non-radiolabelled product was observed (Scheme 2.12c). This result suggests that the precursor itself can serve as a ^{19}F-fluoride source, hence decreasing the specific activity of the reaction.



Scheme 2.12 Methods for preparation of [^{18}F]Ar-CF$_3$ using [^{18}F]fluoride.

Alternatively, [^{18}F]Ar-CF$_3$ can be synthesised by transition metal-mediated cross-coupling reactions. In 2013, Gouverneur and co-workers reported that the combination of [^{18}F]KF/K$_{222}$, methyl chlorodifluoroacetate (ClCF$_2$CO$_2$Me), CuI and *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) at 150 °C leads to the *in situ* formation of reactive "[^{18}F]CuCF$_3$" complex. The reaction of this copper species with aryl iodides affords ^{18}F-labelled trifluoromethylated products in high RCYs with a broad range of substrate scope (Scheme 2.12d).[75] Riss and co-workers also demonstrated the use of CuBr to mediate

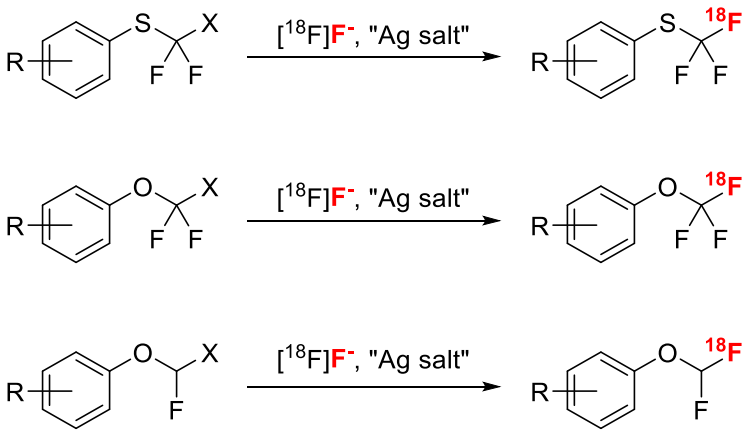
^{18}F-trifluoromethylation of aryl iodides using [^{18}F]trifluoromethane ([^{18}F]HCF$_3$), which is prepared from [^{18}F]KF/K$_{222}$ according to the procedure reported by Vugts and co-workers.[76] The scope of this reaction was expanded to aryl boronic acids, in which the ^{18}F-trifluoromethylation was achieved at room temperature with significantly improved specific activity in the range of 1 to 32 GBq/μmol (Scheme 2.12e).[77]

2.3.4 Strategies for the ^{18}F-Labelling of Ar-SCF$_3$, -OCF$_3$ and -OCF$_2$H

The ^{18}F-radiosynthetic methods described in the previous sections illustrated the advance of ^{18}F-labelling of fluoroalkanes, fluoroarenes and trifluoromethyl arenes. The production of clinically useful radiotracers relies on these technologies to incorporate ^{18}F into organic molecules for PET imaging. Meanwhile, other fluorine-containing functional groups such as di- and trifluoromethyl ethers, as well as thioethers, have recently received increasing attention for the applications in drug developments due to several beneficial properties as mentioned in Chapter 2.1. To date, there is no general procedure for ^{18}F-labelling of these medicinally useful motifs. Hence, the development of a novel method for ^{18}F-labelling of Ar-SCF$_3$, -OCF$_3$ and -OCF$_2$H groups could facilitate the development of potentially high-value radiotracers which lie outside of the currently accessible radiochemical space. In addition, a more diverse range of ^{18}F-tags would provide invaluable information for the selection of lead compounds much earlier in the drug discovery pipeline.

The existing methods for preparation of Ar-SCF$_3$, -OCF$_3$ and -OCF$_2$H groups have been discussed in Chapter 2.2. One of the procedures that is amenable for ^{18}F-radiosynthesis is halogen exchange of the corresponding alkyl halides. However, multiple ^{18}F-fluorination is not viable due to the minute quantity (~ picomolar) of [^{18}F]fluoride available. Therefore, precursors which require only a single fluorine substitution step is needed; i.e. Ar-SCF$_2$X, Ar-OCF$_2$X and Ar-OCHFX. As discussed previously, Suda and Hino have demonstrated that

$AgBF_4$ can induce the halogen exchange of Ar-SCF_2Br at room temperature, although the use of $AgBF_4$ is not suitable for ^{18}F-radiochemistry due to potential isotope scrambling from the BF_4^- anion which can have a detrimental effect on the specific activity. The employment of silver salts as a halogenophilic Lewis acid to facilitate halogen exchange reaction is well established; however, this concept has never been considered as a generic activation manifold to promote halex ^{18}F-fluorination. In the next section, a novel silver-mediated method for the ^{18}F-labelling of Ar-SCF_3, -OCF_3 and -OCF_2H groups under mild reaction conditions will be described (Scheme 2.13). This will include the synthesis of precursors, the development of the ^{18}F-labelling methods as well as the applications of this protocol to the synthesis of the ^{18}F-labelled Umemoto reagent.

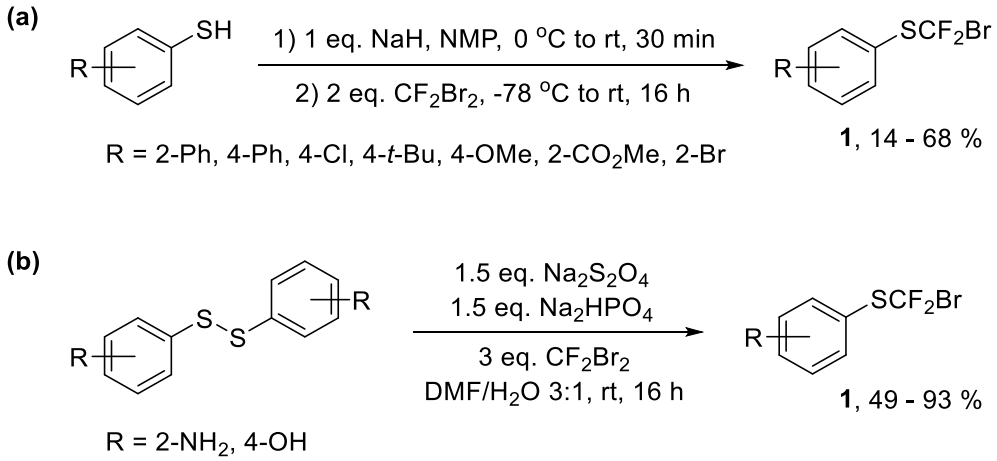


Scheme 2.13 Silver-mediated ^{18}F-labelling of Ar-SCF_3, -OCF_3 and -OCF_2H.

2.4 Silver-Mediated ^{18}F-Labelling of Ar-SCF$_3$ from Ar-SCF$_2$Br

2.4.1 Preparation of Ar-SCF$_2$Br precursors

In this work, most of the Ar-SCF$_2$Br precursors were synthesised using the procedure reported by Burton and Wiemers.[78] A solution of sodium thiophenolates was prepared by reaction of the corresponding thiophenols with 1.5 eq. of NaH using degassed NMP as a solvent. To this solution, 2 eq. of CF_2Br_2 was slowly added at -78 ^oC. After stirring at room temperature overnight, a range of Ar-SCF$_2$Br were obtained in moderate yields (Scheme 2.14a).

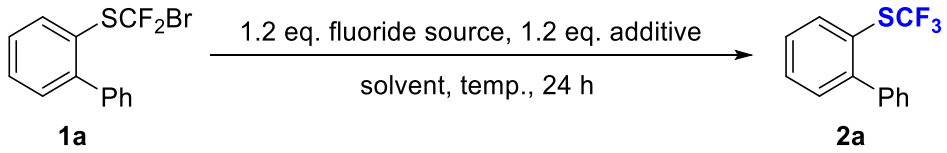


Scheme 2.14 Preparation of Ar-SCF$_2$Br precursors;
These substrates were prepared by S. Verhoog.

The reaction tolerates both electron-donating and electron-withdrawing substituents as well as heterocyclic substrates such as coumarin and benzothiazole. However, substrates with an acidic hydrogen such as -NH_2 or -OH substituents led to a formation of several unknown side-products. These substrates were alternatively prepared from aryl disulfide substrate *via* the procedure reported by Wakselman and co-workers.[79] Sodium thiophenolate can be generated *in situ* by the reaction of aryl disulfide with $Na_2S_2O_4$ and Na_2HPO_4 which subsequently reacts with CF_2Br_2 to give the desired product under mild reaction conditions (Scheme 2.14b).

2.4.2 Optimisation of Reaction Conditions for ^{18}F-Labelling of Ar-SCF$_3$

Compound **1a** with *ortho*-phenyl substituent was chosen as a model substrate for the reaction optimisation because the ^{18}F-labelled product ([^{18}F]**2a**) is a potential precursor for the production of ^{18}F-labelled Umemoto reagent, a prominent electrophilic trifluoromethylating reagent. Preliminary studies were conducted by reacting **1a** with "cold" sources of fluoride at elevated temperature (Table 2.3). The highest yield of **2a** was achieved by using KF and 18-crown-6 as the fluoride source (entry 1).



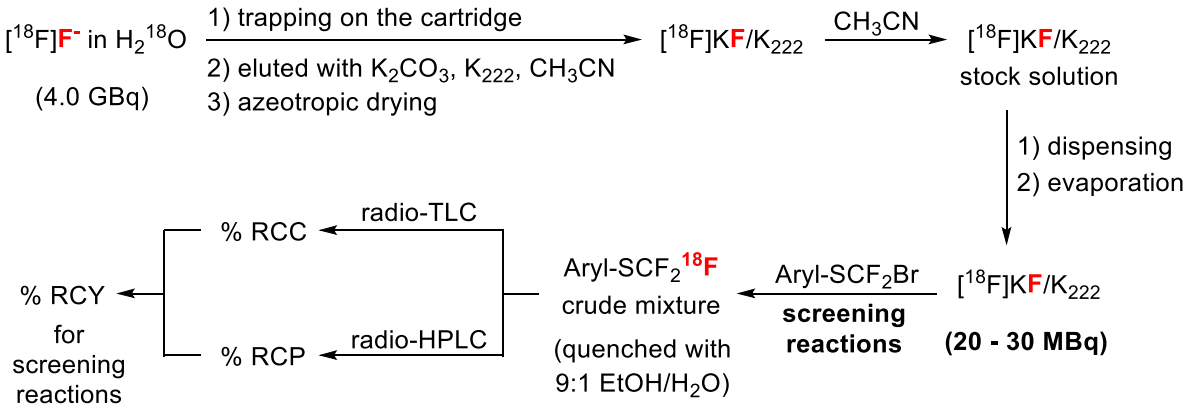
Entry	Fluoride source	Additive	Solvent	Temp.	Conversion [a]	Yield [a]
1	KF	18-crown-6	sulfolane	150 °C	97 %	16 %
2	KF	18-crown-6	DMF	150 °C	61 %	6 %
3	TBAF·3H$_2$O	-	*t*-BuOH	150 °C	10 %	7 %

Table 2.3 Preliminary results for fluorination of **1a**; **1a** (0.10 mmol), KF or TBAF·3H$_2$O (0.12 mmol), 18-crown-6 (0.12 mmol), solvent (100 μL); These reactions were carried out by S. Verhoog; [a] Determined by ^{19}F NMR using PhCF$_3$ as an internal standard.

The promising preliminary results encouraged us to attempt the ^{18}F-fluorination of **1a** using [^{18}F]fluoride. The ^{18}F-labelling reactions were conducted at the Siemens Oxford Molecular Imaging Laboratory (SOMIL), University of Oxford. Due to the safety regulations, the maximum amount of radioactivity allowed is 4.0 GBq. There is no cyclotron in Oxford; therefore, the ^{18}F isotope had to be purchased in the form of [^{18}F]fluoride in H$_2$^{18}O, which was then activated using the standard drying procedures described in Chapter 1.3. For the purpose of the optimisation of reaction conditions and the screening of substrate scope, the

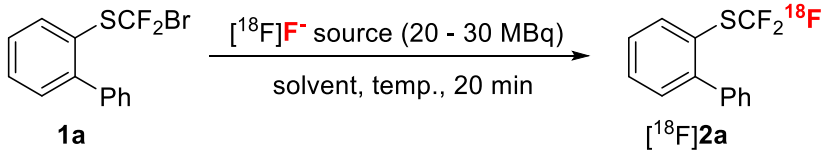
activated [^{18}F]KF/K_{222} complex was re-dissolved in CH_3CN to provide a stock solution. For each screening reaction, an aliquot containing a small amount of radioactivity (20 - 30 MBq) was taken from the stock solution. Subsequently, the CH_3CN was evaporated under a stream of N_2 gas, then a solution of Ar-SCF_2Br precursor in a solvent of choice was added, and subsequently stirred at the required temperature for 20 minutes. The reactions were performed in duplicates in order to minimise experimental errors.

After each screening reaction, 9:1 EtOH/H_2O was added to the reaction mixture to form a homogeneous mixture in which both organic fluorine-containing species and the remaining [^{18}F]fluoride were dissolved. The crude mixture was then analysed by radio-TLC and radio-HPLC. The radio-TLC provides data on radiochemical conversion (RCC), which is determined as the ratio of radioactivity of the unreacted [^{18}F]fluoride on the baseline and the radioactivity of ^{18}F-containing organic material at higher R_f. The radio-HPLC can provide data on radiochemical purity (RCP) of the reaction; by overlaying the UV-trace of the "cold" (non-radiolabelled) product reference with the radio-trace of the crude reaction mixture, the peak of the ^{18}F-labelled product can be located. The ratio of the area under the ^{18}F-labelled product peak against other radioactive species represents the RCP of the reaction. Ultimately, the radiochemical yield (RCY) of the reaction can be calculated by multiplying % RCC and % RCP, then averaged with the RCYs from the other duplicates (Scheme 2.15).



Scheme 2.15 General procedure for the screening reactions of ^{18}F-labelling.

The reaction of **1a** with [^{18}F]KF/K$_{222}$ complex in various solvents at elevated temperatures did not result in ^{18}F-incorporation (Table 2.4, entries 1 - 7). [^{18}F]Et$_4$NF, a reagent prepared by eluting the ion exchange cartridge with Et$_4$NHCO$_3$ instead of K$_2$CO$_3$/K$_{222}$, was employed as an alternative ^{18}F-fluoride source. The reaction of [^{18}F]Et$_4$NF with **1a** gave the ^{18}F-labelled **2a** in trace amount at the temperature as high as 200 ^{o}C (Table 2.4, entry 10)



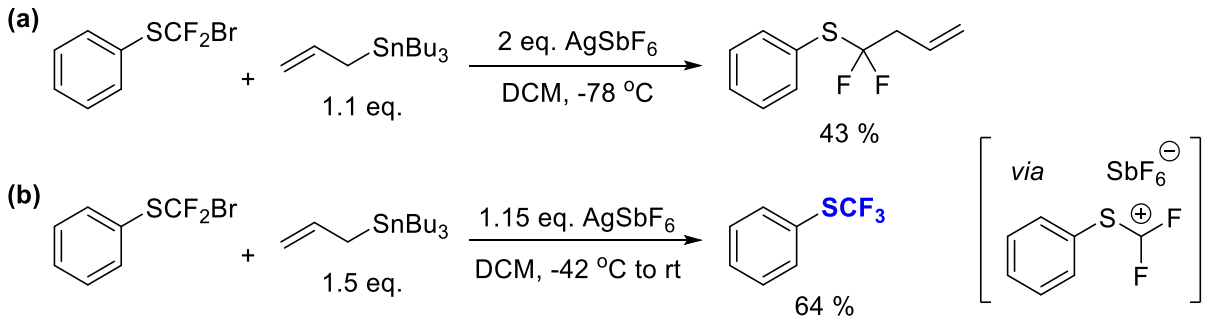
1a [^{18}F]**2a**

Entry	[^{18}F]F$^-$ source	Solvent	Temp.	RCY [a],[b]
1	[^{18}F]KF/K$_{222}$	CH$_3$CN	80 ^{o}C	0 % (*n* = 2)
2	[^{18}F]KF/K$_{222}$	*t*-BuOH	80 ^{o}C	0 % (*n* = 2)
3	[^{18}F]KF/K$_{222}$	DMF	110 ^{o}C	0 % (*n* = 2)
4	[^{18}F]KF/K$_{222}$	DMA	150 ^{o}C	0 % (*n* = 2)
5	[^{18}F]KF/K$_{222}$	NMP	180 ^{o}C	0 % (*n* = 2)
6	[^{18}F]KF/K$_{222}$	DMSO	180 ^{o}C	0 % (*n* = 2)
7	[^{18}F]KF/K$_{222}$	sulfolane	180 ^{o}C	0 % (*n* = 2)
8	[^{18}F]Et$_4$NF	*t*-BuOH	80 ^{o}C	0 % (*n* = 2)
9	[^{18}F]Et$_4$NF	DMF	150 ^{o}C	0 % (*n* = 2)
10	[^{18}F]Et$_4$NF	sulfolane	200 ^{o}C	1 ± 1 % (*n* = 2)

Table 2.4 ^{18}F-Fluorination of **1a** by thermal activation; **1a** (0.04 mmol), [^{18}F]KF/K$_{222}$ or [^{18}F]NEt$_3$F (20 - 30 MBq), solvent (300 µL); *n* represents number of runs; [a] Determined by radio-TLC and radio-HPLC; [b] the error is calculated as a standard deviation.

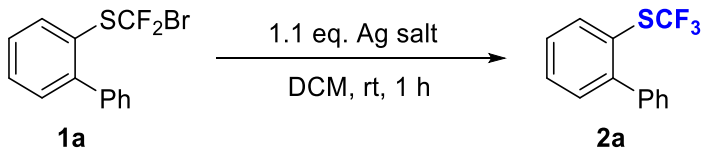
The unsuccessful results on the ^{18}F-fluorination of **1a** using a thermal activation strategy emphasise the requirement for the development of a new activation mode. As described earlier, AgBF$_4$ has been successfully used as a reagent for the fluorination of Ar-SCF$_2$Br. In addition, Reutrakul and co-workers discovered that upon treating Ar-SCF$_2$Br with AgSbF$_6$, difluoro(phenylthio)methylium cation (Ar-SCF$_2^+$) is generated and can be

characterised at low temperature.[80] This electrophilic species can be trapped by many nucleophiles such as allyl tributylstannane at –78 °C, affording the allylated product in 43 % yield (Scheme 2.16a). On the other hand, when the reaction was performed at –42 °C, the Ar-SCF$_3$ by-product was formed exclusively in 64 % yield (Scheme 2.16b). This result suggests that the SbF_6^- anion is a potential source of fluoride ion that can be trapped by highly electrophilic Ar-SCF_2^+ species.



Scheme 2.16 Silver-mediated allylation with the formation of Ar-SCF$_3$ by-product.[80]

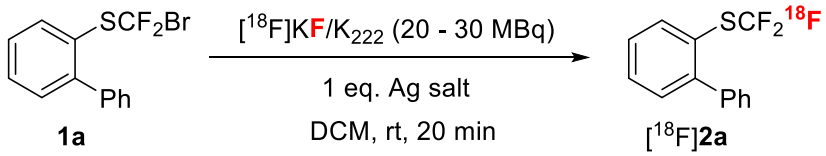
Our preliminary study showed that both $AgBF_4$ and $AgSbF_6$ can efficiently fluorinate **1a** at room temperature, affording **2a** in 54 % and 24 % respectively (Table 2.5). In both cases, the complete consumption of starting materials and the formation of various side-products was observed (see Section 2.9 for more detail).



Entry	Ag salt	Conversion [a],[b]	Yield [b]
1	$AgBF_4$	100 %	54 %
2	$AgSbF_6$	100 %	24 %

Table 2.5 Fluorination of **1a** with silver salts; **1a** (0.10 mmol), Ag salt (0.11 mmol), DCM (1.0 mL); [a] Consumption of the starting material; [b] Determined by ^{19}F NMR using $PhCF_3$ as an internal standard; These reactions were carried out by S. Verhoog.

The silver-mediated halogen exchange was attempted in the presence of [^{18}F]KF/K$_{222}$ (Table 2.6). Pleasingly, the reaction of **1a** with AgBF$_4$ in DCM at room temperature afforded [^{18}F]**2a** in 33 ± 5 % RCY (entry 1). However, the BF_4^- anion can serve as a source of "cold" fluoride and potentially cause isotopic scrambling by ^{18}F-^{19}F exchange. As a result, the specific activity of the ^{18}F-fluorination mediated by AgBF$_4$ is expected to be intrinsically low. Hence, another Ag^+ source with inactive counter-anion is required.

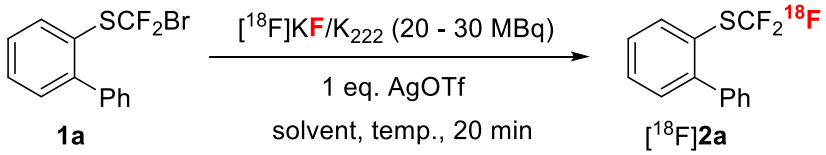


Entry	Ag salt	RCY [a]
1	AgBF$_4$	33 ± 5 % (*n* = 2)
2	AgF	0 % (*n* = 2)
3	Ag$_2$O	0 % (*n* = 2)
4	Ag$_2$CO$_3$	0 % (*n* = 2)
5	CF$_3$CO$_2$Ag	0 % (*n* = 2)
6	AgNO$_3$	0 % (*n* = 2)
7	AgClO$_4$	0 % (*n* = 2)
8	AgOMs	0 % (*n* = 2)
9	AgOTf	60 ± 4 % (*n* = 10)
10	LiOTf	0 % (*n* = 2)
11	Cu(OTf)$_2$	0 % (*n* = 2)

Table 2.6 Silver-mediated ^{18}F-fluorination of **1a** with different silver salts; **1a** (0.04 mmol), Ag salt (0.04 mmol) [^{18}F]KF/K$_{222}$ (20 - 30 MBq), DCM (300 µL); [a] Determined by radio-TLC and radio-HPLC.

A screening of various silver salts revealed that most of these were ineffective to induce ^{18}F-fluorination of **1a** (entries 2 - 8). Gratifyingly, good radiochemical yields of [^{18}F]**2a** were observed when AgOTf was employed (entry 9). The ^{18}F-labelled product was not observed in control experiments using LiOTf and Cu(OTf)$_2$, hence confirming that the presence of Ag^+ is required (entries 10 - 11).

The RCY of the reaction was further improved when DCE was used as a solvent; the maximum RCYs were achieved by using 2 eq. of AgOTf in DCE at either room temperature or 60 ^{o}C (Table 2.7, entries 2 and 3, respectively). Surprisingly, the use of other polar solvents such as Et$_2$O, CH$_3$CN and DMF completely inhibited the ^{18}F-fluorination (Table 2.7, entries 4 - 6). Furthermore, it was found that the reaction was also completely inhibited by the presence of a small amount of CH$_3$CN in DCM (Table 2.7, entry 7).

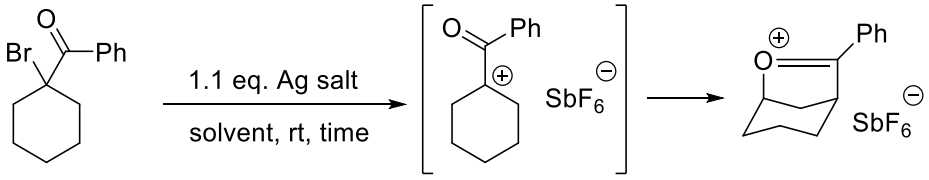


1a [^{18}F]**2a**

Entry	Solvent	Temp.	RCY [a]
1	DCM	rt	60 ± 4 % (*n* = 10)
2	DCE	rt	79 ± 3 % (*n* = 2)
3 [b]	DCE	60 ^{o}C	81 ± 3 % (*n* = 2)
4	Et$_2$O	rt	0 % (*n* = 2)
5	CH$_3$CN	rt	0 % (*n* = 2)
6	DMF	rt	0 % (*n* = 2)
7 [c]	DCM	rt	0 % (*n* = 2)

Table 2.7 Silver-mediated ^{18}F-fluorination of **1a**; **1a** (0.04 mmol), AgOTf (0.04 mmol), [^{18}F]KF/K$_{222}$ (20 - 30 MBq), solvent (300 μL); [a] Obtained by radio-TLC and radio-HPLC; [b] 0.08 mmol AgOTf; [c] CH$_3$CN was not evaporated off after dispensing the [^{18}F]KF/K$_{222}$, hence the reaction was carried out in DCM/CH$_3$CN mixture.

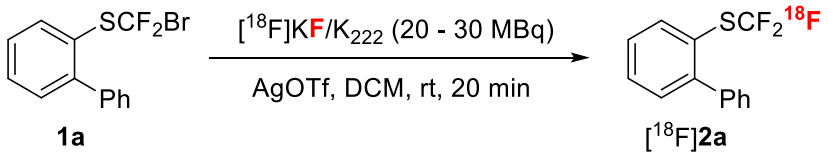
A similar solvent effect in a Ag^+-mediated reaction was also observed by Bégué and Bonnet (Table 2.8).[81] The bromine abstraction of an α-bromoketone substrate mediated by $AgSbF_6$ occurs smoothly in DCM affording a cyclised product in 80 % yield (entry 1). The formation of the cyclised product was fully inhibited when the reaction was carried out in CH_3CN (entry 2). A similar result was observed when the reaction was performed in DCM but with a preformed $AgSbF_6 \cdot nCH_3CN$ complex (entry 3). Such a solvent effect could be explained by the donation of the lone pair on polar solvents such as Et_2O, CH_3CN or DMF to the silver cation, hence reducing the electrophilicity of the Ag^+. The binding enthalpy between CH_3CN and Ag^+ was measured to be as high as 40.1 kcal/mol.[82]



Entry	Ag salt	Solvent	Time	Yield [a]
1	$AgSbF_6$	DCM	2 min	80 %
2	$AgSbF_6$	CH_3CN	72 h	0 %
3	$AgSbF_6 \cdot nCH_3CN$	DCM	72 h	0 %

Table 2.8 Effect of solvent on silver-mediated bromine abstraction.[81]

Minimising the amount of precursor and silver salt employed would be expected to result in the more facile purification of the ^{18}F-labelled product. Therefore, the effect of lowering the amount of **1a** and AgOTf was investigated (Table 2.9). It was found that the RCY of [^{18}F]**2a** was reduced drastically by lowering the amount of **1a** and/or AgOTf (entries 2 - 7). The reaction with half the amounts of **1a**, AgOTf and DCM (hence the concentration remained unchanged) gave only a slight reduction of the RCY from 60 % to 44 % (entry 8). These reaction conditions might be advantageous when the ^{18}F-labelled product is used for clinical PET imaging where high specific activity is of importance.



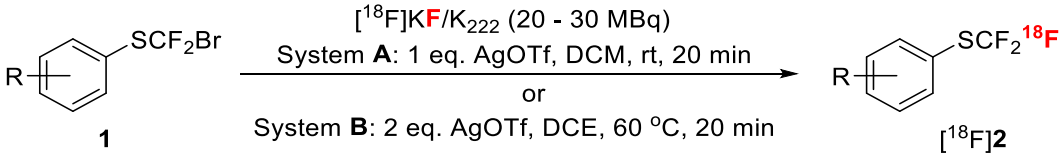
1a [^{18}F]**2a**

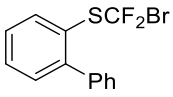
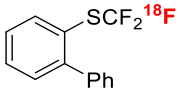
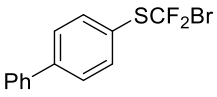
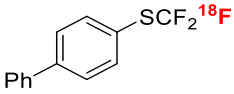
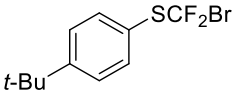
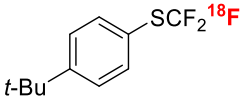
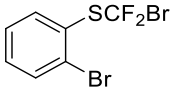
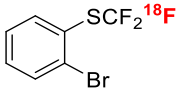
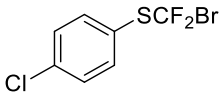
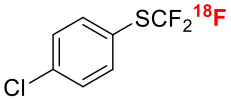
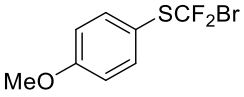
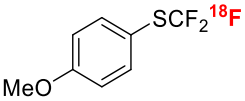
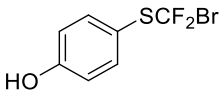
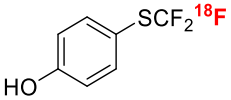
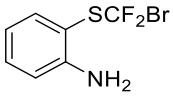
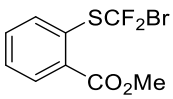
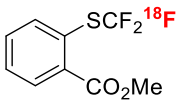
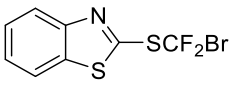
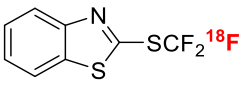
Entry	1a (mmol)	AgOTf (mmol)	DCM	RCY [a]
1	0.04	0.04	300 µL	60 ± 4 % (*n* = 10)
2	0.02	0.04	300 µL	39 ± 2 % (*n* = 2)
3	0.01	0.04	300 µL	18 ± 1 % (*n* = 2)
4	0.04	0.02	300 µL	34 ± 9 % (*n* = 2)
5	0.04	0.004	300 µL	8 ± 8 % (*n* = 2)
6	0.004	0.004	300 µL	18 ± 1 % (*n* = 2)
7	0.02	0.02	300 µL	31 ± 2 % (*n* = 2)
8	0.02	0.02	150 µL	44 ± 2 % (*n* = 2)

Table 2.9 Silver-mediated ^{18}F-fluorination of **1a** with different amount of **1a** and AgOTf and DCM; [a] Determined by radio-TLC and radio-HPLC.

2.4.3 Investigation of the Substrate Scope for ^{18}F-Labelling of Ar-SCF$_3$

The screening of various reaction parameters in the previous section revealed two sets of optimised reaction conditions: System **A** (0.04 mmol precursor, 0.04 mmol AgOTf, 300 µL DCM, rt) which operates at room temperature, and the more forcing conditions, System **B** (0.04 mmol precursor, 0.08 mmol AgOTf, 300 µL DCE, 60 °C). The model substrate **1a** underwent ^{18}F-fluorination under both conditions affording [^{18}F]**2a** in high RCYs (Table 2.10, entry 1). Next, the scope of the reaction was investigated by screening various Ar-SCF$_2$Br substrates bearing different functional groups under both reaction conditions (Table 2.10). The substrate with an electron-neutral substituent such as the *tert*-butyl group in **1c** gave moderate RCYs applying System **A**, but the RCY was dramatically enhanced to 92 % with the System **B** (entry 3).



Entry	Precursor	Product	Product code	RCY [a]	
				System **A**	System **B**
1			[^{18}F]**2a**	60 ± 4 % (*n* = 10)	81 ± 3 % (*n* = 4)
2			[^{18}F]**2b**	12 ± 2 % (*n* = 4)	6 ± 2 % (*n* = 4)
3			[^{18}F]**2c**	34 ± 3 % (*n* = 4)	92 ± 0 % (*n* = 4)
4			[^{18}F]**2d**	2 ± 1 % (*n* = 4)	55 ± 6 % (*n* = 2)
5			[^{18}F]**2e**	2 ± 0 % (*n* = 4)	46 ± 11 % (*n* = 4)
6			[^{18}F]**2f**	36 ± 2 % (*n* = 4)	74 ± 3 % (*n* = 4)
7			[^{18}F]**2k**	16 ± 2 % (*n* = 4)	21 ± 1 % (*n* = 4)
8			[^{18}F]**2j**	35 ± 2 % (*n* = 4)	40 ± 2 % (*n* = 4)
9			[^{18}F]**2g**	1 ± 1 % (*n* = 4)	2 ± 1 % (*n* = 4)
10			[^{18}F]**2h**	0 % (*n* = 4)	0 % (*n* = 4)

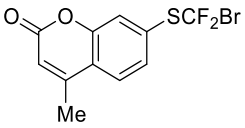
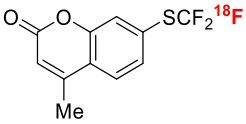
11			[^{18}F]**2i**	1 ± 0 % (*n* = 4)	37 ± 5 % (*n* = 4)

Table 2.10 Investigation of the substrate scope for ^{18}F-labelling of Ar-SCF$_3$; **1** (0.04 mmol), [^{18}F]KF/K$_{222}$ (20 - 30 MBq); System **A** : AgOTf (0.04 mmol), DCM (300 µL), rt; System **B** : AgOTf (0.08 mmol), DCE (300 µL), 60 °C; The precursors and reference compounds were synthesised by S. Verhoog; [a] Determined by radio-TLC and radio-HPLC.

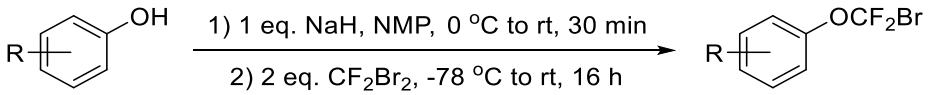
The substrates containing halogen groups such as *para*-chloride (**1d**) and *ortho*-bromide (**1e**) afforded trace amounts of the desired product when System **A** was applied; however, the reactions were greatly improved using System **B**, giving [^{18}F]**2d** and [^{18}F]**2e** in 55 ± 6 % and 46 ± 11 % RCYs, respectively (entries 4 - 5). The reaction was shown to tolerate electron-donating substituents such as a methoxy group (**1f**), a free hydroxy group (**1k**) and a free amino group (**1j**). Applying System **A**, [^{18}F]**2f**, [^{18}F]**2k** and [^{18}F]**2j** were obtained in 36 ± 2 %, 16 ± 2 % and 35 ± 2 % RCYs, respectively (entries 6 - 8). With System **B**, the RCY of [^{18}F]**2f** was doubled; in contrast, the formation of several ^{18}F-radiolabelled side products was observed for substrates **1k** and **1j** which might be caused by reactions at the free-OH and -NH$_2$ groups at elevated temperature.

The electron-withdrawing ester substituent in **1g** completely inhibited the ^{18}F-fluorination under both conditions (entry 9). This result is in agreement with the assumption that the reaction proceeds *via* an Ar-SCF$_2^+$ intermediate in which the carbocation is greatly stabilised by the lone pair electrons of the sulfur atom. The presence of an electron-withdrawing group on the aromatic ring induces more delocalisation of the S-lone pair, hence the extent to which this lone pair stabilises the carbocation intermediate is greatly reduced. The benzothiazole substrate **1h** was also inactive under both conditions due to the high degree of delocalisation of the S-lone pair into thiazole ring system (entry 10). The coumarin substrate **1i**, underwent ^{18}F-fluorination only with System **B**, affording [^{18}F]**2i** in 37 ± 5 % RCY (entry 11).

2.5 Silver-Mediated ^{18}F-Labelling of Ar-OCF$_3$ from Ar-OCF$_2$Br

2.5.1 Preparation of Ar-OCF$_2$Br precursors

The only known procedure for the preparation of Ar-OCF$_2$Br compounds was the reaction of the corresponding phenol with CF_2Br_2 under basic conditions. However, low yielding and limited substrate scope were the major drawbacks of this method.[83] Synthesis of the Ar-OCF$_2$Br precursors from phenols was attempted using slightly modified reaction conditions, but the results were unsatisfactory (Table 2.11). Consequently, a new method for the synthesis of Ar-OCF$_2$Br was required.



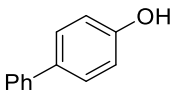
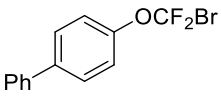
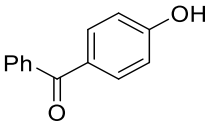
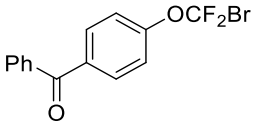
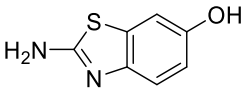
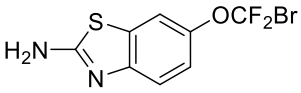
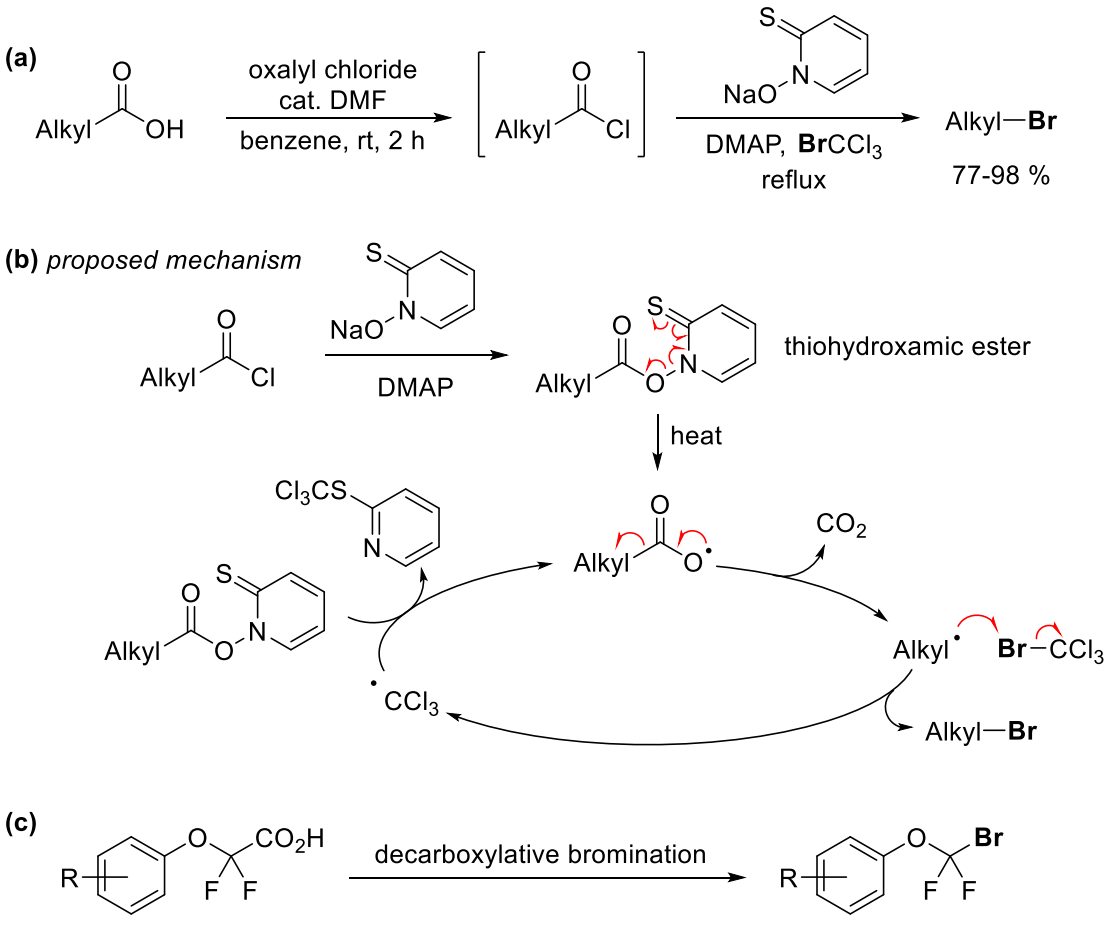
Entry	Phenol	Product	Yield [a]
1			9 %
2			0 %
3			0 %

Table 2.11 Preparation of Ar-OCF$_2$Br precursors from phenols; Phenol (0.10 mmol), NaH (0.10 mmol), CF_2Br_2 (0.20 mmol) and NMP (0.20 mL); [a] Determined by ^{19}F NMR using $PhCF_3$ as an internal standard.

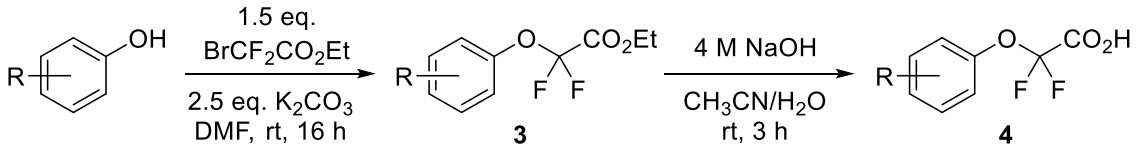
Barton and co-workers reported decarboxylative bromination of various alkyl carboxylic acids *via* thiohydroxamic ester intermediates (Scheme 2.17).[84] The procedure involves the *in situ* formation of the acid chloride by reaction of the corresponding carboxylic acid with oxalyl chloride and a catalytic amount of DMF in benzene at room temperature. The solvent

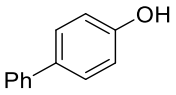
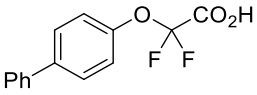
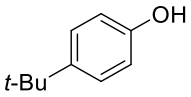
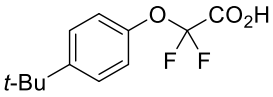
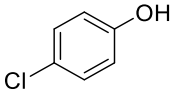
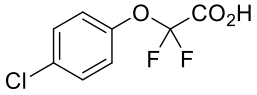
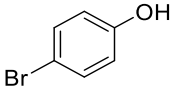
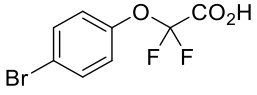
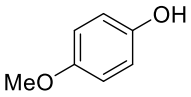
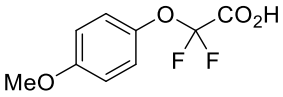
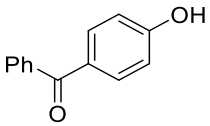
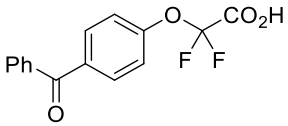
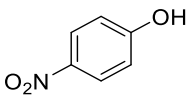
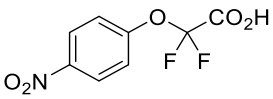
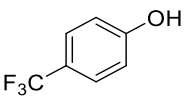
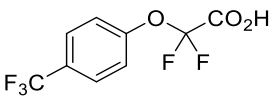
is then evaporated and the acid chloride is re-dissolved in bromotrichloromethane ($BrCCl_3$). Subsequently, 2-mercaptopyridine *N*-oxide sodium salt and DMAP were added and the resulting mixture was heated at reflux, affording the bromodecarboxylated product in high yields (Scheme 2.17a). The mechanism involves the formation of a thiohydroxamic ester containing a relatively weak N–O bond, which undergoes homolytic cleavage under thermal activation. The resulting carboxyl radical then undergoes facile decarboxylation to afford the corresponding alkyl radical which can abstract bromine from the $BrCCl_3$ solvent. This process generates the CCl_3 radical that can initiate a chain reaction by reaction with another molecule of thiohydroxamic ester (Scheme 2.17b). Based on this precedent, we proposed that Ar-OCF_2Br precursors can be synthesised by this methodology starting from *α*,*α*-difluoro-*α*-aryloxyacetic acid derivatives (Ar-OCF_2CO_2H) (Scheme 2.17c).



Scheme 2.17 Bromodecarboxylation of alkyl carboxylic acids *via* thiohydroxamic esters.

The *α,α*-difluoro-*α*-aryloxyacetic acids (**4**) could be prepared by a two-step procedure; the corresponding phenol was reacted with $BrCF_2CO_2Et$ and K_2CO_3 in DMF at room temperature, affording Ar-OCF_2CO_2Et (**3**) which was hydrolysed with NaOH to provide Ar-OCF_2CO_2H precursors (**4**) (Table 2.12).



Entry	Phenol	Product	Product code	Yield [a]
1			**4a**	**55 %** (55 %, 100 %)
2			**4b**	**45 %** (72 %, 62 %)
3			**4c**	**38 %** (38 %, 99 %)
4			**4d**	**26 %** (34 %, 76 %)
5			**4f**	**38 %** (38 %, 98 %)
6			**4i**	**33 %** (35 %, 95 %)
7			**4j**	**6 %** (11 %, 50 %)
8			**4k**	**24 %** (24 %, 98 %)

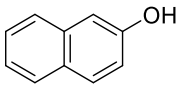
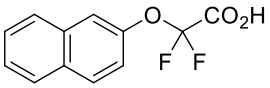
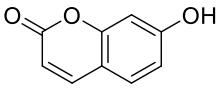
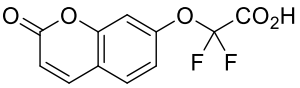
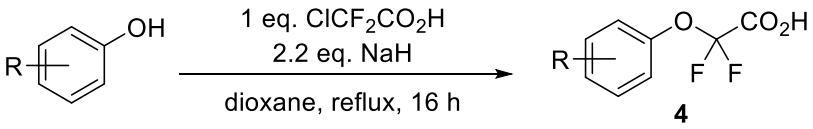
9			**4l**	**31 %** (38 %, 81 %)
10			**4m**	**13 %** [b]

Table 2.12 Preparation of Ar-OCF$_2$CO$_2$H (**4**) from phenol using BrCF$_2$CO$_2$Et; [a] Isolated yields (yield of the first step; yield of the second step); [b] The crude mixture from the first step was used without purification.

The first alkylation step was typically hampered by several side-reactions in which Ar-OCF$_2$H was usually obtained as the main by-product. In several cases, it was impossible to purify **3** by column chromatography; therefore, **4** was instead prepared by an alternative method reported by Fretz.[85] The reaction of phenols with NaH and ClCF$_2$CO$_2$H in dioxane under reflux provided **4** in moderate to good yields (Table 2.13). However, the drawback of this method is the difficulty in removing the high boiling point dioxane and the unreacted ClCF$_2$CO$_2$H reagent.



4

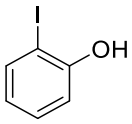
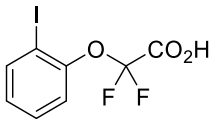
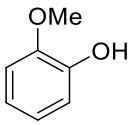
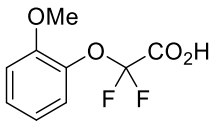
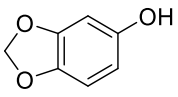
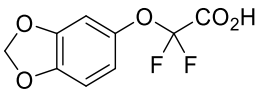
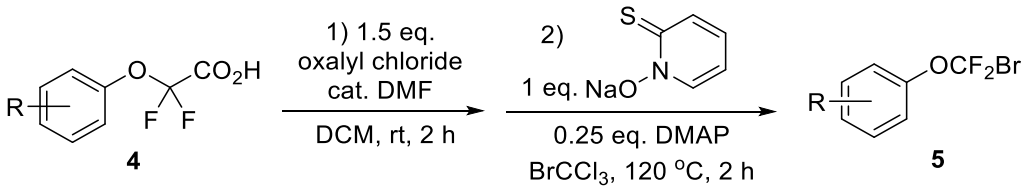
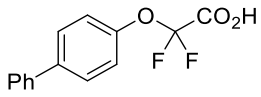
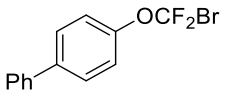
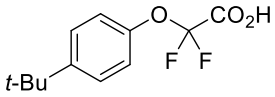
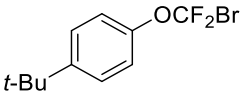
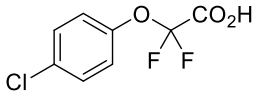
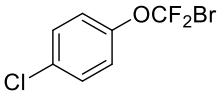
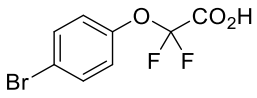
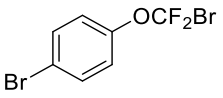
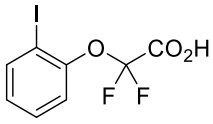
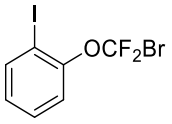
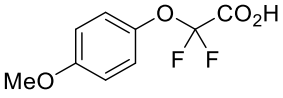
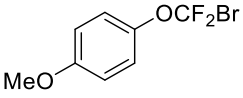
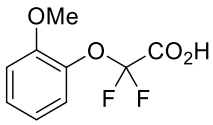
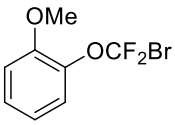
Entry	Phenol	Product	Product code	Yield [a]
1			**4e**	25 %
2			**4g**	75 %
3			**4h**	74 %

Table 2.13 Preparation of Ar-OCF$_2$CO$_2$H from phenol using ClCF$_2$CO$_2$H; [a] Isolated yields.

Under slightly modified conditions, *α*,*α*-difluoro-*α*-aryloxyacetic acids (**4**) underwent bromodecarboxylation, affording the Ar-OCF$_2$Br (**5**) in 31 - 65 % yields (Table 2.14). The reaction tolerates a wide range of substituents including halogens (entries 3 - 5), electron-donating groups (entries 6 - 8) and a ketone (entry 9). However, lower yields were observed with substrates containing strong electron-withdrawing groups such as -NO$_2$ (entry 10) and -CF$_3$ (entry 11) as well as the coumarin substrate leading to **5m** (entry 13).



Entry	Carboxylic acid	Product	Product code	Yield [a]
1			**5a**	65 %
2			**5b**	60 %
3			**5c**	49 %
4			**5d**	61 %
5			**5e**	47 %
6			**5f**	65 %
7			**5g**	58 %

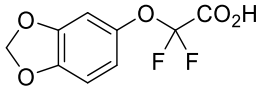
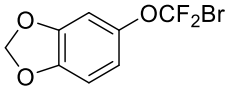
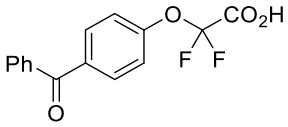
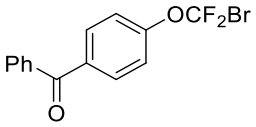
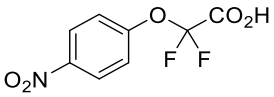
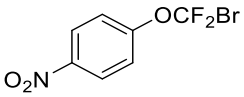
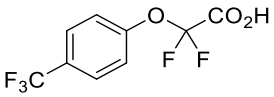
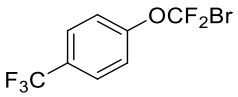
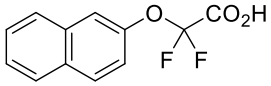
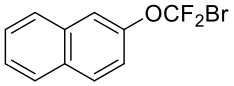
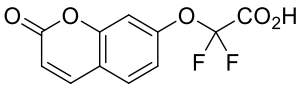
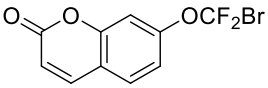
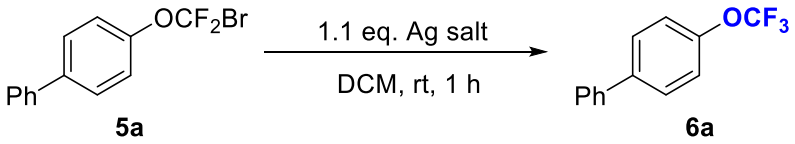
8			**5h**	58 %
9			**5i**	62 %
10			**5j**	38 %
11			**5k**	31 %
12			**5l**	59 %
13			**5m**	35 %

Table 2.14 Bromodecarboxylation of Ar-OCF$_2$CO$_2$H (**4**) providing Ar-OCF$_2$Br (**5**); [a] Isolated yields.

2.5.2 Optimisation of Reaction Conditions for ^{18}F-Labelling of Ar-OCF$_3$

The biphenyl compound **5a** was chosen as a model substrate for the reaction optimisation. The reaction of **5a** with $AgBF_4$ or $AgSbF_6$ gave **6a** in excellent yields (Table 2.15).

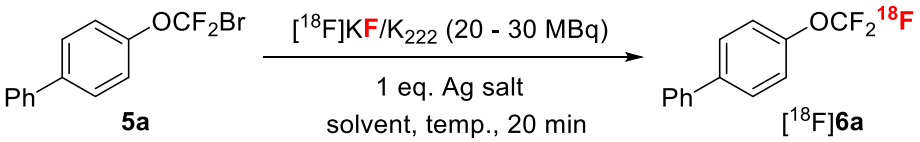


5a **6a**

Entry	Ag salt	Conversion [a]	Yield [a]
1	$AgBF_4$	100 %	98 %
2	$AgSbF_6$	100 %	91 %

Table 2.15 Fluorination of **5a** with silver salts; **5a** (0.10 mmol), Ag salt (0.11 mmol), DCM (1 mL); [a] Determined by ^{19}F NMR using $PhCF_3$ as an internal standard.

However, when similar reaction conditions were tested in the presence of [^{18}F]KF/K$_{222}$, only 9 % of the ^{18}F was incorporated into the product [^{18}F]**6a** (Table 2.16, entry 1). Other silver salts were not effective; for example, the reaction with AgOTf afforded [^{18}F]**6a** in a trace amount along with other ^{18}F-labelled side-products (entry 5). The RCY was improved to 8 ± 2 % when the reaction was carried out in DCE at 60 °C (entry 6) and was further improved to 24 ± 3 % when 2 eq. of AgOTf was used (entry 7). In contrast, a coordinating solvent such as CH$_3$CN completely inhibited the reaction (entry 8). [^{18}F]**6a** was formed in a RCY of 18 ± 3 % when toluene was used as a solvent at 110 °C (entry 9); however, the reaction gave a heterogeneous mixture after being quenched which might lead to inaccuracy in the determination of RCC by radio-TLC.

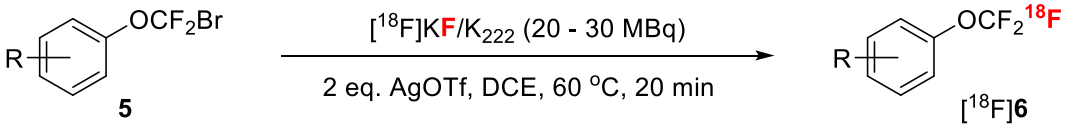


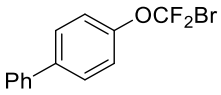
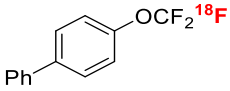
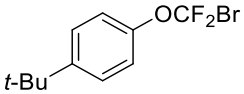
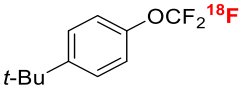
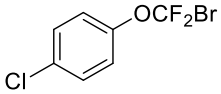
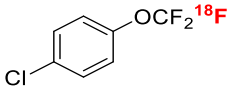
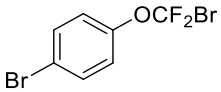
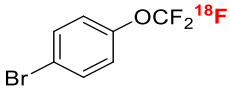
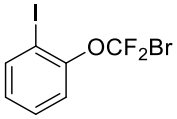
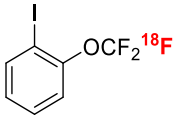
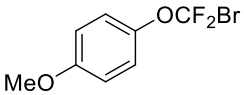
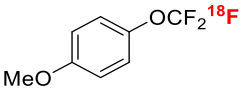
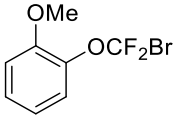
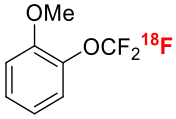
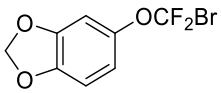
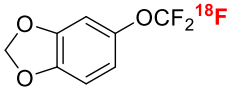
Entry	Ag salt	Solvent	Temp.	RCY [a]
1	1 eq. AgBF$_4$	DCM	rt	9 ± 1 % (*n* = 2)
2	1 eq. AgF	DCM	rt	0 % (*n* = 2)
3	1 eq. AgNO$_3$	DCM	rt	0 % (*n* = 2)
4	1 eq. Ag(CF$_3$CO$_2$)	DCM	rt	2 ± 0 % (*n* = 2)
5	1 eq. AgOTf	DCM	rt	1 ± 0 % (*n* = 2)
6	1 eq. AgOTf	DCE	60 °C	8 ± 2 % (*n* = 2)
7	2 eq. AgOTf	DCE	60 °C	24 ± 3 % (*n* = 4)
8	1 eq. AgOTf	CH$_3$CN	60 °C	0 % (*n* = 2)
9	1 eq. AgOTf	toluene	110 °C	18 ± 3 % (*n* = 2)

Table 2.16 Reaction optimisation for silver-mediated ^{18}F-fluorination of **5a**; **5a** (0.04 mmol), Ag salt (0.04 mmol) [^{18}F]KF/K$_{222}$ (20 - 30 MBq), solvent (300 μL); [a] Determined by radio-TLC and radio-HPLC.

2.5.3 Investigation of the Substrate Scope for ^{18}F-Labelling of Ar-OCF$_3$

With the optimised reaction conditions in hand (Table 2.16, entry 7; 0.04 mmol precursor, 0.08 mmol AgOTf, 300 µL DCE, 60 °C), the scope of the reaction was investigated by screening a range of Ar-OCF$_2$Br substrates (Table 2.17).



Entry	Precursor	Product	Product code	RCY [a]
1			[^{18}F]**6a**	24 ± 2 % (*n* = 4)
2			[^{18}F]**6b**	33 ± 2 % (*n* = 4)
3			[^{18}F]**6c**	7 ± 2 % (*n* = 4)
4			[^{18}F]**6d**	8 ± 2 % (*n* = 4)
5			[^{18}F]**6e**	1 ± 0 % (*n* = 4)
6			[^{18}F]**6f**	48 ± 4 % (*n* = 4)
7			[^{18}F]**6g**	10 ± 2 % (*n* = 4)
8			[^{18}F]**6h**	72 ± 3 % (*n* = 4)

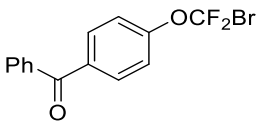
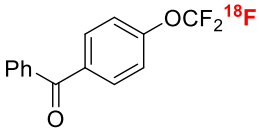
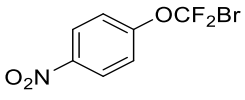
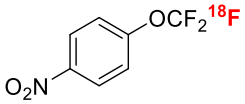
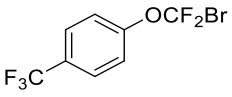
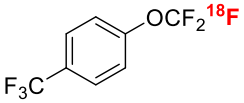
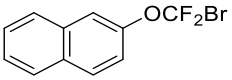
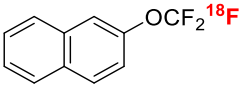
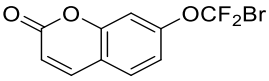
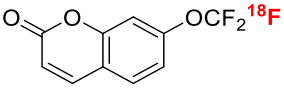
9			[^{18}F]**6i**	15 ± 2 % (*n* = 4)
10			[^{18}F]**6j**	2 ± 1 % (*n* = 4)
11			[^{18}F]**6k**	1 ± 0 % (*n* = 4)
12			[^{18}F]**6l**	29 ± 5 % (*n* = 4)
13			[^{18}F]**6m**	7 ± 0 % (*n* = 4)

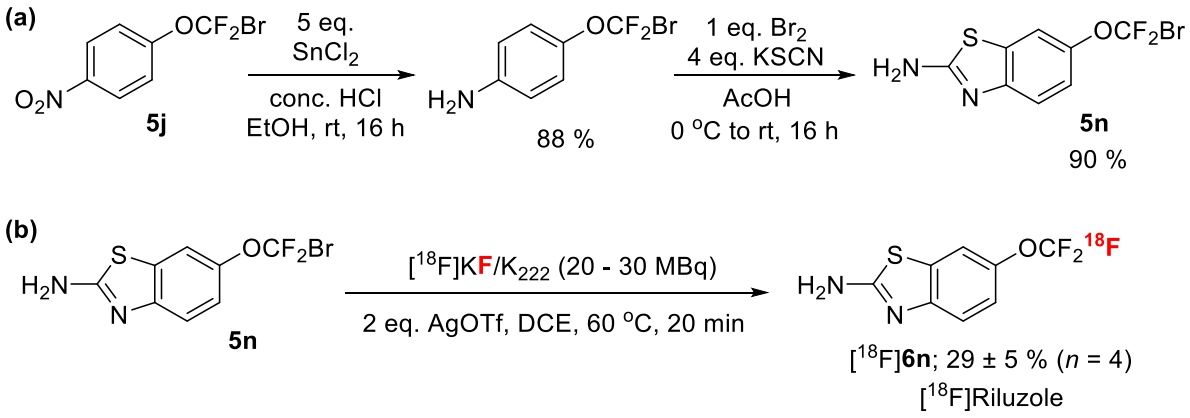
Table 2.17 Investigation of the substrate scope for ^{18}F-labelling of Ar-OCF$_3$; **5** (0.04 mmol), AgOTf (0.08 mmol), [^{18}F]KF/K$_{222}$ (20 - 30 MBq), DCE (300 µL), 60 °C; for the synthesis of reference compounds, see Chapter 5.2.4 [a] Determined by radio-TLC and radio-HPLC.

The reaction of other electron-neutral precursors such as *para-tert*-butyl substituted **5b** and naphthyl substrate **5l** gave the ^{18}F-labelled products in 33 ± 2 % and 29 ± 5 % RCYs, respectively, which are in similar range as the model substrate (entries 2 and 12). The precursors with halogen substituents were less effective; *para*-chloro substituted [^{18}F]**6c** and *para*-bromo substituted [^{18}F]**6d** were obtained in 7 ± 2 % and 8 ± 5 % RCYs, respectively (entries 3 - 4). The substrate with *ortho*-iodo substituent was much less reactive; only a trace amount of [^{18}F]**6e** was obtained after the reaction (entry 5). Electron-donating substituents were beneficial for the reaction; ^{18}F-labelling of the *para*-methoxy substituted **5f** and 1,3-benzodioxole-derived precursor **5h** were achieved in 48 ± 4 % and 72 ± 3 % RCYs, respectively. However, the precursor bearing an *ortho*-methoxy substituent was less reactive, affording [^{18}F]**6g** in 10 ± 2 % RCY. Substrates with electron-withdrawing substituents typically gave lower RCY; the phenyl ketone [^{18}F]**6i** was obtained in 15 ± 2 % RCY.

In particular, the strong electron-withdrawing substituents such as -NO_2 (**5j**) and -CF_3 (**5k**) were detrimental for the reaction (entries 10 - 11). Finally, the heterocyclic coumarin substrate [^{18}F]**6m** was achieved in 7 ± 0 % RCY (entry 13). In summary, the ^{18}F-labelling of Ar-OCF_3 can be achieved in low to moderate yields. The reaction is sensitive to both electronic and steric effects. In general, the electron-rich substrates usually provided higher RCYs of the ^{18}F-labelled product than the electron-poor substrates, which might suggest a mechanism that involves the formation of Ar-OCF_2^+ intermediate. Mechanistic studies will be discussed in Chapter 2.9.

2.5.4 Application of the Methodology to the Synthesis of [^{18}F]Riluzole

Riluzole is the first drug that was approved for the treatment of amyotrophic lateral sclerosis (ALS),[86] a neurological disorder that is caused by the death of neurons that control voluntary muscle.[87] The precursor, 6-(bromodifluoromethoxy)benzo[d]thiazol-2-amine (**5n**), was synthesised from the *para*-NO_2 substituted substrate **5j** by a two-step procedure (Scheme 2.18a). First, the nitro group was reduced by $SnCl_2$ and HCl,[88] affording the corresponding aniline, which was subsequently reacted with KSCN and Br_2 in AcOH to give the 2-amino-benzothiazole precursor **5n** in excellent yield.[89] To our delight, the precursor **5n** underwent ^{18}F-fluorination under the optimised conditions, yielding ^{18}F-labelled Riluzole ([^{18}F]**6n**) in 29 ± 5 % RCY (Scheme 2.18b).

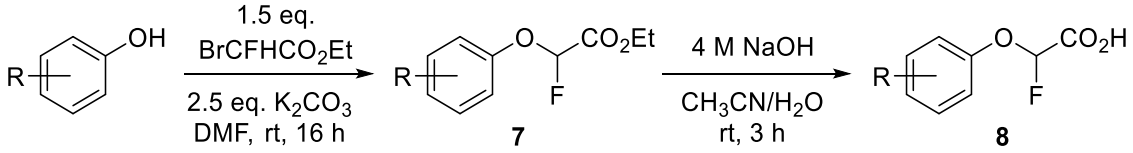


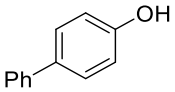
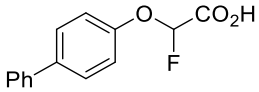
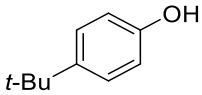
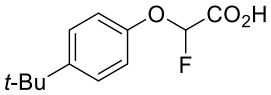
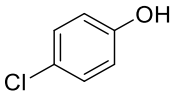
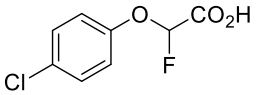
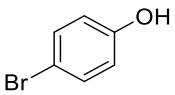
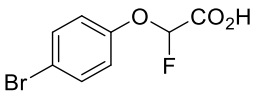
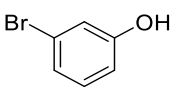
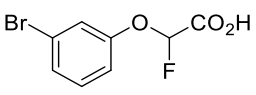
Scheme 2.18 Preparation of the precursor **5n** and the radiosynthesis of [^{18}F]Riluzole.

2.6 Silver-Mediated ^{18}F-Labelling of Ar-OCF$_2$H from Ar-OCFClH

2.6.1 Preparation of Ar-OCFClH precursors

According to the silver-mediated ^{18}F-labelling of Ar-SCF$_3$ and Ar-OCF$_3$ described in the previous sections, we proposed that the Ar-OCF$_2$H group could be radiolabelled using the corresponding Ar-OCFBrH precursor. The synthesis of these precursors was attempted by a modified version of the procedure employed for the synthesis of the Ar-OCF$_2$Br precursors. Firstly, *α*-fluoro-*α*-aryloxyacetic acids (**8**) were prepared in good to excellent yields by alkylation of the corresponding phenols with ethyl bromofluoroacetate followed by hydrolysis with NaOH (Table 2.18).



Entry	Phenol	Product	Product code	Yield [a]
1			**8a**	**94 %** (94 %, 99 %)
2			**8b**	**63 %** (78 %, 81 %)
3			**8c**	**55 %** (72 %, 76 %)
4			**8d**	**45 %** (54 %, 83 %)
5			**8e**	**74 %** (83 %, 89 %)

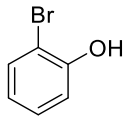
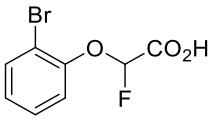
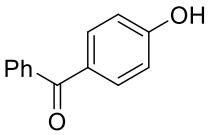
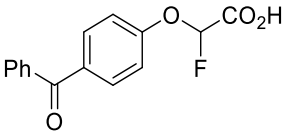
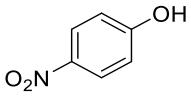
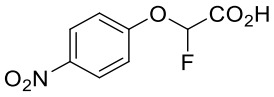
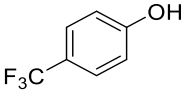
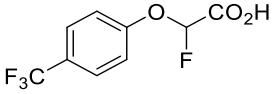
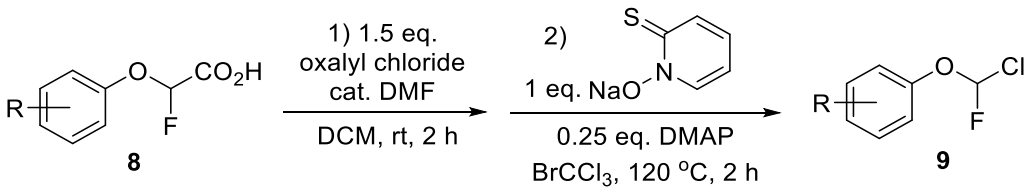
6			**8f**	**71 %** (85 %, 83 %)
7			**8g**	**86 %** (91 %, 94 %)
8			**8h**	**87 %** (92 %, 95 %)
9			**8i**	**85 %** (89 %, 95 %)

Table 2.18 Preparation of Ar-OCFHCO$_2$H (**8**) from phenol using BrCFHCO$_2$Et; [a] Isolated yields (yield of the first step; yield of the second step).

When the α-fluoro-α-aryloxyacetic acids (**8**) were subjected to the bromodecarboxylation conditions used for the synthesis of Ar-OCF$_2$Br precursors, the chlorinated products Ar-OCFClH (**9**) were obtained instead of the expected brominated products (Table 2.19). The identity of the species was confirmed by high-resolution mass spectrum analysis showing peaks that corresponded to the chlorinated substrates. The procedure for chlorodecarboxylation of alkyl carboxylic acid was reported using CCl_4 as a solvent. However, when the $BrCCl_3$ was substituted with CCl_4, no chlorinated product was observed. We propose that the bromodecarboxylation conditions led to the *in situ* formation of the highly electrophilic bromodecarboxylated product, Ar-OCFBrH, which underwent facile halogen exchange with chloride ions produced from the oxalyl chloride to give Ar-OCFClH (**9**). The yields of **9** after flash column chromatography were typically low due to their instability towards moisture and heat; **9a** was slowly hydrolysed upon stirring in a mixture of CH_3CN/H_2O at room temperature. As a result, the Ar-OCFClH precursors were stored at low temperature under an argon atmosphere. Electron-rich substrates such as methoxy substituted **9j** could not be isolated due to rapid decomposition during purification.



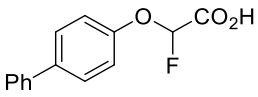
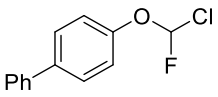
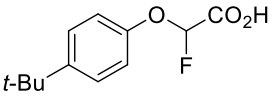
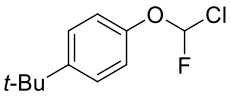
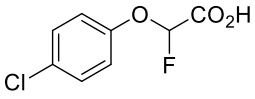
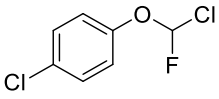
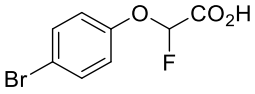
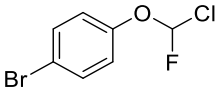
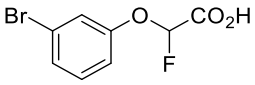
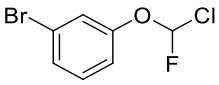
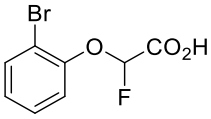
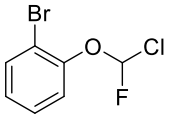
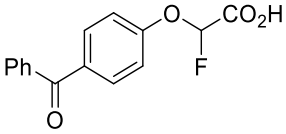
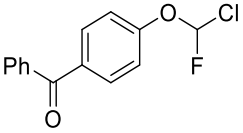
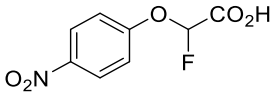
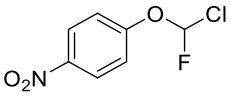
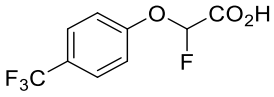
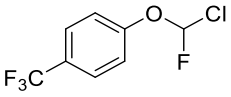
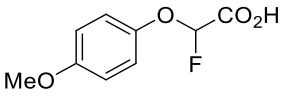
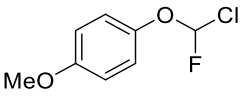
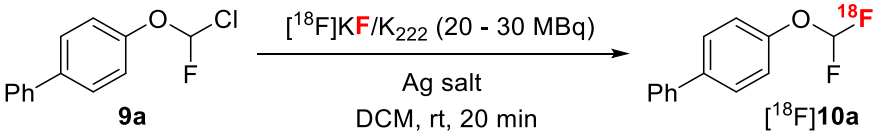
Entry	Carboxylic acid	Product	Product code	Yield [a]
1			**9a**	65 %
2			**9b**	60 %
3			**9c**	49 %
4			**9d**	61 %
5			**9e**	47 %
6			**9f**	65 %
7			**9g**	58 %
8			**9h**	58 %
9			**9i**	62 %
10			**9j**	0 %

Table 2.19 Chlorodecarboxylation of Ar-OCFHCO$_2$H (**8**) providing Ar-OCFClH (**9**); [a] Isolated yields.

2.6.2 Optimisation of Reaction Conditions for ^{18}F-Labelling of Ar-OCF$_2$H

To our delight, when the model substrate **9a** was subjected to the optimised conditions for the ^{18}F-labelling of Ar-SCF$_3$ described in Section 2.4.3 (System **A**: 0.04 mmol precursor, 0.04 mmol AgOTf, 300 µL DCM, rt), the ^{18}F-labelled [^{18}F]**10a** product was observed in 70 ± 3 % RCY (Table 2.20, entry 1). Due to the high reactivity of this precursor, it is worth noting that the ^{18}F-fluorination also occurs in the absence of AgOTf at room temperature, although with much lower RCY (Table 2.20, entry 2).

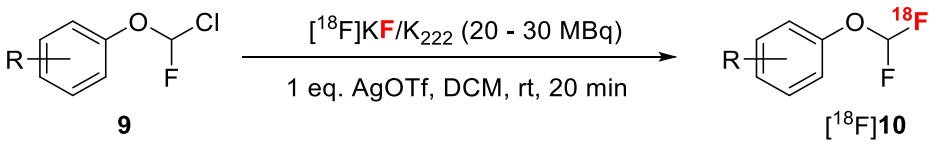


Entry	Ag salt	RCY [a]
1	1 eq. AgOTf	70 ± 3 % (*n* = 4)
2	-	19 ± 4 % (*n* = 2)

Table 2.20 Reaction optimisation for silver-mediated ^{18}F-fluorination of **9a**; **9a** (0.04 mmol), Ag salt (0.04 mmol) [^{18}F]KF/K$_{222}$ (20 - 30 MBq), DCM (300 µL); [a] Determined by radio-TLC and radio-HPLC.

2.6.3 Investigation of the Substrate Scope for ^{18}F-Labelling of Ar-OCF$_2$H

A wide range of Ar-OCFClH precursors (**9**) was subjected to the silver-mediated ^{18}F-fluorination described in the previous section (Table 2.21). Under the optimised reaction conditions, the ^{18}F-labelled Ar-OCF$_2$H ([^{18}F]**10**) was obtained in good to excellent RCYs. The reaction tolerates halogen substituents including *para*-chloro, *para*-bromo, *meta*-bromo and *ortho*-bromo substituents (entries 3 - 6). Pleasingly, the substrates bearing electron-withdrawing groups such as ketone, -NO$_2$ and -CF$_3$ also gave radiolabelled products in excellent RCYs (entries 7 - 9), in contrast to the previously observed results; these classes of substituents were found to be detrimental for the ^{18}F-fluorination of Ar-SCF$_2$Br and Ar-OCF$_2$Br. This switch of reactivity might indicate a change in the reaction mechanism.



9 [^{18}F]**10**

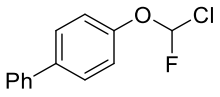
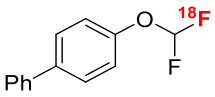
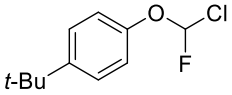
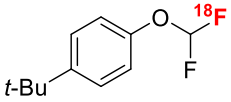
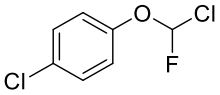
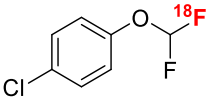
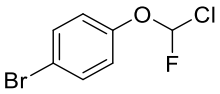
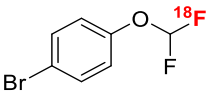
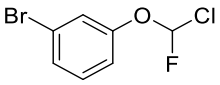
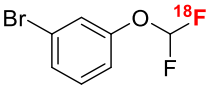
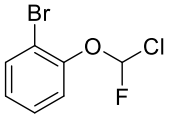
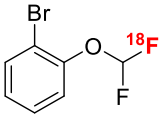
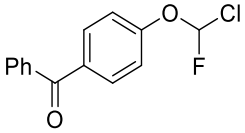
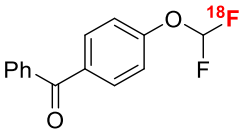
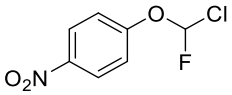
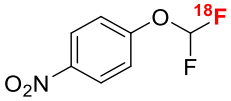
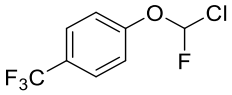
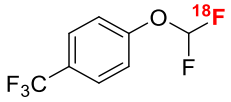
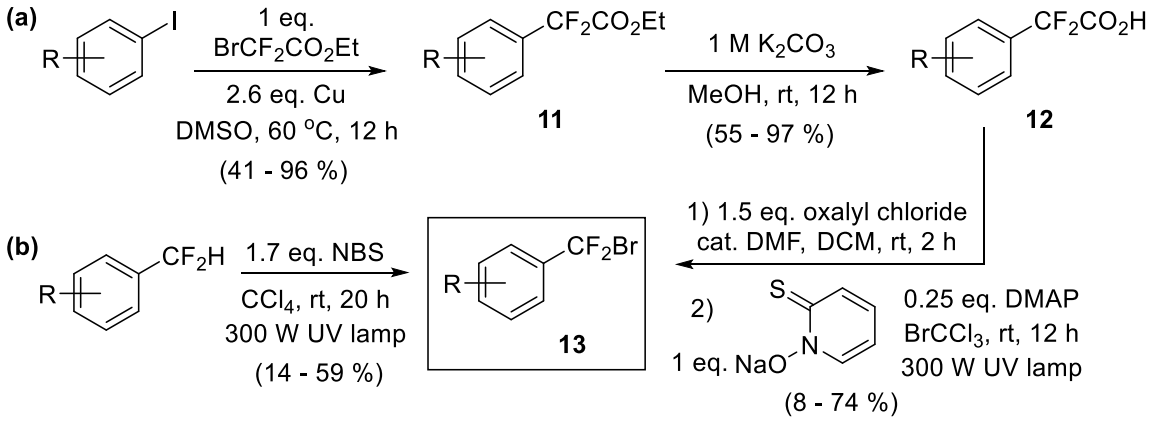
Entry	Precursor	Product	Product code	RCY [a]
1			[^{18}F]**10a**	70 ± 3 % (*n* = 4)
2			[^{18}F]**10b**	75 ± 3 % (*n* = 4)
3			[^{18}F]**10c**	79 ± 5 % (*n* = 4)
4			[^{18}F]**10d**	67 ± 3 % (*n* = 4)
5			[^{18}F]**10e**	68 ± 2 % (*n* = 4)
6			[^{18}F]**10f**	79 ± 3 % (*n* = 4)
7			[^{18}F]**10g**	73 ± 5 % (*n* = 4)
8			[^{18}F]**10h**	66 ± 2 % (*n* = 4)
9			[^{18}F]**10i**	73 ± 4 % (*n* = 4)

Table 2.21 Investigation of the substrate scope for ^{18}F-labelling of Ar-OCF$_2$H; **9** (0.04 mmol), AgOTf (0.04 mmol), [^{18}F]KF/K$_{222}$ (20 - 30 MBq), DCM (300 µL), rt; for the synthesis of reference compounds, see Chapter 5.2.8 [a] Determined by radio-TLC and radio-HPLC.

2.7 Silver-Mediated ^{18}F-Labelling of Ar-CF$_3$ and Ar-CF$_2$H

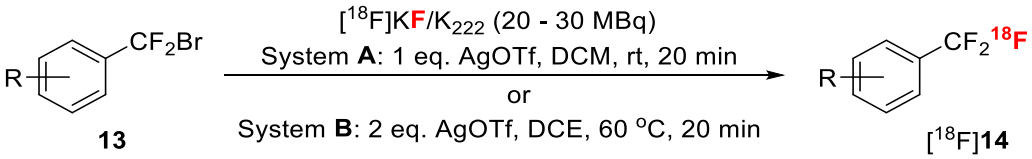
The work described in this section was carried out in collaboration with S. Verhoog, L. Pfeifer and S. Calderwood.[90] To date, there is no general method for the synthesis of ^{18}F-labelled Ar-CF$_2$H from [^{18}F]fluoride and the ^{18}F-labelling of Ar-CF$_3$ *via* halogen exchange typically requires harsh reaction conditions (see Section 2.3.3). Our success in the ^{18}F-labelling of Ar-SCF$_3$, Ar-OCF$_3$ and Ar-OCF$_2$H encouraged us to expand the scope of the silver-mediated ^{18}F-fluorination methodology to Ar-CF$_3$ and Ar-CF$_2$H substrates from Ar-CF$_2$Br and Ar-CFClH precursors.

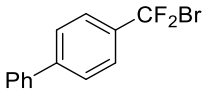
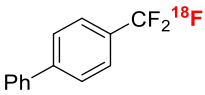
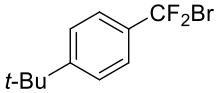
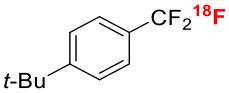
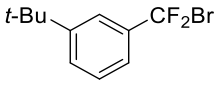
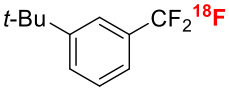
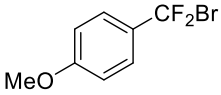
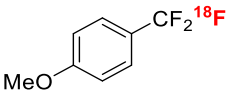
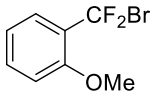
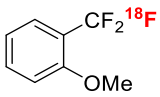
The Ar-CF$_2$Br precursor (**13**) can be prepared from the corresponding aryl iodide by a three-step synthesis (Scheme 2.19a). Copper-mediated cross-coupling reaction of aryl iodide and ethyl bromodifluoroacetate provided Ar-CF$_2$CO$_2$Et (**11**)[91] which can be hydrolysed with K$_2$CO$_3$ to give Ar-CF$_2$CO$_2$H (**12**) in good yields.[92] Bromodecarboxylation of **12** *via* the thermal activation method was not successful; decomposition products were observed. Instead, the mixture was stirred at room temperature under a 300 W UV lamp. As a result, the decarboxylation was induced under milder reaction conditions, providing broader substrate scope and higher yields. Alternatively, the Ar-CF$_2$Br precursors can be prepared by radical bromination of Ar-CF$_2$H substrates, providing **13** in moderate yields (Scheme 2.19b).



Scheme 2.19 Preparation of the Ar-CF$_2$Br **13** for the ^{18}F-labelling of Ar-CF$_3$.

The silver-mediated ^{18}F-fluorination of **13** was performed using the optimised conditions for the ^{18}F-labelling of Ar-SCF$_3$ described in Section 2.4.3 (System **A**: 0.04 mmol precursor, 0.04 mmol AgOTf, 300 µL DCM, rt) (Table 2.22). Electron-neutral and electron-rich substrates both underwent ^{18}F-fluorination in high RCYs at room temperature (entries 1 - 5). Electron-poor substrates usually gave low RCY in the System **A** (entries 6 - 10). However, moderate RCYs of the ^{18}F-labelled products can be obtained under the more forcing conditions (System **B**: 0.04 mmol precursor, 0.08 mmol AgOTf, 300 µL DCE, 60 °C). Strongly electron-withdrawing substituents such as -NO$_2$ and -CF$_3$ fully inhibited the ^{18}F-incorporation even when System **B** was applied (entries 11 - 12).



Entry	Precursor	Product	Product code	RCY [a]	
				System **A**	System **B**
1 [b]			[^{18}F]**14a**	75 ± 1 % (*n* = 27)	-
2			[^{18}F]**14b**	80 ± 3 % (*n* = 4)	-
3 [b]			[^{18}F]**14c**	54 ± 3 % (*n* = 4)	-
4			[^{18}F]**14d**	69 ± 1 % (*n* = 4)	-
5 [b]			[^{18}F]**14e**	44 ± 3 % (*n* = 4)	-

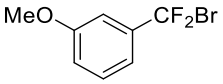
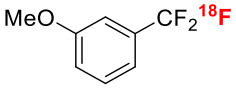
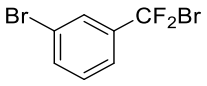
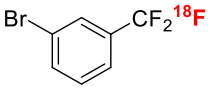
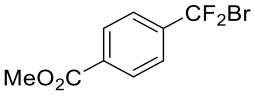
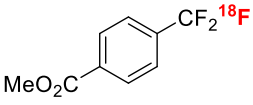
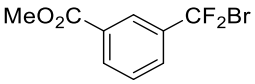
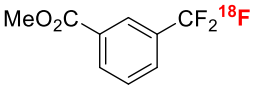
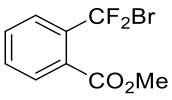
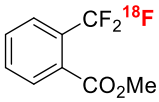
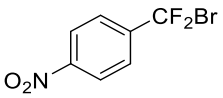
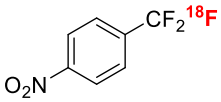
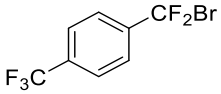
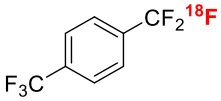
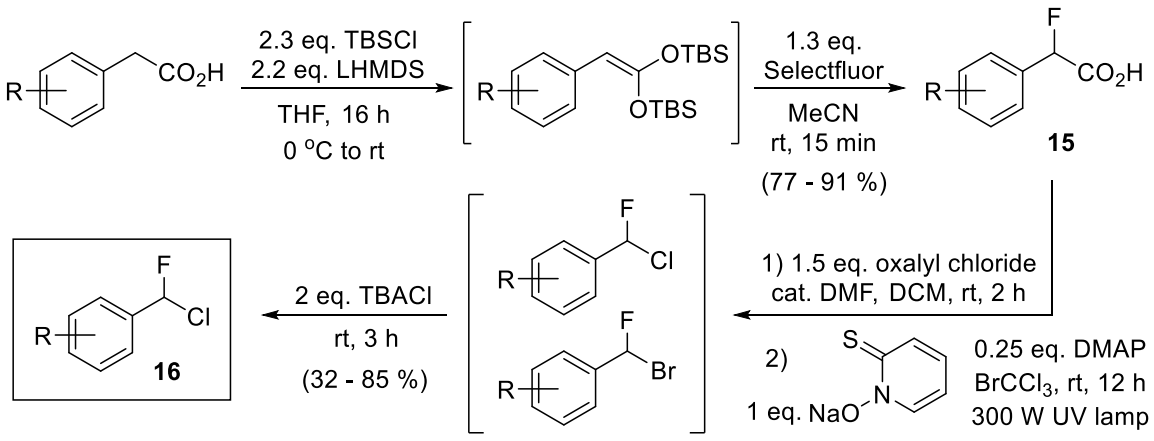
6			[^{18}F]**14f**	25 ± 5 % (*n* = 4)	49 ± 2 % (*n* = 4)
7 [b]			[^{18}F]**14g**	0 % (*n* = 4)	10 ± 3 % (*n* = 4)
8 [b]			[^{18}F]**14h**	0 % (*n* = 4)	26 ± 4 % (*n* = 4)
9			[^{18}F]**14i**	4 ± 1 % (*n* = 4)	36 ± 4 % (*n* = 4)
10 [b]			[^{18}F]**14j**	3 ± 0 % (*n* = 4)	16 ± 2 % (*n* = 4)
11 [b]			[^{18}F]**14k**	0 % (*n* = 2)	0 % (*n* = 2)
12			[^{18}F]**14l**	0 % (*n* = 2)	0 % (*n* = 2)

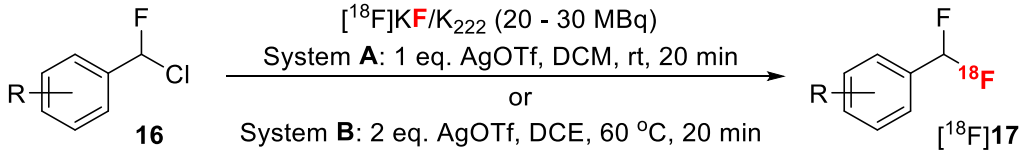
Table 2.22 Investigation of the substrate scope for ^{18}F-labelling of Ar-CF$_3$; **4** (0.04 mmol), [^{18}F]KF/K$_{222}$ (20 - 30 MBq); System **A** : AgOTf (0.04 mmol), DCM (300 µL), rt; System **B** : AgOTf (0.08 mmol), DCE (300 µL), 60 °C; [a] Determined by radio-TLC and radio-HPLC; [b] These precursors were synthesised by S. Calderwood.

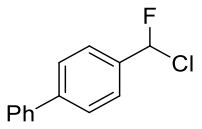
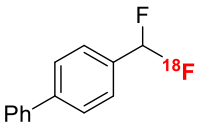
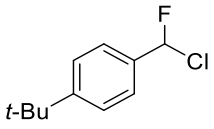
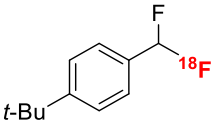
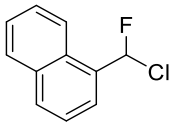
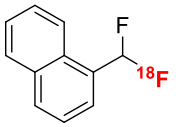
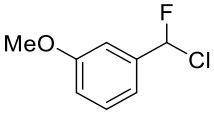
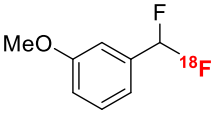
In the synthesis of [^{18}F]Ar-CF$_2$H, the Ar-CFClH precursors (**16**) were prepared by a two-step procedure (Scheme 2.20). First, the corresponding arylacetic acids were reacted with *tert*-butyldimethylsilyl chloride (TBSCl) and LHMDS to form bis(silyl)ketene acetal, which was then fluorinated by Selectfluor to give aryl(fluoro)acetic acids (**15**) in excellent yields. **15** was then subjected to the same bromodecarboxylation conditions to give a mixture of bromo- and chlorodecarboxylated products, which was fully converted into the chlorinated product (**16**) using tetrabutylammonium chloride (TBACl).



Scheme 2.20 Preparation of the Ar-CFClH precursors (**16**).
These precursors were synthesised by L. Pfeifer.

A range of Ar-CFClH precursors (**16**) was tested on both System **A** and System **B** (Table 2.23). The reactions illustrated the same trend as the ^{18}F-labelling of Ar-CF$_3$ where electron-rich substrates displayed significantly higher reactivity; however, the RCYs were relatively lower (in the range of 17 % to 39 %).



Entry	Precursor	Product	Product code	RCY [a]	
				System **A**	System **B**
1			[^{18}F]**17a**	30 ± 4 % (n = 4)	-
2			[^{18}F]**17b**	39 ± 3 % (n = 4)	-
3			[^{18}F]**17c**	37 ± 3 % (n = 4)	-
4			[^{18}F]**17d**	24 ± 6 % (n = 4)	-

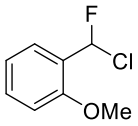
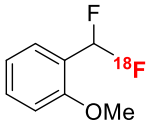
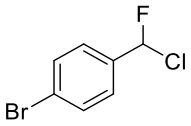
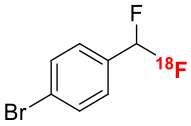
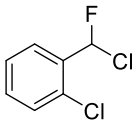
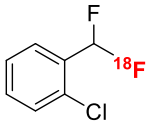
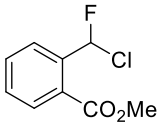
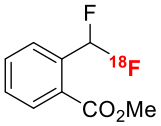
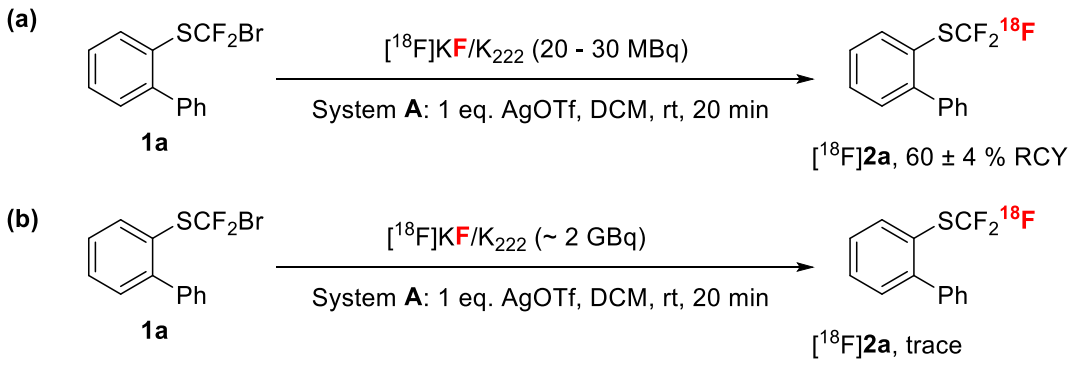
5			[^{18}F]**17e**	27 ± 2 % (*n* = 4)	-
6			[^{18}F]**17f**	17 ± 1 % (*n* = 4)	26 ± 3 % (*n* = 4)
7			[^{18}F]**17g**	0 % (*n* = 2)	17 ± 1 % (*n* = 4)
8			[^{18}F]**17h**	0 % (*n* = 2)	17 ± 3 % (*n* = 4)

Table 2.23 Investigation of the substrate scope for ^{18}F-labelling of Ar-CF$_2$H; **17** (0.04 mmol), [^{18}F]KF/K$_{222}$ (20 - 30 MBq); System **A** : AgOTf (0.04 mmol), DCM (300 µL), rt; System **B** : AgOTf (0.08 mmol), DCE (300 µL), 60 °C; The precursors and reference compounds were synthesised by L. Pfeifer; [a] Determined by radio-TLC and radio-HPLC.

2.8 Isolation Experiments and Determination of Specific Activity

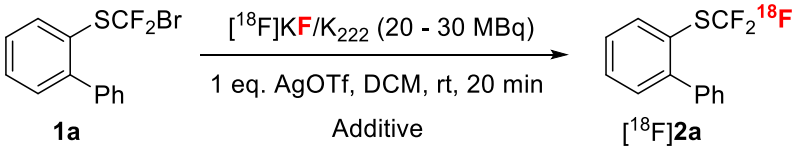
It has been demonstrated that AgOTf can facilitate ^{18}F-labelling of a wide range of substrates including Ar-SCF$_3$, Ar-OCF$_3$, Ar-OCF$_2$H, Ar-CF$_3$ and Ar-CF$_2$H. However, these screening reactions were performed with a small amount of radioactivity (in a range of 20 - 30 MBq) and the radiochemical yields were determined by radio-TLC and radio-HPLC analysis of the crude mixture. In order for the methodology to become practically useful for the production of PET radiotracers, a scale-up protocol that allows for isolation of the ^{18}F-labelled product is required.

The model substrate **1a** was found to efficiently undergo ^{18}F-fluorination when applying System **A** (0.04 mmol precursor, 0.04 mmol AgOTf, 300 µL DCM, rt, 20 min) yielding [^{18}F]**2a** in 60 ± 4 % RCY (Scheme 2.21a). In contrast, only a trace amount of [^{18}F]**2a** was observed when the reaction was performed with a full batch of [^{18}F]KF/K$_{222}$ (~ 2 GBq) (Scheme 2.21b)



Scheme 2.21 The ^{18}F-fluorination of **1a** with a higher amount of radioactivity.

We proposed that the reaction could be inhibited by the higher amount of K_2CO_3 and K_{222} in the reaction mixture. These species were necessary for the elution of the [^{18}F]fluoride from the ion exchange cartridge during the fluoride activation stage (see the end of Chapter 1.3). For screening reactions, the resulting mixture of [^{18}F]KF/K_{222} complex and the remaining K_2CO_3 and K_{222} was dissolved in CH_3CN, then a small aliquot of [^{18}F]KF/K_{222} was taken. As a result, these species were presented in a low amount, hence the reactions were not inhibited. To provide evidence for the detrimental effects of K_2CO_3 and K_{222}, spiking experiments were conducted by adding these species in the same amounts that were used for [^{18}F]fluoride elution (Table 2.24).

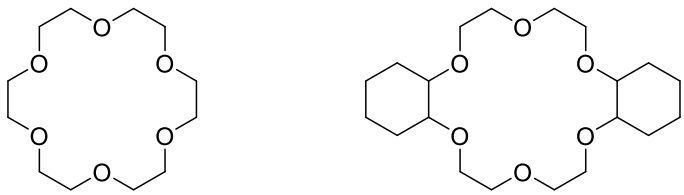


Entry	Additive	RCY [a]
1	-	60 ± 4 % (*n* = 10)
2	0.014 mmol K_2CO_3 0.027 mmol K_{222}	6 ± 1 % (*n* = 2)
3	0.027 mmol K_{222}	6 ± 0 % (*n* = 2)
4	0.014 mmol K_2CO_3	29 ± 1 % (*n* = 2)
5	0.014 mmol $K_2C_2O_4$	51 ± 4 % (*n* = 2)

Table 2.24 The effect of additives on the silver-mediated ^{18}F-fluorination of **1a**.

The results of the spiking experiments confirmed that the presence of either K_2CO_3 or K_{222} can dramatically reduce the RCY of the reaction (entries 2 - 4). Therefore, an alternative base and chelator that did not inhibit the reaction had to be identified. When the reaction was performed in the presence of potassium oxalate ($K_2C_2O_4$), only a slight decrease in RCY was observed (entry 5); hence, it could be used as a substitute for K_2CO_3. However, as $K_2C_2O_4$ is much less basic, a small amount of K_2CO_3 had to be added to prevent the formation of volatile [^{18}F]HF during the subsequent drying step.[93]

In addition, an alternative potassium cation chelator was required for the replacement of Kryptofix-2.2.2. Although 18-crown-6 is a popular choice, the resulting [^{18}F]KF/18-crown-6 complex is known to have limited solubility in organic solvents.[94] To increase the solubility, we considered a more hydrophobic dicyclohexyl substituted crown ether (diCy-18-crown-6) as an alternative chelator (Scheme 2.22).

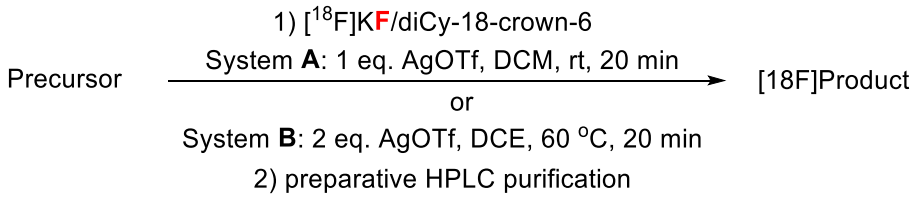


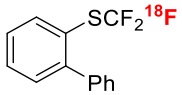
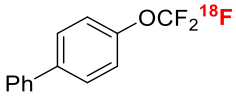
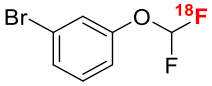
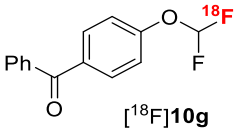
Scheme 2.22 Alternative potassium ion chelators.

The isolation protocol starts with trapping the delivered [^{18}F]fluoride in the anion exchange cartridge, which was flushed by the new eluting mixture : $K_2C_2O_4$ (0.012 mmol, 4 mg), K_2CO_3 (0.0014 mmol, 0.2 mg) and diCy-18-crown-6 (0.038 mmol, 14 mg) in 4:1 CH_3CN/H_2O (1.0 mL). The resulting solution containing approximately 2 GBq of [^{18}F]KF/diCy-18-crown-6 complex was azeotropically dried, dissolved in MeOH then transferred to a vial containing AgOTf. The solvent was removed at 100 ^{o}C under a stream of nitrogen, then a solution of the precursor in either DCM or DCE was added. After stirring for 20 min at the specified temperature, the crude mixture was filtered through a syringe

filter to remove the silver salt and purified by preparative HPLC using CH_3CN/H_2O eluent system. The fraction containing the major radioactive peak was collected and analysed by radio-HPLC to confirm the identity of the radiolabelled product. The isolated radiochemical yield was determined by comparing the radioactivity of this fraction to the starting activity. In addition, specific activity (SA), the radioactivity per unit mass (for more details, see Section 1.3), can be calculated by taking the ratio of the isolated radioactivity and the mass of "cold" product. The mass can be calculated by comparing the area under the UV-trace with a calibration curve made by known amounts of the product references.

A selection of Ar-SCF$_2$Br, Ar-OCF$_2$Br, Ar-OCFClH, Ar-CF$_2$Br and Ar-CFClH substrates was subjected to the isolation protocol and the isolated yields as well as the specific activities were determined (Table 2.25).



Entry	Product	System	Starting Activity (MBq) [a]	Isolated Activity (MBq) [b]	RCY	SA (GBq/μmol)
1	 [^{18}F]**2a**	**A**	2080 1890 1942	169 197 79	8 ± 2 % (*n* = 3)	0.32
2	 [^{18}F]**6a**	**B**	1725 588	237 40	10 ± 3 % (*n* = 2)	0.08
3	 [^{18}F]**10e**	**A**	1510 685	509 195	32 ± 2 % (*n* = 2)	0.04
4	 [^{18}F]**10g**	**A**	1982 327	242 106	22 ± 10 % (*n* = 2)	0.17

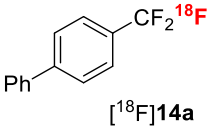
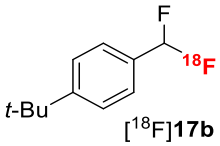
5	 [^{18}F]**14a**	**A**	1090	272	24 % (n = 1)	0.25
6	 [^{18}F]**17b**	**A**	1690	363	21 % (n = 1)	0.03

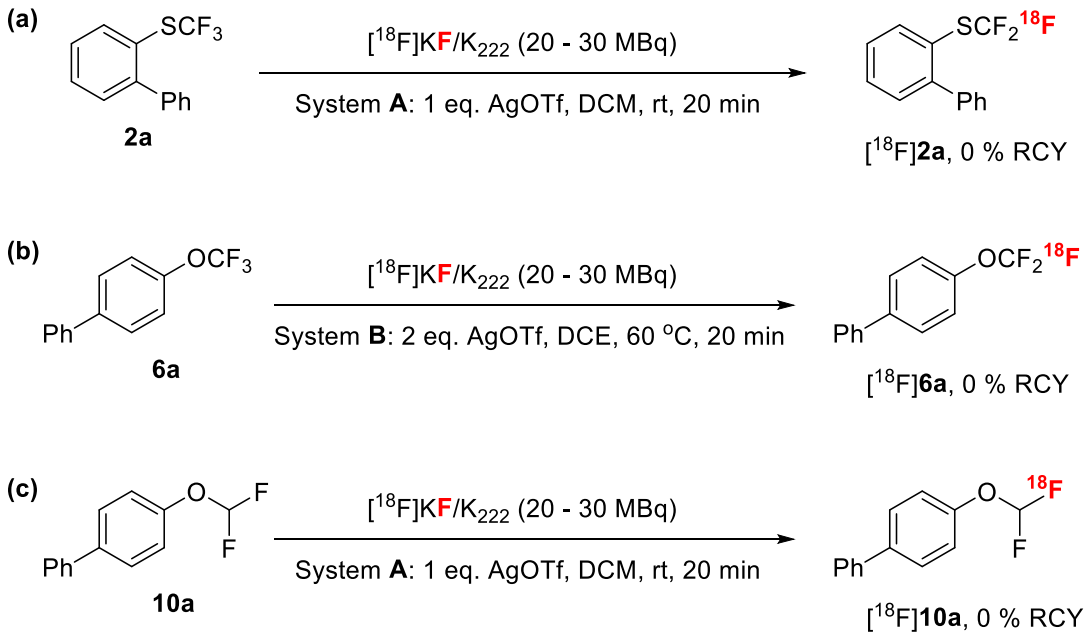
Table 2.25 Isolation of the ^{18}F-labelled products; [a] Measured after drying procedure; [b] Measured after isolated by preparative HPLC.

All ^{18}F-labelled products were successfully isolated in 8 - 32 % RCYs. There are many reasons why these numbers are significantly lower than those obtained from the screening conditions. The main difference is that the isolated yields were not decay corrected (i.e. did not take into account the decay of the radioisotope over time). The additives such as $K_2C_2O_4$ and diCy-18-crown-6 could also impede the reaction. Moreover, the ^{18}F-labelled products could be lost during transfers and during the HPLC purification step. Nevertheless, the final activities were in the range of 40 MBq to 509 MBq, which are sufficient for application in PET imaging. The specific activities of the isolated products were determined to be in the range of 0.03 GBq/µmol to 0.32 GBq/µmol which are comparable to those reported for the ^{18}F-labelling of Ar-CF$_3$ applying the previously reported [^{18}F]CuCF$_3$ strategy.[73] The relatively low SA values suggest that the protocol is only suitable for supporting drug development studies.

The silver content of the ^{18}F-labelled product prepared with this methodology was determined in collaboration with PhosphonicS Limited. The isolated products were analysed by inductively coupled plasma atomic emission spectrometry (ICP-AES). The silver contents of [^{18}F]**6a** and [^{18}F]**10e** were found to be 0.02 µg/g and 0.05 µg/g, respectively, confirming that the AgOTf can be efficiently removed by the preparative HPLC.

2.9 Investigation of Reaction Mechanism

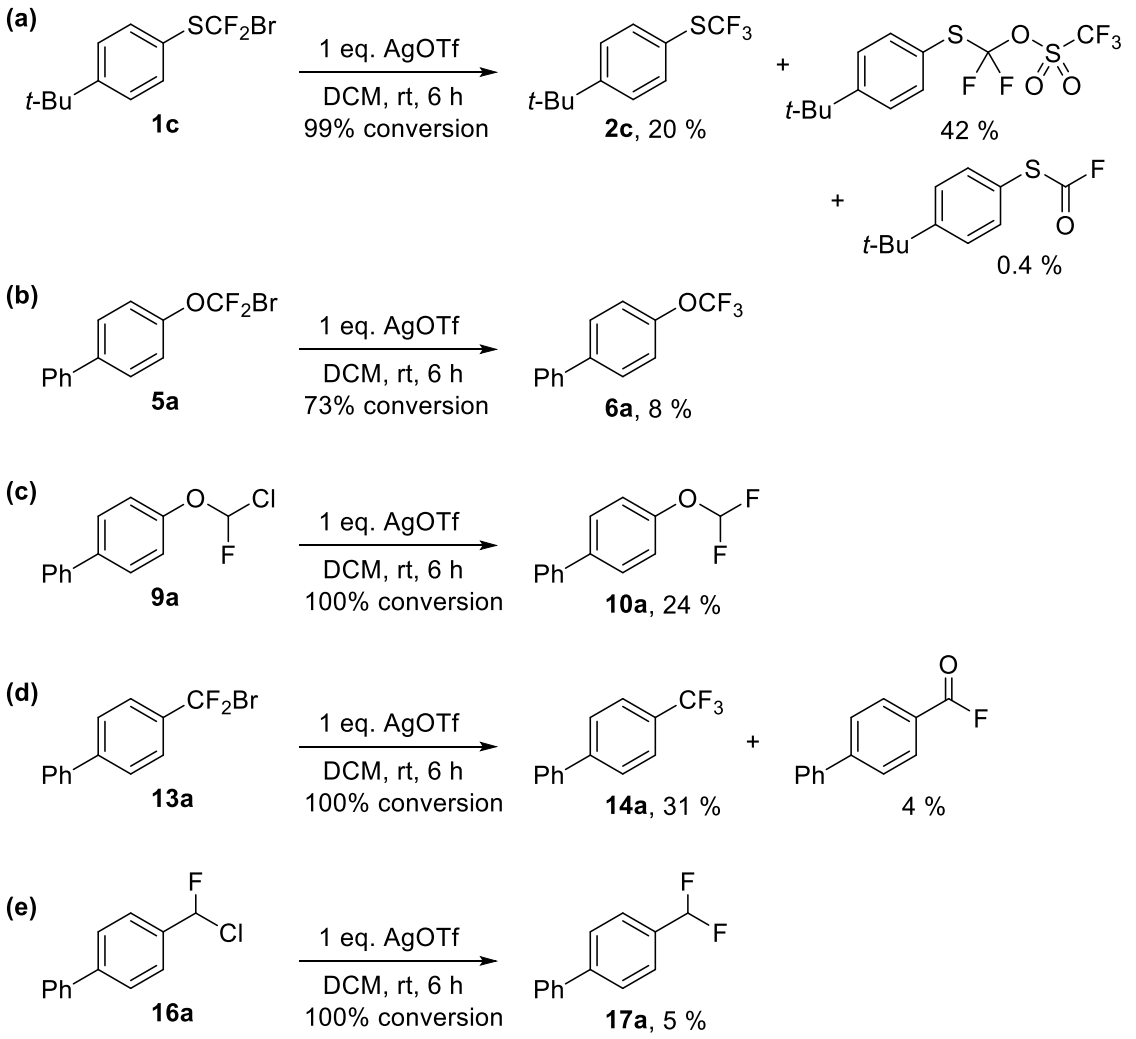
The low specific activities observed for the isolated ^{18}F-labelled products suggested the occurrence of side reactions that led to the formation of ^{19}F-fluoride. One of the possibilities is the isotopic scrambling caused by the ^{18}F-^{19}F exchange. Control experiments were performed by subjecting the non-radiolabelled products **2a**, **6a** and **10a** under the optimised silver-mediated ^{18}F-fluorination conditions (Scheme 2.23). Incorporation of ^{18}F into the substrates was not observed in these experiments, suggesting that direct isotopic exchange is not the cause of the low specific activity.



Scheme 2.23 Control experiments on the isotopic exchange of **2a**, **6a** and **10a**.

Surprisingly, the reaction of precursors (Ar-SCF$_2$Br **1c**, Ar-OCF$_2$Br **5a**, Ar-OCFClH **9a**, Ar-CF$_2$Br **13a** and Ar-CFClH **16a**) with AgOTf in the absence of a fluoride source led to decomposition of the precursors in high conversions, with concomitant formation of the corresponding fluorinated products (Scheme 2.24). In the case of Ar-SCF$_2$Br substrate **1a**, the ^{19}F NMR analysis revealed the formation of Ar-SCF$_2$OTf (a triplet {J_{F-F} = 5.2 Hz} at –42.8 ppm and a quartet {J_{F-F} = 5.2 Hz} at –74.4 ppm)[95] in 42 % ^{19}F NMR yield, as well as a

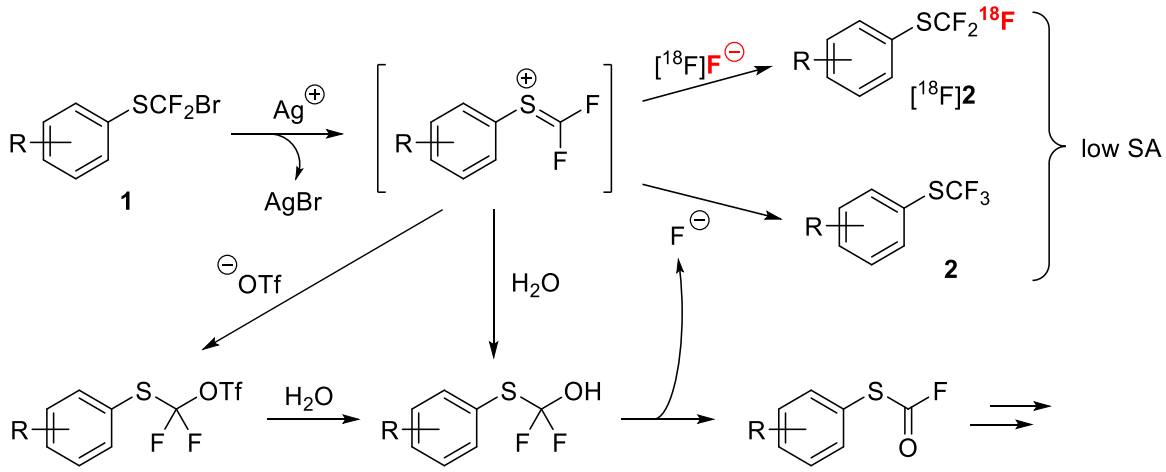
trace amount of Ar-SCOF (a singlet at +42.8 ppm)[96] (Scheme 2.24a). The formation of an acyl fluoride moiety was also observed in the reaction of the Ar-CF_2Br substrate **13a** (Scheme 2.24d).



Scheme 2.24 Reactions of precursors with AgOTf in the absence of fluoride source; Yields determined by ^{19}F NMR using $PhCF_3$ as an internal standard.

The formation of the fluorinated products suggests that the starting materials can act as fluoride sources under the reaction conditions. From these results, we proposed a mechanism that involves the abstraction of bromide or chloride of the starting material by the halogenophilic silver salt, leading to the formation of a carbocation that is partially stabilised by neighbouring fluorine atom(s) and a heteroatom (sulfur or oxygen). This carbocation can be trapped by [^{18}F]fluoride to afford the desired ^{18}F-labelled product. Alternatively, it can

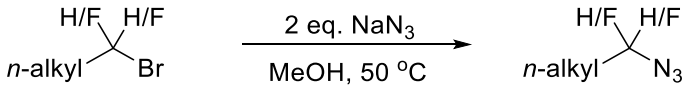
also be trapped by a triflate anion or a water molecule, which can eventually hydrolyse the starting material to form an acyl fluoride with a concomitant release of the "cold" fluoride. This "cold" fluoride can compete with the [^{18}F]fluoride, causing low specific activity.



Scheme 2.25 Proposed mechanism of the silver-mediated ^{18}F-labelling of Ar-SCF$_3$.

The formation of the carbocation intermediate is in agreement with the results of the substrate screening study. In most cases, the reactions of the substrates containing electron-donating substituents afforded significantly higher RCY and the presence of strong electron-withdrawing substituents such as -NO$_2$ and -CF$_3$ is typically highly detrimental for the reaction. In contrast, all of the Ar-OCFClH substrates underwent silver-mediated ^{18}F-fluorination in high RCYs, including the -NO$_2$ and -CF$_3$ substituted precursors (see Section 2.6.3). This result suggests that the reaction of Ar-OCFClH substrates might operate with a different mechanism. Dolbier and co-workers have studied the quantitative effect of adjacent fluorine substituents on the rates of S$_N$2 reactions.[97] The reaction of a weakly basic anion, azide ion (N_3^-), with different *n*-alkyl bromides revealed that the substrate with a single fluorine substituent at the *α*-position reacted approximately 5 times slower than the non-fluorinated substrate (Table 2.26, entry 2). However, the *α*,*α*-difluorinated analogue showed a dramatic 13250 times decrease in the reactivity towards S$_N$2 reaction (Table 2.26, entry 3). The authors suggested that the classical electron-electron

Coulomb repulsive interaction is the main contribution the inhibition effect of the *α,α*-difluorinated substrate.



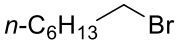
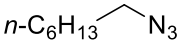
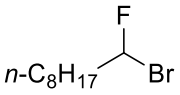
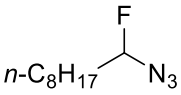
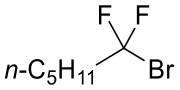
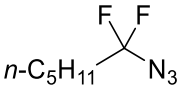
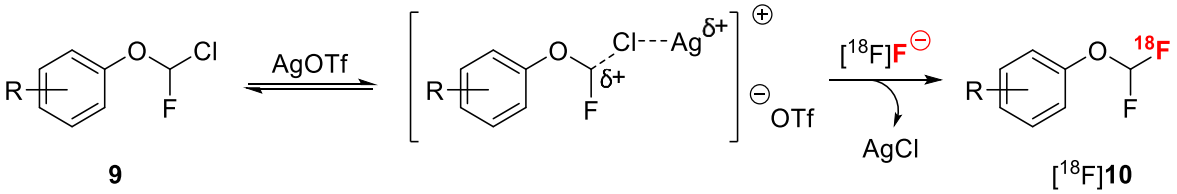
Entry	Alkyl bromide	Product	10^5 k S_N2	k_H/k_F
1			6.89	1
2			1.42	5
3			5.2 x 10^{-4}	13250

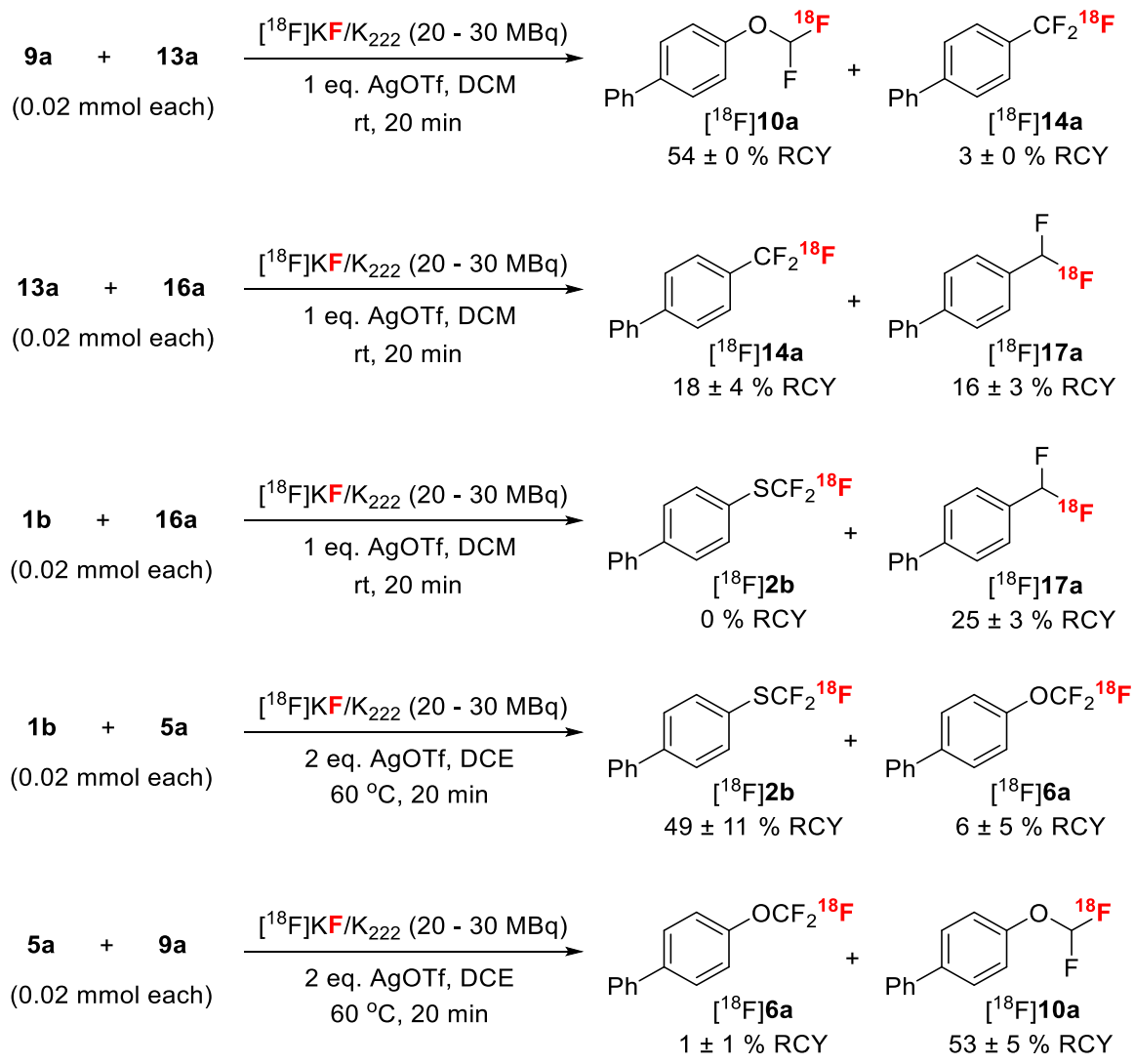
Table 2.26 Effect of adjacent fluorine substituents on the rates of S_N2 reactions.[96]

From this evidence, we proposed that the silver-mediated ^{18}F-fluorination of Ar-OCFClH proceed with more S_N2 character; hence the requirement for the stabilisation of the carbocation intermediate is less pronounced. Nevertheless, the fact that the RCY of the reaction was greatly enhanced in the presence of AgOTf (see Section 2.6.2) underlined the role of the silver salt. The reaction between the Ar-OCFClH precursor and the silver cation could result in the Ag(I)-halogen complex which partially activates the precursor, facilitating the subsequent substitution with [^{18}F]fluoride (Scheme 2.26).



Scheme 2.26 Proposed mechanism of the silver-mediated ^{18}F-labelling of Ar-OCF$_2$H.

In addition, competition experiments were conducted to compare the reactivity between Ar-SCF$_2$Br, Ar-OCF$_2$Br, Ar-OCFClH, Ar-CF$_2$Br and Ar-CFClH precursors towards the silver-mediated ^{18}F-fluorination. An equimolar mixture of a pair of substrates was subjected to the optimised reaction conditions (System **A** or **B**), then the ratio of the ^{18}F-labelled products was investigated (Scheme 2.27).

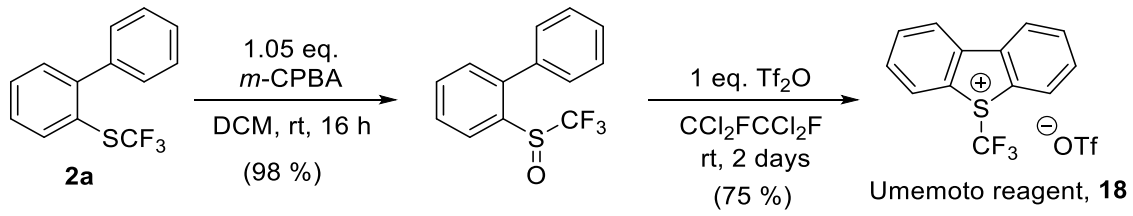


Scheme 2.27 Competition experiments between **1b**, **5a**, **9a**, **13a** and **16a** towards the silver-mediated ^{18}F-fluorination (n = 2).

The outcomes of these experiments revealed the reactivity towards ^{18}F-fluoride in the order of: Ar-OCFClH (**9**) > Ar-CF$_2$Br (**13**) ~ Ar-CFClH (**16**) > Ar-SCF$_2$Br (**1**) > Ar-OCF$_2$Br (**5**).

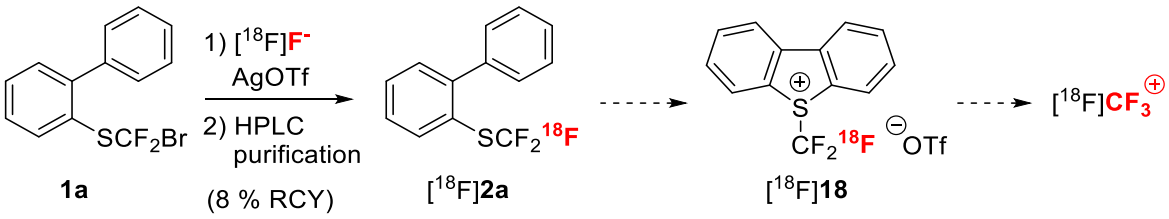
2.10 Production of ^{18}F-Labelled Umemoto Reagent

5-(trifluoromethyl)dibenzothiophenium trifluoromethanesulfonate (Umemoto reagent, **18**), developed by Umemoto and Ishihara, has been utilised as a potent electrophilic trifluoromethylating reagent, allowing the transfer of the trifluoromethyl group to various substrates (see Chapter 3 for more details).[98] It can be synthesised by a two-step procedure starting from 2-(trifluoromethylthio)biphenyl (**2a**) (Scheme 2.28).[99] The oxidation of **2a** using *meta*-chloroperbenzoic acid (*m*-CPBA) in DCM at room temperature overnight provided the corresponding sulfoxide in excellent yield. Subsequent cyclisation mediated by trifluoromethanesulfonic anhydride (Tf_2O) at room temperature over 2 days afforded the Umemoto reagent in 75 % yield.



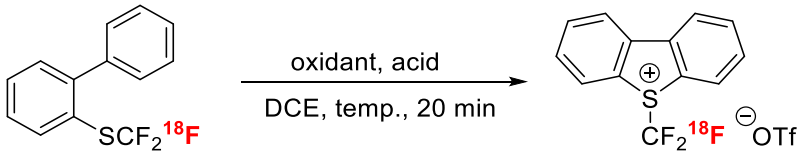
Scheme 2.28 Method for the preparation of Umemoto reagent from **2a**.

We envisaged that compound [^{18}F]**2a**, which was isolated in 8 % RCY with a specific activity of 0.32 GBq/µmol (Section 2.8, Table 2.25, entry 1), could serve as a precursor for the synthesis of the ^{18}F-labelled Umemoto reagent ([^{18}F]**18**). The ultimate goal of this would be to employ [^{18}F]**18** as a novel electrophilic source of [^{18}F]trifluoromethyl group (Scheme 2.29), complementing the nucleophilic [^{18}F]$CuCF_3$ methods (Scheme 2.12d and e).



Scheme 2.29 Method for the preparation of [^{18}F]Umemoto reagent from **2a**.

The original two-step procedure for the synthesis of **18** is not suitable for the application in radiochemistry due to the short half-life of fluorine-18. In order to minimise the synthesis time, a one-pot procedure was attempted by treating [^{18}F]**2a** with a combination of oxidant and acid (Table 2.27). Although the radio-HPLC trace of [^{18}F]**18** matched the trace of the "cold" reference, it was partly unstable under the HPLC conditions hence causing radiochemical purity (RCP) determinations by radio-HPLC to be unreliable. Therefore, only the radiochemical conversion (RCC) of [^{18}F]**2a** obtained by the radio-TLC could be measured.

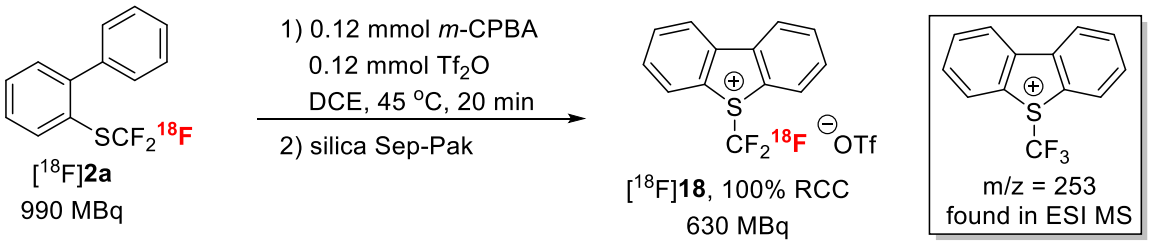


[^{18}F]**2a** [^{18}F]**18**

Entry	Oxidant	Acid	Temp.	RCC [a]
1	0.045 mmol (Mes)I(OCOCF$_3$)$_2$	0.09 mmol TfOH	rt	42 ± 8 % (*n* = 2)
2	0.045 mmol (Mes)I(OAc)$_2$	0.09 mmol TfOH	rt	25 ± 5 % (*n* = 2)
3	0.045 mmol (Mes)I(OAc)$_2$	0.09 mmol TfOH	45 °C	53 ± 2 % (*n* = 2)
4	0.08 mmol *m*-CPBA	-	45 °C	0 % (*n* = 2)
5	0.08 mmol *m*-CPBA	0.08 mmol Tf$_2$O	45 °C	76 ± 19 % (*n* = 4)
6	0.12 mmol *m*-CPBA	0.12 mmol Tf$_2$O	45 °C	99 ± 0 % (*n* = 4)
7	0.16 mmol *m*-CPBA	0.16 mmol Tf$_2$O	45 °C	99 ± 0 % (*n* = 4)

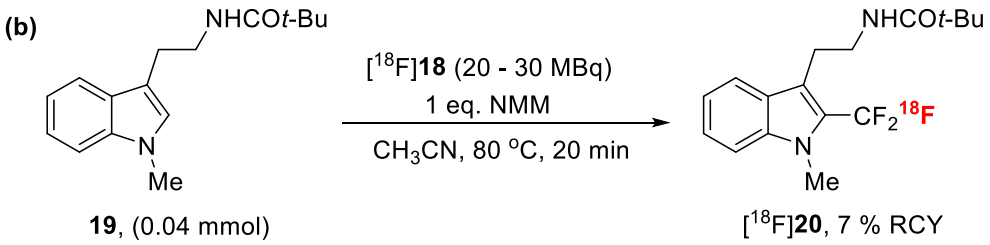
Table 2.27 Synthesis of [^{18}F]**18** *via* the oxidative cyclisation of [^{18}F]**2a**; [a] Determined by radio-TLC; Mes = mesityl (2,4,6-trimethylphenyl).

The combination of hypervalent iodine(III) reagents and trifluoromethanesulfonic acid (TfOH) gave moderate RCC of [^{18}F]**2a** (entries 1 - 3). Gratifyingly, the conversion of [^{18}F]**2a** was significantly improved when the combination of *m*-CPBA and Tf_2O was used (entries 5 - 7). Full conversion was achieved when 3 eq. of both reagents were employed (entry 6). Next, the optimised conditions were attempted on a large-scale synthesis, starting from 990 MBq of the HPLC-isolated [^{18}F]**2a** (Scheme 2.30). After the reaction, the crude mixture was filtered through a silica Sep-Pak to remove other impurities. The radio-TLC analysis of the resulting solution showed a full conversion of the [^{18}F]**2a** with the final activity of 630 MBq (the activity is lost during the transfer and from the decay of ^{18}F-radioisotope). The product was further analysed by ESI mass spectrometry which revealed a peak at 253 m/z corresponding to the 5-(trifluoromethyl)dibenzothiophenium cation.



Scheme 2.30 Synthesis of [^{18}F]**18** from the oxidative cyclisation of [^{18}F]**2a**.

When the isolated [^{18}F]**18** was reacted with *N*-(2-(1-methyl-1H-indol-3-yl)ethyl)pivalamide (**19**) in the presence of *N*-methylmorpholine, the ^{18}F-trifluoromethylated indole product ([^{18}F]**20**) was observed in 7 % RCY (Scheme 2.31). This reaction demonstrated the utility of the ^{18}F-labelled Umemoto reagent as a novel electrophilic ^{18}F-trifluoromethylating reagent, although the development of more efficient reaction conditions is required.



Scheme 2.31 Synthesis of [^{18}F]**18** from the oxidative cyclisation of [^{18}F]**2a**.

2.11 Conclusions

In summary, novel protocols for ^{18}F-labelling of Ar-SCF_3, -OCF_3 and -OCF_2H groups have been developed. These motifs are highly relevant for application in medicinal chemistry due to their unique physical and chemical properties (Section 2.1). In this chapter, we demonstrated that a silver salt can efficiently facilitate halogen exchange, allowing ^{18}F-fluorination of Ar-SCF_2Br, -OCF_2Br and -OCFClH groups under mild reaction conditions (Section 2.4, 2.5 and 2.6). In contrast, ^{18}F-incorporation was not observed in the absence of silver even at the temperatures as high as 180 ^{o}C. The use of a silver salt to promote a halex reaction was unprecedented in the field of radiochemistry. The procedure required the use of a weakly-coordinating counteranion of silver such as AgOTf and non-coordinating solvents such as DCM or DCE. The proposed mechanism involves the formation of a partially stabilised carbocation next to the heteroatom, based on the observation that electron-rich substrates typically gave much higher RCY of the radiolabelled products than electron-poor substrates. In some cases, the presence of a strong electron-withdrawing group such as -NO_2 or -CF_3 completely inhibited the ^{18}F-incorporation. The silver-mediated ^{18}F-fluorination method was successfully applied for the synthesis of [^{18}F]Riluzole, an ^{18}F-labelled version of the registered drug for the treatment of ALS and schizophrenia. In addition, [^{18}F]Ar-CF_3 and [^{18}F]Ar-CF_2H can also be prepared in good RCYs using this methodology (Section 2.7).

Furthermore, the silver-mediated protocol was slightly modified, allowing the large-scale synthesis and isolation of the ^{18}F-labelled Ar-SCF_3, Ar-OCF_3, Ar-OCF_2H, Ar-CF_3 and Ar-CF_2H with a larger amount of radioactivity (Section 2.8). The radiolabelled product was isolated in activities of up to 509 MBq, which is suitable for application in PET imaging. However, the specific activities of the ^{18}F-labelled products were relatively low as a result of the hydrolysis of the precursors under the reaction conditions (Section 2.9).

Finally, the synthesis of the [^{18}F]Umemoto reagent was successfully developed starting from the corresponding [^{18}F]Ar-SCF$_3$ (synthesised *via* the silver-mediated ^{18}F-fluorination method) (Section 2.10). The application of the [^{18}F]Umemoto reagent to the electrophilic ^{18}F-trifluoromethylation will be further investigated in the future work.

2.12 References

[1] (a) T. Khotavivattana,* S. Verhoog,* M. Tredwell, L. Pfeifer, S. Calderwood, K. Wheelhouse, T. L. Collier, V. Gouverneur, *Angew. Chem. Int. Ed.* **2015**, *54*, 9991-9995; * These authors contributed equally to this work. (b) S. Verhoog, L. Pfeifer, T. Khotavivattana, S. Calderwood, T. L. Collier, K. Wheelhouse, M. Tredwell, V. Gouverneur, *Synlett* **2016**, *27*, 25-28.
[2] F. Leroux, P. Jeschke, M. Schlosser, *Chem. Rev.* **2005**, *105*, 827-856.
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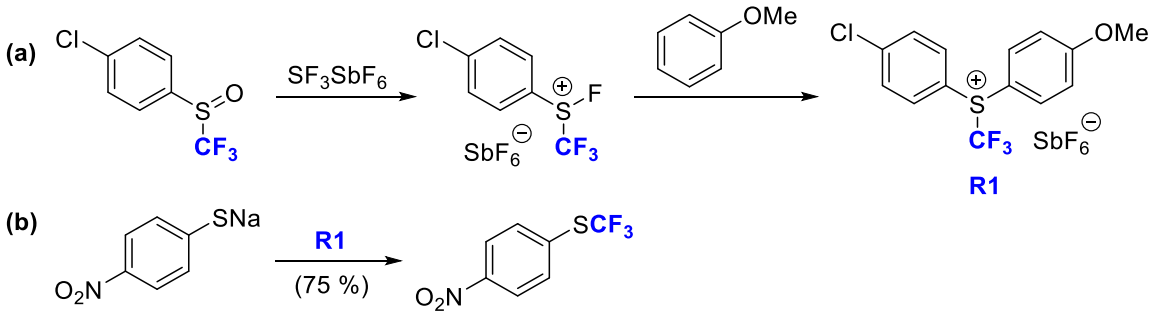
Chapter 3: Trifluoromethylation-Thiocyclisation of Alkenes

The work described in this chapter was carried out in collaboration with Dr. Paolo Ricci.[1] The synthesis of ^{18}F-labelled 5-(trifluoromethyl)dibenzothiophenium trifluoromethane sulfonate ([^{18}F]Umemoto reagent) described in Chapter 2.10 was the first example of the ^{18}F-labelling of an electrophilic trifluoromethylating reagent. Building on this novel approach towards electrophilic ^{18}F-trifluoromethylation, we decided to investigate the synthetic utility of these reagents with the ultimate goal of the translation towards radiochemistry.

3.1 Electrophilic Trifluoromethylating Reagents

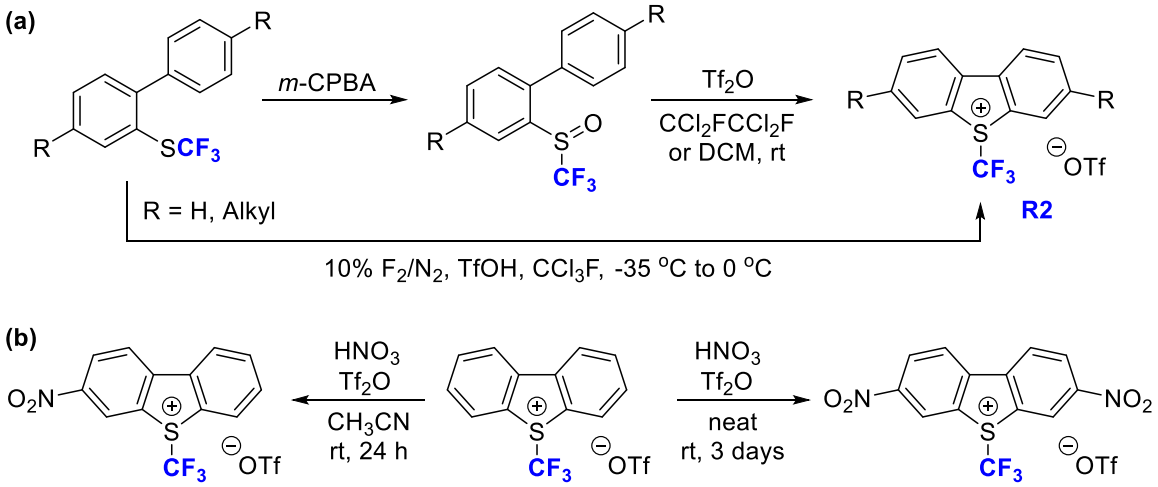
In 1984, Yagupolskii and co-workers reported the first example of electrophilic trifluoromethylation using diaryl(trifluoromethyl)sulfonium salt (**R1**), which was prepared from aryltrifluoromethyl sulfoxide (Scheme 3.1a).[2] The reaction of *para*-nitro-thiophenolate with **R1** afforded the trifluoromethylated product in good yield (Scheme 3.1b).



Scheme 3.1 The preparation and the reaction of the reagent **R1** with thiophenolate.

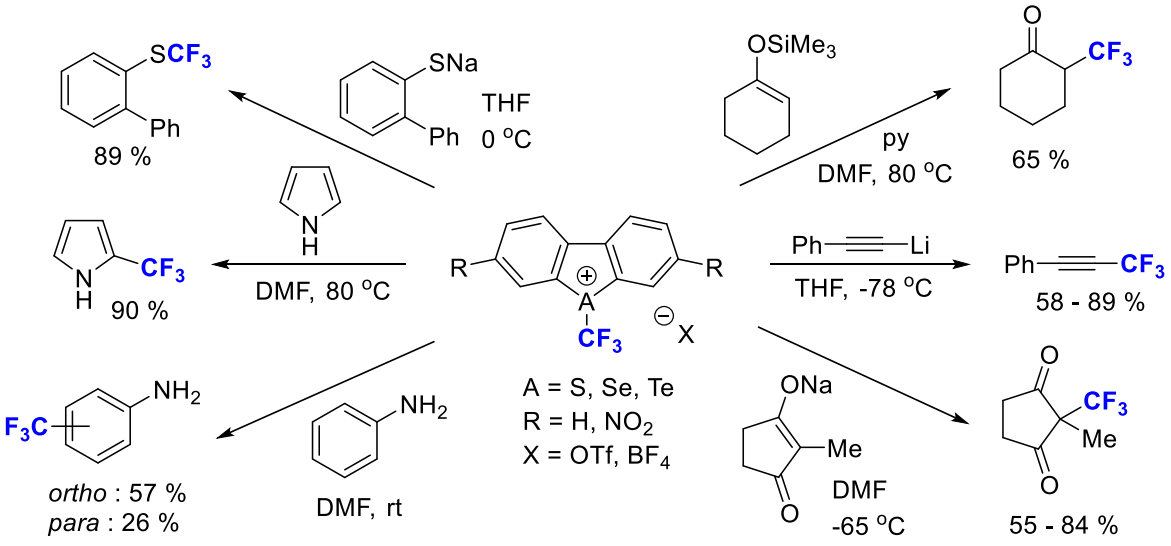
However, the need for the electron-donating methoxy group in order to stabilise the positively charged sulfur atom significantly reduced the electrophilicity of the reagent. In 1990, Umemoto and Ishihara demonstrated that the cyclised (trifluoromethyl)dibenzo thiophenium salts (**R2**) exhibited improved stability. This finding allowed for the installation of various electron-withdrawing or electron-donating substituents in order to modulate the reactivity of the reagent.[3] These classes of substrates can be synthesised either by the two-step procedure as described in Chapter 2.10, or by the reaction of the corresponding

trifluoromethyl sulphide with fluorine gas in the presence of a strong acid (Scheme 3.2a). The reactivity of **R2** can be further enhanced by the synthesis of either mononitro- or dinitro-substituted reagents (Scheme 3.2b). Employing a similar strategy, the selenophenium and tellurophenium analogues were also reported.



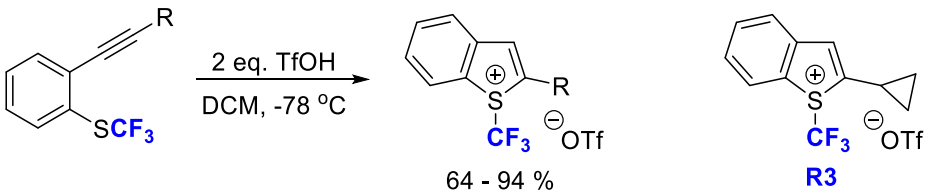
Scheme 3.2 The preparation and modification of the Umemoto reagent (**R2**).

This class of reagents has been shown to lead to the transfer of trifluoromethyl group to various nucleophiles such as thiolates, anilines, silyl enol ethers and carbanions in good yields (Scheme 3.3).[4]



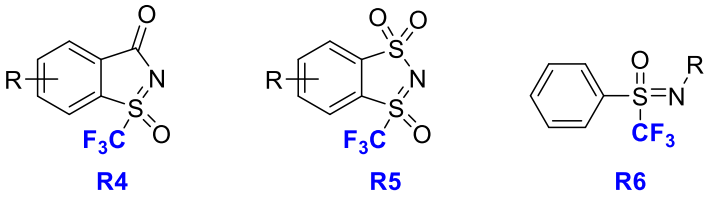
Scheme 3.3 The reactivity of the Umemoto reagent towards various nucleophiles.[4]

Following on from this discovery, a large scale preparation of the Umemoto reagent (**R2**) was successfully developed with a modified protocol,[5] hence making it one of the few commercially available trifluoromethylating reagents. In 2010, Shibata and co-workers developed a similar trifluoromethylating reagent based on benzothiophenium salts.[6] In particular, the cyclopropyl-substituted reagent **R3** showed much greater reactivity than **R2** (Scheme 3.4). However, this class of reagent is relatively unstable and readily undergo decomposition in *N*,*N*-dimethylformamide solvent.[7]



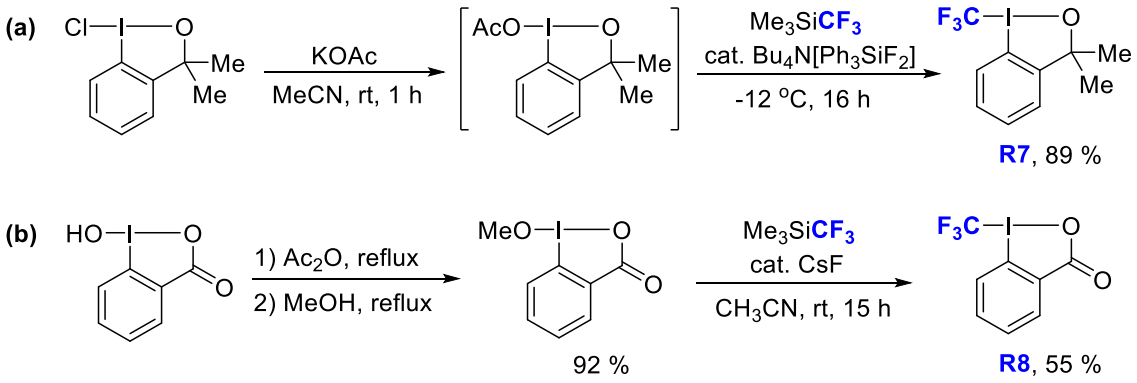
Scheme 3.4 The preparation the Shibata reagent (**R3**).[7]

Adachi and Ishihara demonstrated the first neutral electrophilic trifluoromethylating reagents **R4**, **R5** and **R6** based on trifluoromethyl sulfoximine motif (Scheme 3.5).[8] However, these reagents were significantly less reactive compared to the positively charged reagents such as **R2**.



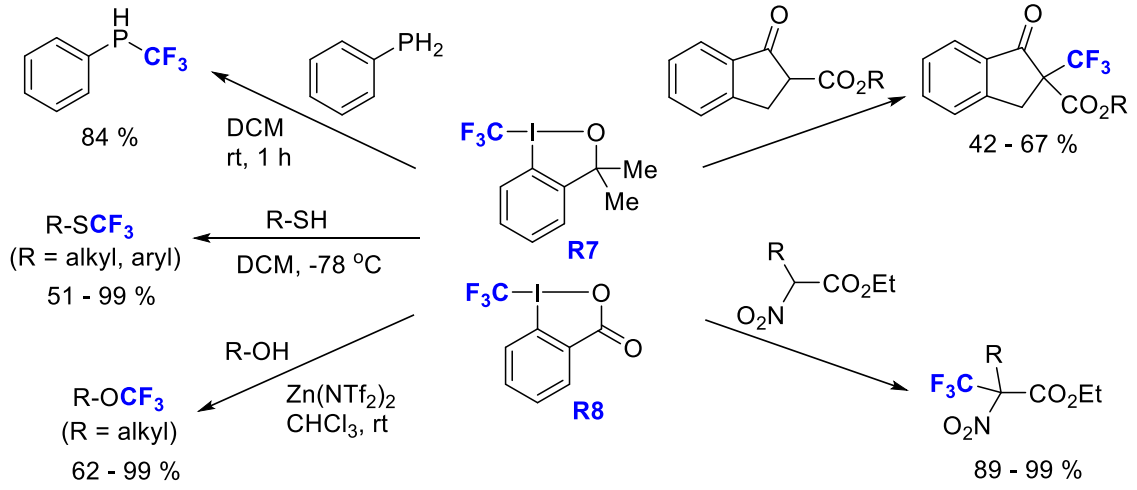
Scheme 3.5 The first neutral reagents for electrophilic trifluoromethylation.

A new class of trifluoromethylating reagents based on neutral hypervalent iodine(III)-CF_3 reagent was disclosed in 2006 by Togni and co-workers. The overall concept relies on umpolung chemistry, in which the reagents were synthesised by the nucleophilic ligand replacement with the Ruppert-Prakash reagent (Me_3SiCF_3). This method led to the development of 3,3-dimethyl-1-(trifluoromethyl)-1,2-benziodoxole (Togni I, **R7**, Scheme 3.6a) and 1-trifluoromethyl-1,2-benziodoxol-3-(1H)-one (Togni II, **R8**, Scheme 3.6b).[9]



Scheme 3.6 The synthesis of the Togni reagents I (**R7**) and II (**R8**) from Me_3SiCF_3.

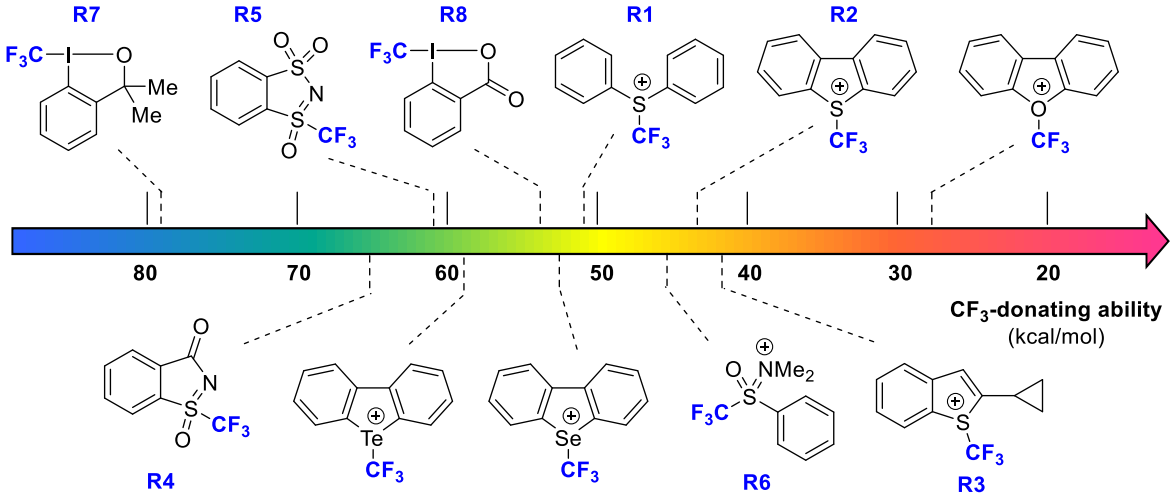
These reagents were reported to react with various nucleophiles such as thiols, phosphines, alcohols, *β*-keto esters and *α*-nitro esters under mild reaction conditions (Scheme 3.7).[10] Moreover, the reactivity of these reagents can be further enhanced by activation of both Lewis and Brønsted Acids as well as transition metal catalysis. Due to the superior reactivity, these hypervalent iodine reagents have been employed for the development of new synthetic methodologies and both **R7** and **R8** can be supplied on a multi-kilogram scale. Due to these reagents having been reported to undergo violent decomposition when heated at elevated temperatures, they should be handled with precautions.[11]



Scheme 3.7 The reactivity of the Togni reagents towards various nucleophiles.

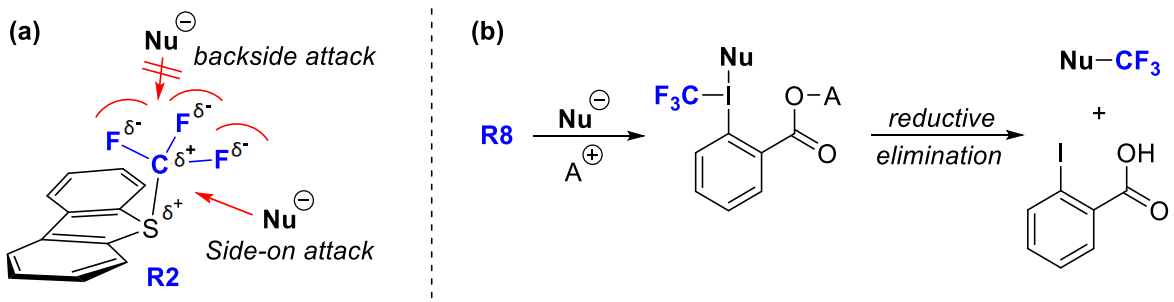
In order to compare the reactivity among various electrophilic trifluoromethylating reagents, Cheng and co-workers suggested a potential correlation between the CF_3^+ donating ability

and the calculated X–CF_3 bond heterolytic dissociation enthalpies. As a result, an estimate reactivity guide was proposed (Scheme 3.8).[12]



Scheme 3.8 Estimated reactivity guide for electrophilic trifluoromethylating reagents.

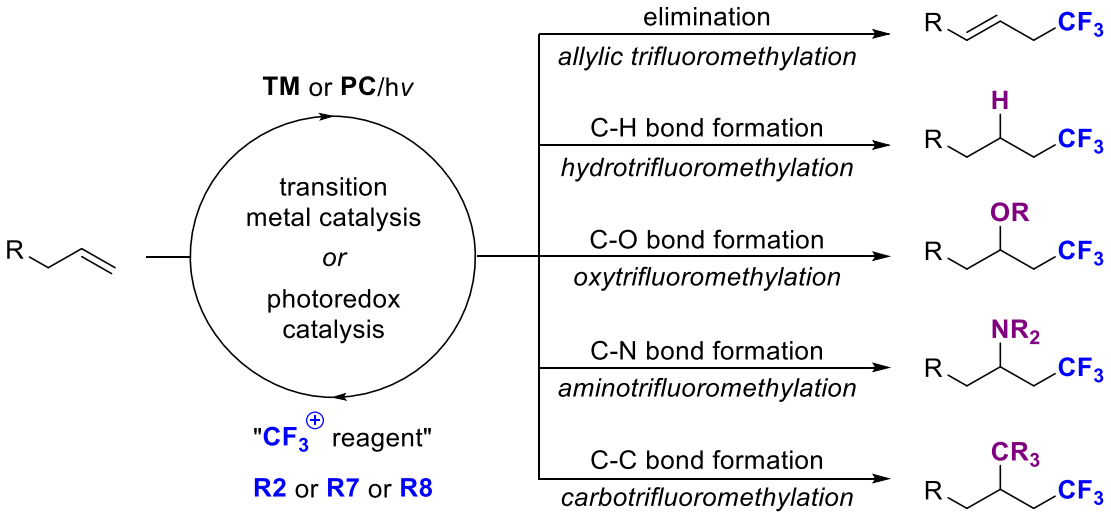
It has been suggested that the mechanism of the electrophilic trifluoromethylation reactions does not proceed through the conventional S_N2 attack of nucleophiles at the CF_3 group. The results of molecular orbital calculations of the Umemoto reagent (**R2**) in conjunction with kinetic studies comparing to the S-CH_3 analogue suggests that the nucleophile attacks side-on to avoid the electronic repulsion from the three fluorine substituents (Scheme 3.9a).[13] In the case of the Togni reagents **R7** and **R8**, the mechanism involves attack of the nucleophile at the iodine centre, resulting in the formation of λ^3-iodane species. This subsequently undergoes rapid reductive elimination leading to the transfer of the CF_3 group onto the nucleophile (Scheme 3.9b).[14]



Scheme 3.9 Proposed mechanism for electrophilic trifluoromethylation with **R2** and **R8**.

3.2 Trifluoromethylation of Alkenes with Electrophilic CF_3 Reagents

Trifluoromethylation of alkenes has recently become a major research focus due to the addition of CF_3 across C=C bond being one of the most reliable methods to access structurally diverse compounds containing Csp^3–CF_3 bonds.[15] This area benefits from the fact that olefins are easily accessible and robust feedstocks. The electrophilic trifluoromethylating reagents, particularly the Umemoto reagent (**R2**) and Togni reagents (**R7** and **R8**), have been employed as sources of trifluoromethyl groups in both transition metal catalysis,[16] as well as photoredox catalysis,[17] in the trifluoromethylation of alkenes. The formation of Csp^3–CF_3 bond is usually accompanied by an elimination reaction to give allylic trifluoromethylation products or C–H, C–C or C–heteroatom bond formation, affording dual functionalised products (Scheme 3.10).[18]

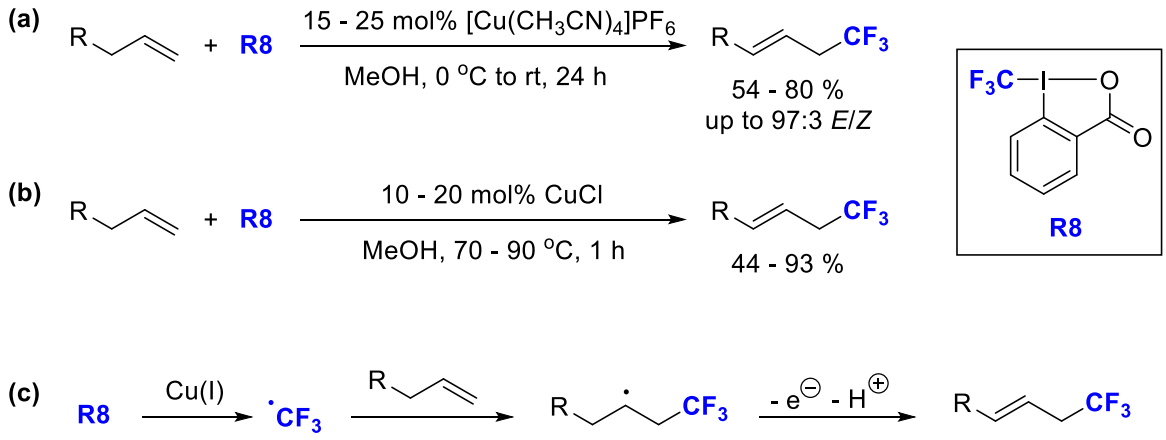


Scheme 3.10 Trifluoromethylation of alkenes with electrophilic CF_3 reagents (TM = transition metal; PC = photocatalyst).

3.2.1 Allylic Trifluoromethylation of Unactivated Alkenes

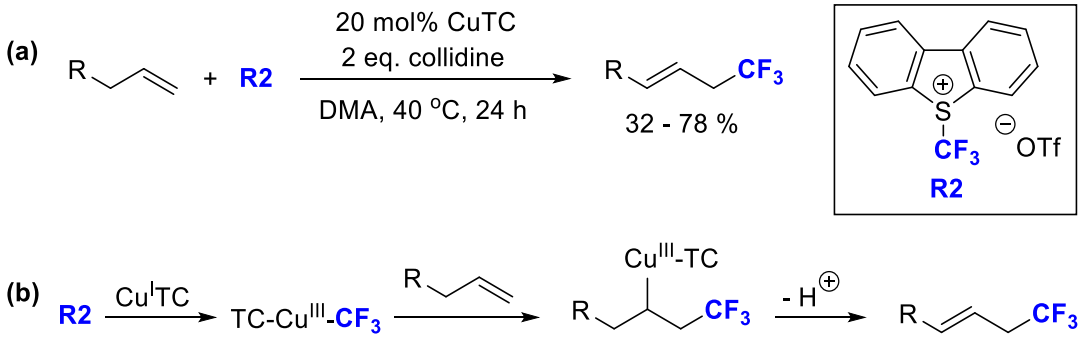
In 2011, several research groups simultaneously reported the first examples of trifluoromethylation of alkenes with electrophilic CF_3 reagent. Buchwald *et al.*[19] and Wang *et al.*[20] demonstrated that Togni reagent II (**R8**), in the presence of a copper catalyst can efficiently transfer the CF_3 group onto unactivated alkene. The subsequent allylic Csp^3–H

bond activation led to the formation of allyl-CF_3 products with good *E*/*Z* regioselectivity (Scheme 3.11a and b). The authors proposed that the reaction proceeds through a complex reaction mechanism that may involve multiple pathways. After a series of mechanistic experiments, there was strong evidence for the generation of a CF_3 radical, which could be trapped by the alkene, followed by oxidation and subsequent deprotonation to form the allyl-CF_3 product (Scheme 3.11c).



Scheme 3.11 Copper-catalysed allylic trifluoromethylation of unactivated alkenes with **R8**.

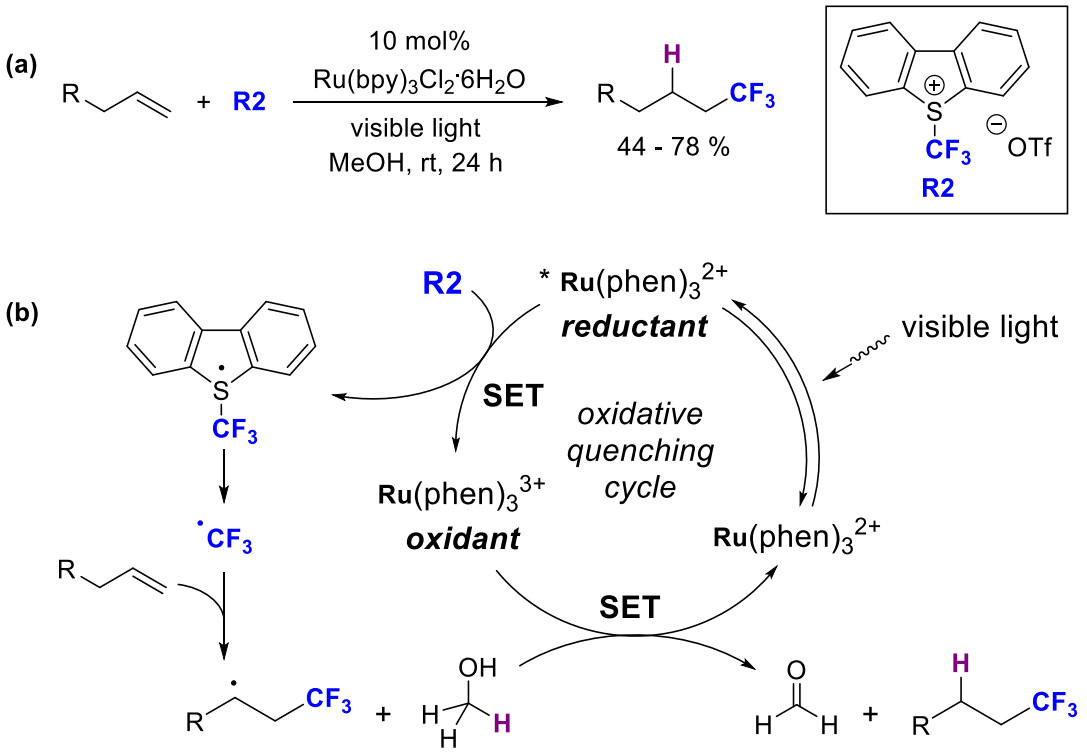
Building on this, Liu and co-workers reported the same transformation using Umemoto reagent (**R2**) with copper-thiophene-2-carboxylate (CuTC) as a catalyst (Scheme 3.12a).[21] Based on theoretical calculations, the authors proposed a mechanism that involves the formation of Cu^{III}-CF_3 species which subsequently undergoes alkene insertion, following by deprotonation to form the allyl-CF_3 product (Scheme 3.12b).



Scheme 3.12 Copper-catalysed allylic trifluoromethylation of unactivated alkenes with **R2**.

3.2.2 Hydrotrifluoromethylation of Unactivated Alkenes

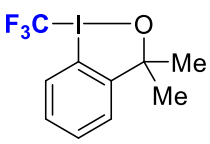
In 2013, Gouverneur and co-workers demonstrated that $Ru(bpy)_3Cl_2{\cdot}6H_2O$ under visible light is an efficient photoredox catalytic system to induce hydrotrifluoromethylation of unactivated alkenes using the Umemoto reagent (**R2**) as the CF_3 source (Scheme 3.13a).[22]



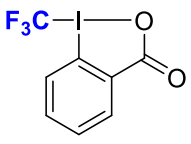
Scheme 3.13 Photoredox-catalysed hydrotrifluoromethylation of unactivated alkenes.

The proposed mechanism (Scheme 3.13b) involves the excitation of the $Ru(bpy)_3^{2+}$ photocatalyst by visible light, generating the excited-state species $Ru(bpy)_3^{2+}*$, which itself can act as both a strong oxidant and a strong reductant. Based on the measured reduction potentials, the authors suggested that the reaction went through an oxidative quenching cycle by single electron transfer (SET) from the $Ru^{II}*$ species to the Umemoto reagent (**R2**). The resulting Umemoto radical species could readily collapse to generate an electrophilic CF_3 radical which can be added regioselectively to the alkenes. The resulting carbon radical can then abstract a hydrogen atom from methanol, a process which is facilitated by the strong oxidant $Ru(bpy)_3^{3+}$.

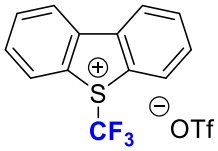
In this transformation, it was demonstrated that the Togni reagents (**R7** or **R8**) were inferior to the Umemoto reagent (**R2**). To find out the reasoning behind this observation, the reduction potentials of these reagents were measured by cyclic voltammetry in different solvents (Table 3.1).[23] The result revealed **R2** to be a superior electron acceptor due to the higher value of the reduction potential (–0.63 V in CH_3CN, entry 3), which is compatible with the reduction potential of the oxidation of $Ru(bpy)_3^{2+}$* to $Ru(bpy)_3^{3+}$ (–0.81 V in CH_3CN).[24] This compared favourably to the reduction potential of both **R7** and **R8** for which neither value was high enough to be efficiently reduced by the excited $Ru(bpy)_3^{2+}$*.



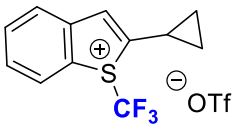
R7



R8



R2



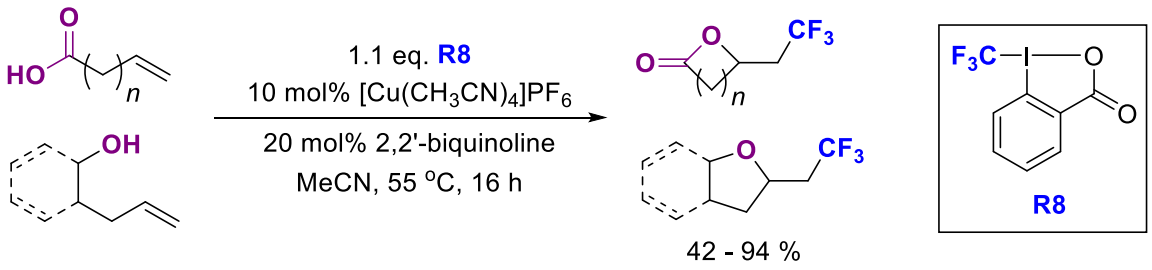
R3

Entry	CF_3 reagent	E_{pc1} in CH_3CN [a]	E_{pc1} in DMF [a]	E_{pc1} in MeOH [a]
1	**R7**	–1.82 V	–2.66 V	-
2	**R8**	–1.10 V	–1.98 V	–1.55 V
3	**R2**	–0.63 V	–0.85 V	–0.90 V
4	**R3**	–0.72 V	–0.78 V	–1.17 V

Table 3.1 Reduction potentials for the first reduction of different electrophilic CF_3 reagents; [a] cathodic peak potential at 293 K with a glassy carbon electrode and 0.1 M *n*-Bu_4NPF_6 as the supporting electrolyte; all potentials are quoted vs. Ag/Ag^+ in CH_3CN, scan rate: 0.2 V/s.

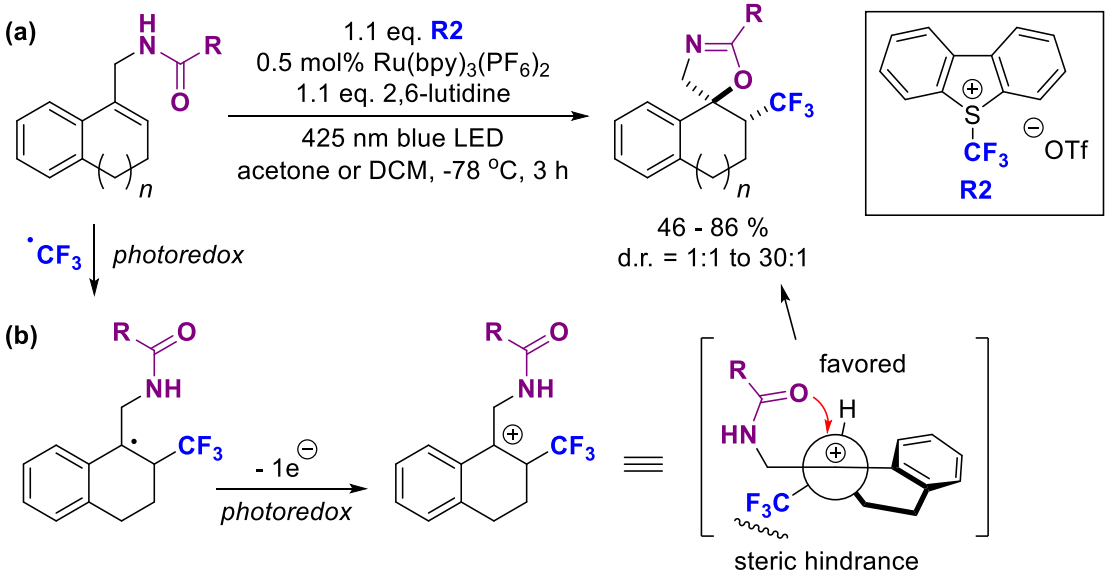
3.2.3 Trifluoromethylation-Heterocyclisation of Alkenes

In 2012, Buchwald and co-workers developed the first oxytrifluoromethylation of unactivated alkenes using the Togni reagent II (**R8**) based on the copper-catalysed allylic trifluoromethylation described earlier in Section 3.2.1.[25] The oxytrifluoromethylated products can be obtained by the reaction of **R8** with the corresponding terminal alkenes with adjacent oxygen nucleophiles such as alcohols, phenols or carboxylic acids in the presence of catalytic amounts of $Cu(CH_3CN)_4PF_6$ and 2,2'-biquinoline ligand (Scheme 3.14).



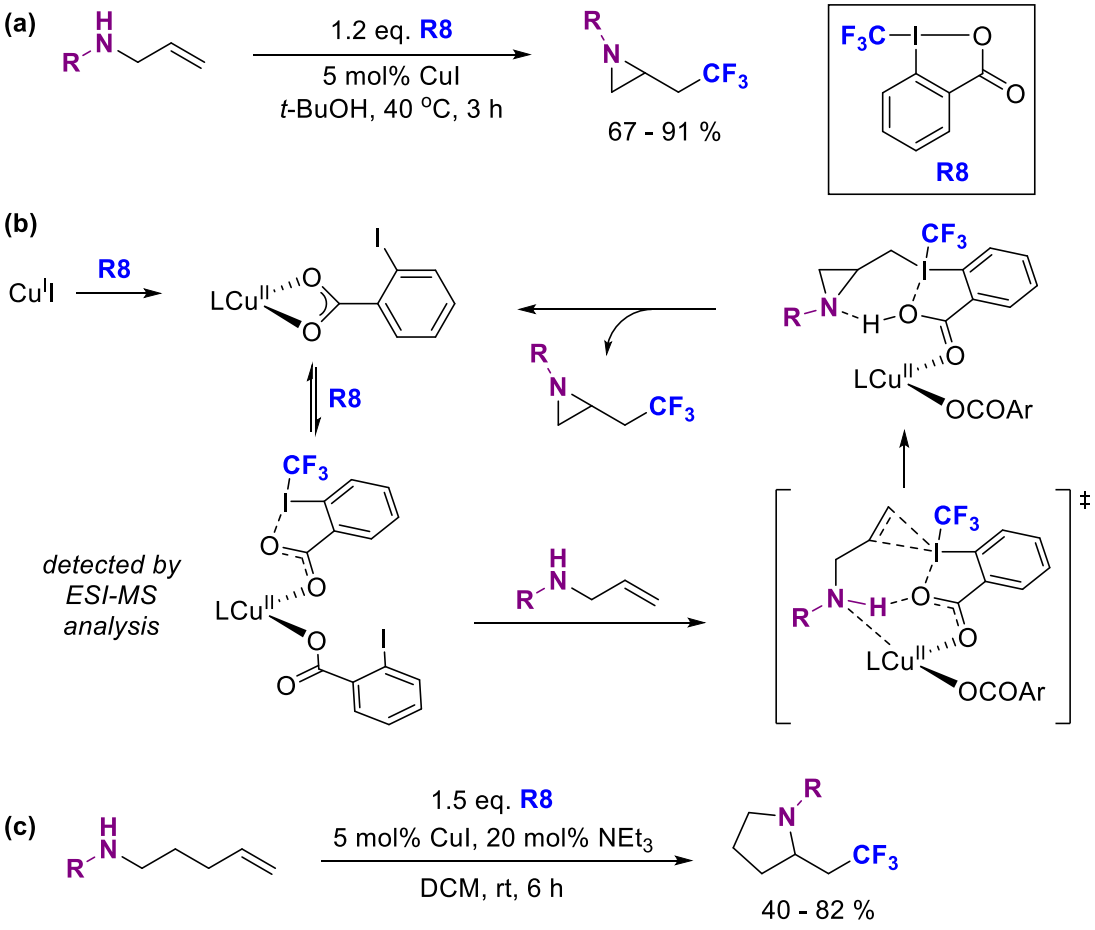
Scheme 3.14 Copper-catalysed oxytrifluoromethylation of unactivated alkenes with **R8**.

More recently in 2015, Koike and Akita *et al.* reported a photoredox-catalysed trifluoromethylation-oxycyclisation of conjugated alkenes with pendant amide group, affording spirooxazolines and spirooxazines using the Umemoto reagent (**R2**) (Scheme 3.15a).[26] The reaction exhibits good *anti*-diastereoselectivity with the diastereomer ratios (d.r.) ranging from 1:1 to 30:1. The reactions were carried out at –78 °C to maximise the diastereoselectivity. The proposed reaction mechanism is similar to the photocatalytic hydrotrifluoromethylation described in the Section 3.2.2. However, in this case, the resultant benzylic radical can be readily oxidised to generate an α-CF_3-substituted carbocationic intermediate which undergoes nucleophilic cyclisation with the adjacent amide group. The *anti*-selectivity of the cyclisation process was hypothesised to be controlled by the steric factor of the CF_3 substituent (Scheme 3.15b).



Scheme 3.15 Photoredox-catalysed CF_3-oxycyclisation of conjugated alkenes with **R2**.

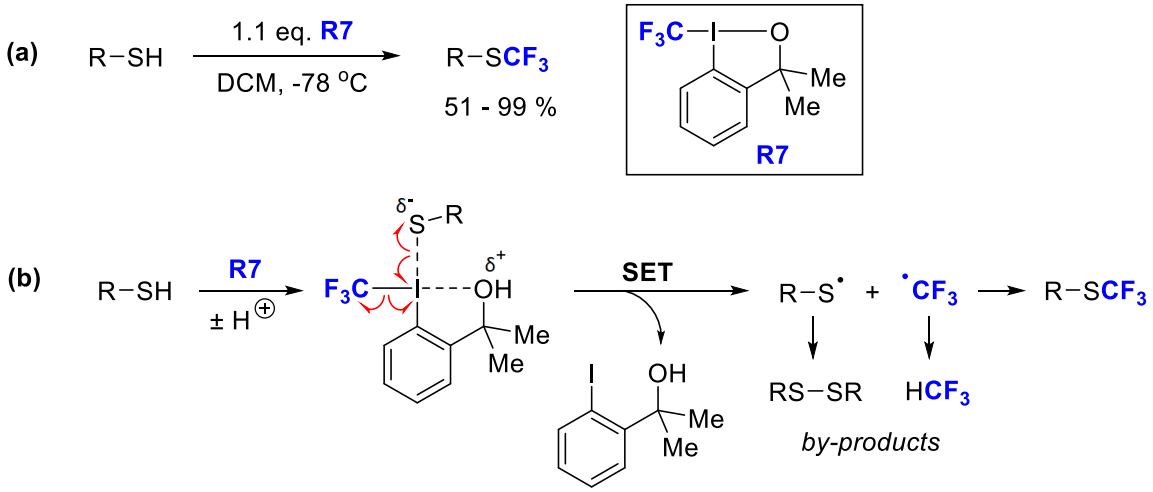
The first trifluoromethylation aminocyclisation of allylamine derivatives was developed by Sodeoka and co-workers in 2013 using the Togni reagent II (**R8**) under Cu(I) catalysis (Scheme 3.16a).[27] The in-depth mechanistic investigation provided evidence for a reactive Cu(II) species which acts as a Lewis acid catalyst to activate **R8** (Scheme 3.16b).[28] The authors proposed that the electrophilic hypervalent iodine centre could induce an intramolecular nucleophilic attack of the adjacent amine group onto the alkene. The resulting alkyl-I(III)-CF_3 intermediate then underwent reductive elimination to afford the trifluoromethylated aziridine product. The scope of the reaction was also extended to the synthesis of trifluoromethylated pyrrolidines (Scheme 3.1c). It was found that the yield of the reaction was dramatically improved in the presence of NEt_3 as a co-catalyst.



Scheme 3.16 Copper-catalysed CF_3-aminocyclisation of unactivated alkenes with **R8**.

3.2.4 Thiotrifluoromethylation of Alkenes

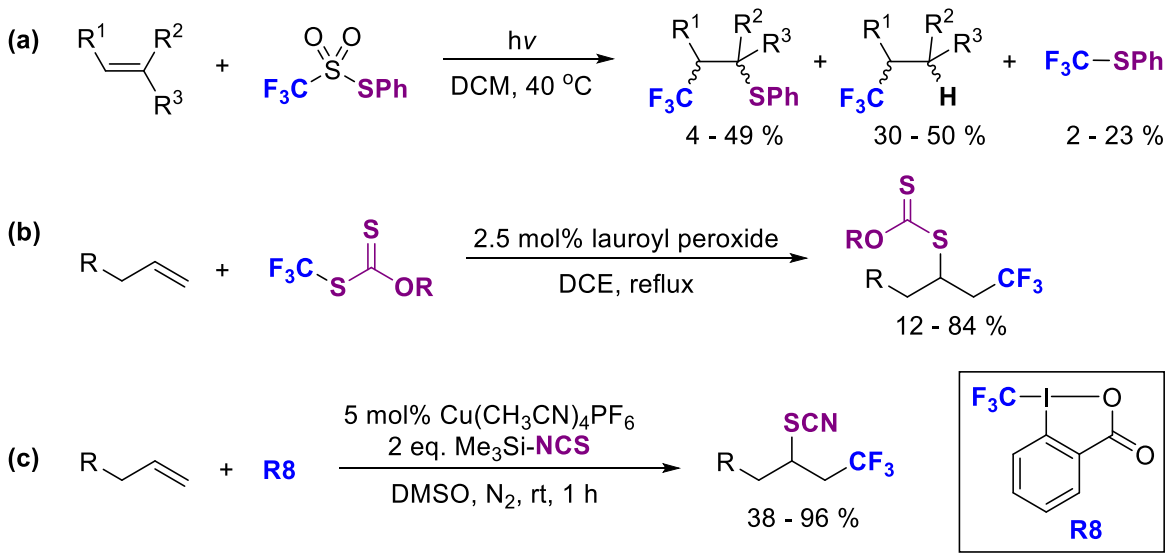
Although many research groups have disclosed various methods for the oxy- and aminotrifluoromethylation of alkenes, alkene difunctionalisation *via* C–CF_3 and C–S bond formation are notoriously rare. In contrast to amines and alcohols, thiols readily react with Togni or Umemoto reagents to give S-trifluoromethylated product; [29] as a result, trifluoromethylation of alkenes in the presence of a sulfur atom is much more challenging. For instance, thiols and thiophenols have been shown to undergo trifluoromethylation in high yields with the Togni reagent I (**R7**) at –78 °C in the absence of a catalyst (Scheme 3.17a).[30] The reaction featured an extensive substrate scope including cysteine side chains in complex peptide molecules.[31]



Scheme 3.17 Trifluoromethylation of thiols with **R7**.

The formation of disulfide and HCF_3 as by-products suggested that the reaction proceeds *via* a radical-based mechanism, which was confirmed by electron paramagnetic resonance (EPR) analysis. Extensive mechanistic investigation experiments, as well as computational studies, were performed and several pathways were considered.[32] One of the most likely pathways involves the protonation of **R7** followed by the coordination of thiol at the hypervalent iodine centre. The resulting λ^4-iodane then undergoes facile SET to generate a CF_3 radical and a thiyl radical, which recombine to form the SCF_3 product (Scheme 3.17b).

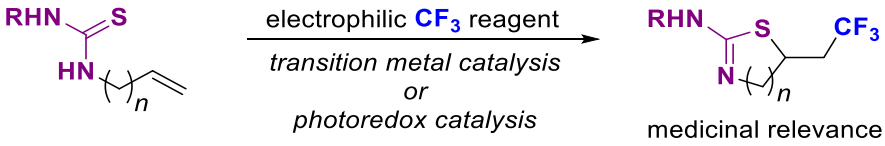
The first example of alkene thiotrifluoromethylation was reported by Langlois and co-workers in 2000 (Scheme 3.18a).[33] It was demonstrated that CF_3SO_2SPh can undergo photolysis, leading to the generation of a CF_3 radical that adds to the alkene. The resulting carbon radical subsequently reacts with another molecule of CF_3SO_2SPh to afford the thioether product and the chain propagating trifluoromethylsulfonyl radical. In this process, the undesired S–CF_3 bond formation was suppressed, since the reagent serves both as CF_3 and S-source. Zard and co-workers also reported the net addition of S-trifluoromethyl xanthates reagents onto unactivated alkenes using lauroyl peroxide as a radical initiator (Scheme 3.18b).[34]



Scheme 3.18 Alkene difunctionalisation *via* C–CF_3 and C–S bond formation.

In 2015, Liu and co-workers reported the first intermolecular thiotrifluoromethylation in which the CF_3 and SR groups did not stem from a single reagent. By using copper as a catalyst, a wide range of alkenes underwent trifluoromethylthiocyanation in good yields using trimethylsilyl isothiocyanate (Me_3SiNCS) as the S-source and the Togni reagent II (**R8**) as the CF_3 source. The silicon atom of the Me_3SiNCS reagent acts as Lewis acid to activate **R8**. Mechanistic studies revealed that the reaction involves the formation of CF_3 radical which adds regioselectively to the alkene.

While in the previous section, a few examples of broadly applicable oxy- and aminotrifluoromethylation of alkenes were discussed, there is no general protocol for trifluoromethylation-thiocyclisation despite the abundance of sulfur-containing heterocycles in medicinal chemistry.[35] We envisaged that the electrophilic CF_3 reagents under transition metal or photoredox catalysis could facilitate trifluoromethylation-thiocyclisation of olefins with pendant thioureas, which would afford novel trifluoromethylated 2-amino-thiazolines and 2-amino-thiazines (Scheme 3.19). These class of substrates could serve as important motifs for applications in medicinal chemistry (for more details, see Chapter 3.3).[36]

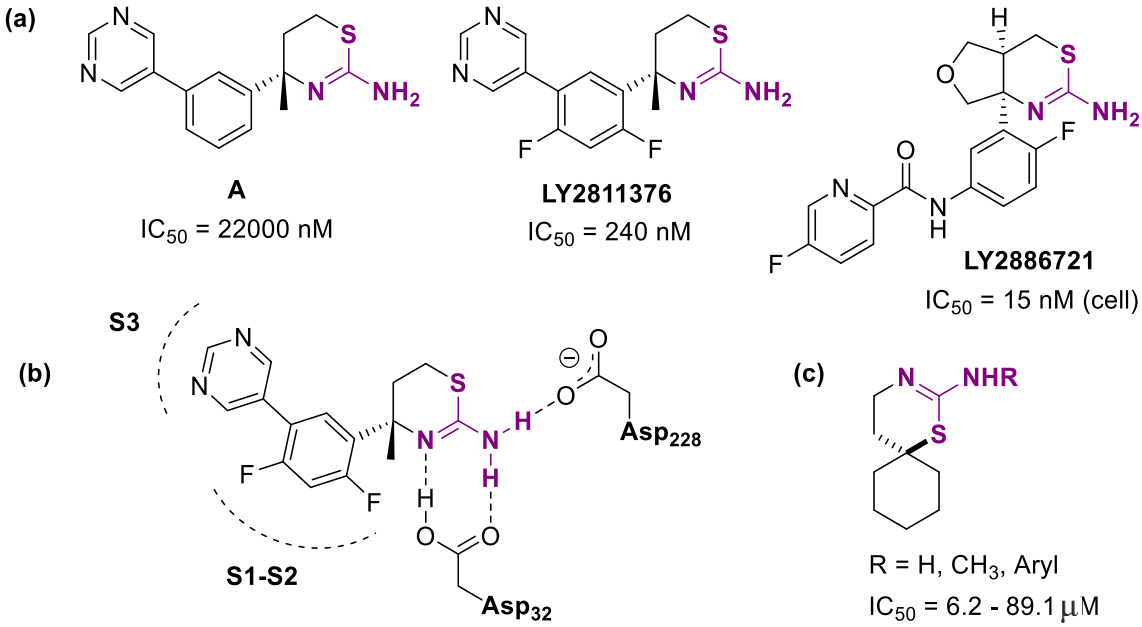


Scheme 3.18 Alkene difunctionalisation *via* C–CF_3 and C–S bond formation.

3.3 2-Amino-Thiazolines and Thiazines for Medicinal Chemistry

2-Amino-thiazolines and thiazines are important scaffolds in the development of aspartate *β*-secretase enzyme (BACE-1) inhibitors, a therapeutic target for Alzheimer's disease.[37] Alzheimer's disease (AD) nowadays is the most common neurodegenerative disease with more than 45 million cases worldwide and an estimated cost of US$ 800 billion in terms of healthcare.[38] World Health Organization (WHO) estimates that the number of patients affected by the AD will triple by 2050, due to the exponential growth of the elderly population.[39] The neuropathological characteristics of the disease involve the deposition of amyloid *β*-peptides plaques (A*β*P) in the brain.[40] It is widely accepted that the formation of A*β*P is caused by the cleavage of the amyloid protein precursor (APP) by aspartate *β*-secretase enzyme (BACE-1).[41] As a result, BACE-1 has become a privileged therapeutic key-target for inhibiting the formation of the AβP, hence preventing the progression of AD.

This concept has inspired the design and development of BACE-1 inhibitors.[42] Although none of the inhibitors is currently FDA approved, some of them are currently in the human clinical trial phase. A breakthrough in the development of nonpeptidomimetic BACE-1 inhibitors came from the identification of 2-amino-thiazine containing molecules **A** as potent bioactive scaffolds (Scheme 3.19a).[43] Further fragment-based drug discovery on **A** revealed that the introduction of fluorine on the aromatic rings lead to improved metabolic stability, Log P and potency.[44] Finally, LY2886721 demonstrated the highest inhibiting activity and hence became the first BACE inhibitor to reach Phase II clinical trials.[45] It was found that the amino-thiazine group can engage in a network of hydrogen bonds with the catalytic aspartates Asp_{32} and Asp_{228} of BACE-1, while the hydrophobic backbone can fill S1-S2 and S3 pockets of the enzyme (Scheme 3.19b).[46]



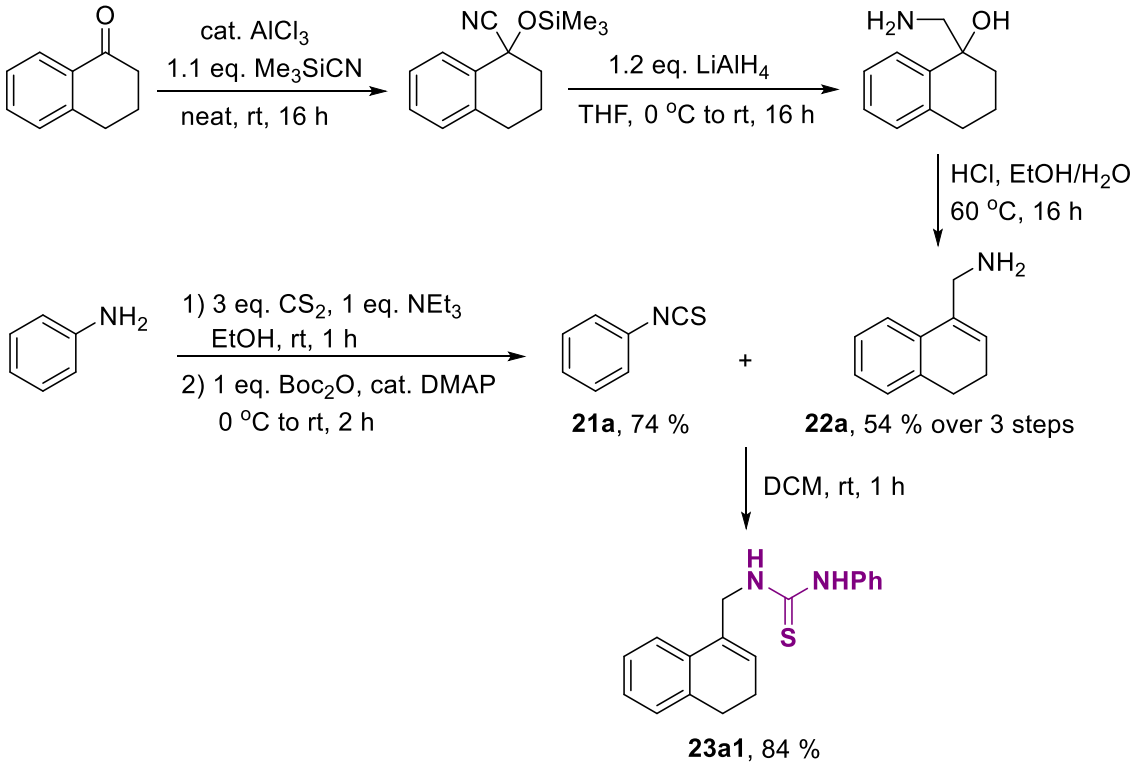
Scheme 3.19 Examples of 2-amino-thiazine-containing medicinally-relevant compounds.

Blokhina and co-workers reported the use of novel spiro-amino-thiazines as potent neuroprotectors (Scheme 3.19c).[47] These compounds are capable of blocking the glutamate-induced calcium ion uptake into synaptosomes of rat brain cortex, leading to the inhibitory activity being greatly affected by the identity of the substituents.

3.4 Optimisation of the Reaction Conditions

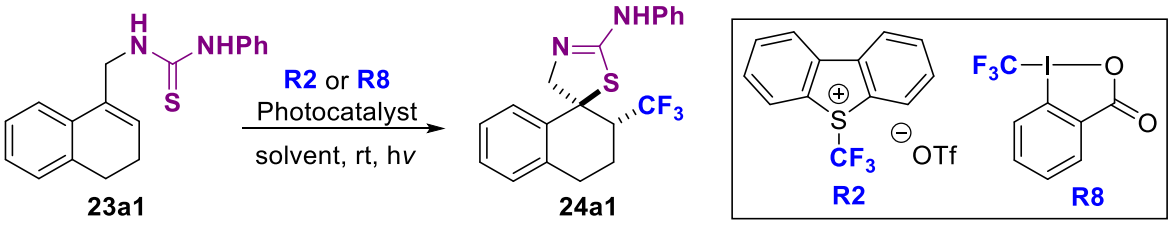
3.4.1 Photoredox-Catalysed Trifluoromethylation-Thiocyclisation

The photoredox-catalysed trifluoromethylation-oxycyclisation of conjugated alkenes reported by Koike and Akita *et al.* was described in Section 3.2.3. We proposed that replacing the amide group with a thiourea group could lead to a novel trifluoromethylation-thiocyclisation, resulting in the trifluoromethylated spiro-amino-thiazine, a new class of compound that could be applied in medicinal chemistry. 1-((3,4-Dihydronaphthalen-1-yl)methyl)-3-phenylthiourea (**23a1**) was selected as a model substrate for reaction optimisation. **23a1** was synthesised by the reaction of phenyl isothiocyanate **21a** with (3,4-dihydronaphthalen-1-yl)methanamine **22a** which was prepared from α-tetralone using a three-step procedure reproduced in the literature (Scheme 3.20).[48] **21a** was prepared by the reaction of aniline with carbon disulfide (CS_2) and trimethylamine (NEt_3), following by di-*tert*-butyl dicarbonate (Boc_2O).[49]



Scheme 3.20 Preparation of the model substrate **23a1**.

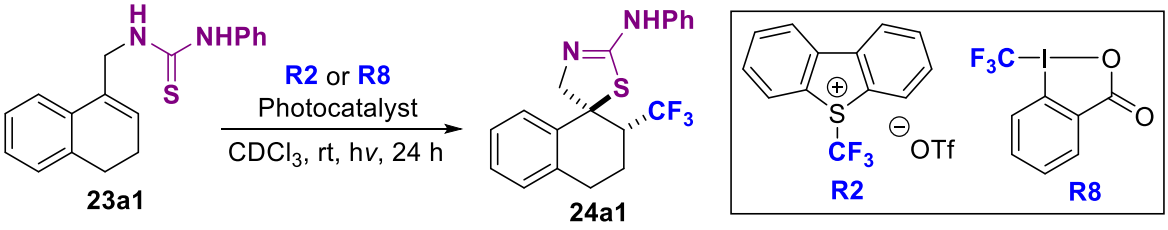
23a1 was reacted with the electrophilic CF_3 source (Umemoto Regent (**R2**) or Togni Reagent II (**R8**)) under photoredox catalysis conditions using either $Ru(bpy)_3(PF_6)_2$ or methylene blue (MB) as a photocatalyst (Table 3.2). ^{19}F NMR analysis of the crude reaction mixture showed a doublet at –66 ppm (J_{F-H} = 9 Hz), corresponding to a single diastereomer of the trifluoromethylated product **24a1** (the determination of the stereochemistry will be discussed in Section 3.5.4).



Entry	Solvent	CF_3^+ reagent [a]	Photocatalyst [b]	Yield of 24a1 [c]	
				2 h	24 h
1	CD_3CN	**R2**	$Ru(bpy)_3(PF_6)_2$	52 %	55 %
2	CD_3CN	**R2**	MB	46 %	49 %
3	CD_3CN	**R8**	$Ru(bpy)_3(PF_6)_2$	20 %	44 %
4	CD_3CN	**R8**	MB	27 %	27 %
5	$CDCl_3$	**R2**	$Ru(bpy)_3(PF_6)_2$	66 %	60 %
6	$CDCl_3$	**R2**	MB	68 %	74 % (65 %)
7	$CDCl_3$	**R8**	$Ru(bpy)_3(PF_6)_2$	32 %	68 %
8	$CDCl_3$	**R8**	MB	69 %	72 %

Table 3.2 Reaction optimisation for photoredox-catalysed CF_3-thiocyclisation of **23a1**; **23a1** (0.05 mmol), solvent (0.50 mL), 14 W white lamp; [a] 1.2 eq. **R2** or **R8**; [b] 5 mol% $Ru(bpy)_3(PF_6)_2$ or 2 mol% MB; [c] Determined by ^{19}F NMR using $PhCF_3$ as an internal standard; Isolated yield in parentheses.

The reaction of **23a1** with the Umemoto reagent (**R2**) in CD_3CN afforded **24a1** in moderate yields with both photocatalysts (entries 1 - 2). In contrast, the reaction with the Togni reagent II (**R8**) gave lower yields (entries 3 - 4). When the reactions were performed in $CDCl_3$, the yields were significantly improved; **R2** and **R8** afforded the desired product in 74 % and 72 %, respectively (entries 5 - 8). When MB was used as a photocatalyst, the reaction was more efficient, which is advantageous since MB is cheaper and less toxic than the $Ru(bpy)_3(PF_6)_2$. In most cases, the yields improved slightly when the reactions were carried out over 24 hours. Finally, under our optimised conditions, **24a1** was isolated in 65 % yield (Table 3.2, entry 6). When eosin Y or rose bengal was employed as an alternative photocatalyst (Table 3.3, entries 2 - 3 and 5 - 6), the yields of **24a1** were slightly lower.



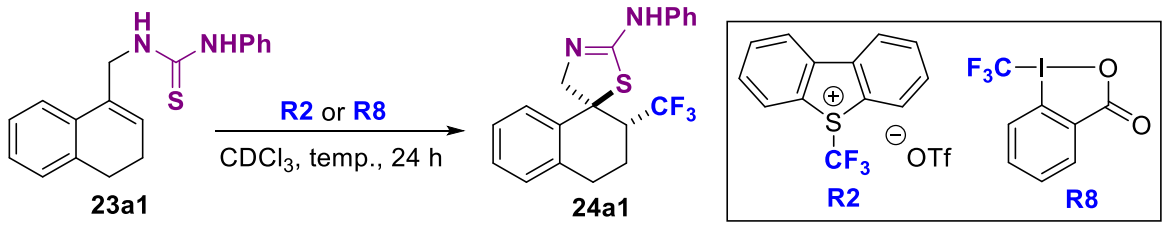
Entry	CF_3^+ reagent [a]	Photocatalyst [b]	Conversion of 23a1 [c]	Yield of 24a1 [d]
1	**R2**	-	35 %	17 %
2	**R2**	eosin Y	100 %	50 %
3	**R2**	rose bengal	100 %	58 %
4	**R8**	-	27 %	11 %
5	**R8**	eosin Y	100 %	50 %
6	**R8**	rose bengal	100 %	52 %

Table 3.3 Reaction optimisation for photoredox-catalysed CF_3-thiocyclisation of **23a1**; **23a1** (0.05 mmol), $CDCl_3$ (0.50 mL), 14 W white lamp; [a] 1.2 eq. **R2** or **R8**; [b] 2 mol%; [c] Determined by ^1H NMR using mesitylene as an internal standard; [d] Determined by ^{19}F NMR using $PhCF_3$ as an internal standard.

It was also observed that the trifluoromethylated product **24a1** was formed in the absence of the photocatalyst (Table 3.3, entries 1 and 4). The yields, however, were much lower than the reactions with the photocatalyst.

3.4.2 Thermal-Activated Trifluoromethylation-Thiocyclisation

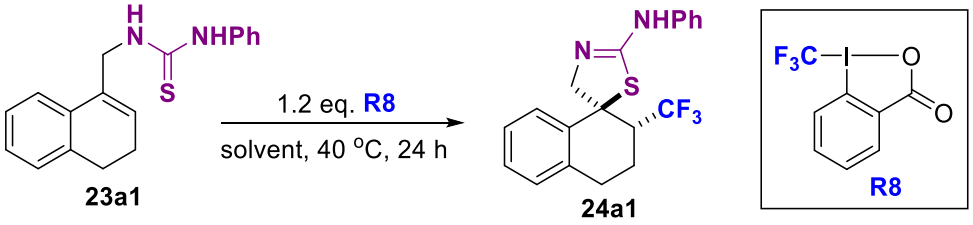
The trifluoromethylation-cyclisation of **23a1** was attempted at elevated temperatures in the absence of light or photocatalyst (Table 3.4).



Entry	CF_3^+ reagent	Temp.	Conversion of 23a1 [b]	Yield of 24a1 [c]
1	1.2 eq. **R2**	rt	35 %	17 %
2	1.2 eq. **R2**	40 ºC	35 %	22 % (d.r. = 18:1)
3	1.5 eq. **R2**	40 ºC	92 %	57 % (d.r. = 18:1)
4	1.5 eq. **R2**	60 ºC	100 %	58 % (d.r. = 5:1)
5	1.2 eq. **R8**	rt	27 %	11 %
6	1.2 eq. **R8**	40 ºC	58 %	43 %
7	1.5 eq. **R8**	40 ºC	100 %	51 %
8	1.5 eq. **R8**	60 ºC	100 %	63 %

Table 3.4 Reaction optimisation for thermal activation CF_3-thiocyclisation of **23a1**; **23a1** (0.05 mmol), $CDCl_3$ (0.50 mL); [a] Determined by ^{1}H NMR using mesitylene as an internal standard; [c] Determined by ^{19}F NMR using $PhCF_3$ as an internal standard; Diastereomeric ratio (d.r.) determined by ^{19}F NMR (the identity of the minor isomer was confirmed by ^{1}H NMR and is in agreement with the literature).[26]

Both **R2** and **R8** can induce the CF_3-thiocyclisation of **23a1** at the elevated temperatures, for which the highest yield of 63 % was achieved using 1.5 eq. of **R8** at 60 °C (entry 8). While the use of the Umemoto reagent (**R2**) gave rise to good yields also, the reaction showed erosion of diastereoselectivity at high temperatures (entry 4). In most cases, the conversion of **23a1** was much higher than the yield of **24a1** but no other fluorinated product was observed in the ^{19}F NMR; a result which could be accounted for due to the decomposition or polymerisation of the starting material under the reaction conditions. While the reaction also proceeds in a range of solvents including DCE, THF, CH_3CN, DMF, MeOH and EtOH, none of them led to the improvement in the yield of **24a1** (Table 3.5).

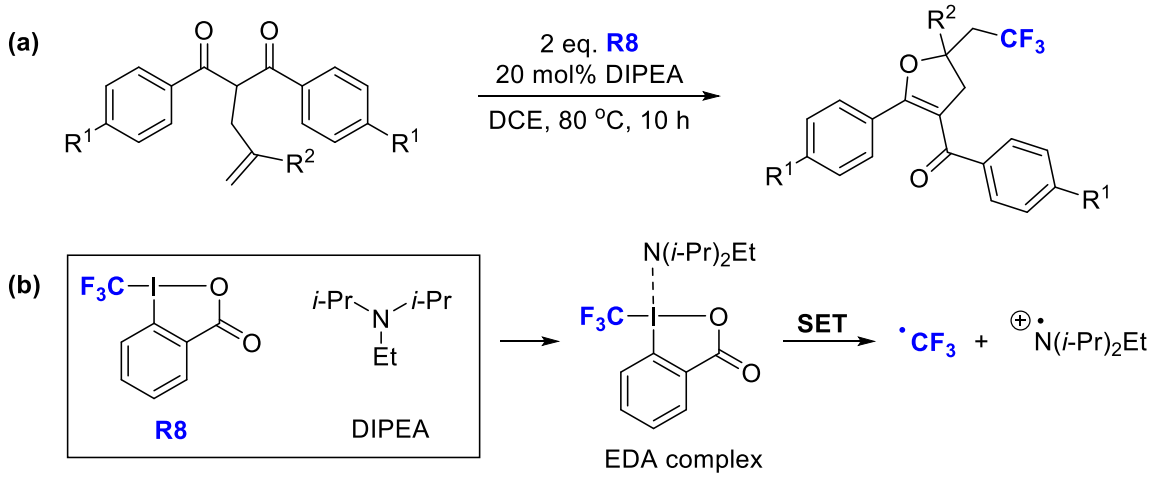


Entry	Solvent	Conversion of 23a1 [a]	Yield of 24a1 [b]
1	$CHCl_3$	63 %	46 %
2	DCE	54 %	35 %
3	THF	51 %	28 %
4	CH_3CN	74 %	35 %
5	DMF	70 %	9 %
7	MeOH	100 %	42 %
8	EtOH	66 %	43 %

Table 3.5 Solvent screening for thermal activation CF_3-thiocyclisation of **23a1**; **23a1** (0.05 mmol), solvent (0.50 mL); [a] Determined by ^1H NMR using mesitylene as an internal standard; [b] Determined by ^{19}F NMR using $PhCF_3$ as an internal standard.

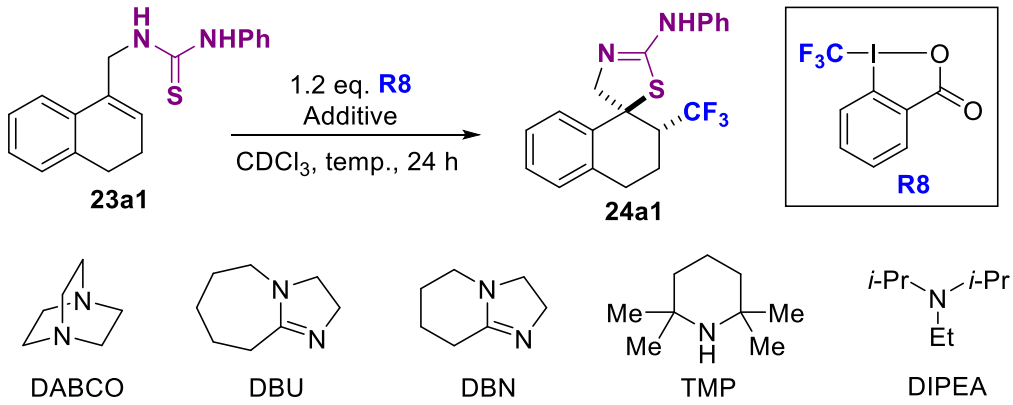
3.4.3 Base-Mediated Trifluoromethylation-Thiocyclisation

Very recently, Liu and co-workers demonstrated that organic bases such as *N*,*N*-diisopropylethylamine (DIPEA) and 1,5-diazabicyclo(4.3.0)non-5-ene (DBN) can induce CF_3 radical formation from the Togni reagent II (**R8**), leading to trifluoromethyl-oxycyclisation of an alkene with pendant 1,3-diketone group (Scheme 3.21a).[50] The author proposed that the amine and **R8** readily form an electron donor-acceptor (EDA) complex, which can undergo single electron transfer (SET) to provide CF_3 radical and amino radical cation (Scheme 3.21b).



Scheme 3.21 Organic base-catalysed trifluoromethyl-oxycyclisation.

In addition, since the N-H hydrogen on the thiourea group of **23a1** is removed upon trifluoromethylation-thiocyclisation, the presence of base should facilitate this deprotonation step after the cyclisation, hence increasing the yield of the reaction. Based on these observations, trifluoromethylation-thiocyclisation of **23a1** in the presence of various bases were investigated (Table 3.6). The inorganic bases, Cs_2CO_3 and $K_2C_2O_4$, did not affect the reaction (entries 2 - 3). On the other hand, the reactions in the presence of organic bases including DABCO, DBU, DBN, TMP and DIPEA at 40 °C gave significantly improved results with the maximum yield of 62 % (entries 4 - 9). Increasing the temperature or the amount of base did not increase the yield further (entries 10 - 12).

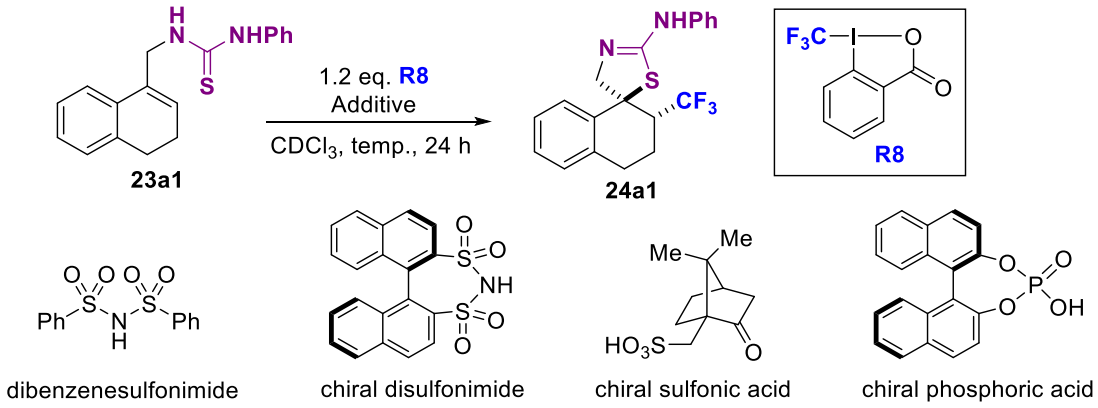


Entry	Temp.	Additive	Conversion of 23a1 [a]	Yield of 24a1 [b]
1	40 °C	-	58 %	43 %
2	40 °C	20 mol% Cs_2CO_3	77 %	43 %
3	40 °C	20 mol% $K_2C_2O_4$	62 %	42 %
4	40 °C	20 mol% DABCO	92 %	60 %
5	40 °C	20 mol% DBU	89 %	57 %
7	40 °C	20 mol% DBN	88 %	54 %
8	40 °C	20 mol% TMP	88 %	59 %
9	40 °C	20 mol% DIPEA	84 %	62 %
10	60 °C	20 mol% DIPEA	98 %	63 %
11	60 °C	50 mol% DIPEA	100 %	56 %
12	60 °C	100 mol% DIPEA	100 %	59 %

Table 3.6 Reaction optimisation for base-mediated CF_3-thiocyclisation of **23a1**; **23a1** (0.05 mmol), CD_3Cl (0.50 mL); [a] Determined by ^1H NMR using mesitylene as an internal standard; [b] Determined by ^{19}F NMR using $PhCF_3$ as an internal standard.

3.4.4 Brønsted Acid-Mediated Trifluoromethylation-Thiocyclisation

The activation of the Togni reagent by Brønsted acids has been utilised for the S–CF_3 bond formation (see Section 3.2.4); however, this concept has never been applied to the trifluoromethylation of alkenes. To investigate this effect, the CF_3-thiocyclisation of **23a1** was carried out in the presence of different acids (Table 3.7)



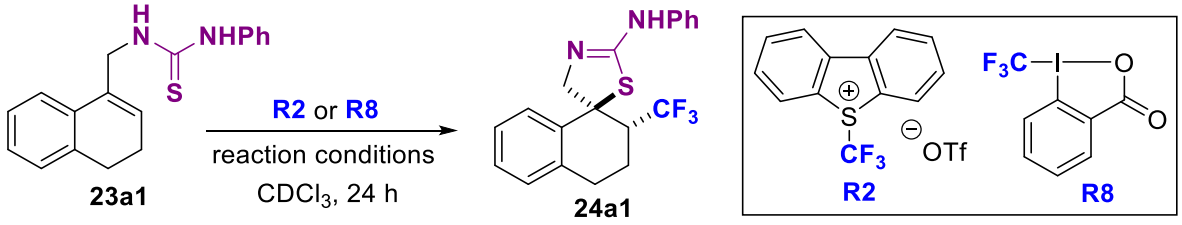
Entry	Temp.	Additive	Yield of 24a1 [a]
1	rt	-	11 %
2	rt	20 mol% TFA	49 %
3	rt	50 mol% TFA	61 %
4	rt	1 eq. TFA	74 %
5	rt	2 eq. TFA	79 %
7	40 °C	2 eq. TFA	77 %
8	60 °C	2 eq. TFA	80 %
9	rt	2 eq. dibenzenesulfonimide	76 %
10	rt	2 eq. chiral disulfonimide	48 % [b]
11	rt	2 eq. chiral sulfonic acid	52 % [b]
12	rt	2 eq. chiral phosphoric acid	14 % [b]

Table 3.7 Reaction optimisation for acid-mediated CF_3-thiocyclisation of **23a1**; **23a1** (0.05 mmol), CD_3Cl (0.50 mL); [a] Determined by ^{19}F NMR using $PhCF_3$ as an internal standard; [b] Enantiomeric ratio (e.r.) = 1:1 (determined by chiral HPLC analysis).

The addition of trifluoroacetic acid (TFA) led to a dramatic increase in the yield of **24a1** even at room temperature (entries 2 - 5). The yield reached 79 % when 2 eq. of TFA was used (entry 5). The reaction did not benefit from increasing the temperature (entries 6 - 7). Other strong organic acids such as bissulfonimide and sulfonic acid also significantly enhanced the yields (entries 9 - 11). However, a weaker acid such as phosphoric acid[51] was not effective (entry 12). The possibility to perform the CF_3-thiocyclisation in an asymmetric fashion was investigated by employing chiral Brønsted acids such as (*R*)-1,1′-binaphthyl-2,2′-disulfonimide (entry 10), (1*S*)-(+)-camphorsulfonic acid (entry 11) and (*R*)-(−)-1,1′-binaphthyl-2,2′-diyl hydrogenphosphate (entry 12); unfortunately, the reaction did not exhibit any enantioselectivity.

3.4.5 Optimised Reaction Conditions for Trifluoromethylation-Thiocyclisation

In summary, we have identified a selection of reaction conditions that can efficiently facilitate the trifluoromethylation-thiocyclisation of the model substrate **23a1** (Table 3.8). These conditions include the photoredox catalysis system (System **C** and **D**) and Brønsted acid mediation using TFA (System **E**).



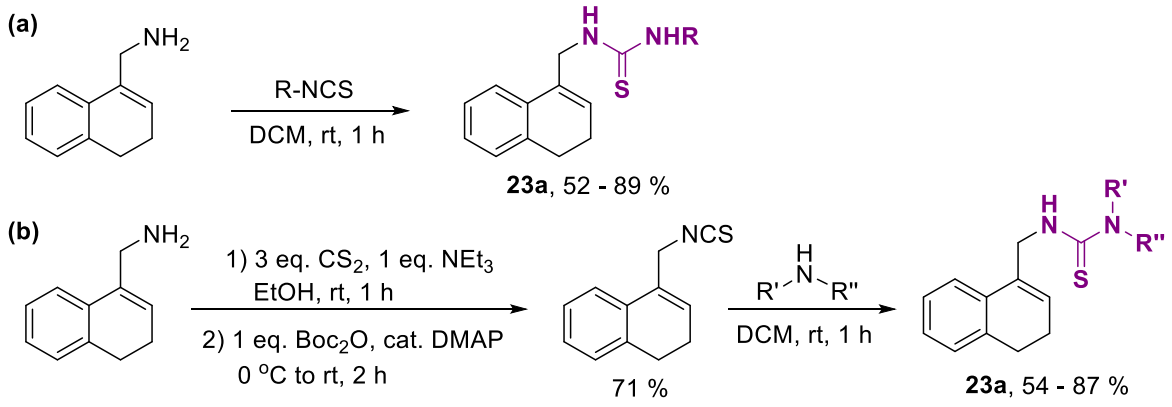
System	Conditions	Yield of 24a1 [a]
C	1.2 eq. **R2**, 2 mol% MB, rt, 14W white lamp	74 %
D	1.2 eq. **R8**, 2 mol% MB, rt, 14W white lamp	72 %
E	1.2 eq. **R8**, 2 eq. TFA, rt	79 %

Table 3.8 The optimised reaction conditions for CF_3-thiocyclisation of **23a1**; **23a1** (0.05 mmol), CD_3Cl (0.50 mL); [a] Determined by ^{19}F NMR using $PhCF_3$ as an internal standard.

3.5 Investigation of the Substrate Scope

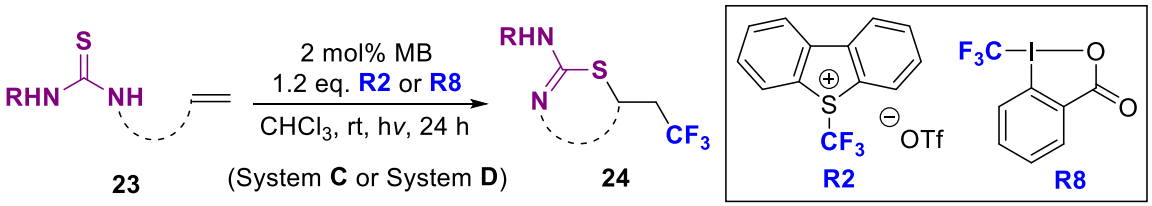
3.5.1 Photoredox-Catalysed Trifluoromethylation-Thiocyclisation

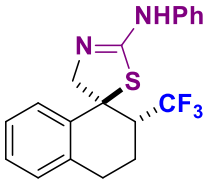
3,4-Dihydro-naphthalene substrates with different thiourea substituents at a C-1 position were readily prepared by the reaction of (3,4-dihydronaphthalen-1-yl)methanamine and the corresponding isothiocyanates (Scheme 3.22a). The substrate with two substituents on the nitrogen was synthesised by converting the (3,4-dihydronaphthalen-1-yl)methanamine into 4-(isothiocyanatomethyl)-1,2-dihydronaphthalene, followed by the reaction with the corresponding secondary amines (Scheme 3.22b).



Scheme 3.22 Preparation of thiourea substrates **23**.

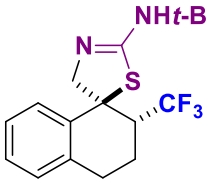
To investigate the substrate scope of the photoredox-catalysed trifluoromethylation-thiocyclisation, a wide range of conjugated alkenes with pendant thiourea groups were reacted with the Umemoto reagent (**R2**) or Togni reagent II (**R8**) under the optimised conditions (System **C** or **D**, respectively) (Table 3.9). In general, **R2** and **R8** exhibited very similar reactivity, although the reaction using **R2** gave slightly lower yields of the respective products. Alkyl substituents on the nitrogen atom such as *tert*-butyl (**23a2**) and benzyl (**23a3**) as well as di-substituted compound (**23a4**) gave the desired products in comparable yields as the model substrate. However, electron-withdrawing substituents such as benzoyl (**23a5**), 2-pyridyl (**23a6**) or 2-oxazolidinone (**23a7**) led to the decrease in reactivity. Unfortunately, no reaction occurred with **23a8**, a substrate possessing the free NH_2 motif.





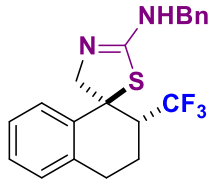
24a1

System **C:** 74 % (65 %)
System **D:** 78 % (65 %)



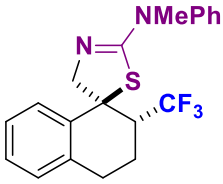
24a2

System **C:** 70 %
System **D:** 75 % (73 %)



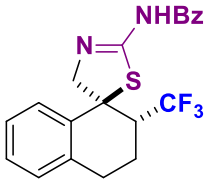
24a3

System **C:** 54 %
System **D:** 53 % (50 %)



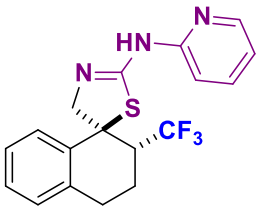
24a4

System **C:** 69 %
System **D:** 82 % (74 %)



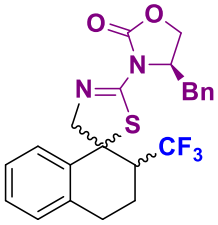
24a5

System **C:** 49 %
System **D:** 42 % (23 %)



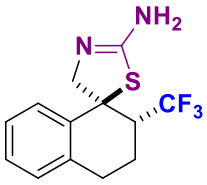
24a6

System **C:** 20 %
System **D:** 40 % [b]



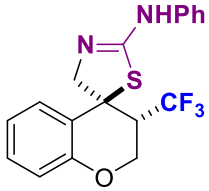
24a7

System **C:** 0 %
System **D:** 0 %



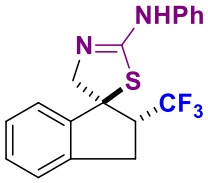
24a8 [a]

System **C:** 0 %
System **D:** 0 %



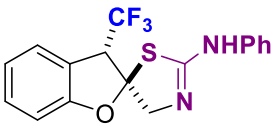
24b1 [a]

System **C:** 71 %
System **D:** 77 % (73 %)



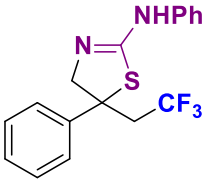
24c1 [a]

System **C:** 38 %
System **D:** 40 % (39 %)



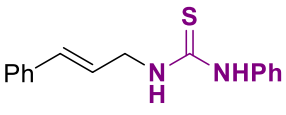
24d [a]

System **C:** 0 %
System **D:** 0 %

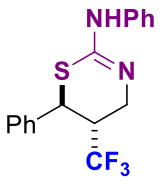


24e1 [a]

System **C:** 61 %
System **D:** 78 % (73 %)

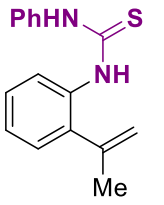


23f1

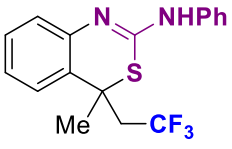


24f1

System **C:** 6 %
System **D:** 10 % (7 %)



23g1



24g1

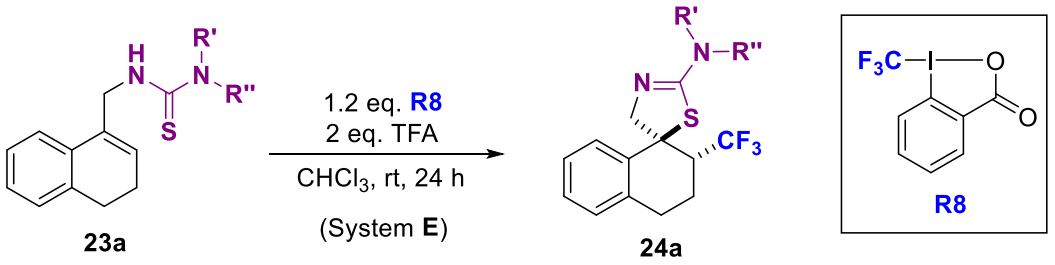
System **C:** 26 %
System **D:** 24 % (18 %)

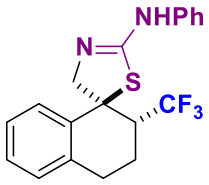
Table 3.9 Investigation of the substrate scope for photoredox-catalysed CF_3-thiocyclisation; System **C**: 1.2 eq. **R2**; System D: 1.2 eq. **R8**; MB = methylene blue; Yields determined by ^{19}F NMR using $PhCF_3$ as an internal standard with 0.30 mmol scale; Isolated yields in parentheses; d.r. > 20:1 [a] The starting materials for these reactions were synthesised by Dr. P. Ricci; [b] The compound could not be isolated by column chromatography.

The reaction of 2H-chromene **23b1** and indene **23c1** gave the corresponding spiro[6.5] and spiro[5.5] products in 73 % and 39 % isolated yields, respectively. Benzofuran substrate (**23d**) possessing electron-rich alkene led to a complex mixture due to the decomposition of the starting material. The reaction displayed a high degree of regioselectivity where the sulfur atom reacted at the α-carbon attached to the phenyl ring; for example, the reaction of the styrene substrate (**23e1**) afforded the 5-membered ring product (**24e1**) in 73 % yield, while the 1-cinnamyl-thiourea substrate (**23f1**) exclusively provided of the 6-membered ring product (**24f1**) in 7 % with the recovery of the starting material. The reaction of 1-phenyl-3-(2-(prop-1-en-2-yl)phenyl)thiourea (**23g1**) where the thiourea is substituted at the *ortho* position of the aromatic ring also gave the 6-membered ring product (**24g1**) in 18 % yield. To summarise, the substrate scope for the photoredox-catalysed reaction conditions is fairly limited; although the reaction provided moderate to good yields and excellent d.r. of the CF_3-substituted thiazolines, the syntheses of the CF_3-substituted thiazines were less efficient.

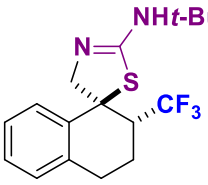
3.5.2 Brønsted Acid-Mediated Trifluoromethylation-Thiocyclisation

Now, the optimised reaction conditions described in Section 3.4.5 using TFA as an activator (System **E**; 1.2 eq. **R8**, 2 eq. TFA, rt, 24 h) were applied to various conjugated alkenes. First, the tolerance of the reaction to the variation of the thiourea *N*–substituent was investigated based on the 1,2-dihydro-naphthalene scaffold (**23a**) (Table 3.10). The alkyl substituted substrates (**23a2**, **23a3** and **23a4**) showed superior reactivity in the TFA-mediated conditions compared to the photoredox-catalysed conditions described in Section 3.5.1. No reaction was observed for the benzoyl substrate (**23a5**). The reaction tolerated various functional groups on the phenyl ring such as halogens (**23a9** and **23a10**), electron-donating methoxy (**23a11**), electron-withdrawing CF_3 (**23a12**) and ester (**23a13**). The reaction also tolerates heterocycles such as pyridine (**23a15**) and benzothiazole (**23a16**) although the yields were slightly lower. The d.r. is higher than 20:1 in all cases.

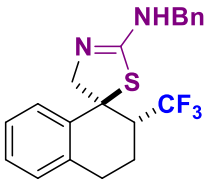




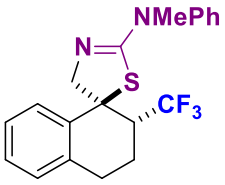
24a1
86 % (83 %)



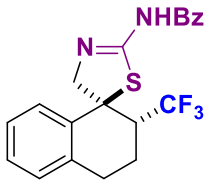
24a2
85 % (82 %)



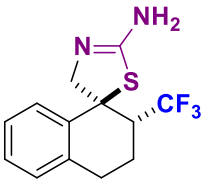
24a3
80 % (75 %)



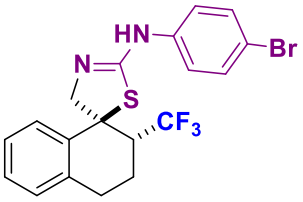
24a4
87 % (85 %)



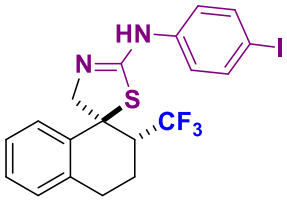
24a5
0 %



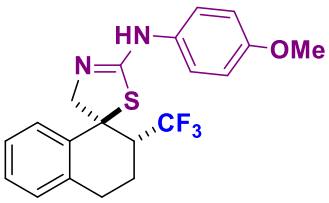
24a8 [a]
0 %



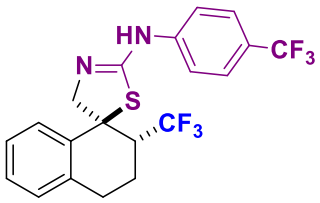
24a9
81 % (82 %)



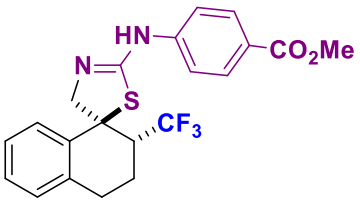
24a10
76 % (70 %)



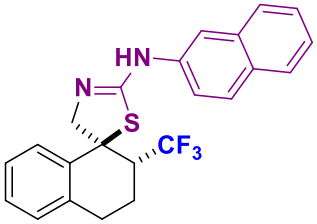
24a11 [a],[b]
nd (79 %)



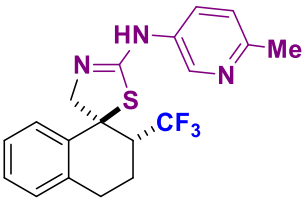
24a12 [a],[b]
nd (64 %)



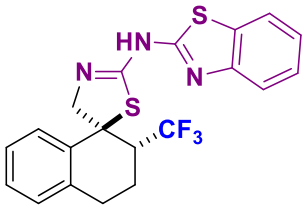
24a13 [a],[b]
nd (58 %)



24a14 [a],[b]
nd (82 %)



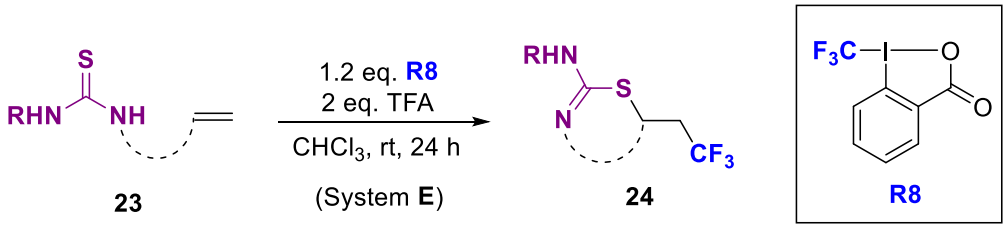
24a15 [a]
57 % (53 %)

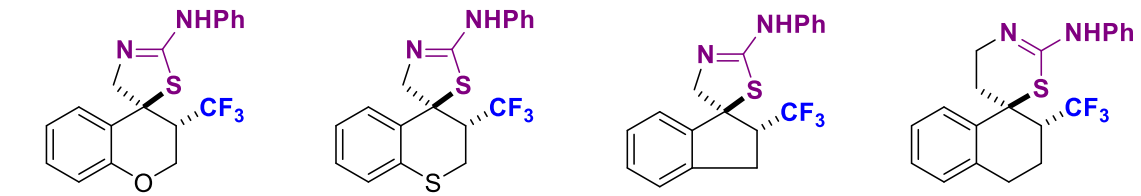


24a16
57 % (58 %)

Table 3.10 Investigation of the substrate scope for acid-mediated CF_3-thiocyclisation; Yields determined by ^{19}F NMR using $PhCF_3$ as an internal standard with 0.30 mmol scale; Isolated yields in parentheses; d.r. > 20:1 [a] The starting materials for these reactions were synthesised by Dr. P. Ricci; [b] These reactions were performed by Dr. P. Ricci.

Next, the variation on the substrate scaffold was examined (Table 3.11). The reaction of 2*H*-chromene **23b1** and 2*H*–thiochromene **23b2** led to the formation of the corresponding trifluoromethylated spiro-thiazoline products in excellent yields and diastereoselectivity. When the indene substrate (**23c1**) was subjected to the reaction, the spiro[5.5] thiazoline (**24c1**) could be isolated as a single diastereomer in 75 % yield. The spiro[6.6] thiazine (**24c2**) can also be accessed in good yield from 1-(2-(3,4-dihydronaphthalen-1-yl)ethyl)-3-phenylthiourea (**23c2**), although the reaction exhibited the erosion in diastereoselectivity (d.r. = 6:1). The reaction of 3-(2-phenylallyl)thiourea with different substituents (**23e1** - **23e4**) provided trifluoromethylated thiazolines in excellent yields.





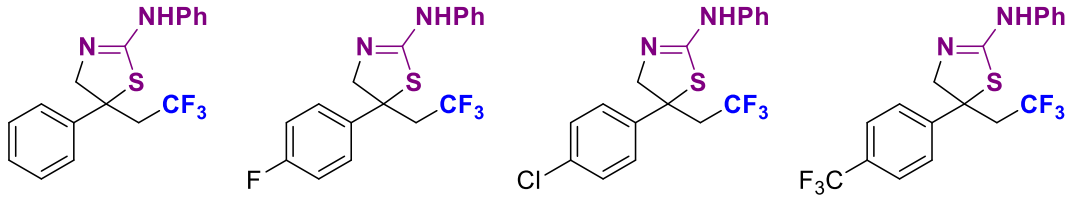
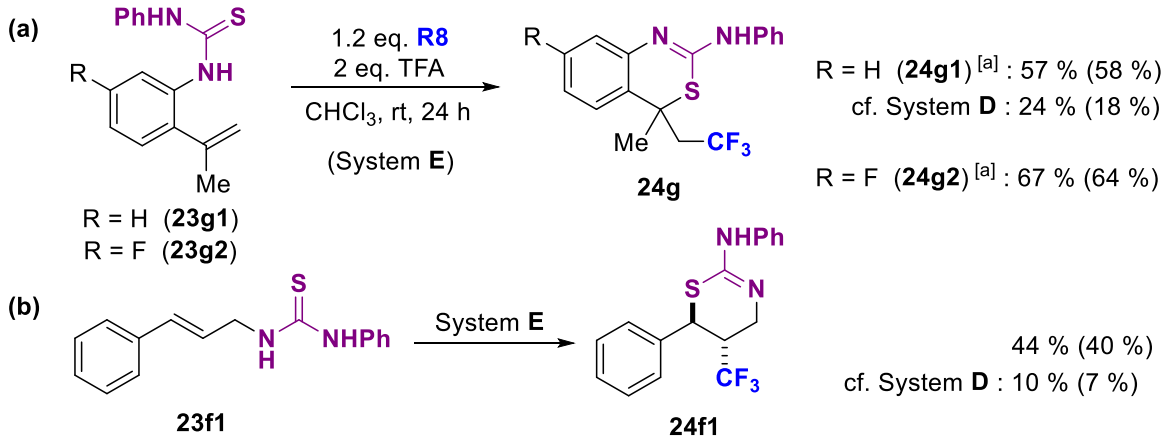


Table 3.11 Investigation of the substrate scope for acid-mediated CF_3-thiocyclisation; Yields determined by ^{19}F NMR using $PhCF_3$ as an internal standard with 0.30 mmol scale; Isolated yields in parentheses; d.r. > 20:1 unless specified [a] The starting materials for these reactions were synthesised by Dr. P. Ricci; [b] These reactions were performed by Dr. P. Ricci. [c] d.r. determined by ^{19}F NMR of the crude mixture.

The reaction of the 1-phenyl-3-(2-(prop-1-en-2-yl)phenyl)thiourea (**23g1**) showed a significant increase in reactivity compared to the photoredox-catalysed conditions; the yield of **24g1** was improved from 18 % to 58 % (Scheme 3.23a). The fluorinated analogue (**23g2**) also gave a similar yield of the trifluoromethylated product.



Scheme 3.23 Investigation of the substrate scope for acid-mediated CF_3-thiocyclisation; Yields determined by ^{19}F NMR using $PhCF_3$ as an internal standard with 0.30 mmol scale; Isolated yields in parentheses; [a] The starting materials for these reactions were synthesised by Dr. P. Ricci.

The 1-cinnamyl-thiourea substrate (**23f1**) also showed a dramatic improvement; **24f2** was isolated as a single diastereomer in 40 % yield compared to 7 % by the photoredox catalysis system (Scheme 2.23b). The 1-cinnamyl-thiourea substrate was chosen as a scaffold for the investigation of the electronic effect on the reaction (Table 3.12). Various substituents were placed at the *para* position of the aromatic rings of both the styrene core and the substituent on the thiourea group. It was found that these substituents had minor effects on the reactivity towards trifluoromethylation-thiocyclisation for which the yields of all the substrates including both electron-rich and electron-poor (**23f1** - **23f8**) were in the range of 40 - 55 %. The substrates with electron-donating substituent such as *para*-methoxy (**23f2** and **23f5**) showed slightly higher reactivity compared to the electron-neutral and electron-withdrawing substituted substrates. This result is in agreement with radical/cationic mechanism (more mechanistic studies will be described in Section 3.6).

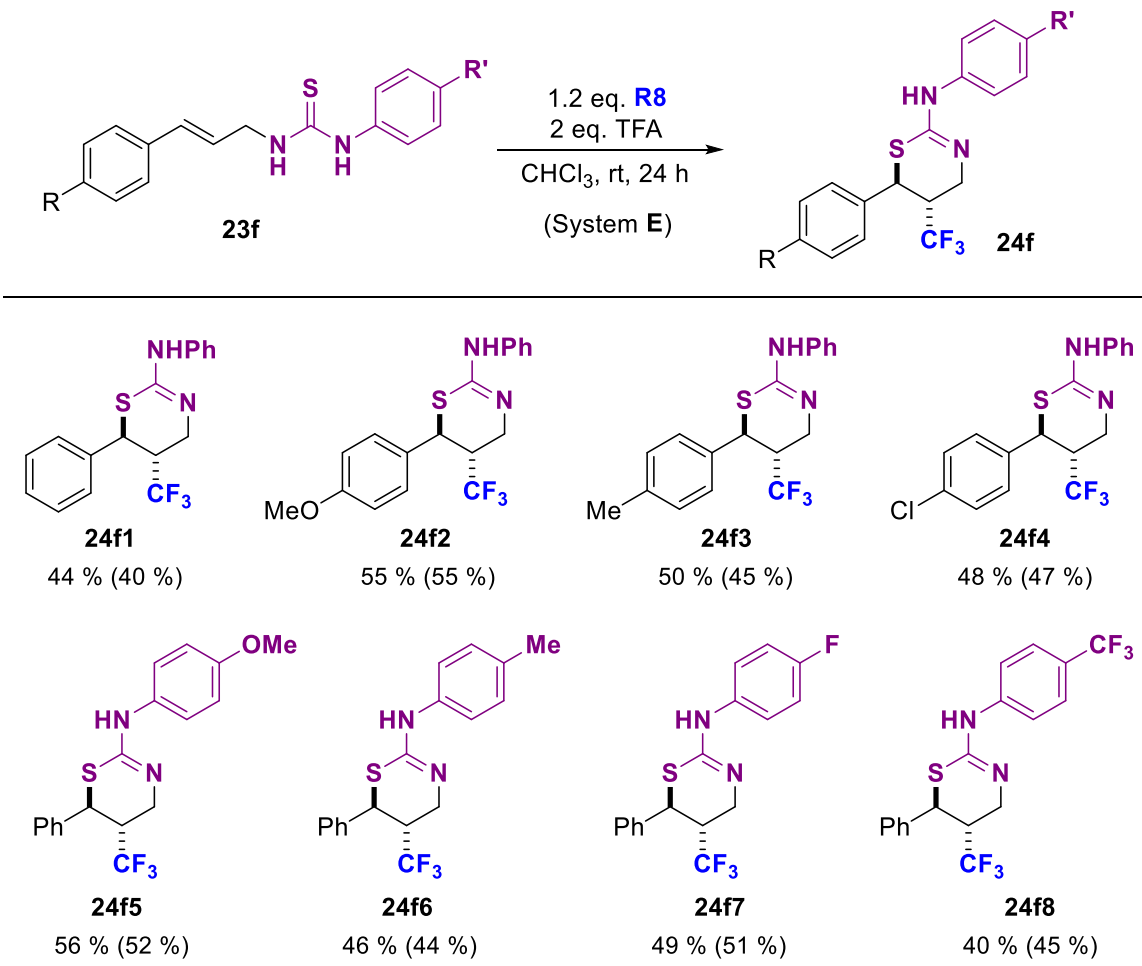
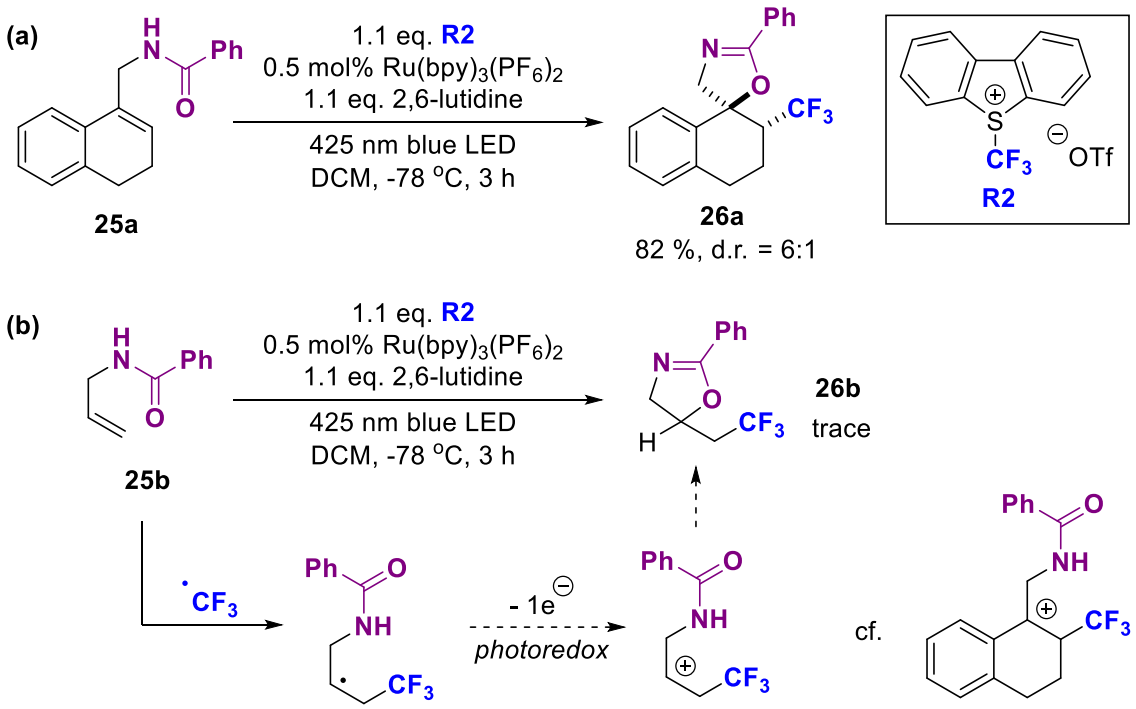


Table 3.12 Investigation of the substrate scope for acid-mediated CF_3-thiocyclisation; Yields determined by ^{19}F NMR using $PhCF_3$ as an internal standard with 0.30 mmol scale; Isolated yields in parentheses; d.r. > 20:1.

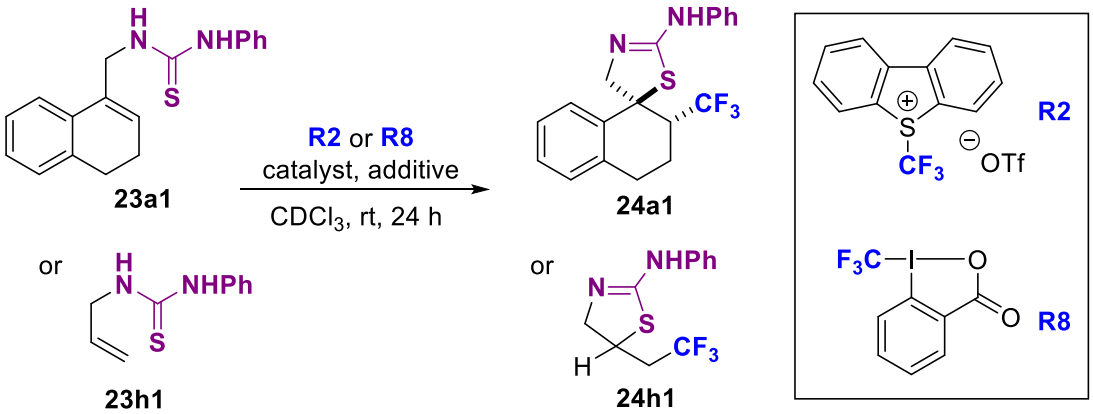
3.5.3 Unactivated Alkene Substrates

Unactivated alkenes are typically more challenging to undergo trifluoromethylation cyclisation. Repeating the reaction conditions reported by Akita and co-workers (described in Section 3.2.3) with the conjugated alkene substrate containing pendant amide group (**25a**) gave the cyclised product (**26a**) with the yield of 82 % which is similar to the reported value (Scheme 3.24a). However, no reaction occurred when the non-conjugated alkene substrates (**25b**) was employed (Scheme 3.24b). This could be explained by the difficulty in the oxidation of the carbo-radical intermediate to generate non-stabilised carbocation in the reaction of **25b** compared to the benzylic carbocation of **25a**.



Scheme 3.24 Investigation of the substrate scope for acid-mediated CF_3-thiocyclisation; Yields determined by ^{19}F NMR using $PhCF_3$ as an internal standard with 0.05 mmol scale.

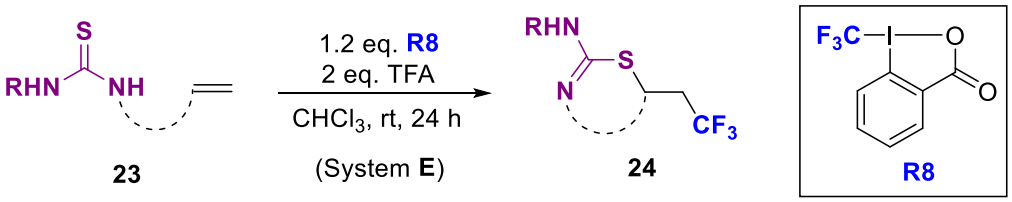
Subsequently, both conjugated (**23a1**) and non-conjugated (**23h1**) alkene substrates containing thiourea substituent were subjected to various reaction conditions for the investigation of their relative reactivity (Table 3.13). The reaction of **23a1** and **23h1** with the Umemoto reagent (**R2**) or Togni reagent II (**R8**) gave small amounts of the CF_3 product in the absence of the catalyst (entries 1 and 5). Remarkably, the reactions of **23a1** under photoredox catalysis conditions were significantly more efficient than **23h1** with the yields of **24a1** in the range of 60 - 74 % compared to 20 - 40 % of **24h1** (entries 2 - 3 and 6 - 7). The same trend was also observed for the thermal-activation conditions (entry 8). The addition of TFA led to the highest improvement of the yields of both substrates (entries 9 - 10); **24a1** and **24h1** were observed in 79 % and 76 %, respectively. The reactions in the presence of $Cu(CH_3CN)_4PF_6$ and 1,10-phenanthroline did not give rise to any significant increase in the yield of products **24a1** or **24h1** (entry 11).



Entry	CF_3^+ reagent	Catalyst & Additive	Yield of 24a1 [a], [b] (starting from 23a1)	Yield of 24h1 [a] (starting from 23h1)
1	1.2 eq. **R2**	-	11 %	12 %
2 [c]	1.2 eq. **R2**	5 mol% $Ru(bpy)_3(PF_6)_2$	60 %	40 %
3 [c]	1.2 eq. **R2**	2 mol% methylene blue	74 %	38 %
4	1.2 eq. **R2**	2 eq. TFA	10 %	13 %
5	1.2 eq. **R8**	-	17 %	21 %
6 [c]	1.2 eq. **R8**	5 mol% $Ru(bpy)_3(PF6)_2$	68 %	20 %
7 [c]	1.2 eq. **R8**	2 mol% methylene blue	72 %	31 %
8 [d]	1.2 eq. **R8**	-	63 %	38 %
9	1.2 eq. **R8**	1 eq. TFA	74 %	69 %
10	1.2 eq. **R2**	2 eq. TFA	79 %	76 %
11	1.2 eq. **R2**	1 eq. $Cu(CH_3CN)_4PF_6$, 1 eq. phen	23 %	33 %

Table 3.13 Reaction optimisation for trifluoromethylation-thiocyclisation of **23a1** and **23h1**; substrate (0.05 mmol), $CDCl_3$ (0.50 mL); [a] Determined by ^{19}F NMR using $PhCF_3$ as an internal standard; [b] d.r. > 20:1 determined by ^{19}F NMR; [c] The reactions were performed with a 14W white lamp as a light source; [d] The reaction was performed at 60 ^oC.

The screening experiments revealed System **E** (Brønsted acid-mediated) was the most efficient for the CF_3-thiocyclisation of non-conjugated alkene substrate. Next, the substrate scope was investigated using various scaffolds on the starting materials (Table 3.14). When the reaction of the allyl thiourea (**23h1**) was performed in a scale-up conditions, **24h1** was isolated in 80 % yield with no formation of the 6-membered ring product. The reaction of methallyl substrate (**23h2**) also led to an almost quantitative yield of trifluoromethylated thiazoline product (**24h2**). The increase in reactivity was expected since the more substituted alkene has higher affinity towards the electron-deficient CF_3 radical.



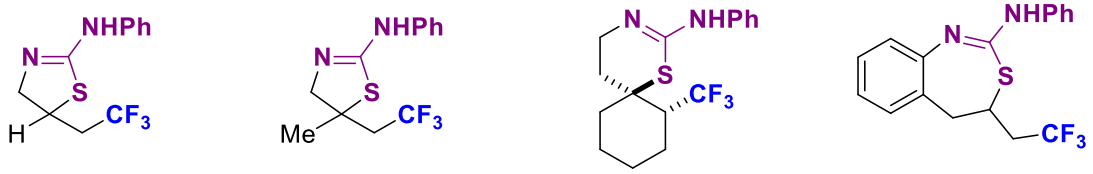
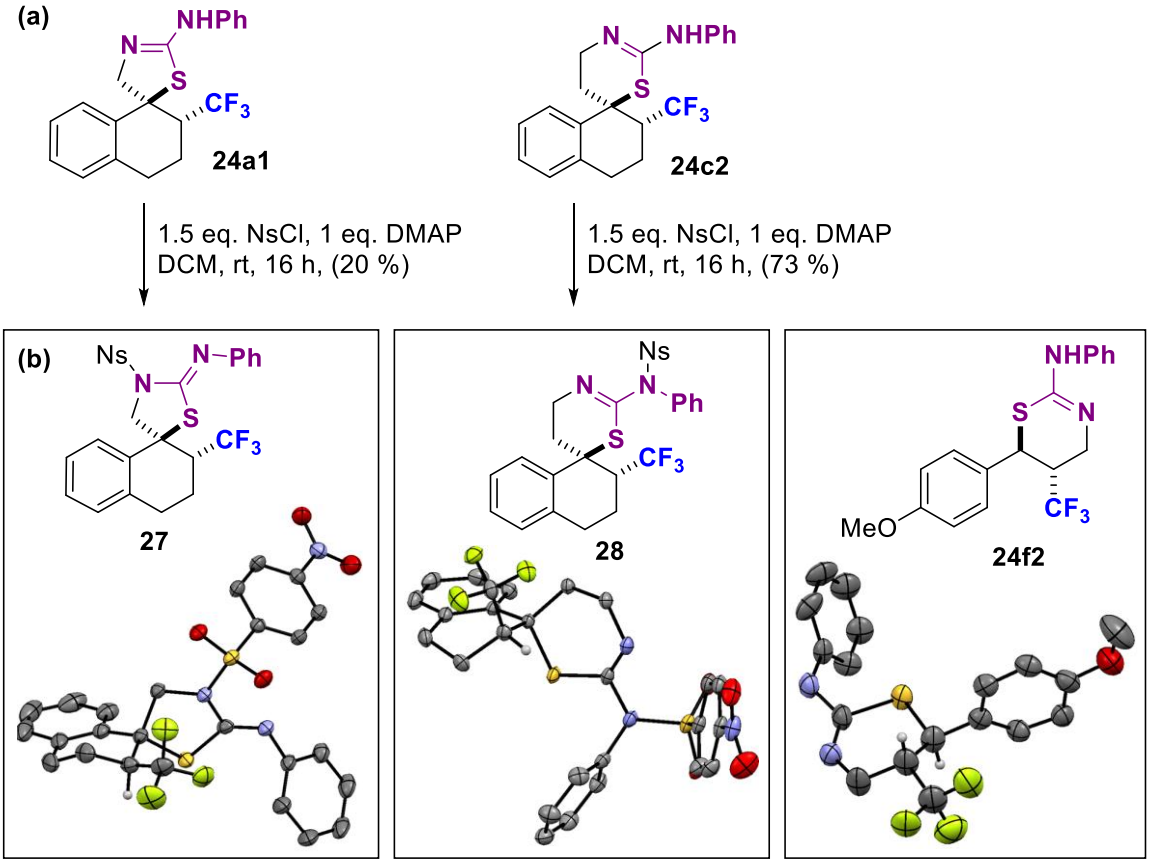


Table 3.14 Investigation of the substrate scope for acid-mediated CF_3-thiocyclisation; Yields determined by ^{19}F NMR using $PhCF_3$ as an internal standard with 0.30 mmol scale; Isolated yields in parentheses; [a] The starting materials for these reactions were synthesised by Dr. P. Ricci; [b] d.r. determined by ^{19}F NMR of the crude mixture.

The preparation of spiro[6,6] thiazine **24i**, a CF_3-substituted analogue of neuroprotectors (as described in Section 3.3), showed erosion in diastereoselectivity. However, the product was isolated in 60 % yield with d.r. >20:1 after purification. A larger scale reaction on 2.3 mmol (0.6 g) afforded **24i** in a reproducible yield of 61 %, an indicator of the robustness of the process. Finally, the method also gave access to the 7-membered ring product; CF_3-containing thiazepine **24j** was achieved in 59 % isolated yield.

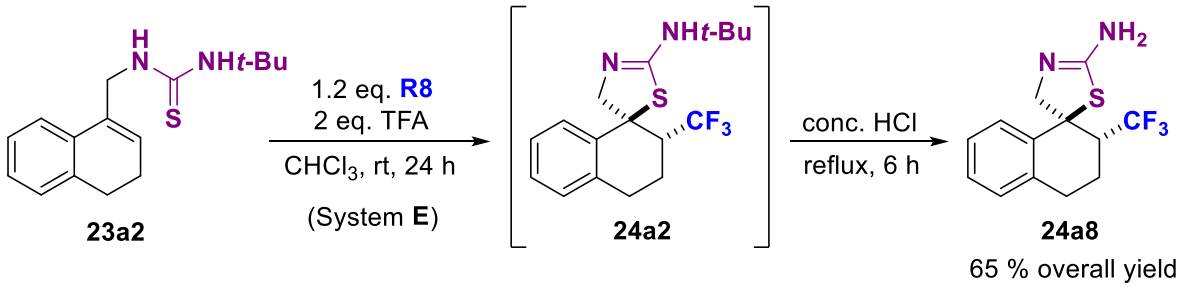
3.5.4 Post-Functionalisation Reactions

The stereochemistry determination of the products was initially attempted by nuclear overhauser effect (NOE) experiment, but the results were inconclusive. X-ray crystallography was chosen as an alternative technique to elucidate the stereochemistry. The CF_3-substituted spiro-thiazoline and spiro-thiazine products formed amorphous solids which were very difficult to recrystallize. As a result, these compounds were further functionalised with 4-nitrobenzenesulfonyl chloride (NsCl) to provide highly crystalline nosylated products (Scheme 3.25a). The spiro-thiazoline **24a1** underwent nosylation at the internal nitrogen position (**27**), whereas the reaction of spiro-thiazine **24c2** gave nosyl group at the external nitrogen position (**28**). The single crystal X-ray diffraction analysis of **27** and **28**, as well as the CF_3-substittuted thiazine **24f2**, unambiguously revealed the *anti*-diastereoselectivity of these reactions (Scheme 3.25b)



Scheme 3.25 Single crystal X-ray diffraction analysis of **27**, **28** and **24f2**.

The majority of the medical relevance thiazines and thiazolines contain unsubstituted NH_2 group (see Section 3.3). However, the substrate containing free-NH_2 thiourea (**23a8**) did not undergo CF_3-thiocyclisation under the optimised reaction conditions. Gratifyingly, **24a8** can be alternatively prepared from the *tert*-butyl substrate (**24a2**) by *in-situ* deprotection under acidic conditions in 65 % overall yield (Scheme 3.26).

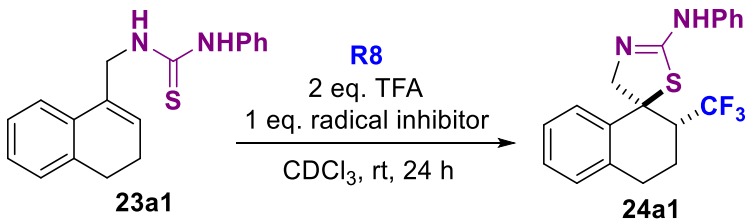


Scheme 3.26 Preparation of free-NH_2 substrate (**24a8**) *via* deprotection of *tert*-butyl group.

3.6 Investigation of Reaction Mechanism

3.6.1 Radical Inhibition Experiment

In order to confirm the hypothesis that the reaction proceeds *via a* radical mechanism, the trifluoromethyl-thiocyclisation were performed in the presence of various radical inhibitors (Scheme 3.27). The reaction was not affected by 1,4-dinitrobenzene, but the presence of benzoquinone inhibited the reaction completely. 2,2,6,6-Tetramethyl-1-piperidinyloxy (TEMPO) also led to a significant decrease in the yield of **24a1**. In addition, the ^{19}F NMR of the crude mixture revealed the formation of 23 % of TEMPO-CF_3 due to the characteristic peak found at –56.3 ppm.[52] These results are consistent with the formation of a CF_3 radical.

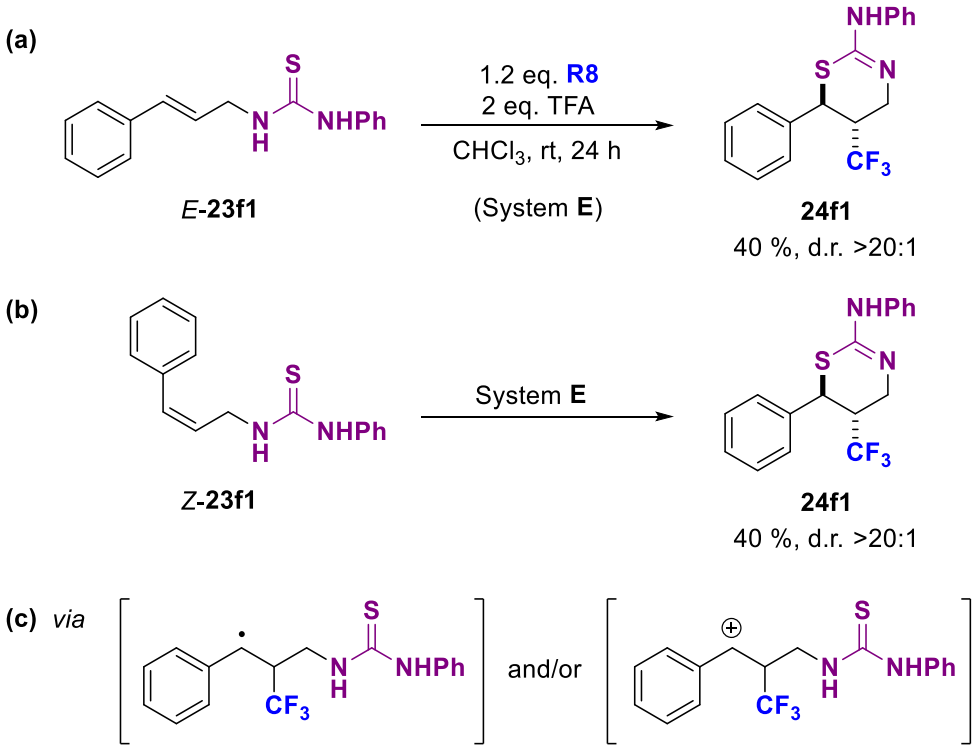


Inhibitor	Yield of **24a1**
-	79 %
1,4-DNB	71 %
benzoquinone	0 %
TEMPO	6 % [a]

Scheme 3.27 Radical inhibition experiments; [a] 23 % of TEMPO-CF_3 was observed.

3.6.2 Reaction on *E*- and *Z*-Alkene Substrates

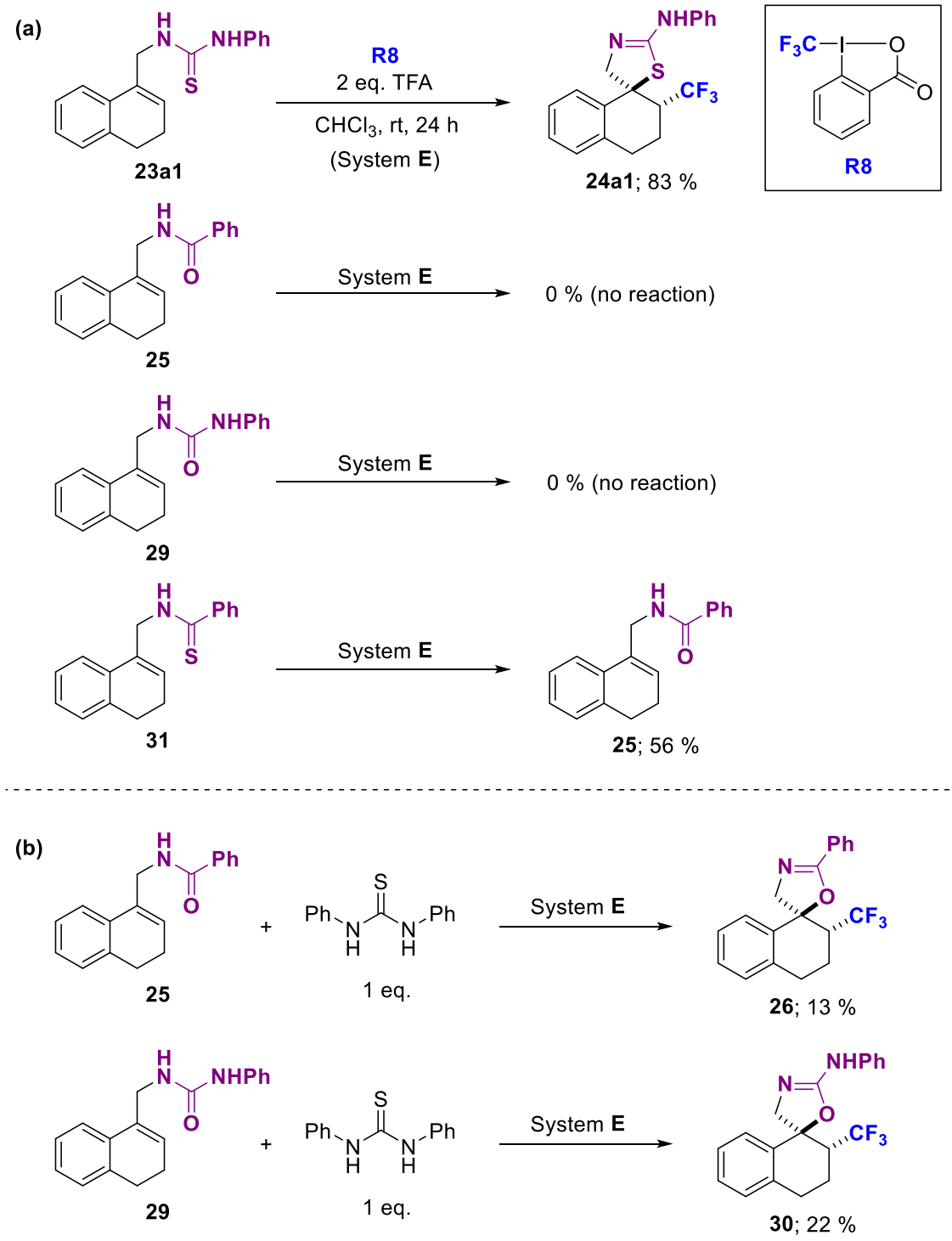
In Section 3.5.2, we demonstrated that the substrate *E*-**23f1** underwent trifluoromethylation-thiocyclisation to afford the CF_3-substituted thiazine substrate (**24f1**) in 40 % yield with *anti*-stereochemistry (Scheme 3.28a). When the reaction was repeated with *Z*-**23f1** as a starting material, the same stereochemical outcome was observed where *anti*-**24f1** was isolated in 40 % yield with d.r. >20:1 (Scheme 3.28b). This result suggested that the reaction proceeds through a step-wise mechanism in which the C–CF_3 and C–S bonds formed do not occur simultaneously. The fact that the reaction exclusively yielded the 6-membered ring substrate suggested that the C–CF_3 bond was formed prior to the C–S bond since it would lead to a more stable benzylic radical/carbocation intermediate (Scheme 3.28c). The mechanism suggested by Sodeoka and co-workers (see Section 3.2.3) which involves the activation of an alkene by the electrophilic hypervalent iodine followed by an intramolecular nucleophilic attack of the adjacent nucleophile was ruled out, since *E*- and *Z*-alkene substrates would yield the products with the different stereochemistry.



Scheme 3.28 Trifluoromethylation-thiocyclisation of *E*- and *Z*-**23f1**.

3.6.3 The Role of Thiourea

In order to investigate the role of the thiourea group in the reaction, the optimised reaction conditions using Togni reagent II (**R8**) and TFA were attempted on the amide (**25**), urea (**29**) and thioamide (**31**) substrates (Scheme 3.29a).

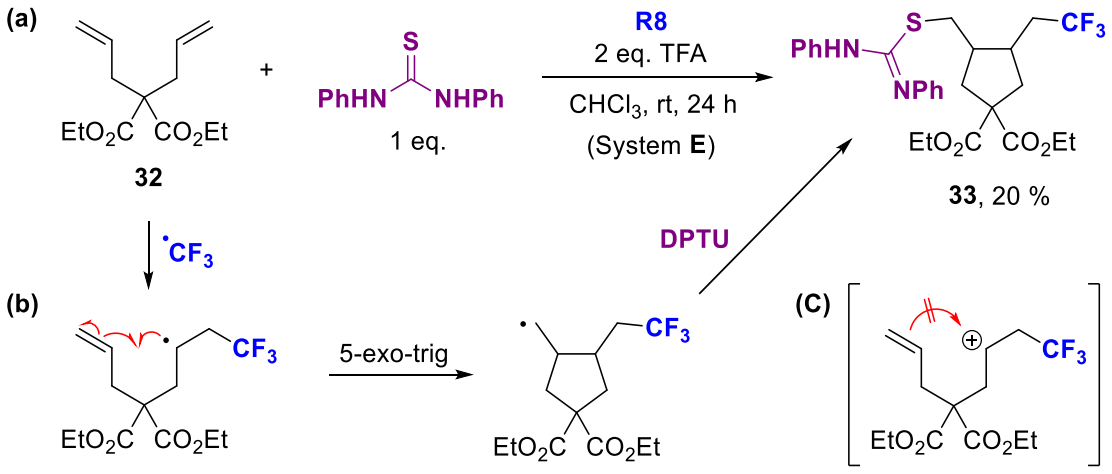


Scheme 3.29 CF_3-thiocyclisation of amide (**25**), urea (**29**) and thioamide (**31**) substrates.

The thioamide substrate (**31**) underwent hydrolysis under acidic conditions to afford **25** in 56 % yield. On the other hand, no reaction was observed when the amide (**25**) or urea (**29**) substrates were employed. The fact that no trifluoromethylated product (or by-product) were observed in the ^{19}F NMR of the crude mixture when thiourea is absent suggested that the thiourea could act as an activator for the Togni reagent. To confirm this hypothesis, the reaction of **25** and **29** were repeated in the presence of diphenylthiourea (Scheme 3.29b). The reaction yielded the corresponding CF_3-cyclised products (**26** and **30**, respectively), along with several unknown trifluoromethylated side-products (several doublets at around – 60 to – 70 ppm with $J_{F\text{-}H}$ ~ 10 Hz corresponding to the RR'CH-CF_3 moiety). These results underlined the importance of the thiourea group to initiate the trifluoromethylation step.

3.6.4 Radical Clock Experiment

To provide further evidence on the radical pathway, the substrate with two terminal alkenes (**32**) was subjected to the optimised reaction conditions in the presence of 1 eq. of diphenylthiourea (DPTU) (Scheme 3.30a). The ^{19}F NMR analysis of the crude mixture revealed several sets of triplets at around –60 to –70 ppm with $J_{F\text{-}H}$ ~ 10 Hz corresponding to the RCH_2-CF_3 moiety. Purification by column chromatography afforded the **33** in 20 % yield as a major product.

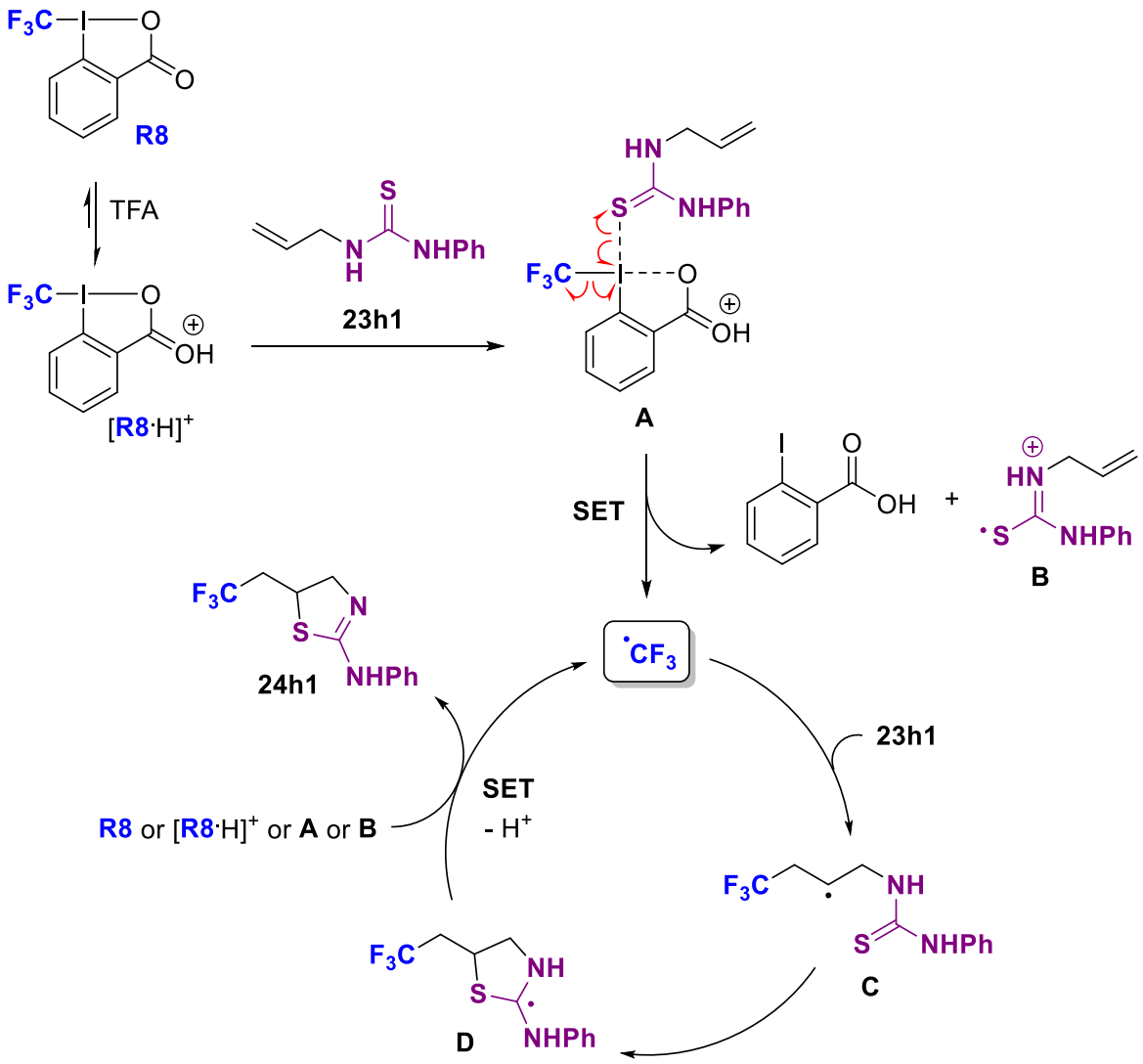


Scheme 3.30 Radical clock experiment using **32** as a starting material.

It was therefore proposed that the reaction of the terminal alkene on **32** with the CF_3 radical can lead to the formation of a carbon radical which can readily undergo facile 5-*exo*-trig radical cyclisation. The resultant carbon radical can then be trapped by the DPTU to form **33** (Scheme 3.30b). This result provided solid evidence for the radical pathway since it is unfavourable for the carbocation intermediate to undergo such cyclisation (Scheme 3.30c).

3.6.5 Proposed Reaction Mechanism

Based on the previous mechanistic experiments, the proposed reaction mechanism is described in Scheme 3.31.



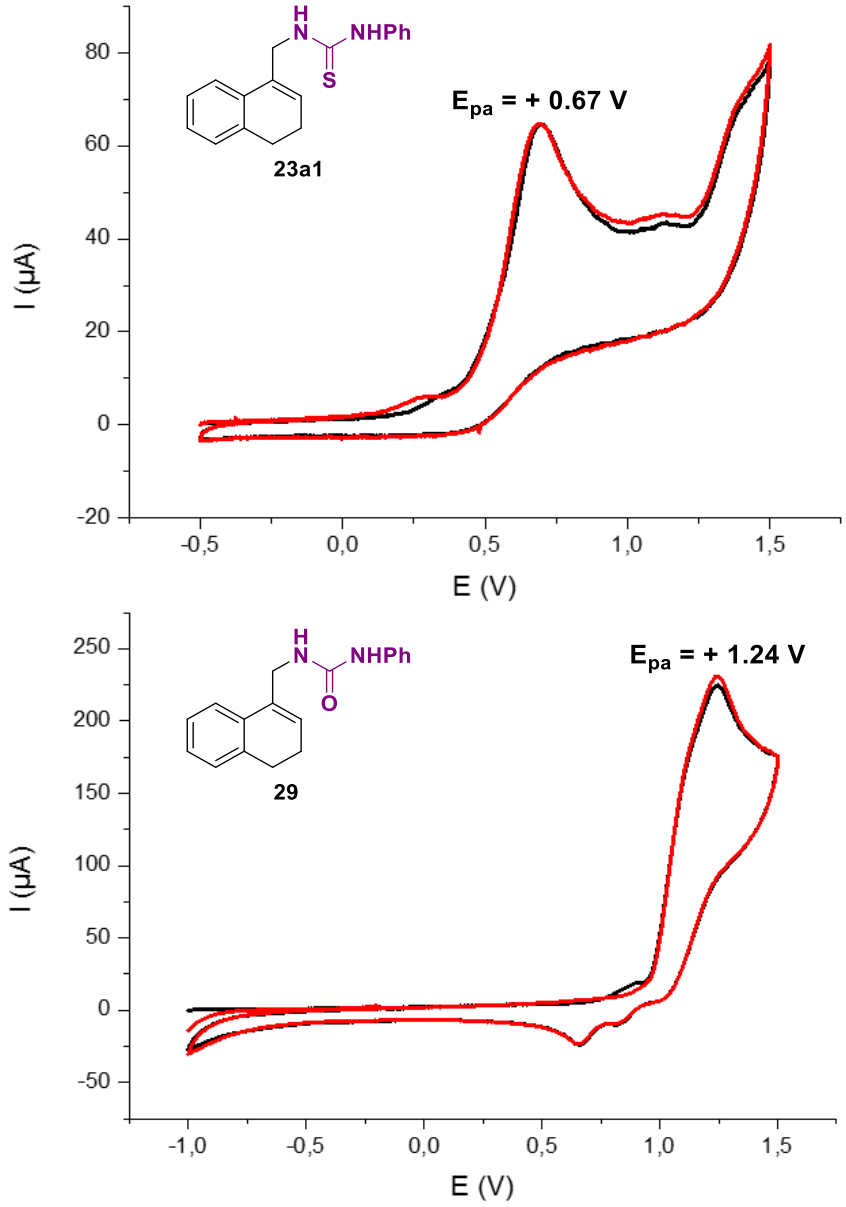
Scheme 3.31 Proposed mechanism for the trifluoromethylation-thiocyclisation of **23h1**.

The proposed reaction mechanism involves the protonation of Togni reagent (**R8**) with TFA to afford the highly electrophilic iodine (III) species [**R8**·H]$^+$. This species can coordinate to the thiourea starting material (in this case, **23h1**) to form **A** which can then undergo homolytic dissociation to form **B**, iodobenzoic acid and the electrophilic CF_3 radical. Although the coordination of thiourea with I(III) centre in **A** is unprecedented, the S–I(III) coordination has been evoked by Togni and co-workers in the S–CF_3 bond formation for thiols (Section 3.2.4, Scheme 3.17a). The alternative pathway towards CF_3 radical formation involving a single electron transfer from the thiourea to [**R8**·H]$^+$ is also possible. The CF_3 radical generated from these processes can regioselectively add to the alkene substrate (in this case, **23h1**) to form **C** for which it is well-documented that thiourea is an efficient radical scavenger.[53] Therefore, we proposed that the carbon radical in **C** can readily undergo ring closure by the pendant thiourea, leading to the C–S bond formation to provide adduct **D**. Oxidation of **D**, possibly *via* a single electron transfer to **R8**, [**R8**·H]$^+$ or **A**, and subsequent proton transfer could lead to the formation of the product **24h1**, and the CF_3 radical that starts a new reaction cycle (alternatively, **D** could be oxidised by **B** to give **24h1** and the regenerated starting material **23h1**). It is worth noting that in the cases of conjugated alkene substrates where the addition of the CF_3 radical would generate a benzylic carbon radical, oxidation into benzylic carbocation prior to S-cyclisation is also viable.

3.6.6 Cyclic Voltammetry Measurement

The work described in this section was carried out in by M. Médebielle. In Section 3.6.3, the contrasting reactivity between thiourea (**23a1**, 83 % of **24a1** isolated) and urea (**29**, no reaction) has been demonstrated. We surmised that this result could be explained by the fact that electron transfer from the thiourea to the Togni reagent (**R8**) is more facile than from the urea group (Konasiewicz and co-workers reported that the ionisation potential of unsubstituted thiourea and unsubstituted urea is 8.5 eV and 10.27 eV, respectively).[54]

To confirm this hypothesis, cyclic voltammetry measurements of the thiourea **23a1** (Scheme 3.32a) and the urea **29** (Scheme 3.32b) were performed. The readings were consistent with the reported ionisation potentials in which the oxidation potential of the thiourea **23a1** (+ 0.67 V *vs* Ag/Ag^+; + 0.98 V *vs* SCE) is much lower than the urea **29** (+ 1.24 V *vs* Ag/Ag^+; + 1.56 V *vs* SCE). Similar values were found for cyclic voltammetry measurements performed in the presence of TFA.



Scheme 3.32 Cyclic voltammetry measurements in CH_3CN + 0.10 M *n*-Et_4NBF_4 in the absence (black curve) and presence (red curve) of 2 eq. TFA; glassy carbon electrode at 0.2 V/s; (a) Thiourea **23a1**: E_{pox} = + 0.67 V *vs* Ag/Ag^+ = + 0.98 V *vs* SCE; (b) Urea **29**: E_{pox} = + 1.24 V *vs* Ag/Ag^+ = + 1.56 V *vs* SCE; E_{pa} = peak potential for the anodic sweep.

3.7 Conclusions

In summary, the first trifluoromethylation followed by S-cyclisation across C=C π bonds has been developed using thiourea as the source of sulfur. The reaction can operate under the standard photoredox catalysis with both Umemoto reagent or Togni reagent II (System **C** and System **D**, respectively) using methylene blue as a non-metal photocatalyst. However, the scope of the reaction was limited to the conjugated alkene substrates leading to trifluoromethylated spiro-thiazolines; the formation of CF_3-substituted thiazines was much less efficient under these systems.

Alternatively, Togni reagent II can be activated by the combination of trifluoroacetic acid as a Brønsted acid and the substrate itself, through its thiourea functionality. This mode of activation allowed the formation of the CF_3 radical that adds to the alkene in the absence of any metal species or light/photoredox catalysts. It was demonstrated that the reaction tolerates a wide range of substrates, leading to the formation of novel trifluoromethylated spiro[5,5] and [5,6] thiazolines, as well as spiro[6,6] thiazines in good to excellent yields. This protocol also allowed for the trifluoromethylation-thiocyclisation of unactivated alkenes in excellent yields, including the synthesis of trifluoromethylated spiro-amino-thiazine (**24i**), a CF_3-substituted analogue of a potent neuroprotector. The reaction possesses a high degree of regioselectivity for which only a single product was observed due to the formation of more stable carbon radical after the addition of the CF_3 radical across the alkene. The reaction exhibits an excellent degree of *anti*-selectivity; the CF_3-substituted thiazoline products were isolated in d.r. > 20:1, although the erosion of d.r. was observed in the thiazine products. Mechanistic experiments confirmed that the reaction operates *via* a radical pathway involving the formation of the CF_3 radical intermediate. The importance of the thiourea functionality for the activation of the Togni reagent was also confirmed.

3.8 References

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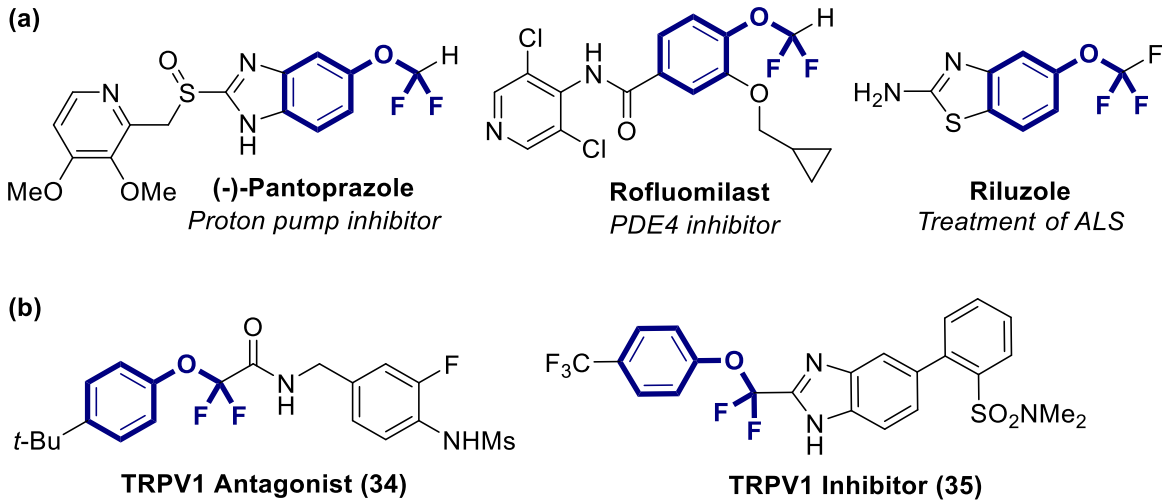
Chapter 4: ^{18}F-Labelling and Functionalisation of Ar-OCF$_2$CO$_2$H

The radiochemical reactions described in this chapter were carried out in collaboration with S. Calderwood or S. Verhoog.[1]

4.1 Ar-OCF$_2$ Motif in Drug Discovery

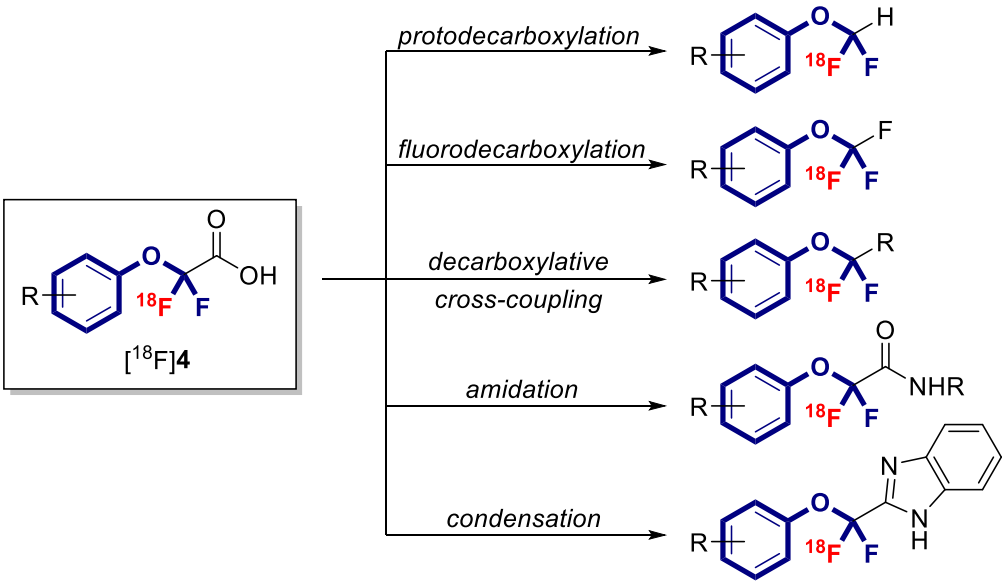
Compounds containing *α*,*α*-difluorinated aryl ethers (Ar-OCF$_2$) are becoming increasingly prevalent in pharmacological compounds, as exhibited by a range of drugs that contain Ar-OCF$_2$H and Ar-OCF$_3$ groups; for example, Pantoprazole, Roflumilast and Riluzole (Scheme 4.1a).[2] These groups can be viewed as the attachment of the Ar-OCF$_2$ motif with a hydrogen and a fluorine atom, respectively, and the method for ^{18}F-labelling these functional groups has been described in Chapter 2. However, the ^{18}F-labelling of the compounds derived from the attachment of the ArOCF$_2$ motif bearing more complex functionalities is unprecedented, despite the increasing number of applications of this sub-group in drug discovery; for example, the TRPV1 antagonist (**34**)[3] and the TRPV1 inhibitor (**35**)[4] which can target pain receptors (Scheme 4.1b). In the case of **34**, it has been found that *α*,*α*-difluoroamide derivative exhibited 3-fold more potent TRPV1 antagonistic activity (IC_{50} = 0.06 μM) than the parent non fluorine-containing amide analogue (IC_{50} = 0.17 μM).



Scheme 4.1 Pharmacologically relevant compounds containing Ar-OCF$_2$ motif.

4.2 Functionalisation of Carboxylic Acid

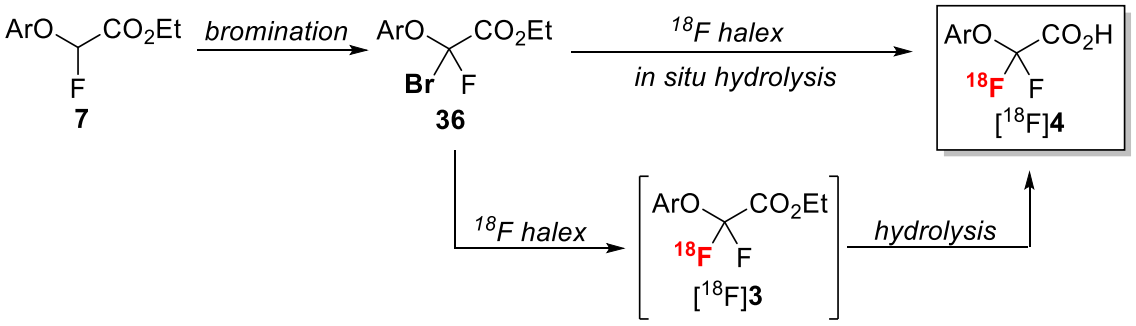
Carboxylic acid is a versatile functional group that can be transformed into various functional groups; for example, reduction to aldehydes and alcohols, reaction with alcohols/amines to form esters/amides, condensation to form a wide range of heterocycles, as well as numerous metal-catalysed reactions.[5] In addition, reactions by extrusion of carbon dioxide (decarboxylative transformations) have also been widely studied.[6] The simplest case of such transformation is the protodecarboxylation using either thermal activation with or without Brønsted acid/base catalysis,[7] or transition-metal mediators such as copper,[8] silver,[9] or mercury salts.[10] Fluorodecarboxylation can also be achieved using F_2,[11] XeF_2,[12] and other milder electrophilic fluorinating reagents such as NFSI (*N*-fluorobenzenesulfonimide) and Selectfluor (1-chloromethyl-4-fluorodiazoniabicyclo[2.2.2]octane bis(tetrafluoroborate)).[13] Moreover, carboxylic acids have also been used as a replacement of organometallic reagents in cross-coupling reactions with various carbon electrophiles.[14] In this chapter, we propose that [^{18}F]*α*,*α*-difluoro-*α*-aryloxyacetic acids ([^{18}F]**4**) could serve as a divergent reagent for the synthesis of the other relevant ^{18}F-labelled targets *via* subsequent post-fluorination functionalisation transformations (Scheme 4.2).



Scheme 4.2 Suggested functionalisation of [^{18}F]Ar-OCF$_2$CO$_2$H ([^{18}F]**4**).

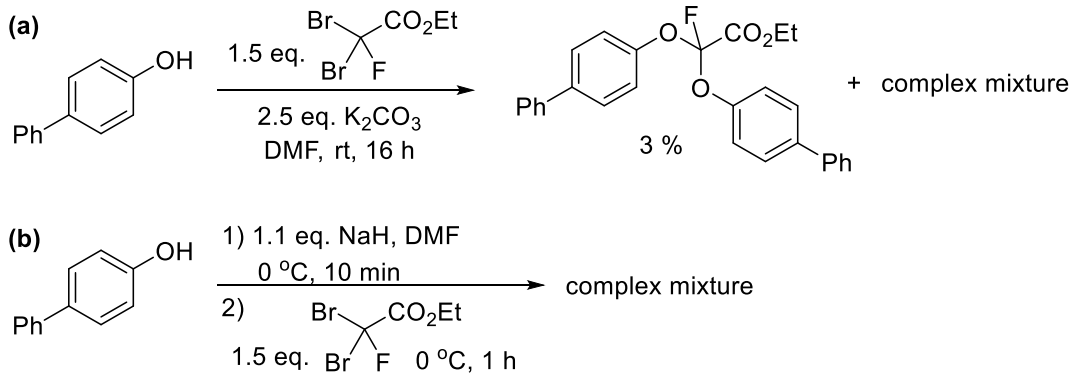
4.3 Preparation of Precursors

In order to prepare [^{18}F]**4**, we considered the halex ^{18}F-fluorination of ethyl *α*-bromo-*α*-fluoro-*α*-aryloxyacetate **36** to give ^{18}F-labelled ethyl *α,α*-difluoro-*α*-aryloxyacetate [^{18}F]**3**, which would afford [^{18}F]**4** upon subsequent hydrolysis (Scheme 4.3). Although the synthesis of **36** was unprecedented, we proposed that **36** could be obtained by bromination of the ethyl *α*-fluoro-*α*-aryloxyacetate **7** (see Chapter 2.6.1 for the preparation of **7**).



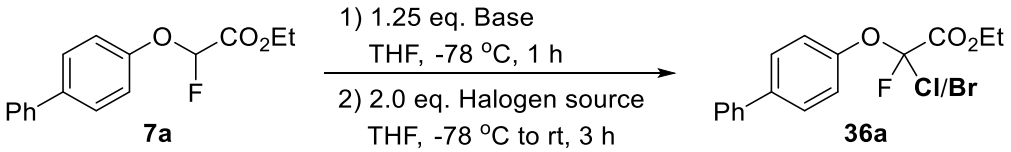
Scheme 4.3 Preparation of [^{18}F]*α,α*-difluoro-*α*-aryloxyacetic acids ([^{18}F]**4**).

Initially, an attempt to prepare **36** by the reaction of phenol with ethyl dibromofluoroacetate in the presence of K_2CO_3 led to a complex mixture (Scheme 4.4a). The reaction of the pre-generated phenoxide ion with NaH at 0 °C also led to several by-products (Scheme 4.4b). The isolation of the di-substituted product indicates that the phenoxide ion could potentially react with **36** to give this side product; therefore, the nucleophilic route is not suitable.



Scheme 4.4 Preparation of [^{18}F]*α,α*-difluoro-*α*-aryloxyacetic acids ([^{18}F]**4**).

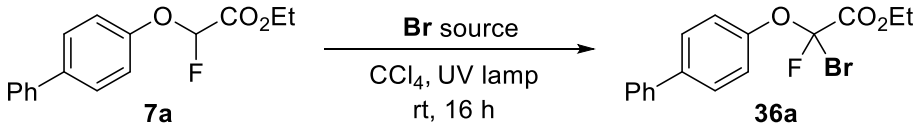
An alternative electrophilic bromination strategy was considered for the synthesis of **36**; deprotonation of **7** to form an enolate intermediate followed by addition of an electrophilic bromine source could lead to the desired brominated precursor (Table 4.1). NaH was not effective to promote the bromination of **7a** and the starting material was fully recovered (entry 1). The reaction of **7a** with lithium diisopropylamide (LDA) or lithium bis(trimethylsilyl)amide (LHMDS) followed by addition of *N*-bromosuccinimide (NBS) or carbon tetrabromide (CBr_4) led to total decomposition of the starting material with no other signal in ^{19}F NMR (entries 2 - 4). The addition of trimethylsilyl chloride (TMSCl) as an additive to form a silyl enol ether was also unsuccessful (entry 5). No chlorinated product was observed when *N*-chlorosuccinimide (NCS) was employed (entry 6). When the enolate solution was quenched with D_2O, 65 % of the deuterated product was observed, indicating that deprotonation is occurring, though this intermediate is not being trapped by the electrophilic halogen source (entry 7).



Entry	Base	Halogen source	Conversion [a]	Yield [a]
1	NaH	NBS	0 %	0 %
2	LDA	NBS	100 %	0 %
3	LHMDS	NBS	100 %	0 %
4	LDA	CBr_4	100 %	0 %
5[b]	LDA	NBS	100 %	0 %
6	LDA	NCS	100 %	0 %
7[c]	LHMDS	-	75 %	- [d]

Table 4.1 Halogenation of **7a** using electrophilic halogen sources; 0.25 mmol scale; [a] Determined by ^{19}F NMR using $PhCF_3$ as an internal standard; [b] The first step was performed in the presence of 1.25 eq. TMSCl; [c] After the first step, the reaction was quenched by the addition of D_2O; [d] 65 % of the deuterated product was observed.

An alternative approach using radical bromination reaction was also investigated (Table 4.2). The reaction of **7a** with bromine (Br_2) in CCl_4 under UV lamp led to total decomposition of the starting material with no trace of the desired product (entry 1). Gratifyingly, 19 % of **36a** was detected in ^{19}F NMR along with 58 % of the remaining **7a** when the reaction was performed using NBS, a reagent which releases Br_2 slowly under the reaction conditions (entry 2). The addition of a catalytic amount of benzoyl peroxide as a radical initiator did not affect the reaction (entry 3). No reaction occurred in the absence of light (entry 4). In order to improve the yield, the amount of NBS was increased to 4.0 equivalent (entry 5). Although the conversion and yield of **36a** rose to 90 % and 31 %, respectively, several fluorine-containing side products were detected in the ^{19}F NMR (30 % overall yield) at the same region of **36a**; these by-products are considered to arise from bromination on the electron-rich aromatic ring.

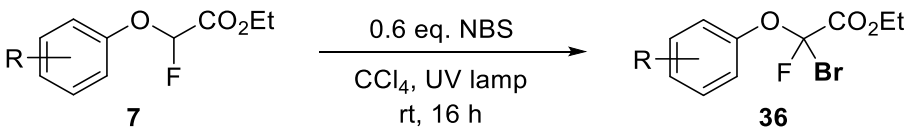


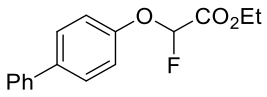
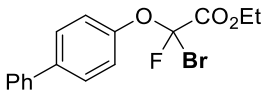
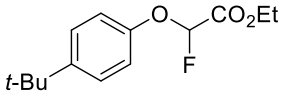
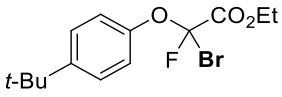
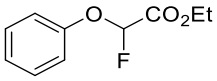
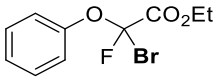
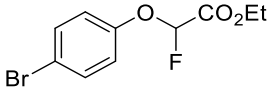
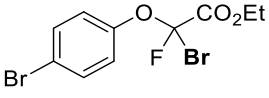
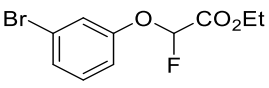
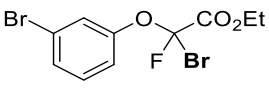
Entry	Br source	Temp	Conversion [a]	Yield [a],[b]
1	1.2 eq. Br_2	80 ºC	100 %	0
2	1.2 eq. NBS	80 ºC	42 %	19 % (13 %) [c]
3[d]	1.2 eq. NBS	80 ºC	46 %	18 % [c]
4[e]	1.2 eq. NBS	80 ºC	0 %	0 %
5	4.0 eq. NBS	80 ºC	90 %	31 % [c]
6	2 x 1.2 eq. NBS	80 ºC	66 %	45 % (16 %) [c]
7	1.2 eq. NBS	rt	38 %	15 % [c]
8	0.6 eq. NBS	rt	nd	nd (12 %)

Table 4.2 Radical bromination of **8a**; 0.25 mmol scale; [a] Determined by ^{19}F NMR using $PhCF_3$ as an internal standard; [b] Isolated yield of the 2.0 mmol scale in parenthesis; [c] Several by-products were detected in ^{19}F NMR; [d] Reaction in the presence of 1 mol% of benzoyl peroxide; [e] Reaction in the absence of light.

When the NBS was added in two portions to avoid these side reactions, the amount of the by-products were reduced (21 % overall yield) and the yield of **36a** was further improved to 45 % (entry 6). Isolation of **36a** by column chromatography was unsuccessful due to the similar polarity between **36a** and the side-products. The reaction was instead performed at room temperature using a substoichiometric amount of NBS (entry 8); 12 % of **36a** was successfully isolated along with the recovery of **7a** in 73 %.

The optimised reaction conditions for radical bromination (0.6 eq. NBS in CCl_4 at room temperature overnight under UV lamp) were applied to a range of ethyl *α*-fluoro-*α*-aryloxyacetates **7** (Table 4.3).



Entry	Phenol	Product	Product code	Yield [a]
1			**36a**	38 %
2			**36b**	37 %
3			**36o**	32 %
4			**36d**	35 %
5			**36p**	26 %

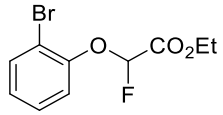
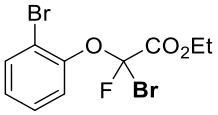
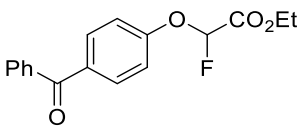
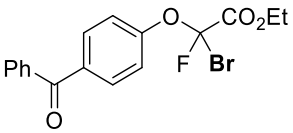
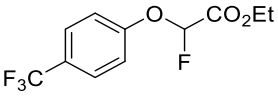
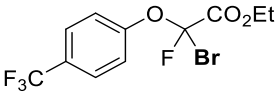
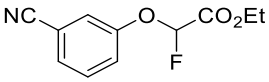
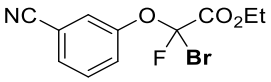
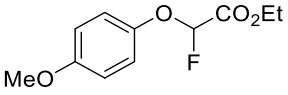
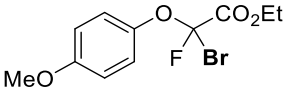
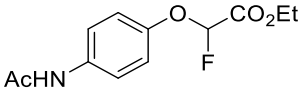
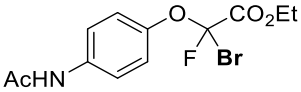
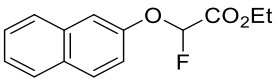
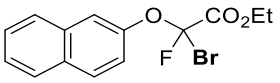
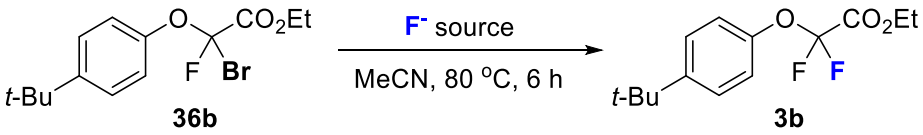
6			**36q**	23 %
7			**36i**	23 %
8			**36k**	19 %
9			**36t**	16 %
10			**36f**	0 % [b]
11			**36u**	0 % [b]
12			**36l**	0 % [b]

Table 4.3 Preparation of ethyl *α*-bromo-*α*-fluoro-*α*-aryloxyacetate **36** from **7** using radical bromination conditions; 4.0 mmol scale; [a] Isolated yields (yield based on NBS); [b] Complex reaction mixture was observed.

Electron-neutral (entries 1 - 3), halogenated (entries 4 - 6) and electron-poor (entries 7 - 9) substrates gave the corresponding brominated products in low yields. These products were isolated by column chromatography without contamination with by-products. In contrast, the electron-rich (entries 10 - 11) and naphthyl (entry 12) substrates were not successful due to the formation of several by-products. It is important to note that these brominated products are highly moisture sensitive and are kept under an argon atmosphere at low temperature.

4.4 Optimisation of Reaction Conditions for ^{18}F-Fluorination of 36b

A preliminary study was conducted by reacting **36b** with "cold" sources of fluoride in acetonitrile at 80 °C (Table 4.4). The reaction of **36b** with silver fluoride (AgF) led to the formation of the fluorinated product (**3b**) in 65 % isolated yield (entry 1). Surprisingly, 38 % of **3b** was also detected when KF was employed as the source of fluoride (entry 2) (cf. the fluorination of Ar-OCF$_2$Br did not occur in the absence of silver). This result is in line with the fact that the rate of nucleophilic substitution at the *α*-position of a carbonyl group is much faster due to stabilisation of the transition state and the interaction between π* from C=O and σ* from C-Br, leading to the reduction in the LUMO energy level.[15]

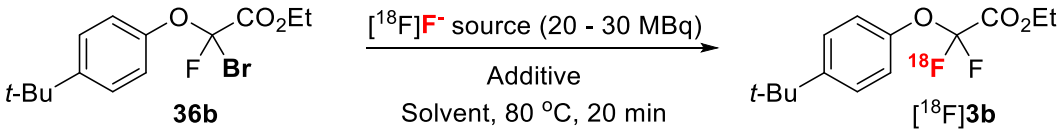


Entry	Fluoride source	Conversion [a]	Yield [a],[b]
1	1.5 eq. AgF	100 %	75 % (65 %)
2	1.5 eq. KF	67 %	38 %

Table 4.4 Preliminary results for fluorination of **36b**; 0.25 mmol scale; [a] Determined by ^{19}F NMR using PhCF$_3$ as an internal standard; [b] Isolated yield in parenthesis.

The preliminary study on the source of ^{18}F-fluoride revealed that [^{18}F]Et$_4$NF was not efficient for this transformation even with the temperature as high as 150 °C (Table 4.5, entries 1 - 3). Gratifyingly, [^{18}F]**3b** was detected in 28 % radiochemical yield (RCY) when **36b** was treated with [^{18}F]KF/K$_{222}$ in CH$_3$CN at 80 °C for 10 minutes (entry 4). The reaction finished in 20 minutes with the RCY of [^{18}F]**3b** increased to 57 % (entries 5 - 6). After varying the amount of the precursor and solvent, the RCY was further improved to 70 % (entries 6 - 10). Decreasing the temperature to 50 °C led to a slight decrease in RCY

(entries 11 - 13). No ^{18}F-incorporation was observed when the reaction was performed in the presence of $AgNO_3$ as a halogen abstractor (entry 14) or NaI as a nucleophilic mediator (entry 15).

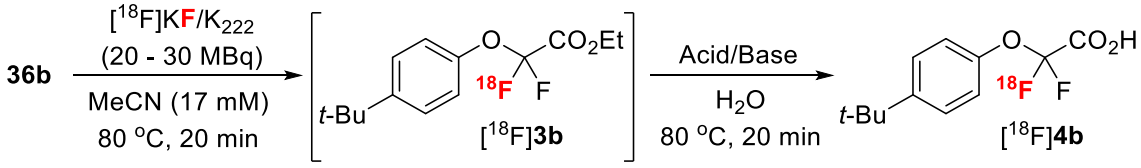


Entry	[^{18}F]F$^-$ source	Solvent	Concentration	Additive	RCY [a]	*n*
1	[^{18}F]Et$_4$NF	CH_3CN	100 mM	-	1 ± 0 %	2
2	[^{18}F]Et$_4$NF	*t*-BuOH	100 mM	-	4 ± 0 %	2
3 [b]	[^{18}F]Et$_4$NF	DMF	100 mM	-	0 %	2
4 [c]	[^{18}F]KF/K$_{222}$	CH_3CN	100 mM	-	28 ± 2 %	2
5	[^{18}F]KF/K$_{222}$	CH_3CN	100 mM	-	57 ± 10 %	4
6 [d]	[^{18}F]KF/K$_{222}$	CH_3CN	100 mM	-	56 ± 16 %	2
7	[^{18}F]KF/K$_{222}$	CH_3CN	200 mM	-	53 ± 4 %	2
8	[^{18}F]KF/K$_{222}$	CH_3CN	33 mM	-	64 ± 6 %	2
9	[^{18}F]KF/K$_{222}$	CH_3CN	17 mM	-	70 ± 6 %	4
10	[^{18}F]KF/K$_{222}$	*t*-BuOH	100 mM	-	32 ± 10 %	2
11 [e]	[^{18}F]KF/K$_{222}$	CH_3CN	100 mM	-	64 ± 8 %	4
12 [e]	[^{18}F]KF/K$_{222}$	CH_3CN	33 mM	-	69 ± 8 %	2
13 [e]	[^{18}F]KF/K$_{222}$	CH_3CN	17 mM	-	30 ± 3 %	2
14	[^{18}F]KF/K$_{222}$	CH_3CN	100 mM	1.0 eq. $AgNO_3$	1 ± 0 %	2
15	[^{18}F]KF/K$_{222}$	CH_3CN	100 mM	1.0 eq. NaI	1 ± 0 %	2

Table 4.5 ^{18}F-Fluorination of **36b**; **36b** (0.01 mmol); [a] Obtained by radio-TLC and radio-HPLC, repeated *n* times; [b] Reaction performed at 150 °C; [c] Reaction time = 10 minutes; [d] Reaction time = 30 minutes; [e] Reaction performed at 50 °C.

4.5 Optimisation of Reaction Conditions for Hydrolysis of [^{18}F]3b

In order to synthesise the acid [^{18}F]**4b**, we initially considered a one-pot hydrolysis procedure. The intermediate [^{18}F]**3b** was prepared using the optimised conditions (Section 4.4, Table 4.5, entry 9), then the crude mixture was treated with 1 M HNO_3 or 1 M NaOH and stirred for further 20 minutes at 80 °C (Table 4.6). Under the acidic conditions, [^{18}F]**4b** was detected in 22 % RCY along with 19 % RCY of the remaining ester [^{18}F]**3b** (entry 1). In the case of basic hydrolysis, [^{18}F]**3b** was fully hydrolysed; however, the desired acid was only observed in 26 % RCY (entry 2).

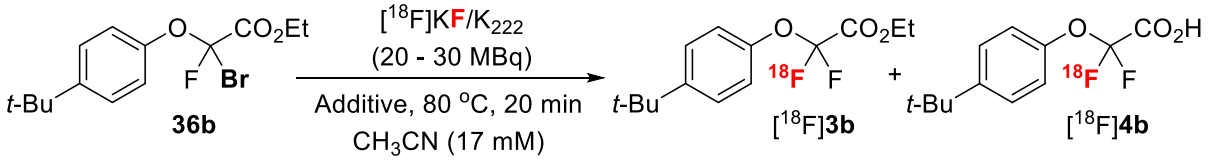


Entry	Acid/Base	[^{18}F]3a RCY [a],[b]	[^{18}F]4a RCY [a]	*n*
1	10 eq. 1 M HNO_3	19 ± 18 %	22 ± 14 %	2
2	5 eq. 1 M NaOH	-	26 ± 0 %	2

Table 4.6 ^{18}F-Fluorination of **36a** followed by hydrolysis using acid/base; **36a** (0.01 mmol); [a] Obtained by radio-TLC and radio-HPLC, repeated *n* times; [b] RCY of **3a** after the hydrolysis step.

An alternative *in situ* hydrolysis approach was considered by conducting the ^{18}F-fluorination of **36b** in the presence of bases (Table 4.7). A mixture of [^{18}F]**3b** and [^{18}F]**4b** was obtained under these conditions (entries 1 - 6) with the best results being obtained when Cs_2CO_3 (entry 5, 36 % RCY) and K_2CO_3 (entry 6, 40 % RCY) were employed as the base. Increasing the amount of base was detrimental to the reaction (entry 7). It is known that certain crown ethers and cryptands can serve as a chelator for potassium ion, hence enhancing the solubility of the base.[16] Although the addition of 18-crown-6 did not lead to a significant improvement (entry 8), the RCY of [^{18}F]**4b** was dramatically increased to 70 % when the

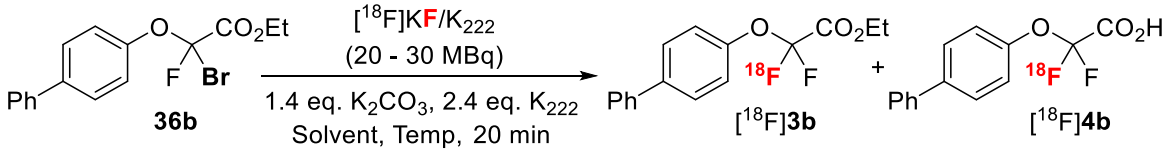
reaction was performed in the presence of 1.4 equivalent of Kryptofix-2.2.2 (K_{222}) (entry 9). The RCY was further improved to 82 % with full consumption of [^{18}F]**4b** being observed when the K_{222} was used in excess (entry 10). The RCY remained at 80 % even when the reaction time was reduced from 20 to 5 minutes. (entries 11 - 12). Increasing the concentration led to decrease in the RCY of [^{18}F]**3b** (entry 13).



Entry	Additive	[^{18}F]3b RCY [a]	[^{18}F]4b RCY [a]	*n*
1	1.4 eq. NBu_4OH	20 ± 0 %	1 ± 0 %	2
2	1.4 eq. LiOH	9 ± 4 %	22 ± 1 %	2
3	1.4 eq. $CsOH{\cdot}H_2O$	31 ± 22 %	16 ± 6 %	2
4	1.4 eq. NEt_4HCO_3	38 ± 8 %	6 ± 2 %	2
5	1.4 eq. Cs_2CO_3	15 ± 1 %	36 ± 0 %	2
6	1.4 eq. K_2CO_3	24 ± 20 %	40 ± 18 %	2
7	2.8 eq. K_2CO_3	22 ± 6 %	14 ± 2 %	2
8	1.4 eq. K_2CO_3, 2.4 eq. 18-crown-6	34 ± 13 %	37 ± 18 %	2
9	1.4 eq. K_2CO_3, 1.4 eq. K_{222}	4 ± 3 %	70 ± 13 %	2
10	1.4 eq. K_2CO_3, 2.4 eq. K_{222}	< 1 %	82 ± 4 %	4
11 [b]	1.4 eq. K_2CO_3, 2.4 eq. K_{222}	< 1 %	80 ± 4 %	4
12 [c]	1.4 eq. K_2CO_3, 2.4 eq. K_{222}	< 1 %	80 ± 8 %	2
13 [d]	1.4 eq. K_2CO_3, 2.4 eq. K_{222}	< 1 %	73 ± 10 %	2

Table 4.7 ^{18}F-Fluorination of **36b**; **36b** (0.01 mmol); [a] Obtained by radio-TLC and radio-HPLC, repeated *n* times; [b] Reaction time = 10 minutes; [c] Reaction time = 5 minutes; [d] Concentration = 33 mM.

The ^{18}F-fluorination with *in situ* hydrolysis of **36b** using 1.4 eq. K_2CO_3 and 2.4 eq. K_{222} was performed in different solvents, temperatures, and concentrations (Table 4.8). Only a trace of the radiolabelled product was detected when DMSO was used as a solvent (entry 2). DMF and *t*-BuOH led to the reduction in RCY of [^{18}F]**4b** compared to CH_3CN (entries 3 - 4). Excellent RCY of [^{18}F]**4b** was achieved when the reaction was conducted in acetone at 50 ^{o}C (entry 5); the RCY improved further to 83 % with higher concentration (entry 7). The RCY decreased slightly when the reaction time was reduced from 20 to 10 minutes (entry 8). As expected, control experiments demonstrated the importance of both K_2CO_3 and K_{222} as additives when the reaction was conducted in acetone (entries 9 - 10).

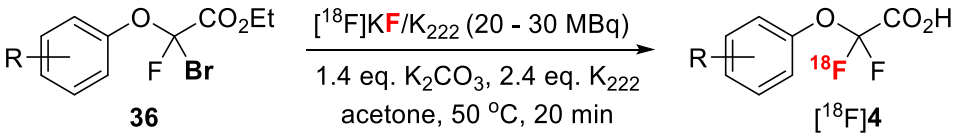


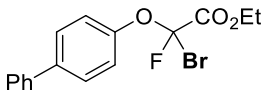
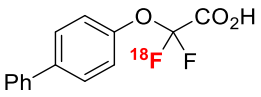
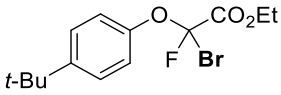
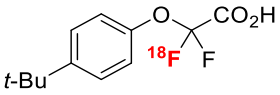
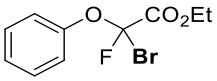
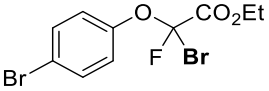
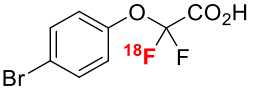
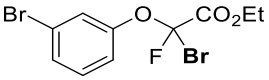
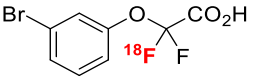
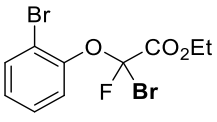
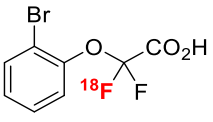
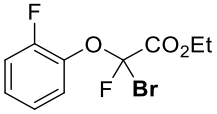
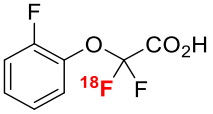
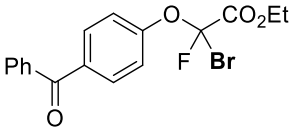
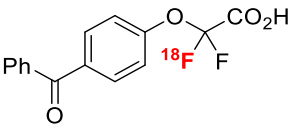
Entry	Solvent	Temp	Concentration	[^{18}F]3a RCY [a]	[^{18}F]4a RCY [a]	*n*
1	CH_3CN	80 ^{o}C	17 mM	< 1 %	82 ± 4 %	2
2	DMSO	80 ^{o}C	17 mM	< 1 %	2 ± 1 %	2
3	DMF	80 ^{o}C	17 mM	< 1 %	60 ± 11 %	2
4	*t*-BuOH	80 ^{o}C	17 mM	< 1 %	45 ± 10 %	2
5	acetone	50 ^{o}C	17 mM	< 1 %	81 ± 6 %	2
6	acetone	50 ^{o}C	33 mM	< 1 %	74 ± 0 %	2
7	acetone	50 ^{o}C	50 mM	< 1 %	83 ± 2 %	4
8 [b]	acetone	50 ^{o}C	50 mM	< 1 %	79 ± 5 %	6
9 [c]	acetone	50 ^{o}C	17 mM	20 ± 10 %	6 ± 1 %	2
10 [d]	acetone	50 ^{o}C	17 mM	4 ± 4 %	-	2

Table 4.8 ^{18}F-Fluorination of **36b**; **36b** (0.01 mmol); [a] Obtained by radio-TLC and radio-HPLC, repeated *n* times; [b] Reaction time = 10 minutes; [c] Reaction in the absence of K_{222}; [d] Reaction in the absence of K_2CO_3.

4.6 Investigation of the Substrate Scope

The optimised reaction conditions for the ^{18}F-labelling of **4b** described in Table 4.8, entry 7 (0.01 mmol **4b**, 0.014 mmol K_2CO_3, 0.024 mmol K_{222}, acetone (200 μL), 50 °C, 20 min) was applied to a range of brominated ester precursors (Table 4.9).



Entry	Phenol	Product	Product code	RCY [a]
1			[^{18}F]**4a**	83 ± 2 % (n = 4)
2			[^{18}F]**4b**	84 ± 2 % (n = 4)
3			[^{18}F]**4o**	80 ± 3 % (n = 4)
4			[^{18}F]**4d**	82 ± 4 % (n = 4)
5			[^{18}F]**4p**	83 ± 3 % (n = 4)
6			[^{18}F]**4q**	35 ± 1 % (n = 4)
7 [b]			[^{18}F]**4r**	44 ± 6 % (n = 4)
8			[^{18}F]**4i**	36 ± 6 % (n = 4)

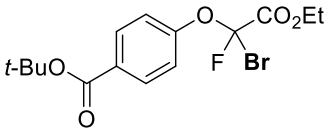
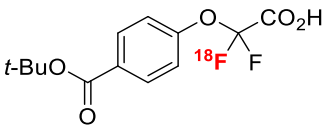
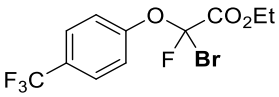
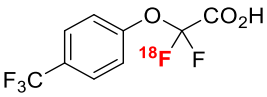
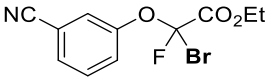
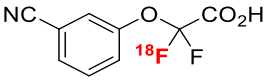
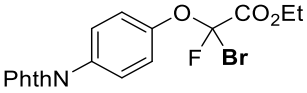
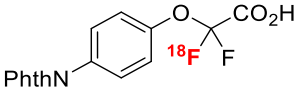
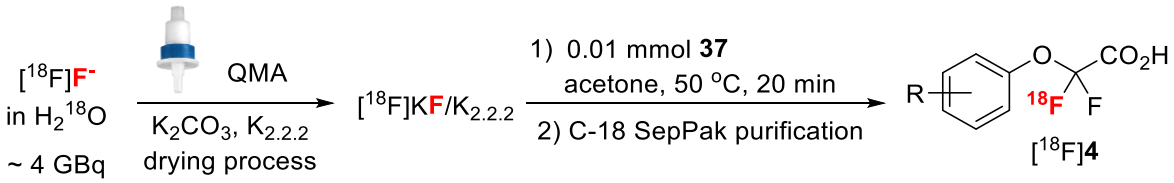
9 [b]			[^{18}F]**4s**	58 ± 4 % (*n* = 4)
10			[^{18}F]**4k**	62 ± 5 % (*n* = 4)
11			[^{18}F]**4t**	65 ± 3 % (*n* = 4)
12 [b]			[^{18}F]**4u**	47 ± 8 % [c] (*n* = 4)

Table 4.9 Substrate scope for the ^{18}F-labelling of **4**; 0.01 mmol **4a**, 0.014 mmol K_2CO_3, 0.024 mmol K_{222}, acetone (200 µL), 50 °C, 20 min; [a] Obtained by radio-TLC and radio-HPLC, repeated *n* times; [b] Precursor synthesised by L. Pfeifer; [c] Product was observed along with 28 ± 8 % of another radiolabeled by-product occurred from the partial hydrolysis of the phthalimide group.

Electron neutral precursors gave excellent RCYs under the optimised reaction conditions (entries 1 - 3). The precursors with bromine substituent at *para* and *meta* positions also gave excellent RCYs (entries 4 - 5). However, the *ortho*-brominated precursor was much less reactive, affording [^{18}F]**4q** in 35 % RCY (entry 6), which could be accounted for by evoking the steric bulk of the large bromine atom which hinders the nucleophilic attack of the [^{18}F]fluoride. The reaction also tolerates a wide range of functional groups such as ketone, ester, trifluoromethyl, nitrile and protected amine, although the RCYs were lower (entries 7 - 12). In the case of the precursor containing phthalimide protected amine **36u**, partial hydrolysis of the phthalimide group was observed in 28 %. Electron-rich arene precursors could not be synthesised for this substrate scope study due to the difficulties during the radical bromination reaction (see Section 4.3).

4.7 Isolation Experiments and Determination of Specific Activity

The radiosynthesis of [^{18}F]**4b** and [^{18}F]**4k** were attempted on a large scale, using ~4 GBq of ^{18}F-fluoride (Table 4.10). In these processes, the addition of K_2CO_3 and K_{222} as the additional additives were not necessary since they were used in the eluent system during the drying process of the [^{18}F]fluoride (see Chapter 1.3 for more details). After the reactions, the products were isolated by C-18 SepPak purification to remove K_2CO_3 and K_{222} which were proved to be detrimental for further post-fluorination functionalisations (see Section 4.8 for more details). [^{18}F]**4b** and [^{18}F]**4k** were obtained in 42 % and 36 % non-decay corrected radiochemical yields (ndc RCY) with specific activities (SA) of 0.37 GBq/μmol and 0.51 GBq/μmol, respectively. The low specific activities could be accounted for by the hydrolysis of the starting material, releasing ^{19}F-fluoride, which can act in competition with ^{18}F-fluoride. The final activities were in the range of 900 MBq to 1820 MBq, which are sufficient for further post-fluorination functionalisation. The SA values were comparable to the silver-mediated halogen exchange reaction described in Section 2.8.



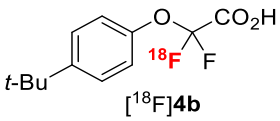
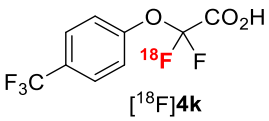
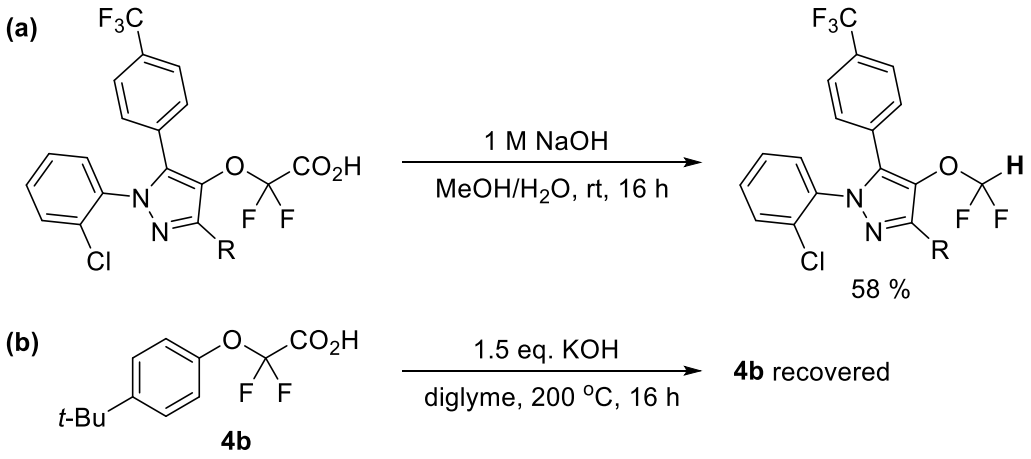
Entry	Product	Starting Activity (MBq) [a]	Isolated Activity (MBq) [b]	RCY	SA (GBq/μmol)
1	 [^{18}F]**4b**	4500 2260	1820 971	42 ± 2 % (*n* = 2)	0.37
2	 [^{18}F]**4k**	4400 2440	1550 900	36 ± 1 % (*n* = 2)	0.51

Table 4.10 Isolation of the ^{18}F-labelled products; [a] Measured after drying procedure; [b] Measured after isolated by C-18 SepPak purification.

4.8 Protodecarboxylation of Ar-OCF$_2$CO$_2$H

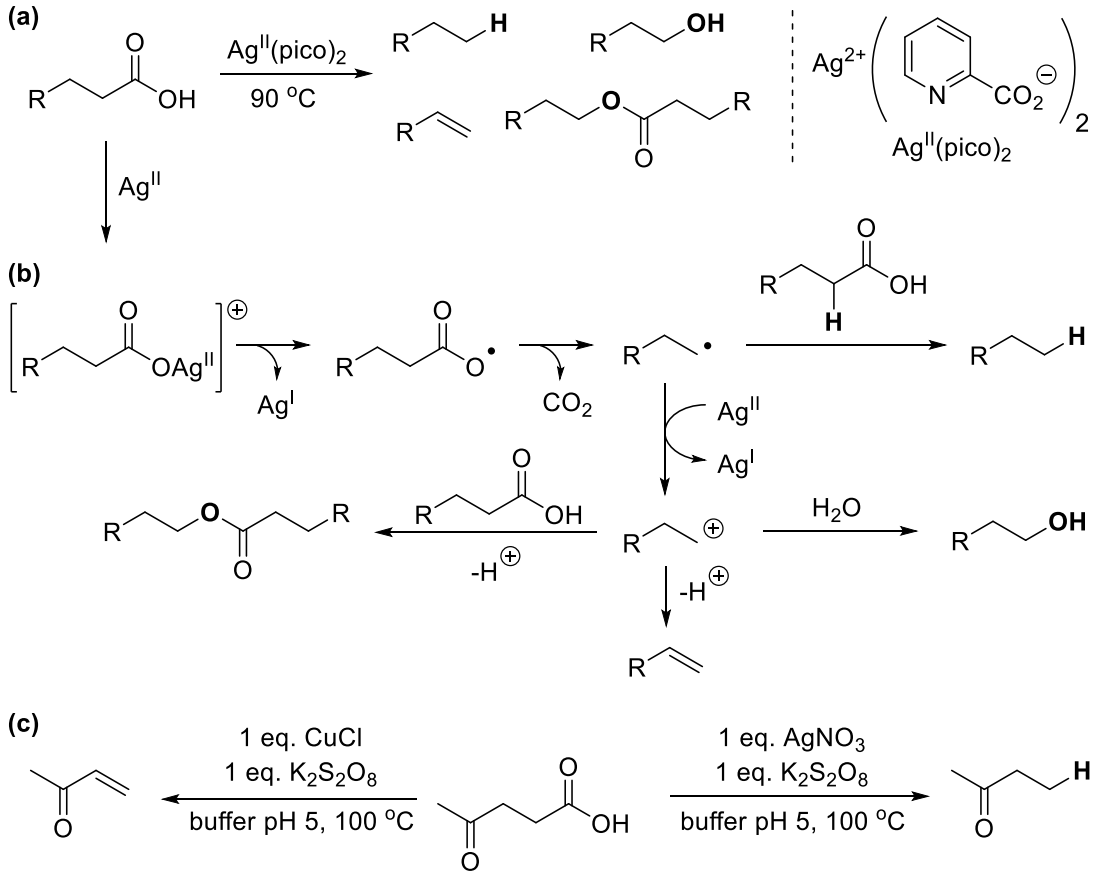
The initial study for the protodecarboxylation of Ar-OCF$_2$CO$_2$H (**4**) was conducted in the "cold" mode using **4b** as a model substrate. An example of protodecarboxylation of Ar-OCF$_2$CO$_2$H was reported on a pyrazole substrate under basic conditions (Scheme 4.5a).[17] We found that no reaction occurred when **4b** was reacted with an excess amount of KOH even at the temperature as high as 200 ^{o}C; full recovery of the starting material was observed (Scheme 4.5b).



Scheme 4.5 Protodecarboxylation under basic conditions.

Although many methods for protodecarboxylation of carboxylic acids have been reported (see Section 4.2), most of these protocols focused on the aromatic substrates. Aliphatic carboxylic acids can undergo decarboxylation *via* radical mechanism or under oxidative conditions. One of the method reported by Anderson and Kochi in 1970 utilised silver(II), which is one of the most powerful oxidants available for organic chemistry.[18] The reaction of aliphatic carboxylic acids with silver(II) salts led to the formation of the protodecarboxylated (alkane) product along with various side-products such as alkene, alcohol and ester (Scheme 4.6a).[19] The suggested mechanism involved the oxidation of the carboxylic acid by silver(II), leading to an acyloxy radical which is known to undergo rapid fragmentation with the extrusion of CO_2 to give an alkyl radical intermediate

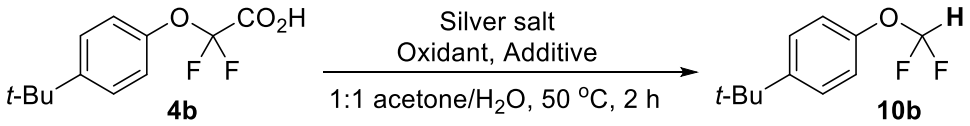
(Scheme 4.6b).[20] The alkyl radical intermediate can undergo hydrogen abstraction (predominantly from the α-position from another molecule of the carboxylic acid), giving the terminal -CH_3. Alternatively, the alkyl radical can be further oxidised by a second silver(II) species to afford the carbocation; this can undergo elimination to form the alkene, or nucleophilic attack by water or another molecule of the carboxylic acid to form the alcohol and the ester, respectively.



Scheme 4.6 Protodecarboxylation under basic conditions.

The silver(II) species can also be generated *in situ* by the reaction between silver nitrate ($AgNO_3$) and peroxydisulfate ion ($S_2O_8^{2-}$).[21] Interestingly, it was found that the addition of copper(II) salt as a co-catalyst has a synergistic effect by promoting the formation of the alkene as a major product. In 2011, Gong and Lin successfully applied this procedure to levulinic acid, affording butanone under silver-mediated conditions and methyl vinyl ketone under copper-mediated conditions (Scheme 4.6c).[22]

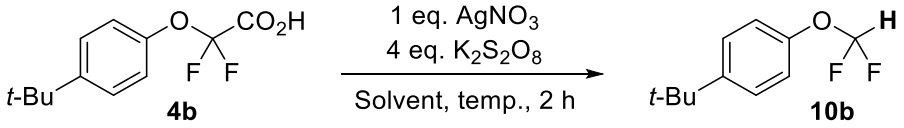
The model substrate **4b** was subjected to various protodecarboxylation conditions using different silver salts and oxidants (Table 4.11). The formation of the Ar-OCF$_2$H product was not observed when 1 eq. of silver(II) picolinate was used (entry 1), though **10b** was detected in 26 % when 1 eq. of $AgNO_3$ and $K_2S_2O_8$ were used (entry 2). The yield was further improved to 53 % using 4 eq. of the oxidant (entries 3 - 4). It is important to note that both K_2CO_3 and K_{222} which were used for the ^{18}F-labelling of **4** were detrimental to the decarboxylation (entries 5 - 6); therefore, these additives must be removed prior to further functionalisation. Both Ag_2CO_3 and $(NH_4)_2S_2O_8$ can also be used as an alternative silver source and oxidant (entries 7 - 8). An addition of CuI had no significant effect on the reaction (entry 10).



Entry	Silver salt	Oxidant	Additive	Conversion [a]	Yield [a]
1	1 eq. $Ag(pico)_2$	-	-	55 %	0 %
2	1 eq. $AgNO_3$	1 eq. $K_2S_2O_8$	-	38 %	26 %
3	1 eq. $AgNO_3$	2 eq. $K_2S_2O_8$	-	93 %	50 %
4	1 eq. $AgNO_3$	4 eq. $K_2S_2O_8$	-	99 %	53 %
5	1 eq. $AgNO_3$	4 eq. $K_2S_2O_8$	1 eq. K_2CO_3	0 %	0 %
6	1 eq. $AgNO_3$	4 eq. $K_2S_2O_8$	2 eq. K_{222}	16 %	9 %
7	1 eq. Ag_2CO_3	4 eq. $K_2S_2O_8$	-	98 %	37 %
8	1 eq. $AgNO_3$	4 eq. $(NH_4)_2S_2O_8$	-	99 %	41 %
9	1 eq. $AgNO_3$	4 eq. PIDA [b]	-	1 %	1 %
10	1 eq. $AgNO_3$	4 eq. $K_2S_2O_8$	1 eq. CuI	81 %	47 %

Table 4.11 Optimisation of reaction conditions for the protodecarboxylation of **4b**; **4b** (0.10 mmol), 1:1 acetone/H_2O (0.4 mL); [a] Determined by ^{19}F NMR using $PhCF_3$ as an internal standard; [b] PIDA = (diacetoxyiodo)benzene.

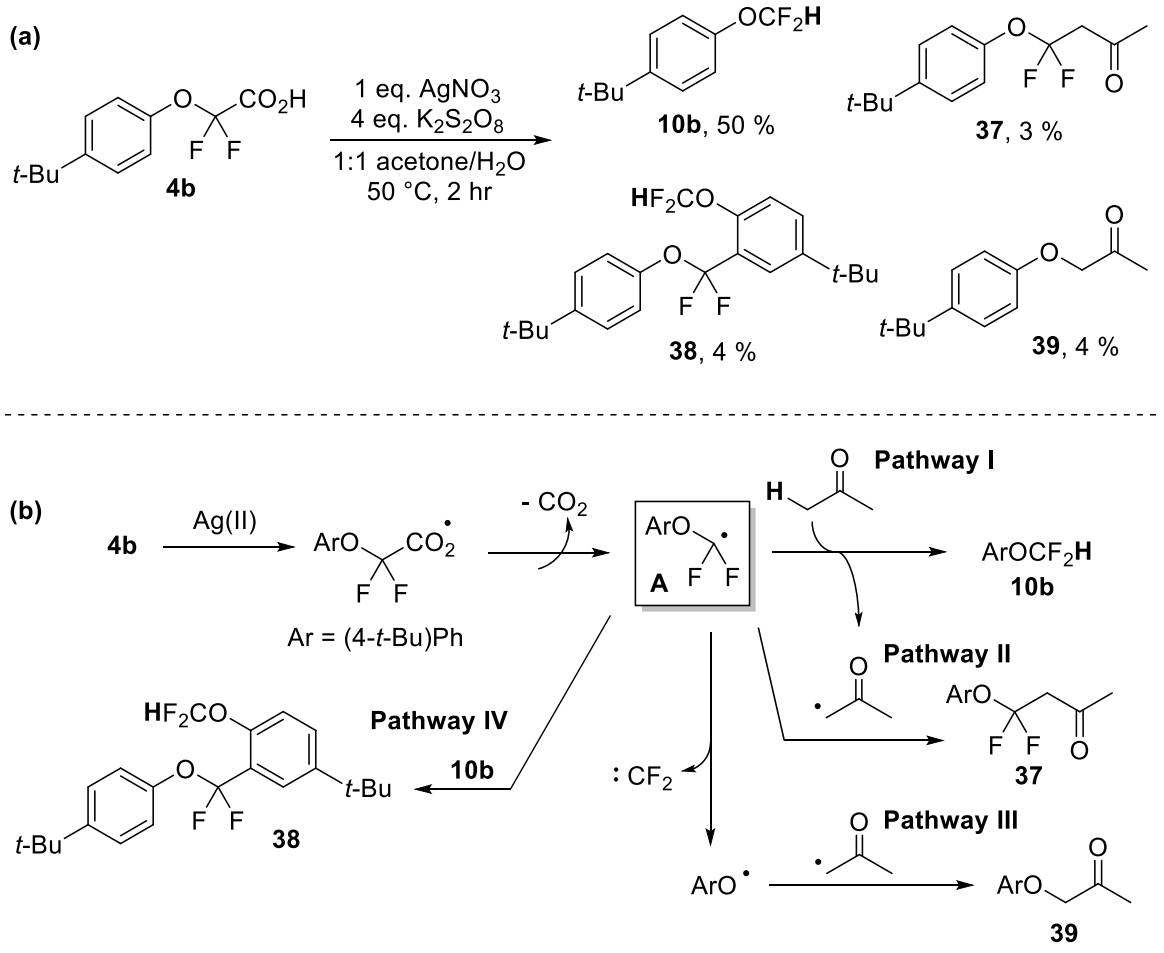
Next, the screening of solvent and temperature was performed using 1 eq. of $AgNO_3$ and 4 eq. of $K_2S_2O_8$ (Table 4.12). The 1:1 mixture of water with other water-miscible organic solvents such as CH_3CN, THF, dioxane, DMF and DMSO did not give a satisfactory result (entries 2 - 6). No reaction occurred when acetone alone was used as a solvent due to insolubility of the inorganic salts (entry 7). The reaction proceeded at room temperature, but the rate was much slower with only 22 % of **4b** being consumed after 2 hours (entry 10). Deuterium labelling revealed that acetone is the source of hydrogen (entries 11 - 12).



Entry	Solvent	Temp.	Conversion [a]	Yield [a]
1	1:1 acetone/H_2O	50 °C	99 %	53 %
2	1:1 CH_3CN/H_2O	80 °C	100 %	6 %
3	1:1 THF/H_2O	80 °C	7 %	1 %
4	1:1 dioxane/H_2O	100 °C	46 %	17 %
5	1:1 DMF/H_2O	100 °C	64 %	9 %
6	1:1 DMSO/H_2O	100 °C	78 %	12 %
7	acetone	50 °C	0 %	0 %
8	4:1 acetone/H_2O	50 °C	4 %	4 %
9	1:4 acetone/H_2O	50 °C	98 %	38 %
10	1:1 acetone/H_2O	rt	22 %	4 %
11	1:1 acetone/D_2O	50 °C	82 %	47 %
12	1:1 acetone-d6/H_2O	50 °C	96 %	4 % [b]

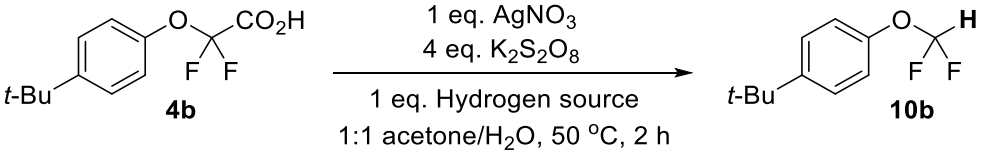
Table 4.12 Optimisation of reaction conditions for the protodecarboxylation of **4b**; **4b** (0.10 mmol), solvent (0.4 mL); [a] Determined by ^{19}F NMR using $PhCF_3$ as an internal standard; [b] 5 % of deuterated **10b** was observed in ^{19}F NMR.

In all cases, the yields of **10b** were significantly lower than the conversion of **4b**, indicating the occurrence of competing side reactions. In order to identify these side reactions, the optimised reaction conditions were repeated on a larger scale using 2.0 mmol of **4b** (Scheme 4.7a). After purification by column chromatography, **10b** was successfully isolated in 50 % yield along with three other by-products; **37**, **38** and **39** in 3 %, 4 % and 4 %, respectively. The oxidative decarboxylation induced by *in situ* generated Ag^{2+} could lead to the formation of the alkyl radical **A** which can abstract hydrogen from acetone to form **10b** (Scheme 4.7b, Pathway I). Alternatively, **A** can also react with other species in the mixture (Pathways II-IV), leading to the formation of these by-products. Notably, the identity of **39** illustrated the loss of the difluoromethyl motif possibly *via* the extrusion of a difluorocarbene.



Scheme 4.7 Oxidative protodecarboxylation of **4b** using $AgNO_3$ and $K_2S_2O_8$.

We envisaged that the yield of the protodecarboxylated product **10b** could be enhanced if hydrogen abstraction step is accelerated by the addition of a more potent hydrogen source (Table 4.13). Unfortunately, none of the hydrogen sources led to a higher yield of **10b** with only diisopropyl ketone not detrimentally affecting the reaction (entry 7).



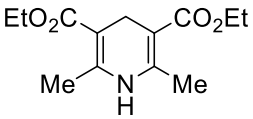
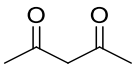
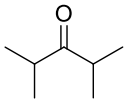
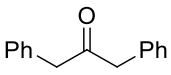
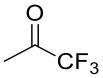
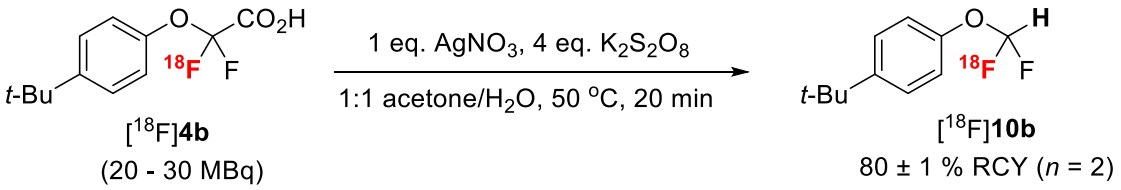
Entry	Hydrogen source	Conversion [a]	Yield [a]
1	HCl	0 %	0 %
2		62 %	25 %
3		1 %	1 %
4		9 %	8 %
5	H-Si(SiMe$_3$)$_3$	34 %	1 %
6		4 %	4 %
7		84 %	53 %
8		89 %	35 %
9		62 %	19 %

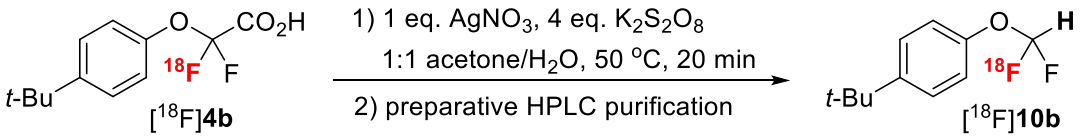
Table 4.13 Optimisation of reaction conditions for the protodecarboxylation of **4b**; **4b** (0.10 mmol), solvent (0.4 mL); [a] Determined by ^{19}F NMR using PhCF$_3$ as an internal standard.

With the optimised protodecarboxylation conditions in hand (Table 4.12, entry 1; 1 eq. $AgNO_3$, 4 eq. $K_2S_2O_8$, 1:1 acetone/H_2O (400 µL), 50 °C), the radiosynthesis of ^{18}F-labelled Ar-OCF$_2$H ([^{18}F]**10**) was explored starting from the isolated [^{18}F]**4b** (see Section 4.7). When a small amount of [^{18}F]**4b** (20 - 30 MBq) was subjected to the optimised conditions, [^{18}F]**10** was observed in 80 ± 1 % RCY (n = 2) with full consumption of [^{18}F]**4b** (Scheme 4.8).



Scheme 4.8 Oxidative protodecarboxylation of [^{18}F]**4b**; RCY determined by radio-HPLC.

The isolation of [^{18}F]**10b** was also attempted by repeating the protodecarboxylation using a full batch of [^{18}F]**4b** (~1 GBq) (Table 4.14). After the reaction, the crude mixture was purified by preparative HPLC to afford [^{18}F]**10b** in 22 ± 1 % non-decay corrected RCY (n = 2). The specific activity was determined using the procedure described in Section 2.8, giving the value of 0.30 GBq/µmol, which is higher than the Ar-OCF$_2$H products obtained using the silver-mediated halogen exchange procedure (0.04 - 0.17 GBq/µmol; Table 2.25, entries 3 - 4)

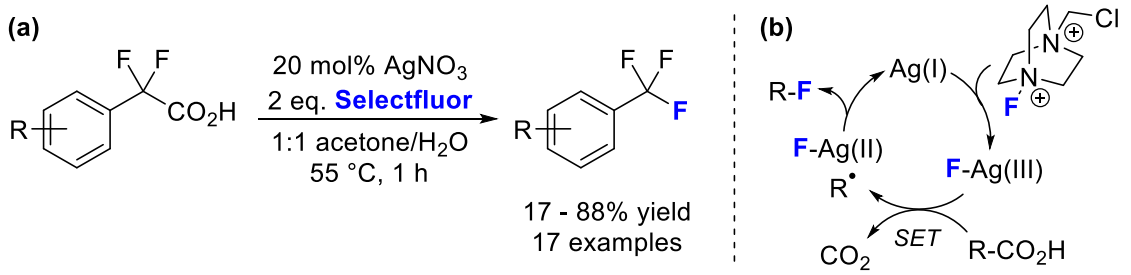


Entry	Starting Activity (MBq) [a]	Isolated Activity (MBq) [b]	RCY	SA (GBq/µmol)
1	1756	408	22 ± 1 % (n = 2)	0.30
2	836	179		

Table 4.14 Isolation of the [^{18}F]**10b**; [a] Measured after drying procedure; [b] Measured after isolated by preparative HPLC.

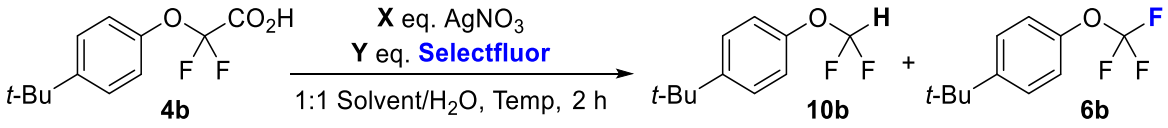
4.9 Fluorodecarboxylation of Ar-OCF$_2$CO$_2$H

In 2013, Gouverneur and co-workers demonstrated that *α,α*-difluoroarylacetic acids can undergo silver-catalysed oxidative fluorodecarboxylation to give trifluoromethyl arenes (Ar-CF$_3$) using Selectfluor as oxidant and fluorine source (Scheme 4.9a).[23] This transformation was inspired by the work of Li and co-workers where the reaction was proposed to proceed *via* an oxidative radical decarboxylation mechanism (Scheme 4.9b).[24]



Scheme 4.9 Fluorodecarboxylation of *α,α*-difluoroarylacetic acids.

When the Ar-OCF$_2$CO$_2$H substrate **4b** was subjected to the reported conditions, the reaction afforded, unexpectedly, the protodecarboxylation product **10b** in 18 % with no desired trifluoromethyl ether **6b** being observed (Table 4.15, Entry 1).

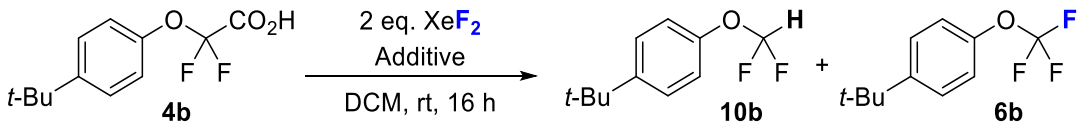


Entry	X	Y	Solvent	Temp	Conversion [a]	Yield 10b [a]	Yield 6b [a]
1 [b]	0.2	2	acetone	50 °C	68 %	18 %	0 %
2 [c]	1	4	acetone	50 °C	100 %	33 %	12 %
3 [c]	1	4	CH$_3$CN	80 °C	100 %	7 %	12 %

Table 4.15 Optimisation of reaction conditions for the Ag-mediated fluorodecarboxylation of **4b**; **4b** (0.10 mmol); [a] Determined by ^{19}F NMR using PhCF$_3$ as an internal standard; [b] solvent 2 mL; [c] Solvent 0.4 mL.

By increasing both $AgNO_3$ and Selectfluor, as well as the reaction concentration, 12 % of **6b** was detected; however, the yield of the protodecarboxylation side-product **10b** was increased to 33 % (entry 2). Replacing acetone with CH_3CN as a solvent suppressed the formation of **10b**, but the yield of **6b** did not improve (entry 3).

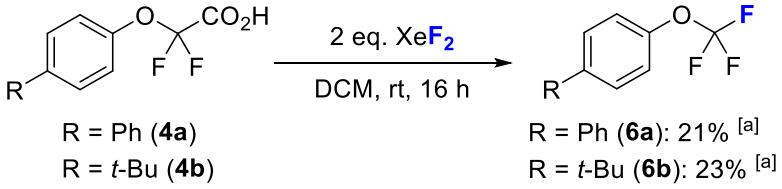
The fluorodecarboxylation with XeF_2 was considered as an alternative method (Table 4.16).[25] When **4b** was allowed to react with 2 eq. XeF_2 in DCM overnight, **6b** was formed in moderate yield (25 % ^{19}F NMR yield, Entry 1). It was reported that in many cases, an external source of fluoride is beneficial for this transformation.[26] However, the addition of NEt_4F or HF·pyridine did not improve the yield of **6b** (entries 2 - 3).



Entry	Additive	Conversion [a]	Yield 10b [a]	Yield 6b [a]
1	-	100 %	-	25 %
2	2 eq. NEt_4F	68 %	-	13 %
3	2 eq. HF·pyridine	100 %	-	0 %

Table 4.16 Optimisation of reaction conditions for the fluorodecarboxylation of **4b**; **4b** (0.20 mmol), DCM (3 mL); [a] Determined by ^{19}F NMR using $PhCF_3$ as an internal standard.

The optimised reaction conditions were repeated at larger scale starting from **4a** and **4b**; the corresponding Ar-OCF_3 products, **6a** and **6b**, were successfully isolated in 21 % and 23 % yields, respectively (Scheme 4.10).



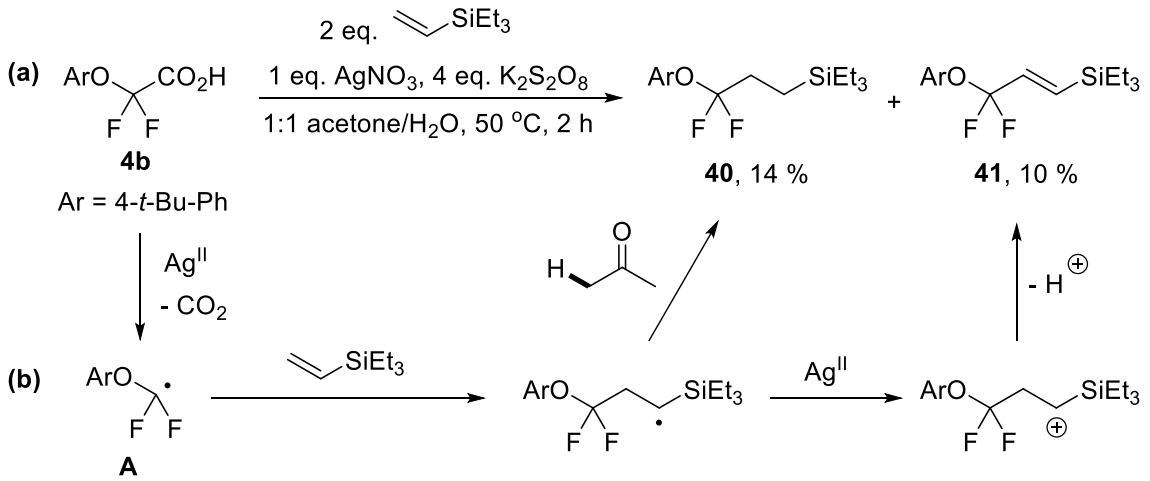
Scheme 4.10 Fluorodecarboxylation of **4a** and **4b** with XeF_2; [a] isolated yields.

Both of the fluorodecarboxylation conditions (silver-mediated and XeF_2) were applied to the isolated ^{18}F-labelled Ar-OCF$_2$CO$_2$H ([^{18}F]**4**). However, neither of the conditions led to the formation of the desired [^{18}F]**6**.

4.10 Decarboxylation of Ar-OCF$_2$CO$_2$H with C–C bond formation

In Section 4.8, we identified **37** as a side product in the oxidative protodecarboxylation reaction of **4b** (Scheme 4.7). This product suggested that the alkyl radical intermediate can be trapped with other nucleophilic species. With this hypothesis in mind, the silver-mediated protodecarboxylation of **4b** was repeated in the presence of triethylvinylsilane (Scheme 4.11a), which enabled the isolation of the addition products **40** and **41** in 14 % and 10 %, respectively.

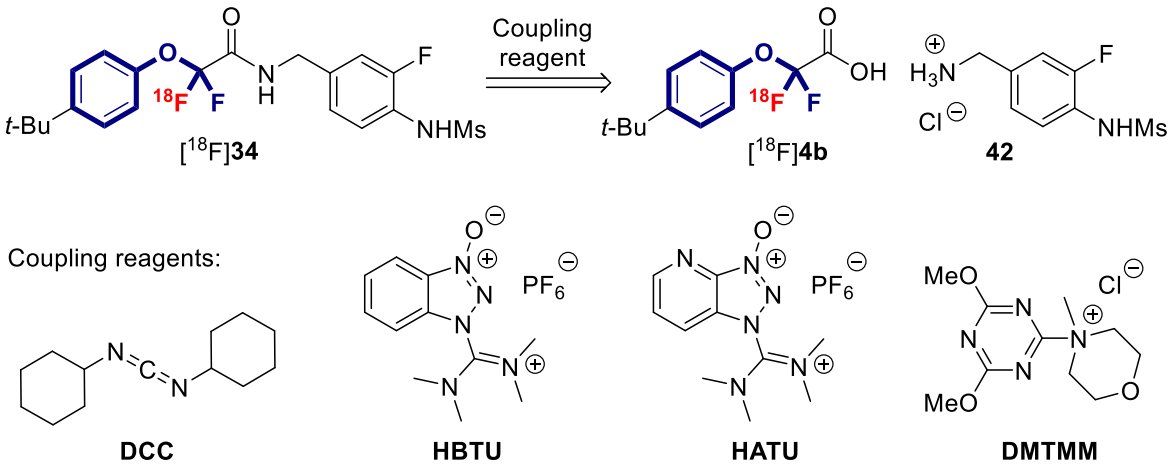
Mechanistically, it is proposed that after the decarboxylation step, the radical intermediate **A** can be trapped by the electron-rich alkene, generating another carbon radical intermediate which abstracts hydrogen from acetone to provide **40** (Scheme 4.11b). Alternatively, the carbon radical can be further oxidised to generate a carbocation intermediate, which generates **41** upon elimination.



Scheme 4.11 Silver-mediated decarboxylation of **4b** in the presence of triethylvinylsilane.

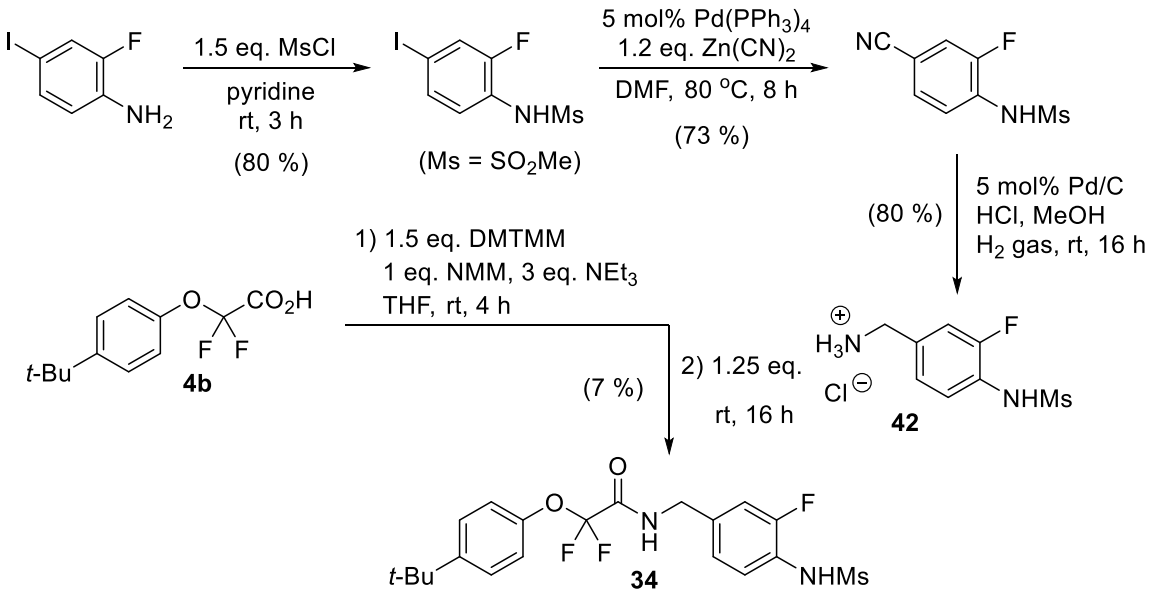
4.11 ^{18}F-Labelling of a TRPV1 Antagonist 34

The TRPV1 antagonist **34** consists of an Ar-OCF$_2$ motif connected with an amide group. We envisaged that the radiosynthesis of [^{18}F]**34** can be achieved by the coupling reaction between [^{18}F]**4b** and the corresponding amine **42**, facilitated by a range of amide coupling reagents such as *N*,*N*'-dicyclohexylcarbodiimide (DCC),[27] *O*-(benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU),[28] *O*-(7-azabenzotriazol-1-yl)-1,1,3,3-tetra-methyluronium hexafluorophosphate (HATU),[29] or 4-(4,6-dimethoxy[1,3,5] triazin-2-yl)-4-methylmorpholinium chloride (DMTMM)[30] (Scheme 4.12).[31]



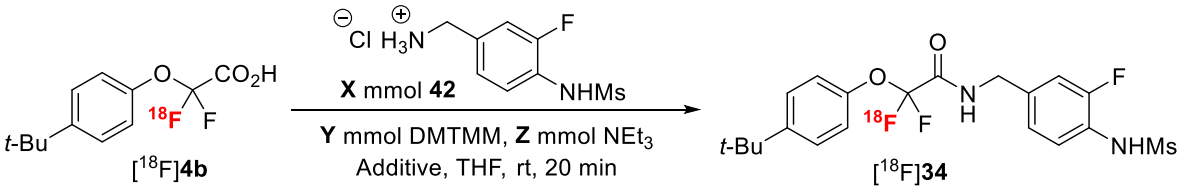
Scheme 4.12 Synthesis of the [^{18}F]**34** from [^{18}F]**4b** using amide coupling reagents.

The ammonium salt **42** and the "cold" reference **34** were synthesised according to the procedure reported by Wang and co-workers,[32] starting from 2-fluoro-4-iodoaniline (Scheme 4.13). The mesylation of aniline by methanesulfonyl chloride in pyridine affords the desired product in 80 % yield. This was then subjected to a palladium-catalysed cyanation of aryl iodide, using Zn(CN)$_2$ in the presence of a catalytic amount of Pd(PPh$_3$)$_4$, yielding the aryl nitrile in 73 %. Subsequent reduction of the nitrile with palladium on carbon and hydrogen afforded the ammonium salt **42** in 80 % yield. The coupling of **42** with **4b** was facilitated by DMTMM with excess trimethylamine (NEt$_3$) and *N*-methylmorpholine (NMM), yielding **34** in 7 %.



Scheme 4.13 Synthesis of the ammonium salt **42** and the "cold" reference **34**.

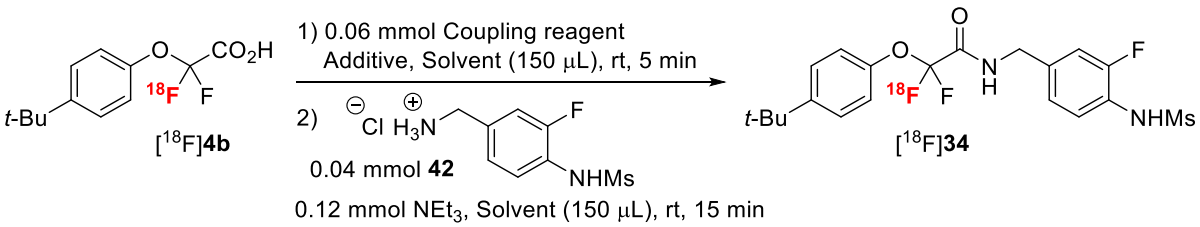
The amide coupling using DMTMM was attempted on isolated [^{18}F]**4b** (Table 4.17), yielding [^{18}F]**4** in 16 % RCY using **42** (0.04 mmol), DMTMM (0.06 mmol) and NEt_3 (0.12 mmol) in THF (300 µL) (entry 1). The RCY improved slightly to 18 % with the addition of NMM (0.04 mmol) (entry 2), though increasing the concentration did not affect the RCY of the product (entries 3 - 4).



Entry	X	Y	Z	Additive	[^{18}F]34 RCY [a]	*n*
1	0.04	0.06	0.12	-	16 ± 1 %	2
2	0.04	0.06	0.12	0.04 mmol NMM	18 ± 4 %	2
3	0.08	0.12	0.24	-	12 ± 5 %	2
4	0.08	0.12	0.24	0.08 mmol NMM	10 ± 1 %	2

Table 4.17 Synthesis of [^{18}F]**34** from [^{18}F]**4b** (20 - 30 MBq); THF (300 µL); [a] Obtained by radio-TLC and radio-HPLC, repeated *n* times.

The coupling of [^{18}F]**4b** with **42** was also investigated with other coupling reagents such as DCC, HATU and HBTU (Table 4.18). The reactions facilitated by DCC and HATU led to a complex mixture of several unidentified ^{18}F-labelled products (entries 1 - 2). On the other hand, HBTU was not reactive under these conditions since only a small portion of the starting [^{18}F]**4b** was consumed (entry 3)

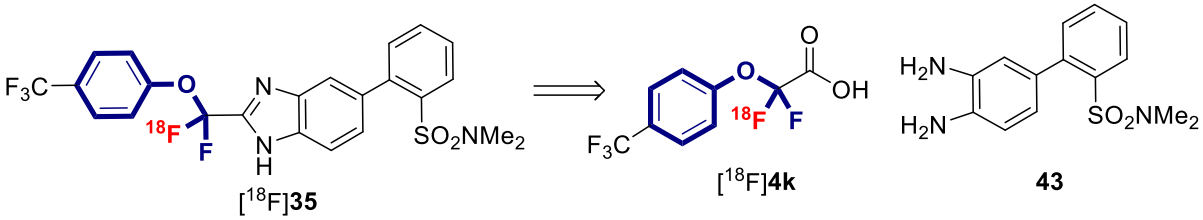


Entry	Coupling reagent	Additive	Solvent	[^{18}F]34 RCY [a]	*n*
1	DCC	0.04 mmol HOBt [b]	DMF	6 ± 1 %	2
2	HATU	-	DMF	8 ± 1 %	2
3	HBTU	-	DMSO	2 ± 0 %	2

Table 4.18 Synthesis of [^{18}F]**34** from [^{18}F]**4b** (20 - 30 MBq); THF (300 µL); [a] Obtained by radio-TLC and radio-HPLC, repeated *n* times; [b] HOBt = 1-hydroxybenzotriazole.

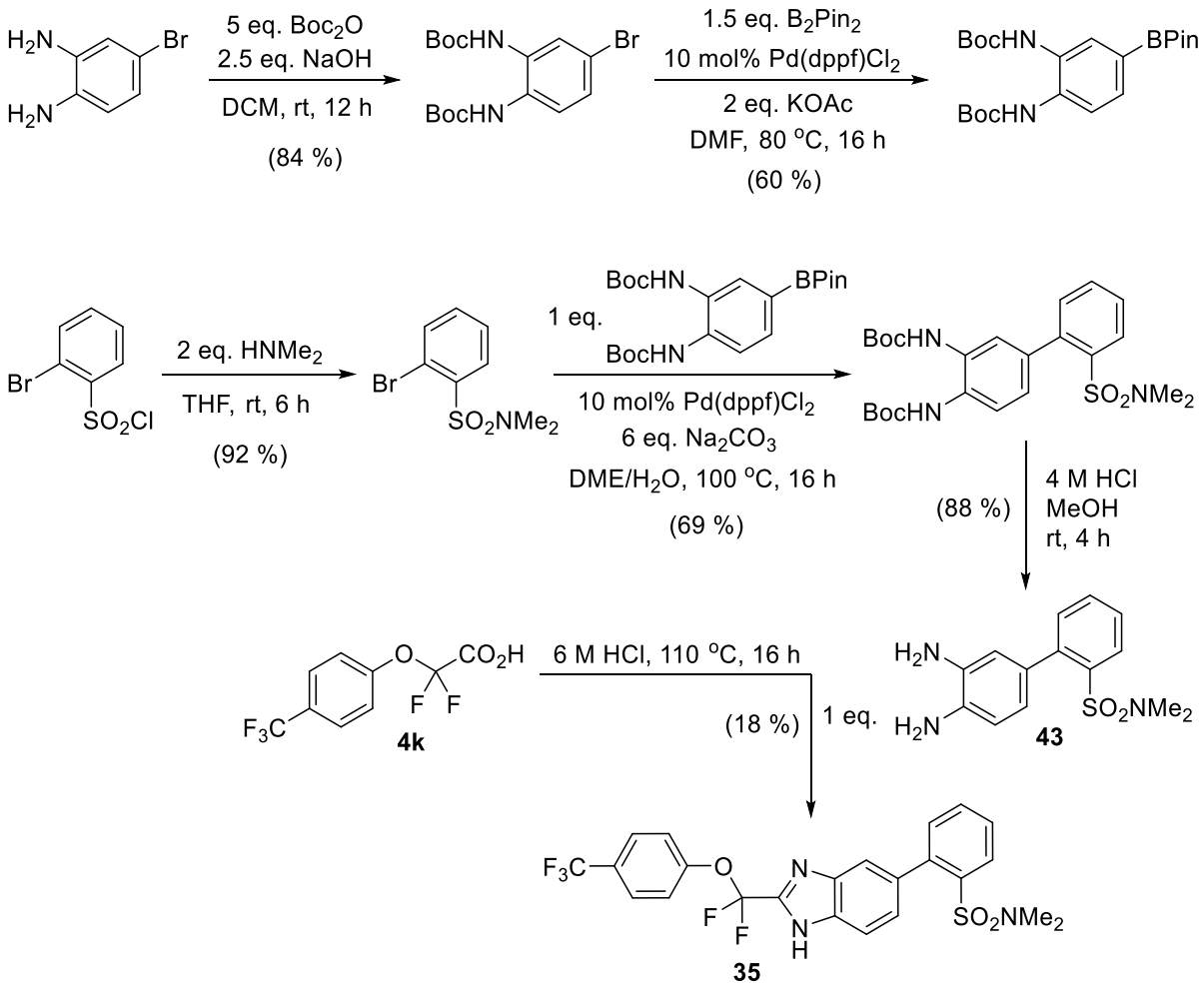
4.12 ^{18}F-Labelling of a TRPV1 Inhibitor 35

The TRPV1 inhibitor **35** consists of an Ar-OCF$_2$ motif connected with a benzimidazole group. It was hypothesised that [^{18}F]**35** could be radiosynthesised by the condensation of the ^{18}F-labelled carboxylic acid [^{18}F]**4k** with the 1,2-diaminobenzene **43** under acidic conditions (Scheme 4.14).



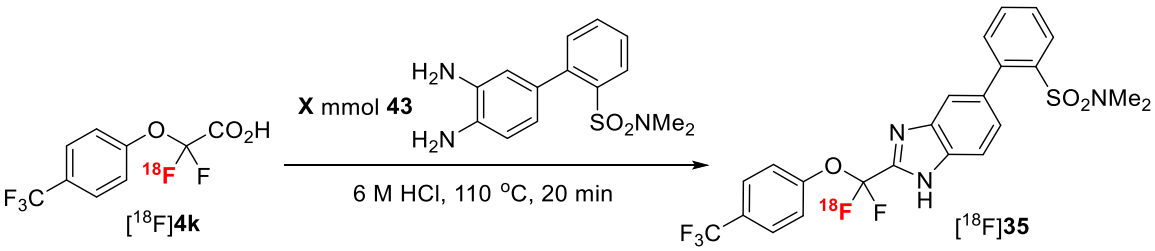
Scheme 4.14 Synthesis of the [^{18}F]**35** from [^{18}F]**4k** and **43**.

The 1,2-diaminobenzene **43** and the "cold" reference was synthesised as described in Scheme 4.15. First, the amine groups of 4-bromobenzene-1,2-diamine were protected with *tert*-butyloxycarbonyl (Boc) groups using di-*tert*-butyl dicarbonate (Boc_2O). Next, the aryl bromide was subjected to a Miyaura borylation using bis(pinacolato)diboron (B_2Pin_2) and a catalytic amount of $Pd(dppf)Cl_2$. The aryl boronic ester product was subsequently subjected to Suzuki coupling conditions with 2-bromo-*N*,*N*-dimethylbenzenesulfonamide. After the deprotection of the Boc groups, the desired diamine **43** was finally obtained. The reaction of **43** with the carboxylic acid **4k** in 6 M HCl under reflux conditions afforded the TRPV1 inhibitor **35** in 18 % yield.



Scheme 4.15 Synthesis of the 1,2-diaminobenzene **43** and the "cold" reference **35**.

Next, the condensation between the 1,2-diaminobenzene **43** and the isolated ^{18}F-labelled carboxylic acid [^{18}F]**4k** to form [^{18}F]**35** was investigated (Table 4.19). Gratifyingly, [^{18}F]**35** was observed in 6 % RCY when 0.02 mmol of **43** was used (entry 1). The RCY could be further improved to 16 % with 0.04 mmol of **43** (entry 2).



Entry	X	[^{18}F]34 RCY [a]	*n*
1	0.02	6 ± 1 %	2
2	0.04	16 ± 9 %	2

Table 4.19 Synthesis of [^{18}F]**35** from [^{18}F]**4k** (20 - 30 MBq); 6 M HCl (200 µL); [a] Obtained by radio-TLC and radio-HPLC, repeated *n* times.

4.13 Conclusions

In summary, we have successfully developed a mild and efficient protocol for preparation of ^{18}F-labeled *α,α*-difluoro-*α*-aryloxyacetic acids *via* halogen exchange ^{18}F-fluorination with *in situ* hydrolysis of the brominated ester precursors (Section 4.3 - 4.5). The reaction tolerates a wide range of substituents (Section 4.6) and can be reproduced at a larger scale, allowing the isolation of the carboxylic acid to be used as a novel ^{18}F-building block (Section 4.7). Subsequent functionalisation of the acid has been investigated; the protodecarboxylation to give [^{18}F]Ar-OCF$_2$H was successfully developed (Section 4.8), although the fluorodecarboxylation and decarboxylative C–C bond formation were unsuccessful (Section 4-9 - 4.10). Finally, the acid can also be transformed into the amide-containing TRPV1 antagonist (Section 4.11) and the benzimidazole-containing TRPV1 inhibitor (Section 4.12).

4.14 Reference

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Future work

In Chapter 2, we have developed the route for the synthesis of ^{18}F-labelled Umemoto reagent, which can successfully transfer the [^{18}F]CF_3 motif to indole. We are aiming to investigate the reactivity of the "hot" Umemoto reagent towards ^{18}F-trifluoromethylation of other substrates such as alkenes and heterocycles. In addition, the ^{18}F-trifluoromethylation of thiols could lead to application in protein labelling by targeting the cysteine amino acid. Moreover, the [^{18}F]Riluzole synthesised by our procedure can potentially serve as a radioligand for brain imaging. In order to verify this assumption, a collaboration with a PET center is required.

Chapter 5: Experimental Data

In this chapter, the full characterisation of the compounds that were synthesised by T. Khotavivattana is provided. The characterisation of the compounds that were synthesised by S. Verhoog, L. Pfeifer, S. Calderwood and Dr. P. Ricci, as well as the spectra of the novel compounds can be found in the corresponding publications.[1]

5.1 General Experimental Information

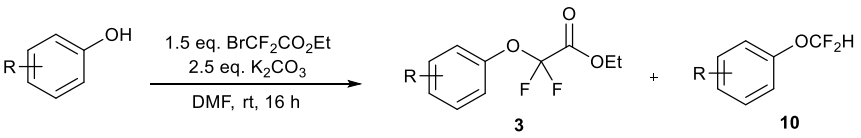
All solvents and chemicals were used as purchased unless stated otherwise. All NMR spectra were recorded on Bruker DPX200, AVF400, AVB400 or AVB500 spectrometers. NMR data were processed using ACD and MestReNova software. Proton and carbon-13 NMR spectra are reported as chemical shifts (δ) in parts per million (ppm) relative to residual undeuterated 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) and are rounded to the nearest 0.1. The following abbreviations are used to describe multiplets: s (singlet), d (doublet), t (triplet), q (quartet), qn (quintet), sex (sextet), sept (septet), m (multiplet), br (broad). High resolution mass spectra (HRMS, m/z) were recorded on a Bruker MicroTOF spectrometer using positive electrospray ionization (ESI), a Micromass GCT spectrometer using chemical ionisation (CI), or a Waters GCT TOF (temperature programmed solid's probe) spectrometer using field ionisation (FI) or electron impact (EI). Infrared spectra were recorded as neat compound using a Bruker Tensor 27 FT-IR spectrometer. Absorptions are reported in wavenumbers (cm^{-1}) and only peaks of interest are reported. Melting points of solids were measured on a Griffin apparatus and are uncorrected. IUPAC names were obtained using the ACD I-Lab 2.0 service. All solvents were dried on a column of alumina prior to use. Thin layer chromatography (TLC) was performed using Merck aluminium-foil baked plates precoated with Kieselgel 60 F245. The

products were visualized using UV fluorescence (254 nm) or potassium permanganate stain. ^{19}F NMR yields were obtained by integrating the product peak(s) relative to 1.0 equivalent internal standard. The relaxation time D1 was set to 10 s for these experiments. Flash column chromatography was performed over Merck silica gel C60 (40-60 μm) using eluent systems as described for each experiment. Known compounds have been checked against literature references and only three pieces of analytical data are given.

5.2 Experimental Procedures and Characterisation Data for Chapter 2

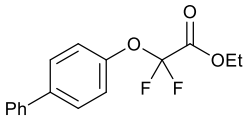
5.2.1 Synthesis of $ArOCF_2CO_2Et$ (3)

General Procedure A



To a suspension of K_2CO_3 (25 mmol) in a solution of the appropriate phenol (10 mmol) in DMF (20 mL) was slowly added ethyl bromodifluoroacetate (15 mmol) at room temperature. The reaction mixture was stirred at room temperature for 16 hours under nitrogen atmosphere. The reaction mixture was poured onto water, extracted with Et_2O (3 × 100 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography.

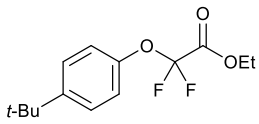
Ethyl (biphenyl-4-yloxy)(difluoro)acetate (3a)



The title compound was prepared following General Procedure A using potassium carbonate (3.46 g, 25.0 mmol), 4-phenylphenol (1.70 g, 10.0 mmol), ethyl bromodifluoroacetate (3.21 mL, 25.0 mmol) and DMF (20 mL). The crude product was purified by silica gel column chromatography (eluent: 3 % EtOAc in *n*-hexane) to provide the title compound (1.60 g, 55 % yield) as a white solid.

(^{1}H NMR, 400 MHz, $CDCl_3$): δ = 7.61–7.56 (m, 4H), 7.48–7.44 (m, 2H), 7.40–7.37 (m, 1H), 7.31 (d, *J* = 8.8 Hz, 2H), 4.42 (q, *J* = 7.1 Hz, 2H), 1.40 (t, *J* = 7.2 Hz, 3H); (^{13}C NMR, 101 MHz, $CDCl_3$): δ = 159.8 (t, *J* = 41.3 Hz), 148.8, 140.0, 139.4, 128.8, 128.2, 127.5, 127.1, 121.9, 114.0 (t, *J* = 272.6 Hz), 63.7, 13.8; (^{19}F NMR, 377 MHz, $CDCl_3$): δ = –76.3 (s, 2F); IR: ν 1775, 1515, 1486, 1378, 1341, 1171, 1134, 1008, 854; HRMS (ESI) for $C_{16}H_{14}F_2NaO_3$ $[M+Na]^+$ requires 315.0803 found 315.0803; Mp. 59−60 °C.

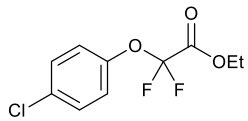
Ethyl (4-*tert*-butylphenoxy)(difluoro)acetate (3b)



The title compound was prepared following General Procedure A using potassium carbonate (3.46 g, 25.0 mmol), 4-*tert*-butylphenol (1.50 g, 10.0 mmol), ethyl bromodifluoroacetate (3.21 mL, 25.0 mmol) and DMF (20 mL). The crude product was purified by silica gel column chromatography (eluent: 4 % Et_2O in *n*-pentane) to provide the title compound (1.97 g, 72 % yield) as a colourless oil.

(^{1}H NMR, 400 MHz, $CDCl_3$): δ = 7.38 (dt, J_1 = 2.6 Hz, J_2 = 8.8 Hz, 2H), 7.15 (d, J = 8.8 Hz, 2H), 4.39 (q, J = 7.1 Hz, 2H), 1.36 (t, J = 7.1 Hz, 3H), 1.33 (s, 9H); (^{13}C NMR, 101 MHz, $CDCl_3$): δ = 159.9 (t, J = 41.3 Hz), 149.3, 147.1, 126.4, 121.1, 114.0 (t, J = 271.4 Hz), 63.5, 34.5, 31.3, 13.8; (^{19}F NMR, 377 MHz, $CDCl_3$): δ = –76.3 (s, 2F); IR: ν 2966, 1777, 1509, 1377, 1341, 1179, 1136, 1108, 1016, 853; HRMS (ESI) for $C_{14}H_{18}F_2NaO_3$ $[M+Na]^+$ requires 295.1116 found 295.1113.

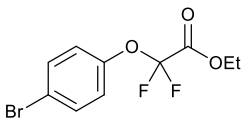
Ethyl 2-(4-chlorophenoxy)-2,2-difluoroacetate (3c)



The title compound was prepared following General Procedure A using potassium carbonate (13.8 g, 100.0 mmol), 4-chlorophenol (5.14 g, 40.0 mmol), ethyl bromodifluoroacetate (7.70 mL, 60.0 mmol) and DMF (80 mL). The crude product was purified by silica gel column chromatography (eluent: 3 % Et_2O in *n*-pentane) to provide the title compound (3.75 g, 38 % yield) as a colourless oil.

(^{1}H NMR, 400 MHz, $CDCl_3$): δ = 7.35 (dt, J_1 = 2.7 Hz, J_2 = 9.1 Hz, 2H), 7.18–7.16 (m, 2H), 4.40 (q, J = 7.2 Hz, 2H), 1.38 (t, J = 7.2 Hz, 3H); (^{13}C NMR, 101 MHz, $CDCl_3$): δ = 159.5 (t, J = 40.9 Hz), 147.9, 131.9, 129.7, 123.1, 113.8 (t, J = 273.4 Hz), 63.8, 13.8; (^{19}F NMR, 377 MHz, $CDCl_3$): δ = –76.7 (s, 2F); IR: ν 1776, 1488, 1378, 1342, 1198, 1167, 1134, 1089, 1014, 850; HRMS (ESI) for $C_{10}H_9ClF_2O_3Na$ $[M+Na]^+$ requires 273.0101 found 273.0101.

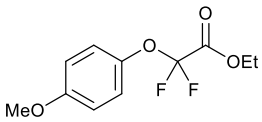
Ethyl (4-bromophenoxy)(difluoro)acetate (3d)



The title compound was prepared following General Procedure A using potassium carbonate (6.91 g, 50.0 mmol), 4-bromophenol (3.46 g, 20.0 mmol), ethyl bromodifluoroacetate (3.85 mL, 30.0 mmol) and DMF (40 mL). The crude product was purified by silica gel column chromatography (eluent: 3 % Et_2O in *n*-pentane) to provide the title compound (2.02 g, 34 % yield) as a colourless oil.

(^{1}H NMR, 400 MHz, $CDCl_3$): δ = 7.49 (dt, J_1 = 2.7 Hz, J_2 = 9.1 Hz, 2H), 7.13–7.10 (m, 2H), 4.40 (q, J = 7.2 Hz, 2H), 1.38 (t, J = 7.2 Hz, 3H); (^{13}C NMR, 101 MHz, $CDCl_3$): δ = 159.5 (t, J = 40.9 Hz), 148.4, 132.7, 123.4, 119.6, 113.7 (t, J = 273.4 Hz), 63.8, 13.8; (^{19}F NMR, 377 MHz, $CDCl_3$): δ = –76.6 (s, 2F); IR: ν 1777, 1485, 1378, 1342, 1198, 1136, 1069, 1012, 848; HRMS (EI/FI) for $C_{10}H_9BrF_2O_3$ $[M]^+$ requires 293.9703 found 293.9706.

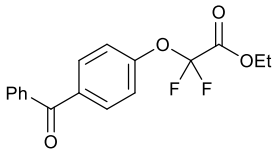
Ethyl 2,2-difluoro-2-(4-methoxyphenoxy)acetate (3f)



The title compound was prepared following General Procedure A using potassium carbonate (13.8 g, 100.0 mmol), 4-methoxyphenol (4.97 g, 40.0 mmol), ethyl bromodifluoroacetate (7.70 mL, 60.0 mmol) and DMF (80 mL). The crude product was purified by silica gel column chromatography (eluent: 10 % Et_2O in *n*-pentane) to provide the title compound (5.46 g, 55 % yield) as a colourless oil.

(^{1}H NMR, 400 MHz, $CDCl_3$): δ = 7.15 (dt, J_1 = 3.1 Hz, J_2 = 9.3 Hz, 2H), 6.87 (dt, J_1 = 3.1 Hz, J_2 = 9.3 Hz, 2H), 4.37 (q, J = 7.3 Hz, 2H), 3.78 (s, 3H), 1.36 (t, J = 7.2 Hz, 3H); (^{13}C NMR, 101 MHz, $CDCl_3$): δ = 159.9 (t, J = 41.3 Hz), 157.8, 142.6, 123.0, 114.4, 114.0 (t, J = 271.0 Hz), 63.5, 55.5, 13.8; (^{19}F NMR, 377 MHz, $CDCl_3$): δ = –76.6 (s, 2F); IR: ν 1774, 1505, 1466, 1378, 1341, 1299, 1252, 1173, 1133, 1033, 845; HRMS (ESI) for $C_{11}H_{12}F_2O_4Na$ $[M+Na]^+$ requires 269.0596 found 269.0596.

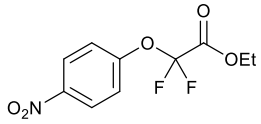
Ethyl (4-benzoylphenoxy)(difluoro)acetate (3i)



The title compound was prepared following General Procedure A using potassium carbonate (6.91 g, 50.0 mmol), 4-hydroxybenzophenone (3.96 g, 20.0 mmol), ethyl bromodifluoroacetate (3.85 mL, 30.0 mmol) and DMF (40 mL). The crude product was purified by silica gel column chromatography (eluent: 5 % Et_2O in *n*-pentane) to provide the title compound (2.26 g, 35 % yield) as a colourless oil.

(^{1}H NMR, 400 MHz, $CDCl_3$): δ = 7.84 (dt, J_1 = 2.2 Hz, J_2 = 8.8 Hz, 2H), 7.79–7.77 (m, 2H), 7.61–7.57 (m, 1H), 7.49 (t, *J* = 7.6 Hz, 2H), 7.33 (d, *J* = 8.8 Hz, 2H), 4.41 (q, *J* = 7.2 Hz, 2H), 1.38 (t, *J* = 7.1 Hz, 3H); (^{13}C NMR, 101 MHz, $CDCl_3$): δ = 195.3, 159.3 (t, *J* = 41.0 Hz), 152.6, 137.2, 135.3, 132.6, 131.8, 129.9, 128.3, 120.8, 113.8 (d, J = 274.2 Hz), 63.8, 13.8; (^{19}F NMR, 377 MHz, $CDCl_3$): δ = –76.5 (s, 2F); IR: ν 1776, 1660, 1599, 1502, 1448, 1378, 1276, 1167, 1014, 938, 924, 855; HRMS (ESI) for $C_{17}H_{15}F_2O_4$ $[M+H]^+$ requires 321.0933 found 321.0926.

Ethyl difluoro(4-nitrophenoxy)acetate (3j)

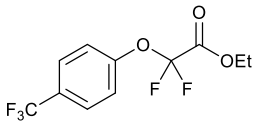


The title compound was prepared following General Procedure A using potassium carbonate (10.4 g, 75.0 mmol), 4-nitrophenol (4.17 g, 30.0 mmol), ethyl bromodifluoroacetdate (5.77 mL, 45.0 mmol) and DMF (60 mL). The crude product was purified by silica gel column chromatography (eluent: 20 % DCM in *n*-pentane) to provide the title compound (879 mg, 11 % yield) as a yellow oil.

(^{1}H NMR, 400 MHz, $CDCl_3$): δ = 8.27 (dt, J_1 = 2.6 Hz, J_2 = 9.1 Hz, 2H), 7.38 (d, *J* = 9.1 Hz, 2H), 4.42 (q, *J* = 7.1 Hz, 2H), 1.39 (t, *J* = 7.1 Hz, 3H); (^{13}C NMR, 101 MHz, $CDCl_3$): δ = 158.9 (t, *J* = 40.5 Hz), 154.2, 145.5, 125.5, 121.4, 113.7 (t, *J* = 276.2 Hz), 64.1, 13.8; (^{19}F

NMR, 377 MHz, $CDCl_3$): δ = –77.0 (s, 2F); IR: ν 1777, 1485, 1378, 1342, 1198, 1136, 1069, 1012, 848; HRMS (EI/FI) for $C_{10}H_9BrF_2O_3$ $[M]^+$ requires 293.9703 found 293.9706.

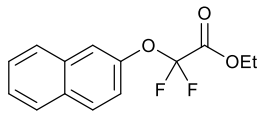
Ethyl difluoro[4-(trifluoromethyl)phenoxy]acetate (3k)



The title compound was prepared following General Procedure A using potassium carbonate (6.91 g, 50.0 mmol), 4-(trifluoromethyl)phenol (3.24 g, 20.0 mmol), ethyl bromodifluoroacetate (3.85 mL, 30.0 mmol) and DMF (40 mL). The crude product was purified by silica gel column chromatography (eluent: 1 % Et_2O in *n*-pentane) to provide the title compound (1.36 g, 24 % yield) as a colourless oil.

(^{1}H NMR, 400 MHz, $CDCl_3$): δ = 7.66 (d, *J* = 8.6 Hz, 2H), 7.34 (d, *J* = 8.6 Hz, 2H), 4.41 (q, *J* = 7.2 Hz, 2H), 1.38 (t, *J* = 7.2 Hz, 3H); (^{13}C NMR, 101 MHz, $CDCl_3$): δ = 159.3 (t, *J* = 40.5 Hz), 152.02, 128.5 (q, *J* = 33.1 Hz), 127.0 (q, *J* = 3.7 Hz), 123.7 (q, *J* = 271.8 Hz), 121.6, 113.8 (t, *J* =274.2 Hz), 63.4, 13.8; (^{19}F NMR, 377 MHz, $CDCl_3$): δ = –62.4 (s, 3F), –76.7 (s, 2F); IR: ν 1779, 1617, 1515, 1379, 1325, 1212, 1126, 1065, 1017, 857; HRMS (EI/FI) for $C_{11}H_9F_5O_3$ $[M]^+$ requires 284.0472 found 284.0479.

Ethyl 2,2-difluoro-2-(naphthalen-2-yloxy)acetate (3l)

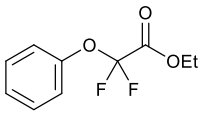


The title compound was prepared following General Procedure A using potassium carbonate (6.91 g, 50.0 mmol), 2-naphthol (2.88 g, 20.0 mmol), ethyl bromodifluoroacetate (3.85 mL, 30.0 mmol) and DMF (40 mL). The crude product was purified by silica gel column chromatography (eluent: 3 % Et_2O in *n*-pentane) to provide the title compound (2.00 g, 38 % yield) as a colourless oil.

(^{1}H NMR, 400 MHz, $CDCl_3$): δ = 7.88–7.82 (m, 3H), 7.70 (s, 1H), 7.56–7.48 (m, 2H), 7.38 (dd, J_1 = 2.5 Hz, J_2 = 9.1 Hz, 1H), 4.41 (q, *J* = 7.1 Hz, 2H), 1.39 (t, *J* = 7.1 Hz, 3H); (^{13}C

NMR, 101 MHz, $CDCl_3$): δ = 159.8 (t, *J* = 41.3 Hz), 147.1, 133.6, 131.5, 129.7, 127.7, 126.8, 126.0, 121.0, 118.6, 114.2 (t, *J* = 272.2 Hz), 63.7, 13.8; (^{19}F NMR, 377 MHz, $CDCl_3$): δ = –76.1 (s, 2F); IR: ν 1774, 1601, 1511, 1466, 1377, 1339, 1158, 1011, 961, 855; HRMS (ESI) for $C_{14}H_{12}O_3F_2Na$ $[M+Na]^+$ requires 289.0647 found 289.0643.

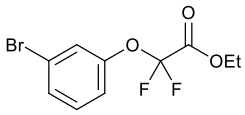
Ethyl difluoro(phenoxy)acetate (3o)



The title compound was prepared following General Procedure A using potassium carbonate (6.91 g, 50.0 mmol), phenol (1.88 g, 20.0 mmol), ethyl bromodifluoroacetate (3.85 mL, 30.0 mmol) and DMF (40 mL). The crude product was purified by silica gel column chromatography (eluent: 2 % Et_2O in *n*-pentane) to provide the title compound (1.37 g, 32 % yield) as a colourless oil.

(^{1}H NMR, 400 MHz, $CDCl_3$): δ = 7.42–7.37 (m, 2H), 7.31–7.25 (m, 3H), 4.41 (q, *J* = 7.2 Hz, 2H), 1.39 (t, *J* = 7.2 Hz, 3H); (^{13}C NMR, 101 MHz, $CDCl_3$): δ = 159.8 (t, *J* = 41.3 Hz), 149.5, 129.6, 126.3, 121.6, 114.0 (t, *J* = 272.2 Hz), 63.6, 13.8; (^{19}F NMR, 377 MHz, $CDCl_3$): δ = –76.2 (s); IR: ν 1776 1592. 1492, 1378, 1341, 1191, 1130, 1005, 858; HRMS (ESI) for $C_{10}H_{10}F_2NaO_3$ $[M+Na]^+$ requires 239.0492 found 239.0489.

Ethyl (3-bromophenoxy)(difluoro)acetate (3p)

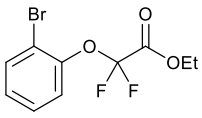


The title compound was prepared following General Procedure A using potassium carbonate (6.91 g, 50.0 mmol), 3-bromophenol (3.46 g, 20.0 mmol), ethyl bromodifluoroacetate (3.85 mL, 30.0 mmol) and DMF (40 mL). The crude product was purified by silica gel column chromatography (eluent: 1 % Et_2O in *n*-pentane) to provide the title compound (1.15 g, 20 % yield) as a colourless oil.

(^{1}H NMR, 400 MHz, $CDCl_3$): δ = 7.42–7.40 (m, 2H), 7.26–7.23 (m, 1H), 7.19–7.17 (m, 1H), 4.40 (q, *J* = 7.1 Hz, 2H), 1.38 (t, *J* = 7.1 Hz, 3H); (^{13}C NMR, 101 MHz, $CDCl_3$): δ = 159.4

(t, *J* = 40.9 Hz), 149.9, 130.6, 129.6, 125.1, 122.5, 120.3, 113.8 (t, *J* = 273.8 Hz), 63.8, 13.8; (^{19}F NMR, 377 MHz, $CDCl_3$): δ = –76.6 (s); IR: ν 1776, 1585, 1472, 1341, 1136, 1012, 858; HRMS (EI/FI) for $C_{10}H_9BrF_2O_3$ $[M]^+$ requires 293.9703 found 293.9709.

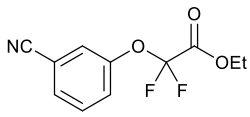
Ethyl (2-bromophenoxy)(difluoro)acetate (3q)



The title compound was prepared following General Procedure A using potassium carbonate (6.91 g, 50.0 mmol), 2-bromophenol (3.46 g, 20.0 mmol), ethyl bromodifluoroacetate (3.85 mL, 30.0 mmol) and DMF (40 mL). The crude product was purified by silica gel column chromatography (eluent: 2 % Et_2O in *n*-pentane) to provide the title compound (2.11 g, 36 % yield) as a colourless oil.

(^{1}H NMR, 400 MHz, $CDCl_3$): δ = 7.63 (dd, J_1 = 1.2 Hz, J_2 = 7.8 Hz, 1H), 7.37–7.30 (m, 1H), 7.26–7.23 (m, 1H), 7.14 (ddd, J_1 = 2.0 Hz, J_2 = 6.9 Hz, J_3 = 7.8 Hz, 1H), 4.42 (q, *J* = 7.1 Hz, 2H), 1.38 (t, *J* = 7.1 Hz, 3H); (^{13}C NMR, 101 MHz, $CDCl_3$): δ = 159.6 (t, *J* = 40.9 Hz), 146.8, 133.8, 128.4, 127.5, 123.0, 116.5, 113.9 (t, *J* = 275.0 Hz), 63.8, 13.8; (^{19}F NMR, 377 MHz, $CDCl_3$): δ = –76.0 (s); IR: ν 1776, 1473, 1446, 1378, 1341, 1212, 1136, 1048, 1031 857; HRMS (EI/FI) for $C_{10}H_9BrF_2O_3$ $[M]^+$ requires 293.9703 found 293.9700.

Ethyl (3-cyanophenoxy)(difluoro)acetate (3t)



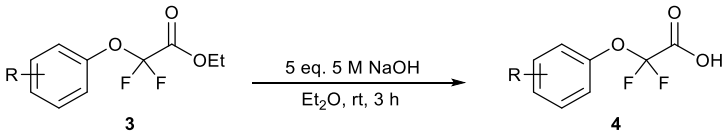
The title compound was prepared following General Procedure A using potassium carbonate (6.91 g, 50.0 mmol), 3-cyanophenol (2.38 g, 20.0 mmol), ethyl bromodifluoroacetate (3.85 mL, 30.0 mmol) and DMF (40 mL). The crude product was purified by silica gel column chromatography (eluent: 20 % Et_2O in *n*-pentane) to provide the title compound (197 mg, 4 % yield) as a pale yellow oil.

(^{1}H NMR, 400 MHz, $CDCl_3$): δ = 7.59–7.56 (m, 1H), 7.53–7.47 (m, 3H), 4.41 (q, *J* = 7.1 Hz, 2H), 1.39 (t, *J* = 7.2 Hz, 3H); (^{13}C NMR, 101 MHz, $CDCl_3$): δ = 159.0 (t, *J* = 40.1 Hz),

149.5, 130.7, 130.0, 126.3, 125.1, 117.5, 113.8, 113.7 (t, J = 275.0 Hz), 64.0, 13.8; (^{19}F NMR, 377 MHz, $CDCl_3$): δ = –76.8 (s); IR: ν 2236, 1775, 1582, 1483, 1432, 1378, 1342, 1238, 1148, 1010, 854; HRMS (EI/FI) for $C_{11}H_9F_2NO_3$ $[M]^+$ requires 241.0550 found 241.0551.

5.2.2 Synthesis of $ArOCF_2CO_2H$ (4)

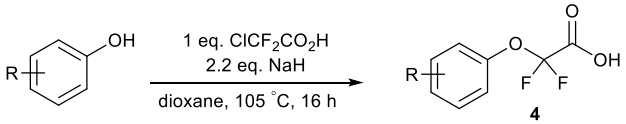
General Procedure B



3 **4**

To a solution of the appropriate ester (5.0 mmol) in specified solvent (25 mL) was added 5 M aq. NaOH (25.0 mmol). The mixture was stirred at room temperature for 3 hours before diluting with Et_2O (25 mL). The reaction mixture was extracted with sat. aq. $NaHCO_3$ (3 x 20 mL). The combined aqueous layers were acidified to pH 1 with 1 M HCl and extracted with Et_2O (3 x 20 mL), then the combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. Products were purified by washing with *n*-pentane.

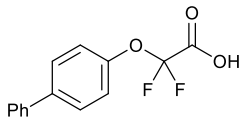
General Procedure C



4

To a solution of an appropriate phenol (10.0 mmol) in dioxane (30 mL) was added chlorodifluoroacetic acid (10.0 mmol). The mixture was cooled to 0 °C and NaH (60 % in mineral oil, 22.0 mmol) was slowly added. The reaction mixture was heated under reflux for 16 hours. The mixture was extracted with sat. $NaHCO_3$ then the combined aqueous layers were acidified with 5 M HCl, and extracted with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*.

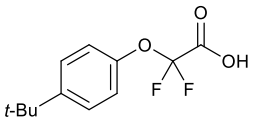
(Biphenyl-4-yloxy)(difluoro)acetic acid (4a)



The title compound was prepared following General Procedure B using ethyl (biphenyl-4-yloxy)(difluoro)acetate (640 mg, 2.19 mmol), 4 M aq. NaOH (5.5 mL, 22.0 mmol) and MeCN (25 mL); (588 mg, 100 % yield, grey solid).

(^{1}H NMR, 400 MHz, $CDCl_3$): δ = 9.77 (brs, 1H), 7.62–7.57 (m, 4H), 7.49–7.45 (m, 2H), 7.41–7.36 (m, 1H), 7.33 (d, *J* = 8.6 Hz, 2H); (^{13}C NMR, 101 MHz, $CDCl_3$): δ = 163.1 (t, *J* = 42.9 Hz), 148.5, 139.9, 139.7, 128.9, 128.4, 127.6, 127.1, 121.9, 113.7 (t, *J* = 272.2 Hz); (^{19}F NMR, 377 MHz, $CDCl_3$): δ = –76.6 (s, 2F); IR: ν 3063, 1776, 1519, 1487, 1452, 1248, 1208, 1190, 1174, 1155, 1101, 1008, 850; HRMS (ESI) for $C_{14}H_9F_2O_3$ $[M-H]^-$ requires 263.0525 found 263.0521; Mp. 103−105 °C.

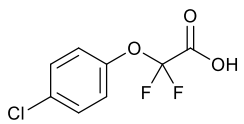
(4-*tert*-Butylphenoxy)(difluoro)acetic acid (4b)



The title compound was prepared following General Procedure B using ethyl (4-*tert*-butylphenoxy)(difluoro)acetate (1.63 g, 6.0 mmol), 5 M aq. NaOH (6 mL, 30.0 mmol) and MeCN (30 mL); (1.40 g, 96 % yield, white solid).

(^{1}H NMR, 400 MHz, $CDCl_3$): δ = 9.90 (brs, 1H), 7.40 (dt, J_1 = 2.6 Hz, J_2 = 9.1 Hz, 2H), 7.17 (d, *J* = 8.8 Hz, 2H), 1.33 (s, 9H); (^{13}C NMR, 101 MHz, $CDCl_3$): δ = 164.2 (t, *J* = 42.9 Hz), 149.6, 146.7, 126.6, 121.1, 113.6 (t, *J* = 274.6 Hz), 34.5, 31.3; (^{19}F NMR, 377 MHz, $CDCl_3$): δ = –76.6 (s, 2F); IR: ν 2965, 1765, 1509, 1366, 1176, 1105, 1016, 833, 804; HRMS (ESI) for $C_{12}H_{14}F_2NaO_3$ $[M+Na]^+$ requires 267.0803 found 267.0810; Mp. 66−68 °C.

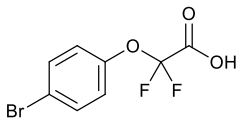
2-(4-Chlorophenoxy)-2,2-difluoroacetic acid (4c)



The title compound was prepared following General Procedure B using ethyl 2-(4-chlorophenoxy)-2,2-difluoroacetate (3.01 g, 12.0 mmol), 5 M aq. NaOH (12 mL, 60.0 mmol) and Et_2O (60 mL); (2.64 mg, 99 % yield, pale yellow solid).

(^{1}H NMR, 400 MHz, $CDCl_3$): δ = 7.77 (brs, 1H), 7.37 (dt, J_1 = 2.7 Hz, J_2 = 9.1 Hz, 2H), 7.19 (dt, J_1 = 2.7 Hz, J_2 = 9.1 Hz, 2H); (^{13}C NMR, 101 MHz, $CDCl_3$): δ = 163.4 (t, J = 41.7 Hz), 147.5, 132.3, 129.8, 123.1, 113.4 (t, J = 273.0 Hz); (^{19}F NMR, 377 MHz, $CDCl_3$): δ = –77.0 (s, 2F); IR: ν 3104, 1766, 1487, 1196, 1145, 1088, 1015, 832; HRMS (ESI) for $C_8H_4ClF_2O_3$ $[M-H]^-$ requires 220.9823 found 220.9828; Mp. 59–61 °C.

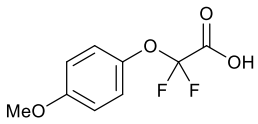
(4-Bromophenoxy)(difluoro)acetic acid (4d)



The title compound was prepared following General Procedure B using ethyl (4-bromophenoxy)(difluoro)acetate (1.48 g, 5.0 mmol), 5 M aq. NaOH (5 mL, 25.0 mmol) and MeCN (25 mL); (880 mg, 76 % yield, white solid).

(^{1}H NMR, 400 MHz, $CDCl_3$): δ = 10.21 (brs, 1H), 7.52 (dt, J_1 = 2.7 Hz, J_2 = 8.8 Hz, 2H), 7.15–7.12 (m, 2H); (^{13}C NMR, 101 MHz, $CDCl_3$): δ = 163.6 (t, J = 42.1 Hz), 148.1, 132.8, 123.4, 120.0, 113.4 (t, J = 273.0 Hz); (^{19}F NMR, 377 MHz, $CDCl_3$): δ = –77.0 (s, 2F); IR: ν 1765, 1484, 1194, 1068, 1013; HRMS (EI/FI) for $C_8H_5BrF_2O_3$ $[M]^+$ requires 265.9390 found 265.9393; Mp. 56−58 °C.

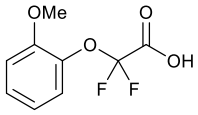
2,2-Difluoro-2-(4-methoxyphenoxy)acetic acid (4f)



The title compound was prepared following General Procedure B using ethyl 2,2-difluoro-2-(4-methoxyphenoxy)acetate (2.95 g, 12.0 mmol), 5 M aq. NaOH (12 mL, 60.0 mmol) and Et_2O (60 mL); (2.57 g, 98 %, white solid).

(^{1}H NMR, 400 MHz, $CDCl_3$): δ = 10.20 (brs, 1H), 7.18 (d, J = 9.1 Hz, 2H), 6.90 (dt, J_1 = 2.9 Hz, J_2 = 9.1 Hz, 2H), 3.83 (s, 3H); (^{13}C NMR, 101 MHz, $CDCl_3$): δ = 163.6 (t, J = 42.5 Hz), 157.8, 142.5, 123.0, 114.7, 113.6 (t, J = 271.9 Hz), 55.7; (^{19}F NMR, 377 MHz, $CDCl_3$): δ = –77.0 (s, 2F); IR: ν 2987, 1775, 1506, 1466, 1379, 1342, 1299, 1252, 1192, 1033, 844; HRMS (ESI) for $C_9H_7F_2O_4$ $[M-H]^-$ requires 217.0318 found 217.0323; Mp. 55–57 °C.

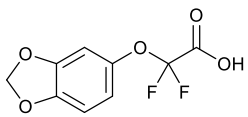
2,2-Difluoro-2-(2-methoxyphenoxy)acetic acid (4g)



The title compound was prepared following General Procedure C using guaiacol (1.10 mL, 10.0 mmol), dioxane (30 mL), chlorodifluoroacetic acid (0.85 mL, 10.0 mmol) and NaH (60 % in mineral oil, 0.88 g, 22.0 mmol); (1.64 g, 75 % yield, beige solid).

(^{1}H NMR, 400 MHz, $CDCl_3$): δ = 9.29 (brs, 1H), 7.30−7.23 (m, 2H), 7.02–6.95 (m, 2H), 3.90 (s, 3H); (^{13}C NMR, 101 MHz, $CDCl_3$): δ = 162.7 (t, *J* = 42.6 Hz), 151.6, 138.0, 127.5, 123.5, 121.1, 113.6 (t, *J* = 273.4 Hz), 112.9, 56.1; (^{19}F NMR, 377 MHz, $CDCl_3$): δ = –77.3 (s, 2F); IR: ν 3512, 1768, 1502, 1261, 1176, 1108; HRMS (ESI) for $C_9H_8F_2NaO_4$ $[M+Na]^+$ requires 241.0288 found 241.0280; Mp. 46−48 °C.

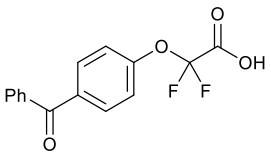
(1,3-Benzodioxol-5-yloxy)(difluoro)acetic acid (4h)



The title compound was prepared following General Procedure C using sesamol (1.38 g, 10.0 mmol), dioxane (30 mL), chlorodifluoroacetic acid (0.85 mL, 10.0 mmol) and NaH (60 % in mineral oil, 0.88 g, 22.0 mmol); (1.72 g, 74 % yield, orange solid).

(^{1}H NMR, 400 MHz, $CDCl_3$): δ = 10.35 (brs, 1H), 7.30−7.23 (m, 1H), 6.79–6.76 (m, 1H), 6.73–6.71 (m, 1H), 6.02 (s, 2H); (^{13}C NMR, 101 MHz, $CDCl_3$): δ = 163.7 (t, *J* = 42.5 Hz), 148.1, 146.1, 143.1, 114.8, 113.6 (t, *J* = 271.4 Hz), 108.0, 104.2, 101.9; (^{19}F NMR, 377 MHz, $CDCl_3$): δ = –77.2 (s, 2F); IR: ν 3511, 2905, 1766, 1614, 1503, 1249, 1089, 861; HRMS (ESI) for $C_9H_5F_2O_5$ $[M-H]^-$ requires 231.0111 found 231.0110; Mp. 64−65 °C.

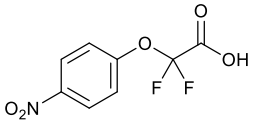
(4-Benzoylphenoxy)(difluoro)acetic acid (4i)



The title compound was prepared following General Procedure B using ethyl (4-benzoylphenoxy)(difluoro)acetate (1.28 g, 4.0 mmol), 5 M aq. NaOH (4 mL, 20.0 mmol) and Et_2O (20 mL); (1.05 mg, 95 % yield, white solid).

(^{1}H NMR, 400 MHz, $CDCl_3$): δ = 8.59 (brs, 1H), 7.86 (d, *J* = 8.6 Hz, 2H), (d, *J* = 7.3 Hz, 2H), 7.64 (t, *J* = 7.3 Hz, 1H), 7.51 (t, *J* = 7.7 Hz, 2H), 7.35 (d, *J* = 8.6 Hz, 2H); (^{13}C NMR, 101 MHz, $CDCl_3$): δ = 197.1, 161.1 (t, *J* = 41.3 Hz), 153.0, 136.8, 134.9, 133.1, 132.2, 130.2, 128.5, 120.9, 113.8 (t, *J* = 273.8 Hz); (^{19}F NMR, 377 MHz, $CDCl_3$): δ = –77.0 (s, 2F); IR: ν 1774, 1645, 1598, 1503, 1448, 1279, 1168, 1016, 926, 851; HRMS (ESI) for $C_{15}H_9F_2O_4$ $[M-H]^-$ requires 291.0474 found 291.0469.

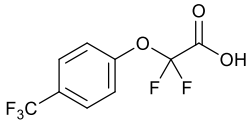
2,2-Difluoro-2-(4-nitrophenoxy)acetic acid (4j)



The title compound was prepared following General Procedure B using ethyl 2,2-difluoro-2-(4-nitrophenoxy)acetate (522 mg, 2.0 mmol), 5 M NaOH (2 mL, 10.0 mmol) and Et_2O (10 mL); (314 mg, 67 %, yellow solid).

(^{1}H NMR, 400 MHz, $CDCl_3$): δ = 8.30 (dt, J_1 = 2.7 Hz, J_2 = 9.3 Hz, 2H), 7.42–7.39 (m, 3H); (^{13}C NMR, 101 MHz, $CDCl_3$): δ = 161.4 (t, *J* = 42.1 Hz), 154.0, 145.6, 125.6, 121.5, 113.5 (t, *J* = 273.0 Hz); (^{19}F NMR, 377 MHz, $CDCl_3$): δ = –77.3 (s, 2F); IR: ν 3125, 1789, 1615, 1592,1517, 1490, 1347, 1160, 1076, 856; HRMS (EI/FI) for $C_8H_5F_2NO_5$ $[M]^+$ requires 233.0136 found 233.0144; Mp. 116–118 °C.

Difluoro[4-(trifluoromethyl)phenoxy]acetic acid (4k)

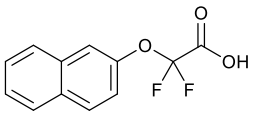


The title compound was prepared following General Procedure B using ethyl difluoro[4-(trifluoromethyl)phenoxy]acetate (1.14 g, 4.0 mmol),

5 M aq. NaOH (4 mL, 20.0 mmol) and MeCN (20 mL); (508 mg, 50 % yield, white solid).

(^{1}H NMR, 400 MHz, $CDCl_3$): δ = 8.80 (brs, 1H), 7.67 (d, *J* = 8.6 Hz, 2H), 7.36 (d, *J* = 8.6 Hz, 2H); (^{13}C NMR, 101 MHz, $CDCl_3$): δ = 163.0 (t, *J* = 41.71 Hz), 151.7, 129.3 (q, *J* = 33.1 Hz), 127.2 (q, *J* = 3.7 Hz), 128.6 (q, *J* = 271.8 Hz), 121.7, 113.5 (t, *J* =274.2 Hz); (^{19}F NMR, 377 MHz, $CDCl_3$): δ = –62.5 (s, 3F), –71.2 (s, 2F); IR: ν 1769, 1615, 1515, 1326, 1125, 1065, 1018, 846, 807; HRMS (EI/FI) for $C_9H_5F_5O_3$ $[M]^+$ requires 256.0159 found 256.0164; Mp. 36−38 °C.

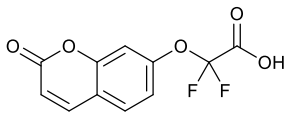
2,2-Difluoro-2-(naphthalen-2-yloxy)acetic acid (4l)



The title compound was prepared following General Procedure B using ethyl 2,2-difluoro-2-(naphthalen-2-yloxy)acetate (1.07 g, 4.0 mmol), 5 M aq. NaOH (4 mL, 20.0 mmol) and MeCN (20 mL); (773 mg, 81 % yield, white solid).

(^{1}H NMR, 400 MHz, $CDCl_3$): δ = 9.10 (brs, 1H), 7.89–7.83 (m, 3H), 7.72 (s, 1H), 7.57–7.50 (m, 2H), 7.39 (dd, J_1 = 2.2 Hz, J_2 = 9.1 Hz, 1H); (^{13}C NMR, 101 MHz, $CDCl_3$): δ = 163.8 (t, *J* = 41.7 Hz), 146.8, 133.6, 131.7, 129.9, 127.8, 127.0, 126.2, 120.9, 118.7, 113.8 (t, *J* = 272.2 Hz); (^{19}F NMR, 377 MHz, $CDCl_3$): δ = –76.4 (s, 2F); IR: ν 3544, 2362, 1711, 1636, 1598, 1466, 1338, 1245, 1133, 961, 893; HRMS (EI/FI) for $C_{12}H_7O_3F_2$ $[M-H]^-$ requires 237.0369 found 237.0367; Mp. 75−77 °C.

Difluoro[(2-oxo-2H-chromen-7-yl)oxy]acetic acid (4m)

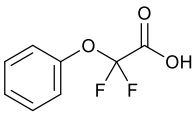


The title compound was prepared following General Procedure B using potassium carbonate (6.91 g, 50.0 mmol), umbeliferone (3.24 g, 20.0 mmol), ethyl bromodifluoroacetate (3.85 mL, 30.0 mmol) and DMF (40 mL). The crude mixture was subjected to conditions described by General Procedure B using 5 M aq.

NaOH (4 mL, 20.0 mmol) and Et_2O (20 mL) to provide the title compound (677 mg, 13 % yield) as a white solid.

(^{1}H NMR, 400 MHz, DMSO-d6): δ = 8.09 (d, *J* = 9.5 Hz, 1H), 7.82 (d, *J* = 8.6 Hz, 1H), 7.30–7.24 (m, 2H), 6.51 (d, *J* = 9.5 Hz, 1H); (^{13}C NMR, 101 MHz, DMSO-d6): δ = 160.6 (t, *J* = 39.5 Hz), 160.0, 154.7, 151.9, 144.0, 130.5, 117.6, 117.4, 116.4, 114.6 (t, *J* = 274.2 Hz), 109.2; (^{19}F NMR, 377 MHz, DMSO-d6): δ = –76.6 (s, 2F); IR: ν 3667, 3071, 2980, 2867m 1776, 1654, 1621, 1604, 1563, 1502, 1156, 1127, 1079, 990; HRMS (ESI) for $C_{11}H_6O_5F_2Na$ $[M+Na]^+$ requires 279.0076 found 279.0075; Mp. 132−135 °C.

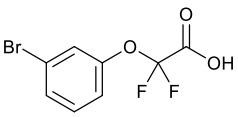
Difluoro(phenoxy)acetic acid (4o)



The title compound was prepared following General Procedure B using ethyl difluoro(phenoxy)acetate (865 mg, 4.0 mmol), 5 M aq. NaOH (4 mL, 20.0 mmol) and MeCN (20 mL); (742 mg, 99 % yield, yellow oil).

(^{1}H NMR, 400 MHz, $CDCl_3$): δ = 8.81 (brs, 1H), 7.45–7.40 (m, 2H), 7.34–7.26 (m, 3H); (^{13}C NMR, 101 MHz, $CDCl_3$): δ = 164.3 (t, *J* = 42.9 Hz), 149.1, 129.7, 126.6, 121.6, 113.6 (t, *J* = 270.6 Hz); (^{19}F NMR, 377 MHz, $CDCl_3$): δ = –76.7 (s); IR: ν 1762, 1591, 1491, 1189, 1025, 1004, 855; HRMS (EI/FI) for $C_8H_6F_2O_3$ $[M]^+$ requires 188.0285 found 188.0286.

(3-Bromophenoxy)(difluoro)acetic acid (4p)

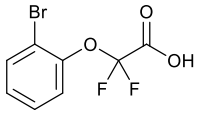


The title compound was prepared following General Procedure B using ethyl (3-bromophenoxy)(difluoro)acetate (590 mg, 2.0 mmol), 5 M aq. NaOH (2 mL, 10.0 mmol) and MeCN (10 mL); (382 mg, 71 % yield, pale yellow solid).

(^{1}H NMR, 400 MHz, $CDCl_3$): δ = 8.37 (brs, 1H), 7.42–7.40 (m, 2H), 7.25–7.23 (m, 1H) , 7.19–7.17 (m, 1H); (^{13}C NMR, 101 MHz, $CDCl_3$): δ = 163.7 (t, *J* = 41.3 Hz), 149.5, 130.8, 129.9, 125.1, 122.6, 120.3, 113.4 (t, *J* = 274.2 Hz); (^{19}F NMR, 377 MHz, $CDCl_3$): δ = –76.9

(s); IR: ν 3574, 1761, 1580, 1462, 1245, 1191, 1142, 1062, 873; HRMS (ESI) for $C_8H_4BrF_2O_3$ $[M-H]^-$ requires 264.9306 found 264.9318; Mp. 40−41 °C.

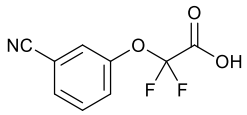
(2-Bromophenoxy)(difluoro)acetic acid (4q)



The title compound was prepared following General Procedure B using ethyl (2-bromophenoxy)(difluoro)acetate (1.18 g, 4.0 mmol), 5 M aq. NaOH (4 mL, 20.0 mmol) and MeCN (20 mL); (1.03 g, 96 % yield, pale yellow oil).

(^{1}H NMR, 400 MHz, $CDCl_3$): δ = 10.35 (brs, 1H), 7.65 (dd, J_1 = 1.2 Hz, J_2 = 7.8 Hz, 1H), 7.39–7.33 (m, 2H) , 7.18 (ddd, J_1 = 2.0 Hz, J_2 = 6.9 Hz, J_3 = 7.8 Hz, 1H); (^{13}C NMR, 101 MHz, $CDCl_3$): δ = 164.0 (t, J = 41.1 Hz), 146.4, 133.9, 128.5, 127.9, 1231, 116.5, 113.4 (t, J = 275.0 Hz); (^{19}F NMR, 377 MHz, $CDCl_3$): δ = –76.5 (s); IR: ν 1766, 1472, 1445, 1149, 1047, 1030, 855; HRMS (EI/FI) for $C_8H_5BrF_2O_3$ $[M]^+$ requires 265.9390 found 265.9403.

(3-Cyanophenoxy)(difluoro)acetic acid (4t)

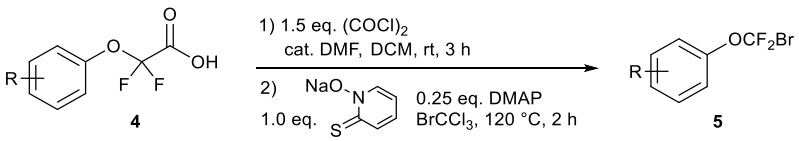


The title compound was prepared following General Procedure B using ethyl (3-cyanophenoxy)(difluoro)acetate (145 mg, 0.6 mmol), 5 M aq. NaOH (0.6 mL, 3.0 mmol) and MeCN (30 mL); (125 mg, 98 % yield, white solid).

(^{1}H NMR, 400 MHz, $CDCl_3$): δ = 9.94 (brs, 1H), 7.63–7.52 (m, 4H); (^{13}C NMR, 101 MHz, $CDCl_3$): δ = 161.5 (t, J = 40.5 Hz), 149.4, 130.9, 130.4, 126.7, 125.3, 117.2, 113.5 (t, J = 274.2 Hz), 113.5; (^{19}F NMR, 377 MHz, $CDCl_3$): δ = –77.2 (s); IR: ν 2242, 1770, 1582, 1483, 1433, 1239, 1160, 931; HRMS (ESI) for $C_8H_4BrF_2O_3$ $[M-H]^-$ requires 212.0165 found 212.0160; Mp. 46−48 °C.

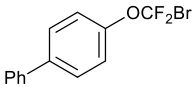
5.2.3 Synthesis of $ArOCF_2Br$ (5)

General Procedure D



To a solution of an appropriate carboxylic acid (1.0 mmol) in CH_2Cl_2 (2 mL) was added DMF (0.10 mmol) and oxalyl chloride (1.5 mmol) at 0 ˚C. The reaction mixture was stirred at room temperature for 3 hours, then concentrated *in vacuo*. To the crude acyl chloride was added $BrCCl_3$ (3 mL), 4-dimethylaminopyridine (0.25 mmol) and sodium-*N*-hydroxy-2-thiopyridone (1.0 mmol). The reaction mixture was refluxed at 120 ˚C for 2 hours then concentrated *in vacuo*. The crude product was purified by silica gel column chromatography.

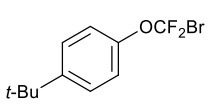
4-[Bromo(difluoro)methoxy]biphenyl (5a)



The title compound was prepared following General Procedure D using (biphenyl-4-yloxy)(difluoro)acetic acid (1.19 g, 4.5 mmol), DCM (7.5 mL), DMF (34.7 µL, 0.45 mmol), oxalyl chloride (579 µL, 6.75 mmol), $BrCCl_3$ (12 mL), 4-Dimethylaminopyridine (137 mg, 1.125 mmol) and sodium-*N*-hydroxy-2-thiopyridone (671 mg, 4.5 mmol). The crude product was purified by silica gel column chromatography (eluent: 1 % Et_2O in *n*-pentane) to provide the title compound (871 mg, 65 % yield) as a white solid.

(^{1}H NMR, 400 MHz, $CDCl_3$): δ = 7.65–7.57 (m, 4H), 7.49–7.45 (m, 2H), 7.41–7.37 (m, 1H), 7.34–7.32 (m, 2H); (^{13}C NMR, 101 MHz, $CDCl_3$): δ = 150.2, 140.1, 139.8, 128.9, 128.4, 127.7, 127.1, 121.6, 114.6 (t, *J* = 308.8 Hz); (^{19}F NMR, 377 MHz, $CDCl_3$): δ = –15.4 (s); IR: ν 1516, 1486, 1212, 1141, 993, 866, 845; HRMS (EI/FI) for $C_{13}H_9BrF_2O$ $[M]^+$ requires 297.9805 found 297.9811; Mp. 44-45 °C.

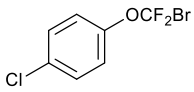
1-(Bromodifluoromethoxy)-4-(*tert*-butyl)benzene (5b)



The title compound was prepared following General Procedure D using (4-*tert*-butylphenoxy)(difluoro)acetic acid (733 mg, 3.0 mmol), DCM (5 mL), DMF (23.1 µL, 0.3 mmol), oxalyl chloride (386 µL, 4.5 mmol), $BrCCl_3$ (8 mL), 4-dimethylaminopyridine (91 mg, 0.75 mmol) and sodium-*N*-hydroxy-2-thiopyridone (447 mg, 3.0 mmol). The crude product was purified by silica gel column chromatography (eluent: 1 % Et_2O in *n*-pentane) to provide the title compound (501 mg, 60 % yield) as a pale yellow oil.

(^{1}H NMR, 400 MHz, $CDCl_3$): δ = 7.43 (dt, J_1 = 2.7 Hz, J_2 = 8.8 Hz, 2H), 7.19–7.17 (m, 2H), 1.35 (s, 9H); (^{13}C NMR, 101 MHz, $CDCl_3$): δ = 150.0, 148.5, 126.6, 120.8, 114.7 (t, J = 308.4 Hz), 34.6, 31.3; (^{19}F NMR, 377 MHz, $CDCl_3$): δ = –15.3 (s, 2F); IR: ν 2965, 1509, 1366, 1268, 1195, 1143, 1107, 1044, 998, 869, 834; HRMS (EI/FI) for $C_{11}H_{13}BrF_2O$ $[M]^+$ requires 278.0118 found 278.0115.

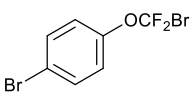
1-(Bromodifluoromethoxy)-4-chlorobenzene (5c)



The title compound was prepared following General Procedure D using 2-(4-chlorophenoxy)-2,2-difluoroacetic acid (890 mg, 4.0 mmol), DCM (8.0 mL), DMF (30.8 µL, 0.4 mmol), oxalyl chloride (515 µL, 6.0 mmol), $BrCCl_3$ (12 mL), 4-dimethylaminopyridine (122 mg, 1.0 mmol) and sodium-*N*-hydroxy-2-thiopyridone (596 mg, 4.0 mmol). The crude product was purified by silica gel column chromatography (eluent: 100 % *n*-pentane) to provide the title compound (509 mg, 49 % yield) as a colourless oil.

(^{1}H NMR, 400 MHz, $CDCl_3$): δ = 7.40 (dt, J_1 = 2.8 Hz, J_2 = 9.1 Hz, 2H), 7.22–7.18 (m, 2H); (^{13}C NMR, 101 MHz, $CDCl_3$): δ = 149.2, 132.7, 129.9, 122.8, 114.5 (t, J = 309.2 Hz); (^{19}F NMR, 377 MHz, $CDCl_3$): δ = –16.1 (s, 2F); IR: ν 1488, 1210, 1144, 1092, 1049, 1006, 863, 831; HRMS (EI/FI) for $C_7H_4BrClF_2O$ $[M]^+$ requires 255.9102 found 255.9101.

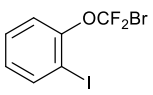
1-Bromo-4-(bromodifluoromethoxy)benzene (5d)



The title compound was prepared following General Procedure D using (4-bromophenoxy)(difluoro)acetic acid (401 mg, 1.5 mmol), DCM (2.5 mL), DMF (11.6 µL, 0.15 mmol), oxalyl chloride (194 µL, 2.25 mmol), $BrCCl_3$ (9 mL), 4-dimethylaminopyridine (46 mg, 0.375 mmol) and sodium-*N*-hydroxy-2-thiopyridone (224 mg, 1.5 mmol). The crude product was purified by silica gel column chromatography (eluent: 0.5 % Et_2O in *n*-pentane) to provide the title compound (278 mg, 61 % yield) as a colourless oil.

(^{1}H NMR, 400 MHz, $CDCl_3$): δ = 7.55 (dt, J_1 = 2.7 Hz, J_2 = 9.1 Hz, 2H), 7.16–7.12 (m, 2H); (^{13}C NMR, 101 MHz, $CDCl_3$): δ = 149.7, 132.9, 123.2, 120.4, 114.3 (t, J = 309.2 Hz); (^{19}F NMR, 377 MHz, $CDCl_3$): δ = –16.1 (s, 2F); IR: ν 1484, 1207, 1142, 1068, 1004, 861; HRMS (EI/FI) for $C_7H_4Br_2F_2O$ $[M]^+$ requires 299.8597 found 299.8595.

Bromo(difluoro)methyl 2-iodophenyl ether (5e)

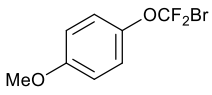


The title compound was prepared following General Procedure C using 2-iodophenol (2.20 g, 10.0 mmol), dioxane (30 mL), chlorodifluoroacetic acid (0.85 mL, 10.0 mmol) and NaH (1.00 g, 25.0 mmol). The crude mixture was then subjected to conditions described by General Procedure D using DCM (4 mL), DMF (18.5 µL, 0.24 mmol), oxalyl chloride (309 µL, 3.6 mmol), $BrCCl_3$ (7 mL), 4-dimethylaminopyridine (73 mg, 0.6 mmol) and sodium-*N*-hydroxy-2-thiopyridone (358 mg, 2.4 mmol). The crude product was purified by silica gel column chromatography (eluent: 0.5 % Et_2O in *n*-pentane) to provide the title compound (393 mg, 47 % yield) as a colourless oil.

(^{1}H NMR, 400 MHz, $CDCl_3$): δ = 7.90 (dd, J_1 = 1.5 Hz, J_2 = 7.8 Hz, 1H), 7.43–7.33 (m, 2H), 7.08–7.04 (m, 1H); (^{13}C NMR, 101 MHz, $CDCl_3$): δ = 151.1, 140.3, 129.7, 128.4, 121.5, 121.4, 114.2 (t, J = 309.9 Hz); (^{19}F NMR, 377 MHz, $CDCl_3$): δ = –14.9 (s, 2F); IR: ν

1468, 1440, 1186, 1136, 865; HRMS (EI/FI) for $C_7H_4BrF_2IO$ $[M]^+$ requires 347.8458 found 347.8463.

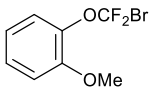
1-(Bromodifluoromethoxy)-4-methoxybenzene (5f)



The title compound was prepared following General Procedure D using 2,2-difluoro-2-(4-methoxyphenoxy)acetic acid (873 mg, 4.0 mmol), DCM (8.0 mL), DMF (30.8 µL, 0.4 mmol), oxalyl chloride (515 µL, 6.0 mmol), $BrCCl_3$ (12 mL), 4-dimethylaminopyridine (122 mg, 1.0 mmol) and sodium-*N*-hydroxy-2-thiopyridone (596 mg, 4.0 mmol). The crude product was purified by silica gel column chromatography (eluent: 2 % Et_2O in *n*-pentane) to provide the title compound (658 mg, 65 % yield) as a colourless oil.

(^{1}H NMR, 400 MHz, $CDCl_3$): δ = 7.19–7.17 (m, 2H), 6.92 (dt, J_1 = 3.1 Hz, J_2 = 9.1 Hz, 2H), 3.83 (s, 3H); (^{13}C NMR, 101 MHz, $CDCl_3$): δ = 158.2, 144.4, 122.7, 115.3 (t, J = 308.0 Hz), 114.6, 55.6; (^{19}F NMR, 377 MHz, $CDCl_3$): δ = –15.7 (s, 2F); IR: ν 1596, 1505, 1464, 1301, 1255, 1196, 1142, 998, 869, 832; HRMS (EI/FI) for $C_8H_7BrF_2O_2$ $[M]^+$ requires 251.9597 found 251.9598.

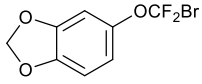
1-(Bromodifluoromethoxy)-2-methoxybenzene (5g)



The title compound was prepared following General Procedure D using 2,2-difluoro-2-(2-methoxyphenoxy)acetic acid (655 mg, 3.0 mmol), DCM (5 mL), DMF (23.1 µL, 0.3 mmol), oxalyl chloride (386 µL, 4.5 mmol), $BrCCl_3$ (8 mL), 4-dimethylaminopyridine (91 mg, 0.75 mmol) and sodium-*N*-hydroxy-2-thiopyridone (447 mg, 3.0 mmol). The crude product was purified by silica gel column chromatography (eluent: 1 % Et_2O in *n*-pentane) to provide the title compound (443 mg, 58 % yield) as a colourless oil.

(^{1}H NMR, 400 MHz, $CDCl_3$): δ = 7.32–7.26 (m, 2H), 7.02 (dd, J_1 = 1.5 Hz, J_2 = 8.3 Hz, 1H), 6.97 (td, J_1 = 1.5 Hz, J_2 = 7.8 Hz, 1H), 3.89 (s, 3H); (^{13}C NMR, 101 MHz, $CDCl_3$): δ = 151.7, 139.7, 127.9, 122.9, 120.6, 114.9 (t, J = 309.5 Hz), 113.0, 56.0; (^{19}F NMR, 377 MHz, $CDCl_3$): δ = –15.2 (s, 2F); IR: ν 1607, 1503, 1264, 1139, 999, 866; HRMS (EI/FI) for $C_8H_7BrF_2O_2$ $[M]^+$ requires 251.9597 found 251.9597.

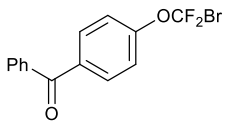
5-(Bromodifluoromethoxy)-1,3-benzodioxole (5h)



The title compound was prepared following General Procedure D using (1,3-benzodioxol-5-yloxy)(difluoro)acetic acid (929 mg, 4.0 mmol), DCM (8 mL), DMF (30.8 µL, 0.4 mmol), oxalyl chloride (515 µL, 6.0 mmol), $BrCCl_3$ (12 mL), 4-dimethylaminopyridine (122 mg, 1.0 mmol) and sodium-*N*-hydroxy-2-thiopyridone (596 mg, 4.0 mmol). The crude product was purified by silica gel column chromatography (eluent: 10 % Et_2O in *n*-pentane) to provide the title compound (622 mg, 58 % yield) as a colourless oil.

(^{1}H NMR, 400 MHz, $CDCl_3$): δ = 6.81–6.71 (m, 3H), 6.03 (s, 2H); (^{13}C NMR, 101 MHz, $CDCl_3$): δ = 148.1, 146.4, 145.0, 115.2 (t, J = 308.0 Hz), 114.6, 108.0, 103.8, 102.0; (^{19}F NMR, 377 MHz, $CDCl_3$): δ = –16.0 (s, 2F); IR: ν 2901, 1504, 1445, 1361, 1250, 1176, 1145, 1122, 1095, 946, 933, 852; HRMS (EI/FI) for $C_8H_5BrF_2O_3$ $[M]^+$ requires 265.9390 found 265.9393.

(4-(Bromodifluoromethoxy)phenyl)(phenyl)methanone (5i)

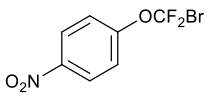


The title compound was prepared following General Procedure D using (4-benzoylphenoxy)(difluoro)acetic acid (415 mg, 1.5 mmol), DCM (2.5 mL), DMF (11.6 µL, 0.15 mmol), oxalyl chloride (194 µL, 2.25 mmol), $BrCCl_3$ (9 mL), 4-dimethylaminopyridine (46 mg, 0.375 mmol) and sodium-*N*-hydroxy-2-thiopyridone (224

mg, 1.5 mmol). The crude product was purified by silica gel column chromatography (eluent: 10 % Et_2O in *n*-pentane) to provide the title compound (303 mg, 62 % yield) as a white solid.

(^{1}H NMR, 400 MHz, $CDCl_3$): δ = 7.90 (dt, J_1 = 2.3 Hz, J_2 = 8.8 Hz, 2H), 7.83–7.80 (m, 2H), 7.63 (tt, J_1 = 1.9 Hz, J_2 = 7.5 Hz, 1H), 7.54–7.50 (m, 2H), 7.38–7.35 (m, 2H); (^{13}C NMR, 101 MHz, $CDCl_3$): δ = 195.2, 153.5, 137.1, 136.0, 132.7, 131.9, 130.0, 128.4, 120.8, 113.9 (t, J = 309.9 Hz); (^{19}F NMR, 377 MHz, $CDCl_3$): δ = –15.9 (s, 2F); IR: ν 1661, 1599, 1501, 1277, 1191, 1138, 1007, 924, 865; HRMS (EI/FI) for $C_{14}H_9BrF_2O_2$ $[M]^+$ requires 325.9754 found 325.9753; Mp. 42–43 °C.

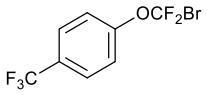
1-(Bromodifluoromethoxy)-4-nitrobenzene (5j)



The title compound was prepared following General Procedure D using 2,2-difluoro-2-(4-nitrophenoxy)acetic acid (233 mg, 1.0 mmol), DCM (2 mL), DMF (7.7 µL, 0.1 mmol), oxalyl chloride (129 µL, 1.5 mmol), $BrCCl_3$ (3 mL), 4-dimethylaminopyridine (30.7 mg, 0.25 mmol) and sodium-*N*-hydroxy-2-thiopyridone (149 mg, 1.0 mmol). The crude product was purified by silica gel column chromatography (eluent: 1 % Et_2O in *n*-pentane) to provide the title compound (103 mg, 38 % yield) as a colourless oil.

(^{1}H NMR, 400 MHz, $CDCl_3$): δ = 8.33 (dt, J_1 = 2.7 Hz, J_2 = 9.3 Hz, 2H), 7.44–7.40 (m, 2H); (^{13}C NMR, 101 MHz, $CDCl_3$): δ = 154.8, 145.9, 125.6, 121.6, 113.5 (t, J = 311.1 Hz); (^{19}F NMR, 377 MHz, $CDCl_3$): δ = –16.7 (s, 2F); IR: ν 1594, 1525, 1491, 1347, 1187, 1136, 1008, 877, 856, 837; HRMS (EI/FI) for $C_7H_4BrF_2NO_3$ $[M]^+$ requires 266.9343 found 266.9340.

1-(Bromodifluoromethoxy)-4-(trifluoromethyl)benzene (5k)

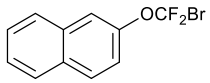


The title compound was prepared following General Procedure D using 2,2-difluoro-2-(4-(trifluoromethyl)phenoxy)acetic acid (1.03 g, 4.0

mmol), DCM (8.0 mL), DMF (30.8 µL, 0.4 mmol), oxalyl chloride (515 µL, 6.0 mmol), $BrCCl_3$ (12 mL), 4-dimethylaminopyridine (122 mg, 1.0 mmol) and sodium-*N*-hydroxy-2-thiopyridone (596 mg, 4.0 mmol). The crude product was purified by silica gel column chromatography (eluent: 100 % *n*-pentane) to provide the title compound (364 mg, 31 % yield) as a colourless oil.

(^{1}H NMR, 400 MHz, $CDCl_3$): δ = 7.71 (dt, *J* = 8.3 Hz, 2H), 7.38 (dt, *J* = 8.3 Hz, 2H); (^{13}C NMR, 126 MHz, $CDCl_3$): δ = 153.0, 129.2 (q, *J* = 33.8 Hz), 127.2 (q, *J* = 3.8 Hz), 123.1 (q, *J* = 271.8 Hz), 121.5, 113.9 (t, *J* = 309.9 Hz); (^{19}F NMR, 377 MHz, $CDCl_3$): δ = –16.2 (s, 2F), –62.5 (s, 3F); IR: ν 1616, 1514 1324, 1217, 1128, 1065, 1005, 867, 843; HRMS (EI/FI) for $C_8H_4BrF_5O$ $[M]^+$ requires 289.9366 found 289.9372.

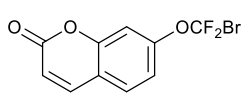
2-(Bromodifluoromethoxy)naphthalene (5l)



The title compound was prepared following General Procedure D using 2,2-difluoro-2-(naphthalen-2-yloxy)acetic acid (357 mg, 1.5 mmol), DCM (2.5 mL), DMF (11.6 µL, 0.15 mmol), oxalyl chloride (194 µL, 2.25 mmol), $BrCCl_3$ (9 mL), 4-dimethylaminopyridine (46 mg, 0.375 mmol) and sodium-*N*-hydroxy-2-thiopyridone (224 mg, 1.5 mmol). The crude product was purified by silica gel column chromatography (eluent: 1 % Et_2O in *n*-pentane) to provide the title compound (241 mg, 59 % yield) as a yellow solid.

(^{1}H NMR, 400 MHz, $CDCl_3$): δ = 7.92–7.87 (m, 3H), 7.73 (s, 1H), 7.59–7.53 (m, 2H), 7.40–7.37 (m, 1H); (^{13}C NMR, 101 MHz, $CDCl_3$): δ = 148.4, 133.5, 131.8, 129.9, 127.9, 127.8, 127.1, 126.4, 120.4, 118.7, 114.7 (t, *J* = 308.8 Hz); (^{19}F NMR, 377 MHz, $CDCl_3$): δ = –15.2 (s, 2F); IR: ν 1512, 1193, 1145, 1003, 963, 906, 811; HRMS (EI/FI) for $C_{11}H_7BrF_2O$ $[M]^+$ requires 271.9648 found 271.9641; Mp. 42–43 °C.

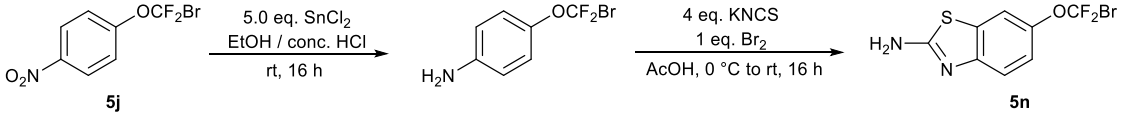
7-(Bromodifluoromethoxy)-2H-chromen-2-one (5m)



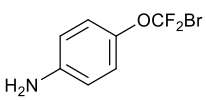
The title compound was prepared following General Procedure D using difluoro[(2-oxo-2H-chromen-7-yl)oxy]acetic acid (512 mg, 2.0 mmol), DCM (3.5 mL), DMF (15.4 µL, 0.2 mmol), oxalyl chloride (257 µL, 3.0 mmol), $BrCCl_3$ (5.5 mL), 4-dimethylaminopyridine (60.9 mg, 0.5 mmol) and sodium-*N*-hydroxy-2-thiopyridone (298 mg, 2.0 mmol). The crude product was purified by silica gel column chromatography (eluent: 30 % Et_2O in *n*-pentane) to provide the title compound (204 mg, 35 % yield) as a pale yellow solid.

(^{1}H NMR, 400 MHz, $CDCl_3$): δ = 7.73 (d, *J* = 9.5 Hz, 1H), 7.55 (d, *J* = 8.6 Hz, 1H), 7.24–7.17 (m, 2H), 6.46 (d, *J* = 9.5 Hz, 1H); (^{13}C NMR, 101 MHz, $CDCl_3$): δ = 159.8, 154.6, 152.6, 142.5, 129.2, 129.0, 117.4, 116.8, 113.8 (t, *J* = 310.3 Hz), 109.8; (^{19}F NMR, 377 MHz, $CDCl_3$): δ = –16.4 (s, 2F); IR: ν 1733, 1614, 1568, 1499, 1425, 1399, 1279, 1231, 1182, 1121, 1099, 1009, 984, 891, 842; HRMS (EI/FI) for $C_{10}H_6BrF_2O_3$ $[M]^+$ requires 290.9463 found 290.9459; Mp. 40-42 °C.

Synthesis of 6-[Bromo(difluoro)methoxy]-1,3-benzothiazol-2-amine (5n)



4-(Bromodifluoromethoxy)aniline

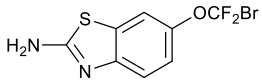


To a solution of 1-(bromodifluoromethoxy)-4-nitrobenzene (961 mg, 3.6 mmol) in EtOH (18 mL) was added $SnCl_2$ (3.29 g, 18.0 mmol) and conc. HCl (2.6 mL). The reaction mixture was stirred at room temperature for 16 hours under nitrogen atmosphere. The reaction mixture was poured on to sat. $NaHCO_3$ (200 mL) then extracted with EtOAc (3 × 50 mL). Combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by silica gel column

chromatography (eluent: 25 % EtOAc in *n*-pentane) to provide the title compound (739 mg, 86 % yield) as pale yellow oil.

(^{1}H NMR, 400 MHz, $CDCl_3$): δ = 7.04 (d, *J* = 8.8 Hz, 2H), 6.66 (d, *J* = 8.8 Hz, 2H), 3.69 (brs, 2H); (^{13}C NMR, 101 MHz, $CDCl_3$): δ = 145.4, 142.9, 122.6, 115.5 (t, *J* = 307.2 Hz), 115.4; (^{19}F NMR, 377 MHz, $CDCl_3$): δ = –15.5 (s, 2F); IR: ν 3378, 1624, 1507, 1188, 1139, 990, 867, 829; HRMS (EI/FI) for $C_7H_6BrF_2NO$ $[M]^+$ requires 236.9601 found 236.9598.

6-[Bromo(difluoro)methoxy]-1,3-benzothiazol-2-amine (5n)

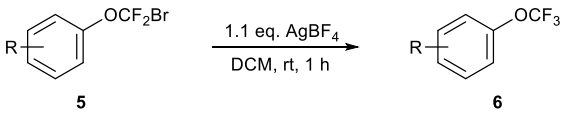


To a solution of 4-(bromodifluoromethoxy)aniline (714 mg, 3 mmol) in AcOH (5 mL) was added KSCN (1.17 g, 12 mmol) and a solution of Br_2 (0.154 mL, 3 mmol) in AcOH (3 mL) at 0 ˚C. The reaction mixture was stirred at room temperature for 16 hours under nitrogen atmosphere. The reaction mixture was poured on to sat. $NaHCO_3$ (200 mL) then extracted with EtOAc (3 × 50 mL). Combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by silica gel column chromatography (eluent: 50 % EtOAc in *n*-pentane) to provide the title compound (798 mg, 90 % yield) as pale yellow solid.

(^{1}H NMR, 400 MHz, $CDCl_3$): δ = 7.50 (d, *J* = 8.80 Hz, 2H), 7.19 (d, *J* = 8.30 Hz, 1H), 5.98 (brs, 2H); (^{13}C NMR, 101 MHz, $CDCl_3$): δ = 167.0, 150.8, 145.7, 132.0, 120.0, 119.3, 115.2 (t, *J* = 308.0 Hz), 114.4; (^{19}F NMR, 377 MHz, $CDCl_3$): δ = –15.8 (s, 2F); IR: ν 3432, 3411, 3287, 3076, 1637, 1599, 1532, 1455, 1319, 1250, 1136, 1095, 1055, 997, 925, 863, 831; HRMS (EI/FI) for $C_8H_5BrF_2N_2OS$ $[M]^+$ requires 293.9274 found 293.9281; Mp. 68−70 °C.

5.2.4 Synthesis of $ArOCF_3$ (6)

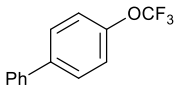
General Procedure E



5 6

To a solution of the appropriate bromide (0.25 mmol) in CH_2Cl_2 (2.5 mL) was added $AgBF_4$ (0.28 mmol) at room temperature. The reaction mixture was stirred at room temperature for 1 hour. The reaction mixture was concentrated *in vacuo*. The crude product was purified by silica gel column chromatography.

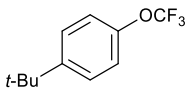
4-(Trifluoromethoxy)biphenyl (6a)



The title compound was prepared following General Procedure E using 4-[bromo(difluoro)methoxy]biphenyl (29.9 mg, 0.1 mmol), $AgBF_4$ (21.4 mg, 0.11 mmol) and dry DCM (1 mL). The crude product was purified by silica gel column chromatography (eluent: 1 % Et_2O in *n*-pentane) to provide the title compound (22.1 mg, 93 % yield) as a white solid.

(^{1}H NMR, 400 MHz, $CDCl_3$): δ = 7.63–7.57 (m, 4H), 7.47 (t, *J* = 7.6 Hz, 2H), 7.39 (t, *J* = 7.3 Hz, 1H), 7.31 (d, *J* = 8.6 Hz, 2H); (^{13}C NMR, 101 MHz, $CDCl_3$): δ = 148.7, 140.0, 139.9, 128.9, 128.5, 127.7, 127.1, 121.2, 120.5 (q, *J* = 256.70 Hz); (^{19}F NMR, 377 MHz, $CDCl_3$): δ = –57.8 (s, 3F). Data consistent with literature values.[2]

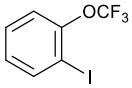
1-*tert*-Butyl-4-(trifluoromethyl)benzene (6b)



The title compound was prepared following General Procedure E using 4-[1-(bromodifluoromethoxy)-4-(*tert*-butyl)benzene (69.8 mg, 0.25 mmol), $AgBF_4$ (53.5 mg, 0.275 mmol) and dry DCM (2.5 mL). The crude product was purified by silica gel column chromatography (eluent: 0.5 % Et_2O in *n*-pentane) to provide the title compound (34.3 mg, 63 % yield) as a pale yellow oil.

(^{1}H NMR, 400 MHz, $CDCl_3$): δ = 7.40 (dt, J_1 = 2.7 Hz, J_2 = 8.8 Hz, 2H), 7.15 (d, J = 8.1 Hz, 2H), 1.34 (s, 9H); (^{13}C NMR, 101 MHz, $CDCl_3$): δ = 149.8, 147.0, 126.6, 120.6 (q, J = 256.4 Hz), 120.4, 34.5, 31.3; (^{19}F NMR, 377 MHz, $CDCl_3$): δ = –57.9 (s, 3F); IR: ν 2963, 2365, 1963, 1507, 1262, 1222, 1170, 805; HRMS (EI/FI) for $C_{11}H_{13}F_3O$ $[M]^+$ requires 218.0981 found 218.0913.

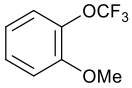
1-Iodo-2-(trifluoromethoxy)benzene (6e)



The title compound was prepared following General Procedure E using bromo(difluoro)methyl 2-iodophenyl ether (87.2 mg, 0.25 mmol), DCM (2.5 mL) and silver tetrafluoroborate (53.5 mg, 0.275 mmol). The crude product was purified by silica gel column chromatography (eluent: 2 % Et_2O in *n*-pentane) to provide the title compound (43.3 mg, 60 % yield) as a colourless oil.

(^{1}H NMR, 400 MHz, $CDCl_3$): δ = 7.89 (dd, J_1 = 1.5 Hz, J_2 = 7.8 Hz, 1H), 7.41–7.37 (m, 1H), 7.31–7.27 (m, 1H), 7.04 (dt, J_1 = 1.5 Hz, J_2 = 7.7 Hz, 1H); (^{13}C NMR, 101 MHz, $CDCl_3$): δ = 149.5, 140.3, 129.7, 128.3, 121.1, 120.5 (q, J = 259.3 Hz), 89.6; (^{19}F NMR, 377 MHz, $CDCl_3$): δ = –57.0 (s, 3F); IR: ν 1470, 1383, 1252, 1211, 1170, 954; HRMS (EI/FI) for $C_7H_4F_3IO$ $[M]^+$ requires 287.9259 found 287.9256.

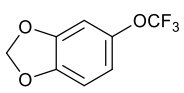
1-Methoxy-2-(trifluoromethoxy)benzene (6g)



The title compound was prepared following General Procedure E using 1-(bromodifluoromethoxy)-2-methoxybenzene (63.3 mg, 0.25 mmol), DCM (2.5 mL) and silver tetrafluoroborate (53.5 mg, 0.275 mmol). The crude product was purified by silica gel column chromatography (eluent: 2 % Et_2O in *n*-pentane) to provide the title compound (25.2 mg, 52 % yield) as a yellow oil.

(^{1}H NMR, 400 MHz, $CDCl_3$): δ = 7.29–7.25 (m, 2H), 7.02 (dd, J_1 = 1.5 Hz, J_2 = 8.3 Hz, 1H), 6.96 (td, J_1 = 1.5 Hz, J_2 = 7.8 Hz, 1H), 3.90 (s, 3H); (^{13}C NMR, 101 MHz, $CDCl_3$): δ = 152.0, 138.1, 127.9, 122.9, 120.7 (q, J = 257.5 Hz), 120.6, 112.9, 56.0; (^{19}F NMR, 377 MHz, $CDCl_3$): –58.2 (s, 3F). Data consistent with literature values.[3]

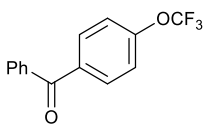
5-(Trifluoromethoxy)-1,3-benzodioxole (6h)



To a solution of 5-(bromodifluoromethoxy)-1,3-benzodioxole (160 mg, 0.6 mmol) in DCM (1.2 mL) was added $AgBF_4$ (128 mg, 0.66 mmol) at –20 ˚C. The reaction mixture was stirred at that temperature for 10 min before quenching with water. The mixture was extracted with DCM (3 x 5 mL). The combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography (eluent: 2 % Et_2O in *n*-pentane) to provide 101 mg of an inseparable mixture of the title compound (56 % yield) and the bromodifluoromethoxy starting material (20 % yield).

(^{1}H NMR, 400 MHz, $CDCl_3$): δ = 6.81–6.69 (m, 3H), 6.02 (s, 2H); (^{13}C NMR, 101 MHz, $CDCl_3$): δ = 148.2, 146.3, 143.4, 120.5 (q, J = 265.4 Hz), 114.2, 108.0, 103.6, 102.0; (^{19}F NMR, 377 MHz, $CDCl_3$): δ = –58.6 (s, 3F); IR: ν 2925, 1505, 1448, 1362, 1263, 1223, 1098, 1007, 852; HRMS (EI/FI) for $C_8H_5F_3O_3$ $[M]^+$ requires 206.0191 found 206.0188.

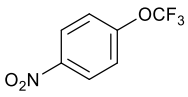
Phenyl(4-(trifluoromethoxy)phenyl)methanone (6i)



The title compound was prepared following General Procedure E using (4-(bromodifluoromethoxy)phenyl)(phenyl)methanone (77.8 mg, 0.25 mmol), DCM (2.5 mL) and silver tetrafluoroborate (53.5 mg, 0.275 mmol). The crude product was purified by silica gel column chromatography (eluent: 20 % Et_2O in *n*-pentane) to provide the title compound (56.5 mg, 85 % yield) as a white solid.

(^{1}H NMR, 400 MHz, $CDCl_3$): δ = 7.88 (dt, J_1 = 2.4 Hz, J_2 = 8.8 Hz, 2H), 7.82–7.79 (m, 2H), 7.62 (tt, J_1 = 1.9 Hz, J_2 = 7.5 Hz, 1H), 7.53–7.49 (m, 2H), 7.34–7.32 (m, 2H); (^{13}C NMR, 101 MHz, $CDCl_3$): δ = 195.1, 152.1, 137.1, 135.8, 132.7, 131.9, 129.9, 128.4, 120.3 (t, J = 258.3 Hz), 120.2; (^{19}F NMR, 377 MHz, $CDCl_3$): δ = –57.6 (s, 3F). Data consistent with literature values.[4]

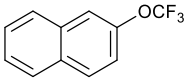
1-Nitro-4-(trifluoromethoxy)benzene (6j)



The title compound was prepared following General Procedure E using 1-(bromodifluoromethoxy)-4-nitrobenzene (26.8 mg, 0.1 mmol), DCM (1 mL) and silver tetrafluoroborate (21.4 mg, 0.11 mmol). The crude product was purified by silica gel column chromatography (eluent: 2 % Et_2O in *n*-pentane) to provide the title compound (14.4 mg, 70 % yield) as a yellow oil.

(^{1}H NMR, 400 MHz, $CDCl_3$): δ = 8.32 (dt, J_1 = 2.7 Hz, J_2 = 9.3 Hz, 2H), 7.40–7.37 (m, 2H); (^{13}C NMR, 101 MHz, $CDCl_3$): δ = 153.5, 145.8, 125.7, 120.9, 120.1 (q, J = 260.7 Hz); (^{19}F NMR, 377 MHz, $CDCl_3$): δ = –57.8 (s, 3F); IR: ν 1619, 1597, 1529, 1494, 1352, 1253, 1203, 1167, 1109, 855; HRMS (EI/FI) for $C_7H_4F_3NO_3$ $[M]^+$ requires 207.0143 found 207.0149.

2-(Trifluoromethoxy)naphthalene (6l)

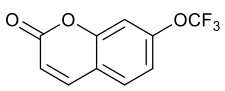


The title compound was prepared following General Procedure E using 2-(bromodifluoromethoxy)naphthalene (59.5 mg, 0.25 mmol), DCM (2.5 mL), and silver tetrafluoroborate (53.5 mg, 0.275 mmol). The crude product was purified by silica gel column chromatography (eluent: 1 % Et_2O in *n*-pentane) to provide the title compound (37.9 mg, 72 % yield) as a pale yellow oil.

(^{1}H NMR, 400 MHz, $CDCl_3$): δ = 7.90–7.84 (m, 3H), 7.70 (s, 1H), 7.58–7.51 (m, 2H), 7.37 (d, J = 9.1 Hz, 1H); (^{13}C NMR, 101 MHz, $CDCl_3$): δ = 146.8, 133.5, 131.7, 130.0, 127.8,

127.0, 126.3, 120.7 (q, *J* = 256.7 Hz), 120.1, 118.1; (^{19}F NMR, 377 MHz, $CDCl_3$): δ = –57.7 (s, 3F). Data consistent with literature values.[3]

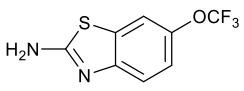
7-(Trifluoromethoxy)-2H-chromen-2-one (6m)



The title compound was prepared following General Procedure E using 7-(bromodifluoromethoxy)-2H-chromen-2-one (58.2 mg, 0.2 mmol), DCM (2 mL) and silver tetrafluoroborate (42.8 mg, 0.22 mmol). The crude product was purified by silica gel column chromatography (eluent: 50 % Et_2O in *n*-pentane) to provide the title compound (38.7 mg, 84 % yield) as a white solid.

(^{1}H NMR, 400 MHz, $CDCl_3$): δ = 7.72 (d, *J* = 9.8 Hz, 1H), 7.53 (d, *J* = 8.6 Hz, 1H), 7.20–7.14 (m, 2H), 6.44 (d, *J* = 9.5 Hz, 1H); (^{13}C NMR, 101 MHz, $CDCl_3$): δ = 159.8, 154.7, 151.3, 142.4, 129.0, 120.2 (q, *J* = 259.9 Hz), 117.3, 116.8, 116.7, 109.2; (^{19}F NMR, 377 MHz, $CDCl_3$): δ = –57.8 (s, 3F); IR: ν 3086, 1720, 1625, 1509, 1404, 1344, 1307, 1273, 1180, 1157, 1104, 1000, 910, 892; HRMS (EI/FI) for $C_{10}H_6F_3O_3$ $[M]^+$ requires 231.0264 found 231.0264; Mp. 64-65 °C.

2-Amino-6-(trifluoromethoxy)-1,3-benzothiazole (6n)

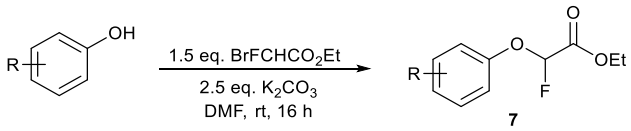


To a solution of 4-(trifluoromethoxy)aniline (177 mg, 1 mmol) in AcOH (2 mL) was added KSCN (389 mg, 4 mmol) and a solution of Br_2 (0.051 mL, 1 mmol) in AcOH (1 mL) at 0 ˚C. The reaction mixture was stirred at room temperature for 16 hours under nitrogen atmosphere. The reaction mixture was poured on to sat. $NaHCO_3$ (200 mL) then extracted with EtOAc (3 × 50 mL). Combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by silica gel column chromatography (eluent: 50 % EtOAc in *n*-pentane) to provide the title compound (230 mg, 98 % yield) as pale yellow solid.

(^{1}H NMR, 400 MHz, $CDCl_3$): δ = 7.48 (d, *J* = 8.80 Hz, 2H), 7.17 (dd, J_1 = 1.5 Hz, J_2 = 8.8 Hz, 1H), 5.99 (brs, 2H); (^{13}C NMR, 101 MHz, $CDCl_3$): δ = 167.0, 150.7, 144.0, 132.0, 120.5 (q, *J* = 256.7 Hz), 119.7, 119.2, 114.1; (^{19}F NMR, 377 MHz, $CDCl_3$): δ = –58.2 (s, 3F). Data consistent with literature values.[5]

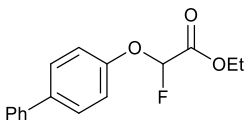
5.2.5 Synthesis of ArOCFHCO$_2$Et (7)

General Procedure F



To a suspension of K_2CO_3 (25 mmol) in a solution of the appropriate phenol (10 mmol) in DMF (20 mL) was slowly added ethyl bromofluoroacetate (15 mmol) at room temperature. The reaction mixture was stirred at room temperature for 16 hours under nitrogen atmosphere. The reaction mixture was poured on to water, extracted with Et_2O (3 × 100 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography.

Ethyl (biphenyl-4-yloxy)(fluoro)acetate (7a)

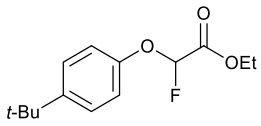


The title compound was prepared following General Procedure F using potassium carbonate (3.46 g, 25.0 mmol), 4-phenylphenol (1.70 g, 10.0 mmol), ethyl bromofluoroacetate (1.77 mL, 15.0 mmol) and DMF (20 mL). The crude product was purified by silica gel column chromatography (eluent: 15 % Et_2O in 30-40 petroleum ether) to provide the title compound (2.57 g, 94 % yield) as a white solid.

(^{1}H NMR, 400 MHz, $CDCl_3$): δ = 7.62−7.58 (m, 4H), 7.49−7.45 (m, 2H), 7.40−7.36 (m, 1H), 7.24 (d, *J* = 8.6 Hz, 2H), 6.04 (d, *J* = 59.9 Hz, 1H), 4.40 (q, *J* = 7.1 Hz, 2H), 1.41 (t, *J* = 7.1 Hz, 3H); (^{13}C NMR, 101 MHz, $CDCl_3$): δ = 163.9 (d, *J* = 31.0 Hz), 155.1, 140.1, 137.5,

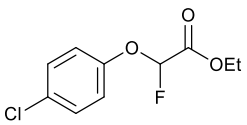
128.9, 128.4, 127.2, 126.8, 117.7, 102.5 (d, J = 231.3 Hz), 62.5, 13.9; (^{19}F NMR, 377 MHz, $CDCl_3$): δ = −129.3 (d, J = 60.7 Hz, 1F); IR: ν 1768, 1608, 1518, 1486, 1217, 1103, 1007, 838; HRMS (ESI) for $C_{16}H_{15}FNaO_3$ $[M+Na]^+$ requires 297.0897 found 297.0891; Mp. 28−29 °C.

Ethyl (4-*tert*-butylphenoxy)(fluoro)acetate (7b)



The title compound was prepared following General Procedure F using potassium carbonate (13.8 g, 100.0 mmol), 4-*tert*-butylphenol (6.00 g, 40.0 mmol), ethyl bromofluoroacetate (7.10 mL, 60.0 mmol) and DMF (80 mL). The crude product was purified by silica gel column chromatography (eluent: 10 % Et_2O in 30-40 petroleum ether) to provide the title compound (7.92 g, 78 % yield) as a colourless oil. (^{1}H NMR, 400 MHz, $CDCl_3$): δ = 7.37 (dt, J_1 = 2.6 Hz, J_2 = 8.8 Hz, 2H), 7.08 (d, J = 8.8 Hz, 2H), 5.95 (d, J = 60.1 Hz, 1H), 4.37 (q, J = 7.1 Hz, 2H), 1.37 (t, J = 7.1 Hz, 3H), 1.32 (s, 9H); (^{13}C NMR, 101 MHz, $CDCl_3$): δ = 164.1 (d, J = 31.8 Hz), 153.6 (d, J = 3.2 Hz), 147.3, 126.6, 117.0, 102.8 (d, J = 231.3 Hz), 62.5, 34.3, 31.4, 13.9; (^{19}F NMR, 377 MHz, $CDCl_3$): δ = −128.9 (d, J = 60.7 Hz, 1F); IR: ν 2964, 1769, 1608, 1511, 1364, 1216, 1185, 1097, 1014, 965, 833; HRMS (ESI) for $C_{14}H_{19}FNaO_3$ $[M+Na]^+$ requires 277.1210 found 277.1208.

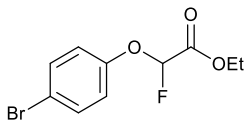
Ethyl (4-chlorophenoxy)(fluoro)acetate (7c)



The title compound was prepared following General Procedure F using potassium carbonate (6.91 g, 50.0 mmol), 4-chlorophenol (2.57 g, 20.0 mmol), ethyl bromofluoroacetate (3.55 mL, 30.0 mmol) and DMF (40 mL). The crude product was purified by silica gel column chromatography (eluent: 10 % Et_2O in *n*-pentane) to provide the title compound (3.38 g, 72 % yield) as a colourless oil.

(^{1}H NMR, 400 MHz, $CDCl_3$): δ = 7.30 (dt, J_1 = 2.8 Hz, J_2 = 9.1 Hz, 2H), 7.07 (dt, J_1 = 2.8 Hz, J_2 = 9.1 Hz, 2H), 5.91 (d, J = 59.4 Hz, 1H), 4.35 (q, J = 7.2 Hz, 2H), 1.35 (t, J = 7.1 Hz, 3H); (^{13}C NMR, 101 MHz, $CDCl_3$): δ = 163.6 (d, J = 31.0 Hz), 154.2 (d, J = 3.2 Hz), 129.8, 129.7, 118.9, 102.5 (d, J = 232.9 Hz), 62.6, 13.9; (^{19}F NMR, 377 MHz, $CDCl_3$): δ = −129.9 (d, J = 60.7 Hz, 1F); IR: ν 2986, 1765, 1588, 1489, 1383, 1298, 1211, 1173, 1089, 1010, 965, 827; HRMS (ESI) for $C_{10}H_{10}ClFNaO_3$ $[M+Na]^+$ requires 255.0195 found 255.0196.

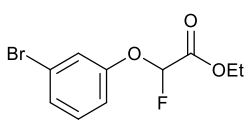
Ethyl (4-bromophenoxy)(fluoro)acetate (7d)



The title compound was prepared following General Procedure F using potassium carbonate (10.4 g, 75.0 mmol), 4-bromophenol (5.19 g, 30.0 mmol), ethyl bromofluoroacetate (5.32 mL, 45.0 mmol) and DMF (60 mL). The crude product was purified by silica gel column chromatography (eluent: 10 % Et_2O in *n*-pentane) to provide the title compound (4.46 g, 54 % yield) as a colourless oil.

(^{1}H NMR, 400 MHz, $CDCl_3$): δ = 7.47 (dt, J_1 = 2.7 Hz, J_2 = 9.1 Hz, 2H), 7.03 (dt, J_1 = 2.4 Hz, J_2 = 9.1 Hz, 2H), 5.91 (d, J = 59.7 Hz, 1H), 4.37 (q, J = 7.1 Hz, 2H), 1.37 (t, J = 7.1 Hz, 3H); (^{13}C NMR, 101 MHz, $CDCl_3$): δ = 163.6 (d, J = 31.0 Hz), 154.8 (d, J = 3.2 Hz), 132.8, 119.3 (d, J = 1.6 Hz), 117.2, 102.4 (d, J = 232.9 Hz), 62.7, 14.0; (^{19}F NMR, 377 MHz, $CDCl_3$): δ = −129.9 (d, J = 60.7 Hz, 1F); IR: ν 1765, 1584, 1486, 1384, 1211, 1175, 1099, 1071, 1008, 965, 825; HRMS (ESI) for $C_{10}H_{10}BrFNaO_3$ $[M+Na]^+$ requires 298.9690 found 298.9688.

Ethyl (3-bromophenoxy)(fluoro)acetate (7e)

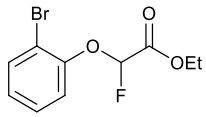


The title compound was prepared following General Procedure F using potassium carbonate (10.4 g, 75.0 mmol), 3-bromophenol (5.19 g, 30.0 mmol), ethyl bromofluoroacetate (5.32 mL, 45.0 mmol) and DMF (60 mL). The crude

product was purified by silica gel column chromatography (eluent: 10 % Et_2O in *n*-pentane) to provide the title compound (6.88 g, 83 % yield) as a colourless oil.

(^{1}H NMR, 400 MHz, $CDCl_3$): δ = 7.32−7.29 (m, 2H), 7.24−7.20 (m, 1H), 7.09−7.07 (m, 1H), 5.94 (q, *J* = 59.2, 1H), 4.37 (q, *J* = 7.1 Hz, 2H), 1.37 (t, *J* = 7.1 Hz, 3H); (^{13}C NMR, 101 MHz, $CDCl_3$): δ = 163.5 (d, *J* = 31.0 Hz), 156.2 (d, *J* = 2.4 Hz), 130.9, 127.6, 122.8, 121.0, 116.1, 102.2 (d, *J* = 233.7 Hz), 62.7, 13.9; (^{19}F NMR, 377 MHz, $CDCl_3$): δ = −130.0 (d, *J* = 59.0 Hz, 1F); IR: ν 1761, 1582, 1474, 1382, 1209, 1102, 1023, 965, 884; HRMS (ESI) for $C_{10}H_{10}BrFNaO_3$ $[M+Na]^+$ requires 298.9690 found 298.9686.

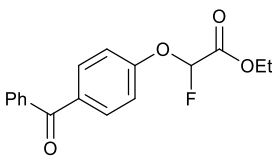
Ethyl (2-bromophenoxy)(fluoro)acetate (7f)



The title compound was prepared following General Procedure F using potassium carbonate (6.91 g, 50.0 mmol), 2-bromophenol (3.46 g, 20.0 mmol), ethyl bromofluoroacetate (3.55 mL, 30.0 mmol) and DMF (40 mL). The crude product was purified by silica gel column chromatography (eluent: 20 % Et_2O in *n*-pentane) to provide the title compound (4.68 g, 85 % yield) as a colourless oil.

(^{1}H NMR, 400 MHz, $CDCl_3$): δ = 7.60 (dd, J_1 = 1.5 Hz, J_2 = 7.8 Hz, 1H), 7.34−7.30 (m, 1H), 7.23 (dt, J_1 = 1.4 Hz, J_2 = 8.1 Hz, 1H), 7.08−7.04 (m, 1H), 5.91 (d, *J* = 59.2 Hz, 1H), 4.44−4.33 (m, 2H), 1.38 (t, *J* = 7.1 Hz, 3H); (^{13}C NMR, 101 MHz, $CDCl_3$): δ = 163.5 (d, *J* = 31.0 Hz), 152.5 (d, *J* = 3.2 Hz), 133.8, 128.8, 126.0, 119.2, 114.0 (d, *J* = 1.6 Hz), 103.0 (d, *J* = 233.7 Hz), 62.6, 14.0; (^{19}F NMR, 377 MHz, $CDCl_3$): δ = −130.0 (d, *J* = 59.0 Hz, 1F); IR: ν 1766, 1579, 1477, 1445, 1384, 1218, 1134, 1095, 1028, 965, 857; HRMS (EI/FI) for $C_{10}H_{10}BrFO_3$ $[M]^+$ requires 275.9797 found 275.9795.

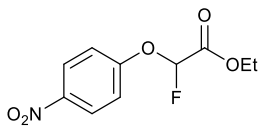
Ethyl (4-benzoylphenoxy)(fluoro)acetate (7g)



The title compound was prepared following General Procedure F using potassium carbonate (6.91 g, 50.0 mmol), 4-hydroxybenzo phenone (3.96 g, 20.0 mmol), ethyl bromofluoroacetate (3.55 mL, 30.0 mmol) and DMF (40 mL). The crude product was purified by silica gel column chromatography (eluent: 30 % Et_2O in *n*-pentane) to provide the title compound (5.50 g, 91 % yield) as a pale yellow oil.

(^{1}H NMR, 400 MHz, $CDCl_3$): δ = 7.85 (dt, J_1 = 2.3 Hz, J_2 = 8.8 Hz, 2H), 7.78–7.76 (m, 2H), 7.59 (tt, J_1 = 1.9 Hz, J_2 = 7.5 Hz, 1H), 7.51–7.47 (m, 2H), 7.21 (d, *J* = 8.6 Hz, 2H), 6.08 (d, *J* = 59.2 Hz, 1H), 4.38 (q, *J* = 7.2 Hz, 2H), 1.38 (t, *J* = 7.2 Hz, 3H); (^{13}C NMR, 101 MHz, $CDCl_3$): δ = 195.3, 163.5 (d, *J* = 31.0 Hz), 158.6 (d, *J* = 2.4 Hz), 137.5, 133.5, 132.4, 132.3, 129.8, 128.3, 116.6, 101.6 (d, J = 233.7 Hz), 62.8, 13.9; (^{19}F NMR, 377 MHz, $CDCl_3$): δ = –130.8 (d, *J* = 59.0 Hz, 1F); IR: ν 1766, 1656, 1600, 1505, 1447, 1278, 1218, 1174, 1151, 1096, 1025, 939, 924, 848; HRMS (ESI) for $C_{17}H_{16}FNaO_3$ $[M+H]^+$ requires 303.1027 found 303.1022.

Ethyl 2-fluoro-2-(4-nitrophenoxy)acetate (7h)

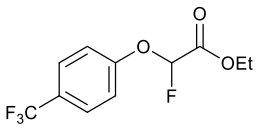


The title compound was prepared following General Procedure F using potassium carbonate (6.91 g, 50.0 mmol), 4-nitrophenol (2.78 g, 20.0 mmol), ethyl bromofluoroacetate (3.55 mL, 30.0 mmol) and DMF (40 mL). The crude product was purified by silica gel column chromatography (eluent: 50 % Et_2O in *n*-pentane) to provide the title compound (4.48 g, 92 % yield) as a pale yellow oil.

(^{1}H NMR, 400 MHz, $CDCl_3$): δ = 8.25 (dt, J_1 = 2.8 Hz, J_2 = 9.1 Hz, 2H), 7.23 (dt, J_1 = 2.6 Hz, J_2 = 9.1 Hz, 2H), 6.07 (d, *J* = 58.4 Hz, 1H), 4.38 (q, *J* = 7.2 Hz, 2H), 1.37 (t, *J* = 7.1 Hz, 3H); (^{13}C NMR, 101 MHz, $CDCl_3$): δ = 163.0 (d, *J* = 30.2 Hz), 159.8 (d, *J* = 2.4 Hz), 144.0,

125.9, 117.1 (d, *J* = 1.6 Hz), 101.2 (d, *J* = 235.2 Hz), 63.0, 13.9; (^{19}F NMR, 377 MHz, $CDCl_3$): δ = −132.0 (d, *J* = 59.0 Hz, 1F); IR: ν 1762, 1615, 1594, 1520, 1494, 1345, 1297, 1218, 1174, 1092, 1011, 965, 851; HRMS (ESI) for $C_{10}H_{10}ClFNaO_3$ $[M+Na]^+$ requires 243.0543 found 243.0.544.

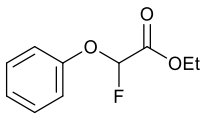
Ethyl fluoro[4-(trifluoromethyl)phenoxy]acetate (7i)



The title compound was prepared following General Procedure F using potassium carbonate (6.91 g, 50.0 mmol), 4-(trifluoromethyl)phenol (3.24 g, 20.0 mmol), ethyl bromofluoroacetate (3.55 mL, 30.0 mmol) and DMF (60 mL). The crude product was purified by silica gel column chromatography (eluent: 10 % Et_2O in *n*-pentane) to provide the title compound (4.74 g, 89 % yield) as a colourless oil.

(^{1}H NMR, 400 MHz, $CDCl_3$): δ = 7.63 (d, *J* = 8.6 Hz, 2H), 7.22 (d, *J* = 8.8 Hz, 2H), 6.02 (d, *J* = 59.2 Hz, 1H), 4.38 (q, *J* = 7.1 Hz, 2H), 1.37 (t, *J* = 7.2 Hz, 3H); (^{13}C NMR, 101 MHz, $CDCl_3$): δ = 163.3 (d, *J* = 31.0 Hz), 157.9, 127.3 (q, *J* = 4.0 Hz), 126.6 (q, *J* = 32.9 Hz), 123.9 (q, *J* = 271.5 Hz), 117.3 (d, *J* = 1.6 Hz), 101.8 (d, *J* = 233.7 Hz), 62.8, 13.9; (^{19}F NMR, 377 MHz, $CDCl_3$): δ = −62.1 (s, 3F), −130.9 (d, *J* = 59.0 Hz, 1F); IR: ν 1766, 1616, 1517, 1325, 1222, 1166, 1113, 1065, 1113, 1065, 1014, 966, 840; HRMS (EI/FI) for $C_{11}H_{10}F_4O_3$ $[M]^+$ requires 266.0566 found 266.0558.

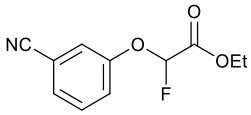
Ethyl fluoro(phenoxy)acetate (7o)



The title compound was prepared following General Procedure F using potassium carbonate (6.91 g, 50.0 mmol), phenol (1.88 g, 20.0 mmol), ethyl bromofluoroacetate (3.55 mL, 30.0 mmol) and DMF (40 mL). The crude product was purified by silica gel column chromatography (eluent: 20 % Et_2O in *n*-pentane) to provide the title compound (1.28 g, 32 % yield) as a colourless oil.

(^{1}H NMR, 400 MHz, $CDCl_3$): δ = 7.38–7.34 (m, 2H), 7.18–7.13 (m, 3H), 5.98 (d, *J* = 59.9 Hz, 1H), 4.37 (q, *J* = 7.1 Hz, 2H), 1.37 (t, *J* = 7.1 Hz, 3H); (^{13}C NMR, 101 MHz, $CDCl_3$): δ = 164.0 (d, *J* = 31.0 Hz), 155.8 (d, *J* = 3.2 Hz), 129.8, 124.4, 117.4, 102.6 (*J* = 232.1 Hz), 62.5, 14.0; (^{19}F NMR, 377 MHz, $CDCl_3$): δ = –129.2 (d, *J* = 60.7 Hz).

Ethyl (3-cyanophenoxy)(fluoro)acetate (7t)

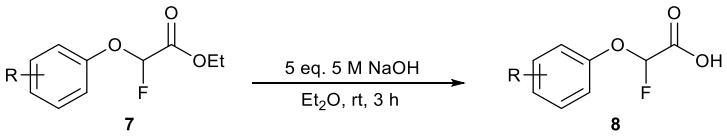


The title compound was prepared following General Procedure F using potassium carbonate (6.91 g, 50.0 mmol), 3-cyanophenol (2.38 g, 20.0 mmol), ethyl bromofluoroacetate (3.55 mL, 30.0 mmol) and DMF (40 mL). The crude product was purified by silica gel column chromatography (eluent: 25 % Et_2O in *n*-pentane) to provide the title compound (2.33 g, 52 % yield) as a white crystal.

(^{1}H NMR, 400 MHz, $CDCl_3$): δ = 7.50−7.44 (m, 2H), 7.41−7.36 (m, 2H), 5.97 (q, *J* = 58.9, 1H), 4.36 (q, *J* = 7.1 Hz, 2H), 1.36 (t, *J* = 7.1 Hz, 3H); (^{13}C NMR, 101 MHz, $CDCl_3$): δ = 163.1 (d, *J* = 30.2 Hz), 155.5 (d, *J* = 2.4 Hz), 130.8, 128.1, 122.1, 120.8, 117.8, 113.7, 101.9 (d, *J* = 233.7 Hz), 62.8, 13.9; (^{19}F NMR, 377 MHz, $CDCl_3$): δ = −130.9 (d, *J* = 59.0 Hz); IR: ν 2234, 1762, 1582, 1482, 1436, 1384, 1228, 1156, 1095, 1018, 966, 859; HRMS (EI/FI) for $C_{11}H_{10}FNO_3$ $[M]^+$ requires 223.0645 found 223.0647; Mp. 32−34 °C.

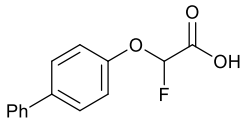
5.2.6 Synthesis of ArOCFHCO$_2$H (8)

General Procedure G



To a solution of the appropriate ester (5.0 mmol) in Et_2O (25 mL) was added 5 M aq. NaOH (25.0 mmol). The reaction mixture was stirred at room temperature for 3 hours before diluting with Et_2O (25 mL). The reaction mixture was extracted with sat. aq. $NaHCO_3$ (3 x 20 mL). The combined aqueous layers were acidified to pH 1 with 1 M HCl and extracted with Et_2O (3 x 20 mL), then the combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. Products were purified by washing with *n*-pentane.

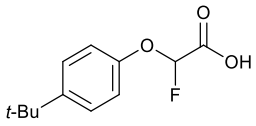
(Biphenyl-4-yloxy)fluoroacetic acid (8a)



The title compound was prepared following General Procedure G using ethyl (biphenyl-4-yloxy)fluoroacetate (2.19 g, 8.0 mmol), 5 M aq. NaOH (8 mL, 40.0 mmol) and Et_2O (40 mL); (1.89 g, 96 % yield, white solid).

(^{1}H NMR, 400 MHz, $CDCl_3$): δ = 7.53–7.47 (m, 4H), 7.37 (t, *J* = 7.6 Hz, 2H), 7.28 (tt, J_1 = 2.1 Hz, J_2 = 7.3 Hz, 1H) , 7.16 (d, *J* = 8.3 Hz, 2H), 6.15 (brs, 1H), 6.00 (d, *J* = 59.7 Hz, 1H); (^{13}C NMR, 101 MHz, $CDCl_3$): δ = 167.5 (d, *J* = 31.8 Hz), 155.1 (d, *J* = 2.4 Hz), 140.1, 138.0, 128.9, 128.6, 127.4, 127.0, 117.8, 102.5 (d, *J* = 232.1 Hz); (^{19}F NMR, 377 MHz, $CDCl_3$): δ = –129.5 (d, *J* = 59.0 Hz, 1F); IR: ν 3047, 1745, 1518, 1487, 1221, 1107, 1018, 838; HRMS (ESI) for $C_{14}H_{10}FO_3$ $[M-H]^-$ requires 245.0609 found 245.0618; Mp. 126−127 °C.

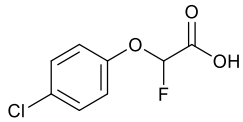
2-(4-(*tert*-Butyl)phenoxy)-2-fluoroacetic acid (8b)



The title compound was prepared following General Procedure G using ethyl (4-*tert*-butylphenoxy)(fluoro)acetate (2.03 g, 8.0 mmol), 5 M aq. NaOH (8 mL, 40.0 mmol) and Et_2O (40 mL); (1.48 g, 81 % yield, white solid).

(^{1}H NMR, 400 MHz, $CDCl_3$): δ = 9.15 (brs, 1H), 7.39 (dt, J_1 = 2.6 Hz, J_2 = 9.1 Hz, 2H), 7.09 (dt, J_1 = 2.3 Hz, J_2 = 8.6 Hz, 2H), 6.02 (d, J = 59.7 Hz, 1H), 1.33 (s, 9H); (^{13}C NMR, 101 MHz, $CDCl_3$): δ = 168.4 (d, J = 31.8 Hz), 153.4 (d, J = 3.2 Hz), 147.7, 126.7, 117.0, 102.3 (d, J = 231.3 Hz), 34.4, 31.4; (^{19}F NMR, 377 MHz, $CDCl_3$): δ = –129.2 (d, J = 60.7 Hz, 1F); IR: ν 3050, 2965, 1748, 1510, 1351, 1265, 1219, 1184, 1129, 1103, 1028, 961, 905, 830; HRMS (ESI) for $C_{12}H_{14}FO_3$ $[M\text{-}H]^-$ requires 225.0933 found 225.0931; Mp. 63−65 °C. Data consistent with literature values.[6]

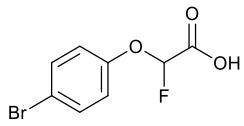
2-(4-Chlorophenoxy)-2-fluoroacetic acid (8c)



The title compound was prepared following General Procedure G using ethyl (4-chloromophenoxy)(fluoro)acetate (1.86 g, 8.0 mmol), 5 M aq. NaOH (8 mL, 40.0 mmol) and Et_2O (40 mL); (1.24 g, 76 % yield, white solid).

(^{1}H NMR, 400 MHz, DMSO-d6): δ = 14.20 (brs, 1H), 7.44 (dt, J_1 = 2.8 Hz, J_2 = 9.1 Hz, 2H), 7.18 (dt, J_1 = 2.8 Hz, J_2 = 9.1 Hz, 2H), 6.40 (d, J = 58.7 Hz, 1H); (^{13}C NMR, 101 MHz, DMSO-d6): δ = 165.2 (d, J = 29.4 Hz), 154.0 (d, J = 2.4 Hz), 129.8, 127.9, 118.6, 101.7 (d, J = 229.7 Hz); (^{19}F NMR, 377 MHz, DMSO-d6): δ = –132.8 (d, J = 59.0 Hz, 1F); IR: ν 3102, 2987, 1755, 1589, 1489, 1214, 1173, 1090, 1011, 962, 827; HRMS (ESI) for $C_8H_5ClFO_3$ $[M\text{-}H]^-$ requires 202.9917 found 202.9924; Mp. 77−79 °C.

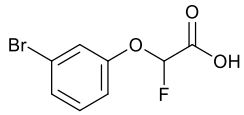
2-(4-Bromophenoxy)-2-fluoroacetic acid (8d)



The title compound was prepared following General Procedure G using ethyl (4-bromophenoxy)(fluoro)acetate (2.22 g, 8.0 mmol), 5 M aq. NaOH (8 mL, 40.0 mmol) and Et_2O (40 mL); (1.65 g, 83 % yield, white solid).

(^{1}H NMR, 400 MHz, DMSO-d6): δ = 14.25 (brs, 1H), 7.57 (dt, J_1 = 2.8 Hz, J_2 = 9.1 Hz, 2H), 7.13 (dt, J_1 = 2.6 Hz, J_2 = 9.1 Hz, 2H), 6.39 (d, J = 58.7 Hz, 1H); (^{13}C NMR, 101 MHz, DMSO-d6): δ = 165.1 (d, J = 29.4 Hz), 154.4, 132.7, 119.0, 115.7, 100.6 (d, J = 228.9 Hz); (^{19}F NMR, 377 MHz, DMSO-d6): δ = –132.8 (d, J = 59.0 Hz, 1F). Data consistent with literature values.[6]

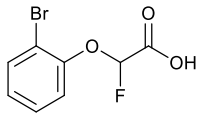
2-(3-Bromophenoxy)-2-fluoroacetic acid (8e)



The title compound was prepared following General Procedure G using ethyl (3-bromophenoxy)(fluoro)acetate (2.22 g, 8.0 mmol), 5 M aq. NaOH (8 mL, 40.0 mmol) and Et_2O (40 mL); (1.77 g, 89 % yield, white solid).

(^{1}H NMR, 400 MHz, $CDCl_3$): δ = 9.63 (brs, 1H), 7.36–7.35 (m, 2H), 7.27 (t, J = 8.3 Hz, 1H), 7.12 (dd, J_1 = 2.2 Hz, J_2 = 8.3 Hz, 1H), 6.04 (d, J = 58.9 Hz, 1H); (^{13}C NMR, 101 MHz, $CDCl_3$): δ = 168.0 (d, J = 31.8 Hz), 156.0 (d, J = 3.2 Hz), 131.0, 128.0, 123.0, 121.0, 116.1, 101.8 (d, J = 232.9 Hz); (^{19}F NMR, 377 MHz, $CDCl_3$): δ = –130.3 (d, J = 59.0 Hz, 1F); IR: ν 3550, 3083, 1772, 1709, 1589, 1473, 1357, 1272, 1223, 1106, 1049, 965, 908, 866; HRMS (EI/FI) for $C_8H_6BrFO_3$ $[M]^+$ requires 247.9484 found 247.9488; Mp. 64−67 °C. Data consistent with literature values.[6]

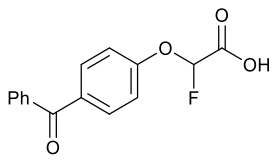
2-(2-Bromophenoxy)-2-fluoroacetic acid (8f)



The title compound was prepared following General Procedure G using ethyl (2-bromophenoxy)(fluoro)acetate (2.22 g, 8.0 mmol), 5 M aq. NaOH (8 mL, 40.0 mmol) and Et_2O (40 mL); (1.65 g, 83 % yield, white solid).

(^{1}H NMR, 400 MHz, DMSO-d6): δ = 14.28 (brs, 1H), 7.68 (dd, J_1 = 1.5 Hz, J_2 = 7.8 Hz, 1H), 7.43 (td, J_1 = 1.5 Hz, J_2 = 7.8 Hz, 2H), 7.33 (d, J = 8.3 Hz, 1H), 7.11 (td, J_1 = 1.5 Hz, J_2 = 7.2 Hz, 1H); (^{13}C NMR, 101 MHz, DMSO-d6): δ = 165.0 (d, J = 29.4 Hz), 151.8, 133.6, 129.8, 125.6, 117.2, 112.2, 102.0 (d, J = 230.5 Hz); (^{19}F NMR, 377 MHz, DMSO-d6): δ = –132.5 (d, J = 59.0 Hz, 1F); IR: ν 2978, 2362, 1755, 1580, 1479, 1442, 1359, 1281, 1228, 1170, 1140, 1114, 1022, 920; HRMS (EI/FI) for $C_8H_5O_3BrF$ $[M-H]^-$ requires 246.9401 found 246.9393; Mp. 58−60 °C.

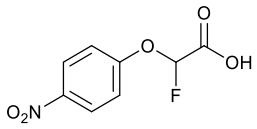
2-(4-Benzoylphenoxy)-2-fluoroacetic acid (8g)



The title compound was prepared following General Procedure G using ethyl (4-benzoylphenoxy)(fluoro)acetate (2.42 g, 8.0 mmol), 5 M aq. NaOH (8 mL, 40.0 mmol) and Et_2O (40 mL); (2.07 g, 94 % yield, white solid).

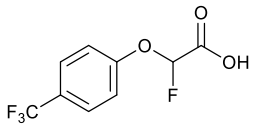
(^{1}H NMR, 400 MHz, DMSO-d6): δ = 7.81 (dt, J_1 = 2.4 Hz, J_2 = 9.1 Hz, 2H), 7.73–7.71 (m, 2H), 7.67 (tt, J_1 = 1.9 Hz, J_2 = 7.3 Hz, 1H), 7.56 (t, J = 7.6 Hz, 2H), 7.32 (d, J = 8.6 Hz, 2H), 6.56 (d, J = 58.2 Hz, 1H); (^{13}C NMR, 101 MHz, DMSO-d6): δ = 194.5, 165.2 (d, J = 29.4 Hz), 158.3 (d, J = 2.4 Hz), 137.2, 132.6, 132.5, 132.2, 129.5, 128.6, 116.3, 101.0 (d, J = 230.5 Hz); (^{19}F NMR, 377 MHz, DMSO-d6): δ = –133.5 (d, J = 59.0 Hz, 1F); IR: ν 3550, 2362, 1708, 1647, 1599, 1281, 1227, 1108, 1043, 923, 845; HRMS (ESI) for $C_{15}H_{12}FO_4$ $[M+H]^+$ requires 275.0714 found 275.0715; Mp. 106−108 °C.

2-Fluoro-2-(4-nitrophenoxy)acetic acid (8h)



The title compound was prepared following General Procedure G using ethyl 2-fluoro-2-(4-nitrophenoxy)acetate (2.92 g, 12.0 mmol), 5 M aq. NaOH (12 mL, 60.0 mmol) and Et_2O (60 mL); (2.44 g, 95 % yield, white solid). (^{1}H NMR, 400 MHz, DMSO-d6): δ = 8.29 (dt, J_1 = 2.8 Hz, J_2 = 9.3 Hz, 2H), 7.38 (dt, J_1 = 2.6 Hz, J_2 = 9.1 Hz, 2H), 6.61 (d, J = 57.7 Hz, 1H); (^{13}C NMR, 101 MHz, DMSO-d6): δ = 164.8 (d, J = 28.6 Hz), 159.7 (d, J = 2.4 Hz), 143.3, 126.0, 117.0, 100.9 (d, J = 230.5 Hz); (^{19}F NMR, 377 MHz, DMSO-d6): δ = –134.7 (d, J = 57.2 Hz, 1F); IR: ν 3226, 1787, 1594, 1512, 1494, 1347, 1240, 1171, 1114, 1017, 856; HRMS (ESI) for $C_8H_5FNO_5$ $[M-H]^-$ requires 214.0157 found 214.0162; Mp. 113−115 °C.

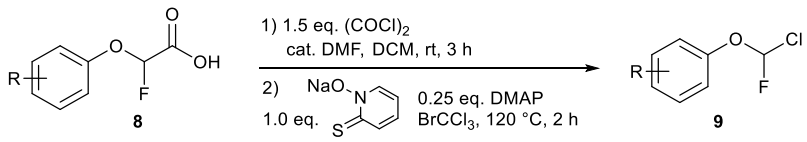
2-Fluoro-2-(4-(trifluoromethyl)phenoxy)acetic acid (8i)



The title compound was prepared following General Procedure G using ethyl fluoro[4-(trifluoromethyl)phenoxy]acetate (2.13 g, 8.0 mmol), 5 M aq. NaOH (8 mL, 40.0 mmol) and Et_2O (40 mL); (1.81 g, 95 % yield, white solid). (^{1}H NMR, 400 MHz, $CDCl_3$): δ = 9.47 (brs, 1H), 7.66 (d, J = 8.6 Hz, 2H), 7.25 (d, J = 8.6 Hz, 2H), 6.10 (d, J = 58.9 Hz, 1H); (^{13}C NMR, 101 MHz, $CDCl_3$): δ = 168.0 (d, J = 31.8 Hz), 157.7, 127.7 (q, J = 3.7 Hz), 127.0 (q, J = 33.4 Hz), 123.8 (q, J = 271.8 Hz), 117.3, 101.4 (d, J = 234.4 Hz); (^{19}F NMR, 377 MHz, $CDCl_3$): δ = –62.1 (s, 3F), –131.2 (d, J = 59.0 Hz, 1F); IR: ν 2929, 1745, 1614, 1517, 1357, 1324, 1275, 1230, 1171, 1122, 1063, 1044, 1015, 836; HRMS (EI/FI) for $C_{10}H_6F_4O_3$ $[M]^+$ requires 238.0253 found 238.0254; Mp. 72−75 °C.

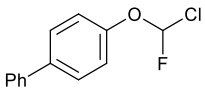
5.2.7 Synthesis of ArOCFClH (9)

General Procedure H



To a solution of an appropriate carboxylic acid (1.0 mmol) in CH_2Cl_2 (2 mL) was added DMF (0.10 mmol) and oxalyl chloride (1.5 mmol) at 0 ˚C. The reaction mixture was stirred at room temperature for 3 hours, then concentrated *in vacuo*. To the crude acyl chloride was added $BrCCl_3$ (3 mL), 4-dimethylaminopyridine (0.25 mmol) and sodium-*N*-hydroxy-2-thiopyridone (1.0 mmol). The reaction mixture was refluxed at 120 ˚C for 2 hours then concentrated *in vacuo*. The crude product was purified by silica gel column chromatography.

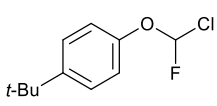
4-(Chlorofluoromethoxy)-1,1'-biphenyl (9a)



The title compound was prepared following General Procedure H using biphenyl-4-yloxy)fluoroacetic acid (246 mg, 1.0 mmol), DCM (2 mL), DMF (7.7 µL, 0.1 mmol), oxalyl chloride (129 µL, 1.5 mmol), $BrCCl_3$ (3 mL), 4-dimethylaminopyridine (30.5 mg, 0.25 mmol) and sodium-*N*-hydroxy-2-thiopyridone (149 mg, 1.0 mmol). The crude product was purified by silica gel column chromatography (eluent: 1 % Et_2O in *n*-pentane) to provide the title compound (70.2 mg, 30 % yield) as a white solid.

(^{1}H NMR, 400 MHz, $CDCl_3$): δ = 7.51–7.45 (m, 5H), 7.37–7.33 (m, 2H), 7.15 (d, *J* = 60.6 Hz, 1H), 7.15–7.11 (m, 2H); (^{13}C NMR, 101 MHz, $CDCl_3$): δ = 151.6, 140.0, 138.7, 128.8, 128.4, 127.4, 127.0, 120.1, 112.2 (d, *J* = 273.4 Hz); (^{19}F NMR, 377 MHz, $CDCl_3$): δ = –73.3 (d, *J* = 60.7 Hz, 1F); IR: ν 3034, 1608, 1516, 1485, 1451, 1353, 1294, 1213, 1186, 1105, 1008, 860; HRMS (EI/FI) for $C_{13}H_{10}ClFO$ $[M]^+$ requires 236.0404 found 236.0365; Mp. 32−34 °C.

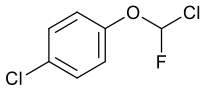
1-(*tert*-Butyl)-4-(chlorofluoromethoxy)benzene (9b)



The title compound was prepared following General Procedure H using 2-(4-(*tert*-butyl)phenoxy)-2-fluoroacetic acid (1.10 g, 4.0 mmol), DCM (8 mL), DMF (30.8 µL, 0.4 mmol), oxalyl chloride (515 µL, 6.0 mmol), $BrCCl_3$ (12 mL), 4-dimethylaminopyridine (122 mg, 1.0 mmol) and sodium-*N*-hydroxy-2-thiopyridone (596 mg, 4.0 mmol). The crude product was purified by silica gel column chromatography (eluent: 1 % Et_2O in *n*-pentane) to provide the title compound (105 mg, 12 % yield) as pale yellow oil.

(^{1}H NMR, 400 MHz, $CDCl_3$): δ = 7.39 (dt, J_1 = 2.7 Hz, J_2 = 8.8 Hz, 2H), 7.10 (d, J = 60.9 Hz, 1H), 7.12–7.08 (m, 2H), 1.33 (s, 9H); (^{13}C NMR, 101 MHz, $CDCl_3$): δ = 150.0, 148.5, 126.6, 119.3, 112.4 (d, J = 272.6 Hz), 34.4, 31.4; (^{19}F NMR, 377 MHz, $CDCl_3$): δ = –73.0 (d, J = 62.4 Hz, 1F); IR: ν 2964, 1510, 1365, 1294, 1203, 1174, 1121, 1093, 1014, 829; HRMS (EI/FI) for $C_{11}H_{14}ClFO$ $[M]^+$ requires 216.0717 found 216.0724.

1-Chloro-4-(chlorofluoromethoxy)benzene (9c)

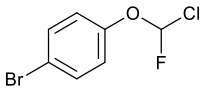


The title compound was prepared following General Procedure H using 2-(4-chlorophenoxy)-2-fluoroacetic acid (818 mg, 4.0 mmol), DCM (8 mL), DMF (30.8 µL, 0.4 mmol), oxalyl chloride (515 µL, 6.0 mmol), $BrCCl_3$ (12 mL), 4-dimethylaminopyridine (122 mg, 1.0 mmol) and sodium-*N*-hydroxy-2-thiopyridone (596 mg, 4.0 mmol). The crude product was purified by silica gel column chromatography (eluent: 0.5 % Et_2O in *n*-pentane) to provide the title compound (248 mg, 32 % yield) as colourless oil.

(^{1}H NMR, 400 MHz, $CDCl_3$): δ = 7.35 (dt, J_1 = 2.8 Hz, J_2 = 8.8 Hz, 2H), 7.20 (d, J = 60.4 Hz, 1H), 7.14–7.10 (s, 2H); (^{13}C NMR, 101 MHz, $CDCl_3$): δ = 150.5, 131.1, 129.7, 121.6, 111.9 (d, J = 275.0); (^{19}F NMR, 377 MHz, $CDCl_3$): δ = –73.9 (d, J = 60.7 Hz, 1F); IR: ν

1414, 1324, 1272, 1172, 1131, 1099, 1070, 1053, 1020, 961, 889, 830; HRMS (EI/FI) for $C_7H_5Cl_2FO$ $[M]^+$ requires 193.9701 found 193.9694.

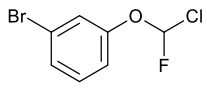
1-Bromo-4-(chlorofluoromethoxy)benzene (9d)



The title compound was prepared following General Procedure H using 2-(4-bromophenoxy)-2-fluoroacetic acid (996 mg, 4.0 mmol), DCM (8 mL), DMF (30.8 µL, 0.4 mmol), oxalyl chloride (515 µL, 6.0 mmol), $BrCCl_3$ (12 mL), 4-dimethylaminopyridine (122 mg, 1.0 mmol) and sodium-*N*-hydroxy-2-thiopyridone (596 mg, 4.0 mmol). The crude product was purified by silica gel column chromatography (eluent: 1 % Et_2O in *n*-pentane) to provide the title compound (283 mg, 30 % yield) as a colourless oil.

(^{1}H NMR, 400 MHz, $CDCl_3$): δ = 7.51 (dt, J_1 = 2.7 Hz, J_2 = 9.1 Hz, 2H), 7.20 (d, J = 60.2 Hz, 1H), 7.51 (dtd, J_1 = 0.7 Hz, J_2 = 2.7 Hz, J_3 = 9.1 Hz, 2H); (^{13}C NMR, 101 MHz, $CDCl_3$): δ = 151.0, 132.7, 121.9, 118.7, 111.8 (d, J = 275.0 Hz); (^{19}F NMR, 377 MHz, $CDCl_3$): δ = –73.9 (d, J = 59.0 Hz, 1F); IR: ν 1484, 1294, 1195, 1099, 1067, 1009, 851, 823; HRMS (EI/FI) for $C_7H_5BrClFO$ $[M]^+$ requires 237.9196 found 237.9198.

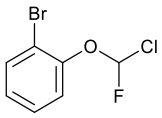
1-Bromo-3-(chlorofluoromethoxy)benzene (9e)



The title compound was prepared following General Procedure H using 2-(3-bromophenoxy)-2-fluoroacetic acid (996 mg, 4.0 mmol), DCM (8 mL), DMF (30.8 µL, 0.4 mmol), oxalyl chloride (515 µL, 6.0 mmol), $BrCCl_3$ (12 mL), 4-dimethylaminopyridine (122 mg, 1.0 mmol) and sodium-*N*-hydroxy-2-thiopyridone (596 mg, 4.0 mmol). The crude product was purified by silica gel column chromatography (eluent: 1 % Et_2O in *n*-pentane) to provide the title compound (308 mg, 32 % yield) as a pale yellow oil.

(^{1}H NMR, 400 MHz, $CDCl_3$): δ = 7.30–7.25 (m, 2H), 7.18–7.14 (m, 1.5H), 7.04–7.01 (m, 1.5H); (^{13}C NMR, 101 MHz, $CDCl_3$): δ = 152.6, 130.8, 128.8, 123.4, 122.7, 118.9, 111.8 (d, *J* = 275.0 Hz); (^{19}F NMR, 377 MHz, $CDCl_3$): δ = –74.1 (d, *J* = 60.7 Hz, 1F); IR: ν 1582, 1472, 1427, 1293, 1189, 1092, 1065, 1017, 877, 832; HRMS (EI/FI) for $C_7H_5BrClFO$ $[M]^+$ requires 237.9196 found 237.9247.

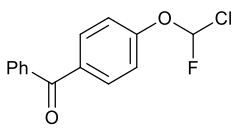
1-Bromo-2-(chlorofluoromethoxy)benzene (9f)



The title compound was prepared following General Procedure H using 2-(2-bromophenoxy)-2-fluoroacetic acid (996 mg, 4.0 mmol), DCM (8 mL), DMF (30.8 µL, 0.4 mmol), oxalyl chloride (515 µL, 6.0 mmol), $BrCCl_3$ (12 mL), 4-dimethylaminopyridine (122 mg, 1.0 mmol) and sodium-*N*-hydroxy-2-thiopyridone (596 mg, 4.0 mmol). The crude product was purified by silica gel column chromatography (eluent: 1 % Et_2O in *n*-pentane) to provide the title compound (385 mg, 40 % yield) as a colourless oil.

(^{1}H NMR, 400 MHz, $CDCl_3$): δ = 7.64 (dd, J_1 = 1.5 Hz, J_2 = 8.1 Hz, 1H), 7.37–7.29 (m, 2.5H), 7.15–7.11 (m, 1.5H); (^{13}C NMR, 101 MHz, $CDCl_3$): δ = 149.4, 133.9, 128.6, 127.0, 121.7, 115.3 (d, *J* = 1.6 Hz), 112.4 (d, *J* = 275.0 Hz); (^{19}F NMR, 377 MHz, $CDCl_3$): δ = –74.0 (d, *J* = 60.7 Hz, 1F); IR: ν 1474, 1444, 1295, 1210, 1084, 1017, 871, 814; HRMS (EI/FI) for $C_7H_5BrClFO$ $[M]^+$ requires 237.9196 found 237.9196.

(4-(Chlorofluoromethoxy)phenyl)(phenyl)methanone (9g)

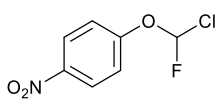


The title compound was prepared following General Procedure H using 2-(4-benzoylphenoxy)-2-fluoroacetic acid (1.10 g, 4.0 mmol), DCM (8 mL), DMF (30.8 µL, 0.4 mmol), oxalyl chloride (515 µL, 6.0 mmol), $BrCCl_3$ (12 mL), 4-dimethylaminopyridine (122 mg, 1.0 mmol) and sodium-*N*-hydroxy-2-thiopyridone (596

mg, 4.0 mmol). The crude product was purified by silica gel column chromatography (eluent: 15 % Et_2O in *n*-pentane) to provide the title compound (210 mg, 20 % yield) as pale yellow oil.

(^{1}H NMR, 400 MHz, $CDCl_3$): δ = 7.79 (dt, J_1 = 2.3 Hz, J_2 = 8.8 Hz, 2H), 7.72–7.70 (m, 2H), 7.53 (tt, J_1 = 2.0 Hz, J_2 = 7.5 Hz, 1H), 7.44–7.40 (m, 2H), 7.30–7.15 (m, 3H); (^{13}C NMR, 101 MHz, $CDCl_3$): δ = 195.3, 155.2, 137.4, 134.5, 132.5, 132.1, 129.9, 128.4, 118.9, 111.5 (d, J = 275.0 Hz); (^{19}F NMR, 377 MHz, $CDCl_3$): δ = –75.2 (d, J = 60.7 Hz, 1F); IR: ν 1656, 1599, 1503, 1447, 1277, 1214, 1170, 1087, 1015, 923, 847; HRMS (EI/FI) for $C_{14}H_{10}ClFO_2$ $[M]^+$ requires 264.0353 found 264.0351.

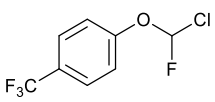
1-(Chlorofluoromethoxy)-4-nitrobenzene (9h)



The title compound was prepared following General Procedure H using 2-fluoro-2-(4-nitrophenoxy)acetic acid (861 mg, 4.0 mmol), DCM (8.0 mL), DMF (30.8 µL, 0.4 mmol), oxalyl chloride (515 µL, 6.0 mmol), $BrCCl_3$ (12 mL), 4-dimethylaminopyridine (122 mg, 1.0 mmol) and sodium-*N*-hydroxy-2-thiopyridone (596 mg, 4.0 mmol). The crude product was purified by silica gel column chromatography (eluent: 20 % Et_2O in *n*-pentane) to provide the title compound (319 mg, 39 % yield) as a pale yellow oil.

(^{1}H NMR, 400 MHz, $CDCl_3$): δ = 8.28 (dt, J_1 = 2.8 Hz, J_2 = 9.3 Hz, 2H), 7.32 (d, J = 60.7 Hz, 1H), 7.30 (dt, J_1 = 2.7 Hz, J_2 = 8.8 Hz, 2H), 7.24; (^{13}C NMR, 101 MHz, $CDCl_3$): δ = 156.4, 144.8, 125.6, 119.7, 111.1 (t, J = 276.6 Hz); (^{19}F NMR, 377 MHz, $CDCl_3$): δ = –76.6 (d, J = 59.0 Hz, 2F); IR: ν 1615, 1594, 1520, 1493, 1344, 1299, 1219, 1173, 1077, 1013, 872, 848; HRMS (EI/FI) for $C_7H_5ClFNO_3$ $[M]^+$ requires 204.9942 found 204.9939.

1-(Chlorofluoromethoxy)-4-(trifluoromethyl)benzene (9i)

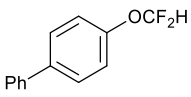


The title compound was prepared following General Procedure H using 2-fluoro-2-(4-(trifluoromethyl)phenoxy)acetic acid (952 mg, 4.0 mmol), DCM (8 mL), DMF (30.8 µL, 0.4 mmol), oxalyl chloride (515 µL, 6.0 mmol), $BrCCl_3$ (12 mL), 4-dimethylaminopyridine (122 mg, 1.0 mmol) and sodium-*N*-hydroxy-2-thiopyridone (596 mg, 4.0 mmol). The crude product was purified by silica gel column chromatography (eluent: 1 % Et_2O in *n*-pentane) to provide the title compound (163 mg, 18 % yield) as a colourless oil.

(^{1}H NMR, 400 MHz, $CDCl_3$): δ = 7.67 (d, *J* = 8.6 Hz, 2H), 7.28 (d, *J* = 8.8 Hz, 2H), 7.27 (d, *J* = 60.2 Hz, 2H); (^{13}C NMR, 101 MHz, $CDCl_3$): δ = 154.4, 128.0 (q, *J* = 3.7 Hz), 127.1 (q, *J* = 33.4 Hz), 123.8 (q, *J* = 271.8 Hz), 119.8 (d, *J* = 1.6 Hz), 111.5 (d, *J* = 275.8 Hz); (^{19}F NMR, 377 MHz, $CDCl_3$): δ = –62.3 (s, 3F), –75.1 (d, *J* = 60.7 Hz, 1F); IR: ν 1616, 1515, 1423, 1325, 1207, 1168, 1104, 1104, 1060, 1015, 865, 838; HRMS (EI/FI) for $C_8H_5ClF_4O$ $[M]^+$ requires 227.9965 found 227.9940.

5.2.8 Synthesis of $ArOCF_2H$ (10)

4-(Difluoromethoxy)biphenyl (10a)

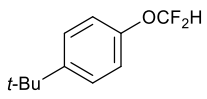


Into a pressure tube containing a mixture of 4-Phenylphenol (85.1 mg, 0.5 mmol) and aqueous KOH (1.5 mL, 25 wt%, ca. 8 mmol), was added chlorodifluoroacetophenone (476 mg, 2.5 mmol) (dissolved in MeCN (1.5 mL)) at -78 °C. The reaction tube was sealed and heated to 80 °C for 4 hr. The reaction was quenched by addition of water, and the aqueous phase was extracted with Et_2O (x2). The combined organic phases were washed with brine, then dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Trifluorotoluene (61.4 µL, 0.50 mmol) was added as an internal standard and the yield was calculated to be 62 % by ^{19}F NMR spectroscopy. Purification by

column chromatography on SiO_2 gel (EtOAc/*n*-hexane = 1:40) gave the title compound (51.3 mg, 47 %) as a colourless crystal.

(^{1}H NMR, 400 MHz, $CDCl_3$): δ = 7.49-7.45 (m, 4H), 7.35 (t, *J* = 7.4 Hz, 2H), 7.26 (tt, J_1 = 2.0 Hz, J_2 = 7.3 Hz, 1H), 7.09 (d, *J* = 8.6 Hz, 2H), 6.44 (t, *J* = 74.0 Hz, 1H); (^{13}C NMR, 101 MHz, $CDCl_3$): δ = 150.6, 140.1, 138.6, 128.9, 128.5, 127.5, 127.1, 119.9, 116.0 (t, *J* = 259.9 Hz); (^{19}F NMR, 377 MHz, $CDCl_3$): δ = –81.9 (d, *J* = 74.6 Hz, 2F). Data consistent with literature values.[7]

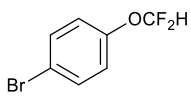
1-*tert*-Butyl-4-(difluoromethoxy)benzene (10b)



To a Schlenck tube was added (4-*tert*-butylphenoxy)(difluoro)acetic acid (122 mg, 0.50 mmol), Selectfluor™ (708 mg, 2.0 mmol) and $AgNO_3$ (17 mg, 0.10 mmol). The Schlenck tube was purged with nitrogen and acetone (8 mL) and water (2 mL) were added, after which the reaction was stirred at 55 °C for 1 h. The reaction mixture was diluted with H_2O (20 mL) and extracted with CH_2Cl_2 (3 × 10 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography (eluent: 1 % Et_2O in *n*-pentane) to provide the title compound (78 mg, 78 % yield) as a colourless oil.

(^{1}H NMR, 400 MHz, $CDCl_3$): δ = 7.38 (dt, J_1 = 2.6 Hz, J_2 = 8.8 Hz, 2H), 7.06 (d, *J* = 8.8 Hz, 2H), 6.49 (t, *J* = 74.3 Hz, 1H), 1.33 (s, 9H); (^{13}C NMR, 101 MHz, $CDCl_3$): δ = 148.9 (t, *J* = 2.8 Hz), 148.4, 126.7, 119.1, 116.1 (t, *J* = 259.1 Hz), 34.4, 31.4; (^{19}F NMR, 377 MHz, $CDCl_3$): δ = –80.4 (d, *J* = 74.6 Hz, 2F). Data consistent with literature values.[8]

1-Bromo-4-(difluoromethoxy)benzene (10d)

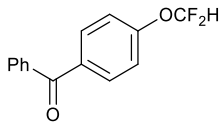


The title compound was prepared following General Procedure A using potassium carbonate (6.91 g, 50.0 mmol), 4-bromophenol (3.46 g, 20.0

mmol), ethyl bromodifluoroacetate (3.85 mL, 30.0 mmol) and DMF (40 mL). The crude product was purified by silica gel column chromatography (eluent: 3 % Et_2O in *n*-pentane) to provide the title compound (1.16 g, 26 % yield) as a colourless oil.

(^{1}H NMR, 400 MHz, $CDCl_3$): δ = 7.49 (dt, J_1 = 2.7 Hz, J_2 = 9.1 Hz, 2H), 7.04–7.01 (m, 2H), 6.49 (t, J = 73.4 Hz, 1H); (^{13}C NMR, 101 MHz, $CDCl_3$): δ = 150.0, 132.8, 121.5, 118.5, 115.6 (t, J = 261.5 Hz); (^{19}F NMR, 377 MHz, $CDCl_3$): δ = –81.2 (d, J = 72.8 Hz, 2F). Data consistent with literature values.[2]

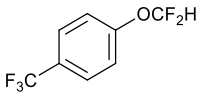
[4-(Difluoromethoxy)phenyl](phenyl)methanone (10g)



The title compound was prepared following General Procedure A using potassium carbonate (6.91 g, 50.0 mmol), 4-hydroxybenzophenone (3.96 g, 20.0 mmol), ethyl bromodifluoroacetate (3.85 mL, 30.0 mmol) and DMF (40 mL). The crude product was purified by silica gel column chromatography (eluent: 5 % Et_2O in *n*-pentane) to provide the title compound (1.33 g, 27 % yield) as a colourless oil.

(^{1}H NMR, 400 MHz, $CDCl_3$): δ = 7.86 (dt, J_1 = 2.3 Hz, J_2 = 8.8 Hz, 2H), 7.80–7.77 (m, 2H), 7.61 (tt, J_1 = 1.9 Hz, J_2 = 7.5 Hz, 1H), 7.52–7.48 (m, 2H), 7.22 (d, J = 8.8 Hz, 2H), 6.63 (t, J = 73.1 Hz, 1H); (^{13}C NMR, 101 MHz, $CDCl_3$): δ = 195.3, 154.2 (t, J = 2.8 Hz), 137.4, 134.4, 132.5, 132.2, 129.9, 128.4, 118.6, 115.4 (t, J = 256.5 Hz); (^{19}F NMR, 377 MHz, $CDCl_3$): δ = –81.7 (d, J = 72.8 Hz, 2F). Data consistent with literature values.[9]

1-(Difluoromethoxy)-4-(trifluoromethyl)benzene (10i)

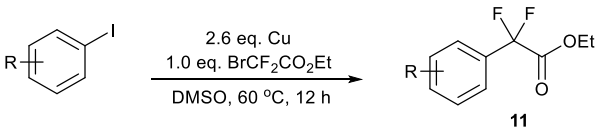


The title compound was prepared following General Procedure A using potassium carbonate (6.91 g, 50.0 mmol), 4-(trifluoromethyl)phenol (3.24 g, 20.0 mmol), ethyl bromodifluoroacetate (3.85 mL, 30.0 mmol) and DMF (40 mL). The crude product was purified by silica gel column chromatography (eluent: 1 % Et_2O in *n*-pentane) to provide the title compound (957 mg, 23 % yield) as a colourless oil.

(^{1}H NMR, 400 MHz, $CDCl_3$): δ = 7.66 (d, *J* = 8.6 Hz, 2H), 7.24 (d, *J* = 8.6 Hz, 2H), 6.58 (t, *J* = 72.9 Hz, 1H); (^{13}C NMR, 101 MHz, $CDCl_3$): δ = 153.5, 127.6 (q, *J* = 33.1 Hz), 127.2 (q, *J* = 3.7 Hz), 123.8 (q, *J* = 271.8 Hz), 119.5, 115.4 (t, *J* = 261.9 Hz); (^{19}F NMR, 377 MHz, $CDCl_3$): δ = –62.3 (s, 3F), –81.8 (d, *J* = 72.8 Hz, 2F) ; IR: ν 2363, 2342, 1327, 1127, 1064, 1017, 843; HRMS (EI/FI) for $C_8H_5F_5O_3$ $[M]^+$ requires 212.0261 found 212.0265.

5.2.9 Synthesis of $ArCF_2CO_2Et$ (11)

General Procedure I

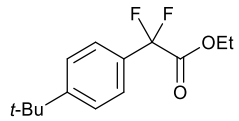


11

To a suspension of activated Cu powder (1.7 g, 26 mmol) in DMSO (26 mL) was added the appropriate aryl iodide (10 mmol) and ethyl bromodifluoroacetate (1.3 mL, 10 mmol) under nitrogen atmosphere. The reaction mixture was stirred at 60 °C for 12 hr. The reaction mixture was filtered through a pad of Celite® and washed with Et_2O. The mixture was washed with sat. aq. NH_4Cl (2 × 50 mL) and brine (2 × 50 mL), then dried over MgSO4, filtered and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography.

Activation of Cu powder: Copper powder (26 mmol) was stirred vigorously in diluted aq. HCl (1 M, 10 mL) for 10 minutes at room temperature and filtered. This procedure was repeated with water (10 mL), MeOH (10 mL) and acetone (10 mL), respectively. Finally, the copper powder was dried under vacuum for 15 minutes before use.

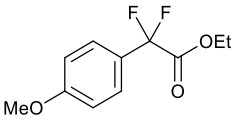
Ethyl 2-(4-(tert-butyl)phenyl)-2,2-difluoroacetate (11b)



The title compound was prepared following General Procedure I using 4-iodobenzotrifluoride (5.20 g, 20 mmol), ethyl bromodifluoroacetate (2.56 mL, 20 mmol), Cu powder (3.30 g, 52 mmol) and DMSO (52 mL). The crude product was purified by silica gel column chromatography (eluent: 5 % Et_2O in *n*-pentane) to provide the title compound (2.22 g, 43 % yield) as a pale yellow oil.

(^{1}H NMR, 400 MHz, $CDCl_3$): δ = 7.55 (d, *J* = 8.8 Hz, 2H), 7.48 (d, *J* = 8.8 Hz, 2H), 4.31 (q, *J* = 7.1 Hz, 2H), 1.35−1.31 (m, 12H); (^{13}C NMR, 101 MHz, $CDCl_3$): δ = 164.4 (t, *J* = 35.4 Hz), 154.3, 129.9 (t, *J* = 25.4 Hz), 125.6, 125.2 (t, *J* = 6.0 Hz), 113.6 (t, *J* = 251.5 Hz), 63.0, 34.8, 31.1, 13.9; (^{19}F NMR, 377 MHz, $CDCl_3$): δ = −103.2 (s, 2F). Data consistent with literature values.[10]

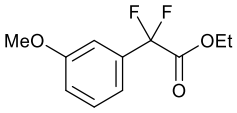
Ethyl 2,2-difluoro-2-(4-methoxyphenyl)acetate (11d)



The title compound was prepared following General Procedure I using 4-iodoanisole (4.68 g, 20 mmol), ethyl bromodifluoroacetate (2.56 mL, 20 mmol), Cu powder (3.30 g, 52 mmol) and DMSO (52 mL). The crude product was purified by silica gel column chromatography (eluent: 10 % Et_2O in *n*-pentane) to provide the title compound (2.05 g, 45 % yield) as a colourless oil.

(^{1}H NMR, 400 MHz, $CDCl_3$): δ = 7.54 (d, *J* = 9.1 Hz, 2H), 6.96 (d, *J* = 8.8 Hz, 2H), 4.30 (q, *J* = 7.1 Hz, 2H), 3.84 (s, 3H), 1.32 (t, *J* = 7.1 Hz, 3H); (^{13}C NMR, 101 MHz, $CDCl_3$): δ = 164.4 (t, *J* = 36.2 Hz), 161.6, 127.0 (t, *J* = 5.9 Hz), 124.9 (t, *J* = 25.8 Hz) 114.0, 113.5 (t, *J* = 251.9 Hz), 63.0, 55.4, 13.9; (^{19}F NMR, 377 MHz, $CDCl_3$): δ = −102.6 (s, 2F). Data consistent with literature values.[11]

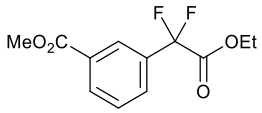
Ethyl 2,2-difluoro-2-(3-methoxyphenyl)acetate (11f)



The title compound was prepared following General Procedure I using 1-iodo-3-methoxybenzene (595 µL, 5.00 mmol), ethyl bromodifluoroacetate (641 µL, 5.00 mmol), Cu powder (826 mg, 13.0 mmol) and DMSO (13 mL). The crude product was purified by silica gel column chromatography (eluent: 0-15 % Et_2O in *n*-pentane) to provide the title compound (897 mg, 3.90 mmol, 78 %) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37 (t, *J* = 8.1 Hz, 1H), 7.19 (d, *J* = 7.8 Hz, 1H), 7.14 (s, 1H), 7.03 (dd, *J* = 2.3, 8.4 Hz, 1H), 4.31 (q, *J* = 7.1 Hz, 2H), 3.84 (s, 3H), 1.32 (t, *J* = 7.1 Hz, 3H); (^{13}C NMR, 101 MHz, $CDCl_3$) δ = 164.2 (t, *J* = 35.2 Hz), 159.7, 134.1 (t, *J* = 25.3 Hz), 129.8, 117.7 (t, *J* = 6.2 Hz), 116.9, 113.2 (t, *J* = 253.4 Hz), 110.7 (t, *J* = 6.4 Hz), 63.2, 55.4, 13.9; (^{19}F NMR, 377 MHz, $CDCl_3$) δ = -103.8 (s, 2F). Data consistent with literature values.[10]

Methyl 3-(2-ethoxy-1,1-difluoro-2-oxoethyl)benzoate (11i)

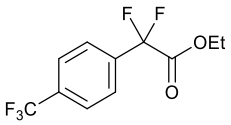


The title compound was prepared following General Procedure I using methyl 3-iodobenzoate (2.36 g, 9.00 mmol), ethyl bromodifluoroacetate (1.15 mL, 9.00 mmol), Cu powder (1.49 g, 23.4 mmol) and DMSO (23 mL). The crude product was purified by silica gel column chromatography (eluent: 0-5 % Et_2O in *n*-pentane) to provide the title compound (1.06 g, 4.11 mmol, 46 %) as a colourless oil.

(^{1}H NMR, 400 MHz, $CDCl_3$): δ = 8.29 (d, *J* = 0.5 Hz, 1H), 8.18 (d, *J* = 7.8 Hz, 1H), 7.81 (dt, *J* = 0.6, 7.8 Hz, 1H), 7.56 (t, *J* = 7.8 Hz, 1H), 4.32 (qd, *J* = 1.1, 7.2 Hz, 2H), 3.95 (d, *J* = 1.6 Hz, 3H), 1.31 (td, *J* = 1.5, 7.1 Hz, 3H); (^{13}C NMR, 101 MHz, $CDCl_3$): δ = 166.0, 163.7 (t, *J* = 35.2 Hz), 133.3 (t, *J* = 26.3 Hz), 132.1, 130.8, 129.8 (t, *J* = 5.9 Hz), 128.9, 126.7 (t, *J* = 6.3

Hz), 112.9 (t, *J* = 252.7 Hz), 63.3, 52.4, 13.8; (^{19}F NMR, 377 MHz, $CDCl_3$): δ = -103.95 (s, 2F); IR: ν 1765, 1727, 1434, 1303, 1232, 1099, 1028, 967, 855, 822, 718; HRMS (ESI^+, *m/z*): $[C_{12}H_{12}O_4F_2Na]$ $(M+Na)^+$ calc. 281.0607, found 281.0596.

Ethyl 2,2-difluoro-2-(4-methoxyphenyl)acetate (11l)

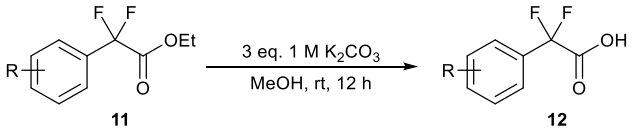


The title compound was prepared following General Procedure I using 4-iodobenzotrifluoride (10.9 g, 40 mmol), ethyl bromodifluoroacetate (5.12 mL, 40 mmol), Cu powder (6.60 g, 104 mmol) and DMSO (104 mL). The crude product was purified by silica gel column chromatography (eluent: 5 % Et_2O in *n*-pentane) to provide the title compound (6.17 g, 56 % yield) as a colourless oil.

(^{1}H NMR, 400 MHz, $CDCl_3$): δ = 7.78−7.73 (m, 4H), 4.32 (q, *J* = 7.1 Hz, 2H), 1.32 (t, *J* = 7.2 Hz, 3H); (^{13}C NMR, 101 MHz, $CDCl_3$): δ = 163.5 (t, *J* = 34.6 Hz), 136.4 (t, *J* = 26.2 Hz), 133.2 (q, *J* = 30.2 Hz), 126.2 (t, *J* = 6.4 Hz), 125.7 (q, *J* = 3.7 Hz), 123.5 (q, *J* = 272.6 Hz), 112.7 (t, *J* = 253.1 Hz), 63.5, 13.8; (^{19}F NMR, 377 MHz, $CDCl_3$): δ = −63.1 (s, 3F), −104.5 (s, 2F). Data consistent with literature values.[12]

5.2.10 Synthesis of $ArCF_2CO_2H$ (12)

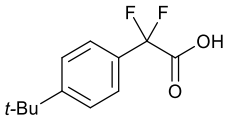
General Procedure J



To a solution of an appropriate ethyl α,α-difluoroaryl acetate (5.0 mmol) in MeOH (15 mL) was added 1 M aq. K_2CO_3 (15 mL, 15 mmol). The reaction mixture was stirred at room temperature for 12 hours before diluting with Et_2O. The reaction mixture was extracted with sat. aq. $NaHCO_3$ (3 x 20 mL). The combined aqueous layers were acidified to pH 1 and extracted with Et_2O (3 x 20 mL), then the combined organic phases were washed with brine,

dried over $MgSO_4$ and concentrated *in vacuo*. Products were purified by washing with *n*-pentane.

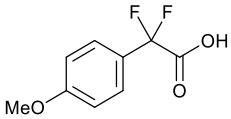
2-(4-(*tert*-Butyl)phenyl)-2,2-difluoroacetic acid (12b)



The title compound was prepared following General Procedure J using ethyl 2-(4-(*tert*-butyl)phenyl)-2,2-difluoroacetate (2.05 g, 8.00 mmol), 1 M K_2CO_3 (24.0 mL, 24.0 mmol) and MeOH (24 mL). After work-up the desired product was obtained as a white solid (1.04 g, 4.56 mmol, 57 %).

(^{1}H NMR, 400 MHz, DMSO-d6): δ = 7.55 (d, *J* = 8.8 Hz, 2H), 7.50 (d, *J* = 8.6 Hz, 2H), 1.28 (s, 9H); (^{13}C NMR, 101 MHz, DMSO-d6): δ = 165.1 (t, J = 34.2 Hz), 153.9, 129.9 (t, J = 25.4 Hz), 125.7, 124.9 (t, J = 6.0 Hz), 113.7 (t, J = 249.5 Hz), 34.6, 30.9; (^{19}F NMR, 377 MHz, DMSO-d6): δ = –102.1 (s, 2F). Data consistent with literature values.[10]

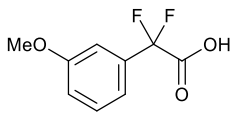
Difluoro(4-methoxyphenyl)acetic acid (12d)



The title compound was prepared following General Procedure J using ethyl 2,2-difluoro-2-(4-methoxyphenyl)acetate (1.84 g, 8.00 mmol), 1 M K_2CO_3 (24.0 mL, 24.0 mmol) and MeOH (24 mL). After work-up the desired product was obtained as a white solid (1.47 g, 7.27 mmol, 91 %).

(^{1}H NMR, 400 MHz, DMSO-d6): δ = 7.50 (d, *J* = 9.1 Hz, 2H), 7.07 (d, *J* = 8.8 Hz, 2H), 3.80 (s, 3H); (^{13}C NMR, 101 MHz, DMSO-d6): δ = 165.2 (t, J = 34.7 Hz), 161.2, 126.8 (t, J = 6.0 Hz), 124.7 (t, J = 26.2 Hz), 114.2, 113.7 (t, J = 250.0 Hz), 55.4; (^{19}F NMR, 377 MHz, DMSO-d6): δ = –101.0 (s, 2F). Data consistent with literature values.[10]

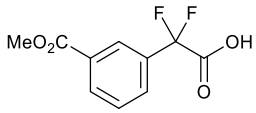
Difluoro(3-methoxyphenyl)acetic acid (12f)



The title compound was prepared following General Procedure J using ethyl 2,2-difluoro-2-(3-methoxyphenyl)acetate (898 g, 3.90 mmol), 1 M K_2CO_3 (11.7 mL, 11.7 mmol) and MeOH (12 mL). After work-up the desired product was obtained as a white solid (436 mg, 2.16 mmol, 55 %).

(^{1}H NMR, 400 MHz, DMSO-d6): δ = 7.46 (t, *J* = 8.0 Hz, 1H), 7.17-7.15 (m, 1H), 7.15-7.13 (m, 1H), 7.07 (t, *J* = 1.9 Hz, 1H), 3.81 (s, 3H); (^{13}C NMR, 101 MHz, DMSO-d6): δ = 165.3 (t, *J* = 33.7 Hz), 159.8, 134.6 (t, *J* = 25.4 Hz), 130.8, 117.6 (t, *J* = 6.1 Hz), 117.1, 113.8 (t, *J* = 250.8), 111.0 (t, *J* = 6.3 Hz), 55.8; (^{19}F NMR, 377 MHz, DMSO-d6): δ = –102.4 (s, 2F). Data consistent with literature values.[10]

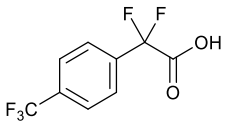
Difluoro[3-(methoxycarbonyl)phenyl]acetic acid (12i)



The title compound was prepared following General Procedure J using methyl 3-(2-ethoxy-1,1-difluoro-2-oxoethyl)benzoate (775 mg, 3.00 mmol), 1 M K_2CO_3 (9.00 mL, 9.00 mmol) and MeOH (9 mL). After work-up the desired product was obtained as a white solid (487 mg, 2.12 mmol, 71 %).

(^{1}H NMR, 400 MHz, $CDCl_3$): δ = 9.66 (brs, 1H), 8.33-8.32 (m, 1H), 8.21 (ddd, *J* = 1.1, 1.7, 7.8 Hz, 1H), 7.86 (dtd, *J* = 0.6, 1.2, 7.8 Hz, 1H), 7.59 (td, *J* = 0.6, 7.8 Hz, 1H), 3.98 (s, 3H); (^{13}C NMR, 101 MHz, $CDCl_3$) δ = 167.4 (t, *J* = 35.8 Hz), 166.4, 132.7 (t, *J* = 21.8 Hz), 132.4, 130.8, 130.0 (t, *J* = 6.1 Hz), 129.1, 126.9 (t, *J* = 6.2 Hz), 112.6 (t, *J* = 253.3 Hz), 52.7; (^{19}F NMR, 377 MHz, $CDCl_3$) δ = -105.0 (s, 2F); IR: ν 1756, 1725, 1431, 1287, 1234, 1120, 1077, 1024, 961, 914, 786, 742; HRMS (ESI$^-$, *m/z*): $[C_{10}H_7O_4F_2]$ $(M-H)^-$ calc. 229.0318, found 229.0324; MP: 68-69°C.

2,2-Difluoro-2-(4-(trifluoromethyl)phenyl)acetic acid (12l)

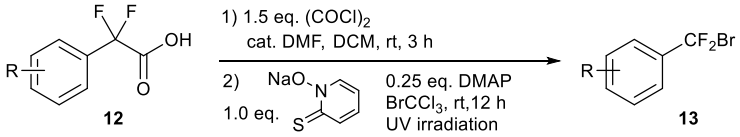


The title compound was prepared following General Procedure J using ethyl 2,2-difluoro-2-(4-methoxyphenyl)acetate (5.54 g, 20 mmol), 1 M K_2CO_3 (60 mL, 60 mmol) and MeOH (60 mL); (3.41 g, 68 % yield, white solid).

(^{1}H NMR, 400 MHz, DMSO-d6): δ = 7.91 (d, *J* = 8.3 Hz, 2H), 7.82 (d, *J* = 8.3 Hz, 2H); (^{13}C NMR, 101 MHz, DMSO-d6): δ = 164.4 (t, *J* = 33.0 Hz), 136.8 (t, *J* = 25.4 Hz), 131.5 (q, *J* = 31.8 Hz), 126.4 (t, *J* = 6.0 Hz), 126.0 (t, *J* = 3.7 Hz), 123.7 (q, *J* = 272.6 Hz), 112.9 (t, *J* = 251.1 Hz); (^{19}F NMR, 377 MHz, DMSO-d6): δ = −61.7 (s, 3F), −103.3 (s, 2F); IR: ν 3026, 2877, 2534, 2362, 1751, 1413, 1322, 1260, 1166, 1122, 1098, 991, 886, 845; HRMS (ESI) for $C_9H_4F_5O_2$ [M-H]$^-$ requires 239.0136 found 239.0135; Mp. 76−79 °C.

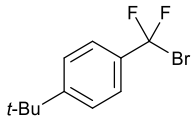
5.2.11 Synthesis of $ArCF_2Br$ (13)

General Procedure K



To a solution of an appropriate carboxylic acid (1.0 mmol) in DCM (2 mL) was added DMF (7.7 µL, 0.1 eq.) and oxalyl chloride (129 µL, 1.5 mmol) at 0 ˚C. The reaction mixture was stirred at room temperature for 3 hours, then concentrated *in vacuo*. The crude acyl chloride was added degassed $BrCCl_3$ (3 mL), 4-Dimethylaminopyridine (30.7 mg, 0.25 mmol) and sodium-*N*-hydroxy-2-thiopyridone (149 mg, 1.0 mmol). The reaction mixture was stirred under 300 W UV lamp for 12 hours and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography.

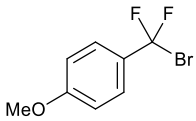
1-(Bromodifluoromethyl)-4-(*tert*-butyl)benzene (13b)



The title compound was prepared following General Procedure K using 2-(4-(*tert*-butyl)phenyl)-2,2-difluoroacetic acid (913 mg, 4.00 mmol), DCM (8 mL), DMF (30.8 µL, 400 µmol), oxalyl chloride (414 µL, 6.00 mmol), $BrCCl_3$ (12 mL), 4-dimethylaminopyridine (122 mg, 1.00 mmol) and sodium-*N*-hydroxy-2-thiopyridone (596 mg, 4.00 mmol). The crude product was purified by silica gel column chromatography (eluent: 1 % Et_2O in *n*-pentane) to provide the title compound (781 mg, 2.97 mmol, 74 %) as a pale yellow oil.

(^{1}H NMR, 400 MHz, $CDCl_3$): δ = 7.56 (d, *J* = 8.8 Hz, 2H), 7.49 (d, *J* = 9.1 Hz, 2H), 1.36 (s, 9H); (^{13}C NMR, 101 MHz, $CDCl_3$): δ = 154.7, 135.4 (t, *J* = 23.4 Hz), 125.6, 124.1 (t, *J* = 5.2 Hz), 118.6 (t, *J* = 303.6 Hz), 34.9, 31.1; (^{19}F NMR, 377 MHz, $CDCl_3$): δ = –42.5 (s, 2F); IR: ν 2966, 1613, 1411, 1366, 1276, 1141, 1100, 1053, 1015, 882, 822; HRMS (EI) for $C_{11}H_{13}BrF_2$ $[M]^+$ requires 262.0169 found 262.0168.

1-(Bromodifluoromethyl)-4-methoxybenzene (13d)

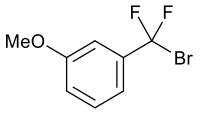


The title compound was prepared following General Procedure K using difluoro(4-methoxyphenyl)acetic acid (1.21 g, 6.00 mmol), DCM (12 mL), DMF (46.2 µL, 600 µmol), oxalyl chloride (773 µL, 9.00 mmol), $BrCCl_3$ (18 mL), 4-dimethylaminopyridine (183 mg, 1.50 mmol) and sodium-*N*-hydroxy-2-thiopyridone (894 mg, 6.00 mmol). The crude product was purified by silica gel column chromatography (eluent: 1 % Et_2O in *n*-pentane) to provide the title compound (118 mg, 498 µmol, 8 %) as a colourless oil.

(^{1}H NMR, 400 MHz, $CDCl_3$): δ = 7.58 (d, *J* = 9.1 Hz, 2H), 6.96 (d, *J* = 9.1 Hz, 2H), 3.86 (s, 3H); (^{13}C NMR, 101 MHz, $CDCl_3$): δ = 161.7, 128.7 (t, *J* = 26.6 Hz), 126.7 (t, *J* = 288.5 Hz) 126.4 (t, *J* = 4.8 Hz), 113.8, 55.4; (^{19}F NMR, 377 MHz, $CDCl_3$): δ = −46.5 (s, 2F); IR: ν

1613, 1516, 1463, 1313, 1255, 1179, 1133, 1093, 1055, 1029, 901, 829; HRMS (EI) for $C_8H_7BrF_2O$ $[M]^+$ requires 235.9648 found 235.9655.

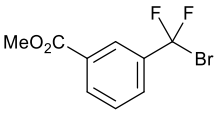
1-[Bromo(difluoro)methyl]-3-methoxybenzene (13f)



The title compound was prepared following General Procedure K using difluoro(3-methoxyphenyl)acetic acid (202 mg, 1.00 mmol), DCM (2 mL), DMF (7.7 µL, 0.10 mol), oxalyl chloride (128 µL, 1.50 mmol), $BrCCl_3$ (3 mL), 4-dimethylaminopyridine (31 mg, 0.25 mmol) and sodium-*N*-hydroxy-2-thiopyridone (149 mg, 1.00 mmol). The crude product was purified by silica gel column chromatography (eluent: *n*-pentane) to provide the title compound (131 mg, 553 µmol, 45 %) as a colourless oil.

(^{1}H NMR, 400 MHz, $CDCl_3$): δ = 7.37 (td, *J* = 0.4, 8.0 Hz, 1H), 7.22-7.19 (m, 1H), 7.12-7.11 (m, 1H), 7.02 (ddt, *J* = 0.4, 2.6, 8.3 Hz, 1H), 3.85 (s, 3H), (^{13}C NMR, 101 MHz, $CDCl_3$) δ = 159.7, 139.5 (t, *J* = 23.7 Hz), 129.9, 118.3 (m, *J* = 304.5 Hz), 117.2, 116.6 (t, *J* = 4.8 Hz), 109.9 (t, *J* = 5.4 Hz) 55.6; (^{19}F NMR, 377 MHz, $CDCl_3$) δ = -43.6 (s, 2F); IR: ν 1605, 1493, 1455, 1434, 1319, 1290, 1221, 1124, 1087, 1038, 917, 807, 771; HRMS (FI) for $C_8H_7{}^{79}BrF_2$ $[M]^+$ requires 235.9648 found 235.9655.

Methyl 3-[bromo(difluoro)methyl]benzoate (13i)

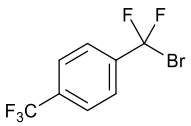


The title compound was prepared following General Procedure K using difluoro[3-(methoxycarbonyl)phenyl]acetic acid (345 mg, 1.50 mmol), DCM (3 mL), DMF (11.6 µL, 0.150 mmol), oxalyl chloride (191 µL, 2.25 mmol), $BrCCl_3$ (4.5 mL), 4-dimethylaminopyridine (46 mg, 0.38 mmol) and sodium-*N*-hydroxy-2-thiopyridone (224 mg, 1.50 mmol). The crude product was purified by silica gel column

chromatography (eluent: *n*-pentane) to provide the title compound (174 mg, 656 µmol, 44 %) as a pale yellow oil.

(^{1}H NMR, 400 MHz, $CDCl_3$): δ = 8.30 (s, 1H), 8.18 (d, J = 7.8 Hz, 1H), 7.81 (dd, J = 0.4, 7.8 Hz, 1H), 7.57 (t, *J* = 7.5 Hz, 1H), 3.98 (dd, *J* = 0.8, 1.9 Hz, 3H); (^{13}C NMR, 101 MHz, $CDCl_3$): δ = 165.72, 138.55 (t, *J* = 24.3 Hz), 132.23, 130.87, 128.96, 128.52 (t, *J* = 4.8 Hz), 125.50 (t, *J* = 5.2 Hz), 117.56 (t, *J* = 303.6 Hz), 52.50; (^{19}F NMR, 377 MHz, $CDCl_3$): δ = -44.33 (s, 2F); IR: ν 1727, 1434, 1307, 1237, 1133, 1082, 1061, 980, 894, 814, 757, 720; HRMS (FI) for $C_9H_7O_2{}^{79}BrF_2$ $[M]^+$ requires 263.9597 found 263.9604.

1-(Bromodifluoromethyl)-4-(trifluoromethyl)benzene (13l)



The title compound was prepared following General Procedure K using 2,2-difluoro-2-(4-(trifluoromethyl)phenyl)acetic acid (2.49 g, 10.0 mmol), DCM (20 mL), DMF (77. µL, 1.0 mmol), oxalyl chloride (1.29 mL, 15.0 mmol), $BrCCl_3$ (30 mL), 4-dimethylaminopyridine (305 mg, 2.5 mmol) and sodium-*N*-hydroxy-2-thiopyridone (1.49 g, 10.0 mmol). The crude product was purified by silica gel column chromatography (eluent: 1 % Et_2O in *n*-pentane) to provide the title compound (520 mg, 18 % yield) as a yellow oil.

(^{1}H NMR, 400 MHz, $CDCl_3$): δ = 7.75 (s, 4H); (^{13}C NMR, 101 MHz, $CDCl_3$): δ = 141.3 (t, *J* = 24.6 Hz), 133.3 (q, *J* = 32.9 Hz), 125.9 (q, *J* = 3.7 Hz), 124.9 (t, *J* = 4.8 Hz), 123.4 (t, *J* = 272.6 Hz), 117.2 (t, *J* = 304.0 Hz); (^{19}F NMR, 377 MHz, $CDCl_3$): δ = –45.5 (s, 2F), –63.2 (s, 3F); IR: ν 1414, 1324, 1272, 1172, 1131, 1099, 1070, 1053, 1020, 960, 889, 830; HRMS (EI/FI) for $C_8H_4BrF_4$ $[M-F]^+$ requires 254.9433 found 254.9460.

5.2.12 General Information for Radiochemical Procedures

[^{18}F]Fluoride was produced by Erigal (UK) and delivered as [^{18}F]fluoride in 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 (MP1, ORTG, Tennessee, USA or Chromafix PS-HCO_3 ^{18}F separation cartridges, 45 mg) and subsequently released with a solution of K_{222}/K_2CO_3 (Kryptofix-2.2.2 (15 mg) and K_2CO_3 (3 mg) in 1 mL of MeCN/H_2O, 4:1) into the concentrator. For large dose applications, [^{18}F]fluoride was eluted from with a solution of dicyclohexano-18-crown-6 (14 mg), potassium oxalate (4 mg) and K_2CO_3 (200 µL of 1 mg/ml in H_2O) in a total volume of 1 mL (4:1 MeCN/H_2O). The solution was dried with five cycles of azeotropic drying with acetonitrile (200 µl) and redissolved in anhydrous acetonitrile (500-1000 µL). HPLC analysis was performed with a Dionex Ultimate 3000 dual channel HPLC system equipped with shared autosampler, parallel UV-detectors and LabLogic NaI/PMT-radiodetectors with Flowram analog output. Radio-TLC was performed on Merck Kieselgel 60 F254 plates. Analysis was performed using a plastic scintillator/PMT detector. All radiochemical yields quoted are decay corrected. Radiochemical yields are calculated by radioTLC, taking into account the radiochemical purity observed by radio-HPLC.

1) General Procedure for the ^{18}F-fluorination of Ar-SCF_2Br

Conditions A: To a V-vial containing AgOTf (10 mg, 0.04 mmol) and a magnetic stirrer bar was added [^{18}F]KF/K_{222} (~30 MBq) in MeCN (~30 µL). The MeCN was removed by heating (100 °C) the vial under a stream of N_2. Upon cooling of the V-vial, a solution of precursor (0.04 mmol) in CH_2Cl_2 (300 µL) was added by syringe. The sealed vial was allowed to stir for 20 minutes at room temperature. The reaction was quenched by addition of EtOH/H_2O

(9:1, 500 μL). An aliquot was removed for analysis by radioTLC and HPLC for radiochemical yield and product identity. Analysis was performed using Gradient A with a Waters Nova-Pak C18 column (4 μm, 3.9 x 150 mm) at a flow rate 1ml/min.

Conditions B: To a V-vial containing AgOTf (20 mg, 0.08 mmol) and a magnetic stirrer bar was added [^{18}F]KF/K_{222} (~30 MBq) in MeCN (~30 μL). The MeCN was removed by heating (100 °C) the vial under a stream of N_2. Upon cooling of the V-vial, a solution of precursor (0.04 mmol) in DCE (300 μL) was added by syringe. The sealed vial was allowed to stir for 20 minutes at 60 °C. The reaction was quenched by addition of EtOH/H_2O (9:1, 500 μL). An aliquot was removed for analysis by radioTLC and HPLC for radiochemical yield and product identity. Analysis was performed using Gradient A with a Waters Nova-Pak C18 column (4 μm, 3.9 x 150 mm) at a flow rate 1ml/min.

2) General Procedure for the [^{18}F]fluorination of Ar-OCF_2Br

To a V-vial containing AgOTf (20 mg, 0.08 mmol) and a magnetic stirrer bar was added [^{18}F]KF/K_{222} (~30 MBq) in MeCN (~30 μL). The MeCN was removed by heating (100 °C) the vial under a stream of N_2. Upon cooling of the V-vial, a solution of precursor (0.04 mmol) in DCE (300 μL) was added by syringe. The sealed vial was allowed to stir for 20 minutes at 60 °C. The reaction was quenched by addition of EtOH/H_2O (9:1, 500 μL). An aliquot was removed for analysis by radioTLC and HPLC for radiochemical yield and product identity. Analysis was performed using Gradient A with a Waters Nova-Pak C18 column (4 μm, 3.9 x 150 mm) at a flow rate 1ml/min.

3) General Procedure for the [^{18}F]fluorination of Ar-OCHFCl

To a V-vial containing AgOTf (10 mg, 0.04 mmol) and a magnetic stirrer bar was added [^{18}F]KF/K_{222} (~30 MBq) in MeCN (~30 μL). The MeCN was removed by heating (100 °C)

the vial under a stream of N_2. Upon cooling of the V-vial, a solution of precursor (0.04 mmol) in CH_2Cl_2 (300 μL) was added by syringe. The sealed vial was allowed to stir for 20 minutes at room temperature. The reaction was quenched by addition of EtOH/H_2O (9:1, 500 μL). An aliquot was removed for analysis by radioTLC and HPLC for radiochemical yield and product identity. Analysis was performed using Gradient A with a Waters Nova-Pak C18 column (4 μm, 3.9 x 150 mm) at a flow rate 1ml/min.

4) General Procedure for the [^{18}F]fluorination of Ar-CF_2Br and Ar-CHFCl

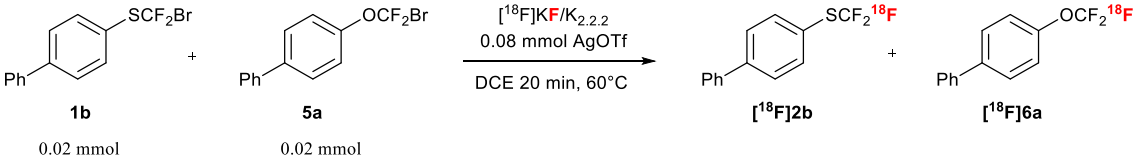
Conditions A: To a V-vial containing AgOTf (10 mg, 0.04 mmol) and a magnetic stirrer bar was added [^{18}F]KF/K_{222} (~30 MBq) in MeCN (~30 μL). The MeCN was removed by heating (100 °C) the vial under a stream of N_2. Upon cooling of the V-vial, a solution of precursor (0.04 mmol) in DCM (300 μL) was added by syringe. The sealed vial was allowed to stir for 20 min at room temperature. The reaction was quenched by addition of EtOH/H_2O (9:1, 500 μL). An aliquot was removed for analysis by radio-TLC and HPLC for radiochemical yield and product identity. Analysis was performed using Gradient A with a Waters Nova-Pak C18 column (4 μm, 3.9 x 150 mm) at a flow rate 1 ml/min.

Conditions B: To a V-vial containing AgOTf (20 mg, 0.08 mmol) and a magnetic stirrer bar was added [^{18}F]KF/K_{222} (~30 MBq) in MeCN (~30 μL). The MeCN was removed by heating (100 °C) the vial under a stream of N_2. Upon cooling of the V-vial, a solution of precursor (0.04 mmol) in DCE (300 μL) was added by syringe. The sealed vial was allowed to stir for 20 min at 60 °C. The reaction was quenched by addition of EtOH/H_2O (9:1, 500 μL). An aliquot was removed for analysis by radio-TLC and HPLC for radiochemical yield and product identity. Analysis was performed using Gradient A with a Waters Nova-Pak C18 column (4 μm, 3.9 x 150 mm) at a flow rate 1 ml/min.

5) General Procedure for the Control Experiment without AgOTf

To a V-vial containing a magnetic stirrer bar was added [^{18}F]KF/K_{222} (~30 MBq) in MeCN (~30 µL). The MeCN was removed by heating (100 °C) the vial under a stream of N_2. Upon cooling of the V-vial, a solution of precursor (0.04 mmol) in DCE (300 µL) was added by syringe. The sealed vial was allowed to stir for 20 min at at 60 °C. The reaction was quenched by addition of EtOH/H_2O (9:1, 500 µL). An aliquot was removed for analysis by radio-TLC and HPLC for radiochemical yield and product identity. Analysis was performed using Gradient A with a Phenomenex Synergi Hydro RP 80 Å column (4 µm, 4.6 x 150 mm) at a flow rate 1 ml/min.

6) General Procedure for the Competition Experiment



To a V-vial containing AgOTf (20 mg, 0.08 mmol) and a magnetic stirrer bar was added [^{18}F]KF/K_{222} (~30 MBq) in MeCN (~30 µL). The MeCN was removed by heating (100 °C) the vial under a stream of N_2. A solution of [1,1'-biphenyl]-4-yl(bromodifluoromethyl) sulfane (6 mg, 0.02 mmol) and 4-[bromo(difluoro)methoxy]biphenyl (6 mg, 0.02 mmol) in DCE (300 µL) was added by syringe. The sealed vial was allowed to stir at 60 °C for 20 minutes. The reaction was quenched with EtOH/H_2O 9/1 (500 µl) and an aliquot was analysed by radio-TLC and radio-HPLC (Zorbax C18 column 250x4.6mm).

5.2.13 Radio-HPLC Traces with Authentic UV References Overlaid

Crude radio-HPLC traces of the crude mixture following the General Procedure, with authentic UV references overlaid are shown below. The solid blue line indicates the UV trace for cold reference material and the solid black line is the crude radio-HPLC trace. All samples were run using HPLC gradient A.

HPLC gradient A:

water/acetonitrile, 1 mL/min, Waters Nova-Pak C18 Column, 4 µm, 3.9 x 150 mm

0-1 min (5 % MeCN) isocratic

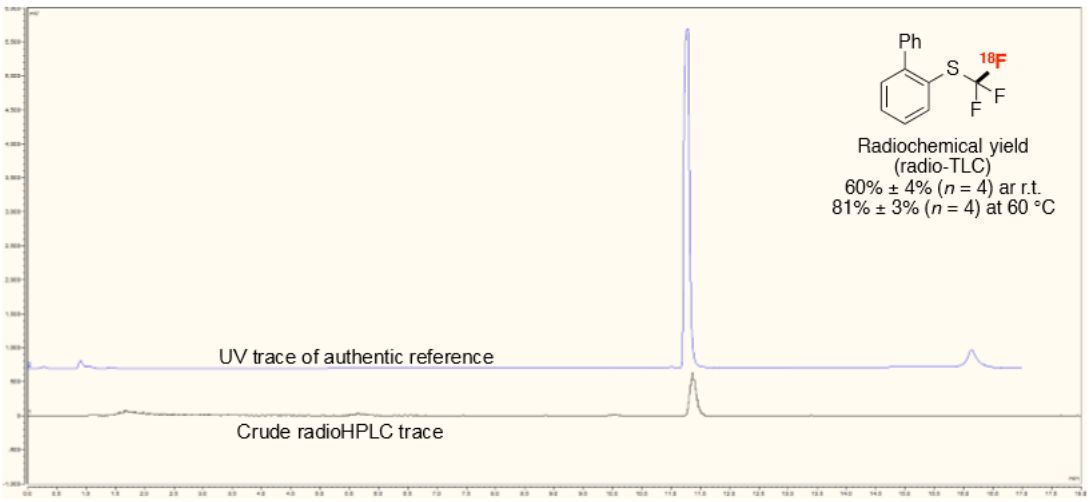
1-10 min (5 % MeCN to 95 % MeCN) linear increase

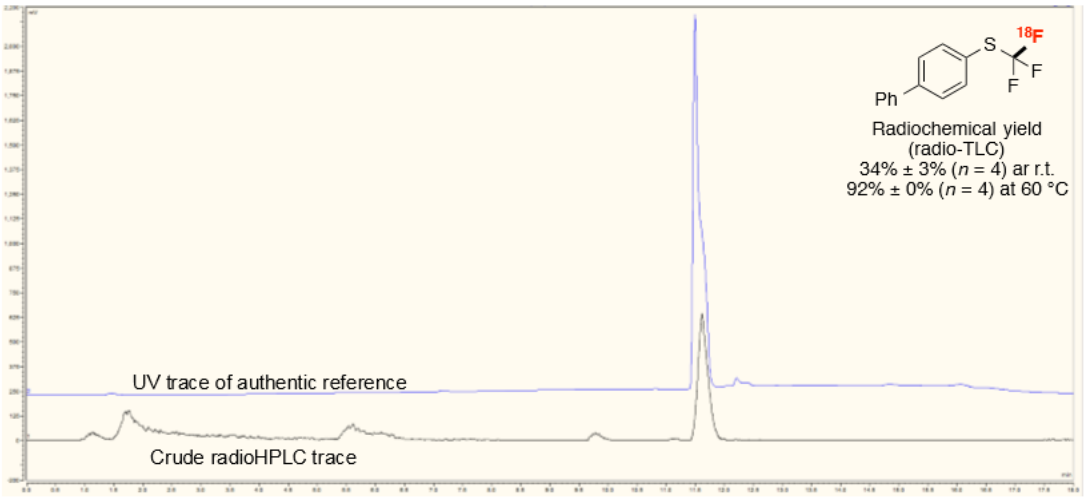
10-14 min (95 % MeCN) isocratic

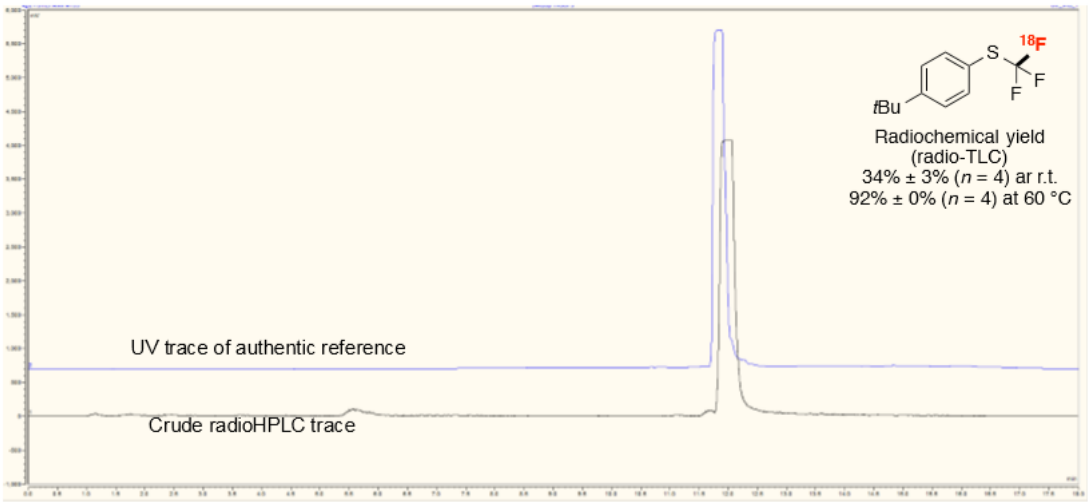
14-15 min (95 % MeCN to 5 % MeCN) linear decrease

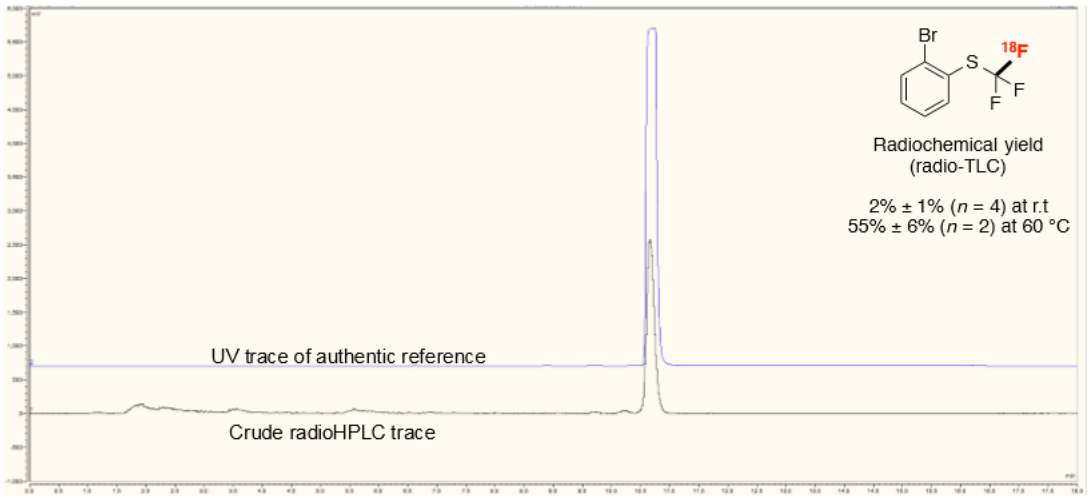
15-17 min (5 % MeCN) isocratic

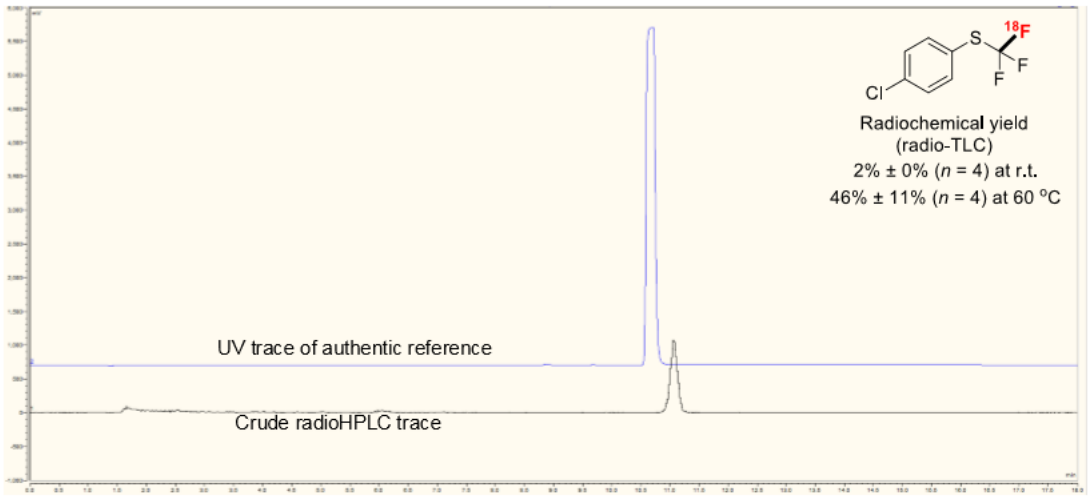
1) [^{18}F]Ar-SCF$_3$ ([^{18}F]2)

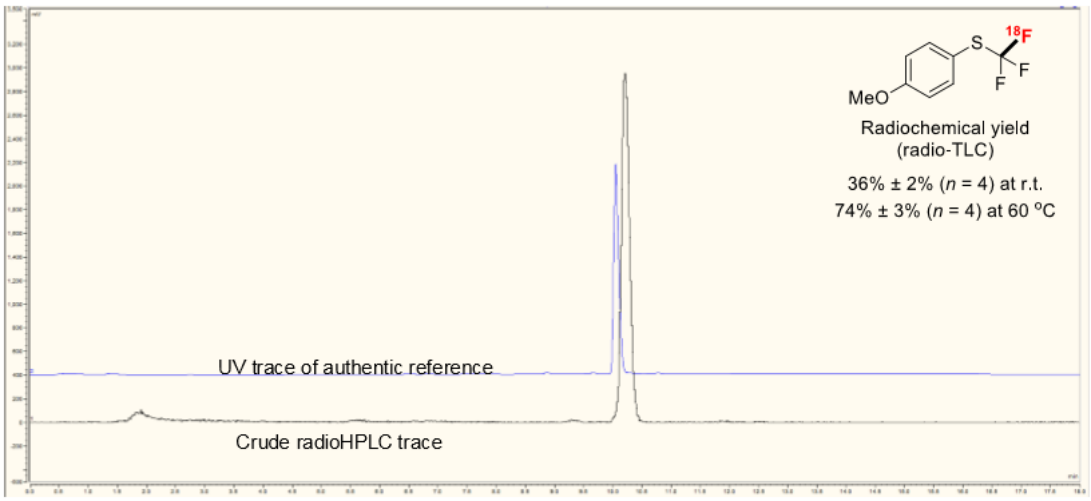


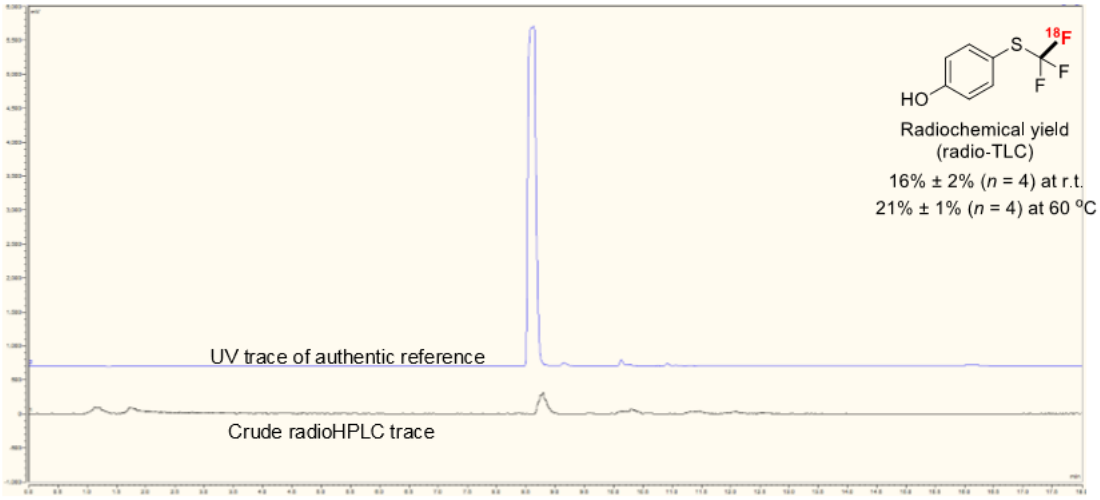


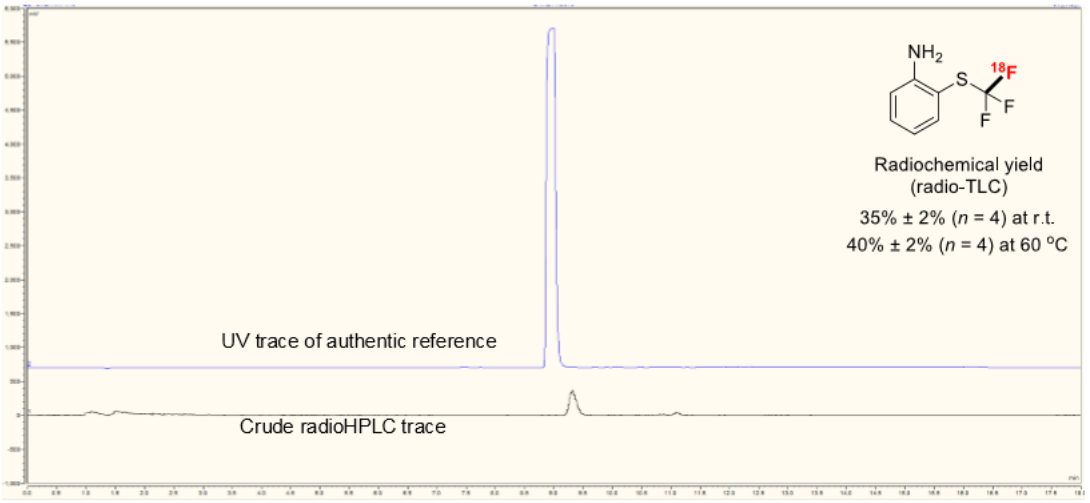


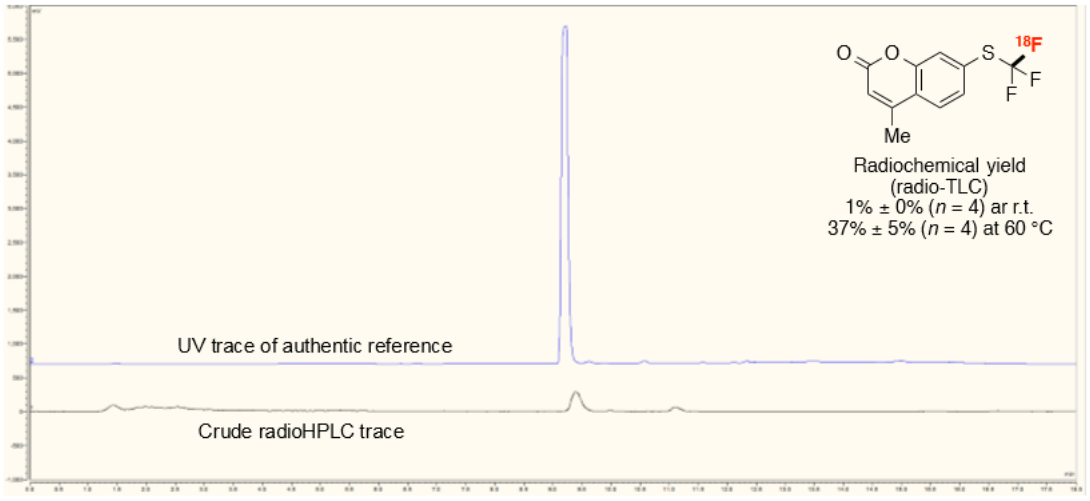

Br
S
18F
F
F
Radiochemical yield
(radio-TLC)
2% ± 1% (n = 4) at r.t
55% ± 6% (n = 2) at 60 °C
UV trace of authentic reference
Crude radioHPLC trace


S
18F
F
F
Cl
Radiochemical yield
(radio-TLC)
2% ± 0% (n = 4) at r.t.
46% ± 11% (n = 4) at 60 °C
UV trace of authentic reference
Crude radioHPLC trace

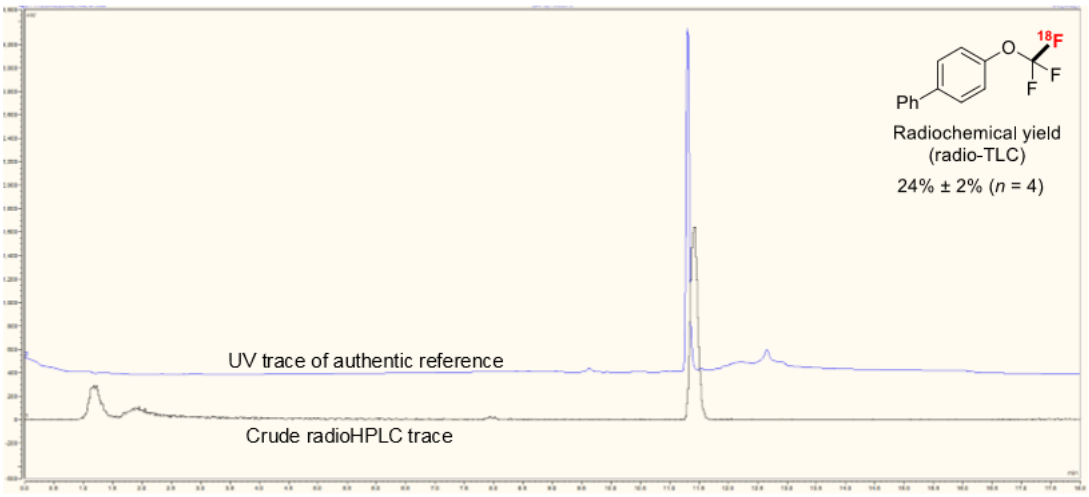

S
18F
F
F
MeO
Radiochemical yield
(radio-TLC)
36% ± 2% (n = 4) at r.t.
74% ± 3% (n = 4) at 60 °C
UV trace of authentic reference
Crude radioHPLC trace

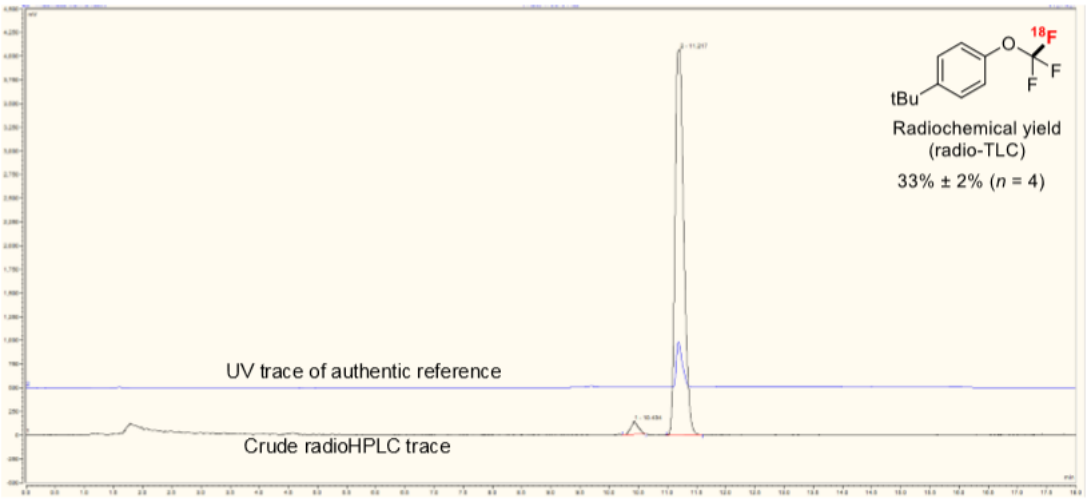

HO
S
18F
F
F
Radiochemical yield
(radio-TLC)
16% ± 2% (n = 4) at r.t.
21% ± 1% (n = 4) at 60 °C
UV trace of authentic reference
Crude radioHPLC trace

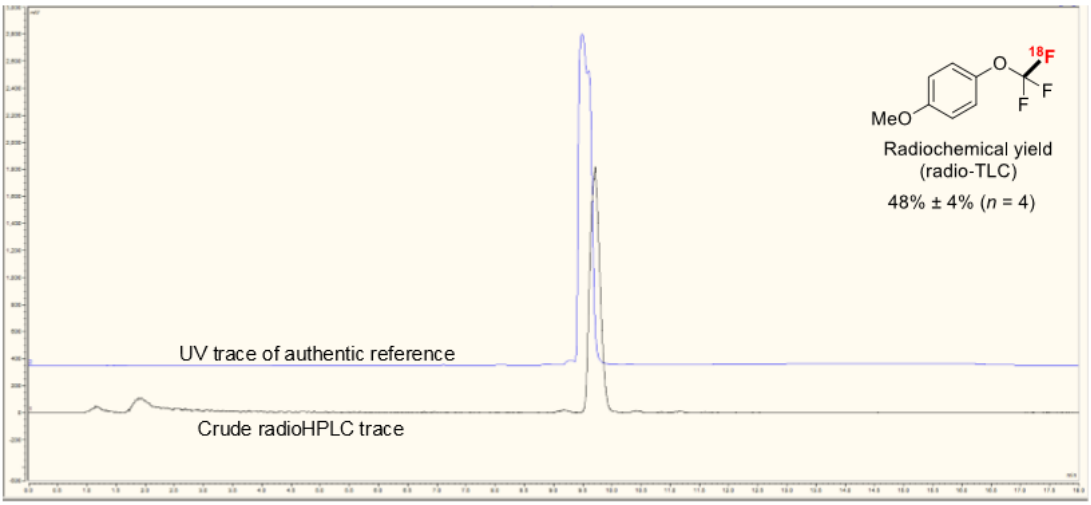

NH2
S
18F
F
F
Radiochemical yield
(radio-TLC)
35% ± 2% (n = 4) at r.t.
40% ± 2% (n = 4) at 60 °C
UV trace of authentic reference
Crude radioHPLC trace

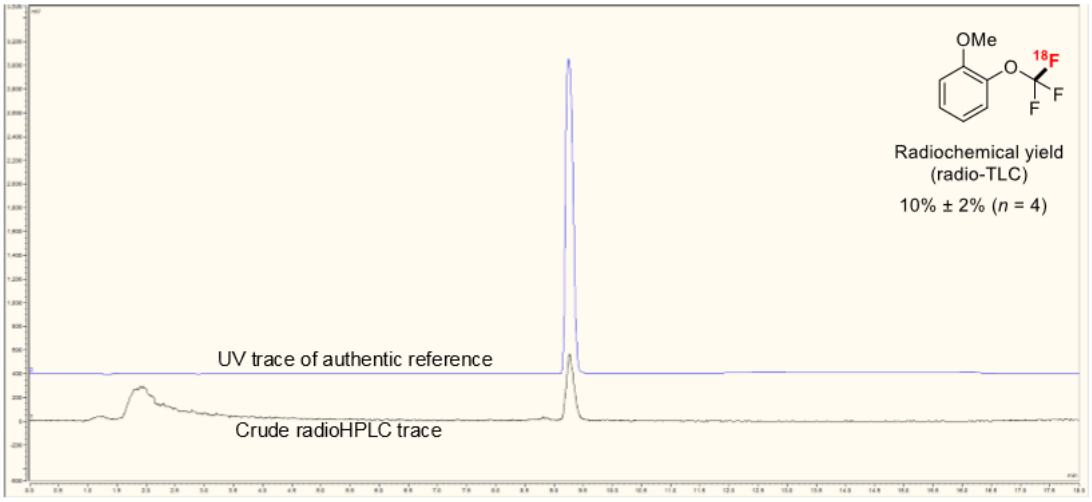

O
O
Me
S
18F
F
F
Radiochemical yield
(radio-TLC)
1% ± 0% (n = 4) ar r.t.
37% ± 5% (n = 4) at 60 °C
UV trace of authentic reference
Crude radioHPLC trace

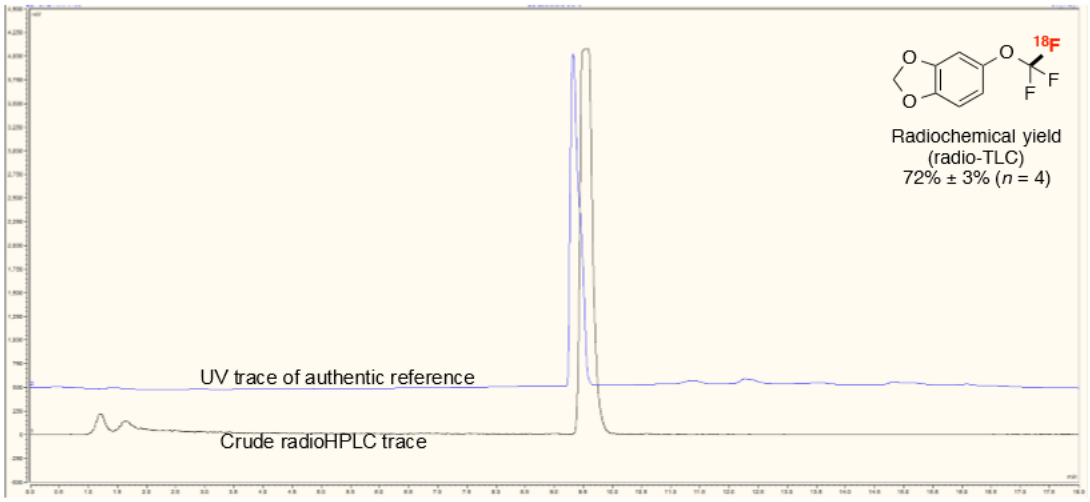
2) [^{18}F]Ar-OCF$_3$ ([^{18}F]6)

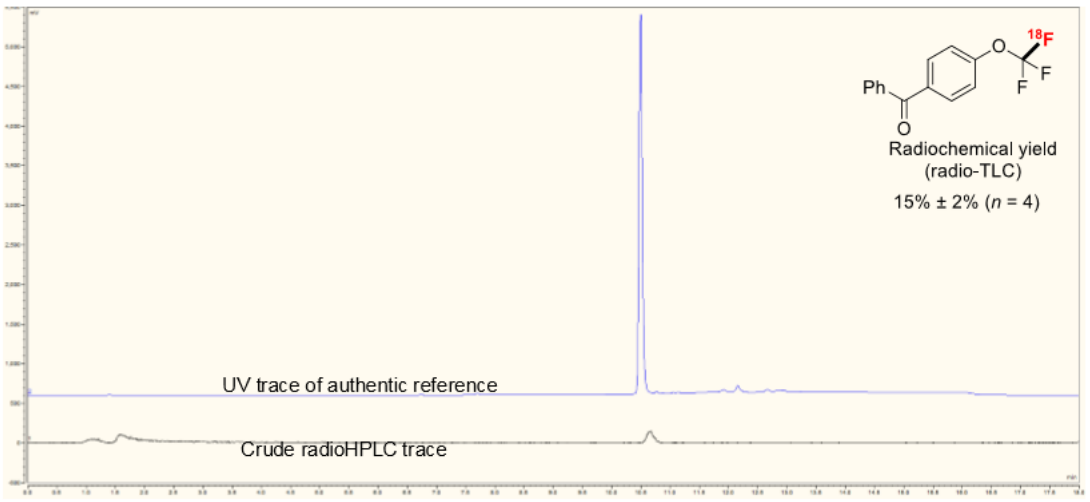


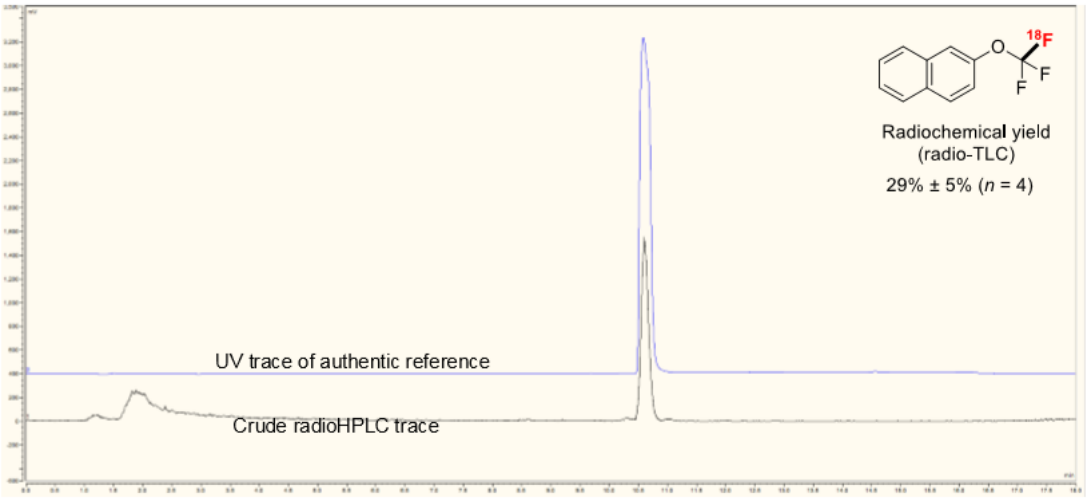


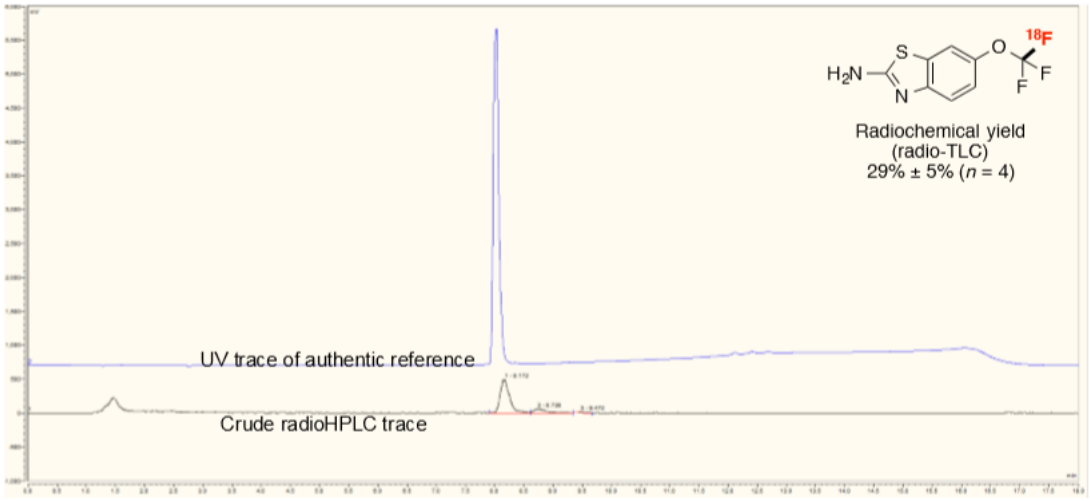



OMe
O
18F
F
F
Radiochemical yield
(radio-TLC)
10% ± 2% (n = 4)
UV trace of authentic reference
Crude radioHPLC trace

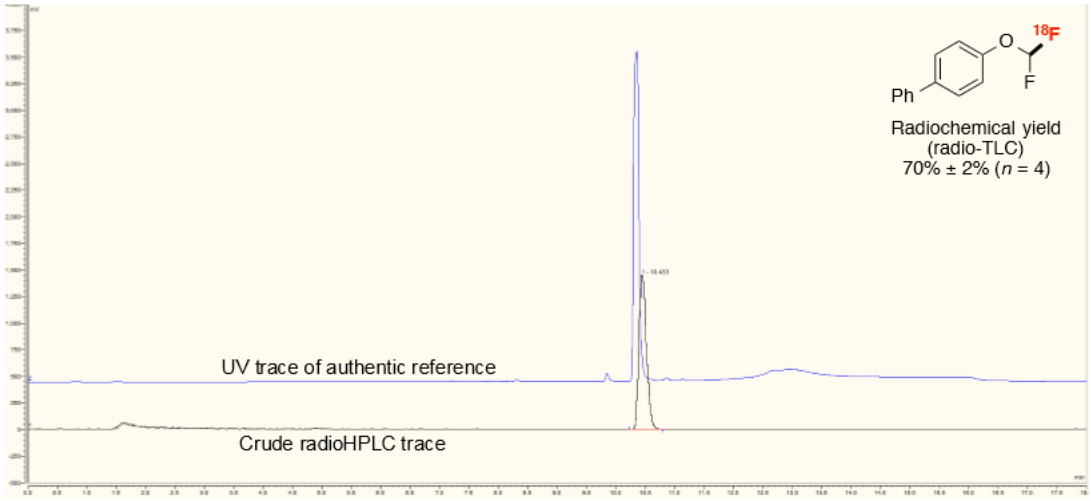

O
O
O
18F
F
F
Radiochemical yield
(radio-TLC)
72% ± 3% (n = 4)
UV trace of authentic reference
Crude radioHPLC trace

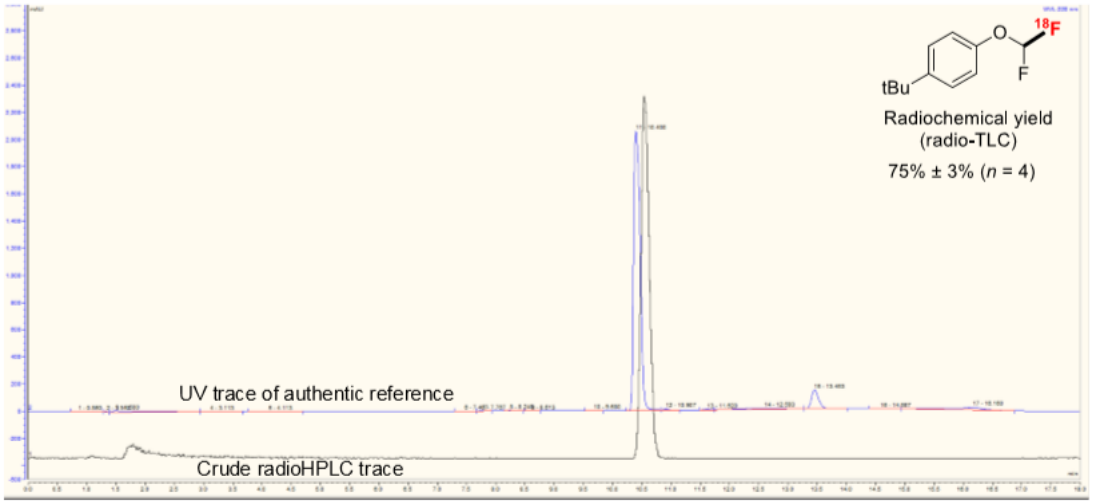

Ph
O
O
18F
F
F
Radiochemical yield
(radio-TLC)
15% ± 2% (n = 4)
UV trace of authentic reference
Crude radioHPLC trace

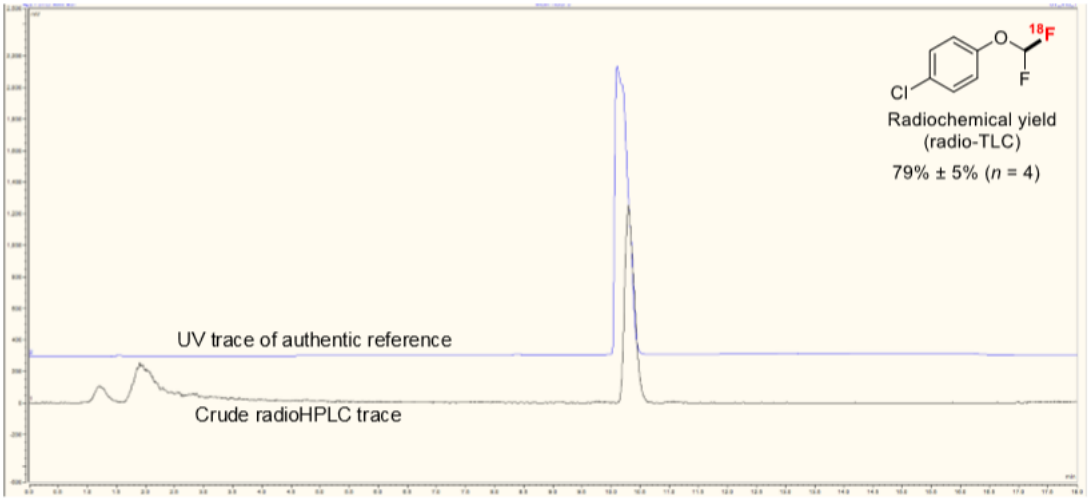

Radiochemical yield
(radio-TLC)
29% ± 5% (n = 4)
UV trace of authentic reference
Crude radioHPLC trace

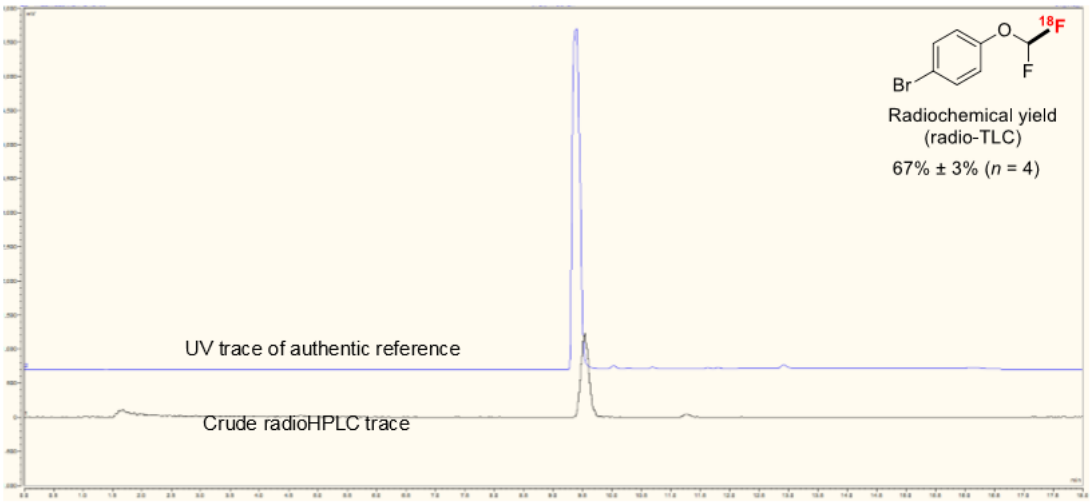

Radiochemical yield
(radio-TLC)
29% ± 5% (n = 4)
UV trace of authentic reference
Crude radioHPLC trace

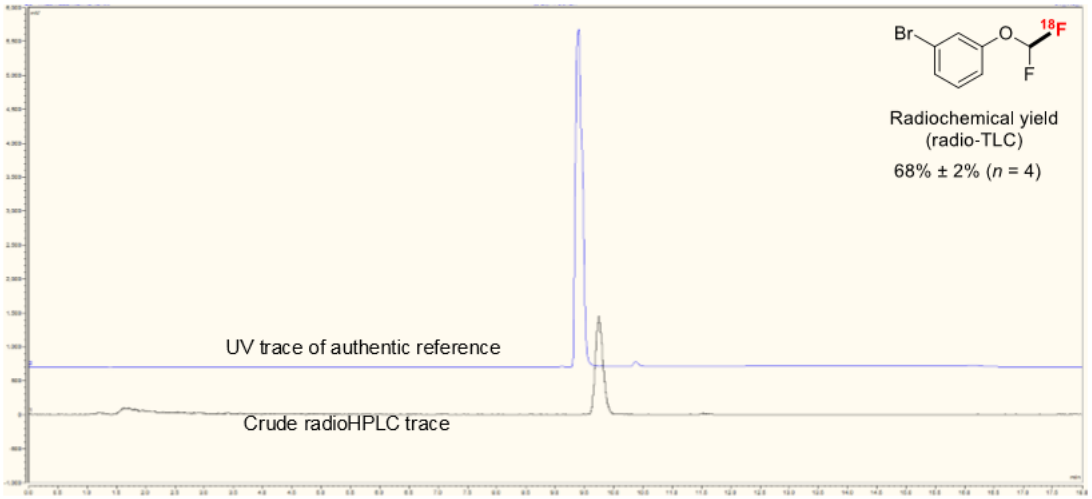
3) [^{18}F]Ar-OCF$_2$H ([^{18}F]10)

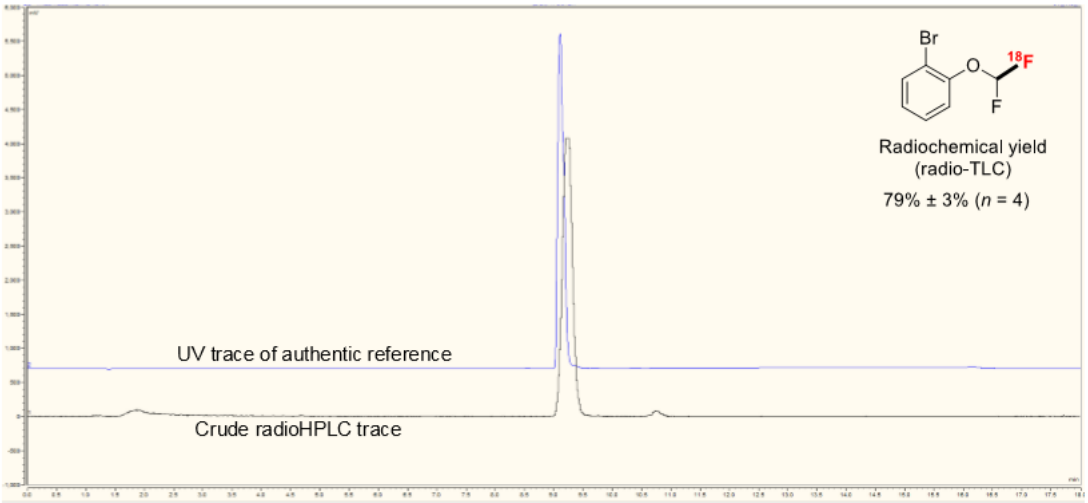


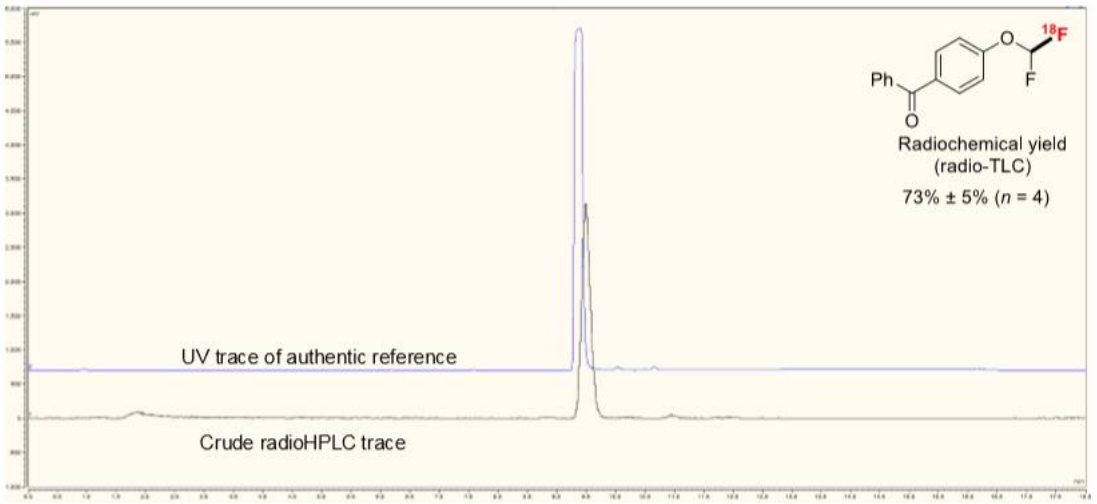


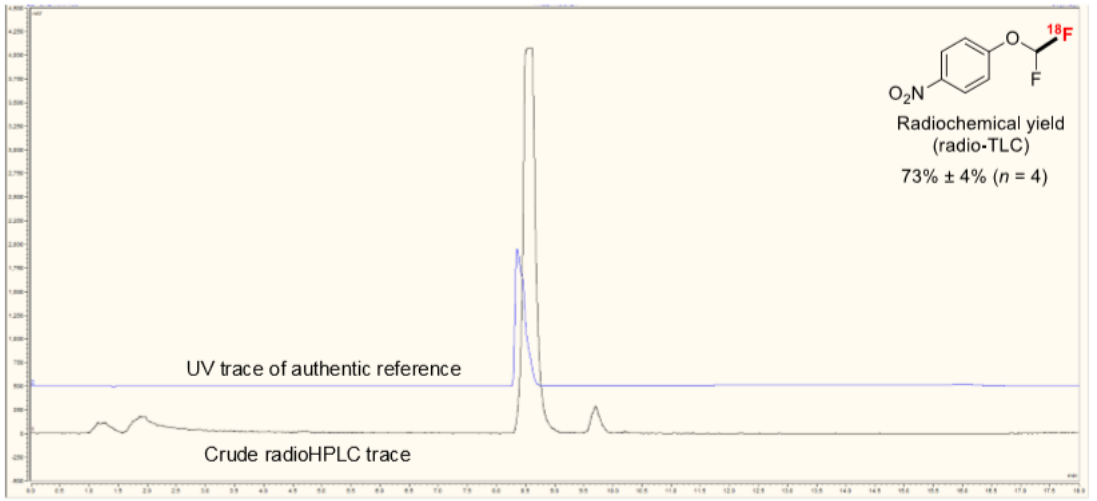


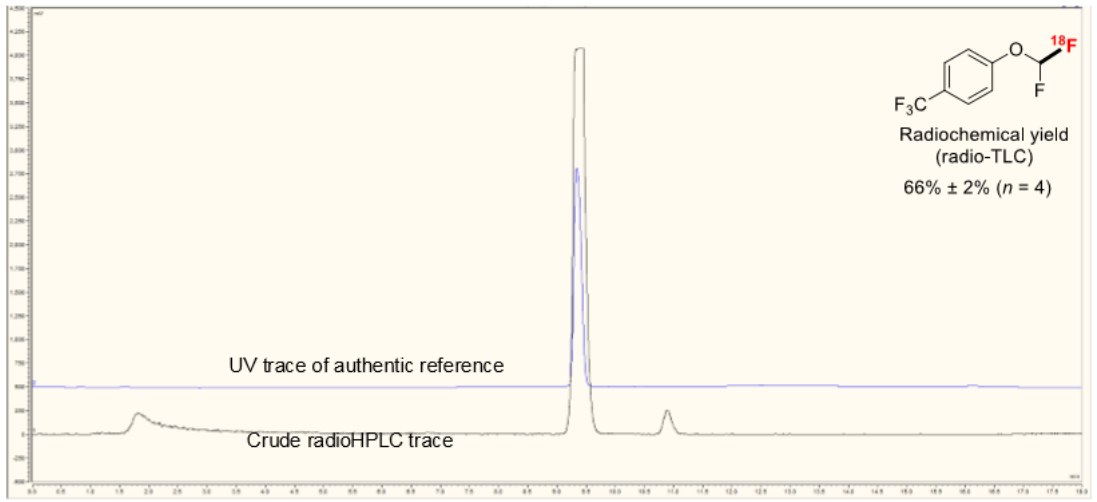

Br
O
18F
F
Radiochemical yield
(radio-TLC)
67% ± 3% (n = 4)
UV trace of authentic reference
Crude radioHPLC trace


Br
O
18F
F
Radiochemical yield
(radio-TLC)
68% ± 2% (n = 4)
UV trace of authentic reference
Crude radioHPLC trace

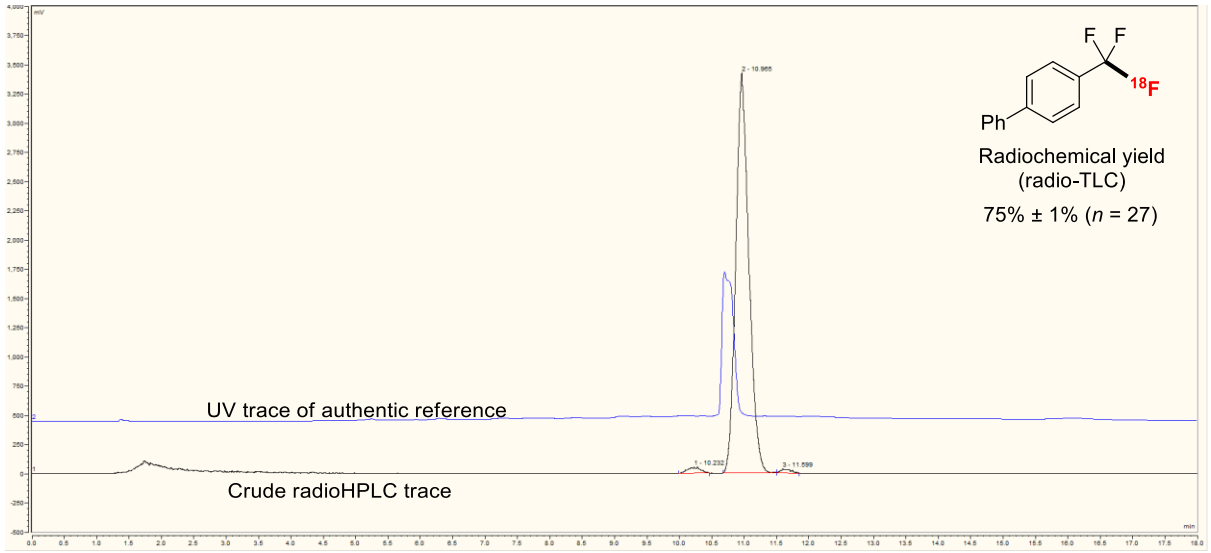

Br
O
18F
F
Radiochemical yield
(radio-TLC)
79% ± 3% (n = 4)
UV trace of authentic reference
Crude radioHPLC trace

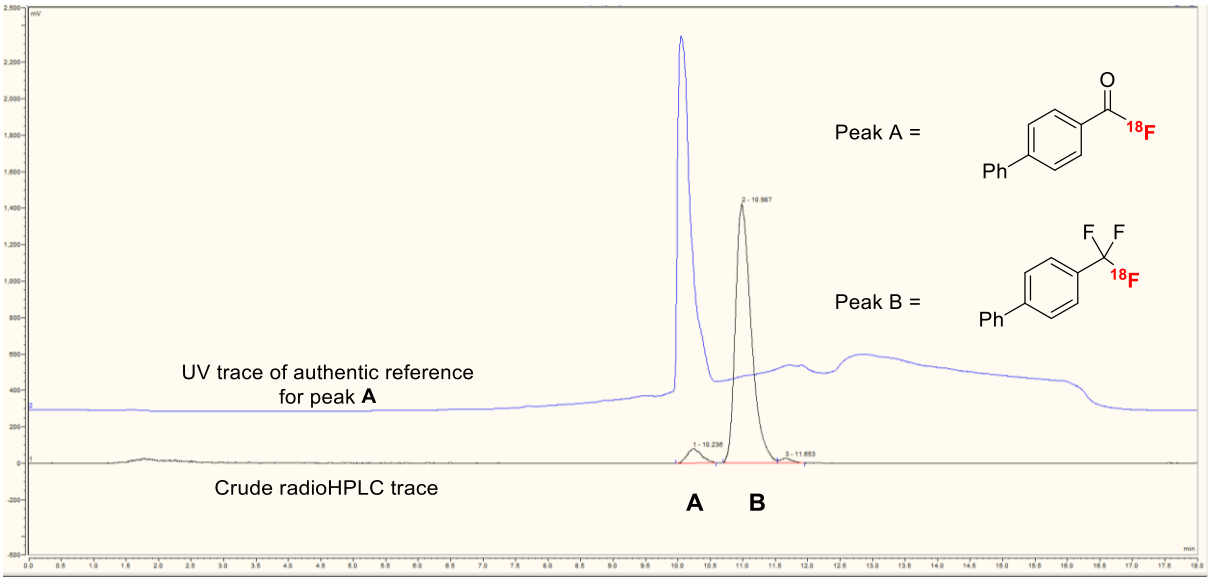

Ph
O
O
18F
F
Radiochemical yield
(radio-TLC)
73% ± 5% (n = 4)
UV trace of authentic reference
Crude radioHPLC trace

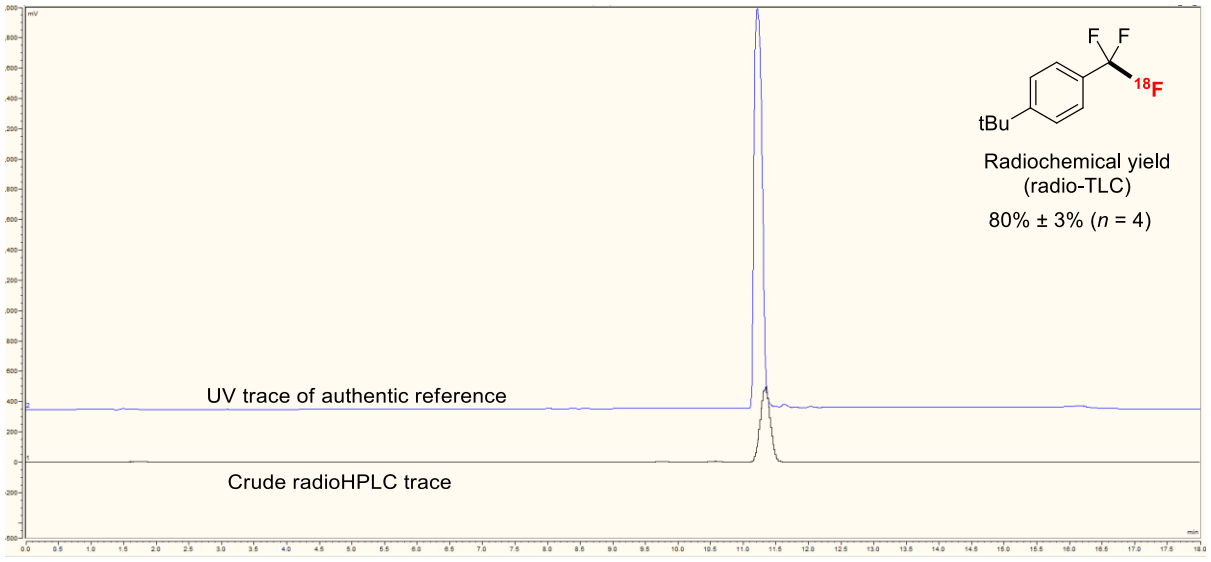

O2N
O
18F
F
Radiochemical yield
(radio-TLC)
73% ± 4% (n = 4)
UV trace of authentic reference
Crude radioHPLC trace

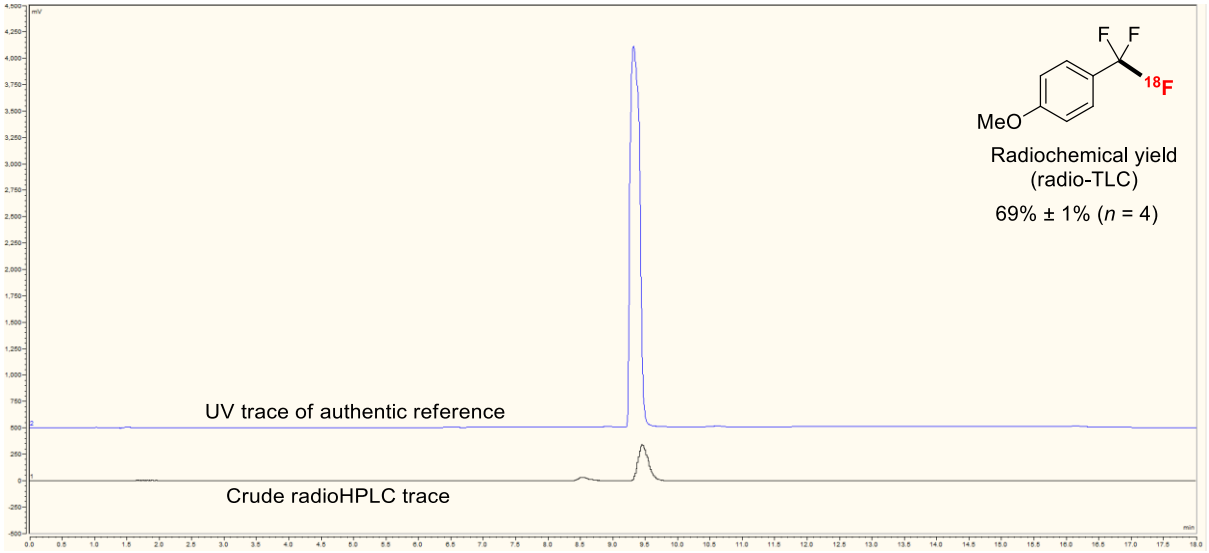

F3C
O
18F
F
Radiochemical yield
(radio-TLC)
66% ± 2% (n = 4)
UV trace of authentic reference
Crude radioHPLC trace

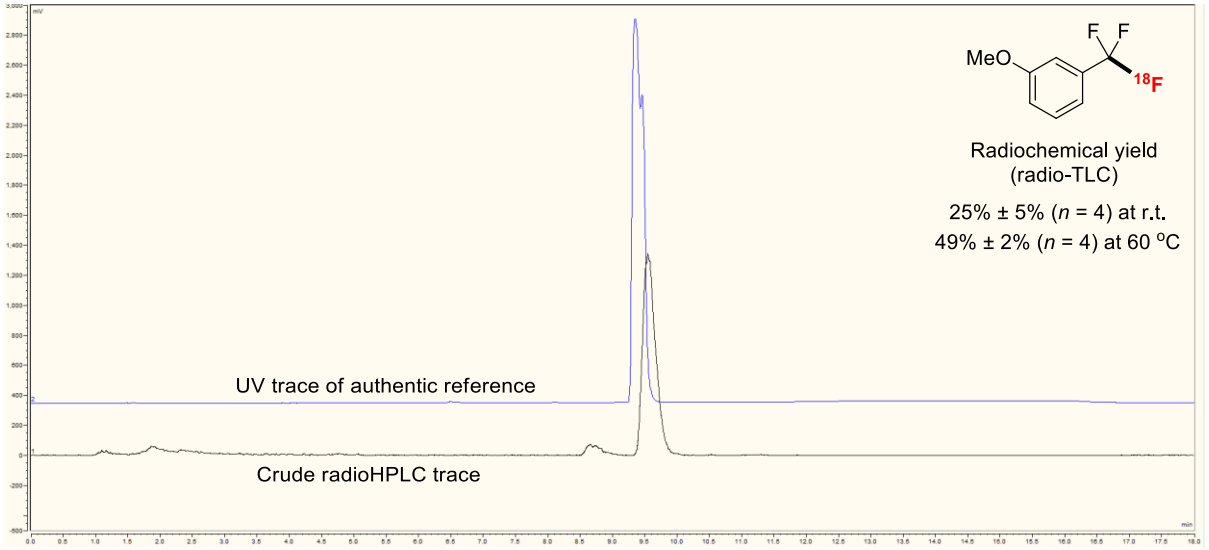
4) [^{18}F]Ar-CF$_3$ ([^{18}F]14)

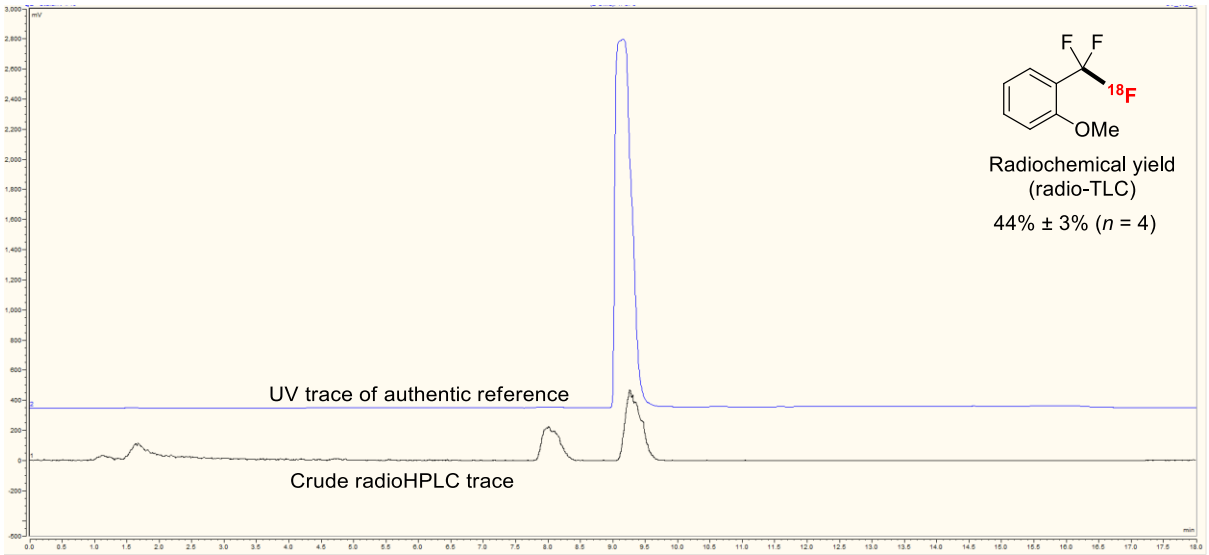


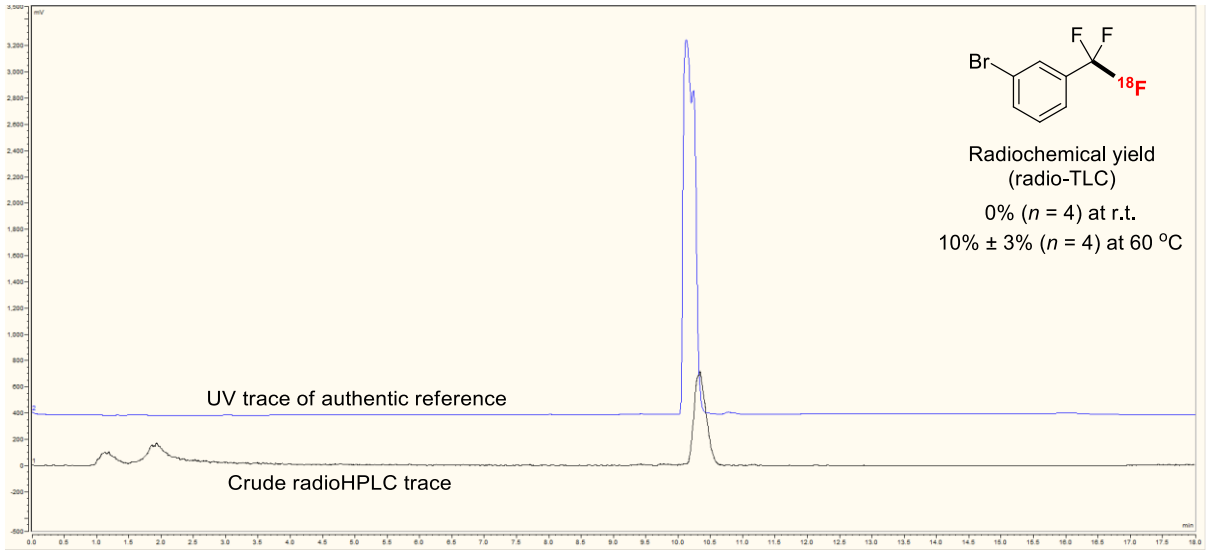


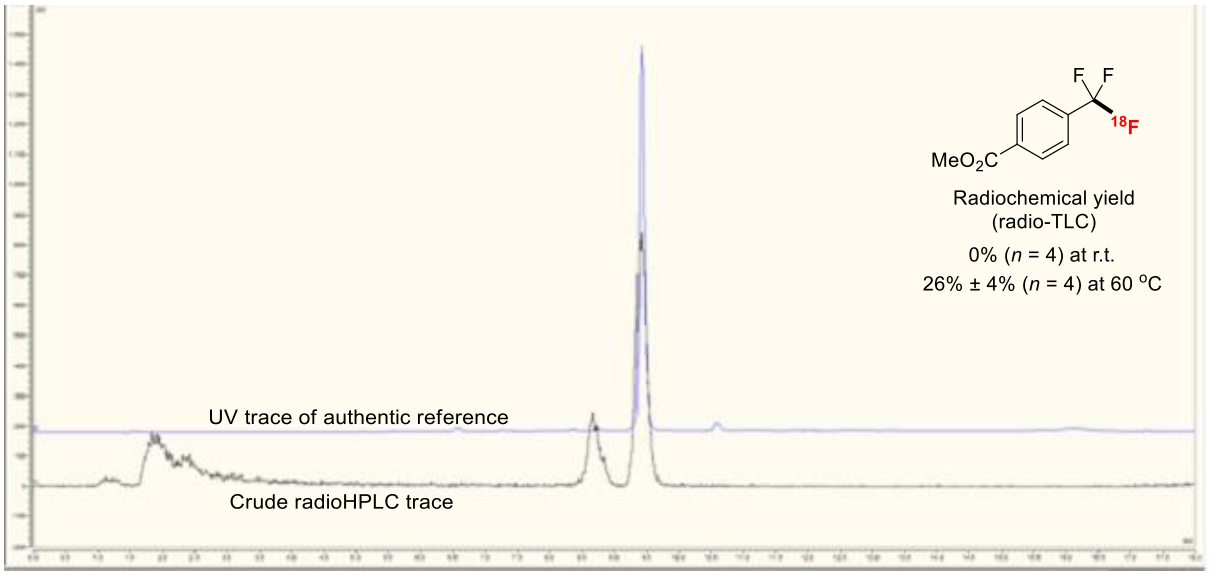


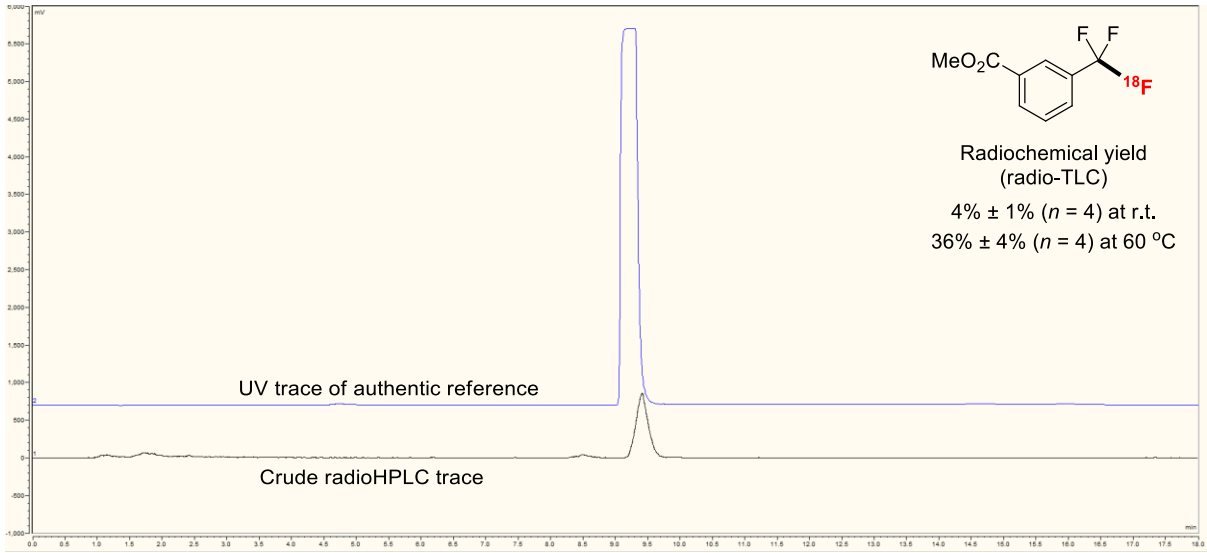

F F
18F
MeO
Radiochemical yield
(radio-TLC)
69% ± 1% (n = 4)
UV trace of authentic reference
Crude radioHPLC trace

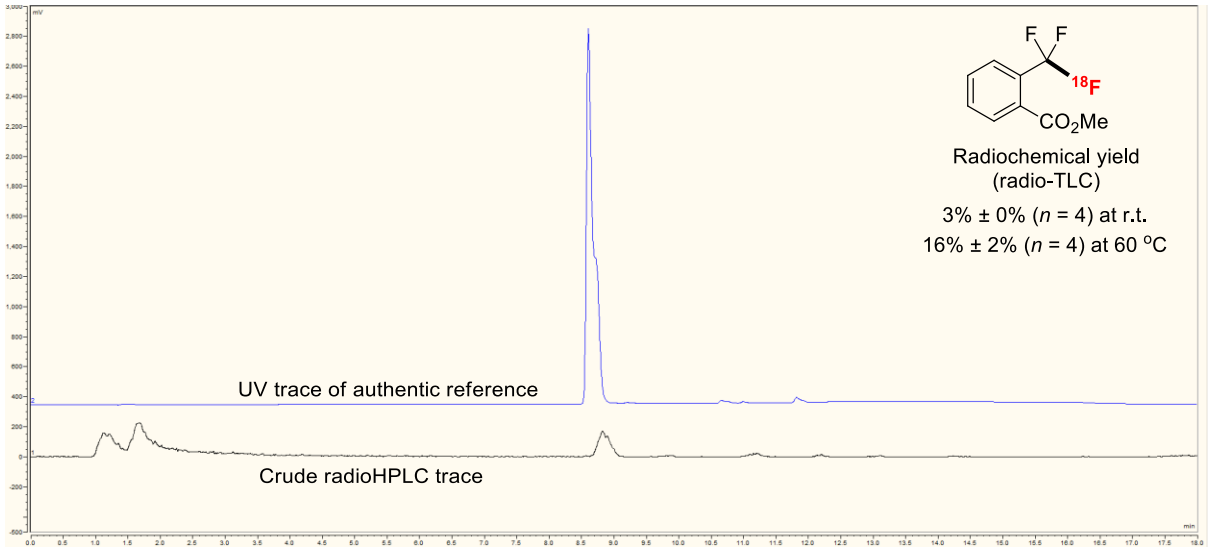

F F
MeO
18F
Radiochemical yield
(radio-TLC)
25% ± 5% (n = 4) at r.t.
49% ± 2% (n = 4) at 60 °C
UV trace of authentic reference
Crude radioHPLC trace


F F
18F
OMe
Radiochemical yield
(radio-TLC)
44% ± 3% (n = 4)
UV trace of authentic reference
Crude radioHPLC trace

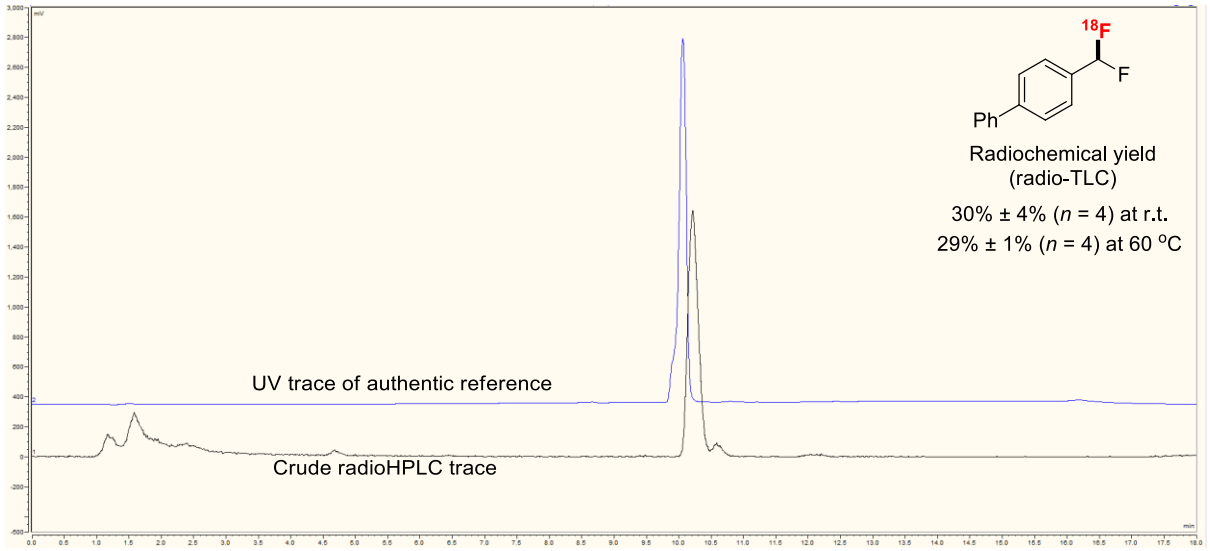

Br
F F
18F
Radiochemical yield
(radio-TLC)
0% (n = 4) at r.t.
10% ± 3% (n = 4) at 60 °C
UV trace of authentic reference
Crude radioHPLC trace

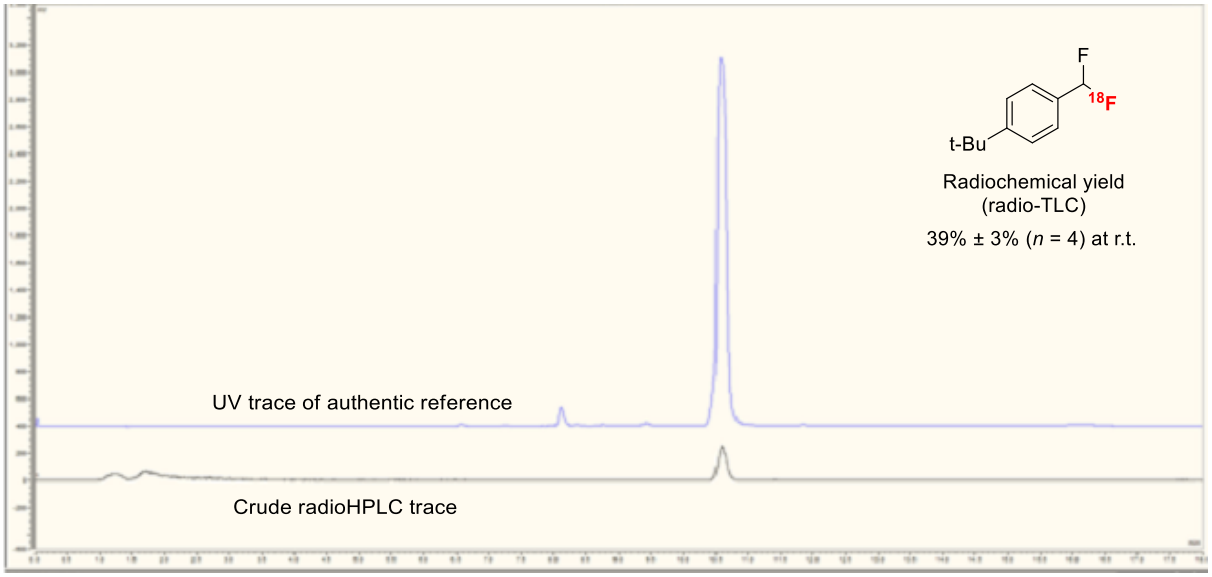

MeO2C
F F
18F
Radiochemical yield
(radio-TLC)
0% (n = 4) at r.t.
26% ± 4% (n = 4) at 60 °C
UV trace of authentic reference
Crude radioHPLC trace

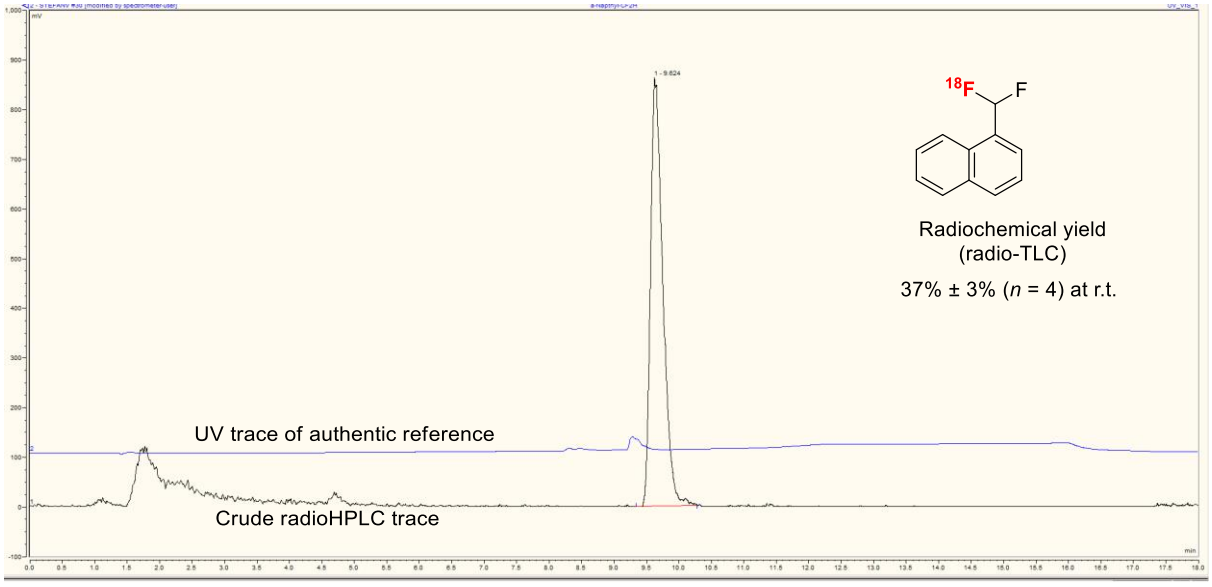

MeO2C
F F
18F
Radiochemical yield
(radio-TLC)
4% ± 1% (n = 4) at r.t.
36% ± 4% (n = 4) at 60 °C
UV trace of authentic reference
Crude radioHPLC trace

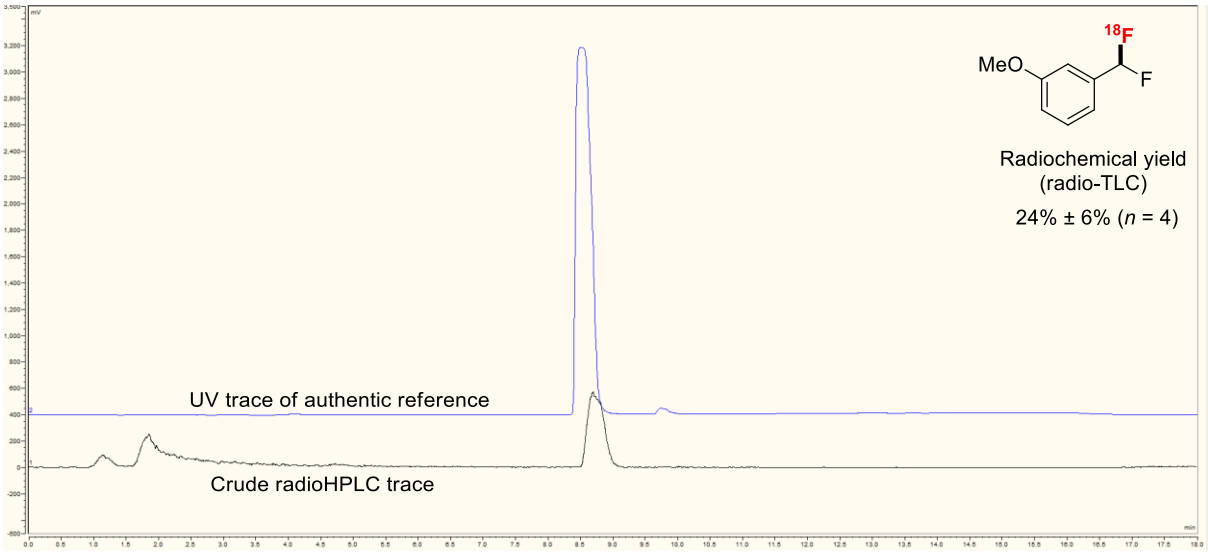


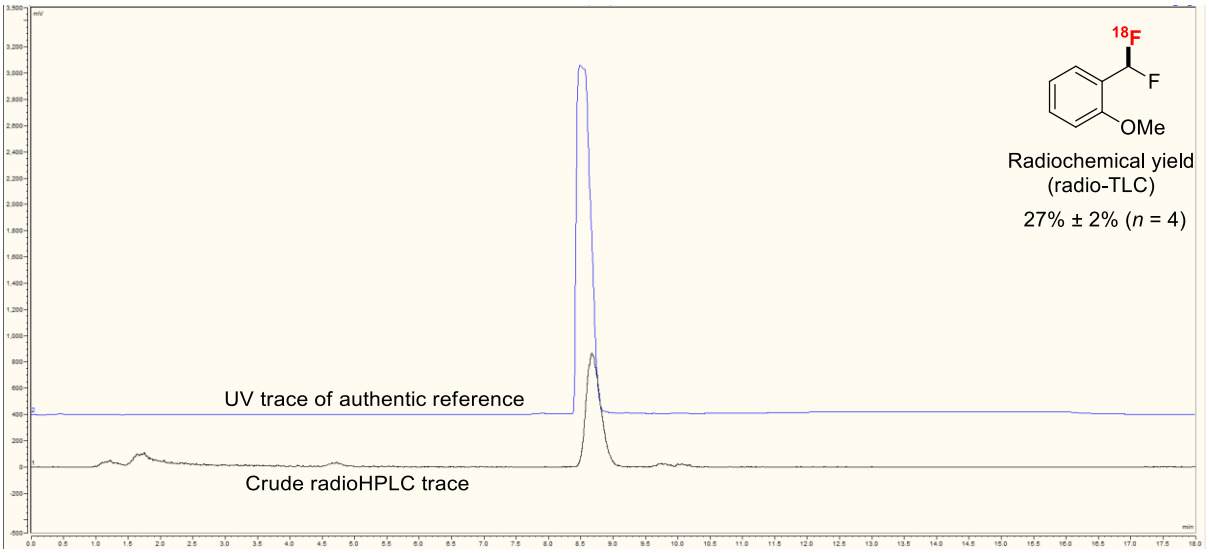
5) [^{18}F]Ar-CF_2H ([^{18}F]17)

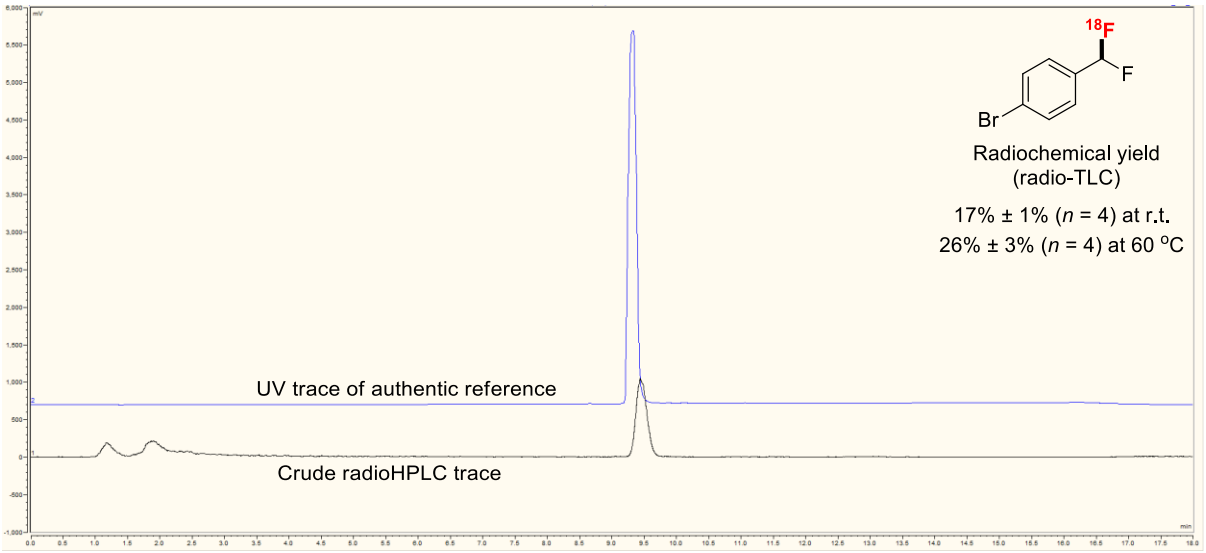


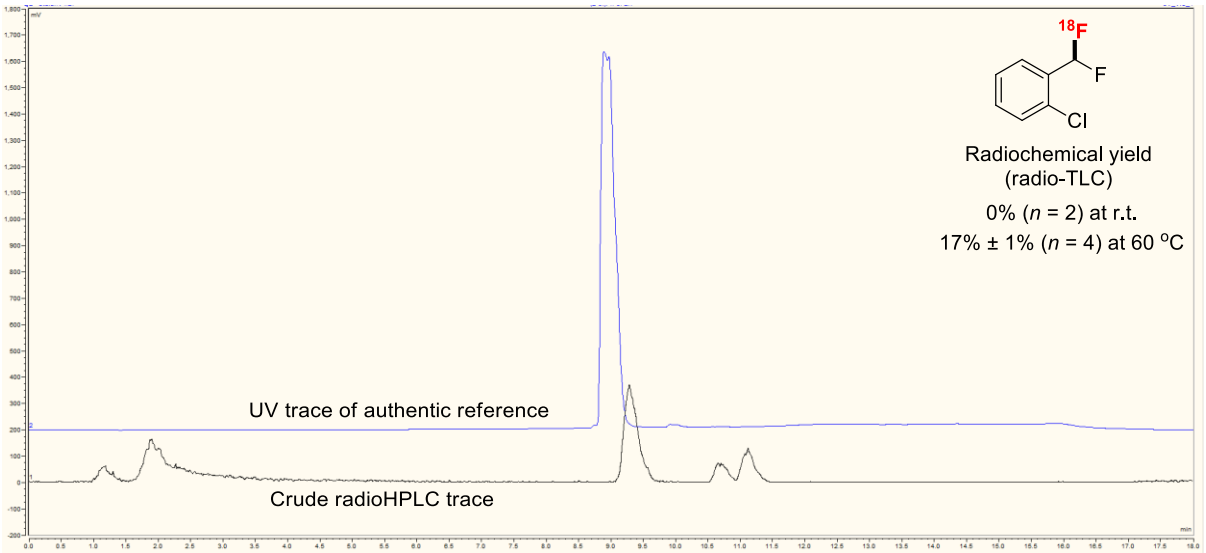


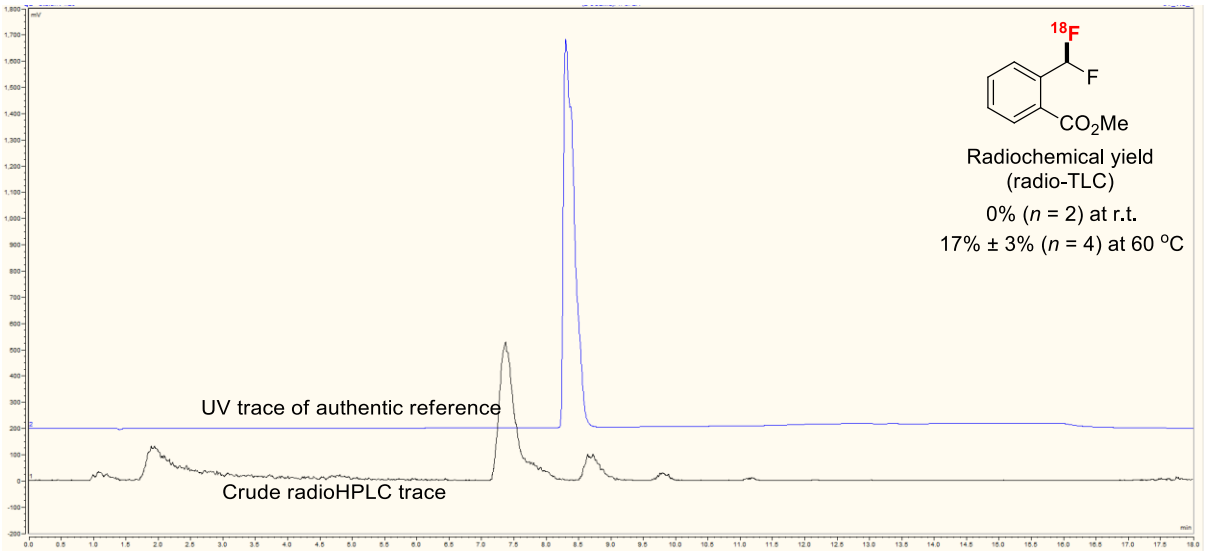

^{18}F
F
Radiochemical yield
(radio-TLC)
37% ± 3% (*n* = 4) at r.t.
UV trace of authentic reference
Crude radioHPLC trace


MeO
^{18}F
F
Radiochemical yield
(radio-TLC)
24% ± 6% (*n* = 4)
UV trace of authentic reference
Crude radioHPLC trace


^{18}F
F
OMe
Radiochemical yield
(radio-TLC)
27% ± 2% (*n* = 4)
UV trace of authentic reference
Crude radioHPLC trace

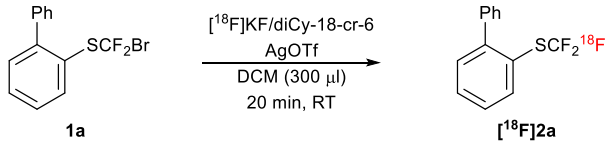

18F
F
Br
Radiochemical yield
(radio-TLC)
17% ± 1% (n = 4) at r.t.
26% ± 3% (n = 4) at 60 °C
UV trace of authentic reference
Crude radioHPLC trace


18F
F
Cl
Radiochemical yield
(radio-TLC)
0% (n = 2) at r.t.
17% ± 1% (n = 4) at 60 °C
UV trace of authentic reference
Crude radioHPLC trace


18F
F
CO2Me
Radiochemical yield
(radio-TLC)
0% (n = 2) at r.t.
17% ± 3% (n = 4) at 60 °C
UV trace of authentic reference
Crude radioHPLC trace

5.2.14 Isolation Procedure and Determination of Isolated RCY and SA

1) [^{18}F]2-[(Trifluoromethyl)sulfanyl]biphenyl ([^{18}F]2a)



Dried [^{18}F]KF/dicyclohexyl-18-crown-6 complex was dissolved in MeOH (300 µl) and added to a V-vial containing AgOTf (10 mg, 0.04 mmol). To this vial was added CH_3CN (400 µL). The solvent was then removed at 100 ˚C under a stream of nitrogen for approximately 5 minutes. The vial was allowed to cool to room temperature and a solution of 2-{[bromo(difluoro)methyl]sulfanyl}biphenyl (12 mg, 0.04 mmol) in CH_2Cl_2 (300 µL) was added by syringe. The resulting suspension was stirred for 20 minutes at room temperature, after which time the solvent was removed under a stream of nitrogen for approximately 2 minutes. The crude mixture was taken up in CH_3CN (2 x 300 µL), filtered through a syringe filter and injected onto a reverse phase HPLC column (Phenomenex Luna C18(2) 100Å, 250 x 10mm).

Flow rate 4 ml/min

0-17 min (50 % MeCN) (isocratic)

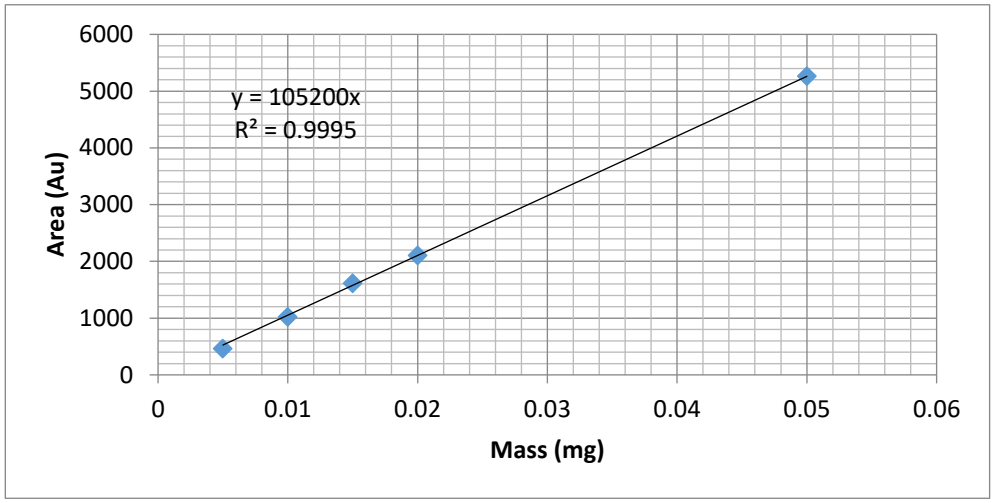
17-27 min (80 % MeCN) (isocratic)

27-32 min (95 % MeCN) (isocratic)

[^{18}F]2-[(trifluoromethyl)sulfanyl]biphenyl was eluted at 28.2 min.

Three reactions were performed, starting from 2080 MBq, 1890 MBq and 1975 MBq of ^{18}F-fluoride (after solvent removal), 197 MBq, 169 MBq and 79 MBq of [^{18}F]2-[(trifluoromethyl)sulfanyl]biphenyl were isolated respectively. RCY = 8 ± 2 % (*n* = 3).

Calibration curve of 2-[(trifluoromethyl)sulfanyl]biphenyl (2a)



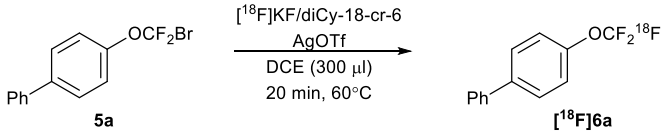
Peak area = 6504.8

Amount of ^{19}F-product **2a** = 6504.8/105200 = 0.062 mg (MW = 254.3) = 0.24 μmol

Activity = 79 MBq

SA = (79/0.24)/1000 = 0.32 GBq/μmol

2) [^{18}F]4-(Trifluoromethoxy)biphenyl ([^{18}F]6a)



Dried [^{18}F]KF/dicyclohexyl-18-crown-6 complex was dissolved in MeOH (300 μl) and added to a V-vial containing AgOTf (10 mg, 0.04 mmol). To this vial was added CH_3CN (400 μL). The solvent was then removed at 100 ˚C under a stream of nitrogen for approximately 5 minutes. The vial was allowed to cool to room temperature and a solution of 4-[bromo(difluoro)methoxy]biphenyl (12 mg, 0.04 mmol) in DCE (300 μL) was added by syringe. The resulting suspension was stirred for 20 minutes at 60 ˚C, after which time the solvent was removed under a stream of nitrogen for 2 minutes at 80 ˚C. The crude mixture was taken up in CH_3CN (2 x 300μL), filtered through a syringe filter and injected onto a reverse phase HPLC column (Phenomenex Luna C18(2) 100Å**,** 250 x 10mm).

Flow rate 4 ml/min

0-17 min (50 % MeCN) (isocratic)

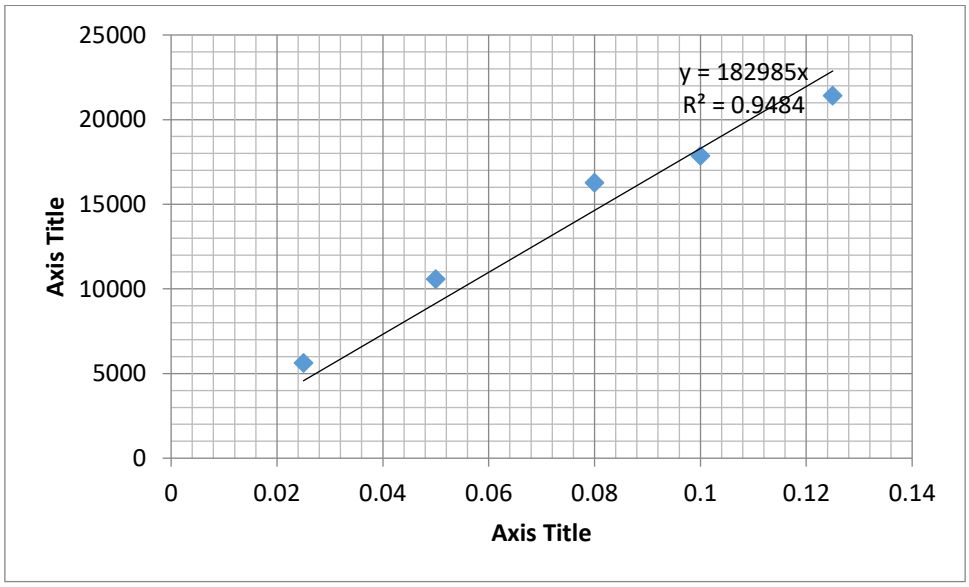
17-27 min (80 % MeCN) (isocratic)

27-32 min (95 % MeCN) (isocratic)

[^{18}F]4-(trifluoromethoxy)biphenyl was eluted at 29.8 min.

Two reactions were performed, starting from 1725 MBq and 588 MBq of ^{18}F-fluoride (after solvent removal), 237 MBq and 40 MBq of [^{18}F]4-(trifluoromethoxy)biphenyl were isolated respectively. RCY = 11 ± 4 % (*n* = 2).

Calibration curve of 4-(Trifluoromethoxy)biphenyl (6a)



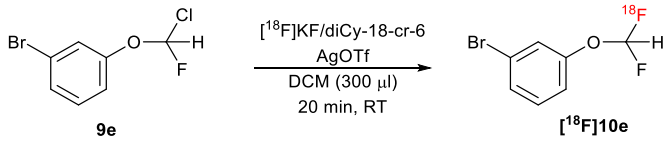
Peak area = 122054

Amount of ^{19}F-product **6a** = 122054/182985 = 0.67 mg (MW = 238.2) = 2.80 μmol

Activity = 237 MBq

SA = (237/2.80)/1000 = 0.08 GBq/μmol

3) [^{18}F]1-Bromo-3-(difluoromethoxy)benzene ([^{18}F]10e)



Dried [^{18}F]KF/dicyclohexyl-18-crown-6 complex was dissolved in MeOH (300 µl) and added to a V-vial containing AgOTf (10 mg, 0.04 mmol). To this vial was added CH_3CN (400 µL). The solvent was then removed at 100 ˚C under a stream of nitrogen for approximately 5 minutes. The vial was allowed to cool to room temperature and a solution of 1-bromo-3-[chloro(fluoro)methoxy]benzene (10 mg, 0.04 mmol) in CH_2Cl_2 (300 µL) was added by syringe. The resulting suspension was stirred for 20 minutes at room temperature, after which time the solvent was removed under a stream of nitrogen for approximately 2 minutes. The crude mixture was taken up in CH_3CN (2 x 300µL), filtered through a syringe filter and injected onto a reverse phase HPLC column (Phenomenex Luna C18(2) 100Å**,** 250 x 10mm).

Flow rate 4 ml/min

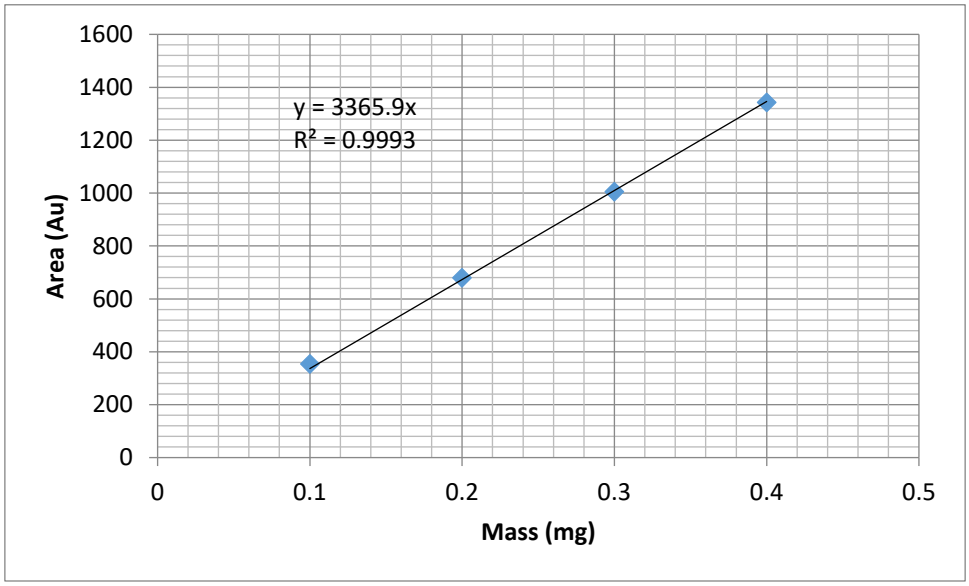
0-16 min (50 % MeCN) (isocratic)

16-27 min (80 % MeCN) (isocratic)

[^{18}F]1-bromo-3-(difluoromethoxy)benzene was eluted at 23.2 min.

Two reactions were performed, starting from 594 MBq and 1510 MBq of ^{18}F-fluoride (after solvent removal), 195 MBq and 509 MBq [^{18}F]1-bromo-3-(difluoromethoxy)benzene was isolated. RCY = 34 ± 1 % (*n* = 2).

Calibration curve of 1-Bromo-3-(difluoromethoxy)benzene (10e)



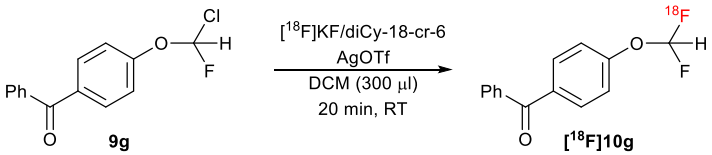
Peak area = 10032.2

Amount of ^{19}F- product **10e** = 10032/3365.9 = 2.98 mg (MW = 223.0) = 13.4 μmol

Activity = 509 MBq

SA = (509/13.4)/1000 = 0.04 GBq/μmol

4) [^{18}F]4-(Difluoromethoxy)phenyl](phenyl)methanone ([^{18}F]10g)



Dried [^{18}F]KF/dicyclohexyl-18-crown-6 complex was dissolved in MeOH (300 μl) and added to a V-vial containing AgOTf (10 mg, 0.04 mmol). To this vial was added CH_3CN (400 μL). The solvent was then removed at 100 ˚C under a stream of nitrogen for approximately 5 minutes. The vial was allowed to cool to room temperature and a solution of {4-[chloro(fluoro)methoxy]phenyl}(phenyl)methanone (11 mg, 0.04 mmol) in CH_2Cl_2 (300 μL) was added by syringe. The resulting suspension was stirred for 20 minutes at room

temperature, after which time the solvent was removed under a stream of nitrogen for approximately 2 minutes. The crude mixture was taken up in CH_3CN (2 x 300µL), filtered through a syringe filter and injected onto a reverse phase HPLC column (Phenomenex Luna C18(2) 100Å**,** 250 x 10mm).

Flow rate 4 ml/min

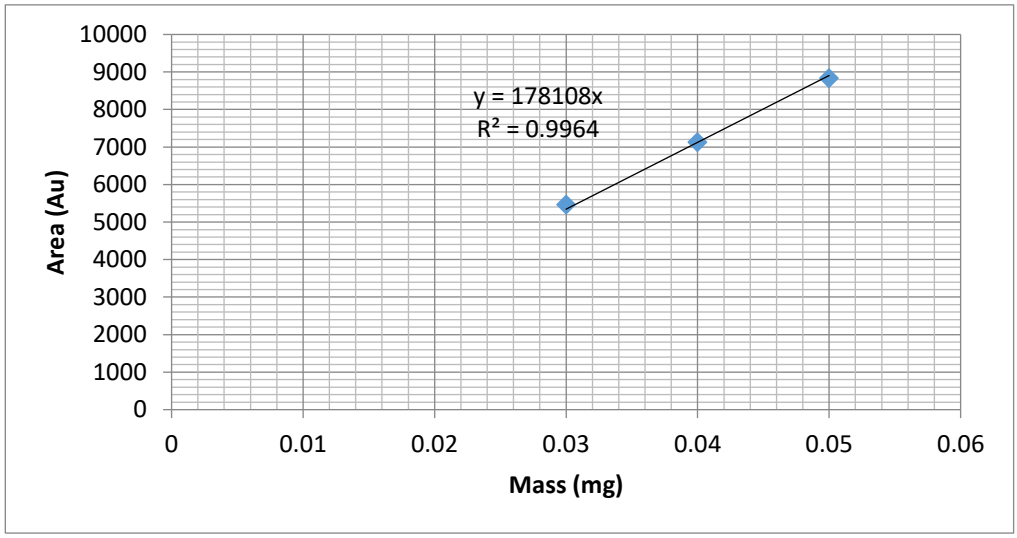
0-17 min (50 % MeCN) (isocratic)

17-25 min (80 % MeCN) (isocratic)

[^{18}F][4-(difluoromethoxy)phenyl](phenyl)methanone was eluted at 22.0 min.

Two reactions were performed, starting from 327 MBq and 1982 MBq of ^{18}F-fluoride (after solvent removal), 106 MBq and 242 MBq of [^{18}F][4-(difluoromethoxy) phenyl](phenyl)methanone was isolated. RCY = 31 ± 2 % (*n* = 2).

Calibration curve of 4-(Difluoromethoxy)phenyl](phenyl)methanone (10g)



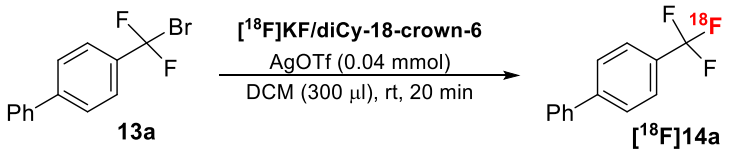
Peak area = 60260.8

Amount of ^{19}F- product **10g** = 60260.8/178108 = 0.34 mg (MW = 247.2)= 1.37 µmol

Activity = 242 MBq

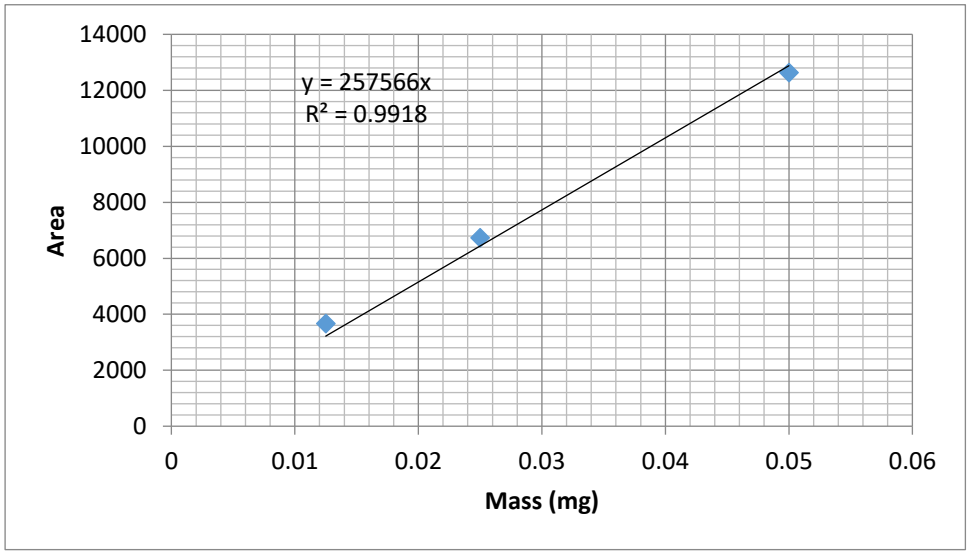
SA = (242/1.37)/1000 = 0.18 GBq/µmol

5) [^{18}F]-4-(Trifluoromethyl)-1,1'-Biphenyl ([^{18}F]14a)

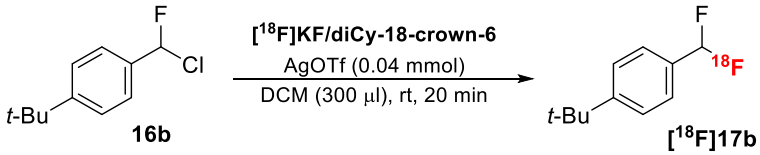


Dried [^{18}F]KF/di-cyclohexyl-18-crown-6 complex was dissolved in MeOH (600 µl) and added to a V-vial containing AgOTf (10 mg, 0.04 mmol). CH_3CN (400 µL) was added and the solvent was removed at 100 °C under a stream of nitrogen (5 min). The mixture was allowed to cool to room temperature and a solution of 4-(bromodifluoromethyl)-1,1'-biphenyl (11 mg, 0.04 mmol) in DCM (300 µL) was added. The resulting suspension was stirred for 20 min at room temperature after which the solvent was removed under a stream of nitrogen (2 min). To the crude mixture was added DMF (300 µL) followed by 60 % CH_3CN/ 40 % H_2O (1.3 mL), filtered through a syringe filter and loaded onto a semi- prep HPLC column (Phenomenex Synergi Hydro RP 80 Å, 250 x 10 mm). Purification was achieved with a 4 ml/min flow eluting the column with eluens A and [^{18}F]-4-(trifluoromethyl)-1,1'-biphenyl was collected (Rt = 15.7 min). Starting from 1090 MBq ^{18}F-fluoride (after solvent removal), 272 MBq [^{18}F]-4-(trifluoromethyl)-1,1'-biphenyl (24 % yield, uncorrected) could be isolated.

Eluents A: 0-20 min (25 % H_2O, CH_3CN 75 %) (isocratic)

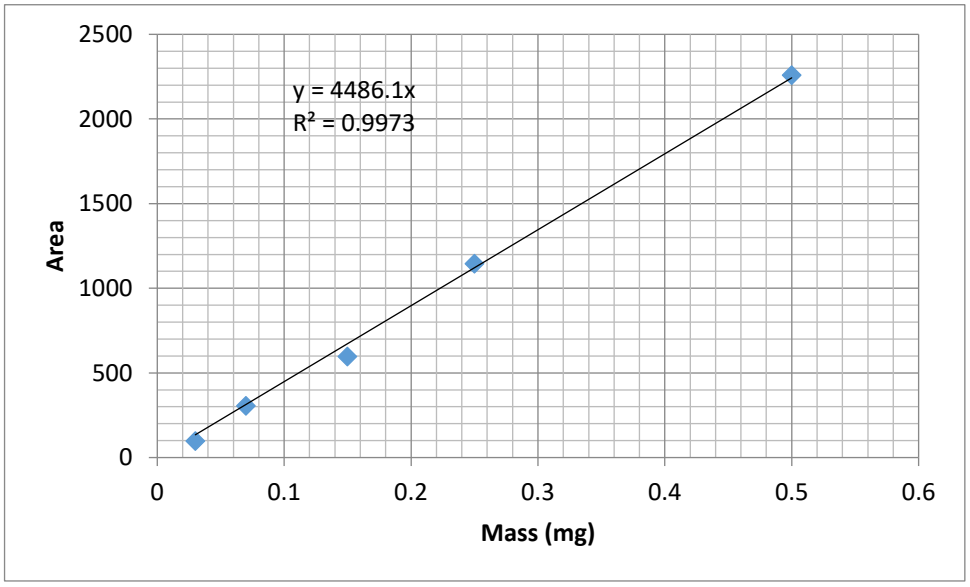


6) [^{18}F]-1-(tert-Butyl)-4-(Difluoromethyl)benzene ([^{18}F]17b)



Dried [^{18}F]KF/di-cyclohexyl-18-crown-6 complex was dissolved in MeOH (600 µl) and added to a V-vial containing AgOTf (10 mg, 0.04 mmol). CH_3CN (400 µL) was added and the solvent was removed at 100 °C under a stream of nitrogen (5 min). The mixture was allowed to cool to room temperature and a solution of 1-(*tert*-butyl)-4-(chlorofluoro methyl)benzene (8 mg, 0.04 mmol) in DCM (300 µL) was added. The resulting suspension was stirred for 20 min at room temperature after which the solvent was removed under a stream of nitrogen (2 min). The crude mixture was taken up in CH_3CN (2x300 µL), filtered through a syringe filter and loaded onto a semi- prep HPLC column (Phenomenex Luna C18(2) 100 Å, 250 x 10 mm). Purification was achieved with a 4 ml/min flow eluting the column with eluents B and [^{18}F]-1-(*tert*-butyl)-4-(difluoromethyl)benzene was collected (Rt = 29.7 min). Starting from 1690 MBq ^{18}F-fluoride (after solvent removal), 363 MBq [^{18}F]-1-(tert-butyl)-4-(difluoromethyl)benzene (21 % yield, uncorrected) could be isolated.

Eluents B: 0-15 min (50 % H_2O, CH_3CN 50 %); 15-35 min (65 % H_2O, CH_3CN 35 %)



5.2.15 Radiosynthesis and Application of [^{18}F]Umemoto Reagent ([^{18}F]18)

General Procedure for the Radiosynthesis of [^{18}F]Umemoto Reagent ([^{18}F]18)

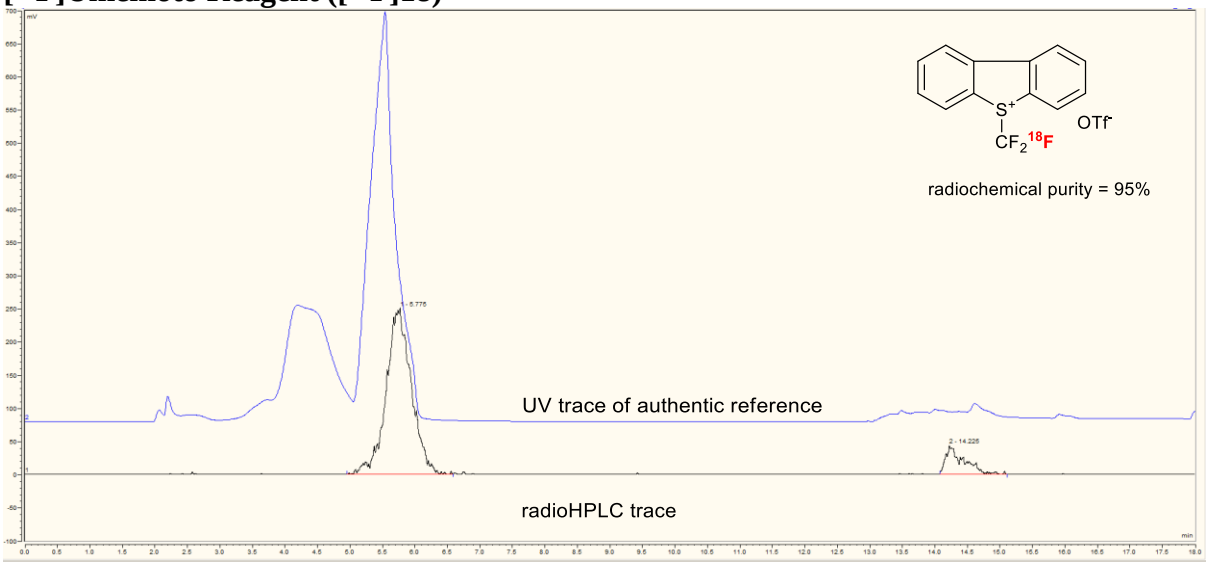
To a V-vial containing a solution of [^{18}F]2-[(trifluoromethyl)sulfanyl]biphenyl ([^{18}F]**2a**) (~500 MBq, obtained after purification by preparative HPLC; see Section 5.2.14) in MeCN was diluted with H_2O (25 mL). The mixture was eluted over a SepPak cartridge (Waters C18-light; activated with 1 mL MeOH and 5 mL H_2O) and a SepPak Dry® cartridge (Waters, Na_2SO_4). The product was flushed off with DCM (4 mL). The solvent was evaporated with a stream of N_2, then a solution of *meta*-chloroperoxybenzoic acid (20 mg, 0.08 mmol) in DCE (300 μL) was added by syringe, followed by a solution of trifluoromethanesulfonic anhydride (20 μL, 0.12 mmol) in DCE (100 μL). The sealed vial was allowed to stir for 20 minutes at 45 °C. After the reaction, the mixture was eluted over a silica SepPak (plus). The cartridge was flushed with DCE (3 mL) then the product was eluted with MeCN (800 μL) to provide a stock solution of the [^{18}F]Umemoto Reagent ([^{18}F]**18**). An aliquot was removed for analysis by radioTLC and HPLC for radiochemical yield and product identity. Analysis was performed using Gradient B with a Merck Chromolith® HighResolution RP-18e 100x4.6mm.

HPLC gradient B:

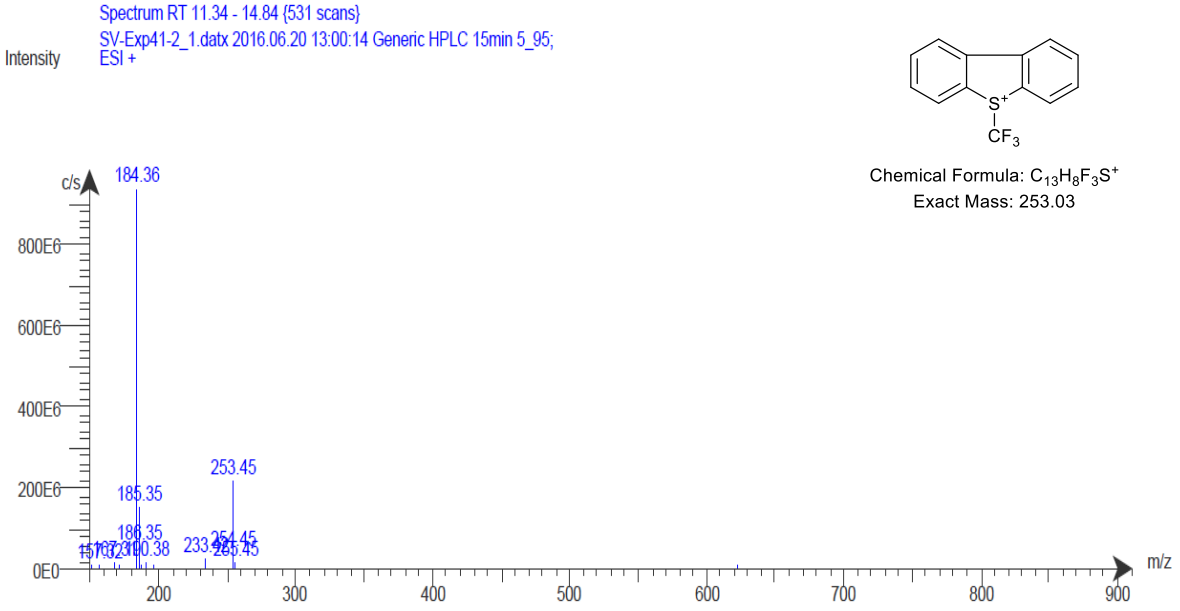
water/acetonitrile, 1 mL/min, Merck Chromolith® HighResolution RP-18e 100x4.6mm.

0-10 min	90 % H_2O/10 % MeCN
10-11 min	90 % H_2O/10 % MeCN to 5 % H_2O/95 % MeCN
11-15 min	5 % H_2O/95 % MeCN
15-16 min	5 % H_2O/95 % MeCN to 90 % H_2O/10 % MeCN
16-18 min	90 % H_2O/10 % MeCN

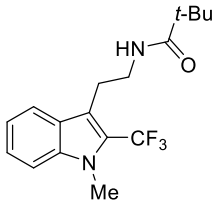
[^{18}F]Umemoto Reagent ([^{18}F]18)



Mass spectrum of the main peak



_N_-(2-(1-methyl-2-(trifluoromethyl)-1H-indol-3-yl)ethyl)pivalamide (20)



A 5 mL vial containing a magnetic stirrer bar was added *N*-[2-(1-methyl-1H-indol-3-yl)ethyl]pivalamide 60 mg, 0.24 mmol) and CuCl (4.6 mg, 0.046 mmol). MeOH (1 mL) and 1-(trifluoromethyl)-1,2-benziodoxol-3(1H)-one (88 mg, 0.28 mmol) were added under an argon atmosphere. The reaction mixture was stirred for 2 hours at 70 ^{o}C. Upon completion of the reaction, sat. aq. $NaHCO_3$ (10 mL) was added at room temperature. The resulting mixture was extracted with EtOAc (2 x 10 mL), and combined organic phases were washed sequentially with distilled water and brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude mixture was purified by silica gel column chromatography (eluent: 20 % EtOAc in *n*-pentane) to provide the title compound (72 mg, 68 % yield) as a white solid.

(1H NMR, 500 MHz, $CDCl_3$): δ = 7.74 (d, J = 8.2 Hz, 1H), 7.40−7.36 (m, 2H), 7.20 (ddd J_1 = 1.9 Hz, J_2 = 6.0 Hz, J_3 = 7.9 Hz, 1H), 5.74 (br s, 1H), 3.84 (s, 3H), 3.53 (q, J = 6.6 Hz, 2H), 3.15 (tq, J_1 = 1.9 Hz, J_2 = 6.6, 2H), 1.12 (s, 9H); (13C NMR, 125 MHz, $CDCl_3$): δ = 178.5, 137.7, 126.5, 124.9, 123.0 (q, J = 35.0 Hz), 122.45 (q, J = 267.2 Hz), 120.5, 120.4, 115.8 (q, J = 2.8 Hz), 109.7, 40.6, 38.6, 30.9 (q, J = 1.8 Hz), 27.4, 24.2; (19F NMR, 377 MHz, $CDCl_3$): δ = −55.8 (s, 3F). Data consistent with literature values.[13]

General Procedure for the Radiosynthesis of [^{18}F]N-(2-(1-methyl-2-(trifluoromethyl)-1H-indol-3-yl)ethyl)pivalamide ([^{18}F]20)

To a V-vial containing a magnetic stirrer bar was added [^{18}F]Umemoto Reagent ([^{18}F]**18**) (~30 MBq) in MeCN (~30 µL). Then a solution of *N*-(2-(1-methyl-1H-indol-3-yl)ethyl)pivalamide (10 mg, 0.04 mmol) and *N*-methyl-morpholine (5 µL, 0.04 mmol) was added by syringe. The sealed vial was allowed to stir for 20 minutes at 80 °C. An aliquot was removed for analysis by radioTLC and HPLC for radiochemical yield and product identity. Analysis was performed using Gradient A with a Waters Nova-Pak C18 column (4 µm, 3.9 x 150 mm) at a flow rate 1ml/min.

HPLC gradient A:

water/acetonitrile, 1 mL/min, Waters Nova-Pak C18 Column, 4 µm, 3.9 x 150 mm

0-1 min (5 % MeCN) isocratic

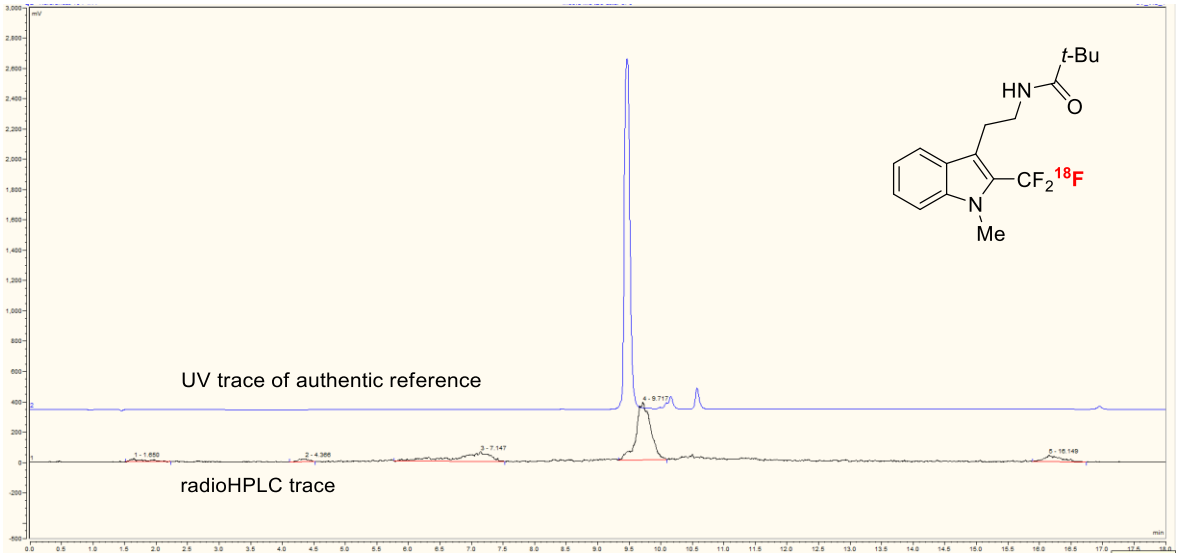
1-10 min (5 % MeCN to 95 % MeCN) linear increase

10-14 min (95 % MeCN) isocratic

14-15 min (95 % MeCN to 5 % MeCN) linear decrease

15-17 min (5 % MeCN) isocratic

[^{18}F]*N*-(2-(1-methyl-2-(trifluoromethyl)-1H-indol-3-yl)ethyl)pivalamide ([^{18}F]20)



5.3 Experimental Procedures and Characterisation Data for Chapter 3

5.3.1 Synthesis of Thioureas (23)

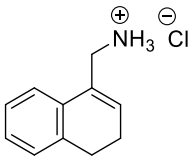
General Procedure L *(Preparation of thioureas from amines)* To a solution of appropriate amine (1.0−1.2 equiv.) in DCM (0.1 M) was added an appropriate isothiocyanate (1.0−1.2 equiv.) and the mixture was stirred at room temperature for 16 hours under nitrogen atmosphere. The reaction mixture was concentrated *in vacuo*. The crude product was purified by silica gel column chromatography or precipitation by redissolving in DCM followed by addition of Et_2O and *n*-pentane. The solid was collected by filtration and washed with *n*-pentane (x2).

General Procedure M *(Reduction of aldehydes with $NaBH_4$)* Into a solution of appropriate aldehyde (12.0 mmol) in MeOH (20 mL) was added $NaBH_4$ (302 mg, 8.0 mmol) at 0 ^oC. The reaction was stirred at room temperature for 3 hours then quenched with water and the mixture was extracted with Et_2O (x2). Combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude alcohol was used in the next step without further purification.

General Procedure N *(Synthesis of N-allyl phthalimides from allyl alcohols)* To the solution of appropriate allyl alcohol (5.0 mmol) in THF (25 mL) was added PPh_3 (1.31 g, 5.0 mmol), phthalimide (736 mg, 5.0 mmol) and diethyl azodicarboxylate (0.79 mL, 5.0 mmol) at 0 ^oC. After stirring for 16 hours at room temperature, the reaction mixture was concentrated *in vacuo*. The crude product was either purified by silica gel column chromatography or used in the next step without further purification.

General Procedure O *(Hydrazinolysis of phathalimides)* Into a solution of appropriate phthalimide (2.5 mmol) in MeOH (25 mL) was added hydrazine monohydrate (0.18 mL, 3.75 mmol) and the reaction mixture was stirred for 16 hours under reflux. The mixture was cooled, concentrated *in vacuo*, re-dissolved in 1 M HCl (20 mL) and the resulting suspension was filtered. The filtrate was basified to pH = 10 using 5 M NaOH and extracted with Et_2O (x2). Combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude amine was used in the next step without further purification.

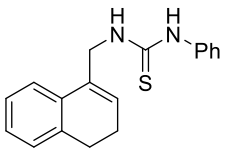
(3,4-Dihydronaphthalen-1-yl)methanammonium chloride



The title compound was prepared following literature reported procedure,[14] using alpha-tetralone (6.65 mL, 50 mmol), $AlCl_3$ (8 mg, 0.06 mmol), TMSCN (6.88 mL, 55 mmol) and LAH (2.28 g, 60 mmol). (3.09 g, 39 % yield, white solid). The salt is then basified and extracted with DCM and used as a free amine in the next steps.

(^{1}H NMR, 400 MHz, CD_3OD): δ = 7.23−7.20 (m, 2H), 7.17−7.14 (m, 2H), 6.22 (t, *J* = 4.5 Hz, 1H), 3.95 (brs, 2H), 2.74 (t, *J* = 8.1 Hz, 2H), 2.31−2.28 (m, 2H); (^{13}C NMR, 101 MHz, CD_3OD): δ = 137.9, 133.1, 131.6, 131.4, 129.2, 129.2, 128.1, 123.3, 41.7, 28.7, 24.1. Data consistent with literature values.[14]

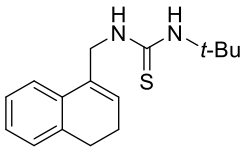
1-((3,4-Dihydronaphthalen-1-yl)methyl)-3-phenylthiourea (23a1)



The title compound was prepared following General Procedure L using (3,4-dihydronaphthalen-1-yl)methanamine (796 mg, 5.0 mmol), DCM (50 mL) and phenyl isothiocyanate (0.60 mL, 5.0 mmol). The crude product was purified by precipitation to give the title compound (1.28 g, 87 % yield) as a white solid.

(^{1}H NMR, 400 MHz, $CDCl_3$): δ (ppm) = 8.45 (br s, 1H), 7.47−7.40 (m, 3H), 7.37−7.23 (m, 6H), 6.20 (br s , 1H), 6.16 (t, *J* = 4.4 Hz, 1H), 4.81 (d, *J* = 4.4 Hz, 2H), 2.87 (t, *J* = 8.1 Hz, 2H), 2.44−2.39 (m, 2H); (^{13}C NMR, 101 MHz, $CDCl_3$): δ (ppm) = 180.1, 136.3, 136.0, 132.6, 132.2, 130.0, 128.5, 127.7, 127.3, 126.9, 126.6, 124.7, 122.7, 48.0, 27.7, 22.9; IR: ν 3382, 3201, 2934, 2883, 2830, 1596, 1530, 1495, 1449, 1344, 1298, 1236, 1185, 1134, 1072, 1022, 970 cm^{-1}; HRMS (ESI) for $C_{18}H_{19}N_2S$ $[M+H]^+$ requires 295.1264 found 295.1264; Mp. 105−108 °C.

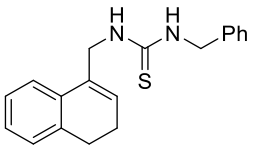
1-(*tert*-Butyl)-3-((3,4-dihydronaphthalen-1-yl)methyl)thiourea (23a2)



The title compound was prepared following General Procedure L using (3,4-dihydronaphthalen-1-yl)methanamine (318 mg, 2.0 mmol), DCM (20 mL) and *tert*-butyl isothiocyanate (0.25 mL, 2.0 mmol). The crude product was purified by precipitation to give the title compound (393 mg, 72 % yield) as a white solid.

(^{1}H NMR, 400 MHz, $CDCl_3$): δ (ppm) = 7.38−7.26 (m, 4H), 6.22 (t, *J* = 4.5 Hz, 1H), 6.17 (br s , 1H), 4.69 (s, 2H), 2.89 (t, *J* = 8.1 Hz, 2H), 2.46−2.41 (m, 2H), 1.43 (s, 9H); (^{13}C NMR, 101 MHz, $CDCl_3$): δ (ppm) = 180.9, 136.3, 132.5 (2C), 128.8, 127.8, 127.4, 126.7, 122.8, 52.7, 48.3, 29.5, 27.8, 23.0; IR 3270, 3061, 2931, 2831, 1535, 1491, 1450, 1392, 1345, 1280, 1198, 1120, 1021, 973, 922, 821 cm^{-1} ; HRMS (ESI) for $C_{16}H_{23}N_2S$ $[M+H]^+$ requires 275.1577 found 275.1575; Mp. 127−129 °C.

1-Benzyl-3-((3,4-Dihydronaphthalen-1-yl)methyl)thiourea (23a3)

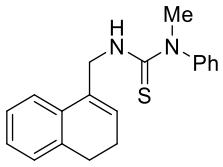


The title compound was prepared following General Procedure L using (3,4-dihydronaphthalen-1-yl)methanamine (318 mg, 2.0 mmol), DCM (20 mL) and benzyl isothiocyanate (0.27 mL, 2.0 mmol). The crude

product was purified by silica gel column chromatography (eluent: 20 % EtOAc in *n*-pentane) to provide the title compound (318 mg, 52 % yield) as white solid.

(^{1}H NMR, 400 MHz, $CDCl_3$): δ (ppm) = 7.46−7.38 (m, 5H), 7.35−7.26 (m, 4H), 6.25 (br s, 1H), 6.15 (t, *J* = 4.3 Hz, 2H), 5.97 (br s , 1H), 4.75 (br s, 2H), 4.57 (br s, 2H), 2.84 (t, *J* = 8.1 Hz, 2H), 2.42−2.37 (m, 2H); (^{13}C NMR, 101 MHz, $CDCl_3$): δ (ppm) = 181.9, 136.7, 136.3, 132.4, 131.9, 128.8, 128.5, 127.8, 127.8, 127.5, 127.4, 126.7, 122.6, 48.5, 47.0, 27.7, 22.9; IR: 3251, 3061, 2932, 2830, 1547, 1492, 1463, 1344, 1277, 1023, 960, 822 cm^{-1}; HRMS (ESI) for $C_{19}H_{21}N_2S$ $[M+H]^+$ requires 309.1420 found 309.1419; Mp. 90−93 °C.

3-((3,4-Dihydronaphthalen-1-yl)methyl)-1-methyl-1-phenylthiourea (23a4)



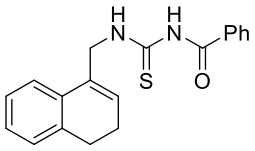
To a solution of (3,4-dihydronaphthalen-1-yl)methanamine[5] (2.0 mmol) in EtOH (4 mL) was added triethylamine (0.28 mL, 2.0 mmol) and carbon disulfide (0.36 mL, 6.0 mmol). The mixture was stirred at room temperature for 2 hours then cooled to 0 ºC. Di-tert-butyl dicarbonate (437 mg, 2.0 mmol) and 4-(dimethylamino)pyridine (7.3 mg, 0.06 mmol) were added then the mixture was stirred at room temperature for 4 hours. The reaction mixture was diluted with EtOAc (20 mL) and the organic layer was washed with H_2O (20 mL) and brine (20 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated in vacuo. The crude product was purified by silica gel column chromatography (eluent: 10 % Et_2O in *n*-pentane) to provide the isothiocyanate (285 mg, 71 % yield) as a colourless oil.

The isothiocyanate (242 mg, 1.2 mmol) was then dissolved in DCM (12 mL) and was added *N*-methylaniline (0.16 mL, 1.44 mmol) and triethylamine (0.25 mL, 1.8 mmol). The mixture was stirred at room temperature for 16 hours. The reaction mixture was concentrated *in vacuo* and the crude product was purified by redissolving in DCM followed by addition of

Et_2O and *n*-pentane. The solid was collected by filtration and washed with *n*-pentane (x2) to give the title compound (324 mg, 87 % yield) as a white solid.

(^{1}H NMR, 400 MHz, $CDCl_3$): δ (ppm) = 7.50−7.40 (m, 3H), 7.32−7.23 (m, 6H), 6.01 (t, *J* = 4.4 Hz, 1H) 5.45 (br s , 1H), 4.74 (dd, *J* = 4.9, 1.0 Hz, 2H), 3.82 (s, 3H), 2.80 (t, *J* = 7.9 Hz, 2H), 2.38−2.32 (m, 2H); (^{13}C NMR, 101 MHz, $CDCl_3$): δ (ppm) = 181.7, 142.6, 136.3, 132.8, 132.7, 130.4, 128.3, 127.5, 127.4, 127.1, 126.9, 126.5, 122.7, 48.4, 43.3, 27.8, 22.9; IR:3396, 3057, 2931, 2829, 1594, 1513, 1490, 1450, 1384, 1345, 1304, 1280, 1236, 1103, 1072, 1051, 1020, 1001, 970, 812 cm^{-1}; HRMS (ESI) for $C_{19}H_{21}N_2S$ $[M+H]^+$ requires 309.1420 found 309.1419; Mp. 108−111 °C.

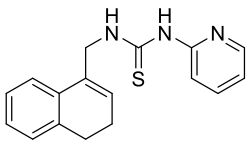
_N_-(((3,4-Dihydronaphthalen-1-yl)methyl)carbamothioyl)benzamide (23a5)



The title compound was prepared following General Procedure L using (3,4-dihydronaphthalen-1-yl)methanamine (318 mg, 2.0 mmol), DCM (20 mL) and benzoyl isothiocyanate (0.54 mL, 4.0 mmol). The crude product was purified by precipitation to give the title compound (451 mg, 68 % yield) as a pale yellow solid.

(^{1}H NMR, 400 MHz, $CDCl_3$): δ = 10.90 (brs, 1H), 9.18 (brs, 1H), 7.93−7.91 (m, 2H), 7.72 (tt, J_1 = 1.1 Hz, J_2 = 7.5 Hz, 1H), 7.61 (t, *J* = 7.7 Hz, 2H), 7.40−7.27 (m, 4H), 6.28 (t, *J* = 4.4 Hz, 1H), 4.86 (dd, J_1 = 1.2 Hz, J_2 = 5.1 Hz, 2H), 2.92 (t, *J* = 8.1 Hz, 2H), 2.49−2.44 (m, 2H); (^{13}C NMR, 101 MHz, $CDCl_3$): δ = 179.6, 166.6, 136.3, 133.5, 132.7, 131.7, 131.4, 129.1, 128.8, 127.4, 127.4, 126.7, 122.5, 48.2, 27.8, 23.0; IR: ν 3240, 2933, 2830, 1669, 1601, 1508, 1489, 1314, 1255, 1155, 1102, 1073, 1023, 1001, 972, 892; HRMS (ESI) for $C_{19}H_{19}ON_2S$ $[M+H]^+$ requires 323.1213 found 323.1212; Mp. 100−105 °C.

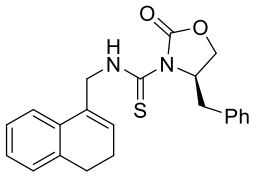
1-((3,4-Dihydronaphthalen-1-yl)methyl)-3-(pyridin-2-yl)thiourea (23a6)



The title compound was prepared following General Procedure L using (3,4-dihydronaphthalen-1-yl)methanamine (318 mg, 2.0 mmol), DCM (20 mL) and benzyl isothiocyanate (0.27 mL, 2.0 mmol). The crude product was purified by silica gel column chromatography (eluent: 20 % EtOAc in *n*-pentane) to provide the title compound (318 mg, 52 % yield) as white solid.

(^{1}H NMR, 400 MHz, $CDCl_3$): δ = 12.01 (s, 1H), 9.16 (s, 1H), 8.01 (d, J = 5.1 Hz, 1H), 7.63 (td, J_1 = 1.9 Hz, J_2 = 7.8 Hz, 1H), 7.37 (d, J = 7.1 Hz, 1H), 7.26−7.18 (m, 3H), 6.93−6.88 (m, 2H), 6.18 (t, *J* = 4.3 Hz, 1H), 4.83 (d, *J* = 5.4 Hz, 2H), 2.82 (t, *J* = 7.9 Hz, 2H), 2.40−2.34 (m, 2H); (^{13}C NMR, 101 MHz, $CDCl_3$): δ = 181.9, 136.7, 136.3, 132.4, 131.9, 128.8, 128.5, 127.8, 127.8, 127.5, 127.4, 126.7, 122.6, 48.5, 47.0, 27.7, 22.9; IR: ν 3251, 3061, 2932, 2830, 1547, 1492, 1463, 1344, 1277, 1023, 960, 822; HRMS (ESI) for $C_{17}H_{18}N_3S$ $[M+H]^+$ requires 309.1420 found 309.1419; Mp. 90−93 °C.

(*R*)-4-Benzyl-*N*-((3,4-dihydronaphthalen-1-yl)methyl)-2-oxooxazolidine-3-carbothioamide (23a7)

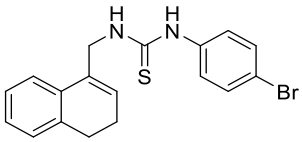


To a solution of (3,4-dihydronaphthalen-1-yl)methanamine (391 mg, 2.0 mmol) in EtOH (15 mL) was added (*R*)-4-Benzyl-*N*-((3,4-dihydronaphthalen-1-yl)methyl)-2-oxooxazolidine-3-carbothioamide (535 mg, 2.0 mmol) and the mixture was stirred at room temperature for 16 hours under nitrogen atmosphere. The reaction mixture was concentrated *in vacuo*. The crude product was purified by silica gel column chromatography (eluent: 5 % EtOAc in *n*-pentane) to provide the title compound (581 mg, 77 % yield) as white solid.

(^{1}H NMR, 400 MHz, $CDCl_3$): δ = 10.04 (brs, 1H), 7.34−7.20 (m, 9H), 6.16 (t, *J* = 3.6 Hz, 1H), 5.28 (t, *J* = 8.3 Hz, 1H), 4.75 (qd, J_1 = 4.2 Hz, J_2 = 15.3 Hz, 2H), 4.30−4.22 (m, 2H),

3.63 (dd, J_1 = 2.0 Hz, J_2 = 13.2 Hz, 1H), 2.96 (dd, J_1 = 9.5 Hz, J_2 = 13.0 Hz, 1H), 2.83 (t, J = 8.1 Hz, 2H), 2.40−2.35 (m, 2H); (^{13}C NMR, 101 MHz, $CDCl_3$): δ = 177.7, 154.3, 136.3, 135.3, 132.7, 131.5, 129.3, 128.8, 128.7, 127.8, 127.4, 127.2, 126.6, 122.4, 66.3, 59.0, 48.9, 27.7, 23.0; IR: ν 3244, 3027, 2930, 1744, 1535, 1490, 1453, 1390, 1348, 1288, 1209, 1193, 1090, 1070, 1007, 911; HRMS (ESI) for $C_{22}H_{23}O_2N_2S$ $[M+H]^+$ requires 379.1475 found 379.1475; Mp. 58−61 °C.

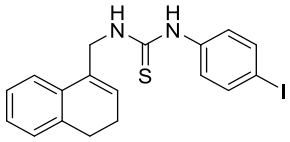
1-(4-Bromophenyl)-3-((3,4-dihydronaphthalen-1-yl)methyl)thiourea (23a9)



The title compound was prepared following General Procedure L using (3,4-dihydronaphthalen-1-yl)methanamine (478 mg, 3.0 mmol), DCM (30 mL) and 4-bromophenyl isothiocyanate (642 mg, 3.0 mmol). The crude product was purified by precipitation to give the title compound (821 mg, 73 % yield) as a white solid.

(^{1}H NMR, 400 MHz, $CDCl_3$): δ (ppm) = 8.36 (br s, 1H), 7.43 (dt, J = 8.6, 2.4 Hz, 2H), 7.29−7.17 (m, 4H), 7.00 (d, J = 8.3 Hz, 2H), 6.06 (t, J = 4.3 Hz, 1H), 6.00 (br s , 1H), 4.67 (d, J = 3.9 Hz, 2H), 2.77 (t, J = 8.1 Hz, 2H), 2.44−2.29 (m, 2H); (^{13}C NMR, 101 MHz, $CDCl_3$): δ (ppm) = 180.1, 136.4, 135.3, 133.2, 132.6, 132.1, 129.1, 127.9, 127.6, 126.8, 126.3, 122.8, 120.3, 48.2, 27.8, 23.0; IR: 3232, 2934, 1534, 1488, 1452, 1308, 1283, 1238, 1099, 1072, 1010, 970, 908, 823 cm^{-1}; HRMS (ESI) for $C_{18}H_{18}N_2BrS$ $[M+H]^+$ requires 373.0369 found 373.0370; Mp. 112−114 °C.

1-(4-Iodophenyl)-3-((3,4-dihydronaphthalen-1-yl)methyl)thiourea (23a10)

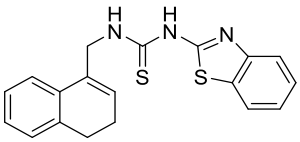


The title compound was prepared following General Procedure L using (3,4-dihydronaphthalen-1-yl)methanamine (478 mg, 3.0 mmol), DCM (30 mL) and 4-iodophenyl isothiocyanate (735 mg,

3.0 mmol). The crude product was purified by precipitation to give the title compound (913 mg, 72 % yield) as a white solid.

(^{1}H NMR, 400 MHz, $CDCl_3$): δ (ppm) = 8.32 (br s, 1H), 7.72 (d, *J* = 8.6 Hz, 2H), 7.39−7.27 (m, 4H), 6.86 (d, *J* = 7.8 Hz, 2H), 6.16 (t, *J* = 3.9 Hz, 1H), 6.11 (br s , 1H), 4.77 (d, *J* = 3.2 Hz, 2H), 2.87 (t, *J* = 7.9 Hz, 2H), 2.44−2.39 (m, 2H); (^{13}C NMR, 101 MHz, $CDCl_3$): δ (ppm) = 180.0, 139.0, 136.4, 135.9, 132.5, 132.0, 129.0, 127.9, 127.5, 126.7, 126.3, 122.7, 91.3, 48.2, 27.7, 22.9; IR: 3237, 3057, 2934, 2830, 2059, 1533, 1485, 1453, 1309, 1281, 1238, 1059, 1007, 970, 820 cm^{-1}; HRMS (ESI) for $C_{18}H_{18}N_2IS$ $[M+H]^+$ requires 421.0230 found 421.0223; Mp. 147−149 °C.

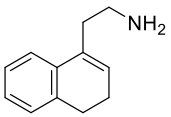
1-(Benzo[d]thiazol-2-yl)-3-((3,4-dihydronaphthalen-1-yl)methyl)thiourea (23a16)



The title compound was prepared following General Procedure L for 48 hours using (3,4-dihydronaphthalen-1-yl)methanamine (478 mg mg, 3.0 mmol), DCM (30 mL) and 2-isothiocyanatobenzo[*d*]thiazole (570 mg, 3.0 mmol). The crude product was purified by precipitation to give the title compound (358 mg, 34 % yield) as a white solid.

(^{1}H NMR, 400 MHz, $CDCl_3$): δ (ppm) = 11.3 (br s, 1H), 7.68 (d, *J* = 7.9 Hz, 1H), 7.42 (d, *J* = 7.9 Hz, 1H), 7.38-7.32 (m, 2H), 7.30-7.17 (m, 4H), 6.23 (t, *J* = 4.5 Hz, 1H), 4.83 (dd, *J* = 4.9, 1.0 Hz, 2H), 2.83 (*J* = 7.9 Hz, 2H), 2.42-2.33 (m, 2H); (^{13}C NMR, 101 MHz, $CDCl_3$ + DMSO-d_6 (5 % v/v)): δ (ppm) = 178.2, 160.5, 149.0, 136.2, 132.8, 131.9, 129.9, 127.7, 127.5, 127.0, 126.4, 125.9, 123.6, 122.5, 120.7, 120.0, 47.4, 27.6, 22.8; IR: 3168, 3031, 1555, 1524, 1457, 1314, 1017, 914 cm^{-1}; HRMS (ESI) for $C_{19}H_{18}N_3S_2$ $[M+H]^+$ requires 352.0937 found 352.0936; Mp.185-187 °C.

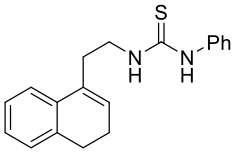
2-(3,4-Dihydronaphthalen-1-yl)ethan-1-amine



The compound was synthesised using literature reported procedure.[15] (1.99 g, 75 % yield, pale yellow oil).

(^{1}H NMR, 400 MHz, $CDCl_3$): δ = 7.29−7.16 (m, 4H), 5.93 (t, *J* = 4.5 Hz, 1H), 2.90 (t, *J* = 6.9 Hz, 2H), 2.77 (t, *J* = 7.9 Hz, 2H), 2.63 (td, J_1 = 1.2 Hz, J_2 = 6.9 Hz, 2H), 2.32−2.27 (m, 2H), 1.15 (brs, 2H); (^{13}C NMR, 101 MHz, $CDCl_3$): δ = 136.6, 134.3, 133.7, 127.5, 126.6, 126.5, 126.2, 122.5, 40.5, 36.9, 28.3, 23.0. Data consistent with literature values.[16]

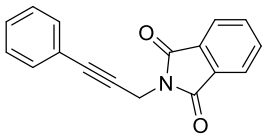
1-(2-(3,4-Dihydronaphthalen-1-yl)ethyl)-3-phenylthiourea (23c2)



The title compound was prepared following General Procedure L using 2-(3,4-dihydronaphthalen-1-yl)ethan-1-amine (520 mg, 3.0 mmol), DCM (30 mL) and phenyl isothiocyanate (0.36 mL, 3.0 mmol). The crude product was purified by silica gel column chromatography (eluent: 20 % EtOAc in *n*-pentane) to provide the title compound (646 mg, 70 % yield) as a white solid.

(^{1}H NMR, 400 MHz, $CDCl_3$): δ (ppm) = 7.96 (br s , 1H), 7.32 (t, *J* = 7.6 Hz, 2H), 7.23−7.16 (m, 2H), 7.13−7.02 (m, 5H), 6.03 (br s , 1H), 5.68 (t, *J* = 4.4 Hz, 1H), 3.71 (q, *J* = 6.0 Hz, 2H), 2.66 (t, *J* = 6.2 Hz, 2H), 2.49 (t, *J* = 7.9 Hz, 2H), 2.08−2.02 (m, 2H); (^{13}C NMR, 101 MHz, $CDCl_3$): δ (ppm) = 180.2, 136.6, 135.9, 133.5, 133.4, 130.1, 127.8, 127.7, 127.4, 127.3, 126.6, 125.6, 122.7, 43.6, 31.9, 28.1, 23.0; IR: 3200, 2934, 1531, 1496, 1450, 1314, 1255, 1179, 1109, 910 cm^{-1}; HRMS (ESI) for $C_{19}H_{21}N_2S$ $[M+H]^+$ requires 309.1420 found 309.1417; Mp. 76−78 °C.

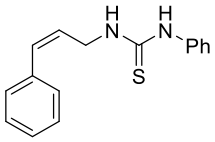
(2-(3-phenylprop-2-yn-1-yl)isoindoline-1,3-dione



The title compound was prepared following General Procedure N using 3-phenyl-2-propyn-1-ol (1.50 mL, 12.0 mmol), THF (60 mL), PPh_3 (3.15 g, 12.0 mmol), phthalimide (1.77 g, 12.0 mmol) and diethyl azodicarboxylate (1.89 mL, 12.0 mmol). The crude product was purified by silica gel column chromatography (eluent: 10 % EtOAc in *n*-pentane) to provide (2-(3-phenylprop-2-yn-1-yl)isoindoline-1,3-dione (1.88 g, 60 % yield) as a white solid.

(^{1}H NMR, 400 MHz, $CDCl_3$): δ (ppm) = 7.83 (dd, *J* = 5.4, 2.9 Hz, 2H), 7.67 (dd, *J* = 5.4, 2.9 Hz, 2H), 7.36−7.33 (m, 2H), 7.23−7.17 (m, 3H), 4.61 (s, 2H); (^{13}C NMR, 101 MHz, $CDCl_3$): δ (ppm) = 167.1, 134.2, 132.1, 131.9, 128.5, 128.2, 123.5, 122.3, 83.0, 82.6, 27.9. Data consistent with literature values.[17]

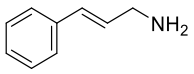
(*Z*)-1-Phenyl-3-m(3-phenylallyl)thiourea (*Z*-23f1)



The title compound was prepared following General Procedure O using (2-(3-phenylprop-2-yn-1-yl)isoindoline-1,3-dione (783 mg, 3.0 mmol), hydrazine monohydrate (161 µL, 3.3 mmol) and MeOH (25 mL). To the solution of crude 3-phenylprop-2-yn-1-amine (347 mg, 2.65 mmol) in DCM (6 mL) and MeOH (6 mL) was added Et_3N (38 µL, 0.1 mmol) and Lindlar catalyst (44 mg). The resulting suspension was stirred under H_2 balloon for 16 hr then filtered through a pad of Celite®, concentrated *in vacuo* to provide crude (*Z*)-3-phenylprop-2-en-1-amine (350 mg) which was used in the next step without further purification. The crude (*Z*)-3-phenylprop-2-en-1-amine (306 mg, 2.3 mmol) was subjected to the conditions described by General Procedure L using phenyl isothiocyanate (0.30 mL, 2.53 mmol) and DCM (23 mL). The crude product was purified by silica gel column chromatography (eluent: 25 % EtOAc in *n*-pentane) to give the title compound (478 mg, 78 % yield) as a white solid.

(^{1}H NMR, 400 MHz, $CDCl_3$): δ (ppm) = 8.18 (brs, 1H), 7.44−7.17 (m, 10H), 6.61 (d, *J* = 11.5 Hz, 1H), 6.09 (br s , 1H), 5.74 (dt, *J* = 11.7, 6.6, 1H), 4.60 (t, *J* = 5.0 Hz, 2H); (^{13}C NMR, 101 MHz, $CDCl_3$): δ (ppm) = 180.4, 136.0, 135.9, 132.2, 130.2, 128.7, 128.3, 127.4, 127.3, 126.9, 125.2, 43.6; IR: 3205, 1596, 1527, 1494, 1448, 1314, 1238, 1190, 1111, 1075, 1028, 915 cm^{-1}; HRMS (ESI) for $C_{16}H_{17}N_2S$ $[M+H]^+$ requires 269.1107 found 269.1109; Mp. 87−88 °C.

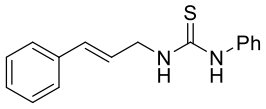
(*E*)-3-phenylprop-2-en-1-amine



The compound was synthesised using literature reported procedure.[17] (1.99 g, 75 % yield, pale yellow oil).

(^{1}H NMR, 400 MHz, $CDCl_3$): δ = 7.39−7.36 (m, 2H), 7.33−7.29 (m, 2H), 7.22 (tt, J_1 = 2.0 Hz, J_2 = 7.2 Hz, 1H), 6.50 (d, *J* = 15.7 Hz, 1H), 6.33 (dt, J_1 = 5.7 Hz, J_2 = 15.7 Hz, 1H), 3.48 (dd, J_1 = 1.5 Hz, J_2 = 5.9 Hz, 2H), 1.34 (brs, 2H); (^{13}C NMR, 101 MHz, $CDCl_3$): δ = 137.1, 131.2, 129.3, 128.4, 127.2, 126.1, 44.2. Data consistent with literature values.[17]

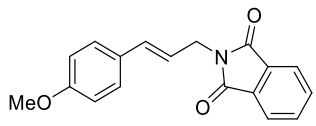
1-Cinnamyl-3-phenylthiourea (*E*-23f1)



The title compound was prepared following General Procedure L using (*E*)-3-phenylprop-2-en-1-amine (666 mg, 5.0 mmol), DCM (50 mL) and phenyl isothiocyanate (0.60 mL, 5.0 mmol). The crude product was purified by precipitation to give the title compound (1.29 g, 96 % yield) as a white solid.

(^{1}H NMR, 400 MHz, $CDCl_3$): δ (ppm) = 8.33 (br s , 1H), 7.48−7.44 (m, 2H), 7.39−7.25 (m, 8H), 6.55 (d, *J* = 15.9 Hz, 1H), 6.27 (dt, *J* = 15.9, 6.4 Hz, 1H), 6.20 (br s , 1H), 4.49 (t, *J* = 5.4 Hz, 2H); (^{13}C NMR, 101 MHz, $CDCl_3$): δ (ppm) = 180.5, 136.2, 135.9, 132.9, 130.2, 128.5, 127.8, 127.3, 126.4, 125.3, 124.3, 47.6; IR: 3211, 3027, 2055, 1596, 1531, 1495, 1450, 1347, 1314, 1260, 1185, 1073, 1028, 966, 910 cm^{-1}; HRMS (ESI) for $C_{16}H_{17}N_2S$ $[M+H]^+$ requires 269.1107 found 269.1110; Mp. 96−97 °C.

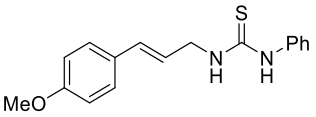
(*E*)-2-(3-(4-methoxyphenyl)allyl)isoindoline-1,3-dione



(*E*)-3-(4-Methoxyphenyl)prop-2-en-1-ol was prepared following General Procedure M using (*E*)-3-(4-methoxyphenyl) acrylaldehyde (813 mg, 5.0 mmol), $NaBH_4$ (126 mg, 3.3 mmol) and (MeOH 10 mL). The crude alcohol was then subjected to conditions described in General Procedure N using THF (25 mL), PPh_3 (1.31 g, 5.0 mmol), phthalimide (736 mg, 5.0 mmol) and diethyl azodicarboxylate (0.79 mL, 5.0 mmol). The crude product was purified by silica gel column chromatography (eluent: 10 % EtOAc in *n*-pentane) to provide (*E*)-2-(3-(4-methoxyphenyl)allyl)isoindoline-1,3-dione (340 mg, 23 % yield) as a white solid.

(^{1}H NMR, 400 MHz, $CDCl_3$): δ (ppm) = 7.86 (dd, *J* = 5.4, 2.9 Hz, 2H), 7.72 (dd, *J* = 5.4, 3.2 Hz, 2H), 7.30 (d, *J* = 8.8 Hz, 2H), 6.83 (d, *J* = 8.8 Hz, 2H), 6.62 (d, *J* = 15.7 Hz, 1H), 6.13 (dt, *J* = 15.7, 6.6 Hz, 1H), 4.43 (dd, J_1 = 1.2 Hz, J_2 = 6.6 Hz, 2H), 3.79 (s, 3H); (^{13}C NMR, 101 MHz, $CDCl_3$): δ (ppm) = 168.0, 159.4, 133.9, 133.3, 132.2, 129.0, 127.7, 123.2, 120.4, 113.9, 55.2, 39.7. Data consistent with literature values.[18]

(*E*)-1-(3-(4-Methoxyphenyl)allyl)-3-phenylthiourea (23f2)

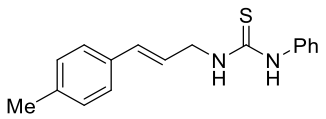


The title compound was prepared following General ProcedureO using (*E*)-2-(3-(4-methoxyphenyl)allyl)isoindoline-1,3-dione (323 mg, 1.1 mmol), hydrazine monohydrate (80 µL, 1.65 mmol) and MeOH (10 mL). The crude amine was subjected to the conditions described by General Procedure L using phenyl isothiocyanate (0.116 mL, 0.97 mmol) and DCM (9 mL). The crude product was purified by precipitation to give the title compound (253 mg, 77 % yield) as a white solid.

(^{1}H NMR, 400 MHz, $CDCl_3$): δ (ppm) = 8.13 (br s , 1H), 7.45 (t, *J* = 7.8 Hz, 2H), 7.34−7.25 (m, 5H), 6.86 (d, *J* = 8.8 Hz, 2H), 6.49 (d, *J* = 15.9 Hz, 1H), 6.13 (dt, *J* = 15.7, 6.5 Hz, 1H), 6.13 (br s , 1H), 4.45 (t, *J* = 5.6 Hz, 2H), 3.82 (s, 3H); (^{13}C NMR, 101 MHz, $CDCl_3$): δ

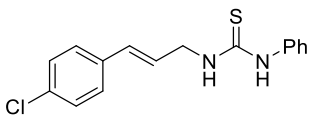
(ppm) = 180.4, 159.4, 135.9, 132.6, 130.2, 128.9, 127.6, 127.4, 125.3, 121.9, 114.0, 55.2, 47.8; IR: 3205, 2981, 2361, 1606, 1529, 1509, 1452, 1420, 1298, 1246, 1175, 1031, 967, 840 cm^{-1}; HRMS (ESI) for $C_{17}H_{19}ON_2S$ $[M+H]^+$ requires 299.1213 found 299.1212; Mp. 130−132 °C.

(*E*)-1-Phenyl-3-(3-(*p*-tolyl)allyl)thiourea (23f3)



(*E*)-3-(*p*-Tolyl)prop-2-en-1-ol was prepared following General Procedure M using (*E*)-3-(*p*-tolyl)acrylaldehyde (1.462 g, 10.0 mmol), $NaBH_4$ (252 mg, 6.7 mmol) and (MeOH 20 mL). The crude alcohol (815 mg, 5.5 mmol) was then dissolved in THF (30 mL) and to the solution was added PPh_3 (1.59 g, 6.05 mmol), phthalimide (890 mg, 6.05 mmol) and diethyl azodicarboxylate (0.95 mL, 6.05 mmol). After stirring for 2 hours at room temperature, hydrazine monohydrate (0.8 mL, 16.5 mmol) was added and the reaction mixture was stirred at room temperature for 16 hours. The mixture was diluted with H_2O (15 mL) and conc. HCl (3 mL) was added. After stirring for 30 minutes, the suspension was filtered and the filtrate was washed with EtOAc (x2), basified to pH = 10 using 5 M NaOH and extracted with Et_2O (x2). Combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude amine (589 mg, 4.0 mmol) was subjected to the conditions described by General Procedure L using phenyl isothiocyanate (0.525 mL, 4.4 mmol) and DCM (40 mL). The crude product was purified by precipitation to give the title compound (819 mg, 72 % yield) as a yellow solid. (^{1}H NMR, 400 MHz, $CDCl_3$): δ (ppm) = 8.11 (br s , 1H), 7.45 (t, *J* = 7.8 Hz, 2H), 7.34−7.25 (m, 5H), 7.14 (d, *J* = 7.8 Hz, 2H), 6.51 (d, *J* = 15.7 Hz, 1H), 6.20 (dt, *J* = 15.7, 6.5 Hz, 1H), 6.14 (br s , 1H), 4.47 (t, *J* = 5.6 Hz, 2H), 2.35 (s, 3H); (^{13}C NMR, 101 MHz, $CDCl_3$): δ (ppm) = 180.5, 137.8, 135.9, 133.4, 132.9, 130.2, 129.3, 127.4, 126.3, 125.3, 123.2, 47.8, 21.2; IR: 3120, 3024, 2360, 1595, 1529, 1496, 1451, 1345, 1313, 1260, 1183, 1119, 968 cm^{-1}; HRMS (ESI) for $C_{17}H_{19}N_2S$ $[M+H]^+$ requires 283.1264 found 283.1266; Mp. 147−149 °C.

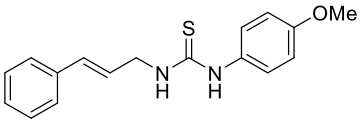
(*E*)-1-(3-(4-Chlorophenyl)allyl)-3-phenylthiourea (23f4)



(*E*)-3-(4-Chlorophenyl)prop-2-en-1-ol was prepared following General Procedure M using (*E*)-3-(4-chlorophenyl)acrylaldehyde (1.00 g, 6.0 mmol), $NaBH_4$ (151 mg, 4.0 mmol) and (MeOH 10 mL). The crude alcohol (742 mg, 4.4 mmol) was then dissolved in THF (25 mL) and to the solution was added PPh_3 (1.27 g, 4.84 mmol), phthalimide (712 mg, 4.84 mmol) and diethyl azodicarboxylate (0.76 mL, 4.84 mmol). After stirring for 2 hours at room temperature, hydrazine monohydrate (0.64 mL, 13.2 mmol) was added and the reaction mixture was stirred at room temperature for 16 hours. The mixture was diluted with H_2O (15 mL) and conc. HCl (3 mL) was added. After stirring for 30 minutes, the suspension was filtered and the filtrate was washed with EtOAc (x2), basified to pH = 10 using 5 M NaOH and extracted with Et_2O (x2). Combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude amine (642 mg, 3.83 mmol) was subjected to the conditions described by General Procedure L using phenyl isothiocyanate (0.50 mL, 4.21 mmol) and DCM (38 mL). The crude product was purified by precipitation to give the title compound (981 mg, 85 % yield) as a pale yellow solid.

(^{1}H NMR, 400 MHz, $CDCl_3$): δ (ppm) = 8.30 (br s , 1H), 7.45 (t, *J* = 7.8 Hz, 2H), 7.34−7.25 (m, 7H), 6.48 (d, *J* = 15.9 Hz, 1H), 6.24 (dt, *J* = 15.9, 6.4 Hz, 1H), 6.20 (br s , 1H), 4.47 (t, *J* = 5.5 Hz, 2H); (^{13}C NMR, 101 MHz, $CDCl_3$): δ (ppm) = 180.6, 135.9, 134.7, 133.4, 131.5, 130.2, 128.7, 127.6, 127.4, 125.3, 125.2, 47.4; IR: ν 3214, 2981, 2360, 1715, 1594, 1531, 1492, 1451, 1380, 1345, 1313, 1258, 1233, 1184, 1091, 1012, 967, 844 cm^{-1}; HRMS (ESI) for $C_{16}H_{16}N_2ClS$ $[M+H]^+$ requires 303.0717 found 303.0720; Mp. 121−123 °C.

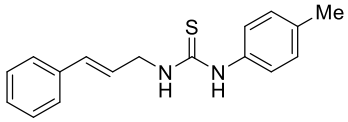
1-Cinnamyl-3-(4-methoxyphenyl)thiourea (23f5)



The title compound was prepared following General Procedure L using (*E*)-3-phenylprop-2-en-1-amine (533 mg, 4.0 mmol), DCM (30 mL) and 4-methoxyphenyl isothiocyanate (727 mg, 4.4 mmol). The crude product was purified by precipitation to give the title compound (1.05 g, 88 % yield) as a white solid.

(^{1}H NMR, 400 MHz, $CDCl_3$): δ (ppm) = 8.06 (br s , 1H), 7.37−7.24 (m, 5H), 7.20 (d, *J* = 8.8 Hz, 2H), 6.95 (d, *J* = 8.8 Hz, 2H), 6.52 (d, *J* = 15.9 Hz, 1H), 6.24 (dt, *J* = 15.9, 6.5 Hz, 1H), 5.96 (br s , 1H), 4.46 (t, *J* = 5.6 Hz, 2H), 3.82 (s, 3H); (^{13}C NMR, 101 MHz, $CDCl_3$): δ (ppm) = 181.1, 159.0, 136.2, 132.7, 128.5, 128.2, 127.8, 127.8, 126.4, 124.5, 115.3, 55.5, 47.5; IR: 3190, 1507, 1292, 1240, 1166, 1105, 1030, 966, 910, 830 cm^{-1}; HRMS (ESI) for $C_{17}H_{19}ON_2S$ $[M+H]^+$ requires 299.1213 found 299.1213; Mp. 97−98 °C.

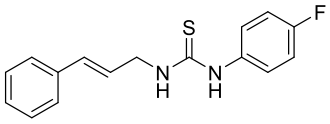
1-Cinnamyl-3-(*p*-tolyl)thiourea (23f6)



The title compound was prepared following General Procedure L using (*E*)-3-phenylprop-2-en-1-amine (533 mg, 4.0 mmol), DCM (30 mL) and *p*-tolyl isothiocyanate (657 mg, 4.4 mmol). The crude product was purified by precipitation to give the title compound (838 mg, 74 % yield) as a white solid.

(^{1}H NMR, 400 MHz, $CDCl_3$): δ (ppm) = 8.09 (br s, 1H), 7.38−7.24 (m, 7H), 7.15 (d, *J* = 8.3 Hz, 2H), 6.53 (d, *J* = 15.9 Hz, 1H), 6.25 (dt, *J* = 15.9, 6.4 Hz, 1H), 6.08 (br s , 1H), 4.47 (t, *J* = 5.5 Hz, 2H), 2.38 (s, 3H); (^{13}C NMR, 101 MHz, $CDCl_3$): δ (ppm) = 180.7, 137.7, 136.2, 133.1, 132.8, 130.8, 128.5, 127.8, 126.4, 125.6, 124.5, 47.6, 21.0; IR: 3198, 3026, 1510, 1449, 1311, 1259, 1188, 966, 910, 819 cm^{-1}; HRMS (ESI) for $C_{17}H_{19}N_2S$ $[M+H]^+$ requires 283.1264 found 283.1268; Mp. 117−118 °C.

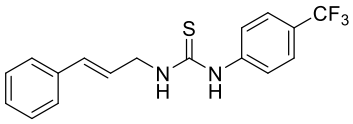
1-Cinnamyl-3-(4-fluorophenyl)thiourea (23f7)



The title compound was prepared following General Procedure L using (*E*)-3-phenylprop-2-en-1-amine (533 mg, 4.0 mmol), DCM (30 mL) and 4-fluorophenyl isothiocyanate (674 mg, 4.4 mmol). The crude product was purified by silica gel column chromatography (eluent: 20 % EtOAc in *n*-pentane) to provide the title compound (879 mg, 77 % yield) as a white solid.

(^{1}H NMR, 400 MHz, $CDCl_3$): δ (ppm) = 8.43 (br s, 1H), 7.37−7.31 (m, 4H), 7.29−7.25 (m, 3H), 7.13 (t, *J* = 8.6 Hz, 2H), 6.54 (d, *J* = 15.9 Hz, 1H), 6.25 (dt, *J* = 15.8, 6.5 Hz, 1H), 6.04 (br s, 1H), 4.46 (t, *J* = 5.6 Hz, 2H); (^{13}C NMR, 101 MHz, $CDCl_3$): δ (ppm) = 180.8, 161.4 (d, *J* = 248.0 Hz), 136.1, 133.0, 131.9, 128.6, 127.9 (d, *J* = 7.2 Hz), 127.7, 126.4, 124.2, 117.0 (d, *J* = 23.1 Hz), 47.5; (^{19}F NMR, 377 MHz, $CDCl_3$): δ (ppm) = −113.0 (br s, 1F); IR: 3216, 1529, 1504, 1340, 1214, 1153, 966, 910, 834 cm^{-1}; HRMS (ESI) for $C_{16}H_{16}N_2FS$ $[M+H]^+$ requires 287.1013 found 287.1015; Mp. 90−91 °C.

1-Cinnamyl-3-(4-(trifluoromethyl)phenyl)thiourea (23f8)

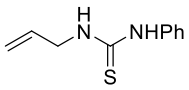


The title compound was prepared following General Procedure L using (*E*)-3-phenylprop-2-en-1-amine (533 mg, 4.0 mmol), DCM (30 mL) and 4-(trifluoromethyl)phenyl isothiocyanate (894 mg, 4.4 mmol). The crude product was purified by precipitation to give the title compound (952 mg, 71 % yield) as a white solid.

(^{1}H NMR, 400 MHz, $CDCl_3$): δ = 8.65 (br s , 1H), 7.68 (d, *J* = 8.3 Hz, 2H), 7.41−7.26 (m, 7H), 6.60 (d, *J* = 15.7 Hz, 1H), 6.35 (br s , 1H), 6.28 (dt, *J* = 15.9, 6.5 Hz, 1H), 4.48 (t, *J* = 4.9 Hz, 2H); (^{13}C NMR, 101 MHz, $CDCl_3$): δ (ppm) = 180.3, 139.6, 136.0, 133.6, 128.6, 128.3, 128.1, 127.3, 126.4, 124.2, 123.7, 123.6 (q, *J* = 271.8 Hz), 47.7; (^{19}F NMR, 377 MHz, $CDCl_3$): δ (ppm) = −62.5 (s, 3F); IR: 3267, 1619, 1552, 1333, 1162, 1115, 1071, 1015, 967,

840 cm^{-1}; HRMS (ESI) for $C_{17}H_{16}N_2F_3S$ $[M+H]^+$ requires 337.0981 found 337.0981; Mp. 123−124 °C.

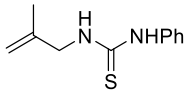
1-Allyl-3-phenylthiourea (23h1)



The title compound was prepared following General Procedure L using allylamine (0.3 ml, 4.0 mmol), DCM (30 mL) and phenyl isothiocyanate (0.53 mL, 4.4 mmol). The crude product was purified by precipitation to give the title compound (705 mg, 92 % yield) as a white solid.

(^{1}H NMR, 400 MHz, $CDCl_3$): δ (ppm) = 8.01 (br s, 1H), 7.43 (t, *J* = 7.6 Hz, 2H), 7.30 (t, *J* = 7.5 Hz, 1H), 7.22 (d, *J* = 7.6 Hz, 2H), 6.05 (br s, 1H), 5.87 (*app.* dq, *J* = 11.0, 5.7 Hz, 1H), 5.21-5.11 (m, 2H), 4.29 (dt, *J* = 5.7, 1.2 Hz, 2H); (^{13}C NMR, 101 MHz, $CDCl_3$): δ (ppm) = 180.4, 136.1, 133.1, 130.0, 127.1, 125.1, 116.9, 47.5; IR: 3208, 2360, 1644, 1529, 1313, 1235, 1192, 918 cm^{-1}; HRMS (ESI) for $C_{10}H_{13}N_2S$ $[M+H]^+$ requires 193.0790 found 193.0797; Mp. = 90−92 °C.

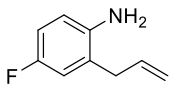
1-(2-Methylallyl)-3-phenylthiourea (23h2)



The title compound was prepared following General Procedure L using 2-methylprop-2-en-1-amine (284 mg, 4.0 mmol), DCM (30 mL) and phenyl isothiocyanate (0.53 mL, 4.4 mmol). The crude product was purified by precipitation to give the title compound (745 mg, 90 % yield) as a white solid.

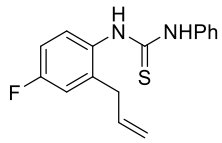
(^{1}H NMR, 400 MHz, $CDCl_3$): δ (ppm) = 8.32 (br s , 1H), 7.45 (t, *J* = 7.7 Hz, 2H), 7.33 (t, *J* = 7.5 Hz, 1H), 7.27 (d, *J* = 7.6 Hz, 2H), 6.12 (br s , 1H), 4.86 (s, 1H), 4.79 (s, 1H), 4.24 (d, *J* = 4.4 Hz, 2H), 1.76 (s, 3H); (^{13}C NMR, 101 MHz, $CDCl_3$): δ (ppm) = 180.9, 141.1, 135.9, 130.2, 127.4, 125.4, 111.1, 50.7, 20.5; IR: 3215, 2980, 2360, 1596, 1533, 1496, 1451, 1349, 1313, 1234, 1189, 1028, 943, 892 cm^{-1}; HRMS (ESI) for $C_{11}H_{15}N_2S$ $[M+H]^+$ requires 207.0951 found 207.0951; Mp. = 83−84 °C.

2-allyl-4-fluoroaniline



A round-bottomed flask equipped with a reflux condenser was charged with *N*-allyl-4-fluoroaniline (1.21 g, 8.0 mmol) and BF_3•OEt_2 (1.48 mL, 12.0 mmol). The reaction mixture was heated at 140 °C for 12 hours, then treated with a sat. $Na_2CO_{3(aq)}$ and extracted with DCM (x2). Combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography (eluent: 10 % Et_2O in *n*-pentane) to provide the title compound (654 mg, 54 % yield) as a yellow oil. (^{1}H NMR, 400 MHz, $CDCl_3$): δ (ppm) = 6.82−6.76 (m, 2H), 6.64−6.60 (m, 1H), 5.99−5.89 (m, 1H), 5.19−5.09 (m, 2H), 3.53 (br s , 2H), 3.29 (dt, *J* = 6.1, 1.6 Hz, 2H); (^{13}C NMR, 101 MHz, $CDCl_3$): δ (ppm) = 156.4 (d, *J* = 235.2 Hz), 140.7 (d, *J* = 1.6 Hz), 135.0, 125.6 (d, *J* = 6.4 Hz), 116.7, 116.6, 116.5 (d, *J* = 8.0 Hz), 116.3 (d, *J* = 23.1 Hz), 36.1. Data consistent with literature values.[19]

1-(2-Allyl-4-fluorophenyl)-3-phenylthiourea (23j)



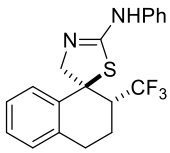
The title compound was prepared following General Procedure L using 2-allyl-4-fluoroaniline (605 mg, 4.0 mmol), DCM (30 mL) and phenyl isothiocyanate (0.53 mL, 4.4 mmol). The crude product was purified by precipitation to give the title compound (853 mg, 74 % yield) as a white solid.

(^{1}H NMR, 400 MHz, $CDCl_3$): δ (ppm)= 8.18 (br s , 1H), 7.68 (br s , 1H), 7.46−7.40 (m, 3H), 7.35 (d, *J* = 7.3 Hz, 2H), 7.30 (t, *J* = 7.2 Hz, 1H), 7.02−6.97 (m, 2H), 5.87−5.77 (m, 1H), 4.99 (d, *J* = 10.0 Hz, 1H), 4.89 (d, *J* = 17.1 Hz, 1H), 3.35 (d, *J* = 6.1 Hz, 2H); (^{13}C NMR, 101 MHz, $CDCl_3$): δ = 180.6, 161.7 (d, *J* = 248.0 Hz), 138.9, 136.7, 135.0, 131.7, 130.2 (d, *J* = 8.7 Hz), 129.7, 127.3, 125.5, 117.2, 117.0, 114.3 (d, *J* = 23.1 Hz), 36.2; (^{19}F NMR, 377 MHz, $CDCl_3$): δ (ppm) = −113.1 (br s , 1F); IR: 3192, 2980, 2361, 1593, 1524, 1496, 1448, 1349, 1314, 1263, 1219, 1147, 998, 967, 922, 867 cm^{-1}; HRMS (ESI) for $C_{16}H_{16}N_2FS$ $[M+H]^+$ requires 287.1013 found 287.1010; Mp. 129−130 °C.

5.3.2 Synthesis of CF_3-Thiocyclised Products (24)

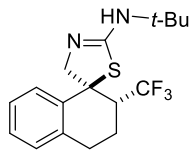
General procedure P *(Trifluoromethylation-cyclisation with Togni reagent II)* Into a vial containing appropriate thiourea (0.3 mmol), 1-trifluoromethyl-1,2-benziodoxol-3-(1H)-one (113.8 mg, 0.36 mmol), 4Å MS (30 mg) and a stirrer bar was added a solution of trifluoroacetic acid (45.9 µL, 0.6 mmol) in $CDCl_3$ (3.0 mL) under Ar atmosphere. The vial was sealed and allowed to stir at room temperature for 24 hours. The reaction mixture was then concentrated and purified by silica gel column chromatography.

(1*S,2*S**)-*N*-Phenyl-2-(trifluoromethyl)-3,4-dihydro-2H,4'H-spiro[naphthalene-1,5'-thiazol]-2'-amine (24a1)**



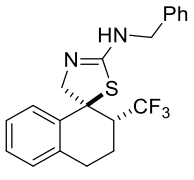
The title compound was prepared following General Procedure P using 1-((3,4-dihydronaphthalen-1-yl)methyl)-3-phenylthiourea (88.2 mg, 0.3 mmol), 1-trifluoromethyl-1,2-benziodoxol-3-(1H)-one (113.8 mg, 0.36 mmol), 4Å MS (30 mg), trifluoroacetic acid (45.9 µL, 0.6 mmol) and $CDCl_3$ (3.0 mL). The crude product was purified by silica gel column chromatography (eluent: 1 % Et_3N and 15 % EtOAc in *n*-pentane) to provide the title compound (90.5 mg, 83 % yield) as a white solid. (^{1}H NMR, 400 MHz, $CDCl_3$): δ (ppm) = 7.66−7.62 (m, 1H), 7.20−7.06 (m, 6H), 7.00−6.93 (m, 2H), 4.30 (d, A of AB, J_{AB} = 13.0 Hz, 1H), 4.23 (d, B of AB, J_{AB} = 13.0 Hz, 1H), 3.13−3.04 (m, 1H), 2.92−2.76 (m, 2H), 2.27−2.19 (m, 1H), 2.09 (br s, 1H); (^{13}C NMR, 101 MHz, $CDCl_3$): δ (ppm) = 158.8, 145.9, 137.9, 134.4, 128.9, 128.8, 127.7, 126.9, 126.5 (q, *J* = 283.7 Hz), 126.0, 123.3, 121.0, 61.1, 60.6, 47.9 (q, *J* = 24.6 Hz), 25.5, 22.7; (^{19}F NMR, 377 MHz, $CDCl_3$): δ (ppm) = −63.7 (d, *J* = 10.4 Hz, 3F); IR: 2931, 1636, 1589, 1491, 1445, 1303, 1263, 1191, 1150, 1117, 1035, 896 cm^{-1}; HRMS (ESI) for $C_{19}H_{18}N_2F_3S$ $[M+H]^+$ requires 363.1137 found 363.1134; Mp. 117−121 °C.

(1*S,2*S**)-*N*-(*tert*-butyl)-2-(trifluoromethyl)-3,4-dihydro-2H,4'H-spiro[naphthalene-1,5'-thiazol]-2'-amine (24a2)**



The title compound was prepared following General Procedure P using 1-(*tert*-butyl)-3-((3,4-dihydronaphthalen-1-yl)methyl)thiourea (82.3 mg, 0.3 mmol), 1-trifluoromethyl-1,2-benziodoxol-3-(1H)-one (113.8 mg, 0.36 mmol), 4Å MS (30 mg), trifluoroacetic acid (45.9 µL, 0.6 mmol) and $CDCl_3$ (3.0 mL). The crude product was purified by silica gel column chromatography (eluent: 1 % Et_3N and 10 % EtOAc in *n*-pentane) to provide the title compound (84.2 mg, 82 % yield) as a white solid. (^{1}H NMR, 400 MHz, $CDCl_3$): δ (ppm) = 7.64 (dt, *J* = 9.3, 3.6 Hz, 1H), 7.19 (dt, *J* = 9.3, 3.6 Hz, 2H), 7.08−7.06 (m, 1H), 4.38 (d, A of AB, J_{AB} = 14.2 Hz, 1H), 4.33 (d, B of AB, J_{AB} = 14.2 Hz, 1H), 4.12 (br s , 1H), 3.19−3.09 (m, 1H), 3.00−2.86 (m, 2H), 2.39−2.31 (m, 1H), 2.15−2.07 (m, 1H), 1.40 (s, 9H); (^{13}C NMR, 101 MHz, $CDCl_3$): δ (ppm) = 155.2, 139.5, 133.7, 128.6, 127.4, 126.7, 126.5 (q, *J* = 283.7 Hz), 125.8, 70.1, 65.3, 53.0, 47.8 (q, *J* = 24.6 Hz), 28.9, 25.6, 24.1 (q, *J* = 2.4 Hz); (^{19}F NMR, 377 MHz, $CDCl_3$): δ (ppm) = −64.1 (d, *J* = 10.4 Hz, 3F); IR: 3279, 2965, 1638, 1490, 1453, 1391, 1364, 1339, 1298, 1247, 1219, 1201 1189, 1178, 1148, 1117, 1106, 1024, 933 cm^{-1}; HRMS (ESI) for $C_{17}H_{22}N_2F_3S$ $[M+H]^+$ requires 343.1450 found 343.1447; Mp. 114−116 °C.

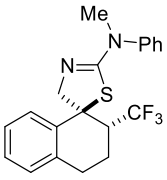
(1*S,2*S**)-*N*-Benzyl-2-(trifluoromethyl)-3,4-dihydro-2H,4'H-spiro[naphthalene-1,5'-thiazol]-2'-amine (24a3)**



The title compound was prepared following General Procedure P using 1-benzyl-3-((3,4-dihydronaphthalen-1-yl)methyl)thiourea (92.5 mg, 0.3 mmol), 1-trifluoromethyl-1,2-benziodoxol-3-(1H)-one (113.8 mg, 0.36 mmol), 4Å MS (30 mg), trifluoroacetic acid (45.9 µL, 0.6 mmol) and $CDCl_3$ (3.0 mL). The crude product was purified by silica gel column chromatography (eluent: 1 % Et_3N and 15 % EtOAc in *n*-pentane) to provide the title compound (84.7 mg, 75 % yield) as a white solid.

(^{1}H NMR, 400 MHz, $CDCl_3$): δ (ppm) = 7.64−7.62 (m, 1H), 7.37−7.27 (m, 5H), 7.24−7.19 (m, 2H), 7.10−7.08 (m, 2H), 4.34 (s, 2H), 4.30 (d, A of AB, J_{AB} = 14.2 Hz, 1H), 4.24 (d, B of AB, J_{AB} = 14.2 Hz, 1H), 3.23−3.13 (m, 1H), 3.02−2.87 (m, 2H), 2.40−2.32 (m, 1H), 2.16−2.08 (m, 1H); (^{13}C NMR, 101 MHz, $CDCl_3$): δ (ppm) = 158.6, 139.3, 138.3, 133.6, 128.6, 128.5, 127.6, 127.5, 127.4, 126.8, 126.5 (q, *J* = 283.7 Hz), 125.8, 68.4, 66.2, 48.5, 47.8 (q, *J* = 24.9 Hz), 25.5, 23.9; (^{19}F NMR, 377 MHz, $CDCl_3$): δ (ppm) = −63.9 (d, *J* = 8.7 Hz, 3F); IR: 3195, 3028, 2938, 1625, 1541, 1491, 1454, 1372, 1338, 1298, 1264, 1178, 1147, 1117, 1032, 933 cm^{-1}; HRMS (ESI) for $C_{20}H_{20}N_2F_3S$ $[M+H]^+$ requires 377.1294 found 377.1303; Mp. 67−68 °C.

(1*S,2*S**)-*N*-Methyl-*N*-phenyl-2-(trifluoromethyl)-3,4-dihydro-2H,4'H-spiro[naphthalene-1,5'-thiazol]-2'-amine (24a4)**

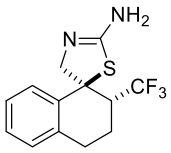


The title compound was prepared following General Procedure P using 3-((3,4-dihydronaphthalen-1-yl)methyl)-1-methyl-1-phenylthiourea (92.5 mg, 0.3 mmol), 1-trifluoromethyl-1,2-benziodoxol-3-(1H)-one (113.8 mg, 0.36 mmol), 4Å MS (30 mg), trifluoroacetic acid (45.9 µL, 0.6 mmol) and $CDCl_3$ (3.0 mL). The crude product was purified by silica gel column chromatography (eluent: 1 % Et_3N and 10 % EtOAc in *n*-pentane) to provide the title compound (95.6 mg, 85 % yield) as a pale yellow oil.

(^{1}H NMR, 400 MHz, $CDCl_3$): δ (ppm) = 7.72 (d, *J* = 7.8 Hz, 1H), 7.33−7.30 (m, 2H), 7.23−7.16 (m, 5H), 7.03 (d, *J* = 7.3 Hz, 1H), 4.58 (d, A of AB, J_{AB} = 15.6 Hz, 1H), 4.54 (d, B of AB, J_{AB} = 15.6 Hz, 1H), 3.46 (s, 3H), 3.16−3.09 (m, 1H), 2.96−2.78 (m, 2H), 2.32−2.24 (m, 1H), 2.06 (br s , 1H); (^{13}C NMR, 101 MHz, $CDCl_3$): δ (ppm) = 160.4, 145.9, 139.6, 133.8, 129.1, 128.7, 127.5, 126.9, 126.7, 126.7 (q, *J* = 283.5 Hz), 126.3, 126.2, 69.4 (q, *J* = 2.4 Hz), 66.5, 48.2 (q, *J* = 24.6 Hz), 40.2, 25.8, 23.8 (q, J = 3.2 Hz); (^{19}F NMR, 377 MHz,

$CDCl_3$): δ (ppm) = −63.9 (d, *J* = 10.4 Hz, 3F); IR: 2938, 1617, 1590, 1496, 1453, 1355, 1264, 1178, 1146, 1116, 1030, 933 cm^{-1}; HRMS (ESI) for $C_{20}H_{20}N_2F_3S$ $[M+H]^+$ requires 377.1294 found 377.1299.

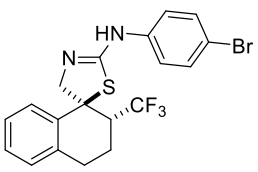
(1*S,2*S**)-2-(Trifluoromethyl)-3,4-dihydro-2H,4'H-spiro[naphthalene-1,5'-thiazol]-2'-amine (24a8)**



Into a vial containing (1*S**,2*S**)-*N*-(*tert*-butyl)-2-(trifluoromethyl)-3,4-dihydro-2H,4'H-spiro[naphthalene-1,5'-thiazol]-2'-amine (57.3 mg, 0.2 mmol) was added conc. HCl (0.5 mL) and the suspension was stirred at 110 °C for 30 min. The mixture was cooled in ice bath and basified to pH 10 with sat. $NaHCO_{3(aq)}$ (5 mL). The mixture was extracted with EtOAc (x2) and combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude solid was dissolved in minimum amount of $CHCl_3$ then precipitated by addition of *n*-pentane. After filtration, the title compound was obtained (44.2 mg, 77 % yield) as a white solid.

(^{1}H NMR, 400 MHz, $CDCl_3$): δ (ppm) = 7.63−7.59 (m, 1H), 7.22−7.18 (m, 2H), 7.09−7.07 (m, 1H), 4.58 (br s , 2H), 4.44 (d, A of AB, J_{AB} = 14.5 Hz, 1H), 4.39 (d, B of AB, J_{AB} = 14.5 Hz, 1H), 3.23−3.14 (m, 1H), 3.01−2.87 (m, 2H), 2.39−2.31 (m, 1H), 2.14−2.08 (m, 1H); (^{13}C NMR, 126 MHz, $CDCl_3$): δ (ppm) = 158.1, 139.2, 133.8, 128.8, 127.8, 127.0, 126.5 (q, *J* = 283.2 Hz), 126.0, 68.9 (q, *J* = 2.9 Hz), 67.7, 48.1 (q, *J* = 24.9 Hz), 25.7, 23.9 (q, *J* = 2.9 Hz); (^{19}F NMR, 377 MHz, $CDCl_3$): δ (ppm) = −64.0 (d, *J* = 10.4 Hz, 3F); IR: 3452, 2937, 1658, 1490, 1458, 1345, 1303, 1262, 1244, 1177, 1145, 1112, 1031, 991, 932, 894, 832 cm^{-1}; HRMS (ESI) for $C_{13}H_{14}N_2F_3S$ $[M+H]^+$ requires 287.0824 found 287.0824; Mp. 180−182 °C.

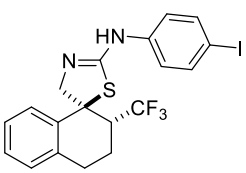
(1*S,2*S**)-*N*-(4-Bromophenyl)-2-(trifluoromethyl)-3,4-dihydro-2H,4'H-spiro[naphthalene-1,5'-thiazol]-2'-amine (24a9)**



The title compound was prepared following General Procedure P using 1-(4-bromophenyl)-3-((3,4-dihydronaphthalen-1-yl)methyl)thiourea (112.0 mg, 0.3 mmol), 1-trifluoromethyl-1,2-benziodoxol-3-(1H)-one (113.8 mg, 0.36 mmol), 4Å MS (30 mg), trifluoroacetic acid (45.9 µL, 0.6 mmol) and $CDCl_3$ (3.0 mL). The crude product was purified by silica gel column chromatography (eluent: 1 % Et_3N and 15 % EtOAc in *n*-pentane) to provide the title compound (109 mg, 82 % yield) as a white solid.

(^{1}H NMR, 400 MHz, $CDCl_3$): δ (ppm) = 7.72 (dt, J_1 = 3.7 Hz, J_2 = 9.3 Hz, 1H), 7.36 (dt, J = 9.3, 2.3 Hz, 2H), 7.21 (dt, J = 9.3, 3.7 Hz, 2H), 7.09 (dd, J_1 = 5.6, 3.9 Hz, 1H), 7.01 (d, J = 8.8 Hz, 2H), 4.25 (d, A of AB, J_{AB} = 12.6 Hz, 1H), 4.18 (d, B of AB, J_{AB} = 12.6 Hz, 1H), 3.19−3.12 (m, 1H), 2.97−2.87 (m, 2H), 2.35−2.27 (m, 1H), 2.19 (br s , 1H); (^{13}C NMR, 126 MHz, $CDCl_3$): δ (ppm) = 157.8, 145.4, 137.6, 134.6, 131.9, 129.0, 127.9, 127.0, 126.5 (q, J = 283.9 Hz), 126.0, 122.5, 116.0, 61.4, 60.3, 48.0 (q, J = 24.9 Hz), 25.6, 22.7; (^{19}F NMR, 377 MHz, $CDCl_3$): δ (ppm) = −63.8 (d, J = 10.4 Hz, 3F); IR: 3059, 2934, 2361, 1636, 1579, 1542, 1487, 1457, 1397, 1373, 1340, 1307, 1263, 1191, 1151, 1117, 1071, 1034, 1007, 934 cm^{-1}; HRMS (ESI) for $C_{19}H_{17}N_2BrF_3S$ $[M+H]^+$ requires 441.0242 found 441.0248; Mp. 179−181 °C.

(1*S,2*S**)-*N*-(4-Iodophenyl)-2-(trifluoromethyl)-3,4-dihydro-2H,4'H-spiro[naphthalene-1,5'-thiazol]-2'-amine (24a10)**

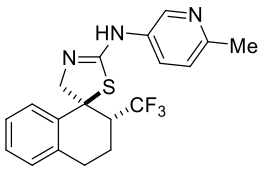


The title compound was prepared following General Procedure P using 1-(4-iodomophenyl)-3-((3,4-dihydronaphthalen-1-yl)methyl)thiourea (126.1 mg, 0.3 mmol), 1-trifluoromethyl-1,2-benziodoxol-3-(1H)-one

(113.8 mg, 0.36 mmol), 4Å MS (30 mg), trifluoroacetic acid (45.9 µL, 0.6 mmol) and $CDCl_3$ (3.0 mL). The crude product was purified by silica gel column chromatography (eluent: 1 % Et_3N and 15 % EtOAc in *n*-pentane) to provide the title compound (103 mg, 70 % yield) as a white solid.

(^{1}H NMR, 400 MHz, $CDCl_3$): δ (ppm) = 7.71 (dt, J_2 = 9.3, 3.7 Hz, 1H), 7.55 (d, J = 8.8 Hz, 2H), 7.21 (dt, J = 9.3, 3.7 Hz, 2H), 7.09 (dd, J = 9.1, 3.7 Hz, 1H), 6.89 (d, J = 8.8 Hz, 2H), 4.23 (d, A of AB, J_{AB} = 12.6 Hz, 1H), 4.16 (d, B of AB, J_{AB} = 12.6 Hz, 1H),3.18−3.11 (m, 1H), 3.01−2.85 (m, 2H), 2.34−2.27 (m, 1H), 2.19 (br s, 1H); (^{13}C NMR, 101 MHz, $CDCl_3$): δ (ppm) = 158.1, 146.2, 137.9, 137.6, 134.6, 129.0, 127.9, 127.0, 126.5 (q, J = 283.2 Hz), 126.0, 123.0, 86.6, 61.3, 60.1, 48.0 (q, J = 24.9 Hz), 25.6, 22.7; (^{19}F NMR, 377 MHz, $CDCl_3$): δ (ppm) = −63.8 (d, J = 8.7 Hz, 3F); IR: 3024, 1635, 1575, 1538, 1514, 1483, 1451, 1394, 1372, 1341, 1308, 1263, 1191, 1150, 1118, 1035, 1003, 935 cm^{-1}; HRMS (ESI) for $C_{19}H_{17}N_2F_3IS$ $[M+H]^+$ requires 489.0104 found 489.0101; Mp. 164−166 °C.

(1*S,2*S**)-*N*-(6-Methylpyridin-3-yl)-2-(trifluoromethyl)-3,4-dihydro-2H,4'H-spiro[naphthalene-1,5'-thiazol]-2'-amine (24a15)**

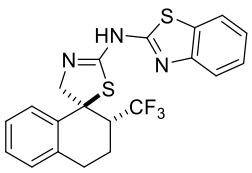


The title compound was prepared following General Procedure P using 1-((3,4-dihydronaphthalen-1-yl)methyl)-3-(6-methylpyridin-3-yl)thiourea (92.8 mg, 0.3 mmol), 1-trifluoromethyl-1,2-benziodoxol-3-(1H)-one (113.8 mg, 0.36 mmol), 4Å MS (30 mg), trifluoroacetic acid (45.9 µL, 0.6 mmol) and $CDCl_3$ (3.0 mL). The crude product was purified by silica gel column chromatography (eluent: 1 % Et_3N and 20 % EtOAc in DCM) to provide the title compound (60.0 mg, 53 % yield) as a white solid.

(^{1}H NMR, 400 MHz, $CDCl_3$): δ (ppm) = 8.21 (d, J = 2.5 Hz, 1H), 7.74−7.71 (m, 1H), 7.37 (dd, J = 8.1, 2.7 Hz, 1H), 7.27−7.17 (m, 2H), 7.08−7.02 (m, 2H), 6.40 (br s , 1H), 4.31 (d, A

of AB, J_{AB} = 12.6 Hz, 1H), 4.25 (d, B of AB, J_{AB} = 12.6 Hz, 1H), 3.17−3.08 (m, 1H), 2.99−2.83 (m, 2H), 2.48 (s, 3H), 2.31−2.23 (m, 1H), 2.16 (br s , 1H); (^{13}C NMR, 101 MHz, $CDCl_3$): δ (ppm) = 160.1, 152.9, 142.3, 141.5, 137.2, 134.7, 129.0, 129.0, 127.9, 126.9, 126.4 (q, *J* = 283.7 Hz), 126.0, 123.0, 60.4, 58.3, 47.9 (q, *J* = 25.4 Hz), 25.6, 23.6, 22.4; (^{19}F NMR, 377 MHz, $CDCl_3$): δ (ppm) = −63.8 (d, *J* = 10.4 Hz, 3F); IR: 3020, 2925, 1633, 1547, 1490, 1451, 1373, 1302, 1264, 1190, 1149, 1117, 1034, 934, 895, 834 cm^{-1}; HRMS (ESI) for $C_{19}H_{19}N_3F_3S$ $[M+H]^+$ requires 378.1246 found 378.1243; Mp. 193−194 °C.

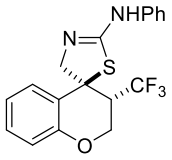
(1*S,2*S**)-*N*-(Benzo[d]thiazol-2-yl)-2-(trifluoromethyl)-3,4-dihydro-2H,4'H-spiro[naphthalene-1,5'-thiazol]-2'-amine (24a16)**



The title compound was prepared following General Procedure P using 1-(benzo[d]thiazol-2-yl)-3-((3,4-dihydronaphthalen-1-yl) methyl)thiourea (105.4 mg, 0.3 mmol), 1-trifluoromethyl-1,2-benziodoxol-3-(1H)-one (113.8 mg, 0.36 mmol), 4Å MS (30 mg), trifluoroacetic acid (45.9 µL, 0.6 mmol) and $CDCl_3$ (3.0 mL). The crude product was purified by silica gel column chromatography (eluent: 1 % Et_3N and 20 % EtOAc in *n*-pentane) to provide the title compound (68.4 mg, 54 % yield) as a yellow solid.

(^{1}H NMR, 400 MHz, DMSO-d6): δ (ppm) = 9.31 (br s , 1H), 7.80 (d, *J* = 7.8 Hz, 1H), 7.70 (d, *J* = 6.1 Hz, 1H), 7.59 (d, *J* = 7.8 Hz, 1H), 7.32 (t, *J* = 7.6 Hz, 1H), 7.25−7.13 (m, 4H), 4.15 (br s , 2H), 3.55−3.49 (m, 1H), 3.10-2.71 (m, 2H), 2.20 (app q, *J* = 5.6 Hz, 2H); (^{13}C NMR, 126 MHz, DMSO-d6): δ (ppm) = 170.9, 165.6, 151.6, 138.1, 135.5, 132.9, 129.4, 128.2, 127.4 (q, *J* = 283.9 Hz), 127.2, 126.3, 126.1, 123.4, 121.9, 120.5, 57.8, 53.7, 46.5 (q, *J* = 24.2 Hz), 25.7, 21.7; (^{19}F NMR, 377 MHz, DMSO-d6): δ (ppm) = −63.3 (d, *J* = 9.5 Hz, 3F); IR: 2980, 1611, 1495, 1441, 1325, 1247, 1178, 1151, 1113, 1093, 1034, 915 cm^{-1}; HRMS (ESI) for $C_{20}H_{17}N_3F_3S_2$ $[M+H]^+$ requires 420.0811 found 420.0808; Mp. cannot be determined due to decomposition at >250 °C.

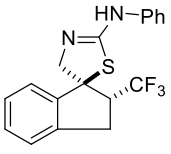
(3S*,4S*)-*N*-Phenyl-3-(trifluoromethyl)-4'H-spiro[chromane-4,5'-thiazol]-2'-amine (24b1)



The title compound was prepared following General Procedure P using 1-((2H-chromen-4-yl)methyl)-3-phenylthiourea (88 mg, 0.3 mmol), 1-trifluoromethyl-1,2-benziodoxol-3-(1H)-one (113.8 mg, 0.36 mmol), 4Å MS (30 mg), trifluoroacetic acid (45.9 µL, 0.6 mmol) and $CDCl_3$ (3.0 mL). The crude product was purified by silica gel column chromatography (eluent: 1 % Et_3N and 20 % EtOAc in *n*-pentane) to provide the title compound (68.4 mg, 54 % yield) as a yellow solid.

(^{1}H NMR, 400 MHz, $CDCl_3$): δ (ppm) = 7.87 (dd, *J* = 8.1, 1.2 Hz, 1H), 7.29 (t, *J* = 7.8 Hz, 2H), 7.20 (td, *J* = 7.7, 1.4 Hz, 1H), 7.15 (d, *J* = 7.6 Hz, 2H), 7.07 (t, *J* = 7.5 Hz, 1H), 6.98 (td, *J* = 7.7, 1.0 Hz, 1H), 6.85 (d, *J* = 8.3 Hz, 1H), 4.65 (dd, *J* = 12.2, 3.2 Hz, 1H), 4.39−4.24 (m, 3H), 3.19−3.12 (m, 1H); (^{13}C NMR, 101 MHz, $CDCl_3$): δ (ppm) = 158.3, 153.3, 145.9, 129.6, 129.1, 127.0, 125.2 (q, *J* = 283.2 Hz), 123.7, 122.1, 121.8, 121.0, 117.3, 64.0 (q, *J* = 2.9 Hz), 59.1, 57.4, 47.2 (q, *J* = 25.7 Hz); (^{19}F NMR, 377 MHz, $CDCl_3$): δ (ppm) = −63.4 (d, *J* = 8.7 Hz, 3F); IR: 3034, 2889, 1639, 1590, 1489, 1449, 1358, 1313, 1277, 1236, 1164, 1130, 1108, 1073, 1040, 908, 856 cm^{-1}; HRMS (ESI) for $C_{18}H_{16}ON_2F_3S$ $[M+H]^+$ requires 365.0930 found 365.0928; Mp. 144−146 °C.

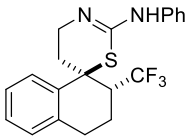
(1S*,2S*)-*N*-Phenyl-2-(trifluoromethyl)-2,3-dihydro-4'H-spiro[indene-1,5'-thiazol]-2'-amine (24c1)



The title compound was prepared following General Procedure P using 1-((1H-inden-3-yl)methyl)-3-phenylthiourea (84.0 mg, 0.3 mmol), 1-trifluoromethyl-1,2-benziodoxol-3-(1H)-one (113.8 mg, 0.36 mmol), 4Å MS (30 mg), trifluoroacetic acid (45.9 µL, 0.6 mmol) and $CDCl_3$ (3.0 mL). The crude product was purified by silica gel column chromatography (eluent: 1 % Et_3N and 20 % EtOAc in DCM) to provide the title compound (78.4 mg, 75 % yield) as a white solid.

(^{1}H NMR, 400 MHz, $CDCl_3$): δ (ppm) = 7.46−7.44 (m, 1H), 7.25−7.15 (m, 6H), 7.09 (d, *J* = 7.9 Hz, 2H) 7.00−6.93 (m, 1H), 4.56 (d, J_{AB} = 13.2 Hz, 1H), 4.12 (d, J_{AB} = 13.2 Hz, 1H), 3.48-3.30 (m, 1H), 3.25 (dd, *J* = 13.4, 2.7 Hz, 2H); (^{13}C NMR, 101 MHz, $CDCl_3$): δ (ppm) = 157.1, 143.6, 134.5, 132.1, 129.1, 128.4, 127.1, 125.6, 125.4 (q, *J* = 284.7 Hz), 125.3, 123.4, 120.1, 62.9, 62.2, 47.1 (q, *J* = 26.0 Hz), 26.0 (q, *J* = 3.0 Hz); (^{19}F NMR, 377 MHz, $CDCl_3$): δ (ppm) = −66.3 (br s, 3F); IR: 2981, 1676, 1589, 1497, 1467, 1345, 1283, 1171, 1130, 1127, 1055, 996 cm^{-1}; HRMS (ESI) for $C_{18}H_{16}N_2F_3S$ $[M+H]^+$ requires 349.0981 found 349.0977; Mp. 138-140 °C.

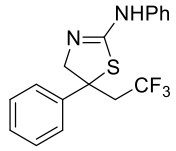
(1*S,2*S**)-*N*-Phenyl-2-(trifluoromethyl)-3,4,4',5'-tetrahydro-2H-spiro[naphthalene-1,6'-[1,3]thiazin]-2'-amine (24c2)**



The title compound was prepared following General Procedure P using *N*-((3,4-dihydronaphthalen-1-yl)methyl)benzamide (92.5 mg, 0.3 mmol), 1-trifluoromethyl-1,2-benziodoxol-3-(1H)-one (113.8 mg, 0.36 mmol), 4Å MS (30 mg), trifluoroacetic acid (45.9 µL, 0.6 mmol) and $CDCl_3$ (3.0 mL). The crude product was purified by silica gel column chromatography (eluent: 1 % Et_3N and 10 % EtOAc in *n*-pentane) to provide the title compound (59.5 mg, 53 % yield) as a white solid.

(^{1}H NMR, 400 MHz, $CDCl_3$): δ (ppm) = 7.47 (d, *J* = 7.6 Hz, 1H), 7.17−7.06 (m, 6H), 6.98 (d, *J* = 7.1 Hz, 1H), 6.90 (t, *J* = 7.2 Hz, 1H), 6.46 (br s , 1H), 3.81−3.71 (m, 2H), 3.08−2.99 (m, 1H), 2.89−2.71 (m, 3H), 2.54 (br s , 1H), 2.34 (d, *J* = 14.4 Hz, 1H), 2.19−2.12 (m, 1H); (^{13}C NMR, 101 MHz, $CDCl_3$): δ (ppm) = 149.7, 143.4, 137.1, 135.8, 129.2, 128.8, 127.6, 126.8 (q, *J* = 284.6 Hz), 126.7, 126.6, 122.8, 121.2, 50.6, 45.7 (q, *J* = 24.0 Hz), 41.8, 30.7, 25.3, 20.0 (q, *J* = 2.9 Hz); (^{19}F NMR, 377 MHz, $CDCl_3$): δ (ppm) = −61.4 (d, *J* = 8.7 Hz, 3F); IR: 2980, 1625, 1587, 1495, 1439, 1367, 1309, 1261, 1200, 1176, 1141, 1121, 1107, 1078, 1019, 947, 837 cm^{-1}; HRMS (ESI) for $C_{20}H_{20}N_2F_3S$ $[M+H]^+$ requires 377.1294 found 377.1299; Mp. 136−139 °C.

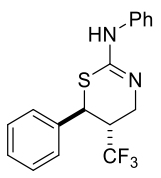
_N_,5-Diphenyl-5-(2,2,2-trifluoroethyl)-4,5-dihydrothiazol-2-amine (24e1)



The title compound was prepared following General Procedure P using 1-phenyl-3-(2-phenylallyl)thiourea (80.5 mg, 0.3 mmol), 1-trifluoromethyl-1,2-benziodoxol-3-(1H)-one (113.8 mg, 0.36 mmol), 4Å MS (30 mg), trifluoroacetic acid (45.9 µL, 0.6 mmol) and $CDCl_3$ (3.0 mL). The crude product was purified by silica gel column chromatography (eluent: 1 % Et_3N and 10 % EtOAc in *n*-pentane) to provide the title compound (90.8 mg, 90 % yield) as a white solid.

(^{1}H NMR, 400 MHz, $CDCl_3$): δ (ppm) = 7.40−7.30 (m, 7H), 7.15−7.09 (m, 3H), 4.16 (dd, J_1 = 11.7 Hz, J_2 = 15.9 Hz, 2H), 3.20−3.00 (m, 2H); (^{13}C NMR, 101 MHz, $CDCl_3$): δ = 160.0, 146.5, 139.6, 129.1, 128.6, 128.0, 126.3, 124.9 (q, J = 279.8 Hz), 123.6, 121.1, 60.8, 60.2, 44.9 (q, J = 26.8 Hz); (^{19}F NMR, 377 MHz, $CDCl_3$): δ (ppm) = −60.4 (t, J = 10.4 Hz, 3F); IR: ν 3030, 2865, 1639, 1590, 1556, 1494, 1446, 1362, 1322, 1256, 1256, 1218, 1183, 1126, 1081, 1037, 995, 857; HRMS (ESI) for $C_{17}H_{16}N_2F_3S$ $[M+H]^+$ requires 337.0981 found 337.0975; Mp. 82−84 °C.

(5*R,6*S**)-*N*,6-Diphenyl-5-(trifluoromethyl)-5,6-dihydro-4H-1,3-thiazin-2-amine (24f1)**

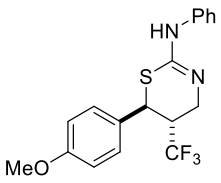


The title compound was prepared following General Procedure P using 1-cinnamyl-3-phenylthiourea (80.5 mg, 0.3 mmol), 1-trifluoromethyl-1,2-benziodoxol-3-(1H)-one (113.8 mg, 0.36 mmol), 4Å MS (30 mg), trifluoroacetic acid (45.9 µL, 0.6 mmol) and $CDCl_3$ (3.0 mL). The crude product was purified by silica gel column chromatography (eluent: 1 % Et_3N and 10 % EtOAc in *n*-pentane) to provide the title compound (40.0 mg, 40 % yield) as a white solid.

(^{1}H NMR, 400 MHz, $CDCl_3$): δ (ppm) = 7.28−7.15 (m, 9H), 6.96−6.92 (m, 1H), 5.65 (br s , 1H), 4.46 (d, J = 8.8 Hz, 1H), 3.88 (dd, A of ABX, J_{AB} = 13.7 Hz, J_{AX} = 4.4 Hz, 1H), 3.56 (B of ABX, J_{AB} = 13.7 Hz, J_{BX} = 7.8 Hz, 1H), 2.89−2.81 (m, 1H); (^{13}C NMR, 101 MHz,

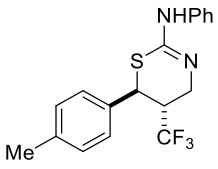
$CDCl_3$): δ (ppm) = 152.7, 142.5, 139.9, 129.0, 128.9, 128.4, 127.7, 126.3 (q, *J* = 281.7 Hz), 123.2, 120.6, 46.1 (q, *J* = 24.2 Hz), 45.4, 44.8; (^{19}F NMR, 377 MHz, $CDCl_3$): δ (ppm) = −68.5 (d, *J* = 6.9 Hz, 3F); IR: 2981, 1626, 1589, 1520, 1496, 1456, 1439, 1382, 1308, 1248, 1167, 1118, 1079, 995, 955 cm^{-1}; HRMS (ESI) for $C_{17}H_{16}N_2F_3S$ $[M+H]^+$ requires 337.0981 found 337.0976; Mp. 116−118 °C.

(5*R,6*S**)-6-(4-Methoxyphenyl)-*N*-phenyl-5-(trifluoromethyl)-5,6-dihydro-4H-1,3-thiazin-2-amine (24f2)**



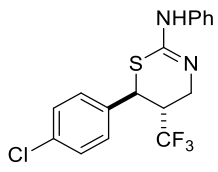
The title compound was prepared following General Procedure P using (*E*)-1-(3-(4-methoxyphenyl)allyl)-3-phenylthiourea (89.5 mg, 0.3 mmol), 1-trifluoromethyl-1,2-benziodoxol-3-(1H)-one (113.8 mg, 0.36 mmol), 4Å MS (30 mg), trifluoroacetic acid (45.9 µL, 0.6 mmol) and $CDCl_3$ (3.0 mL). The crude product was purified by silica gel column chromatography (eluent: 1 % Et_3N and 10 % EtOAc in *n*-pentane) to provide the title compound (60.4 mg, 55 % yield) as a white solid. (^{1}H NMR, 400 MHz, $CDCl_3$): δ (ppm) = 7.33−7.28 (m, 6H), 7.08−7.03 (m, 1H), 6.90 (dt, *J* = 8.6, 2.6 Hz, 2H), 6.07 (br s , 1H), 4.56 (d, *J* = 9.1 Hz, 1H), 4.00 (dd, *J* = 13.9, 4.2 Hz, 1H), 3.83 (s, 3H), 3.67 (dd, *J* = 13.7, 8.1 Hz, 1H), 2.99−2.88 (m, 1H); (^{13}C NMR, 101 MHz, $CDCl_3$): δ (ppm) = 159.6, 153.0, 142.6, 131.6, 129.0, 129.0, 126.3 (q, *J* = 282.1 Hz), 123.2, 120.6, 114.4, 55.3, 46.3 (q, *J* = 27.8 Hz), 45.0, 44.9; (^{19}F NMR, 377 MHz, $CDCl_3$): δ (ppm) = −68.4 (d, *J* = 6.9 Hz, 3F); IR: 2980, 2360, 1611, 1588, 1497, 1459, 1439, 1381, 1306, 1247, 1176, 1109, 1033, 995, 835 cm^{-1}; HRMS (ESI) for $C_{18}H_{18}ON_2F_3S$ $[M+H]^+$ requires 367.1087 found 367.1083; Mp. 136−138 °C.

(5*R,6*S**)-*N*-Phenyl-6-(*p*-tolyl)-5-(trifluoromethyl)-5,6-dihydro-4H-1,3-thiazin-2-amine (24f3)**



The title compound was prepared following General Procedure P using (*E*)-1-Phenyl-3-(3-(*p*-tolyl)allyl)thiourea (84.7 mg, 0.3 mmol), 1-trifluoromethyl-1,2-benziodoxol-3-(1H)-one (113.8 mg, 0.36 mmol), 4Å MS (30 mg), trifluoroacetic acid (45.9 µL, 0.6 mmol) and $CDCl_3$ (3.0 mL). The crude product was purified by silica gel column chromatography (eluent: 1 % Et_3N and 10 % EtOAc in *n*-pentane) to provide the title compound (49.2 mg, 47 % yield) as a white solid. (^{1}H NMR, 400 MHz, $CDCl_3$): δ (ppm) = 7.21−7.13 (m, 6H), 7.06 (d, J = 8.1 Hz, 2H), 6.96−6.92 (m, 1H), 4.44 (d, J = 9.1 Hz, 1H), 3.89 (dd, A of ABX, J_{AB} = 13.7 Hz, J_{AX} = 4.2 Hz, 1H), 3.55 (dd, B of ABX, J_{AB} = 13.7 Hz, J_{BX} = 8.1 Hz, 1H), 2.87−2.82 (m, 1H), 2.25 (s, 3H); (^{13}C NMR, 101 MHz, $CDCl_3$): δ (ppm) = 153.0, 142.6, 138.3, 136.8, 129.6, 128.9, 127.6, 126.3 (q, J = 281.3 Hz), 123.1, 120.5, 46.2 (q, J = 23.8 Hz), 45.2, 44.9, 21.1; (^{19}F NMR, 377 MHz, $CDCl_3$): δ (ppm) = −68.5 (d, J = 6.9 Hz, 3F); IR: 2981, 2360, 1627, 1589, 1515, 1496, 1438, 1438, 1381, 1307, 1248, 1166, 1111, 1074, 995, 955, 844 cm^{-1}; HRMS (ESI) for $C_{18}H_{18}N_2F_3S$ $[M+H]^+$ requires 351.1137 found 351.1140; Mp. 117−119 °C.

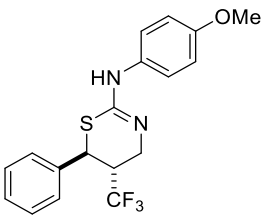
(5*R,6*S**)-6-(4-Chlorophenyl)-*N*-phenyl-5-(trifluoromethyl)-5,6-dihydro-4H-1,3-thiazin-2-amine (24f4)**



The title compound was prepared following General Procedure P using (*E*)-1-(3-(4-chlorophenyl)allyl)-3-phenylthiourea (90.8 mg, 0.3 mmol), 1-trifluoromethyl-1,2-benziodoxol-3-(1H)-one (113.8 mg, 0.36 mmol), 4Å MS (30 mg), trifluoroacetic acid (45.9 µL, 0.6 mmol) and $CDCl_3$ (3.0 mL). The crude product was purified by silica gel column chromatography (eluent: 1 % Et_3N and 10 % EtOAc in *n*-pentane) to provide the title compound (55.8 mg, 50 % yield) as a white solid.

(^{1}H NMR, 400 MHz, $CDCl_3$): δ (ppm) = 7.25−7.17 (m, 8H), 6.95 (t, *J* = 6.7 Hz, 1H), 4.44 (d, *J* = 8.8 Hz, 1H), 3.89 (dd, A of ABX, J_{AB} = 13.9 Hz, J_{AX} = 4.4 Hz, 1H), 3.54 (dd, A of ABX, J_{AB} = 13.9 Hz, J_{AX} = 4.4 Hz, 1H), 2.82−2.75 (m, 1H); (^{13}C NMR, 101 MHz, $CDCl_3$): δ (ppm) = 152.4, 142.3, 138.4, 134.3, 129.2, 129.1, 129.0, 126.1 (q, *J* = 281.3 Hz), 123.3, 120.5, 46.1 (q, *J* = 24.4 Hz), 44.8, 44.8; (^{19}F NMR, 377 MHz, $CDCl_3$): δ (ppm) = −68.4 (d, *J* = 8.7 Hz, 3F); IR: 2981, 2888, 2360, 1628, 1589, 1520, 1493, 1438, 1381, 1310, 1248, 1167, 1119, 1074, 1015, 995, 955, 841 cm^{-1}; HRMS (ESI) for $C_{17}H_{15}N_2ClF_3S$ $[M+H]^+$ requires 371.0591 found 371.0591; Mp. 98−99 °C.

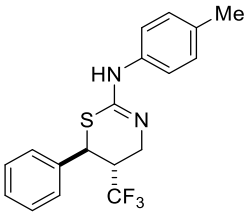
(5*R,6*S**)-*N*-(4-methoxyphenyl)-6-phenyl-5-(trifluoromethyl)-5,6-dihydro-4H-1,3-thiazin-2-amine (24f5)**



The title compound was prepared following General Procedure P using 1-cinnamyl-3-(4-methoxyphenyl)thiourea (89.5 mg, 0.3 mmol), 1-trifluoromethyl-1,2-benziodoxol-3-(1H)-one (113.8 mg, 0.36 mmol), 4Å MS (30 mg), trifluoroacetic acid (45.9 µL, 0.6 mmol) and $CDCl_3$ (3.0 mL). The crude product was purified by silica gel column chromatography (eluent: 1 % Et_3N and 20 % EtOAc in *n*-pentane) to provide the title compound (57.3 mg, 52 % yield) as a white solid.

(^{1}H NMR, 400 MHz, $CDCl_3$): δ (ppm) = 7.38−7.29 (m, 5H), 7.17 (d, *J* = 8.3 Hz, 2H), 6.84 (dt, J_1 = 2.6 Hz, J_2 = 8.8 Hz, 2H), 4.54 (d, *J* = 8.8 Hz, 1H), 3.97 (dd, A of ABX, J_{AB} = 13.2 Hz, J_{AX} = 4.2 Hz, 1H), 3.78 (s, 3H), 3.64 (dd, B of ABX, J_{AB} = 13.9 Hz, J_{AX} = 8.1 Hz, 1H), 2.97−2.90 (m, 1H); (^{13}C NMR, 101 MHz, $CDCl_3$): δ (ppm) = 156.0, 153.6, 139.9, 135.8, 128.9, 128.4, 127.8, 126.3 (q, *J* = 281.3 Hz), 122.8, 114.2, 55.4, 46.2 (q, *J* = 23.8 Hz), 45.3, 44.8; (^{19}F NMR, 377 MHz, $CDCl_3$): δ (ppm) = −68.4 (d, *J* = 6.9 Hz, 3F); IR: 2933, 1625, 1507, 1456, 1382, 1240, 1168, 1117, 1035, 832 cm^{-1}; HRMS (ESI) for $C_{18}H_{18}ON_2F_3S$ $[M+H]^+$ requires 367.1087 found 367.1086; Mp. 140−142 °C.

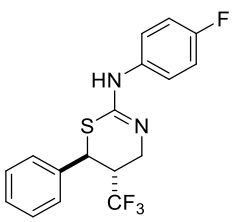
(5*R,6*S**)-6-phenyl-*N*-(*p*-tolyl)-5-(trifluoromethyl)-5,6-dihydro-4H-1,3-thiazin-2-amine (24f6)**



The title compound was prepared following General Procedure P using 1-cinnamyl-3-(*p*-tolyl)thiourea (84.7 mg, 0.3 mmol), 1-trifluoromethyl-1,2-benziodoxol-3-(1H)-one (113.8 mg, 0.36 mmol), 4Å MS (30 mg), trifluoroacetic acid (45.9 µL, 0.6 mmol) and $CDCl_3$ (3.0 mL). The crude product was purified by silica gel column chromatography (eluent: 1 % Et_3N and 20 % EtOAc in *n*-pentane) to provide the title compound (45.6 mg, 44 % yield) as a white solid.

(^{1}H NMR, 400 MHz, $CDCl_3$): δ (ppm) = 7.38−7.29 (m, 5H), 7.15 (d, *J* = 7.6 Hz, 2H), 7.09 (d, *J* = 8.3 Hz, 2H), 4.55 (d, *J* = 9.1 Hz, 1H), 3.99 (dd, A of ABX, J_{AB} = 13.7 Hz, J_{AX} = 3.7 Hz, 1H), 3.65 (dd, B of ABX, J_{AB} = 13.7 Hz, J_{AX} = 8.1 Hz, 1H), 2.98−2.92 (m, 1H), 2.30 (s, 3H); (^{13}C NMR, 101 MHz, $CDCl_3$): δ (ppm) = 152.9, 140.0, 139.8, 132.9, 129.5, 128.9, 128.4, 127.7, 126.3 (q, *J* = 281.3 Hz), 120.8, 46.2 (q, *J* = 24.6 Hz), 45.4 (q, *J* = 24.6 Hz), 44.8 (q, *J* = 1.0 Hz), 20.8; (^{19}F NMR, 377 MHz, $CDCl_3$): δ (ppm) = −68.5 (d, *J* = 8.7 Hz, 3F); IR: 2981, 1628, 1605, 1510, 1456, 1382, 1301, 1247, 1168, 1117, 1048, 998, 825 cm^{-1}; HRMS (ESI) for $C_{18}H_{18}N_2F_3S$ $[M+H]^+$ requires 351.1137 found 351.1133; Mp. 126−128 °C.

(5*R,6*S**)-*N*-(4-Fluorophenyl)-6-phenyl-5-(trifluoromethyl)-5,6-dihydro-4H-1,3-thiazin-2-amine (24f7)**

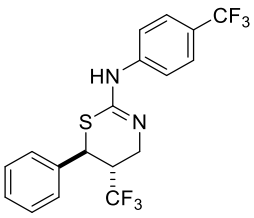


The title compound was prepared following General Procedure P using 1-cinnamyl-3-(4-fluorophenyl)thiourea (85.9 mg, 0.3 mmol), 1-trifluoromethyl-1,2-benziodoxol-3-(1H)-one (113.8 mg, 0.36 mmol), 4Å MS (30 mg), trifluoroacetic acid (45.9 µL, 0.6 mmol) and $CDCl_3$ (3.0 mL). The crude product was purified by silica gel column chromatography (eluent: 1 % 1 %

Et_3N and 10 % EtOAc in *n*-pentane) to provide the title compound (47.8 mg, 45 % yield) as a white solid.

(^{1}H NMR, 400 MHz, $CDCl_3$): δ (ppm) = 7.38−7.30 (m, 5H), 7.17 (dd, *J* = 8.1, 4.7 Hz, 2H), 7.00−6.94 (m, 2H), 4.55 (d, *J* = 9.1 Hz, 1H), 3.94 (dd, A of ABX, J_{AB} = 13.9 Hz, J_{AX} = 4.7 Hz, 1H), 3.64 (dd, B of ABX, J_{AB} = 13.9 Hz, J_{AX} = 7.6 Hz, 1H), 3.03−2.94 (m, 1H); (^{13}C NMR, 101 MHz, $CDCl_3$): δ (ppm) = 159.0 (d, *J* = 241.6 Hz), 153.6, 139.5, 139.2, 129.0, 128.5, 127.7, 126.2 (q, *J* = 282.1 Hz), 122.5 (d, *J* = 8.0 Hz), 115.5 (d, *J* = 23.1 Hz), 46.4 (q, *J* = 24.6 Hz), 45.4, 44.2; (^{19}F NMR, 377 MHz, $CDCl_3$): δ (ppm) = −68.6 (d, *J* = 8.7 Hz, 3F), −119.9 (br s , 1F); IR: 2981, 1625, 1504, 1456, 1382, 1305, 1249, 1215, 1169, 1119, 837 cm^{-1}; HRMS (ESI) for $C_{17}H_{15}N_2F_4S$ $[M+H]^+$ requires 355.0887 found 355.0884; Mp. 131−132 °C.

(5*R,6*S**)-6-Phenyl-5-(trifluoromethyl)-*N*-(4-(trifluoromethyl)phenyl)-5,6-dihydro-4H-1,3-thiazin-2-amine (24f8)**

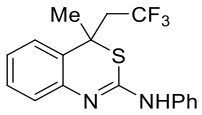


The title compound was prepared following General Procedure P using 1-cinnamyl-3-(4-(trifluoromethyl)phenyl)thiourea (100.9 mg, 0.3 mmol), 1-trifluoromethyl-1,2-benziodoxol-3-(1H)-one (113.8 mg, 0.36 mmol), 4Å MS (30 mg), trifluoroacetic acid (45.9 µL, 0.6 mmol) and $CDCl_3$ (3.0 mL). The crude product was purified by silica gel column chromatography (eluent: 1 % Et_3N and 10 % EtOAc in *n*-pentane) to provide the title compound (49.3 mg, 41 % yield) as a white solid.

(^{1}H NMR, 400 MHz, $CDCl_3$): δ (ppm) = 7.53 (d, *J* = 8.3 Hz, 2H), 7.39−7.33 (m, 7H), 4.58 (d, *J* = 8.8 Hz, 1H), 3.99 (dd, A of ABX, J_{AB} = 13.9 Hz, J_{AX} = 4.2 Hz, 1H), 3.68 (dd, A of ABX, J_{AB} = 13.9 Hz, J_{AX} = 7.6 Hz, 1H), 3.02−2.95 (m, 1H); (^{13}C NMR, 101 MHz, $CDCl_3$): δ (ppm) = 153.0, 146.3, 139.3, 129.1, 128.7, 127.8, 126.3, 126.2 (q, *J* = 282.1 Hz), 126.2,

124.3 (q, *J* = 271.0 Hz), 120.3, 46.2 (q, *J* = 25.4 Hz), 45.6, 44.4; (^{19}F NMR, 377 MHz, $CDCl_3$): δ (ppm) = −61.8 (s, 3F), −68.5 (d, *J* = 6.9 Hz, 3F); IR: 2927, 1631, 1598, 1525, 1456, 1410, 1382, 1249, 1162, 1111, 1064, 1014, 844 cm^{-1}; HRMS (ESI) for $C_{18}H_{15}N_2F_6S$ $[M+H]^+$ requires 405.0855 found 405.0851; Mp. 87−88 °C.

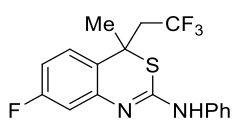
4-Methyl-*N*-phenyl-4-(2,2,2-trifluoroethyl)-4H-benzo[d][1,3]thiazin-2-amine (24g1)



The title compound was prepared following General Procedure P using 1-phenyl-3-(2-(prop-1-en-2-yl)phenyl)thiourea (80.5 mg, 0.3 mmol), 1-trifluoromethyl-1,2-benziodoxol-3-(1H)-one (113.8 mg, 0.36 mmol), 4Å MS (30 mg), trifluoroacetic acid (45.9 µL, 0.6 mmol) and $CDCl_3$ (3.0 mL). The crude product was purified by silica gel column chromatography (eluent: 1 % Et_3N and 5 % EtOAc in *n*-pentane) to provide the title compound (58.8 mg, 58 % yield) as a white solid.

(^{1}H NMR, 400 MHz, $CDCl_3$): δ (ppm) = 7.51 (d, *J* = 7.8 Hz, 2H), 7.37 (t, *J* = 8.1 Hz, 3H), 7.31 (t, *J* = 7.6 Hz, 1H), 7.21−7.11 (m, 3H), 2.69 (ddq, *J* = 63.0, 15.4, 10.8 Hz, 2H), 1.98 (s, 3H); (^{13}C NMR, 101 MHz, $CDCl_3$): δ (ppm) = 150.4, 142.8, 141.3, 129.0, 128.6, 126.8, 125.1 (q, *J* = 279.7 Hz), 124.4, 123.9, 123.8, 122.7, 120.9, 44.7, 43.5 (q, *J* = 27.0 Hz), 23.1; (^{19}F NMR, 377 MHz, $CDCl_3$): δ (ppm) = −60.1 (t, *J* = 10.4 Hz, 3F); IR: 2980, 2361, 1617, 1578, 1521, 1496, 1478, 1439, 1359, 1315, 1257, 1232, 1127, 1105, 1074, 1032, 940 cm^{-1}; HRMS (ESI) for $C_{17}H_{16}N_2F_3S$ $[M+H]^+$ requires 337.0981 found 337.0983; Mp. 82−84 °C.

7-Fluoro-4-methyl-*N*-phenyl-4-(2,2,2-trifluoroethyl)-4H-benzo[d][1,3]thiazin-2-amine (24g2)

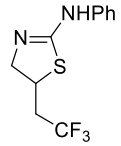


The title compound was prepared following General Procedure P using 1-(5-fluoro-2-(prop-1-en-2-yl)phenyl)-3-phenylthiourea (85.9 mg, 0.3 mmol), 1-trifluoromethyl-1,2-benziodoxol-3-(1H)-one (113.8 mg, 0.36 mmol), 4Å MS (30

mg), trifluoroacetic acid (45.9 µL, 0.6 mmol) and $CDCl_3$ (3.0 mL). The crude product was purified by silica gel column chromatography (eluent: 1 % Et_3N and 10 % EtOAc in *n*-pentane) to provide the title compound (68.3 mg, 64 % yield) as a white solid.

(^{1}H NMR, 400 MHz, $CDCl_3$): δ (ppm) = 7.60 (d, *J* = 7.8 Hz, 2H), 7.37 (t, *J* = 7.9 Hz, 2H), 7.24 (dd, *J* = 8.6, 5.6 Hz, 1H), 7.13 (t, *J* = 7.6 Hz, 1H), 7.09−7.01 (m, 2H), 6.92 (br s , 1H), 2.65 (ddq, *J* = 58.8, 15.4, 10.8 Hz, 2H), 1.95 (s, 3H); (^{13}C NMR, 101 MHz, $CDCl_3$): δ (ppm) = 161.2, 158.8, 149.2, 140.1 (d, *J* = 2.4 Hz), 139.9, 129.0, 126.3 (d, *J* = 8.0 Hz), 125.0 (q, *J* = 279.8 Hz), 123.8, 120.5, 115.3 (d, *J* = 22.3 Hz), 109.7 (d, *J* = 24.6 Hz), 44.5, 43.2 (q, *J* = 27.0 Hz), 23.0; (^{19}F NMR, 377 MHz, $CDCl_3$): δ (ppm) = −60.0 (t, *J* = 10.4 Hz, 3F), −117.5 (q, *J* = 7.5 Hz, 1F); IR: 2981, 2360, 1616, 1587, 1521, 1498, 1480, 1439, 1360, 1316, 1257, 1187, 1145, 1091, 1035, 958 cm^{-1}; HRMS (ESI) for $C_{17}H_{15}N_2F_4S$ $[M+H]^+$ requires 355.0887 found 355.0880; Mp. 133−135 °C.

_N_-Phenyl-5-(2,2,2-trifluoroethyl)-4,5-dihydrothiazol-2-amine (24h1)

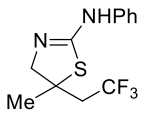


The title compound was prepared following General Procedure P using 1-allyl-3-phenylthiourea (57.7 mg, 0.3 mmol), 1-trifluoromethyl-1,2-benziodoxol-3-(1H)-one (113.8 mg, 0.36 mmol), 4Å MS (30 mg), trifluoroacetic acid (45.9 µL, 0.6 mmol) and $CDCl_3$ (3.0 mL). The crude product was purified by silica gel column chromatography (eluent: 1 % Et_3N and 25 % EtOAc in *n*-pentane) to provide the title compound (62.8 mg, 80 % yield) as a white solid.

(^{1}H NMR, 400 MHz, $CDCl_3$): δ (ppm) = 7.30 (t, *J* = 7.8 Hz, 2H), 7.14 (d, *J* = 7.6 Hz, 2H), 7.08 (t, *J* = 7.3 Hz, 1H), 6.66 (br s, 1H), 4.04−3.95 (m, 2H), 3.69−3.64 (m, 1H), 2.64−2.48 (m, 2H); (^{13}C NMR, 101 MHz, $CDCl_3$): δ (ppm) = 159.9, 146.2, 129.0, 125.5 (q, *J* = 277.4 Hz), 123.5, 120.9, 56.7, 41.9, 38.9 (q, *J* = 27.8 Hz); (^{19}F NMR, 377 MHz, $CDCl_3$): δ (ppm) = −64.9 (t, *J* = 10.4 Hz, 3F); IR: 3246, 3194, 3128, 3008, 2979, 2861, 2362, 1591, 1557, 1497,

1446, 1377, 1331, 1265, 1244, 1191, 1174, 1154, 1141, 1096, 1072, 1036, 982, 904, 839 cm^{-1}; HRMS (ESI) for $C_{11}H_{12}N_2F_3S$ $[M+H]^+$ requires 261.0668 found 261.0667; Mp. 129−130 °C.

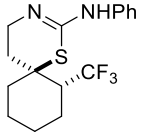
5-Methyl-*N*-phenyl-5-(2,2,2-trifluoroethyl)-4,5-dihydrothiazol-2-amine (24h2)



The title compound was prepared following General Procedure P using 1-(2-methylallyl)-3-phenylthiourea (61.9 mg, 0.3 mmol), 1-trifluoromethyl-1,2-benziodoxol-3-(1H)-one (113.8 mg, 0.36 mmol), 4Å MS (30 mg), trifluoroacetic acid (45.9 µL, 0.6 mmol) and $CDCl_3$ (3.0 mL). The crude product was purified by silica gel column chromatography (eluent: 30 % EtOAc in *n*-pentane) to provide the title compound (78.7 mg, 96 % yield) as a white solid.

(^{1}H NMR, 400 MHz, $CDCl_3$): δ (ppm) = 7.23−7.18 (m, 2H), 7.02−6.95 (m, 3H), 3.60 (d, A of AB J_{AB} = 11.4 Hz, 1H), 3.50 (d, B of AB J_{AB} = 11.4 Hz, 1H), 2.65−2.52 (m, 2H), 1.58 (s, 3H); (^{13}C NMR, 101 MHz, $CDCl_3$): δ (ppm) = 160.4, 147.0, 129.0, 125.4 (q, J = 279.0 Hz), 123.4, 121.1, 61.9, 53.8, 43.6 (q, J = 27.8 Hz), 25.5; (^{19}F NMR, 377 MHz, $CDCl_3$): δ (ppm) = −61.1 (t, J = 11.3 Hz, 3F); IR: 3032, 2858, 2360, 1639, 1590, 1492, 1445, 1390, 1370, 1312, 1257, 1173, 1148, 1106, 1089, 1053, 975, 902, 858 cm^{-1}; HRMS (ESI) for $C_{12}H_{14}N_2F_3S$ $[M+H]^+$ requires 275.0824 found 275.0822; Mp. 118−119 °C.

(6*S,7*S**)-*N*-Phenyl-7-(trifluoromethyl)-1-thia-3-azaspiro[5.5]undec-2-en-2-amine (24i)**

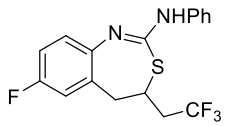


The title compound was prepared following General Procedure P using 1-(2-(cyclohex-1-en-1-yl)ethyl)-3-(4-methoxybenzyl)thiourea (92.0 mg, 0.3 mmol), 1-trifluoromethyl-1,2-benziodoxol-3-(1H)-one (113.8 mg, 0.36 mmol), 4Å MS (30 mg), trifluoroacetic acid (45.9 µL, 0.6 mmol) and $CDCl_3$ (3.0 mL). The crude product (*d.r.* = 8:1) was purified by silica gel column chromatography (eluent: 1 % 1 % Et_3N and 25

% EtOAc in *n*-pentane) to provide the title compound (58.7 mg, 60 % yield) as a white solid (*d.r.* = 20:1).

(^{1}H NMR, 400 MHz, $CDCl_3$): δ (ppm) = 7.18 (t, *J* = 7.8 Hz, 2H), 7.12 (br s , 2H), 6.93−6.89 (m, 1H), 3.72-3.34 (m, 2H), 2.49−2.44 (m, 1H), 2.03−1.72 (m, 6H), 1.63−1.40 (m, 4H); (^{13}C NMR, 101 MHz, $CDCl_3$): δ (ppm) = 149.2, 143.4, 128.8, 127.0 (q, *J* = 283.9 Hz), 122.5, 120.8, 50.0, 48.3 (q, *J* = 23.5 Hz), 41.6, 37.0, 31.4, 22.5 (q, *J* = 2.9 Hz), 21.7, 21.2; (^{19}F NMR, 377 MHz, $CDCl_3$): δ (ppm) = −60.3 (br s , 3F); IR: 2942, 2361, 1624, 1586, 1518, 1496, 1436, 1375, 1342, 1309, 1276, 1238, 1199, 1167, 1138, 1091, 1069, 1037, 987, 899, 832 cm^{-1}; HRMS (ESI) for $C_{16}H_{20}N_2F_3S$ $[M+H]^+$ requires 329.1294 found 329.1290; Mp. 98−99 °C.

7-Fluoro-*N*-phenyl-4-(2,2,2-trifluoroethyl)-4,5-dihydrobenzo[d][1,3]thiazepin-2-amine (24j)



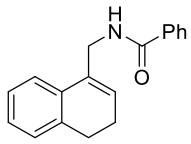
The title compound was prepared following General Procedure P using 1-(2-allyl-4-fluorophenyl)-3-phenylthiourea (85.9 mg, 0.3 mmol), 1-trifluoromethyl-1,2-benziodoxol-3-(1H)-one (113.8 mg, 0.36 mmol), 4Å MS (30 mg), trifluoroacetic acid (45.9 µL, 0.6 mmol) and $CDCl_3$ (3.0 mL). The crude product was purified by silica gel column chromatography (eluent: 20 % Et_2O in *n*-pentane) to provide the title compound (62.3 mg, 59 % yield) as a pale yellow resin.

(^{1}H NMR, 400 MHz, $CDCl_3$): δ (ppm) = 7.73 (d, *J* = 7.6 Hz, 2H), 7.37 (t, *J* = 8.1 Hz, 2H), 7.12 (t, *J* = 7.5 Hz, 1H), 7.05−7.00 (m, 2H), 6.93 (dd, *J* = 8.6, 2.5 Hz, 1H), 4.21−4.14 (m, 1H), 3.07 (dd, A of ABX, J_{AB} = 13.7 Hz, J_{AX} = 5.4 Hz, 1H), 2.82 (dd, A of ABX, J_{AB} = 13.7 Hz, J_{AX} = 8.9 Hz, 1H), 2.73−2.52 (m, 2H); (^{13}C NMR, 101 MHz, $CDCl_3$): δ (ppm) = 158.8 (d, *J* = 242.4 Hz), 146.0, 144.4, 139.7, 130.6 (d, *J* = 7.2 Hz), 129.0, 125.4 (q, *J* = 278.2 Hz), 125.1 (d, *J* = 8.0 Hz), 123.6, 119.5, 115.9 (d, *J* = 22.3 Hz), 114.8 (d, *J* = 22.3 Hz), 49.2, 41.4

(q, *J* = 27.8 Hz), 37.1; (^{19}F NMR, 377 MHz, $CDCl_3$): δ (ppm) = −63.4 (t, *J* = 10.4 Hz, 3F), −119.9 (q, *J* = 7.5 Hz, 1F); IR: 3424, 1619, 1593, 1512, 1486, 1435, 1380, 1345, 1312, 1262, 1212, 1136, 1101, 1006, 964, 873, 829 cm^{-1}; HRMS (ESI) for $C_{17}H_{15}N_2F_4S$ $[M+H]^+$ requires 355.0887 found 355.0883.

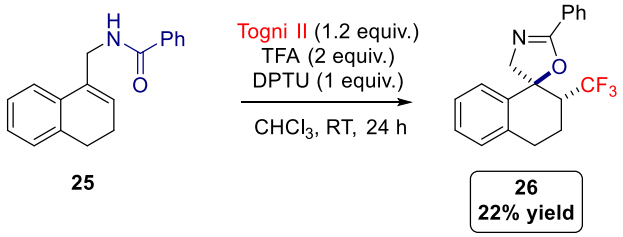
5.3.3 Amide, Urea and Thioamide Substrates

N-((3,4-Dihydronaphthalen-1-yl)methyl)benzamide (25)



To a mixture of (1,2-dihydronaphthalen-4-yl)methanammonium hydrochloride (392 mg, 2.0 mmol), Et_3N (1.12 ml, 8 mmol) and DMAP (24.4 mg, 0.2 mmol), benzoyl chloride (0.23 ml, 2 mmol) was added dropwise at 0 °C. The mixture was stirred for 3h at room temperature. The reaction was quenched by the addition of saturated NH_4Cl aq (50 mL). The aqueous phase was extracted with CH_2Cl_2 (50 mL × 3). The organic phase was combined and reduced to a volume of approximate 20 mL. The solution was washed with K_2CO_3 aq (50 mL) and the aqueous phase was extracted with CH_2Cl_2 (50 mL × 3). The combined organic phase was dried over $MgSO_4$, filtered and concentrated. The crude product was purified by flash column chromatography (25 % EtOAc in hexane) to provide the title compound (390 mg, 70 % yield) as a white solid. (^{1}H NMR, 400 MHz, $CDCl_3$): δ = 7.77 (d, *J* = 7.1 Hz, 2H), 7.48 (t, *J* = 7.3 Hz, 1H), 7.40 (t, *J* = 7.5 Hz, 2H), 7.31 (d, *J* = 6.9 Hz, 1H), 7.23−7.17 (m, 3H), 6.28 (brs, 1H), 6.13 (t, *J* = 4.4 Hz, 1H), 4.50 (d, *J* = 4.7 Hz, 2H), 2.80 (t, *J* = 8.1 Hz, 2H), 2.36−2.31 (m, 2H); (^{13}C NMR, 101 MHz, $CDCl_3$): δ = 167.3, 136.4, 134.4, 132.9, 132.9, 131.4, 128.5, 128.3, 127.8, 127.3, 126.9, 126.7, 122.6, 42.3, 27.8, 23.0. Data consistent with literature values.[20]

(1S*,2R*)-2'-phenyl-2-(trifluoromethyl)-3,4-dihydro-2H,4'H-spiro[naphthalene-1,5'-oxazole] (26)



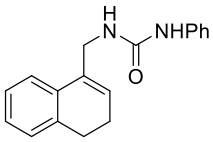
25

26
22% yield

Into a vial containing *N*-((3,4-dihydronaphthalen-1-yl)methyl)benzamide (79.0 mg, 0.3 mmol), *N*,*N*′-diphenylthiourea (68.5 mg, 0.3 mmol), 1-trifluoromethyl-1,2-benziodoxol-3-(1H)-one (113.8 mg, 0.36 mmol), 4Å MS (30 mg) and a stirrer bar was added a solution of trifluoroacetic acid (45.9 µL, 0.6 mmol) in $CDCl_3$ (3.0 mL) under Ar atmosphere. The vial was sealed and allowed to stir at room temperature for 24 hours. The reaction mixture was then concentrated and purified by silica gel column chromatography (eluent: 1 % NEt_3 and 10 % EtOAc in *n*-pentane) to provide the title compound (25.4 mg, 22 % yield) as a colourless oil.

(^{1}H NMR, 400 MHz, $CDCl_3$): δ (ppm) = 7.93 (d, *J* = 8.4 Hz, 2H), 7.44 (t, *J* = 7.3 Hz, 1H), 7.37 (t, *J* = 7.4 Hz, 2H), 7.25−7.22 (m, 1H), 7.18−7.14 (m, 2H), 7.07−7.05 (m, 1H), 4.56 (d, *J* = 15.8 Hz, 1H), 3.97 (d, *J* = 15.8 Hz, 1H), 2.95−2.86 (m, 3H), 2.28−2.22 (m, 1H), 1.95−1.82 (m, 1H); (^{13}C NMR, 126 MHz, $CDCl_3$): δ (ppm) = 163.7, 140.5, 134.2, 131.5, 128.4, 128.4, 128.3, 128.1, 127.6, 127.4, 126.8 (q, *J* = 281.3 Hz), 125.3, 84.8, 65.5, 46.6 (q, *J* = 24.9 Hz), 28.0, 20.9 (q, *J* = 2.9 Hz); (^{19}F NMR, 377 MHz, $CDCl_3$): δ (ppm) = −66.6 (d, *J* = 8.2 Hz, 3F); IR: 2926, 1655, 1494, 1450, 1389, 1347, 1309, 1266, 1227, 1195, 1165, 1137, 1111, 1090, 1064, 1039, 1027, 980, 931, 895, 833 cm^{-1}; HRMS (ESI) for $C_{19}H_{17}ONF_3$ $[M+H]^+$ requires 332.1257 found 332.1256. Data consistent with literature values.[20]

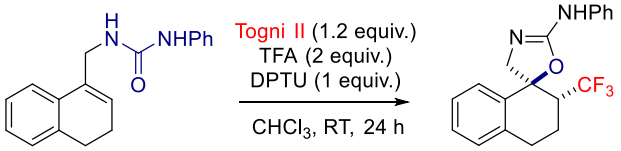
1-((3,4-Dihydronaphthalen-1-yl)methyl)-3-phenylurea (29)



The title compound was prepared following general procedure A using (3,4-dihydronaphthalen-1-yl)methanamine (392 mg, 2.0 mmol), DCM (20 mL) and phenyl isocyanate (0.22 mL, 2.0 mmol). The crude product was purified by precipitation to give the title compound (374 mg, 67 % yield) as a white solid.

(^{1}H NMR, 400 MHz, DMSO-d6): δ (ppm) = 7.41 (d, *J* = 7.6 Hz, 2H), 7.30 (d, *J* = 6.9 Hz, 1H), 7.25−7.18 (m, 5H), 6.90 (t, *J* = 6.6 Hz, 1H), 6.29 (br s , 1H), 6.05 (br s , 1H), 4.15 (br s , 2H), 2.71 (t, *J* = 7.3 Hz, 2H), 2.25 (br s , 2H); (^{13}C NMR, 101 MHz, DMSO-d6): δ (ppm) = 154.9, 140.4, 136.0, 134.0, 133.2, 128.7, 127.6, 127.0, 126.5, 126.0, 122.5, 121.0, 117.5, 40.9, 27.5, 22.4; IR: 3295, 1631, 1596, 1568, 1527, 1495, 1442, 1295, 1264, 1236, 1170, 1053, 1019, 819 cm^{-1}; HRMS (ESI) for $C_{18}H_{19}ON_2$ $[M+H]^+$ requires 279.1492 found 279.1493; Mp. 148−150 °C.

(1*S,2*R**)-*N*-Phenyl-2-(trifluoromethyl)-3,4-dihydro-2H,4'H-spiro[naphthalene-1,5'-oxazol]-2'-amine (30)**



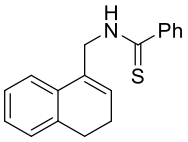
29 **30** **13% yield**

Into a vial containing 1-((3,4-dihydronaphthalen-1-yl)methyl)-3-phenylurea (139 mg, 0.5 mmol) (4), *N*,*N*′-diphenylthiourea (114 mg, 0.5 mmol), 1-trifluoromethyl-1,2-benziodoxol-3-(1H)-one (190 mg, 0.6 mmol) and a stirrer bar was added a solution of trifluoroacetic acid (76.6 µL, 1.0 mmol) in $CHCl_3$ (5.0 mL) under Ar atmosphere. The vial was sealed and allowed to stir at room temperature for 24 hours. The reaction mixture was then concentrated

and purified by silica gel column chromatography (eluent: 25 % EtOAc in *n*-pentane) to provide the title compound (24.8 mg, 14 % yield) as a pale yellow resin.

(^{1}H NMR, 500 MHz, $CDCl_3$): δ (ppm) = 7.45 (d, *J* = 6.9 Hz, 3H), 7.32−7.26 (m, 5H), 7.13 (d, *J* = 6.6 Hz, 1H), 7.02 (t, *J* = 7.3 Hz, 1H), 4.50 (d, *J* = 13.3 Hz, 1H), 3.94 (d, *J* = 13.3 Hz, 1H), 2.99−2.87 (m, 3H), 2.33−2.28 (m, 1H), 1.98−1.90 (m, 1H); (^{13}C NMR, 158 MHz, $CDCl_3$): δ (ppm) = 155.7, 140.0, 139.1, 134.4, 129.0, 128.4, 128.2, 127.4, 126.7 (q, *J* = 281.3 Hz), 125.3, 122.5, 118.3, 84.0, 63.4, 46.5 (q, *J* = 25.8 Hz), 27.9, 20.8 (q, *J* = 2.9 Hz); (^{19}F NMR, 377 MHz, $CDCl_3$): δ (ppm) = −66.6 (d, *J* = 9.0 Hz, 3F); IR: 3063, 2940, 2360, 1676, 1601, 1555, 1499, 1448, 1416, 1389, 1342, 1310, 1269, 1247, 1229, 1188, 1167, 1138, 1112, 1091, 1038, 993, 956, 909, 832 cm^{-1} ; HRMS (CI) for $C_{19}H_{18}ON_2F_3$ $[M+H]^+$ requires 347.1371 found 347.1370.

_N_-((3,4-Dihydronaphthalen-1-yl)methyl)benzothioamide (31)



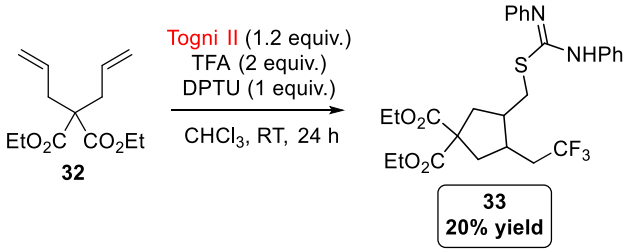
To a solution of (3,4-dihydronaphthalen-1-yl)methanamine (175 mg, 1.1 mmol) in DMF (1 mL) was added benzaldehyde (0.10 mL, 1.0 mmol) and sulfur (35.2 mg, 1.1 mmol). The mixture was stirred at 90 ˚C for 6 hours. The reaction mixture was diluted with Et_2O (20 mL) and the organic layer was washed with sat. $NaHCO_{3(aq)}$ (20 mL), 5 M $HCl_{(aq)}$ (20 mL) and brine (20 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography (eluent: 10 % EtOAc in *n*-pentane) to provide the title compound (239 mg, 57 % yield) as pale yellow solid.

(^{1}H NMR, 400 MHz, $CDCl_3$): δ = 7.70 (d, *J* = 7.3 Hz, 2H), 7.51 (brs, 1H), 7.44 (t, *J* = 7.6 Hz, 1H), 7.35 (t, *J* = 7.6 Hz, 2H), 7.27−7.21 (m, 4H), 6.23 (t, *J* = 4.4 Hz, 1H), 4.81 (d, *J* = 4.2 Hz, 2H), 2.84 (t, *J* = 8.1 Hz, 2H), 2.42−2.37 (m, 2H); (^{13}C NMR, 101 MHz, $CDCl_3$): δ = 198.9, 141.7, 136.3, 132.5, 131.7, 131.0, 130.4, 128.4, 128.0, 127.6, 126.9, 126.6, 122.7, 49.7, 27.7, 23.1; IR: ν 3232, 3025, 2932, 2882, 2829, 1515, 1486, 1384, 1366, 1319, 1281,

1217, 1132, 1096, 1074, 1022, 1001, 971, 940, 819; HRMS (ESI) for $C_{18}H_{18}NS$ $[M+H]^+$ requires 280.1155 found 280.1154; Mp. 82−84 °C.

5.3.4 Radical Clock Experiment

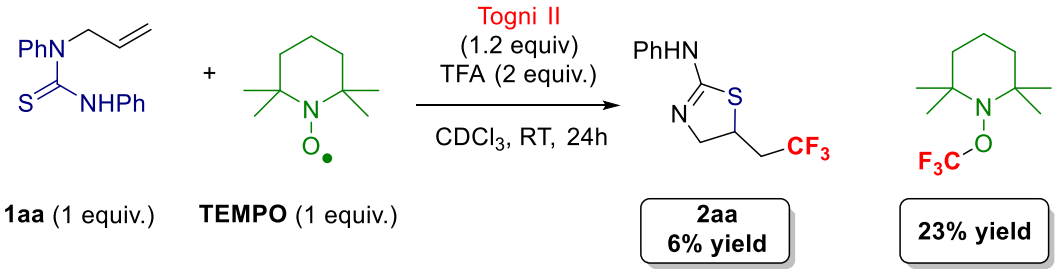
Diethyl-3-(((N,N'-diphenylcarbamimidoyl)thio)methyl)-4-(2,2,2-trifluoroethyl) cyclopentane-1,1-dicarboxylate (33)



The title compound was prepared following General Procedure P using diethyl diallyl malonate (144 mg, 0.6 mmol), diphenylthiourea (136.8 mg, 0.6 mmol), 1-trifluoromethyl-1,2-benziodoxol-3-(1H)-one (113.8 mg, 0.36 mmol), trifluoroacetic acid (45.9 µL, 0.6 mmol) and $CDCl_3$ (3.0 mL). The crude product was purified by silica gel column chromatography (eluent: 15 % EtOAc in *n*-pentane) to provide the title compound (31.7 mg, 20 % yield) as a colourless oil.

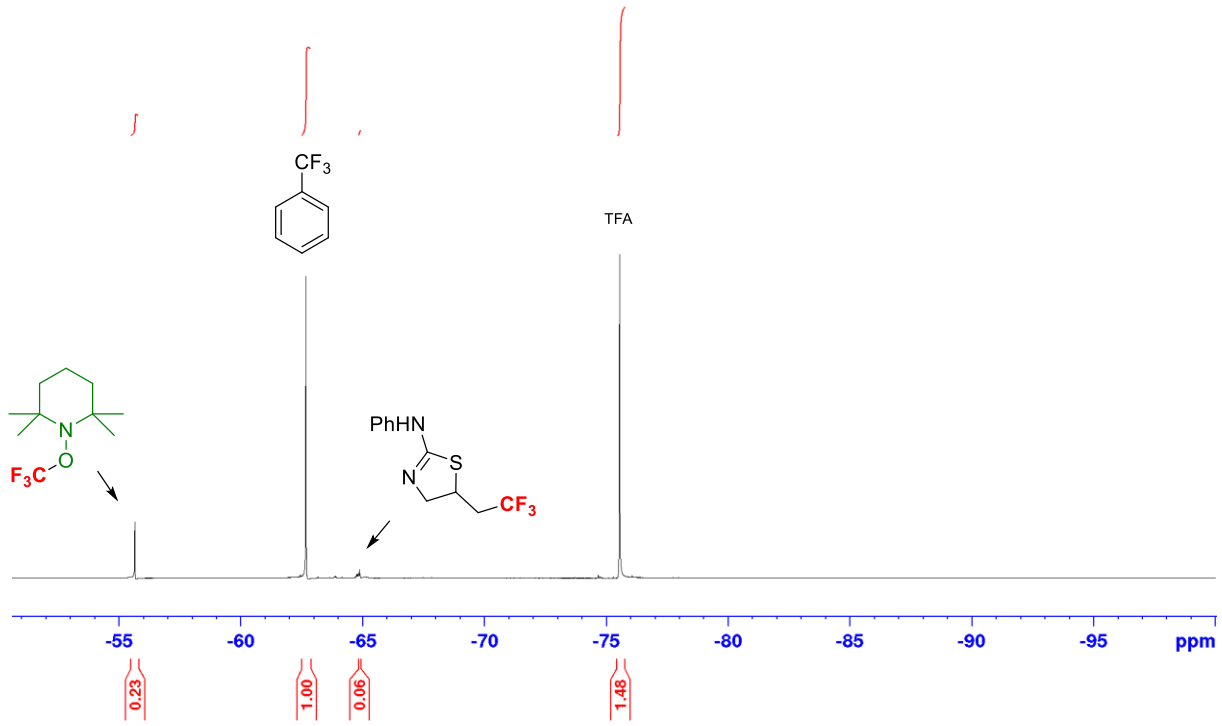
(^{1}H NMR, 400 MHz, CD_3OD): δ (ppm) = 7.16 (t, *J* = 7.8 Hz, 6H), 7.11 (br s, 1H), 6.91 (t, *J* = 7.5 Hz, 4H), 4.06 (q, *J* = 7.1 Hz, 2H), 4.03 (q, *J* = 7.1 Hz, 2H), 2.44−1.76 (m, 10H), 1.11 (t, J = 7.1 Hz, 3H), 1.10 (t, J = 7.1 Hz, 3H); (^{13}C NMR, 101 MHz, CD_3OD): δ (ppm) = 172.2, 172.1, 150.3, 128.4, 127.2 (q, *J* = 276.6 Hz), 122.8, 121.1 (br), 61.5, 61.4, 58.4, 42.0, 37.8, 37.4, 36.0 (q, *J* = 2.2 Hz), 32.7 (q, *J* = 27.9 Hz), 31.3, 12.9; (^{19}F NMR, 377 MHz, CD_3OD): δ (ppm) = −65.8 (t, *J* = 11.5 Hz, 3F); IR: 2982, 2938, 1728, 1627, 1587, 1525, 1515, 1498, 1485, 1437, 1392, 1368, 1312, 1255, 1220, 1184, 1149, 1128, 1095, 1055, 1027, 1007, 914, 861, 838 cm^{-1} ; HRMS (ESI) for $C_{27}H_{32}O_4N_2F_3S$ $[M+H]^+$ requires 537.2029 found 537.2022.

5.3.5 Radical Inhibition Experiment



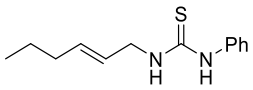
To a vial containing appropriate allyl thiourea **1aa** (0.1 mmol, 19.2 mg), 1-trifluoromethyl-1,2-benziodoxol-3-(1H)-one (37.9 mg, 0.12 mmol), TEMPO (1 equiv.), 4Å MS (10 mg) and a stirrer bar, was added a solution of trifluoroacetic acid (15.3 µL, 0.2 mmol) in $CDCl_3$ (3.0 mL) under Ar atmosphere. The vial was sealed and allowed to stir at room temperature for 24 hours. The reaction mixture was filtered through cotton and analysed by 19F NMR, using $C_6H_5CF_3$ as internal standard (1 equiv.)

^{19}F NMR spectrum of the crude reaction is reported below:



5.3.6 Additional Studies on the Selectivity

(*E*)-1-(Hex-2-en-1-yl)-3-phenylthiourea

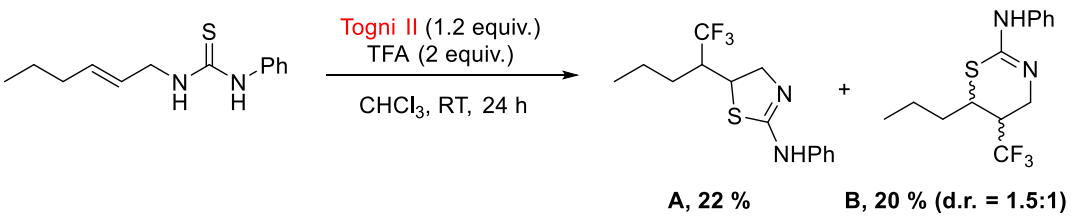


(*E*)-2-(hex-2-en-1-yl)isoindoline-1,3-dione was prepared following General Procedure N using THF (30 mL), PPh_3 (1.59 g, 6.1 mmol), phthalimide (890 mg, 6.1 mmol) and diethyl azodicarboxylate (0.95 mL, 6.1 mmol). The crude product was used on the next reaction without further purification. To the crude mixture was added hydrazine monohydrate (0.8 mL, 16.5 mmol) and stirred at room temperature overnight. The crude amine was subjected to the conditions described by general procedure A using phenyl isothiocyanate (0.78 mL, 6.5 mmol) and DCM (50 mL). The crude product was purified by column chromatography (20 % EtOAc in hexane) to give the title compound **15** (509 mg, 43 % yield) as a pale yellow solid.

(^{1}H NMR, 400 MHz, $CDCl_3$): δ (ppm) = 8.17 (br s, 1H), 7.43–7.30 (m, 2H), 7.26–7.19 (m, 1H), 7.18–7.13 (m, 2H), 5.97 (br s, 1H), 5.62–5.48 (m, 1H), 5.45–5.37 (m, 1H), 4.13 (t, *J* = 5.9 Hz, 2H), 1.97–1.83 (m, 2H), 1.33–1.25 (m, 2H), 0.79 (t, *J* = 7.4 Hz, 3H); (^{13}C NMR, 101 MHz, $CDCl_3$): δ (ppm) = 180.25, 136.16, 134.73, 130.17, 127.20, 125.21, 124.65, 47.53, 34.27, 22.16, 13.61. IR: 3211, 2957, 2927, 2870, 1596, 1528, 1496, 1452, 1346, 1313, 1258, 1235, 1185, 1073, 1028, 969, 934 cm^{-1}; HRMS (ESI) for $C_{13}H_{18}N_2S$ $[M+H]^+$ requires 235.1263 found 235.1263. Mp. 78−79 °C.

***N*-Phenyl-5-(1,1,1-trifluoropentan-2-yl)-4,5-dihydrothiazol-2-amine (A)**

and *N*-phenyl-6-propyl-5-(trifluoromethyl)-5,6-dihydro-4H-1,3-thiazin-2-amine (B)



Into a vial containing (*E*)-1-(hex-2-en-1-yl)-3-phenylthiourea **15** (141 mg, 0.6 mmol), 1-trifluoromethyl-1,2-benziodoxol-3-(1H)-one (228 mg, 0.72 mmol) and a stirrer bar was added a solution of trifluoroacetic acid (91.8 µL, 1.2 mmol) in $CHCl_3$ (6.0 mL) under Ar atmosphere. The vial was sealed and allowed to stir at room temperature for 24 hours. The reaction mixture was then concentrated and purified by silica gel column chromatography (eluent: 25 % EtOAc in *n*-pentane) to provide *N*-phenyl-5-(1,1,1-trifluoropentan-2-yl)-4,5-dihydrothiazol-2-amine **16a** (40.6 mg, 22 % yield) as a pale yellow oil and *N*-phenyl-6-propyl-5-(trifluoromethyl)-5,6-dihydro-4H-1,3-thiazin-2-amine **16b** (36.2 mg, pale yellow oil) as a mixture of diastereomer (d.r. = 1.5:1).

***N*-Phenyl-5-(1,1,1-trifluoropentan-2-yl)-4,5-dihydrothiazol-2-amine (A)**

(^{1}H NMR, 400 MHz, $CDCl_3$): δ (ppm) = 7.28–7.13 (m, 4H), 7.02–6.89 (m, 1H), 4.77 (br s, 1H), 3.71 (dd, J_1 = 4.7 Hz, J_2 = 13.5 Hz, 1H), 3.47 (dd, J_1 = 8.4 Hz, J_2 = 13.4 Hz, 1H), 3.34 (ddd, J_1 = 4.7 Hz, J_2 = 6.2 Hz, J_3 = 9.0 Hz, 1H), 2.45–2.14 (m, 1H), 1.79–1.66 (m, 1H), 1.66–1.51 (m, 1H), 1.51–1.37 (m, 1H), 1.37–1.24 (m, 1H), 0.85 (t, *J* = 7.3 Hz, 3H); (^{13}C NMR, 158 MHz, $CDCl_3$): δ (ppm) = 153.5, 142.3, 129.1, 129.0, 126.5 (q, *J* = 281.3 Hz), 123.1, 120.4, 44.5 (q, *J* = 25.3 Hz), 41.4, 39.8, 19.7, 13.5; (^{19}F NMR, 377 MHz, $CDCl_3$): δ (ppm) = −68.5 (d, *J* = 8.0 Hz, 3F); IR: 2963, 2933, 2875, 2363, 1626, 1590, 1519, 1497, 1459, 1439, 1383, 1311, 1251, 1166, 1128, 1090, 971, 899, 847 cm^{-1} ; HRMS (ESI) for $C_{14}H_{17}N_2SF_3$ $[M+H]^+$ requires 303.1137 found 303.1138.

***N*-Phenyl-6-propyl-5-(trifluoromethyl)-5,6-dihydro-4H-1,3-thiazin-2-amine (B)**

Major: (^{1}H NMR, 400 MHz, $CDCl_3$): δ (ppm) = 7.26–7.19 (m, 2H), 7.10–7.02 (m, 2H), 6.99 (t, *J* = 7.5 Hz, 1H), 5.42 (s, 1H), 4.12–4.01 (m, 1H), 3.80 (dd, J_1 = 7.2 Hz, J_2 = 11.6 Hz, 1H), 3.62 (dd, J_1 = 8.3 Hz, J_2 = 11.6 Hz, 1H), 2.41–2.23 (m, 1H), 1.67–1.25 (m, 4H), 0.83 (t, *J* = 7.2 Hz, 3H); (^{13}C NMR, 158 MHz, $CDCl_3$): δ (ppm) = 158.7, 145.4, 128.0, 126.1 (q, *J* = 281.3 Hz), 122.4, 120.0, 54.8, 47.2, 45.1 (q, *J* = 25.0 Hz), 28.7, 19.4, 13.0 (^{19}F NMR, 377

MHz, $CDCl_3$): δ (ppm) = −67.7 (d, *J* = 9.1 Hz, 3F); Minor: (^{1}H NMR, 400 MHz, $CDCl_3$): δ (ppm) = 7.26–7.19 (m, 2H), 7.10–7.02 (m, 2H), 6.99 (t, *J* = 7.5 Hz, 1H), 5.42 (s, 1H), 4.12–4.01 (m, 1H), 3.89 (dd, J_1 = 7.2 Hz, J_2 = 11.6 Hz, 1H), 3.56 (dd, J_1 = 7.8 Hz, J_2 = 11.8 Hz, 1H), 2.41–2.23 (m, 1H), 1.67–1.25 (m, 4H), 0.86 (t, *J* = 7.2 Hz, 3H); (^{13}C NMR, 158 MHz, $CDCl_3$): δ (ppm) = 158.9, 144.9, 128.0, 126.3 (q, *J* = 281.3 Hz), 122.4, 119.9, 52.9, 45.9, 45.0 (q, *J* = 25.0 Hz), 26.1, 20.0, 13.0; (^{19}F NMR, 377 MHz, $CDCl_3$): δ (ppm) = −67.8 (d, *J* = 9.1 Hz, 3F); IR: 2968, 2876, 2360, 1642, 1591, 1555, 1495, 1468, 1445, 1381, 1321, 1251, 1168, 1132, 1068, 1038, 968, 900, 855 cm^{-1} ; HRMS (ESI) for $C_{14}H_{17}N_2SF_3$ $[M+H]^+$ requires 303.1137 found 303.1139.

5.3.6 Cyclic Voltammetry Analysis

The experiment in this section was performed by Maurice Médebielle. Electrochemical measurements were performed using an EG & G-Princeton Applied Research 263A all-in-one potentiostat, using a standard three-electrode setup with a glassy carbon electrode (diameter = 3 mm) or a platinum electrode (diameter = 1.6 mm), a platinum wire auxiliary electrode and a non-aqueous Ag/Ag^+ (0.1 M NBu_4ClO_4 + 0.01 M $AgNO_3$) system in acetonitrile as the reference electrode. All solutions of the compounds under the study were 0.1 M in the supporting electrolyte *n*-Et_4NBF_4 with the voltage scan rate of 0.2 $V.s^{-1}$. Solutions were thoroughly bubbled with dry argon for 15 minutes to remove any oxygen before any experiment and kept under positive pressure of argon. Under these experimental conditions the ferrocene/ferricinium couple, used as internal reference for potential measurements, was located at $E_{1/2}$ = + 0.046 V in CH_3CN. For conversion factors (SCE *vs* Ag/Ag+), see: V. V. Palvlishchuk and A. W. Adison, *Inorg. Chim. Acta*, **2000**, 298, 97.

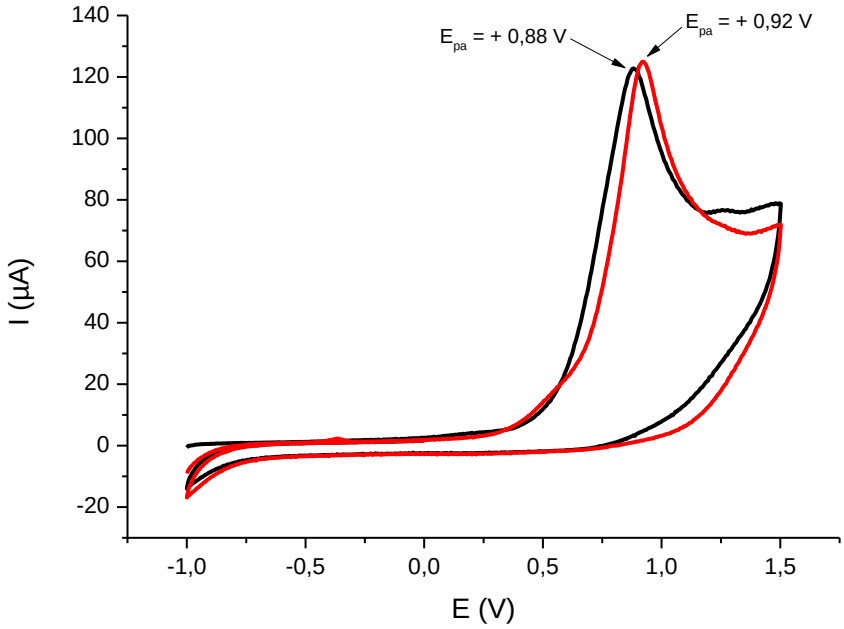


Figure S1. Cyclic voltammetry of thiourea **23h1** *C* = 3.5 mM in CH_3CN + *n*-Et_4NBF_4 0.1 M + in the absence (black curve) and presence (red curve) of TFA (2 eq); glassy carbon electrode at 0.2 V/s. In the absence of TFA, E_{pox} = + 0.88 V *vs* Ag/Ag^+ = + 1.19 V *vs* SCE and in the presence of TFA, E_{pox} = + 0.92 V *vs* Ag/Ag^+ = **+ 1.23 V *vs* SCE**.

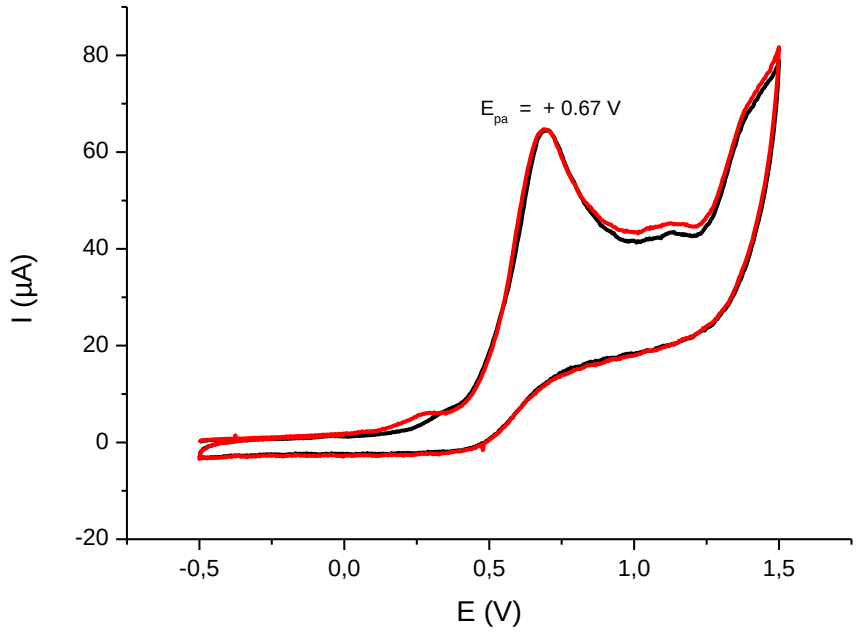


Figure S2. Cyclic voltammetry of thiourea **23a1** *C* = 1.29 mM in CH_3CN + *n*-Et_4NBF_4 0.1 M in the absence (black curve) and presence (red curve) of TFA (2 eq); glassy carbon electrode at 0.2 V/s; E_{pox} = + 0.67 V *vs* Ag/Ag^+ = **+ 0.98 V *vs* SCE**.

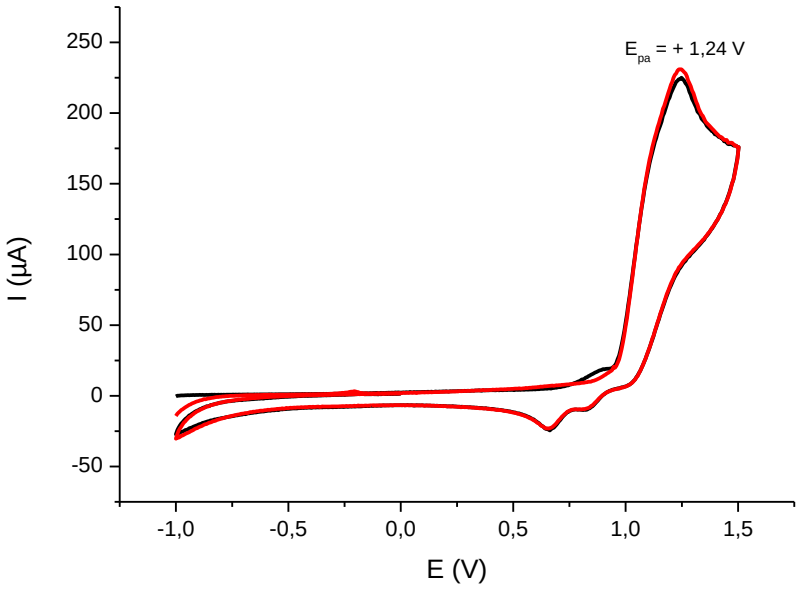


Figure S3. Cyclic voltammetry of urea **29** *C* = 3.06 mM in CH_3CN + *n*-Et_4NBF_4 0.1 M in the absence (black curve) and presence (red curve) of TFA (2 eq); glassy carbon electrode at 0.2 V/s; E_{pox} = + 1.24 V *vs* Ag/Ag^+ = **+ 1.56 V *vs* SCE**.

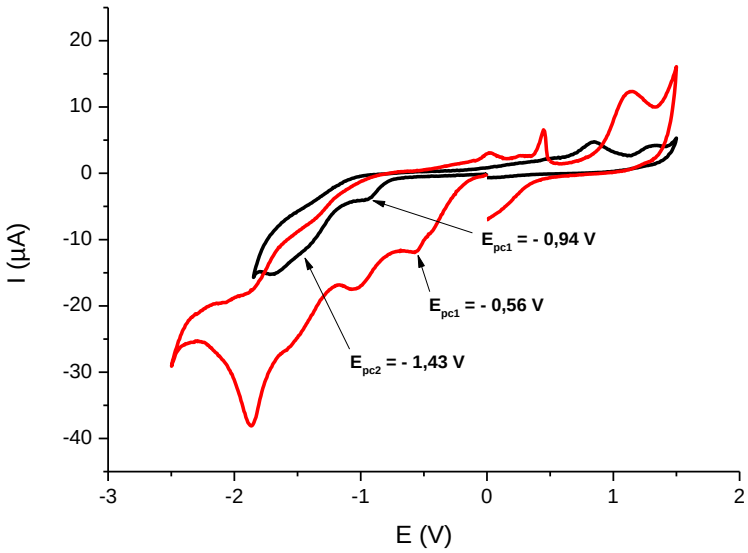
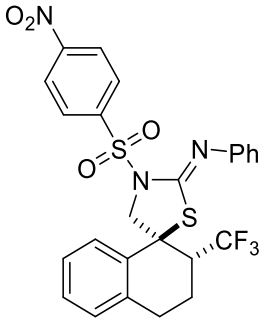


Figure S4. Cyclic voltammetry of Togni reagent **II** *C* = 1.77 mM in CH_3CN + *n*-Et_4NBF_4 0.1 M in the absence (black curve) and presence of TFA (2 eq) (red curve) and presence of TFA (2 eq) + thiourea (1 eq) **1ga**; platinum electrode at 0.2 V/s.

For Togni reagent alone: E_{pc1} = - 0.94 V *vs* Ag/Ag^+ = **- 0.63 V *vs* SCE**; E_{pc2} = - 1.43 V *vs* Ag/Ag^+ = **- 1.12 V *vs* SCE**
For Togni reagent in the presence of TFA: E_{pc1} = - 0.56 V *vs* Ag/Ag^+ = **- 0.25 V *vs* SCE**

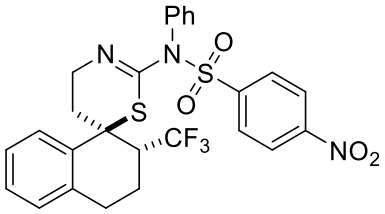
5.3.7 Crystallographic Data

(1*S,2*S**,*Z*)-3'-((4-Nitrophenyl)sulfonyl)-N-phenyl-2-(trifluoromethyl)-3,4-dihydro-2H-spiro[naphthalene-1,5'-thiazolidin]-2'-imine (27)**



4-nitrobenzenesulfonyl chloride (58.9 mg, 0.27 mmol) and 4-dimethylaminopyridine (21.6 mg, 0.18 mmol) were added to a solution of (1*S**,2*S**)-*N*-phenyl-2-(trifluoromethyl)-3,4-dihydro-2H,4'H-spiro[naphthalene-1,5'-thiazol]-2'-amine (64.1 mg, 0.18 mmol) in DCM (1 mL). The reaction mixture was stirred at room temperature for 16 hours. The crude mixture was concentrated *in vacuo* and purified by silica gel column chromatography (eluent: 5 % EtOAc in *n*-pentane) to provide the title compound (19.0 mg, 20 % yield) as a white solid. (^{1}H NMR, 400 MHz, $CDCl_3$): δ (ppm) = 8.49−8.41 (m, 4H), 7.77−7.75 (m, 1H), 7.32−7.10 (m, 4H), 7.15−7.10 (m, 2H), 6.77−6.74 (m, 2H), 4.46 (d, A of AB, J_{AB} = 16.5 Hz, 1H), 4.41 (d, B of AB, J_{AB} = 16.5 Hz, 1H), 3.06−2.85 (m, 2H), 2.89 (dt, J_1 = 6.4 Hz, J_2 = 17.4 Hz, 1H), 2.24 (q, J = 6.4 Hz, 2H); (^{13}C NMR, 126 MHz, $CDCl_3$): δ (ppm) = 150.8, 150.2, 148.9, 143.4, 136.0, 134.6, 133.2, 130.9, 129.4, 129.1, 129.1 (q, J = 282.4 Hz), 128.6, 127.3, 126.4, 124.9, 123.7, 120.7, 57.4, 54.1, 48.2 (q, J = 24.9 Hz), 26.0, 21.3; (^{19}F NMR, 377 MHz, $CDCl_3$): δ (ppm) = −63.8 (d, J = 8.7 Hz, 3F); IR: 2920, 1645, 1592, 1532, 1488, 1349, 1313, 1264, 1177, 1120, 1095, 1044, 1014, 909, 855 cm^{-1}; HRMS (ESI) for $C_{25}H_{21}O_4N_3F_3S_2$ $[M+H]^+$ requires 548.0920 found 548.0915; Mp. >250 (decomp.).

4-Nitro-*N*-phenyl-*N*-((1*S,2*S**)-2-(trifluoromethyl)-3,4,4',5'-tetrahydro-2H-spiro[naphthalene-1,6'-[1,3]thiazin]-2'-yl)benzenesulfonamide (28)**



To the solution of (1*S**,2*S**)-*N*-phenyl-2-(trifluoromethyl)-3,4,4',5'-tetrahydro-2H-spiro[naphthalene-1,6'-[1,3]thiazin]-2'-amine (27.3 mg, 0.073 mmol) in DCM (0.4 mL) was added 4-nitrobenzenesulfonyl chloride (24.1 mg, 0.109 mmol) and 4-dimethylaminopyridine (8.9 mg, 0.073 mmol). The reaction mixture was stirred at room temperature for 16 hours. The crude mixture was concentrated *in vacuo* and purified by silica gel column chromatography (eluent: 10 % EtOAc in *n*-pentane) to provide the title compound (29.6 mg, 73 % yield) as a white solid.

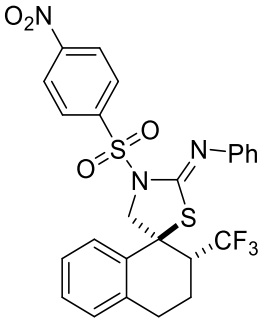
(^{1}H NMR, 400 MHz, $CDCl_3$): δ (ppm) = 8.30 (dt, *J* = 8.8, 2.2 Hz, 2H), 8.00 (dt, *J* = 9.1, 2.1 Hz, 2H), 7.43−7.35 (m, 4H), 7.25−7.23 (m, 2H), 7.19−7.14 (m, 2H), 7.04−7.02 (m, 1H), 4.21−4.02 (m, 2H), 2.93−2.82 (m, 2H), 2.77−2.65 (m, 2H), 2.36−2.25 (m, 2H), 2.18−2.11 (m, 1H); (^{13}C NMR, 126 MHz, $CDCl_3$): δ (ppm) = 150.2, 145.4, 136.1, 135.9, 135.8, 130.4, 129.6, 129.6, 129.3, 129.3, 127.9, 126.8, 126.7 (q, J = 284.6 Hz) 126.5, 123.4, 120.5, 50.9, 45.7 (q, *J* = 2.9 Hz), 45.1 (q, *J* = 23.5 Hz), 28.3, 25.1, 19.8 (q, *J* = 2.9 Hz); (^{19}F NMR, 377 MHz, $CDCl_3$): δ (ppm) = −61.5 (d, *J* = 9.2 Hz, 3F); IR: 2931, 1647, 1531, 1488, 1454, 1402, 1368, 1349, 1313, 1262, 1175, 1119, 1087, 1017, 953, 910, 855 cm^{-1}; HRMS (ESI) for $C_{26}H_{23}O_4N_3F_3S_2$ $[M+H]^+$ requires 562.1077 found 562.1076; Mp. 141−142 °C.

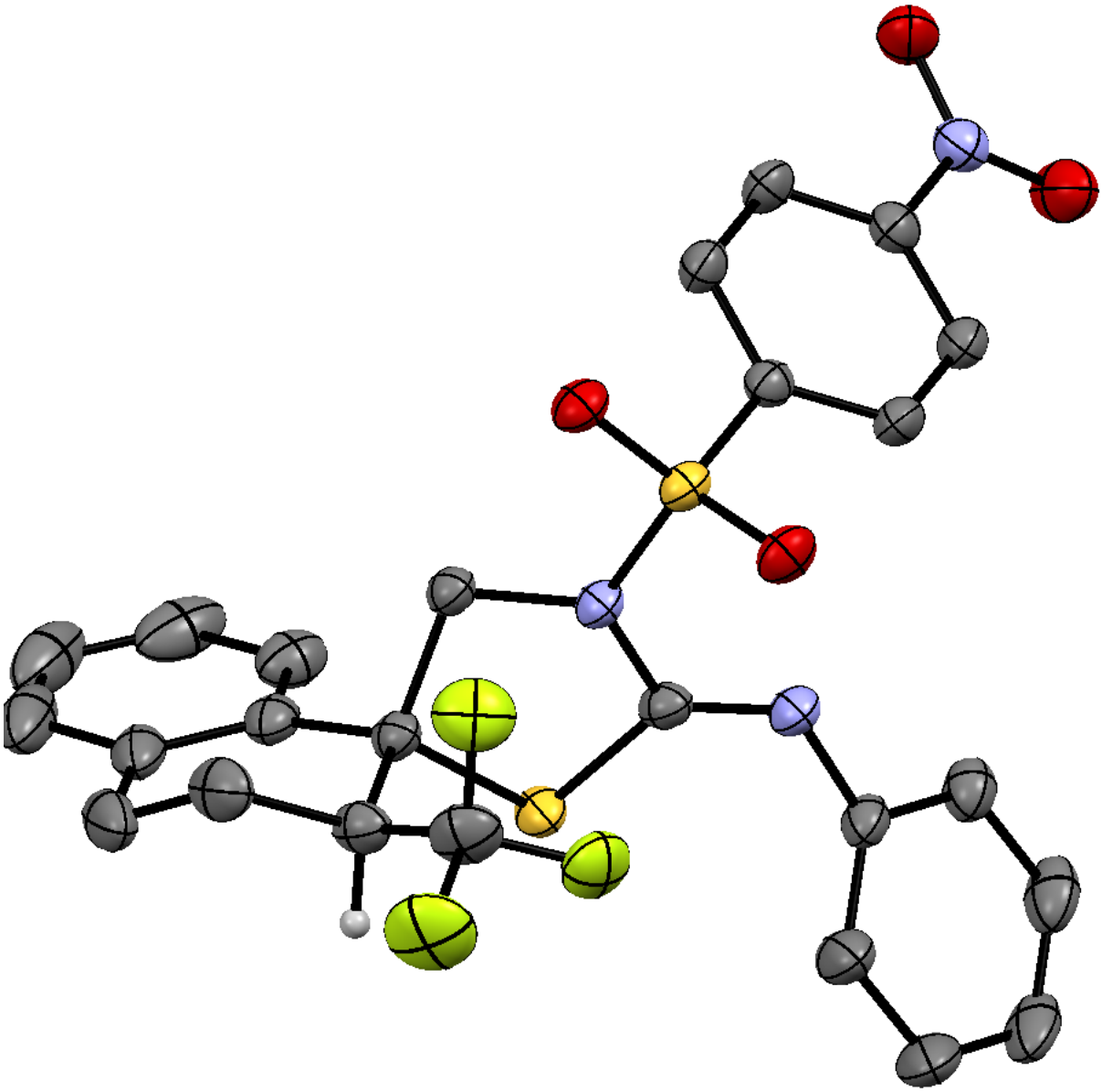
General Information

Low temperature[21] (150 K) single-crystal X-ray diffraction data were collected using or an Oxford Diffraction (Agilent) SuperNova A diffractometer. Raw frame data were reduced using the instrument manufacturer supplied software CrysAlisPro.[22] All structures could be solved *ab initio* using SuperFlip,[23] and full-matrix least-squares refinement was carried out using CRYSTALS.[24] All non-hydrogen atoms were refined using anisotropic displacement ellipsoids, and hydrogen atoms were visible in the difference map. Once the heavy atoms structure was complete, hydrogen atoms were positioned geometrically then refined separately using soft restraints prior to inclusion in the final refinement using a riding model.[25] All structures have been deposited with the Cambridge Crystallographic Data Centre (reference codes CCDC 1474239-1474241); these data can be obtained free of charge *via* www.ccdc.cam.ac.uk/data_request/cif.

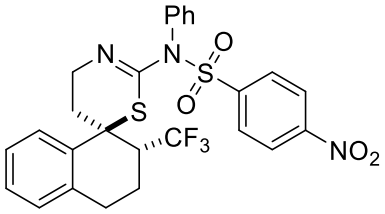
	108lp16	**109lp16**	**107lp16**
Nr.	**27**	**28**	**24f2**
Name			
Formula	$C_{25}H_{20}F_3N_3O_4S_2$	$C_{26}H_{22}F_3N_3O_4S_2$	$C_{18}H_{17}F_3N_2O_1S_1$
Molecular Weight	547.58	561.6	366.41
Crystal System	monoclinic	triclinic	monoclinic
T [K]	150	150	150
Space Group	P 21/n	P -1	P 21/n
a [Å]	6.8480(1)	7.4653(2)	15.2695(4)
b [Å]	20.4301(3)	9.9343(4)	5.9545(2)
c [Å]	17.0570(2)	17.6618(5)	19.0281(7)
α [°]	90	89.239(3)	90
β [°]	90.3040(11)	85.681(2)	91.540(3)
γ [°]	90	72.865(3)	90
V [Å^3]	2386.33(6)	1248.09(7)	1729.45(10)
Z	4	2	4
D_{calc} [g cm^{-3}]	1.524	1.494	1.407
F(0 0 0)	1128	580	760
μ [mm^{-1}]	2.586	2.487	2.022
Crystal Size [mm]	0.10 * 0.10 * 0.25	0.12 * 0.13 * 0.19	0.10 * 0.14 * 0.18
Colour, Shape	clear_pale_colourless, prism	clear_pale_colourless, block	clear_pale_colourless, needle
R_{int}	3.26	3.63	10.33
θ_{min}, θ_{max} [deg]	3.375 - 74.753	4.685 - 74.757	3.664-76.067
Total Reflections	29782	25529	3587
Reflections, Restraints, Parameters (I>-3.0/sigma(I))	4958, 0, 334	5188, 0, 343	3575, 949, 422
S (=GooF)	1.000	1.004	0.983
Min. and Max. Residual Density, [e/Å3]	-0.39	-0.54	-0.86
	0.28	0.58	1.22
Threshold Expression	I>2sigma(I)	I>2sigma(I)	I>2sigma(I)
R_1	0.0313	0.0358	0.0976
wR_2	0.0812	0.0970	0.2580

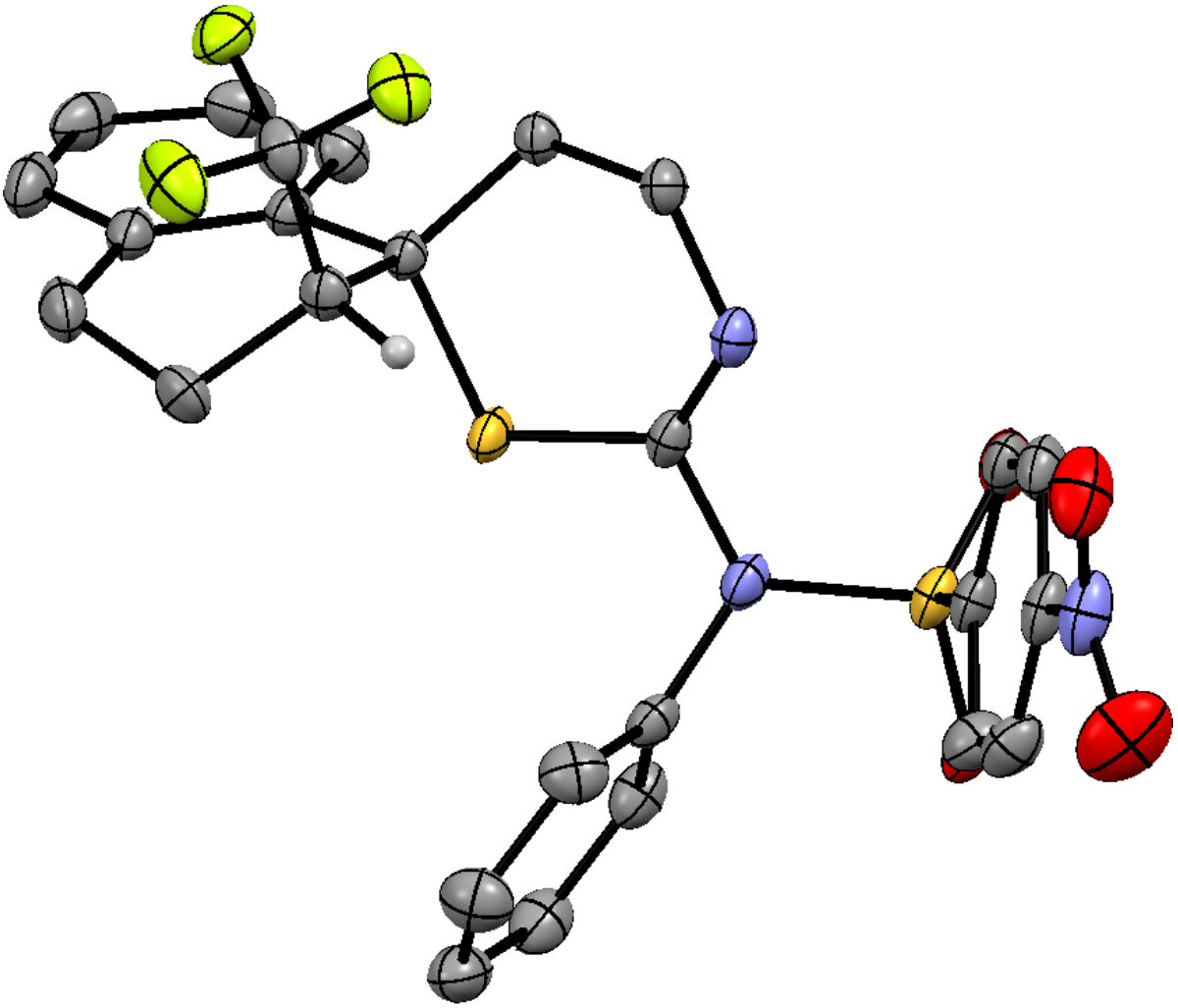
(1*S,2*S**,*Z*)-3'-((4-Nitrophenyl)sulfonyl)-N-phenyl-2-(trifluoromethyl)-3,4-dihydro-2H-spiro[naphthalene-1,5'-thiazolidin]-2'-imine (27)**



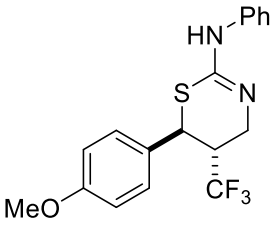


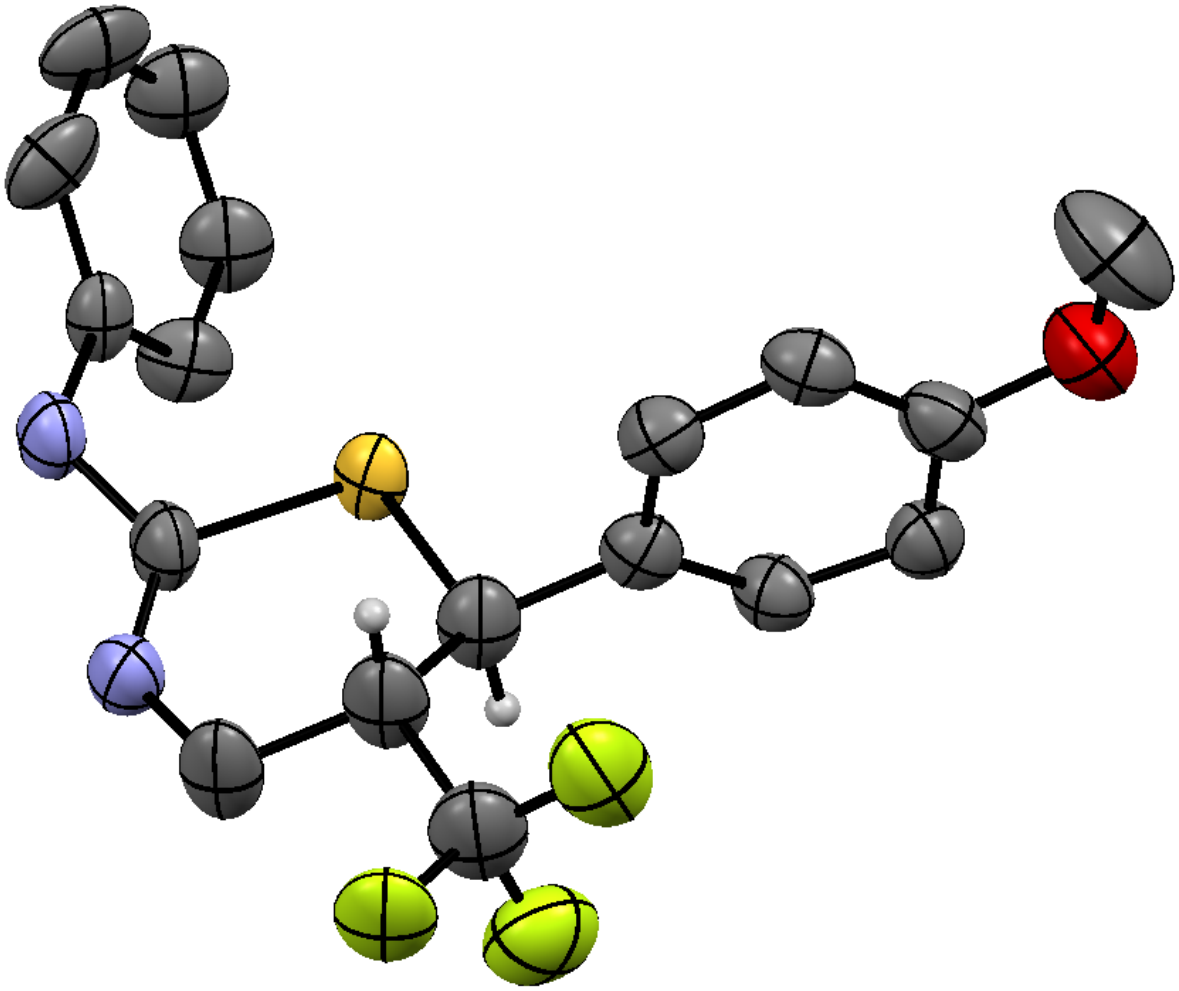
4-Nitro-*N*-phenyl-*N*-((1*S,2*S**)-2-(trifluoromethyl)-3,4,4',5'-tetrahydro-2H-spiro[naphthalene-1,6'-[1,3]thiazin]-2'-yl)benzenesulfonamide (28)**





(5*R,6*S**)-6-(4-Methoxyphenyl)-*N*-phenyl-5-(trifluoromethyl)-5,6-dihydro-4H-1,3-thiazin-2-amine (24f2)**



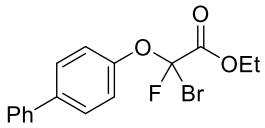


5.4 Experimental Procedures and Characterisation Data for Chapter 4

5.4.1 Synthesis of ArOCFBrCO$_2$Et (36)

General Procedure Q (*Preparation of Ar-OCFBrCO$_2$Et (1) from Ar-OCFHCO$_2$Et)* To a solution of Ar-OCHFCO$_2$Et (4.0 mmol) in CCl_4 (30 mL) was added *N*-bromosuccinimide (2.4 mmol). The reaction was allowed to stir for 16 hours at room temperature under UV light irradiation. The solvent was removed *in vacuo.* The crude product was purified by silica gel column chromatography.

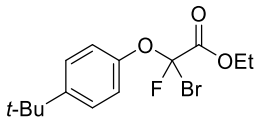
Ethyl (biphenyl-4-yloxy)(bromo)fluoroacetate (36a)



The title compound was prepared following General Procedure K; To a solution of ethyl (biphenyl-4-yloxy)(fluoro)acetate (2.51 g, 9.15 mmol) in CCl_4 (40 mL) was added *N*-bromosuccinimide (979 mg, 5.5 mmol). The reaction was allowed to stir for 16 hours at 70 °C under UV light irradiation. The reaction mixture was cooled to room temperature, then the solvent was removed *in vacuo.* The crude product was purified by silica gel column chromatography (eluent: 5 % Et_2O in *n*-pentane) to provide the title compound (732 mg, 38 % yield) as a white solid.

(^{1}H NMR, 400 MHz, $CDCl_3$): δ = 7.64–7.59 (m, 4H), 7.48–7.45 (m, 2H), 7.40–7.35 (m, 3H), 4.48 (q, *J* = 7.1 Hz, 2H), 1.44 (t, *J* = 7.1 Hz, 3H); (^{13}C NMR, 101 MHz, $CDCl_3$): δ = 161.3 (d, *J* = 31.0 Hz), 151.1, 140.0, 139.6, 128.8, 128.2, 127.6, 127.1, 122.0 (d, *J* = 2.4 Hz), 106.5 (d, *J* = 302.8 Hz), 64.1, 13.8; (^{19}F NMR, 377 MHz, $CDCl_3$): δ = –57.6 (s); IR: ν 1515, 1485, 1371, 1305, 1204, 1171, 1100, 1008, 919, 855; HRMS (EI/FI) for $C_{16}H_{14}BrFO_3$ $[M]^+$ requires 352.0110 found 352.0118; Mp. 44−46 °C.

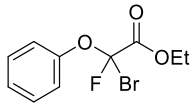
Ethyl (4-*tert*-butylphenoxy)(bromo)fluoroacetate (36b)



The title compound was prepared following General Procedure K; To a solution of ethyl (4-*tert*-butylphenoxy)(fluoro)acetate (1.62 g, 6.37 mmol) in CCl_4 (30 mL) was added *N*-bromosuccinimide (680 mg, 3.82 mmol). The reaction was allowed to stir for 16 hours at room temperature under UV light irradiation. The solvent was removed *in vacuo*. The crude product was purified by silica gel column chromatography (eluent: 2 % Et_2O in *n*-pentane) to provide the title compound (465 mg, 37 % yield) as a pale yellow oil.

(^{1}H NMR, 400 MHz, $CDCl_3$): δ = 7.41 (dt, J_1 = 2.6 Hz, J_2 = 8.8 Hz, 2H), 7.21–7.19 (m, 2H), 4.45 (q, *J* = 7.1 Hz, 2H), 1.42 (t, *J* = 7.1 Hz, 3H), 1.34 (s, 9H); (^{13}C NMR, 101 MHz, $CDCl_3$): δ = 161.4 (d, *J* = 31.0 Hz), 149.5, 149.4, 126.3, 121.2 (d, *J* = 1.6 Hz), 106.6 (d, *J* = 302.8 Hz), 63.9, 34.5, 31.3, 13.8; (^{19}F NMR, 377 MHz, $CDCl_3$): δ = –57.4 (s); IR: ν 2965, 1770, 1510, 1368, 1306, 1207, 1182, 1104, 1015, 919, 859; HRMS (EI/FI) for $C_{14}H_{18}BrFO_3$ $[M]^+$ requires 332.0423 found 332.0426.

Ethyl bromo(phenoxy)fluoroacetate (36o)

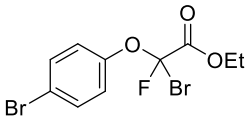


The title compound was prepared following General Procedure K; to a solution of ethyl fluoro(phenoxy)acetate (793 mg, 4.0 mmol) in CCl_4 (20 mL) was added *N*-bromosuccinimide (427 mg, 2.4 mmol). The reaction was allowed to stir for 16 hours at 70 °C under UV light irradiation. The solvent was removed *in vacuo*. The crude product was purified by silica gel column chromatography (eluent: 5 % Et_2O in *n*-pentane) to provide the title compound (208 mg, 31 % yield) as a colourless oil.

(^{1}H NMR, 400 MHz, $CDCl_3$): δ = 7.35–7.31 (m, 2H), 7.25–7.19 (m, 3H), 4.37 (q, *J* = 7.1 Hz, 2H), 1.34 (t, *J* = 7.1 Hz, 3H); (^{13}C NMR, 101 MHz, $CDCl_3$): δ = 161.3 (d, *J* = 31.0 Hz), 151.8, 129.5, 126.5, 121.8, 106.4 (d, *J* = 302.8 Hz), 64.0, 13.8; (^{19}F NMR, 377 MHz,

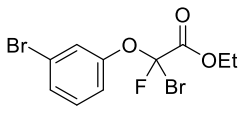
$CDCl_3$): δ = –57.5 (s); IR: ν 1767, 1592, 1488, 1371, 1305, 1193, 1164, 1098, 1013, 924, 848; HRMS (EI/FI) for $C_{10}H_{10}BrFO_3$ $[M]^+$ requires 273.9797 found 275.9793.

Ethyl (4-bromophenoxy)(bromo)fluoroacetate (36d)



The title compound was prepared following General Procedure K; to a solution of ethyl (4-bromophenoxy)(fluoro)acetate (1.11 g, 4.0 mmol) in CCl_4 (20 mL) was added *N*-bromosuccinimide (427 mg, 2.4 mmol). The reaction was allowed to stir for 16 hours at 70 °C under UV light irradiation. The solvent was removed *in vacuo*. The crude product was purified by silica gel column chromatography (eluent: 3 % Et_2O in *n*-pentane) to provide the title compound (299 mg, 35 % yield) as a pale yellow oil. (^{1}H NMR, 400 MHz, $CDCl_3$): δ = 7.53 (dt, J_1 = 2.7 Hz, J_2 = 9.1 Hz, 2H), 7.19–7.15 (m, 2H), 4.45 (q, J = 7.1 Hz, 2H), 1.42 (t, J = 7.1 Hz, 3H); (^{13}C NMR, 101 MHz, $CDCl_3$): δ = 161.1 (d, J = 30.2 Hz), 150.7, 132.6, 123.6, 119.9, 106.2 (d, J = 302.8 Hz), 64.1, 13.8; (^{19}F NMR, 377 MHz, $CDCl_3$): δ = –58.4 (s); IR: ν 3301, 1760, 1666, 1609, 1543, 1509, 1411, 1372, 1312, 1209, 1103, 1016, 835; HRMS (EI/FI) for $C_{10}H_9Br_2FO_3$ $[M]^+$ requires 353.8903 found 353.8904.

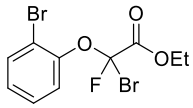
Ethyl (3-bromophenoxy)(bromo)fluoroacetate (36p)



The title compound was prepared following General Procedure K; to a solution of ethyl (3-bromophenoxy)(fluoro)acetate (1.11 g, 4.0 mmol) in CCl_4 (20 mL) was added *N*-bromosuccinimide (427 mg, 2.4 mmol). The reaction was allowed to stir for 16 hours at 70 °C under UV light irradiation. The solvent was removed *in vacuo*. The crude product was purified by silica gel column chromatography (eluent: 5 % Et_2O in *n*-pentane) to provide the title compound (221 mg, 26 % yield) as a colourless oil.

(^{1}H NMR, 400 MHz, $CDCl_3$): δ = 7.39–7.36 (m, 2H), 7.23–7.15 (m, 2H), 4.37 (q, *J* = 7.1 Hz, 2H), 1.34 (t, *J* = 7.2 Hz, 3H); (^{13}C NMR, 101 MHz, $CDCl_3$): δ = 161.0 (d, *J* = 31.0 Hz), 152.1, 130.6, 129.8, 125.2 (d, *J* = 2.4 Hz), 122.4, 120.5, 106.1 (d, *J* = 303.6 Hz), 64.1, 13.8; (^{19}F NMR, 377 MHz, $CDCl_3$): δ = –58.4 (s); IR: ν 2971, 1766, 1582, 1471, 1371, 1304, 1199, 1148, 1100, 1013, 924, 874; HRMS (EI/FI) for $C_{10}H_9Br_2FO_3$ $[M]^+$ requires 353.8903 found 353.8904.

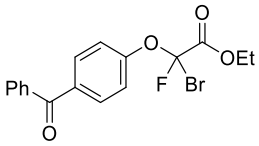
Ethyl (2-bromophenoxy)(bromo)fluoroacetate (36q)



The title compound was prepared following General Procedure K; to a solution of ethyl (2-bromophenoxy)(fluoro)acetate (1.11 g, 4.0 mmol) in CCl_4 (20 mL) was added *N*-bromosuccinimide (427 mg, 2.4 mmol). The reaction was allowed to stir for 16 hours at 70 °C under UV light irradiation. The solvent was removed *in vacuo*. The crude product was purified by silica gel column chromatography (eluent: 5 % Et_2O in *n*-pentane) to provide the title compound (195 mg, 23 % yield) as a colourless oil.

(^{1}H NMR, 400 MHz, $CDCl_3$): δ = 7.65 (dd, J_1 = 1.5 Hz, J_2 = 8.1 Hz, 1H), 7.47 (dt, J_1 = 1.7 Hz, J_2 = 8.3 Hz, 1H), 7.36 (td, J_1 = 1.5 Hz, J_2 = 7.8 Hz, 1H), 7.18 (td, J_1 = 1.5 Hz, J_2 = 7.7 Hz, 1H), 4.46 (qd, J_1 = 1.5 Hz, J_2 = 7.1 Hz, 2H), 1.42 (t, *J* = 7.1 Hz, 3H); (^{13}C NMR, 101 MHz, $CDCl_3$): δ = 161.0 (d, *J* = 31.8 Hz), 149.2, 133.9, 128.4, 127.6, 122.7 (d, *J* = 2.4 Hz), 116.2 (d, *J* = 1.6 Hz), 106.0 (d, *J* =303.6 Hz), 64.1, 13.8; (^{19}F NMR, 377 MHz, $CDCl_3$): δ = –56.7 (s); IR: ν 1767, 1473, 1445, 1371, 1305, 1212, 1147, 1099, 1047, 1031, 1012, 923, 850; HRMS (EI/FI) for $C_{10}H_9Br_2FO_3$ $[M]^+$ requires 353.8902 found 353.8901.

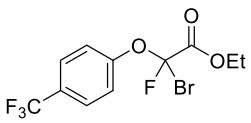
Ethyl (4-benzoylphenoxy)(bromo)fluoroacetate (36i)



The title compound was prepared following General Procedure K; to a solution of ethyl (4-benzoylphenoxy)(fluoro)acetate (1.21 g, 4.0 mmol) in CCl_4 (20 mL) was added *N*-bromosuccinimide (427 mg, 2.4 mmol). The reaction was allowed to stir for 16 hours at 70 °C under UV light irradiation. The solvent was removed *in vacuo*. The crude product was purified by silica gel column chromatography (eluent: 20 % Et_2O in *n*-pentane) to provide the title compound (208 mg, 23 % yield) as a pale yellow oil.

(^{1}H NMR, 400 MHz, $CDCl_3$): δ = 7.89 (dt, J_1 = 2.2 Hz, J_2 = 8.8 Hz, 2H), 7.82–7.80 (m, 2H), 7.62 (tt, J_1 = 1.9 Hz, J_2 = 7.3 Hz, 1H), 7.53–7.49 (m, 2H), 7.42–7.38 (m, 2H), 4.47 (q, *J* = 7.1 Hz, 2H), 1.43 (t, *J* = 7.1 Hz, 3H); (^{13}C NMR, 101 MHz, $CDCl_3$): δ = 195.4, 161.0 (d, *J* = 30.2 Hz), 154.7, 137.3, 135.5, 132.7, 131.8, 130.0, 128.4, 121.2 (d, *J* = 2.4 Hz), 105.7 (d, J = 303.6 Hz), 64.2, 13.8; (^{19}F NMR, 377 MHz, $CDCl_3$): δ = –59.0 (s); IR: ν 1768, 1660, 1599, 1501, 1447, 1372, 1276, 1203, 1164, 1099, 1014, 921, 856; HRMS (EI/FI) for $C_{17}H_{14}BrFO_4$ $[M]^+$ requires 380.0059 found 380.0058.

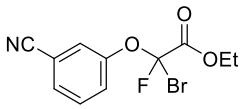
Ethyl bromo(fluoro)[4-(trifluoromethyl)phenoxy]acetate (36k)



The title compound was prepared following General Procedure K; to a solution of ethyl fluoro[4-(trifluoromethyl)phenoxy]acetate (1.06 g, 4.0 mmol) in CCl_4 (20 mL) was added *N*-bromosuccinimide (427 mg, 2.4 mmol). The reaction was allowed to stir for 16 hours at 60 °C under UV light irradiation. The solvent was removed *in vacuo*. The crude product was purified by silica gel column chromatography (eluent: 5 % Et_2O in *n*-pentane) to provide the title compound (160 mg, 19 % yield) as a pale yellow oil.

(^{1}H NMR, 400 MHz, $CDCl_3$): δ = 7.69 (d, *J* = 8.6 Hz, 2H), 7.41 (d, *J* = 8.6 Hz, 2H), 4.46 (q, *J* = 7.1 Hz, 2H), 1.43 (t, *J* = 7.1 Hz, 3H); (^{13}C NMR, 101 MHz, $CDCl_3$): δ = 160.9 (d, *J* = 30.2 Hz), 154.1, 128.7 (q, *J* = 33.1 Hz), 127.0 (q, *J* = 3.7 Hz), 123.7 (q, *J* = 272.1 Hz), 121.9 (d, *J* = 2.4 Hz), 115.7 (d, *J* =304.4 Hz), 64.2, 13.8; (^{19}F NMR, 377 MHz, $CDCl_3$): δ = –59.2 (s, 1F), –62.3 (s, 3F) ; IR: ν 1771, 1615, 1513, 1325, 1211, 1170, 1128, 1065, 1016, 924, 858; HRMS (EI/FI) for $C_{11}H_9BrF_4O_3$ $[M]^+$ requires 343.9671 found 343.9670.

Ethyl (3-cyanophenoxy)(bromo)fluoroacetate (36t)



The title compound was prepared following General Procedure K; to a solution of ethyl (3-cyanophenoxy)(fluoro)acetate (893 mg, 4.0 mmol) in CCl_4 (20 mL) was added *N*-bromosuccinimide (427 mg, 2.4 mmol). The reaction was allowed to stir for 16 hours at 60 °C and UV light irradiation. The solvent was removed *in vacuo*. The crude product was purified by silica gel column chromatography (eluent: 20 % Et_2O in *n*-pentane) to provide the title compound (113 mg, 16 % yield) as a colourless oil.

(^{1}H NMR, 400 MHz, $CDCl_3$): δ = 7.64–7.54 (m, 4H), 4.46 (q, *J* = 7.2 Hz, 2H), 1.42 (t, *J* = 7.2 Hz, 3H); (^{13}C NMR, 101 MHz, $CDCl_3$): δ = 160.7 (d, *J* = 31.0 Hz), 151.7, 130.6, 130.2, 126.5 (d, *J* = 1.6 Hz), 125.4 (d, *J* = 2.4 Hz), 117.5, 113.7, 105.9 (d, *J* = 303.6 Hz), 64.3, 13.8; (^{19}F NMR, 377 MHz, $CDCl_3$): δ = –59.3 (s); IR: ν 2235, 1768, 1581, 1481, 1432, 1372, 1306, 1234, 1158, 1102, 1012, 910, 857; HRMS (EI/FI) for $C_{11}H_9BrFNO_3$ $[M]^+$ requires 300.9750 found 300.9749.

5.4.2 General Information for Radiochemical Procedures

[^{18}F]Fluoride Preparation

[^{18}F]Fluoride was produced by Erigal (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 (MP1, ORTG, Tennessee, USA) and subsequently released with 550 μL of a solution of K_{222}/K_2CO_3 (Kryptofix-2.2.2 (15 mg) and K_2CO_3 (3 mg) in 1 mL of MeCN/H_2O, 4:1) into the concentrator to form [^{18}F]KF/K_{222}. The solution was dried with five cycles of azeotropic drying with acetonitrile (300 μL) and redissolved in anhydrous acetonitrile (1000 μL). [^{18}F]KF/K_{222} (ca. 30 MBq) was dispensed as aliquots of this stock solution into a v-vial containing the necessary reagents and a magnetic stirrer.

Procedure for 'Research Mode' [^{18}F]Fluorination

To a V-vial containing K_2CO_3 (2 mg, 0.014 mmol), K_{222} (9 mg, 0.024 mmol) and a magnetic stirrer bar was added [^{18}F]KF/K_{222} in MeCN. A solution of appropriate starting material (0.01 mmol) in acetone (200 μL) was added *via* syringe. The sealed vial was heated at 50 °C for 20 minutes, before being quenched with water (200 μL). An aliquot was removed for analysis by radio-TLC and radio-HPLC for radiochemical yield and product identification.

Procedure for Large Scale [^{18}F]Fluorination

[^{18}F]Fluoride was dried following the same azeotropic procedure as previously described, however it was not resolubilised in acetonitrile. A solution of ethyl bromo(4-tert-butylphenoxy)fluoroacetate in acetone (250 μL) was added directly into the concentrator vial, which was then heated to 50 °C for 20 minutes. An aliquot was taken for analysis by

radio-TLC and radio-HPLC and the remaining solution was filtered through a Sep-Pak C18 cartridge. The cartridge was rinsed with acetone (200 μL) to give a stock solution of [^{18}F]**4** for post-fluorination studies.

Analysis

For all reactions, an aliquot was removed for analysis by radio-TLC and radio-HPLC. Radio-TLC was carried out on Merck Kiesegel 60 F254 plates in EtOAc/Hexane (1:1) or Methanol and analysed using a plastic scintillator/PMT detector. Radio-HPLC analysis was performed using a Dionex Ultimate 3000 dual channel HPLC system with a shared auto-sampler, parallel UV-detectors and LabLogic NaI/PMTradiodetectors with Flowram analogue output. A representative radio-HPLC trace of the crude reaction mixture, with UV trace (254 nm) of authentic reference material overlaid, is shown below.

HPLC Gradient Settings:

Water + 0.1 % TFA/ MeCN + 0.1 % TFA, 1 mL/min, Waters Nova-Pak C18 Column, 4 μm, 3.9 x 150 mm:

0 – 1 min (5 % MeCN + 0.1 % TFA) isocratic

1 – 11 min (5 % to 95 % MeCN + 0.1 % TFA)

linear increase 11 – 15 min (95 % MeCN + 0.1 % TFA) isocratic

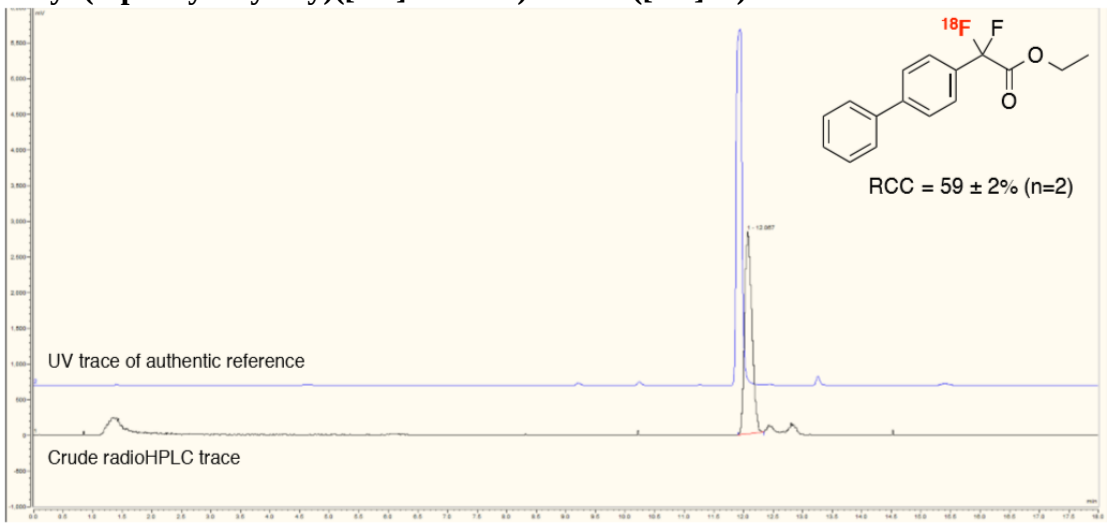
15 – 17 min (95 % to 5 % MeCN + 0.1 % TFA) linear decrease

17 – 18 min (5 % MeCN + 0.1 % TFA) isocratic.

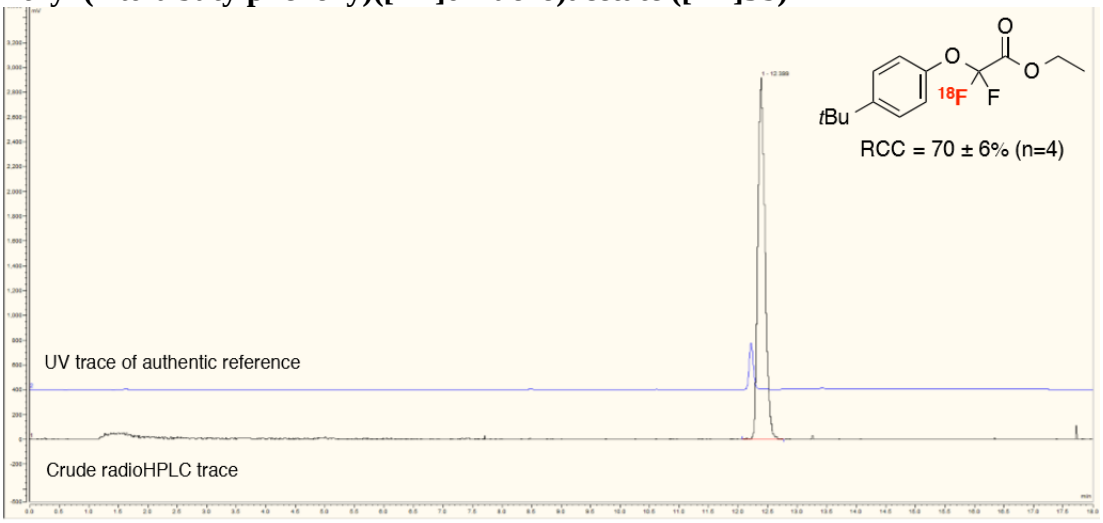
Reported radiochemical conversions are decay corrected and calculated by radio-TLC taking into account the radiochemical purity as determined by radio-HPLC.

5.4.3 Radio-HPLC Traces with Authentic UV References Overlaid

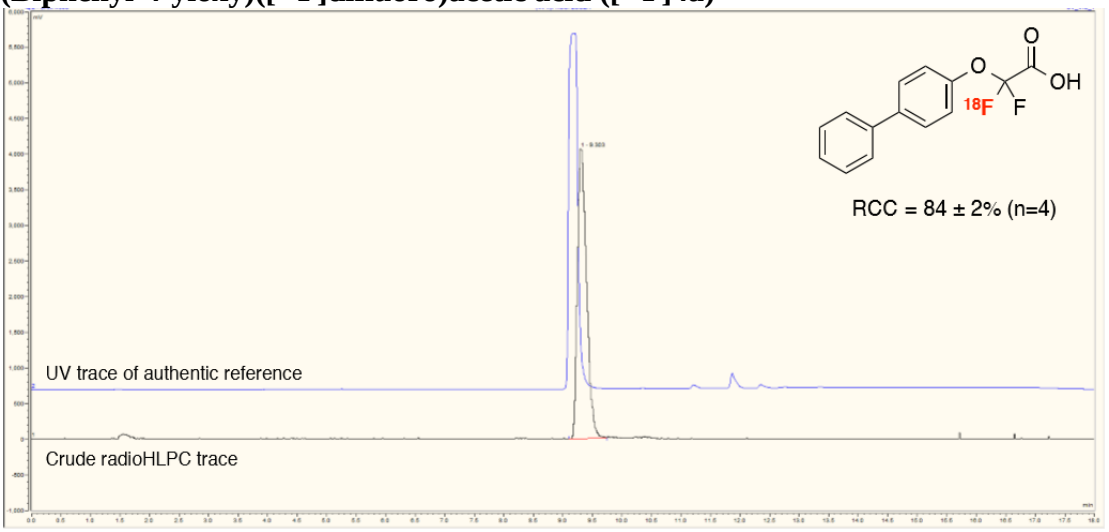
Ethyl (biphenyl-4-yloxy)([^{18}F]difluoro)acetate ([^{18}F]3a)



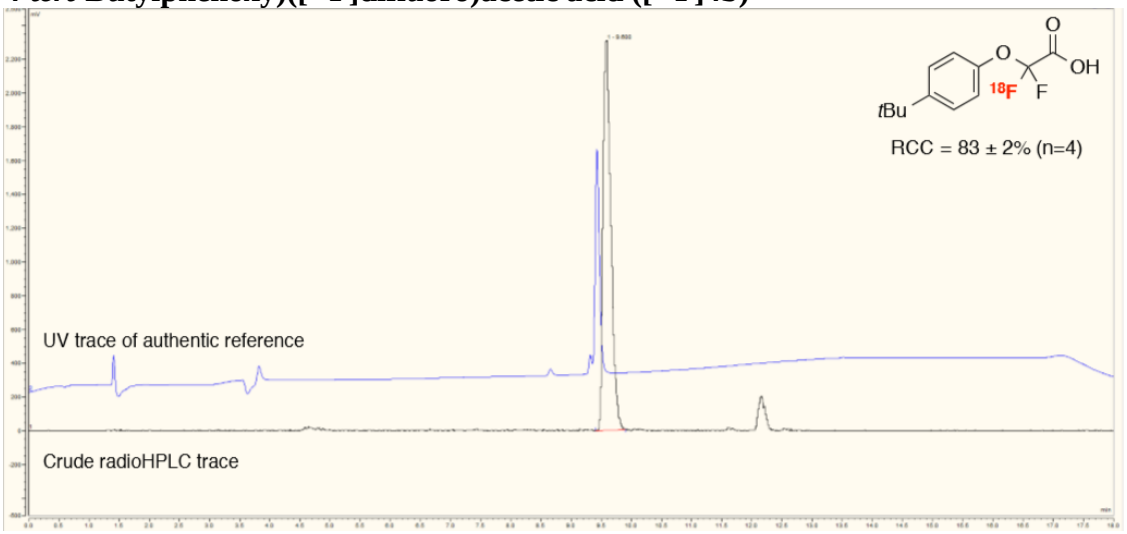
Ethyl (4-*tert*-butylphenoxy)([^{18}F]difluoro)acetate ([^{18}F]3b)



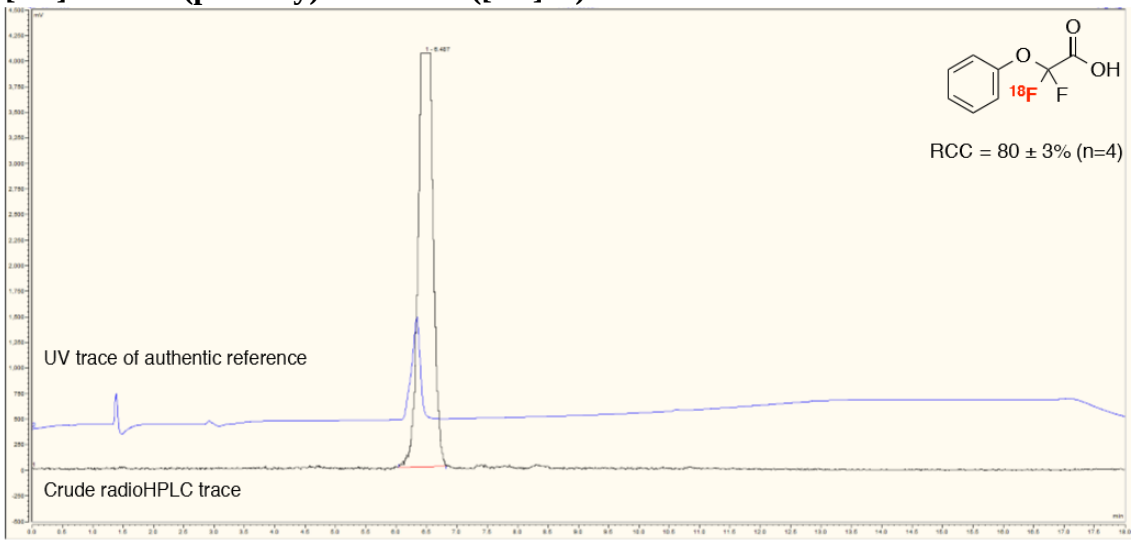
(Biphenyl-4-yloxy)([^{18}F]difluoro)acetic acid ([^{18}F]4a)



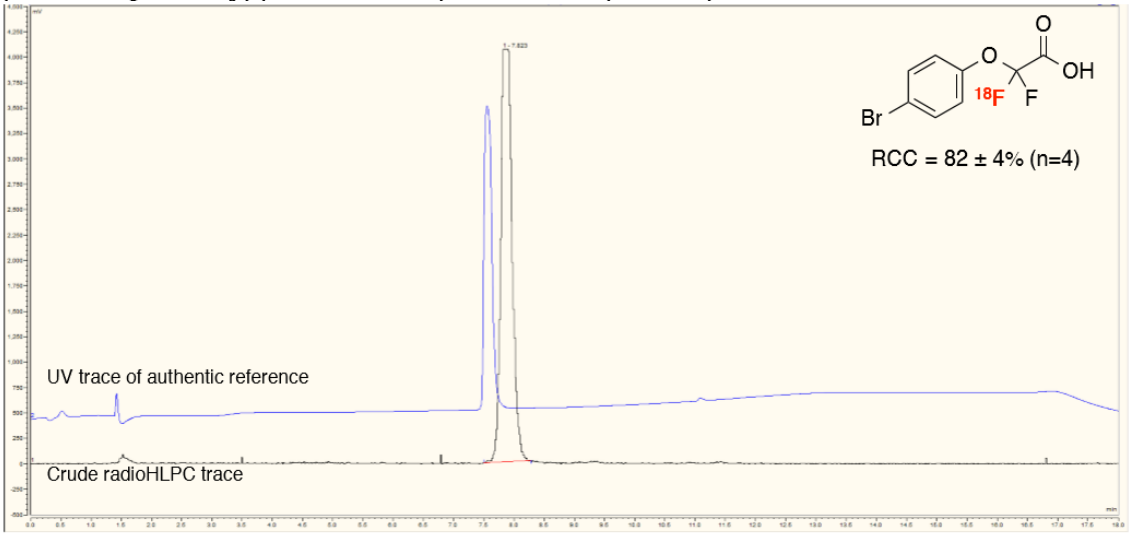
4-*tert*-Butylphenoxy)([^{18}F]difluoro)acetic acid ([^{18}F]4b)



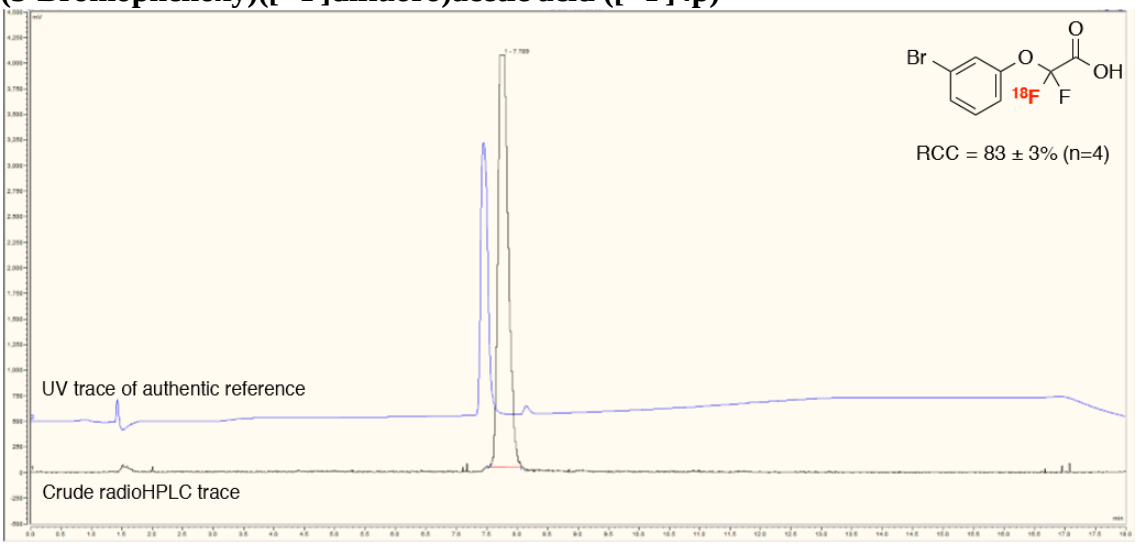
[^{18}F]Difluoro(phenoxy)acetic acid ([^{18}F]4o)



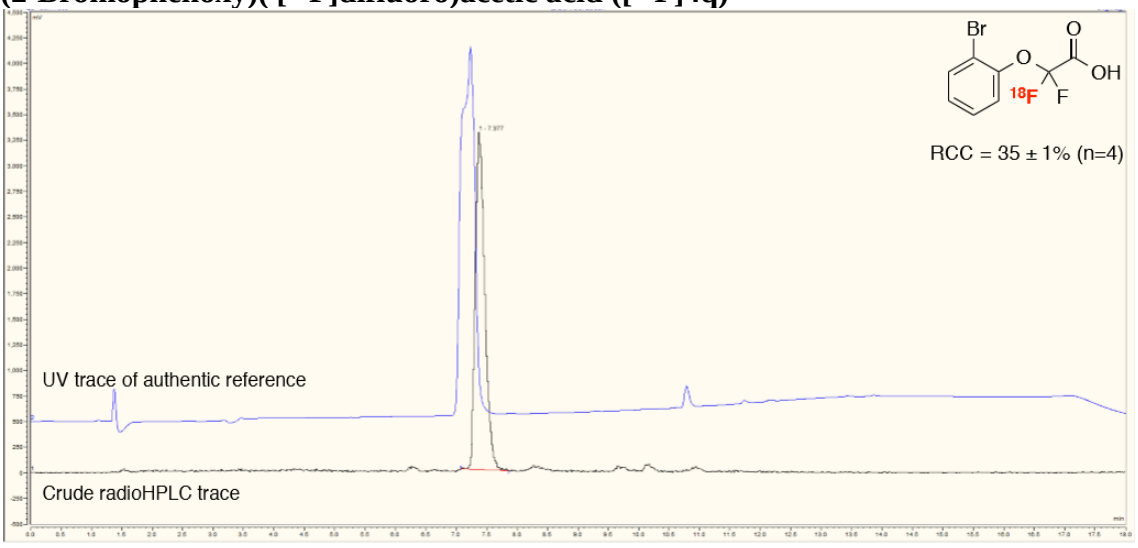
(4-Bromophenoxy)([^{18}F]difluoro)acetic acid ([^{18}F]4d)



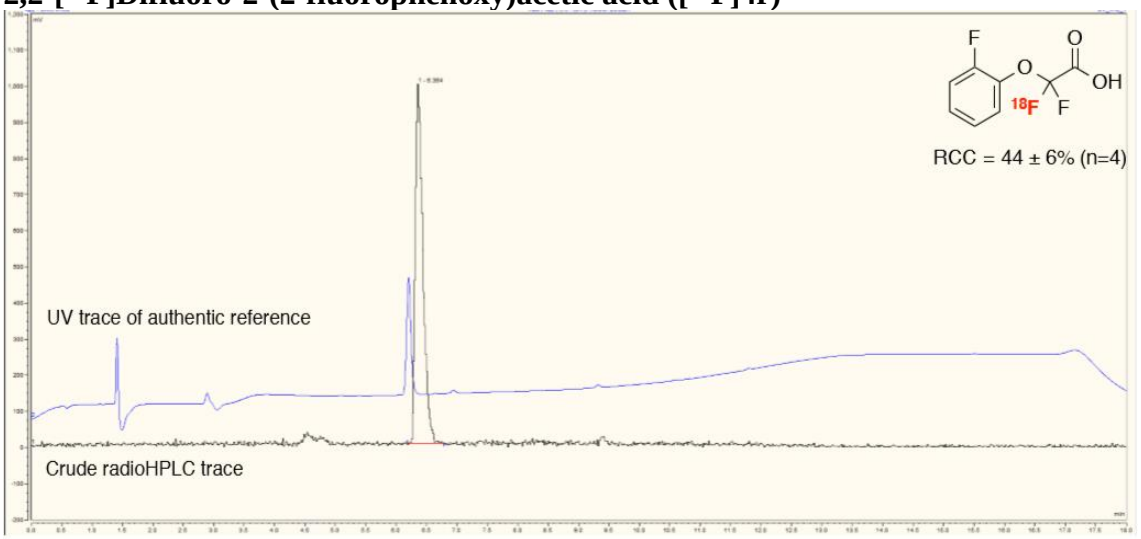
(3-Bromophenoxy)([^{18}F]difluoro)acetic acid ([^{18}F]4p)



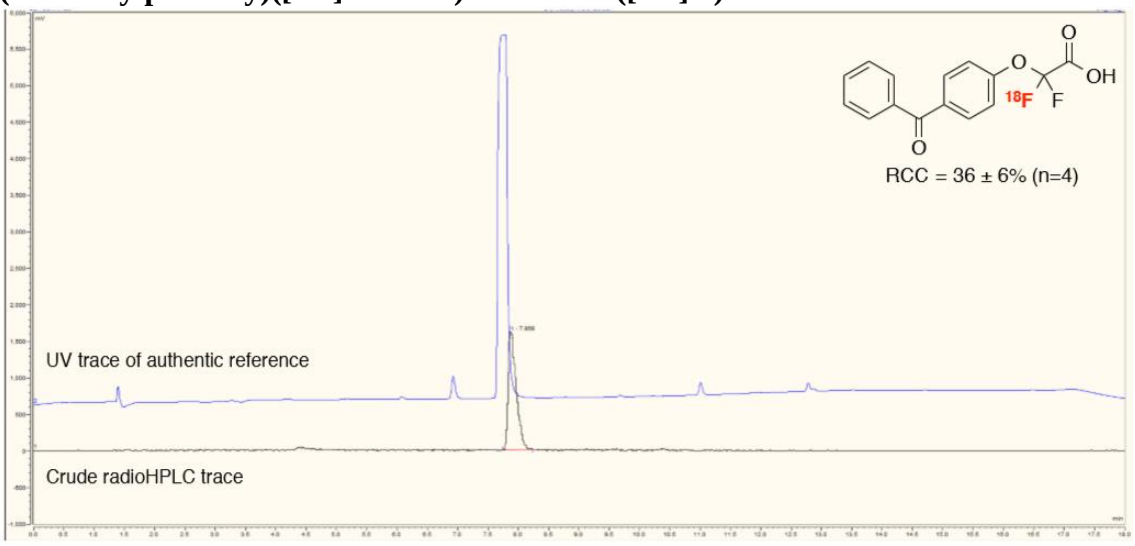
(2-Bromophenoxy)([^{18}F]difluoro)acetic acid ([^{18}F]4q)



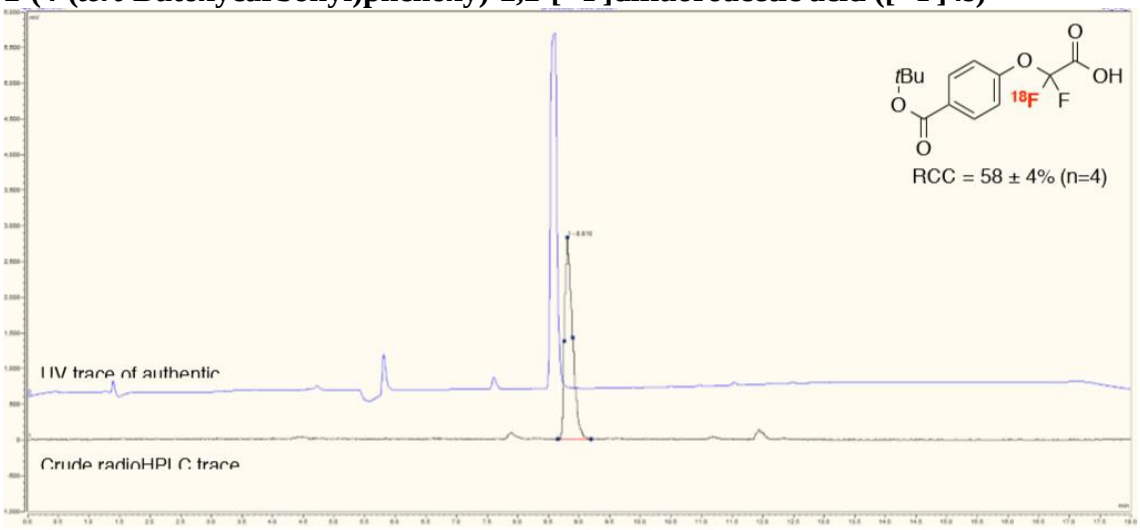
2,2-[^{18}F]Difluoro-2-(2-fluorophenoxy)acetic acid ([^{18}F]4r)



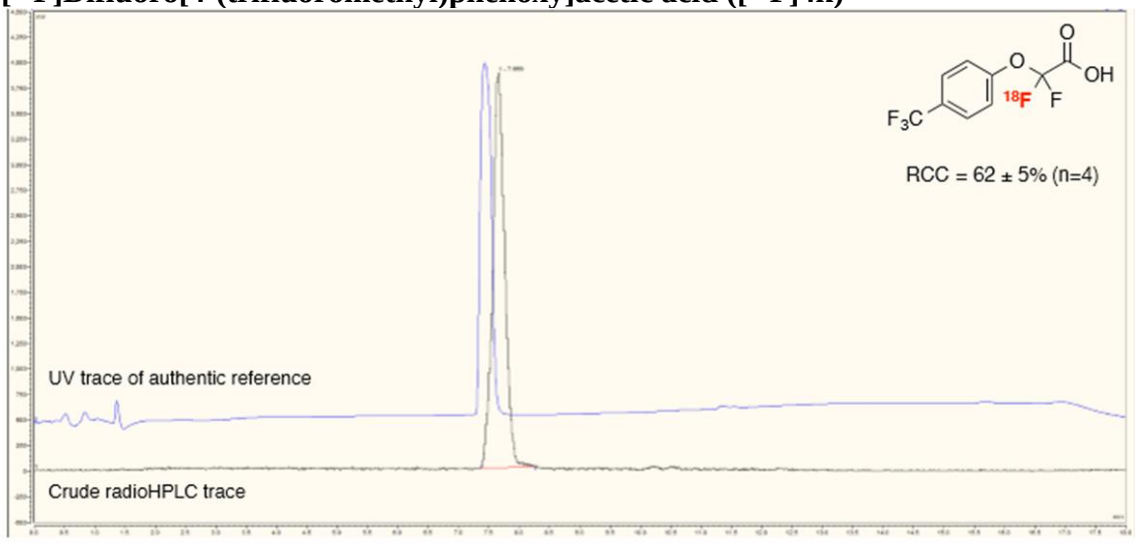
(4-Benzoylphenoxy)([^{18}F]difluoro)acetic acid ([^{18}F]4i)



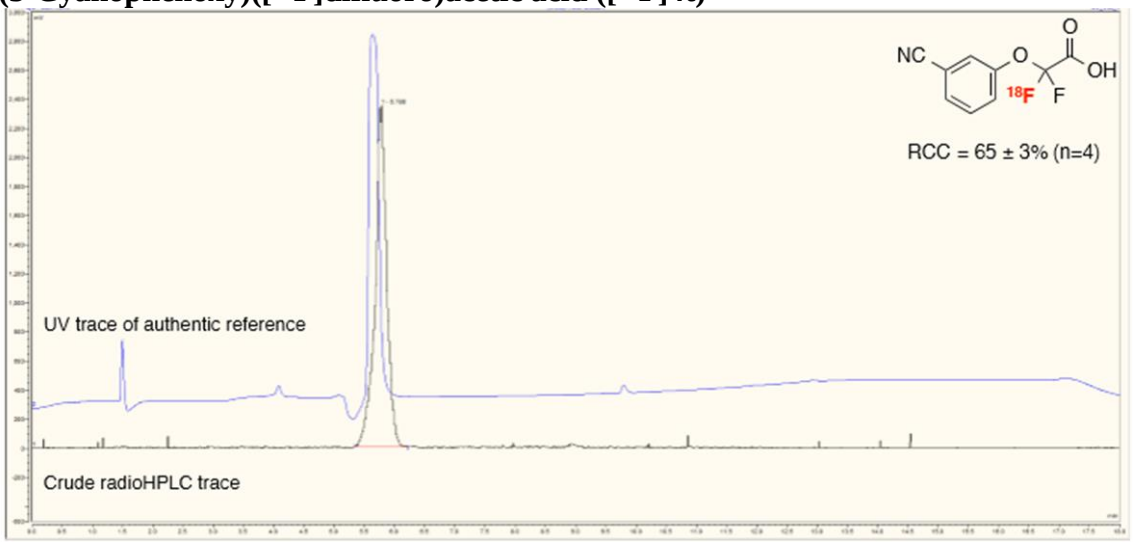
2-(4-(*tert*-Butoxycarbonyl)phenoxy)-2,2-[^{18}F]difluoroacetic acid ([^{18}F]4s)



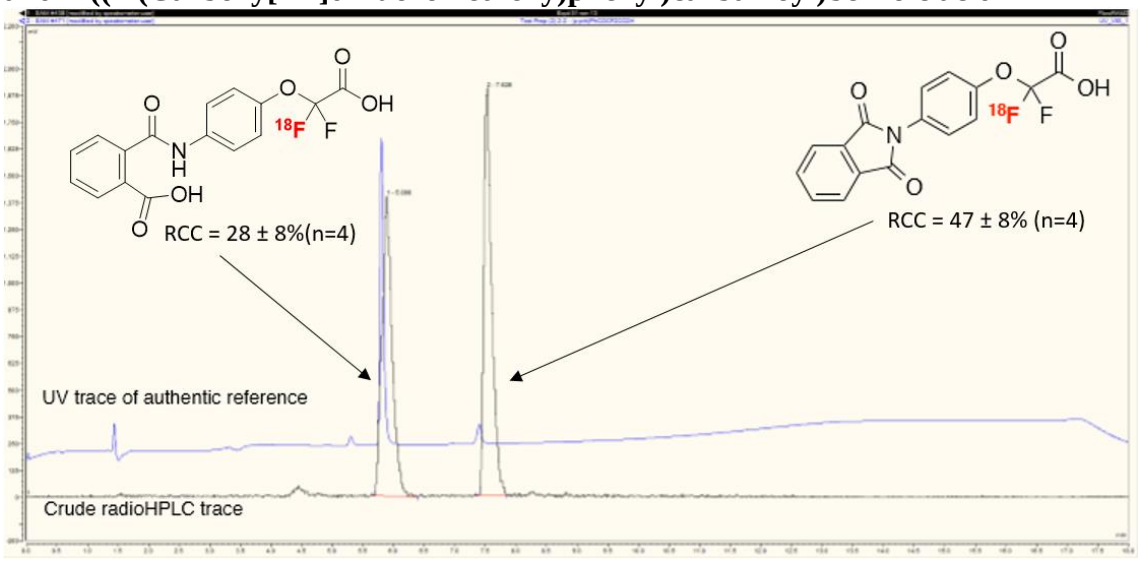
[^{18}F]Difluoro[4-(trifluoromethyl)phenoxy]acetic acid ([^{18}F]4k)



(3-Cyanophenoxy)([^{18}F]difluoro)acetic acid ([^{18}F]4t)

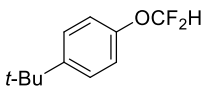


2-(4-(1,3-Dioxoisoindolin-2-yl)phenoxy)-2,2-[^{18}F]difluoroacetic acid ([^{18}F]4u) and 2-((4-(Carboxy[^{18}F]difluoromethoxy)phenyl)carbamoyl)benzoic acid



5.4.4 Silver-Mediated Oxidative Protodecarboxylation

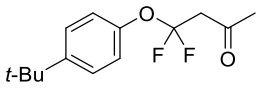
1-*tert*-Butyl-4-(difluoromethoxy)benzene (10b)



To a solution of an appropriate (4-*tert*-butylphenoxy)(difluoro)acetic acid (488.4 mg, 2.0 mmol) in 1:1 acetone/water (8 mL) was added $AgNO_3$ (339.8 mg, 2.0 mmol) and $K_2S_2O_8$ (2.16 g, 8.0 mmol). The reaction mixture was stirred at 50 ^oC for 2 hours before diluting with water. The aqueous layer was extracted with DCM (3 x 10 mL), then the combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by silica gel column chromatography (eluent: 1 % Et_2O in *n*-pentane) to provide the title compound (199.4 mg, 50 % yield) as a colourless oil.

(^{1}H NMR, 400 MHz, $CDCl_3$): δ = 7.38 (dt, J_1 = 2.6 Hz, J_2 = 8.8 Hz, 2H), 7.06 (d, J = 8.8 Hz, 2H), 6.49 (t, J = 74.3 Hz, 1H), 1.33 (s, 9H); (^{13}C NMR, 101 MHz, $CDCl_3$): δ = 148.9 (t, J = 2.8 Hz), 148.4, 126.7, 119.1, 116.1 (t, J = 259.1 Hz), 34.4, 31.4; (^{19}F NMR, 377 MHz, $CDCl_3$): δ = –80.4 (d, J = 74.6 Hz).

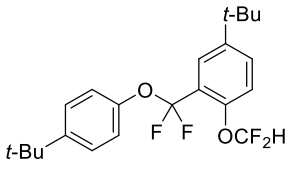
4-(4-(*tert*-Butyl)phenoxy)-4,4-difluorobutan-2-one (37)



The title compound was isolated along with the synthesis of 1-*tert*-butyl-4-(difluoromethoxy)benzene (**10b**); (16.3 mg, 3 % yield) as a colourless oil.

(^{1}H NMR, 400 MHz, $CDCl_3$): δ = 7.37 (dt, J_1 = 2.6 Hz, J_2 = 8.8 Hz, 2H), 7.11 (d, J = 8.8 Hz 1H), 3.26 (t, J = 10.6 Hz, 2H), 2.37 (s, 3H), 1.32 (s, 9H); (^{19}F NMR, 377 MHz, $CDCl_3$): δ = –65.9 (s, 2F); IR: 2964, 1722, 1510, 1412, 1365, 1335, 1265, 1202, 1171, 1121, 1017, 978; HRMS (ESI) for $C_{14}H_{18}F_2NaO_2$ $[M+Na]^+$ requires 279.1167 found 279.1165.

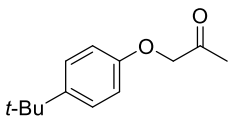
4-(*tert*-Butyl)-2-((4-(*tert*-butyl)phenoxy)difluoromethyl)-1-(difluoromethoxy)benzene (38)



The title compound was isolated along with the synthesis of 1-*tert*-butyl-4-(difluoromethoxy)benzene (**10b**); (14.0 mg, 4 % yield) as a colourless oil.

(^{1}H NMR, 400 MHz, $CDCl_3$): δ = 7.79 (d, *J* = 2.5 Hz, 1H), 7.53 (dd, J_1 = 2.4 Hz, J_2 = 8.5 Hz, 1H), 7.39 (dt, J_1 = 2.5 Hz, J_2 = 8.8 Hz, 2H), 7.25–7.22 (m, 3H), 6.50 (t, *J* = 74.7 Hz, 1H), 1.36 (s, 9H), 1.34 (s, 9H); (^{19}F NMR, 377 MHz, $CDCl_3$): δ = –65.7 (s, 2F), –79.9 (d, *J* = 74.6 Hz, 2F); IR: 2964, 1508, 1366, 1317, 1255, 1131, 1105, 1036; HRMS (EI/FI) for $C_{22}H_{26}F_4O_2$ $[M]^+$ requires 398.1869 found 398.1859.

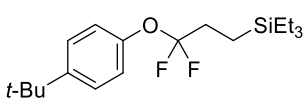
1-(4-(*tert*-Butyl)phenoxy)propan-2-one (39)



The title compound was isolated along with the synthesis of 1-*tert*-butyl-4-(difluoromethoxy)benzene (**10b**); (15.8 mg, 4 % yield) as a colourless oil.

(^{1}H NMR, 400 MHz, $CDCl_3$): δ = 7.41 (dt, J_1 = 2.6 Hz, J_2 = 8.8 Hz, 2H), 7.05 (dt, J_1 = 2.6 Hz, J_2 = 8.8 Hz, 2H), 3.70 (s, 2H), 2.37 (s, 3H), 1.32 (s, 9H); (^{13}C NMR, 126 MHz, $CDCl_3$): δ = 200.1, 149.1, 148.0, 126.4, 120.7, 50.1, 34.5, 31.4, 30.3; IR: 3402, 2962, 1742, 1613, 1515, 1207, 1179, 1145, 1110, 1016, 832; HRMS (EI/FI) for $C_{13}H_{18}O_2$ $[M]^+$ requires 206.1307 found 206.1332.

(3-(4-(*tert*-Butyl)phenoxy)-3,3-difluoropropyl)triethylsilane (40)

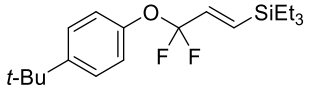


To a solution of (4-*tert*-butylphenoxy)(difluoro)acetic acid (122 mg, 0.5 mmol) in 1:1 acetone/water (2 mL) was added $AgNO_3$ (85.0 mg, 0.5 mmol), $K_2S_2O_8$ (541 mg, 2.0 mmol) and triethylvinylsilane (142 mg, 1.0

mmol). The reaction mixture was stirred at 50 ˚C for 2 hours before diluting with water. The aqueous layer was extracted with DCM (3 x 10 mL), then the combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography (eluent: 1 % Et_2O in *n*-pentane) to provide the title compound (17.0 mg, 10 % yield) as a colourless oil.

(^{1}H NMR, 400 MHz, $CDCl_3$): δ = 7.26 (d, *J* = 8.6 Hz, 2H), 7.03 (d, *J* = 8.4 Hz, 2H), 2.06–1.96 (m, 2H), 1.23 (s, 3H), 0.88 (t, *J* = 7.5 Hz, 6H), 0.79–0.74 (m, 2H), 0.58–0.45 (m, 3H); (^{13}C NMR, 101 MHz, $CDCl_3$): δ = 148.3, 136.0 (t, *J* = 33.4 Hz), 126.2, 125.8 (t, *J* = 265.4 Hz), 121.4, 34.4, 31.4, 30.7 (t, *J* = 30.2 Hz), 7.3, 3.6, 3.1; (^{19}F NMR, 377 MHz, $CDCl_3$): δ = –73.0 (*t*, J = 10.4 Hz).

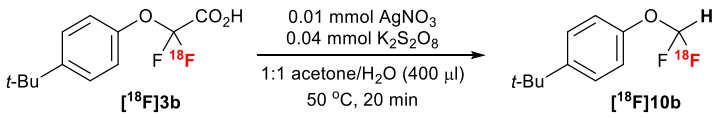
(*E*)-(3-(4-(*tert*-Butyl)phenoxy)-3,3-difluoroprop-1-en-1-yl)triethylsilane (41)



To a solution of (4-*tert*-butylphenoxy)(difluoro)acetic acid (122 mg, 0.5 mmol) in 1:1 acetone/water (2 mL) was added $AgNO_3$ (85.0 mg, 0.5 mmol), $K_2S_2O_8$ (541 mg, 2.0 mmol) and triethylvinylsilane (142 mg, 1.0 mmol). The reaction mixture was stirred at 50 ˚C for 2 hours before diluting with water. The aqueous layer was extracted with DCM (3 x 10 mL), then the combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography (eluent: 1 % Et_2O in *n*-pentane) to provide the title compound (24.0 mg, 14 % yield) as a colourless oil.

(^{1}H NMR, 400 MHz, $CDCl_3$): δ = 7.26 (d, *J* = 8.6 Hz, 2H), 7.02 (d, *J* = 8.4 Hz, 2H), 6.47–6.42 (m, 1H), 6.04 (dt, J_1 = 6.4 Hz, J_2 = 19.1 Hz, 1H), 1.23 (s, 3H), 0.86 (t, *J* = 7.5 Hz, 9H), 0.58–0.45 (m, 6H); (^{13}C NMR, 101 MHz, $CDCl_3$): δ = 148.2, 148.0, 134.8 (t, *J* = 4.4 Hz), 126.1, 121.1, 120.4 (t, *J* = 265.4 Hz), 121.4, 34.4, 31.4, 7.2, 3.0; (^{19}F NMR, 377 MHz, $CDCl_3$): δ = –68.6 (*d*, J = 5.2 Hz).

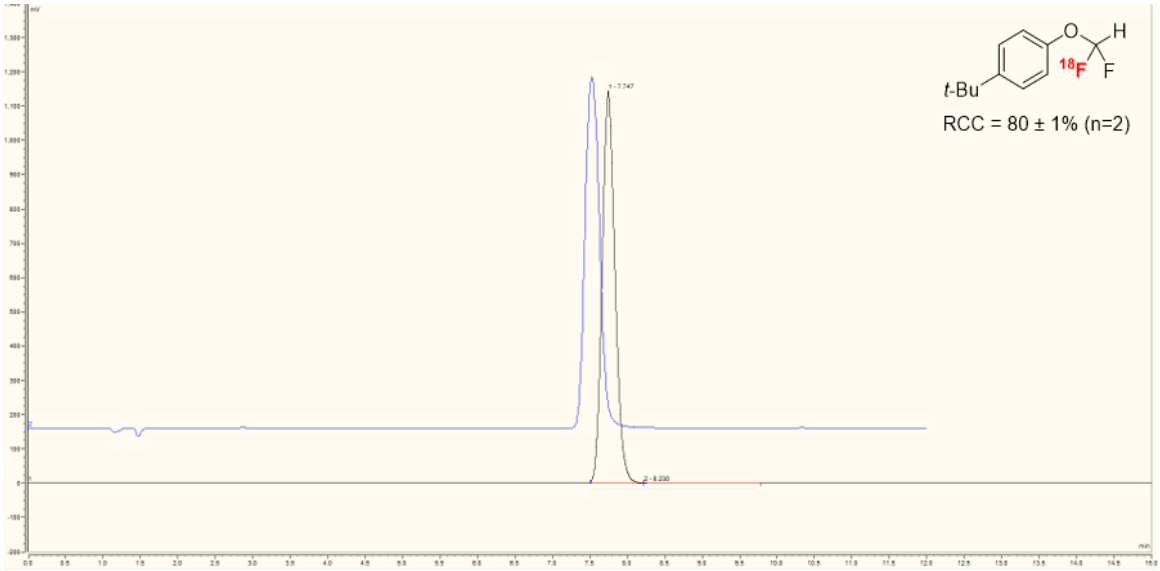
Radiosynthesis of 1-tert-butyl-4-([^{18}F]difluoromethoxy)benzene ([^{18}F]10b)



To a V-vial containing a magnetic stirrer bar was added 4-*tert*-butylphenoxy)([^{18}F]difluoro)acetic acid ([^{18}F]**3b**) in MeCN. The solvent was then removed at 50 ˚C under a stream of nitrogen for approximately 5 minutes. Then acetone (200 µL) was added followed by a solution of $AgNO_3$ (0.2 mg, 0.01 mmol) in H_2O (100 µL) and a solution of $K_2S_2O_8$ (11 mg, 0.04 mmol) in H_2O (100 µL). The sealed vial was allowed to stir for 20 minutes at 50 °C. After the reaction, the mixture was injected onto a reverse phase HPLC column (Phenomenex Luna C18(2) 100Å, 250 x 10mm). Flow rate 4 ml/min (70 % MeCN) [^{18}F]1-*tert*-butyl-4-(difluoromethoxy)benzene ([^{18}F]**10b**) was eluted at 16.5 min.

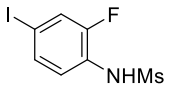
Two reactions were performed, starting from 1756 MBq and 836 MBq of 4-*tert*-butylphenoxy)([^{18}F]difluoro)acetic acid ([^{18}F]**3b**) (after solvent removal); 408 MBq and 179 MBq of 1-*tert*-butyl-4-([^{18}F]difluoromethoxy)benzene ([^{18}F]**10b**) were isolated respectively. RCY = 22 ± 1 % (*n* = 2).

[^{18}F]1-*tert*-Butyl-4-(difluoromethoxy)benzene ([^{18}F]10b): Eluent system = 70 % MeCN isocratic



5.4.5 Synthesis and Radiolabelling of TRPV1 Antagonist (34)

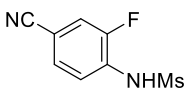
N-(2-Fluoro-4-iodophenyl)methanesulfonamide



The title compound was prepared following a procedure reported in the literature.[26] A cooled solution of 2-fluoro-4-iodoaniline (3.56 g, 15.0 mmol) in pyridine (20 ml) at 0 °C was drop-wise treated with methanesulfonyl chloride (1.74 ml, 22.5 mmol). After being stirred for 3 h at room temperature, the mixture was diluted with water and extracted with ethyl acetate several times. The combined organic layers were washed with water and brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by recrystalisation in DCM/n-pentane to afford the title compound (3.78 g, 80 % yield) as a white solid.

(^{1}H NMR, 400 MHz, $CDCl_3$): δ = 7.42 (d, *J* = 8.3 Hz, 2H), 7.25 (t, *J* = 8.2 Hz, 1H), 6.70 (brs, 1H), 2.97 (s, 3H); (^{19}F NMR, 377 MHz, $CDCl_3$): δ = –126.2 (t, *J* = 8.9 Hz). Data consistent with literature values.[26]

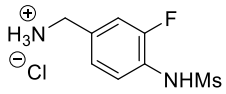
N-(4-Cyano-2-fluorophenyl)methanesulfonamide



A mixture of *N*-(2-fluoro-4-iodophenyl)methanesulfonamide (2.52 g, 8 mmol), zinc cyanide (564 mg, 4.8 mmol), and tetrakis(triphenylphosphine) palladium (462 mg, 0.4 mmol) in dimethylformamide (18 ml) was heated at 80 °C for 8 h. The mixture was diluted with water and extracted with ethyl acetate several times. The combined organic layers were washed with water and brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by recrystalisation in DCM/n-pentane to afford the title compound (1.25 g, 73 % yield) as a white solid.

(^{1}H NMR, 400 MHz, $CDCl_3$): δ = 7.66 (t, *J* = 8.2 Hz, 1H), 7.51–7.30 (m, 2H), 6.91 (brs, 1H), 3.07 (s, 3H); (^{19}F NMR, 377 MHz, $CDCl_3$): δ = –127.6 (t, *J* = 9.1 Hz). Data consistent with literature values.[26]

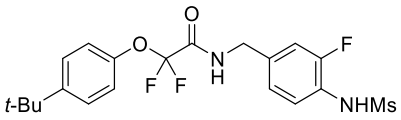
(3-Fluoro-4-(methylsulfonamido)phenyl)methanaminium chloride (42)



The title compound was prepared following a procedure reported in the literature.[26] A stirred suspension of *N*-(4-cyano-2-fluorophenyl) methanesulfonamide (1.07 g, 5 mmol), 5 % palladium on carbon (100 mg) and several drops of concentrated hydrochloric acid in MeOH (25 ml) was hydrogenated under a balloon of hydrogen for 16 h. The reaction mixture was filtered and the filtrate was concentrated *in vacuo* to afford 3-fluoro-4-(methylsulfonylamino)benzyl amine salt as a white solid (1.02 g, 80 % yield).

(^{1}H NMR, 400 MHz, CD_3OD): δ = 7.49 (t, *J* = 8.3 Hz, 1H), 7.28 (dd, J_1 = 2.0 Hz, J_2 = 11.1 Hz, 1H), 7.21 (dd, J_1 = 2.1 Hz, J_2 = 8.3 Hz, 1H), 4.04 (s, 2H), 2.95 (s, 3H); (^{19}F NMR, 377 MHz, CD_3OD): δ = –126.1 (dd, J_1 = 8.3 Hz, J_2 = 11.1 Hz). Data consistent with literature values.[26]

2-(4-(*tert*-Butyl)phenoxy)-2,2-difluoro-*N*-(3-fluoro-4-(methylsulfonamido)benzyl) acetamide (34)



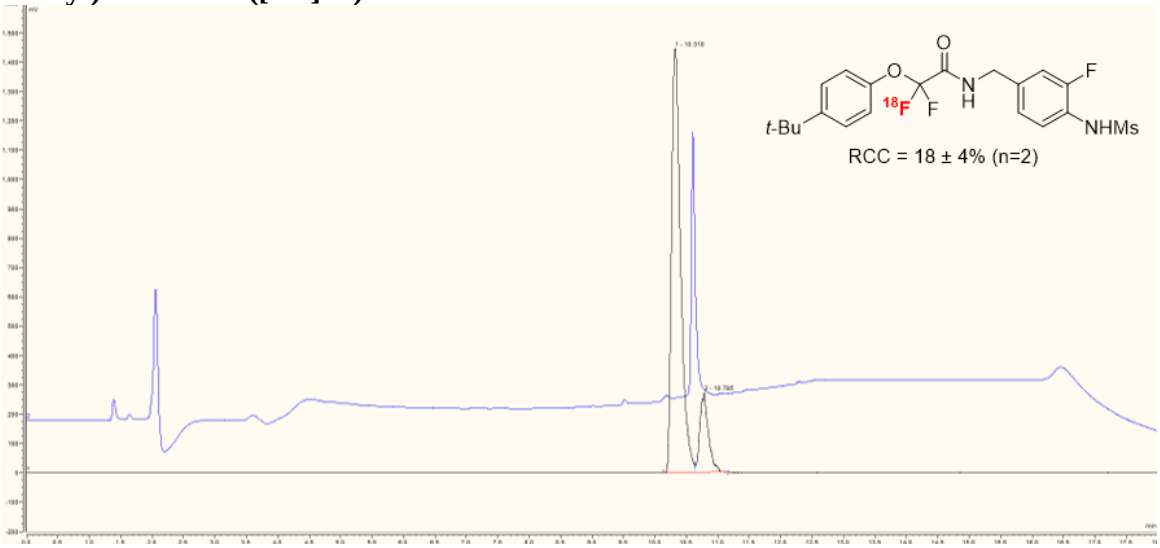
The title compound was prepared following a procedure reported in the literature.[27] To a solution of 4-*tert*-Butylphenoxy)(difluoro)acetic acid (48.8 mg, 0.2 mmol) in THF (2 mL) were added DMTMM (4-(4,6-dimethoxy-1,3,5- triazin-2-yl)-4-methylmorpholinium chloride) (86 mg, 0.3 mmol), NMM (23 μL, 0.2 mmol) and Et_3N (88 μL, 0.6 mmol). After being stirred for 4 h, the reaction mixture was added (3-fluoro-4-(methylsulfonamido)phenyl)methanaminium chloride (64 mg, 0.25 mmol). After additional 10 h, the reaction mixture was diluted with DCM, washed with water and brine, dried over $MgSO_4$, and concentrated *in vacuo*. Purification of the residue by column chromatography (EtOAc/*n*-pentane = 1:1) afforded the title compound (5.8 mg, 7 %) as a white solid.

(^{1}H NMR, 400 MHz, $CDCl_3$): δ = 7.49 (t, *J* = 8.3 Hz, 1H), 7.31 (d, *J* = 8.8 Hz, 2H), 7.15–6.95 (m, 4H), 6.82 (brs, 1H), 6.49 (brs, 1H), 4.46 (d, *J* = 6.1 Hz, 2H), 2.97 (s, 3H), 1.25 (s, 9H); (^{19}F NMR, 377 MHz, $CDCl_3$): δ = –77.0 (s, 2F), –127.9 (t, *J* = 9.1 Hz, 1F). Data consistent with literature values.[27]

***Radiosynthesis of* 2-(4-(*tert*-Butyl)phenoxy)-2,2-[^{18}F]difluoro-*N*-(3-fluoro-4-(methylsulfonamido)benzyl)acetamide ([^{18}F]34)**

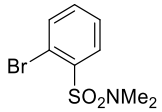
To a V-vial containing a magnetic stirrer bar and 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride (DMTMM) (16.6 mg, 0.06 mmol) and (3-Fluoro-4-(methylsulfonamido)phenyl)methanaminium chloride (**42**) (10 mg, 0.04 mmol) was added [^{18}F]difluoro[4-(trifluoromethyl)phenoxy]acetic acid ([^{18}F]**3b**) in MeCN. A solution of NEt_3 (17 µL, 0.12 mmol) in THF (300 µL) was added, then the sealed vial was allowed to stir for 20 minutes at room temperature. After the reaction, an aliquot was removed for analysis by radio-TLC and HPLC for radiochemical yield and product identity. Analysis was performed using Gradient A with a Phenomenex Synergi Hydro RP 80 Å column (4 µm, 4.6 x 150 mm) at a flow rate 1 ml/min.

2-(4-(*tert*-Butyl)phenoxy)-2,2-[^{18}F]difluoro-*N*-(3-fluoro-4-(methylsulfonamido) benzyl)acetamide ([^{18}F]34)



5.4.6 Synthesis and Radiolabelling of TRPV1 Inhibitor (35)

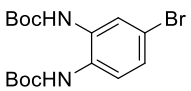
2-Bromo-*N*,*N*-dimethylbenzenesulfonamide



The title compound was prepared following a procedure reported in the literature.[28] To a solution of 2-bromobenzene-1-sulfonyl chloride (7.67 g, 30.0 mmol) in THF (20 mL) was slowly added dimethylamine (6.77 mL, 60.0 mmol) at 0 ˚C. The reaction mixture was stirred at room temperature for 6 hours. The reaction was then poured into water and the mixture was extracted with DCM. The combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo* to provide the title compound (7.30 g, 92 % yield) as a beige solid.

(^{1}H NMR, 400 MHz, $CDCl_3$): δ = 8.08 (dd, J_1 = 1.7 Hz, J_2 = 7.6 Hz, 1H), 7.75 (dd, J_1 = 1.2 Hz, J_2 = 7.8 Hz, 1H), 7.45 (td, J_1 = 1.2 Hz, J_2 = 7.6 Hz, 1H), 7.39 (td, J_1 = 1.7 Hz, J_2 = 7.6 Hz, 1H), 2.90 (s, 6H); (^{13}C NMR, 101 MHz, $CDCl_3$): δ = 137.7, 135.7, 133.5, 132.3, 127.4, 120.3, 37.3. Data consistent with literature values.[28]

Di-*tert*-butyl (4-bromobenzene-1,2-diyl)biscarbamate

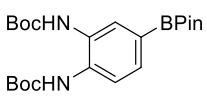


To a solution of 4-bromobenzene-1,2-diamine (2.81 g, 15.0 mmol) in DCM (45 mL) was added di-*tert*-butyl dicarbonate (17.2 mL, 75.0 mmol) and 2 M $NaOH_{(aq)}$ (18.8 mL, 37.5 mmol). The reaction mixture was stirred at room temperature for 12 hours. The reaction mixture was extracted with DCM and the combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography (eluent: 30 % EtOAc in *n*-hexane) to provide the title compound (4.88 g, 84 % yield) as a white solid.

(^{1}H NMR, 400 MHz, $CDCl_3$): δ = 7.77 (s, 1H), 7.33 (s, 1H), 7.23 (dd, J_1 = 2.2 Hz, J_2 = 8.6 Hz, 1H), 6.74 (s, 1H), 6.56 (s, 1H), 1.52 (s, 9H), 1.52 (s, 9H); (^{13}C NMR, 101 MHz, $CDCl_3$): δ = 153.7, 153.4, 146.8, 131.8, 127.9, 126.4, 125.7, 118.2, 81.3, 28.3; IR: ν 3300, 2980,

1700, 1594, 1515, 1413, 1393, 1368, 1238, 1155, 1051, 1024, 910, 855; HRMS (EI/FI) for $C_{16}H_{23}N_2O_4$ $[M]^+$ requires 386.0841 found 386.0842; Mp. 144-146 °C. Data consistent with literature values.[29]

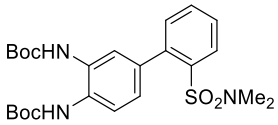
Di-*tert*-butyl (4-(2,2,5,5-tetramethylborolan-1-yl)-1,2-phenylene)dicarbamate



To a mixture of bis(pinacolato)diboron (1.62 g, 6.38 mmol), $Pd(dppf)Cl_2{\cdot}CH_2Cl_2$ (350 mg, 0.43 mmol) and potassium acetate (833 mg, 8.5 mmol) was added degassed DMF (10 mL) under N_2 atmosphere. To the reaction mixture was added di-*tert*-butyl (4-bromobenzene-1,2-diyl)biscarbamate (1.64 g, 4.25 mmol) and stirred at 80 ˚C for 16 hours. The reaction mixture was concentrated *in vacuo*. The crude product was purified by silica gel column chromatography (eluent: 10 % EtOAc in *n*-pentane) to provide the title compound (1.11 g, 60 % yield) as a white solid.

(^{1}H NMR, 400 MHz, $CDCl_3$): δ = 7.75–7.70 (m, 2H), 7.60 (dd, J_1 = 1.0 Hz, J_2 = 8.1 Hz, 1H), 7.13 (s, 1H), 6.51 (s, 1H), 1.50 (s, 9H), 1.50 (s, 9H), 1.32 (s, 6H); (^{13}C NMR, 101 MHz, $CDCl_3$): δ = 154.2, 153.1, 135.0, 132.9, 131.6, 127.3, 121.7, 83.7, 80.9, 80.6, 28.2, 28.2, 24.8; IR: ν 3310, 2972, 1737, 1418, 1366, 1231, 1156, 1095, 855; HRMS (ESI) for $C_{22}H_{35}O_6N_2BNa$ $[M+Na]^+$ requires 456.2517 found 456.2506; Mp. 166-168 °C. Data consistent with literature values.[30]

Di-*tert*-butyl (2'-(*N*,*N*-dimethylsulfamoyl)-[1,1'-biphenyl]-3,4-diyl)dicarbamate

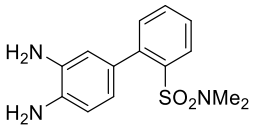


To a solution of di-*tert*-butyl (4-(2,2,5,5-tetramethylborolan-1-yl)-1,2-phenylene)dicarbamate (109 mg, 0.25 mmol) and 2-bromo-*N*,*N*-dimethylbenzenesulfonamide (66.0 mg, 0.25 mmol) in DME (2.0 mL) and H_2O (0.5 mL) was added Na_2CO_3 (126 mg, 1.5 mmol) and $Pd(dppf)Cl_2{\cdot}CH_2Cl_2$ (20.4 mg, 0.025 mmol). The reaction mixture was stirred at 100 ˚C for 16 hours then concentrated *in vacuo*. The

crude product was purified by silica gel column chromatography (eluent: 30 % Et_2O in *n*-pentane) to provide the title compound (84.4 mg, 69 % yield) as a yellow solid.

(^{1}H NMR, 400 MHz, $CDCl_3$): δ = 8.03 (dd, J_1 = 1.2 Hz, J_2 = 7.8 Hz, 1H), 7.57–7.38 (m, 4H), 7.24 (td, J_1 = 1.5 Hz, J_2 = 7.8 Hz, 1H), 7.11 (dd, J_1 = 2.0 Hz, J_2 = 8.3 Hz, 1H), 6.73 (brs, 2H), 2.32 (s, 6H), 1.46 (s, 9H), 1.43 (s, 9H); (^{13}C NMR, 126 MHz, $CDCl_3$): δ = 153.8, 153.7, 140.6, 137.2, 136.5, 132.9, 132.2, 130.4, 130.1, 129.3, 127.7, 126.6, 125.4, 123.0, 81.0, 36.0, 28.3, 28.3; IR: ν 3319, 2977, 2363, 1725, 1702, 1590, 1525, 1480, 1393, 1368, 1323; HRMS (EI/FI) for $C_{24}H_{33}N_3O_6S$ $[M]^+$ requires 491.2090 found 491.1833; Mp. 83-85 °C.

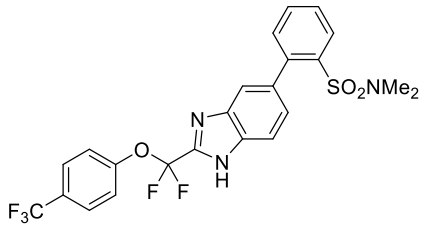
3',4'-Diamino-*N*,*N*-dimethylbiphenyl-2-sulfonamide (43)



To a flask containing di-*tert*-butyl (2'-(*N*,*N*-dimethylsulfamoyl)-[1,1'-biphenyl]-3,4-diyl)dicarbamate (1.02 g, 2.08 mmol) was added 2 M HCl in Et_2O (40 mL, 80 mmol) and 1.25 M HCl in MeOH (16 mL, 20 mmol). The reaction mixture was stirred at room temperature for 4 hours then concentrated *in vacuo*. The residue was dissolved in DCM and the solution was washed with sat. $NaHCO_{3(aq)}$ and brine, dried over $MgSO_4$ and concentrated *in vacuo* to provide the title compound (534 mg, 88 % yield) as a brown solid.

(^{1}H NMR, 400 MHz, $CDCl_3$): δ = 8.08 (dd, J_1 = 1.2 Hz, J_2 = 7.8 Hz, 1H), 7.50 (td, J_1 = 1.5 Hz, J_2 = 7.5 Hz, 1H), 7.41 (td, J_1 = 1.5 Hz, J_2 = 7.5 Hz, 1H), 7.28 (dd, J_1 = 1.2 Hz, J_2 = 7.8 Hz, 1H), 6.81 (t, J = 1.0 Hz, 1H), 6.87 (t, J = 1.2 Hz, 1H), 3.43 (brs, 4H), 2.38 (s, 6H); (^{13}C NMR, 126 MHz, $CDCl_3$): δ = 141.9, 137.4, 134.6, 133.7, 133.2, 132.0, 131.4, 130.3, 127.0, 121.4, 118.4, 115.7, 36.2; IR: ν 3417, 3349, 1627, 1587, 1517, 1465, 1314, 1276, 1153, 1071, 966, 816; HRMS (ESI) for $C_{14}H_{18}O_2N_3S$ $[M+H]^+$ requires 292.1114 found 292.1108; Mp. 121-123 °C.

2-(2-{Difluoro[4-(trifluoromethyl)phenoxy]methyl}-1H-benzimidazol-5-yl)-*N*,*N*-dimethylbenzene sulfonamide (35)



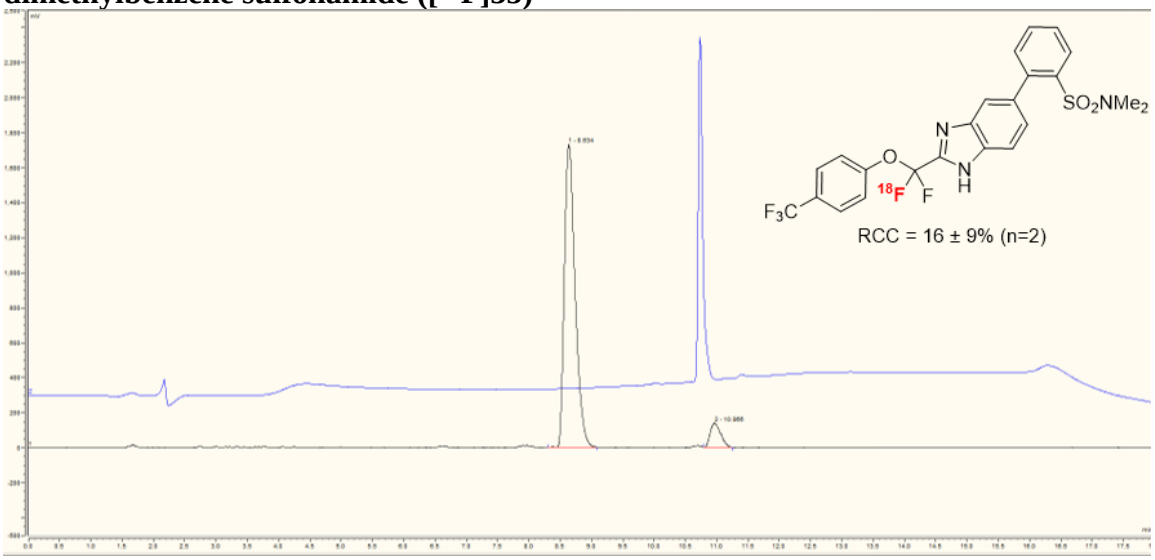
To a mixture of difluoro[4-(trifluoromethyl)phenoxy] acetic acid (218 mg, 0.85 mmol) and 3',4'-diamino-*N*,*N*-dimethylbiphenyl-2-sulfonamide (248 mg, 0.85 mmol) was added 6 M $HCl_{(aq)}$ (2.0 mL). The reaction mixture was stirred at 110 ˚C for 16 hours. The reaction mixture was concentrated *in vacuo* then purified by silica gel column chromatography (eluent: 30 % EtOAc in *n*-pentane) to provide the title compound (80.1 mg, 18 % yield) as a white solid.

(^{1}H NMR, 400 MHz, $CDCl_3$): δ = 10.64 (brs, 1H), 8.02 (dd, J_1 = 8.1 Hz, J_2 = 13.5 Hz, 1H), 7.83 (d, *J* = 8.3 Hz, 1H), 7.70 (d, J = 8.6 Hz, 1H), 7.59 (s, 1H), 7.57 (s, 1H), 7.52 (t, *J* = 7.3 Hz, 1H), 7.45 (td, J_1 = 1.2 Hz, J_2 = 7.6 Hz, 1H), 7.40–7.32 (m, 2H), 7.28 (d, *J* = 7.6 Hz, 1H), 7.22–7.19 (m, 1H), 2.32 (s, 3H), 2.24 (s, 3H); (^{13}C NMR, 126 MHz, $CDCl_3$) 152.0, 144.1 (t, *J* = 39.1 Hz), 141.8, 141.4, 137.3, 136.41, 133.2, 132.3, 128.6 (q, *J* = 33.1 Hz), 127.8 (t, *J* = 6.2 Hz), 127.1 (q, *J* = 3.6 Hz), 125.0, 123.7 (q, *J* = 272.8 Hz), 122.1, 121.2, 120.1, 117.0 (t, *J* = 262.7 Hz), 113.9, 110.8, 36.4, 36.2; (^{19}F NMR, 377 MHz, $CDCl_3$): δ = –62.3 (s, 3F), –65.9 (s, 2F); IR: ν 2974, 1742, 1449, 1370, 1322, 1220, 1162, 1125, 1066, 966; HRMS (ESI) for $C_{23}H_{18}O_3N_3F_5NaS$ $[M+Na]^+$ requires 534.0881 found 534.0869; Mp. 83-85 °C. Data consistent with literature values.[31]

Radiosynthesis of 2-(2-{[^{18}F]difluoro[4-(trifluoromethyl)phenoxy]methyl}-1H-benzimidazol-5-yl)-N,N-dimethylbenzene sulfonamide ([^{18}F]35)

To a V-vial containing a magnetic stirrer bar was added 4-*tert*-butylphenoxy)([^{18}F]difluoro)acetic acid ([^{18}F]**3b**) in MeCN. The solvent was then removed at 50 ˚C under a stream of nitrogen for approximately 5 minutes. A solution of 3',4'-diamino-*N*,*N*-dimethylbiphenyl-2-sulfonamide (**43**) in 6 M HCl (200 µL) was added, then the sealed vial was allowed to stir for 20 minutes at 110 ºC. After the reaction, an aliquot was removed for analysis by radio-TLC and HPLC for radiochemical yield and product identity. Analysis was performed using Gradient A with a Phenomenex Synergi Hydro RP 80 Å column (4 µm, 4.6 x 150 mm) at a flow rate 1 ml/min.

2-(2-{[^{18}F]Difluoro[4-(trifluoromethyl)phenoxy]methyl}-1H-benzimidazol-5-yl)-*N*,*N*-dimethylbenzene sulfonamide ([^{18}F]35)



5.5 References

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