Late-Stage Trifluoromethylation

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

By

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The work described in this thesis was carried out in the Chemistry Research Laboratory and Inorganic Chemistry Laboratory at the University of Oxford from September 2011 until April 2016, under the supervision of Professor Véronique Gouverneur. All of the work is my own unless otherwise stated and has not been submitted previously for any other degree at this or any other university.

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Abstract

Stefan Verhoog D.Phil. Thesis

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This thesis is concerned with the development of methodology for late-stage trifluoromethylation of complex molecules.

Chapter 1 introduces the concept of late-stage trifluoromethylations and details the effect that substitution of a CF_3 group can have on the properties of organic molecules. Methods for generating reactive trifluoromethylating intermediates for use in allylic and aliphatic trifluoromethylation are also discussed.

Chapter 2 examines the photoredox catalysis as a mechanistic manifold for the trifluoromethylation of allylsilanes for the synthesis of branched allylic trifluoromethylated compounds. The stereogenic trifluoromethylation of enantio-enriched allylsilanes through chirality transfer is explored, and mechanistic experiments are performed to investigate the formation of the CF_3 radical intermediate.

Chapter 3 details the development of hydrotrifluoromethylation of terminal alkenes for the synthesis of aliphatic trifluoromethylated compounds under mild conditions using photoredox catalysis. This methodology tolerates a wide range of functional groups and is applicable to the late-stage trifluoromethylation of complex organic compounds.

Chapter 4 explores the synthesis and isolation of ^{18}F-labelled aryl -SCF_3, -OCF_3 and -OCF_2H compounds from high specific activity [^{18}F]fluoride, using Ag(I) mediated halogen exchange as a mode of activation. This methodology can be used for the synthesis and isolation of ^{18}F labelled radiotracers containing new functional groups that have interesting biological and pharmacological properties.

Chapter 5 contains full experimental procedures and characterisation data for compounds synthesised in chapters 2, 3 and 4.

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Matt Tredwell and Benoit, who both became really good friends, and were there for me when I needed it most.

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Abbreviations and Acronyms

$A^{1,3}$	Allylic
A	Steric parameter
Å	Angstroms
Ac	Acetyl
ALS	Amyotrophic lateral sclerosis
app	Apparent
aq	Aqueous
Atm	Atmosphere
BDE	Bond dissociation energy
BHT	3,5-Di-*tert*-4-butylhydroxytoluene
BrettPhos	2-(Dicyclohexylphosphino)3,6-dimethoxy-2',4',6'-triisopropyl-1,1'-biphenyl
BOC	*tert*-Butoxycarbonyl
bpy	2,2'-Bipyridine
Box	Bisoxazoline
BQ	1-4 Benzoquinone
Bq	Becquerels
br	Broad
Bu	Butyl
Bz	Benzoyl
c	Concentration
C	Celsius
cat.	Catalytic
cBZR	Central benzodiazepine receptor
CFL	Compact fluorescent light
CHD	Cyclohexadiene
cm	Centimetres
cm^{-1}	Wavenumber
conc	Concentrated
COD	Cyclooctadiene
CT	Computed tomography
CV	Cyclic voltammetry
D	Dimensional
d	Doublet
DBB	Di-*tert*-butyl biphenyl
DBH	1,3-Dibromo-5,5-dimethylhydantoin
DCC	Dicyclohexylcarbodiimide
DCE	1,2-Dichloroethane
DCM	Dichloromethane
DEAD	Diethyl azodicarboxylate
dec	Decomposes
deg	Degrees
DFT	Density functional theory

DG	Directing group
DIPEA	*N*,*N*-Diisopropylethylamine
DMA	Dimethyl acetamide
DMAP	4-Dimethylaminopyridine
DME	Dimethoxyethane
DMF	*N*,*N*-Dimethylformamide
DMSO	Dimethyl sulfoxide
DOPA	3,4-dihydroxyphenylalanine
dppf	1,1'-Ferrocenediyl-bis(diphenylphosphine)
dr	Diastereoisomeric ratio
dtbpy	4,4'-Di-*tert*-butyl-2,2'-dipyridyl
δ	NMR chemical shift
(*E*)	Entgegen
E	Potential
E_s	Taft steric parameter
ee	Enantiomeric excess
er	Enantiomeric ratio
endo	Endocyclic
ent	Enantiomer
eq	Equivalents
ESI	Electrospray ionisation
Et	Ethyl
exo	Exocyclic
η	Hapticity
fac	Facial
FPPY	2-(2,4-difluorophenyl)pyridine
GBq	Gigabecquerels
GC	Gas chromatography
gem	Geminal
ΔH	Enthalpy change
h	Hours
HMPA	Hexamethylphosphoramide
HOMO	Highest occupied molecular orbital
HPLC	High performance liquid chromatography
HRMS	High resolution mass spectrometry
Hz	Hertz
^{i}	Iso
IR	Infrared
J	Coupling constant
^{2}J	Geminal coupling constant
^{3}J	Vicinal coupling constant
k	Rate constant
kcal	Kilocalories
keV	Kiloelectronvolts
kJ	Kilojoules
K	Kelvin
Kryptofix 2.2.2 ($K_{2.2.2}$)	4,7,13,16,21,24-Hexaoxa-1,10-diazabicyclo[8.8.8]hexacosane

L	Litres
LDA	Lithium diisopropylamide
LED	Light emitting diode
LG	Leaving group
logP, π	Hansch lipophilicity parameter
LUMO	Lowest unoccupied molecular orbital
m	Multiplet
M	Molar
$[M]^+$	Molecular ion
MBq	Megabecquerels
Me	Methyl
mg	Milligrams
mGluR5	Metabotropic glutamate subtybe 5 receptor
MHz	Megahertz
min	Minutes
μL	Microlitres
mL	Millilitres
mol	Moles
μmol	Micromoles
mmol	Millimoles
MMA	Methyl methacrylate
MLCT	Metal to ligand charge transfer
Mp	Melting point
MRI	Magnetic resonance imaging
Ms	Methanesulfonyl
MS	Mass spectrometry, Molecular sieves
MTBE	Methyl *tert*-butyl ether
m/z	Mass to charge ratio
n	Neutron, Number
N, n	Normal
(*S*,*S*)-Noyori catalyst	[*N*-[(1*S*,2*S*)-2-(Amino-κ*N*)-1,2-diphenylethyl]-4-methylbenzenesulfonamidato-κ*N*]chloro[(1,2,3,4,5,6-η)-1-methyl-4-(1-methylethyl)benzene]-ruthenium
nm	Nanometers
NFSI	*N*-Fluorobenzenesulfonimide
Nu	Nucleophile
NMP	N-Methylpyrrolidine
NMR	Nuclear magnetic resonance
Olah's reagent	7:3, HF/py
p	Proton
p	p-Orbital
PCC	Pyridinium chlorochromate
PET	Positron emission tomography
Ph	Phenyl
phen	Phenanthroline
PIDA	**(**Diacetoxyiodo)benzene
Pin	Pinacol

pKa	Acid dissociation constant
ppm	Parts per million
ppy	2-(2-pyridinyl-*N*)phenyl
Pr	Propyl
py	Pyridine
q	Quartet
quant	Quantitative
R	Alkyl
(*R*), *Re*	Rectus
RCC	Radiochemical conversion
RCY	Radiochemical yield
RedAl^{tm}	Sodium bis(2-methoxyethoxy)aluminum hydride
R_f	Retention factor
RT	Room temperature
s	Singlet, s-Orbital, Second
(*S*), *Si*	Sinister
SA	Specific activity
Satd	Saturated
SCE	Saturated calomel electrode
S_E2'	Substitution, electrophilic, bimolecular, allylic
SET	Single electron transfer
SelectFluor	1-Chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate)
SI	Supplementary information
S_N1	Substitution, nucleophilic, unimolecular
S_N2	Substitution, nucleophilic, bimolecular
S_NAr	Substitution, nucleophilic, aromatic
SOMO	Singularly occupied molecular orbital
σ_R	Hammett value
^{t}, *tert*	Tertiary
t	Triplet
t_{2g}	Triple orbital, gerade
$t_{1/2}$	Half life
T	Temperature
TAS	Tris(dimethylamino)sulfonium
TBq	Terabecquerels
TBAF	Tetrabutylammonium fluoride
Tc	Thiophene-2-carboxylate
TCCA	Trichlorocyanuric acid
TDEA	Tetrakis dimethylaminoethane
TEMPO	2,2,6,6-Tetramethylpiperidine 1-oxyl
Tf	Trifluoromethanesulfonate
TFE	2,2,2-Trifluoroethanol
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMAF	Tetramethyl ammonium fluoride
TMS	Trimethylsilyl

ToF	Time of flight
Togni I reagent	3,3-Dimethyl-1-(trifluoromethyl)-1,2-benziodoxole
Togni II reagent	1-Trifluoromethyl-1,2-benziodoxol-3-(1*H*)-one
trig	Trigonal
Ts	*para*-Toluenesulfonyl
Umemoto reagent	5-(Trifluoromethyl)dibenzothiophenium trifluoromethanesulfonate
UV	Ultra-violet
V	Volts
v	Volume
υ	Charton steric parameter
ν_{max}	Infra-red absorption maximum
W	Watts
(*Z*)	Zusammen

Contents

Chapter 1: Introduction to Late-stage Trifluoromethylation

1.1 Properties of the Trifluoromethyl Group

The trifluoromethyl substituent has gained increasing attention in pharmaceutical and agrochemical industries due to its unique ability to alter the electronic and physical properties of bioactive molecules.[1] With this recent interest in trifluoromethylated compounds, the need for mild and selective methods for trifluoromethylation of organic substrates has also increased. In this respect, methods for late-stage trifluoromethylation of complex molecules are advantageous, for example in the context of such approaches for drug discovery (lead optimisation studies) and in ^{18}F-labelling for PET application.

1.1.1 The Size of the Trifluoromethyl Group

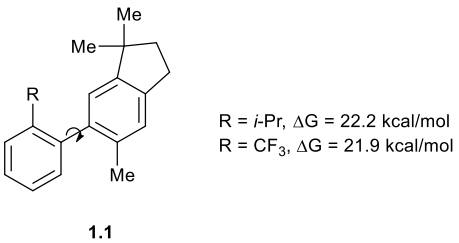
The size of an element or substituent can be determined based on several different steric parameters. The Taft steric parameter E_s of a substituent is calculated based on the logarithm of the relative rate of acid catalysed ester hydrolysis between methyl acetate and the corresponding substituted ester.[2] The Charton steric parameter υ is calculated using a correlation of the E_s value with the van der Waals radius[3] of the substituent, and eliminates resonance and inductive effects that might influence the value of E_s.[4] The value for the steric parameter *A* of a substituent is based upon the difference in Gibbs free energy calculated from equatorial and axial conformers of mono substituted cyclohexanes.[5] Values of these parameters for alkyl and fluorinated alkyl substituents are shown in Table 1.1.

Substituent	**$-E_s$ [a]**	**υ [b]**	***A*** **(kcal/mol)**
H	0	0	0
F	0.46	0.27	0.15
Me	1.24	0.52	1.70
Et	1.31	0.56	1.75
CH_2F	1.48	0.62	1.59
CHF_2	1.91	0.68	1.85
i-Pr	1.71	0.76	2.15
CF_3	2.40	0.91	2.37
t-Bu	2.78	1.24	4.89

[a] Es = Taft steric parameter. [b] υ = Charton steric parameter.

Table 1.1 Steric parameters of alkyl and fluorinated alkyl substituents

These values show that fluorine is a larger substituent compared to hydrogen, and that substitution of the hydrogen atoms of a methyl group with fluorine gradually increases the size. Comparison of the steric values for the CF_3 group with that of other alkyl groups, shows that the steric bulk of the CF_3 group is predicted to be similar to that of an *i*-Pr group. This observation is confirmed by a study of Sternhell *et al*, who related steric bulk to the rotational barrier along the biphenyl axis of indane-derived biphenyls **1-1**.[6] Determination of the rotational barriers by dynamic NMR showed that the CF_3 group has a very similar value to that of an *i*-Pr group (scheme 1.1).



Scheme 1.1 Rotational barriers in substituted indane derivatives

Although the steric bulk of the CF_3 group can be compared to that of an *i*-Pr-group, there is a difference between the two groups in terms of conformation and shape. This can be illustrated by comparing the conformation of the monosubstituted cyclohexanes **1-2** and

1-3, which have been used to determine *A*-values (scheme 1.2). The *i*-Pr group is able to adopt a conformation such as **1-3** in which 1,3-diaxial strain is minimized, whereas the CF_3 group does not have this possibility.

1-2 **1-3**

Scheme 1.2 Conformation of monosubstituted cyclohexanes

1.1.2 Electronic Effects of the Trifluoromethyl Group

Fluorine is the most electronegative of all the elements (Pauling electronegativity = 3.98), and substitution of hydrogen for fluorine in a methyl group can significantly alter the electronic and physicochemical properties of a molecule. The CF_3 group has a strong electron-withdrawing effect when attached to σ-systems (inductive effect, σ_I = +0.46) and π-systems (resonance effect, σ_R = +0.09).[7] The strength of this effect is comparable to that of the NO_2 group (σ_I = +0.64 and σ_R = +0.16). Due to this strong electron-withdrawing effect, the substitution of a CF_3 group can have a marked influence on the pKa values of proximal basic and acidic groups. Comparison of the pKa values for a range of carboxylic acids,[8] alcohols,[9] and amines[10] shows that the introduction of the CF_3 group results in a significant lowering of the pKa (Table 1.2). This inductive effect is strongest when the CF_3 group is substituted on the α-position (Table 1.2 entry 1), and gradually diminishes with added methylene groups between the CF_3 and the corresponding functional group (Table 1.2 entry 2, 3, 7 and 8). Addition of multiple CF_3 groups results in a cumulative effect, as shown for *t*-BuOH in comparison with $(CF_3)_3COH$ (Table 1.2 entry 6). Substitution of a CF_3 group enhances the acidity of carboxylic acids and alcohols as a result of increased stabilisation of the negative charge developing on the oxygen atom. For amines, the

electron-withdrawing effect of the CF_3 group decreases the basicity because of destabilisation of the positive charge developing on protonation of the amine.

Entry		pKa (X = H)[a]	pKa (X = F)[a]
	Carboxylic acids		
1	CX_3COOH	4.8	0.3
2	CX_3CH_2COOH	4.9	3.0
3	$CX_3CH_2CH_2COOH$	4.8	4.2
	Alcohols		
4	CX_3CH_2OH	16.0	12.5
5	$(CX_3)_2CHOH$	16.5	9.3
6	$(CX_3)_3COH$	17.0	5.4
	Amine		
7	$CX_3CH_2NH_3^+$	10.7	5.8
8	$CX_3CH_2CH_2NH_3^+$	10.7	8.7

[a] Measured in H_2O.

Table 1.2 Comparison of pKa values

The σ-inductive effect of the CF_3 group can influence the lipophilicity of aliphatic and aromatic trifluoromethylated compounds. In aliphatic molecules the CF_3 can either reduce or increase the lipophilicity, depending on the substitution pattern. It has been reported that the reduction of basicity upon substitution with a CF_3 group in the α-position for aliphatic alcohols significantly increases the lipophilicity.[11] However, this effect is reversed (reduction of lipophilicity) when the substituted CF_3 group is situated far enough away from the OH group that it does not exert an electronic effect. From experimental data it has been found that introduction of a CF_3 group on an aromatic ring always increases the lipophilicity.[12] For aromatic compounds substituted in the *ortho* or *para* position with Lewis basic substituents such as ethers, amines, alcohols, amides and carbonyls, this can be explained by the electron-withdrawing effect of the CF_3 through resonance. This lowers the Lewis basicity of the substituents on the aromatic ring in the *ortho* and *para* position, and thus decreases the ability of these substituents to engage in hydrogen bonding.

The effects of the trifluoromethyl group on the size, lipophilicity and pKa of bioactive molecules can greatly influence their pharmacological properties such as target binding

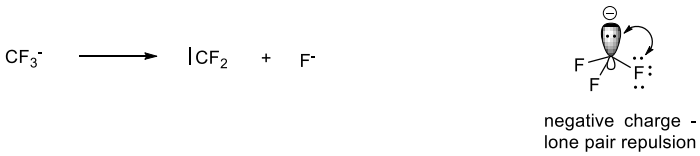
affinity, efficacy, metabolic stability, solubility and bioavailability. Introduction of a CF_3 group in bioactive molecules can therefore be a useful tool for tuning of these properties. Development of efficient methods for the regioselective introduction of the CF_3 group on aromatic and aliphatic substrates is therefore of paramount importance.

1.2 Reagents for Trifluoromethylation

Introduction of the CF_3 group into organic molecules can fundamentally be achieved through nucleophilic, electrophilic or radical trifluoromethylation. Due to the high electronegativity of fluorine, the development of methods and reagents for trifluoromethylation is more challenging compared to alkylation with non-fluorinated reagents. This section will briefly discuss the properties and reactivity of the most important reagents in nucleophilic, electrophilic and radical trifluoromethylation.

1.2.1 Nucleophilic trifluoromethylation

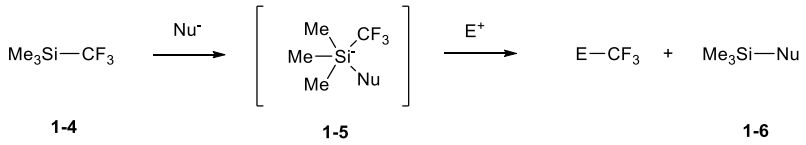
Nucleophilic trifluoromethylation is achieved via the intermediacy of the CF_3 anion. The generation of this anion can be challenging as a result of its low thermal stability.[13] Depending on the conditions, collapse to fluoride ion and singlet difluorocarbene can occur, due to the destabilisation of the negative charge on the carbon atom by the *p*-electrons from the neighbouring fluorine atoms (scheme 1.3).



Scheme 1.3 Negative charge - lone pair repulsion in the CF_3 anion

This decomposition can be prevented by the use of masked CF_3 anion equivalents such as the Ruppert-Prakash reagent, Me_3SiCF_3 **1-4** (Scheme 1.4).[14] This commercially-available, bench-stable, easy to handle liquid can be used to transfer a trifluoromethyl group to a

range of electrophilic substrates through formation of a hypervalent silicate **1-5**. The silicate is formed on activation of Me_3SiCF_3 **1-4** with a nucleophile.

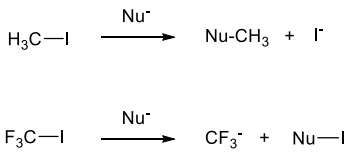


Scheme 1.4 Me_3SiCF_3 **1-4** as masked CF_3 anion equivalent

Since its introduction in 1984, the use of Me_3SiCF_3 **1-4** has led to the development of a wide variety of methods for the synthesis of trifluoromethylated compounds through nucleophilic trifluoromethylation.[15]

1.2.2 Electrophilic Trifluoromethylation

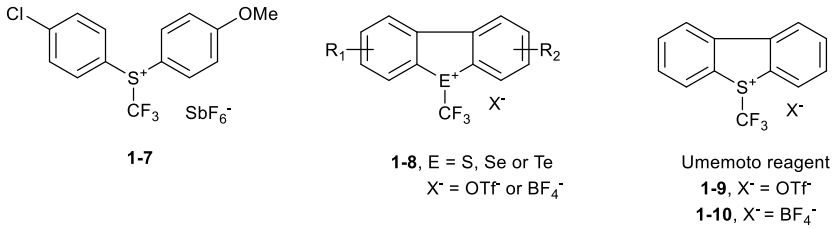
The use of CF_3-X (X = leaving group) in classical substitution reactions does not follow the same pathway as non-fluorinated analogues. Traditional S_N1 and S_N2 processes are inhibited because of the predicted high energy of formation for the CF_3 cation,[16] and hinderance of back-side attack on CF_3-X through steric interactions of the fluorine atoms and repulsion of the nucleophile by the fluorine lone-pairs.[17] As an example, nucleophilic attack on CF_3I has been reported to be directed towards the iodine instead of the CF_3 group (Scheme 1.5).[18]



Scheme 1.5 Reversal of polarisation in CF_3I

Electrophilic trifluoromethylation was first reported in 1984, in the pioneering work of Yagupolskii *et al*, who showed that *S*-(trifluoromethyl)diarylsulfonium salt **1-7** was an effective reagent for the trifluoromethylation of sodium thiophenolates.[19] This report was

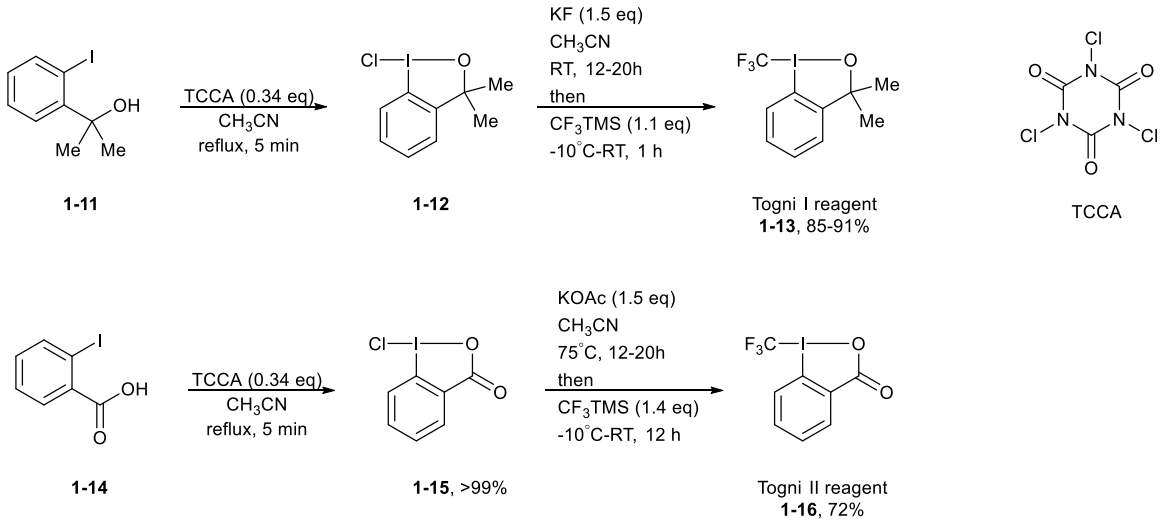
followed by the development of a range of easily available and bench-stable *S*-, *Se*-, and *Te*-(trifluoromethyl)dibenzoheterocyclic onium salts **1-8** by Umemoto, which were shown to be effective electrophilic trifluoromethylation reagents for a range of nucleophiles and activated arenes.[20] The S-(trifluoromethyl)dibenzothiophenium salt **1-9**, the Umemoto reagent, was the preferred reagent in terms of reactivity and ease of synthesis.



Scheme 1.6 Electrophilic trifluoromethylating reagents

Since the development of the Umemoto reagent **1-9**, it has become a very important reagent for the synthesis of both aromatic and aliphatic trifluoromethylated compounds. The Umemoto reagent is commercially available as both the triflate and tetrafluoroborate salts.

Another important class of electrophilic trifluoromethylating reagents based on hypervalent iodine compounds were reported more recently by the group of Togni.[21] These reagents were developed based on the unique properties of organic hypervalent iodine compounds,[22] and could be synthesized through the halogenated precursors **1-12** and **1-15** using oxidation with trichlorocyanuric acid (TCCA), followed by trifluoromethylation with Me_3SiCF_3 (Scheme 1.7).[23] Although both reagent are stable solids at room temperature (Togni I reagent **1-13** gradually decomposes on standing at room temperature and is best kept at 2-8 °C for long-term storage), they have been found to exothermically decompose on heating in the solid state.[24]

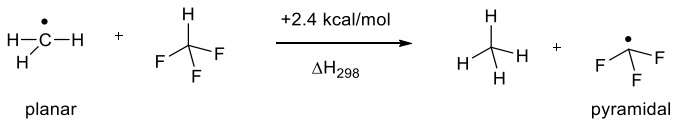


Scheme 1.7 Synthesis of Togni I and II reagent

The Togni I and Togni II reagent **1-13** and **1-16** have found widespread use in the electrophilic trifluoromethylation of sulfur, nitrogen, phosphorous and carbon nucleophiles and are now commercially available.[25]

1.2.3 Properties of the CF_3 radical

Both the strong inductive electron-withdrawing effect and the weaker π-donating resonance effect of fluorine influence the structure and stability of the CF_3 radical.[26] Whereas the CH_3 radical has a planar structure, it was observed that the CF_3 radical has a pyramidal structure (Scheme 1.8).[27] Calculations show that the radical stabilisation energy of the CF_3 radical is 2.4 kcal/mol less than the CH_3 radical.[28]



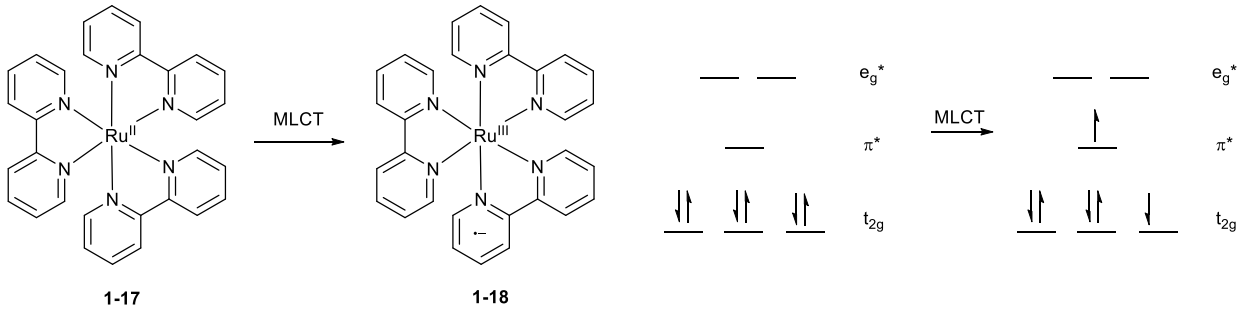
Scheme 1.8 Stability and structure of the CF_3 radical

The CF_3 radical is considered to be an electrophilic radical with a low-lying singly occupied molecular orbital (SOMO), and therefore reacts faster with molecules containing

a high-lying LUMO (lowest unoccupied molecular orbital), such as electron rich arenes and double bonds.[27]

1.2.4 Generation of the CF_3 Radical by Photoredox Catalysis

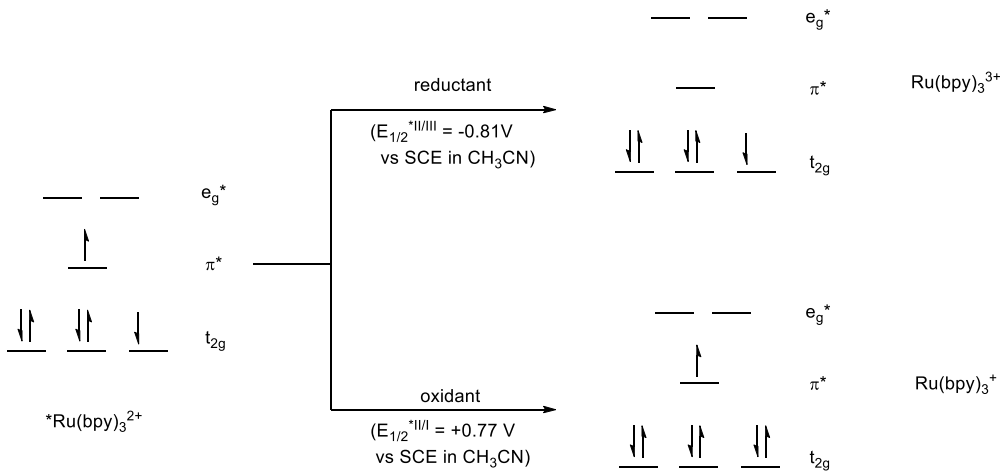
Photoexcitation by visible light of Ruthenium or Iridium polypyridyl complexes, originally developed for splitting of water to give hydrogen and oxygen,[29] has recently attracted much attention in organic chemistry for use in single electron transfer (SET) processes.[30] These complexes, referred to as photoredox catalysts, show poor oxidative or reductive properties in the ground state, but become very efficient electron transfer reagents upon excitation with visible light. When the metal complex absorbs a photon, an electron in the metal centered t_{2g} orbital is excited to the ligand centered π^* orbital, as shown for the complex $Ru(bpy)_3^{2+}$ **1-17** in Scheme 1.9.[31] This metal to ligand charge transfer (MLCT) results in formation of species **1-18** with a Ru^{III} oxidation state.



1-17 **1-18**

Scheme 1.9 Excited state of $Ru(bpy)_3^{2+}$

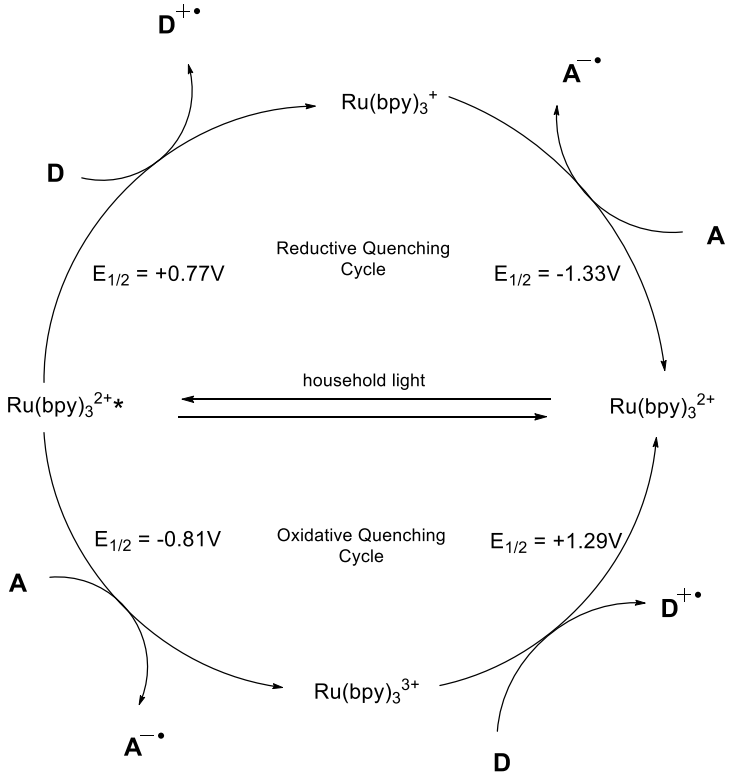
This excited state species **1-18** can then act as a reductant, donating the electron in the ligand centred orbital to another electron acceptor, or as oxidant by filling the vacancy (hole) in the metal centred orbital with an electron from an electron donor (scheme 1.10).



Scheme 1.10 Oxidation or reduction of excited state *$Ru(bpy)_3^{2+}$

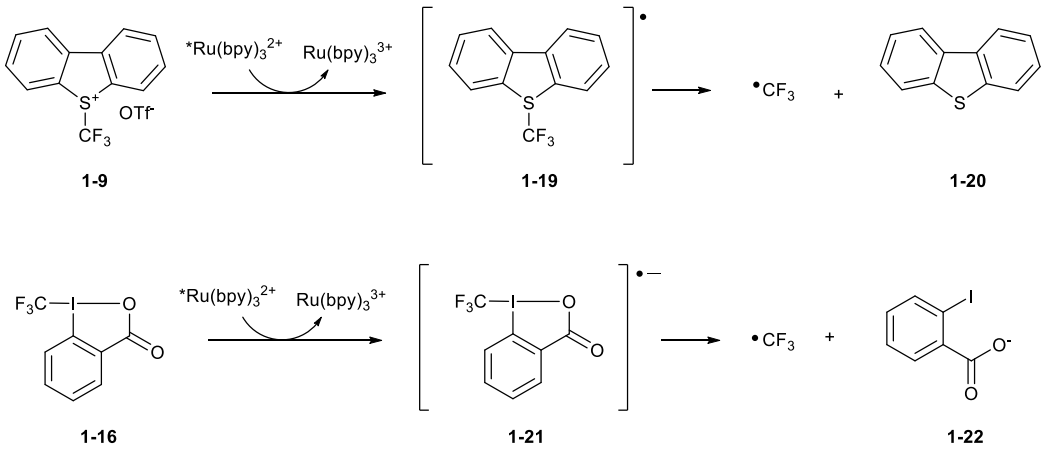
When the excited state *$Ru(bpy)_3^{2+}$ acts as a reductant it enters an oxidative quenching cycle, which results in formation of the radical anion of the electron acceptor (**A**$^{\cdot-}$ in Scheme 1.11) and the strong oxidant $Ru(bpy)_3^{3+}$ ($E_{1/2}^{III/II}$ = +1.29V vs SCE in CH_3CN).[32] The oxidant $Ru(bpy)_3^{3+}$ can then accept an electron from an electron donor (**D** in scheme 1.11) and regenerate the ground state $Ru(bpy)_3^{2+}$.

In the reductive quenching cycle, the excited state *$Ru(bpy)_3^{2+}$ accepts an electron from electron donor **D**, with concomitant formation of the strong reductant $Ru(bpy)_3^{+}$ ($E_{1/2}^{I/II}$ = -1.33 V in CH_3CN).[33] Donation of an electron to electron acceptor **A** by $Ru(bpy)_3^{+}$ regenerates the ground state $Ru(bpy)_3^{2+}$ and completes the catalytic cycle.



Scheme 1.11 Oxidative and reductive quenching cycle

The ability of photoredox catalysts such as $Ru(bpy)_3^{2+}$ to act as efficient single electron transfer reagents under irradiation with visible light, has proven very suitable for the generation of the CF_3 radical under mild conditions. Precursors such as CF_3SO_2Cl, $NaSO_2CF_3$ and CF_3I, in addition to electrophilic trifluoromethylating reagents such as the Umemoto and Togni reagents, have been proposed to generate the CF_3 radical upon SET oxidation or reduction using photoredox catalysts and visible light irradiation.[32e] The proposed pathway for generation of the CF_3 radical from the Umemoto reagent **1-9**, and the Togni II reagent **1-16**, using $Ru(bpy)_3^{2+}$ as a photocatalyst is shown in Scheme 1.12. SET reduction of the Umemoto reagent affords radical intermediate **1-19**, which collapses into the CF_3 radical and dibenzothiophene **1-20**. Generation of the CF_3 radical from SET reduction of the Togni II reagent is accompanied by formation of *ortho*-iodobenzoate **1-22**.

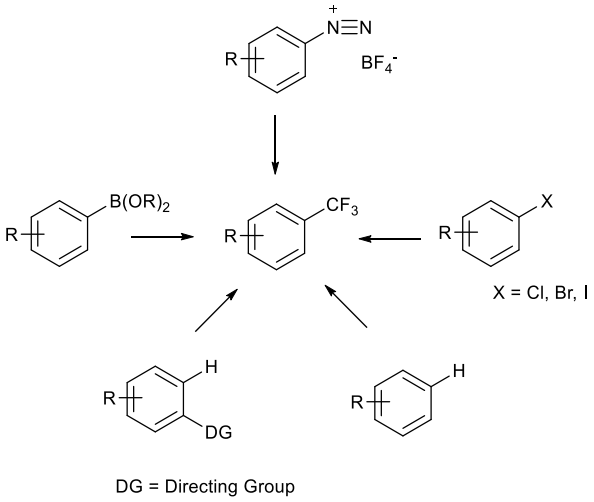


Scheme 1.12 Formation of the CF_3-radical by SET reduction

The generation of the CF_3 radical from widely available, easy to handle and bench stable reagents, under mild conditions using photoredox catalysis, has resulted in a marked increase in the development of new methodology for the trifluoromethylation of Csp^2 and Csp^3 bonds.[26e, 31e]

1.3 Synthesis of Aryl Trifluoromethyl Compounds

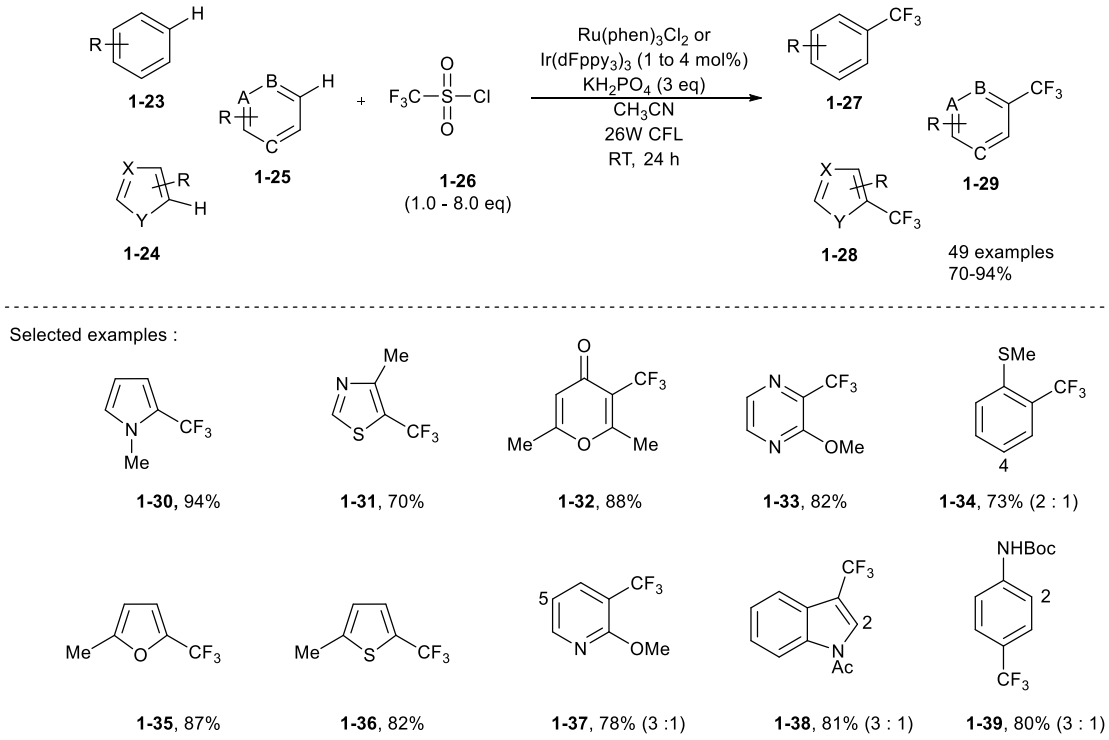
The introduction of the trifluoromethyl group to functionalised arenes and heteroarenes has been well studied since the first reports of Kobayashi and Kumadaki[33] and McLoughlin and Thrower[34] in 1969. This research has led to efficient methods for the trifluoromethylation of (hetero)aryl halides,[35] and (hetero)aryl boronic acid derivatives.[36] In recent years this methodology has also been extended to the use of aryldiazonium salts,[37] and C-H trifluoromethylation of (hetero)aryl precursors bearing a suitable directing group.[38]



Scheme 1.13 Methods for Aryl C*sp*^{2} trifluoromethylation

The direct trifluoromethylation of C-H bonds in unfunctionalised (hetero)arene substrates is a strategy that is very suitable for late-stage trifluoromethylation. In 2011, the group of MacMillan reported the photoredox catalysed C-H trifluoromethylation of a range of unfunctionalised arenes and five- and six-membered heterocycles (Scheme 1.14).[39] The reaction uses CF_3SO_2Cl **1-26** (1-8 eq) as a trifluoromethylation reagent in combination with $Ru(phen)_3Cl_2$ **1-42** (1 to 4 mol%) as the photoredox catalyst, under irradiation with a 26W common household light (CFL) in CH_3CN. The inorganic base KH_2PO_4 (3 eq) was used as an additive. Under these conditions, various five-membered ring heterocycles such as pyrroles, thiophenes and furans could be successfully trifluoromethylated in good yield. More electron-deficient aminothiazoles were also effective substrates, although good yields were only obtained using an excess of CF_3SO_2Cl **1-26** (4.0 eq). The trifluoromethylation of these substrates occured regioselectively in the 2-position. For six-membered heterocycles such as pyridines, pyrimidines, pyrazines and pyrazones, in addition to arenes, it was found that $Ir(Fppy)_3$ **1-43** (Scheme 1.15) provided better yields of trifluoromethylated products. The authors suggested this could be explained by the longer lifetime of the exited state of $Ir(Fppy)_3$ (1.6 μs)[40] in comparison with that of $Ru(phen)_3Cl_2$ **1-42** (0.5 μs).[41] The trifluoromethylation of pyridines required either a large excess of

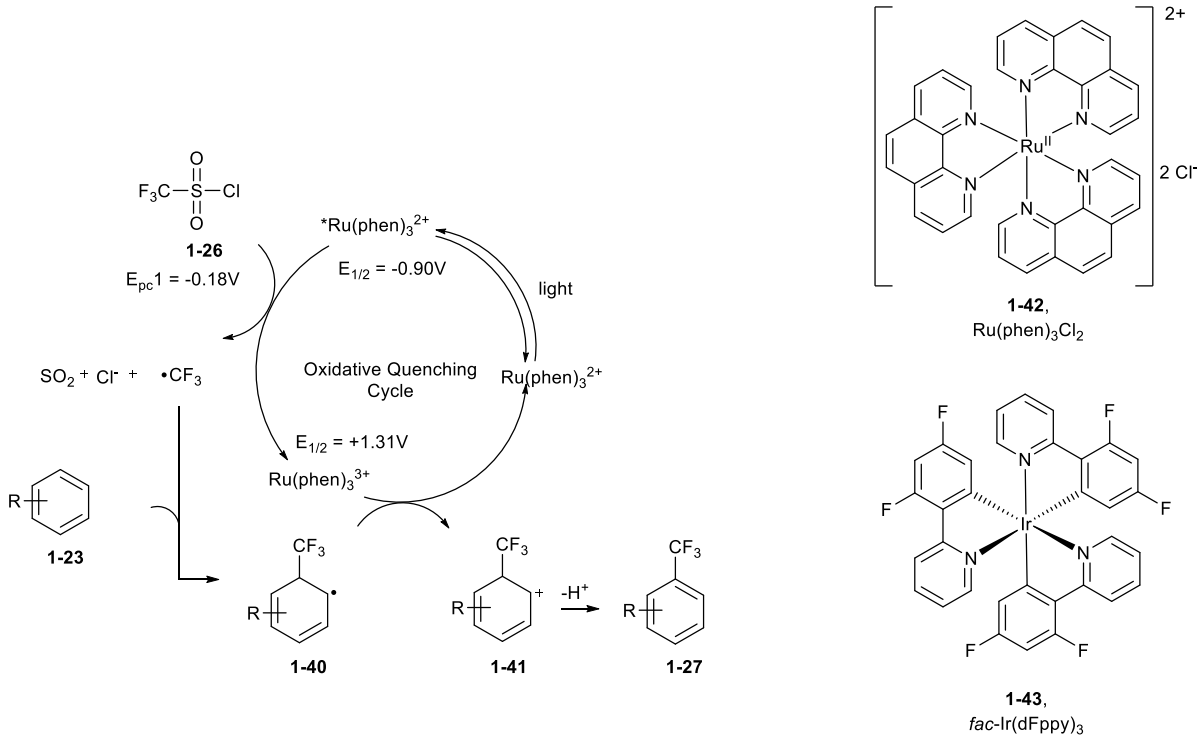
CF_3SO_2Cl **1-26** (8 eq), or inverse stoichiometry to provide good yields. Lower yields were obtained under the standard conditions due to formation of unreactive pyridine.HCl salts during the reaction.



Scheme 1-14 Photoredox catalysed trifluoromethylation of (hetero)arenes

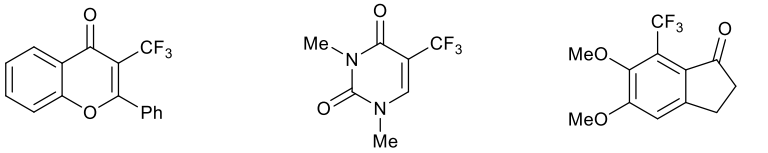
The authors proposed a mechanism in which a CF_3-radical is generated as the reactive intermediate (Scheme 1.15). This radical is formed through single electron transfer from the excited state $*Ru(phen)_3^{2+}$, ($E_{1/2}^{II/III}$ = -0.87V vs SCE in CH_3CN),[42] generated through visible light irradiation of $Ru(phen)_3^{2+}$, to CF_3SO_2Cl **1-26** ($E_{pc}1$ = -0.18V vs SCE in CH_3CN).[31e,32a] This reduction event affords $[CF_3SO_2Cl]^{\cdot-}$, with concomitant formation of the strong oxidant $Ru(phen)_3^{3+}$ ($E_{1/2}^{III/II}$ = +1.36V vs SCE in CH_3CN).[32a] The CF_3 radical is generated from $[CF_3SO_2Cl]^{\cdot-}$ with explusion of SO_2 and Cl^-, and adds to electron rich positions on the arene (see previous section on CF_3 intermediates), affording carbon radical **1-40**. This intermediate radical then undergoes electron transfer from the oxidant

$Ru(phen)_3^{3+}$, which generates the cationic intermediate **1-41** and ground state $Ru(phen)_3^{2+}$, completing the catalytic cycle. Cationic intermediate **1-41** provides the trifluoromethylated product by re-aromatisation through elimination of a proton.



Scheme 1.15 Proposed reaction mechanism for the photoredox catalysed trifluoromethylation of (hetero)arenes

The usefulness of this methodology for late-stage trifluoromethylation was demonstrated by the trifluoromethylation of bioactive compounds and their intermediates (Scheme 1.15). Flavone **1-44** (Vitamine P) could be successfully trifluoromethylated in 85% yield, and methylated CF_3-uracil **1-45**, a perfluorinated DNA-base analogue, could be isolated in 92% yield. Trifluoromethylation of a precursor for the Alzheimer drug Aricept resulted in formation of **1-46** in 94% yield.



1-44, 85%
CF_3-flavone

1-45, 92%
CF_3-Methyluracil

1-46, 94%
CF_3-Aricept precursor

Scheme 1.15 Trifluoromethylation of bioactive compounds

The successful synthesis of trifluoromethylated bioactive compounds such as **1-44** and **1-45** using the photoredox catalysed trifluoromethylation methodology reported by the group of Macmillan demonstrates the potential of late-stage trifluoromethylation for the synthesis of complex molecules.

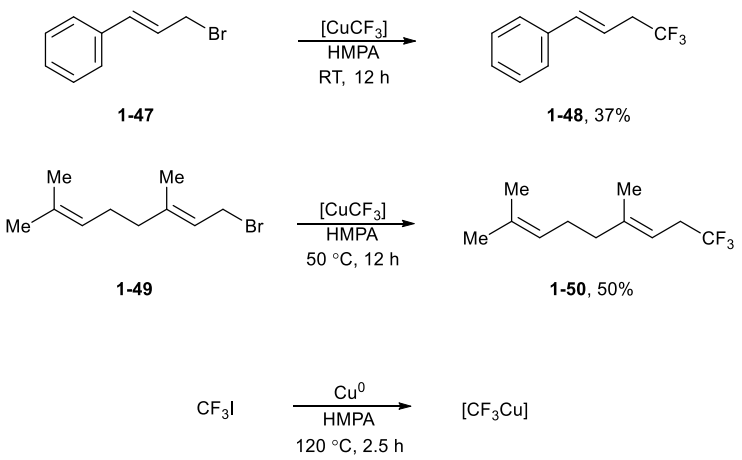
Other notable contributions to C-H activation trifluoromethylation involving generation of a CF_3 radical intermediate have been reported by Baran *et al*.[43] In this methodology, the CF_3 radical is afforded by reaction of $NaSO_2CF_3$ or $Zn(SO_2CF_3)_2$ with *t*-BuOOH in a biphasic system (DCM/H_2O), at room temperature under an atmosphere of air. A range of heterocycles could be efficiently trifluoromethylated, making this method suitable for late-stage trifluoromethylation. Additionally, the innate reactivity of complex natural products towards the CF_3 radical was explored.[44]

1.4 Synthesis of Allylic Trifluoromethyl Compounds

The trifluoromethylation of the Csp^3 bond has been much less developed in comparison with the currently available methodology for (hetero)arene trifluoromethylation. In this respect, the synthesis of allylic trifluoromethylated compounds has received much less attention.

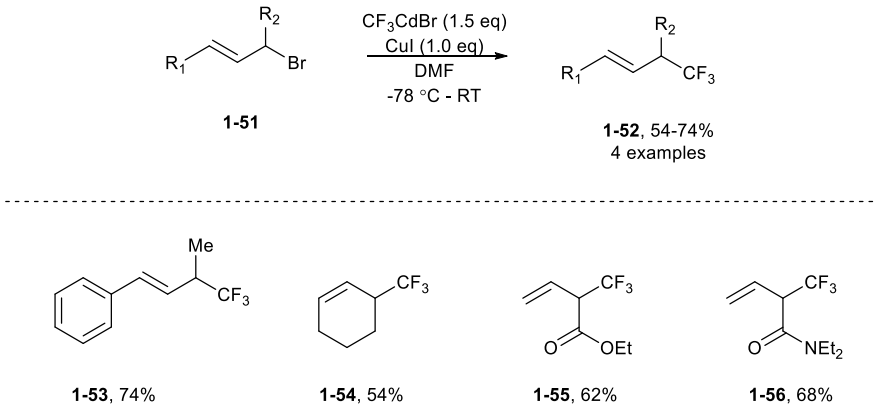
1.4.1 Linear Allylic trifluoromethylation From Pre-functionalised Allyl-Synthons

The first allylic trifluoromethylation reaction was reported in 1979 by the group of Kumadaki.[45] Allylic bromides **1-47** and **1-49** were treated with a solution containing an excess of a $CuCF_3$ reagent (exact amounts were not given), to afford the trifluoromethylated products **1-48** and **1-50** in low to moderate yield (Scheme 1.17). The $CuCF_3$ reagent was prepared from the reaction of CF_3I with metallic copper in HMPA at 120 °C, followed by filtration under inert atmosphere.



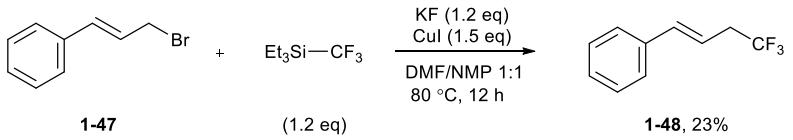
Scheme 1.17 Trifluoromethylation of allylbromides with pre-generated $CuCF_3$

The synthesis of $CuCF_3$ by transmetallation of CF_3CdBr with CuI in DMF developed by Wiemers and Burton[46] allowed for trifluoromethylation under milder conditions, and allyl chloride could be trifluoromethylated at room temperature in 70% yield. This procedure was later extended to the trifluoromethylation of secondary allylic bromides **1-51** by Viehe *et al* (Scheme 1.18).[47]



Scheme 1.18 Allylic trifluoromethylation using $CdCF_3Br$/CuI transmetallation

In the same year, the first use of Et_3SiCF_3 as a nucleophilic trifluoromethylating reagent for allylic halides was reported, which provided **1-48** in low yield.[48] Et_3SiCF_3 was presumably used because of its higher boiling point (bp = 56-58 °C/ 80 mbar) in comparison with Me_3SiCF_3 (bp = 55 °C). The reaction was postulated to proceed through the formation of $CuCF_3$ from the reaction of Et_3SiCF_3 with the fluoride ion in the presence of CuI.

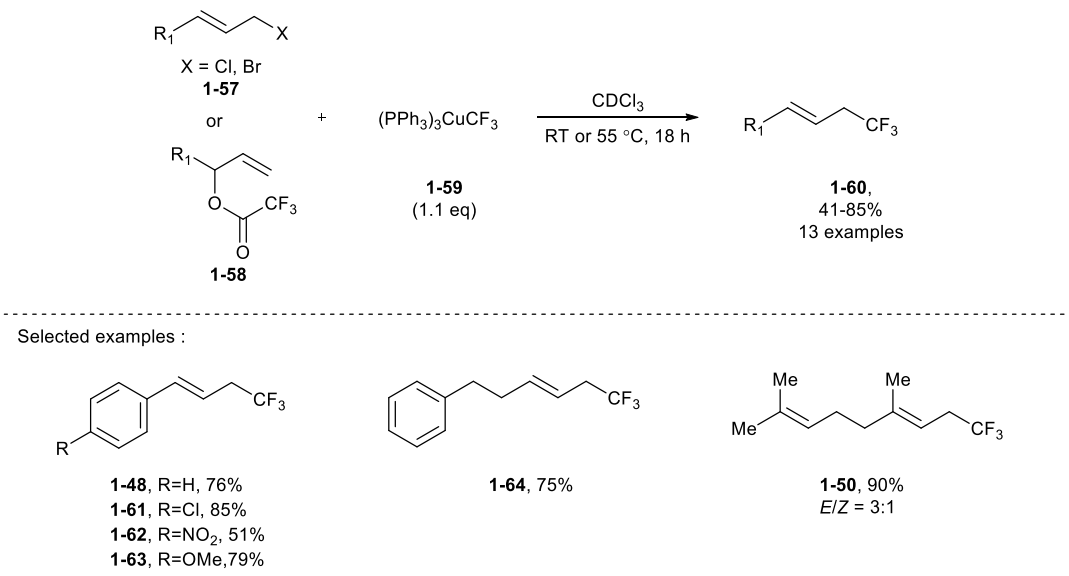


Scheme 1.19 Nucleophilic trifluoromethylation using Et_3SiCF_3

This procedure using a nucleophilic silicon based trifluoromethylation reagent, such as Et_3SiCF_3, for the synthesis of $CuCF_3$ had distinct advantages over the previously reported methods, which used either toxic heavy metals like Cd and Hg, or gaseous reagents under high pressure.

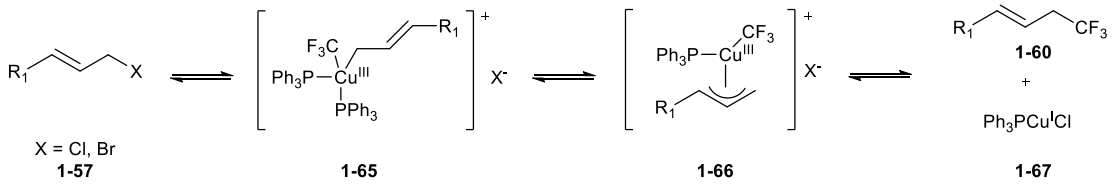
In 2013 the Grushin group reported the synthesis of the $(PPh_3)_3CuCF_3$ complex **1-59** from the reaction of Me_3SiCF_3, $CuF_2.3H_2O$ and PPh_3 in MeOH. The complex was found to be oxygen-sensitive in solution, but stable to air and moisture in the solid state, and could be

used successfully in aromatic trifluoromethylation reactions.[36i] Szábo showed the application of reagent **1-59** as an effective trifluoromethylation reagent for allylic halides **1-57**, and branched allylic trifluoroacetates **1-58**.[49] The reaction provided linear allylic trifluoromethylated products in good yield, regardless of the geometry of the starting material. Branched allylic trifluoroacetate precursors **1-58** were less reactive, and only reacted at elevated temperatures (55 °C).



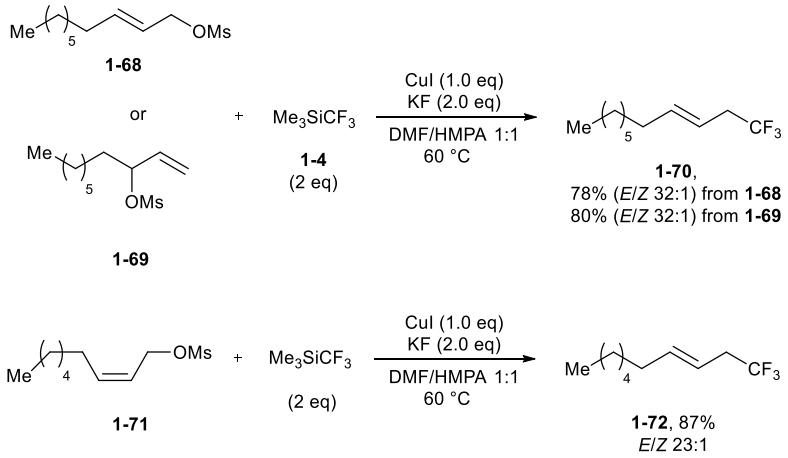
Scheme 1.20 Nucleophilic allylic trifluoromethylation using $(PPh_3)_3CuCF_3$

Based on further experiments, a mechanism involving formation of a Cu-allyl species was postulated (Scheme 1.21). Additional Ph_3P was found to inhibit the reaction, which suggested that dissociation of the phosphine was necessary to initiate the reaction. The formation of Cu-allyl species **1-65**, which could rearrange to the η^3-allyl species **1-66**, was proposed to explain the formation of linear trifluoromethylated products from branched starting materials.



Scheme 1-24 Proposed formation of Cu-allyl complexes

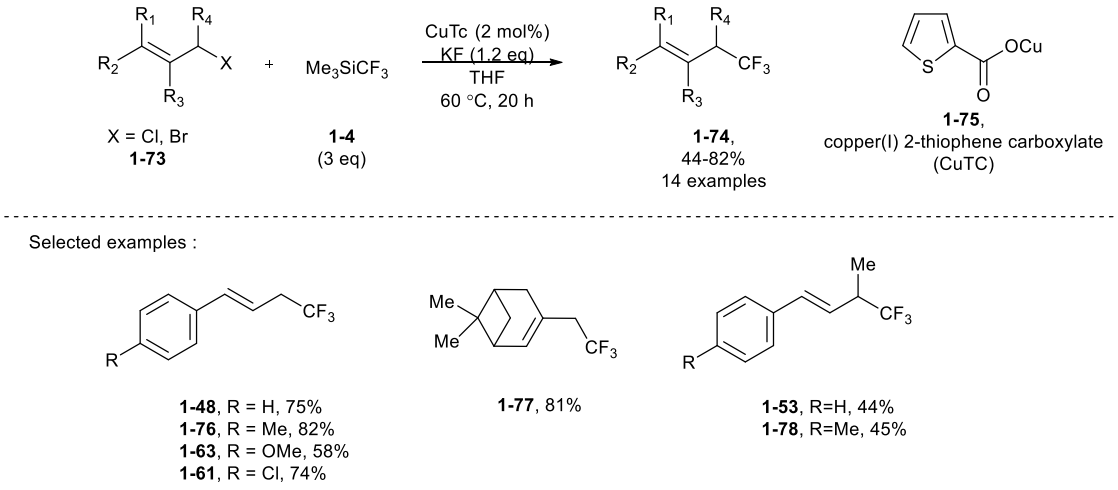
Formation of a Cu-allyl species was also proposed by the group of Qing, based on the experimental outcome of the trifluoromethylation of allylic mesylates **1-68**, **1-69** and **1-71** using the Me_3SiCF_3/KF/CuI system, in a mixture of DMF/HMPA as solvent.[50] Their results showed that both linear and branched allylic mesylates **1-69** and **1-71** provided the linear trifluoromethylated allylic product **1-70** in good yield, and with high selectivity for the *E*-isomer (*E*/*Z* ratio 32:1). The *Z*-isomer **1-71** also provided the *E*-isomer of the allylic trifluoromethylated product with high regioselectivity and *E*/*Z* ratio (23:1).



Scheme 1.22 Nucleophilic trifluoromethylation of allylic mesylates

The group of Nishibayashi reported the first Cu(I)-catalysed nucleophilic allylic trifluoromethylation (Scheme 1.23).[51] They found copper(I) thiophene-2-carboxylate **1-75** to be an efficient catalyst, which could be used at a low loading (2 mol%) in the trifluoromethylation of primary and secondary linear allylic chlorides and bromides. Further mechanistic experiments were again in favour of formation of a Cu-allyl

intermediate. The solvent THF was found to be crucial, as reaction in more polar solvents such as DMF gave only low yields of allylic trifluoromethylated products. The authors proposed that complexation of DMF to the Cu-allyl intermediate inhibited turnover of the copper catalyst.



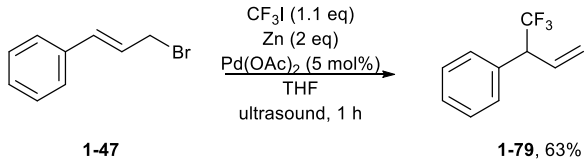
Scheme 1.23 Nucleophilic allylic trifluoromethylation using catalytic copper

All of the methods described in this section provide linear allylic trifluoromethylated products in generally good yields, regardless of the geometry of the starting functionalised allylic synthons. In general, a Cu(I) salt in combination with a nucleophilic CF_3 source is used as the trifluoromethylating reagent. From a limited amount of mechanistic research it has been suggested that $CuCF_3$ is formed as the active trifluoromethylating reagent, with Cu(III)-allyl species being proposed as important intermediates. To date, more detailed studies of this mechanism have not been reported.

1.4.2 Branched Allylic trifluoromethylation From Pre-functionalised Allyl-Synthons

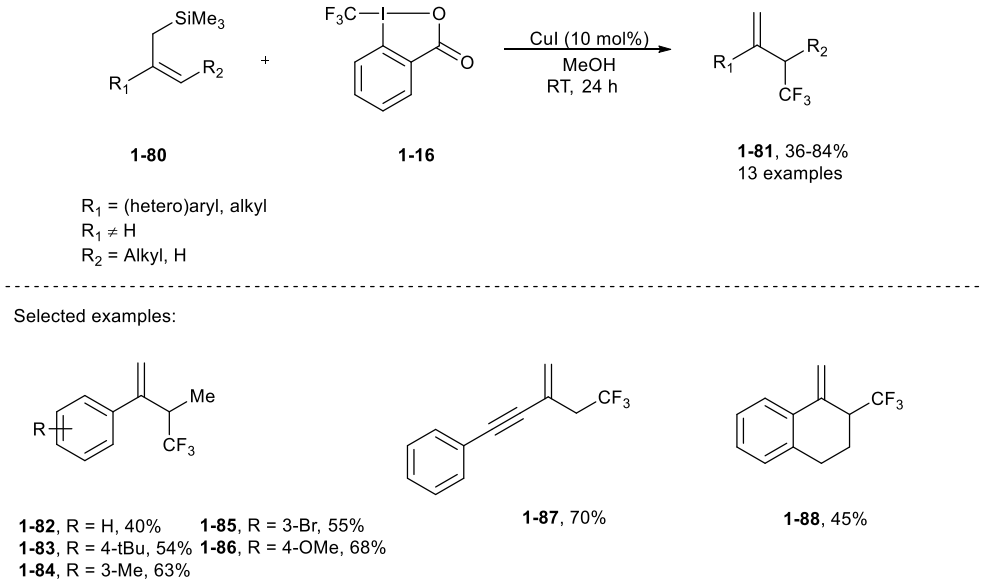
The synthesis of branched allylic trifluoromethylated compounds has received much less attention in comparison with the synthesis of linear products. In 1982, Ishikawa reported the synthesis of branched allylic trifluoromethyl compound **1-79** from the linear allylic

bromide **1-47** using $Pd(OAc)_2$ as a catalyst.[52] The trifluoromethyl group was regioselectively introduced on the benzylic position. A combination of CF_3I and Zn metal was proposed to form $[CF_3ZnI]$ as the active trifluoromethylating reagent, and ultrasonic irradiation was necessary for the reaction to proceed. The authors proposed a Pd(0) species, generated from reduction via $Pd(OAc)_2$ by zinc, as the true catalyst, but did not comment further on the regioselectivity for formation of branched products, which is in marked contrast with the formation of linear trifluoromethylated allylic products using Cu(I) salts (see previous section).



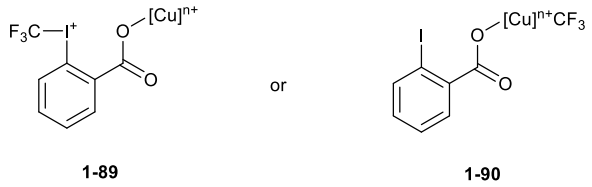
Scheme 1.24 Palladium catalysed allylic trifluoromethylation

With the exception of an isolated example of $Pd(PPh_3)_4$ catalysed trifluoromethylation of allyl tributyltin using CF_3I in low yield (24%),[53] a method for the synthesis of branched allylic trifluoromethylated compounds was not reported until 2012. In this year the group of Sodeoka reported the regioselective trifluoromethylation of allylsilanes, providing branched allylic trifluoromethylated products **1-81** in moderate to good yield.[54] The method showed the trifluoromethylation of allylsilanes **1-80** using CuI as a catalyst, in combination with the Togni II reagent **1-16** as trifluoromethyl source, in MeOH at room temperature (Scheme 1.26). It was found that α-substituted trifluoromethylated products such as **1-88** were obtained in moderate yields. The reaction did not proceed when allylsilanes without a substituent in the β-position were used ($R_1 \neq H$ in Scheme 1.26).



Scheme 1.26 Cu(I) catalysed trifluoromethylation of allylsilanes

A mechanism was proposed involving electrophilic attack of a CF_3^+ type intermediate **1-89** or **1-90**, generated from the combination of Cu(I) and the Togni II reagent (Scheme 1.26), leading to formation of a stabilised β-silylcarbocation (for more details see section 2.1.1), but no experimental data was given to support this proposal.



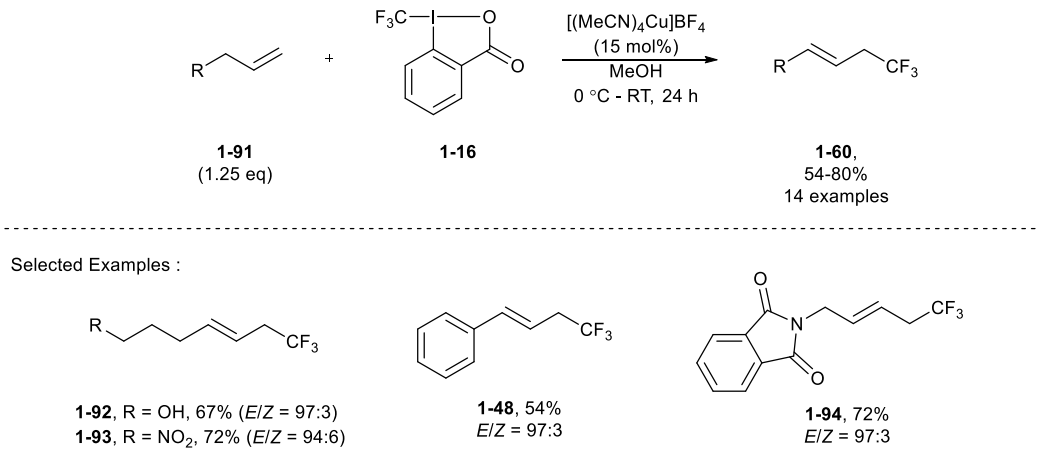
Scheme 1.25 Proposed intermediate

Almost simultaneously, the trifluoromethylation of allylsilanes using CuCl and the Togni II reagent providing branched allylic trifluoromethylated products was reported by the group of Gouveneur.[55] A detailed analysis of this method and the proposed mechanism is given in the next chapter (section 2.1.1).

1.4.3 Allylic C-H Trifluoromethylation

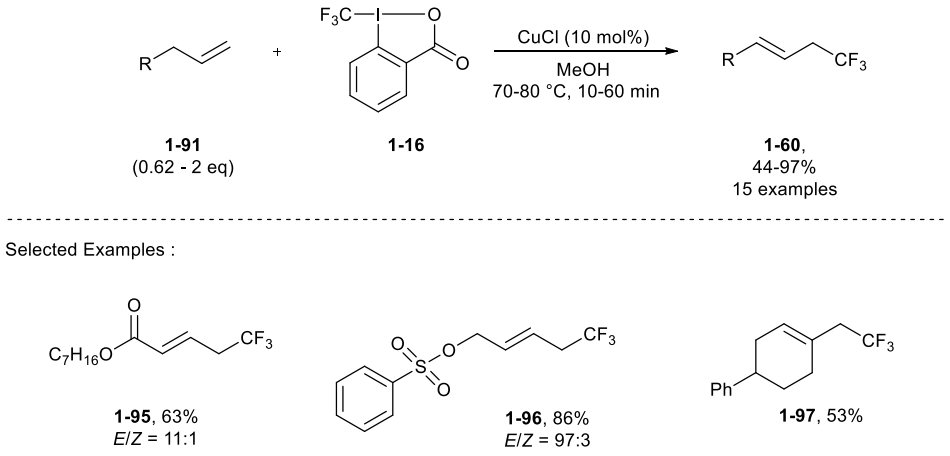
The allylic C-H trifluoromethylation of unfunctionalised alkene precursors was simultaneously reported by the groups of Buchwald[56], Wang[57] and Liu and Fu[58]. All three methods involve of the use of an electrophilic trifluoromethylating reagent in combination with a Cu(I) catalyst.

The group of Buchwald reacted a small excess of allylic precursor **1-91** (1.25 eq) with the Togni II reagent **1-16** (1.0 eq), using $[(MeCN)_4Cu]BF_4$ (15 mol%) as catalyst in MeOH at room temperature (Scheme 1.27). A range of of linear allylic trifluoromethylated compounds **1-60** was obtained in moderate to good yield (54-80%) with good selectivity for the *E*-isomer (*E*/*Z* = 89:11 to 97:3). The method showed a good functional group tolerance, and reactive functionalities such as free hydroxyl groups and epoxides were tolerated under the reaction conditions. It was found that the major side-products formed during the reaction contained two CF_3 groups, and that these products could not be separated from the desired product by silica gel chromatography. For this reason a slight excess of alkene was used, which reduced the formation of by-products to less than 5%, but afforded slighty lower yields of product.



Scheme 1.26 Allylic C-H trifluoromethylation reported by Buchwald

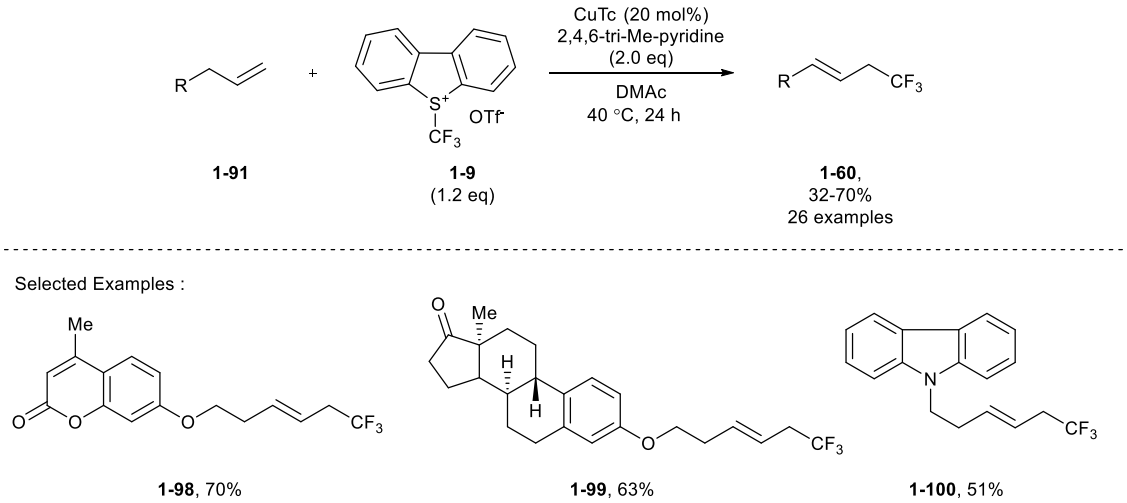
Wang et al reported allylic C-H trifluoromethylation under similar reaction conditions, using CuCl (10 mol%) as catalyst, in combination with the Togni II reagent **1-16** in MeOH. The reaction was performed at 70 °C, and provided the linear allylic trifluoromethylated products in good yields (44-97%). To obtain these yields, the ratio of alkene and Togni II reagent needed to be optimised for every substrate. In most cases an excess of alkene was required. Cyclic alkenes could successfully be trifluoromethylated using a higher temperature (80 °C), and a higher loading of CuCl (20 mol%), although yields were generally lower (44-53%). This type of alkene did not react under the conditions reported by Buchwald.



Scheme 1.28 Allylic C-H trifluoromethylation Wang

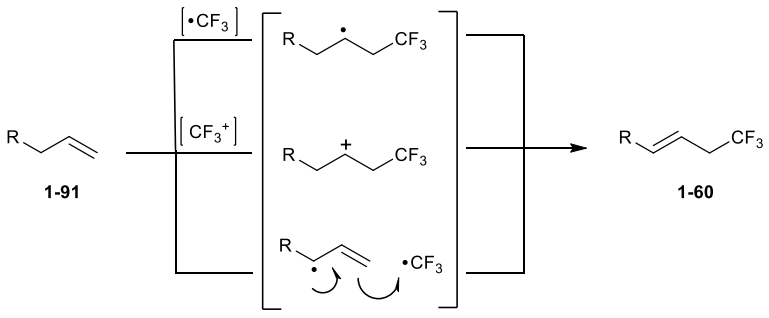
The method developed by Lui and Fu *et al* used a slightly different approach, which was based on conditions from their previously reported method for trifluoromethylation of aryl and vinylboronic acids using a similar reagent combination.[59] Their allylic C-H trifluoromethylation method utilised the Umemoto reagent **1-9** as trifluoromethyl source, in combination with copper(I) thiophene-2-carboxylate **1-75** (20 mol%) as catalyst and 2,4,6-trimethylpyridine (2.0 eq) as ligand. The reactions were stirred for 24 h at 40 °C in DMA, and provided the trifluoromethylated products **1-60** in 32-70% yield. As side-products, vinylic trifluoromethylated products (see Scheme 1.34 further on this section)

and hydrotrifluoromethylated products were formed in up to 10% yield, depending on the substrate. These side-products could not be readily separated from the desired product by silica gel chromatography.



Scheme 1.29 C-H allylic trifluoromethylation

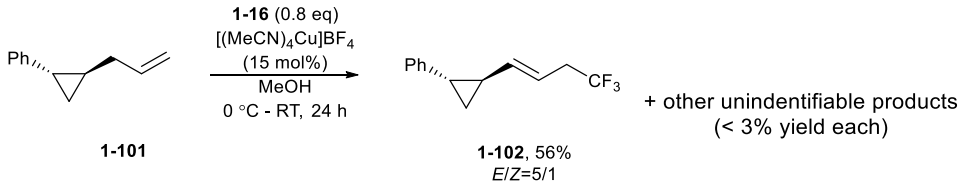
The group of Buchwald proposed three possible mechanistic pathways by which the C-H allylic trifluoromethylation could occur (Scheme 1.30). They envisioned that addition of either a CF_3 radical, or a cationic CF_3 species to the allylic substrates could provide the trifluoromethylated product. A third suggested pathway involved the recombination of the CF_3 radical with an allylic radical.



Scheme 1.30 Mechanistic manifolds for allylic C-H trifluoromethylation

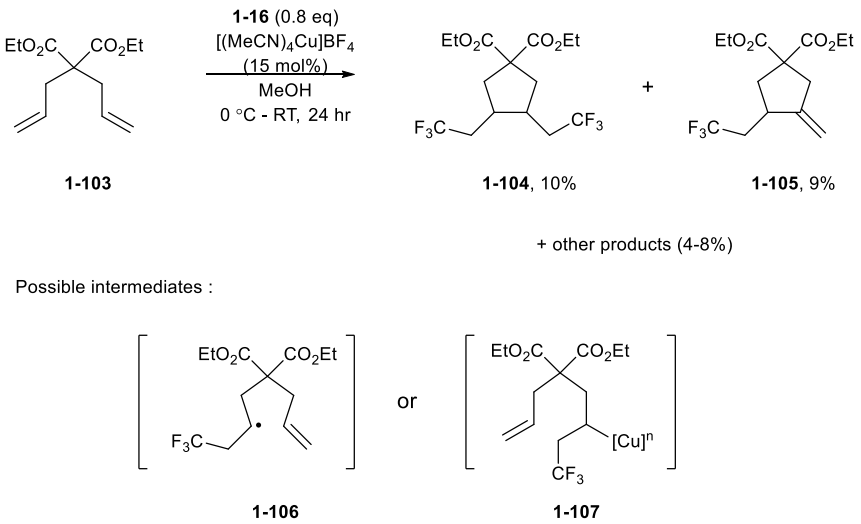
To investigate the possibility of formation of an allylic radical, the cyclopropyl substrate **1-101** was subjected to the trifluoromethylation conditions. Formation of the allylic radical in

substrate **1-101** would be expected to lead to ring opened trifluoromethylated products (see Chapter 2 Section 2.1.1 for a more detailed explanation). The cyclopropyl-containing trifluoromethylated product **1-102** was obtained in 56% yield, with formation of several unidentified trifluoromethylated side-product in 3% yield each. Based on this result, the authors suggested that formation of an allyl radical intermediate was unlikely, but could not be completely ruled out due to the presence of unindentifiable side-products.



Scheme 1.31 Mechanistic investigation into the formation of an allylic radical

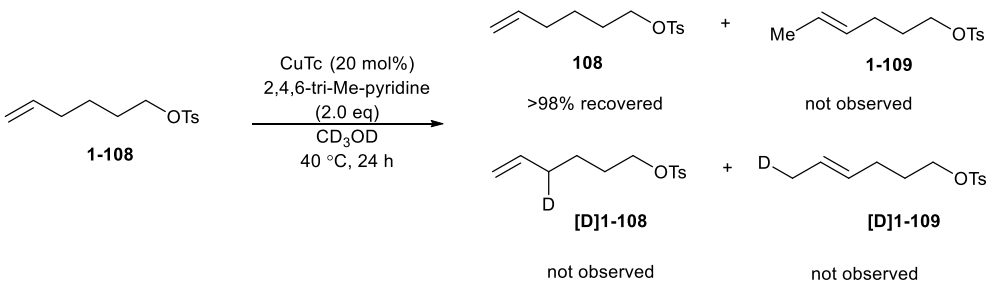
Further mechanistic experiments were conducted to investigate the possibility of product formation via addition of a CF_3 radical to the allylic substrate. To this end, the trifluoromethylation reaction was performed using diene **1-103** as a substrate (Scheme 1.32). Formation of radical **1-06** would result in facile 5-*exo*-trig cyclisation, from which cyclised trifluoromethylated products were expected to form (see Chapter 3, section 3.6.1 for a more detailed explanation). A mixture of products was obtained in low yield, from which the cyclised products **1-104** and **1-105** could be isolated as major components. This result indicated that a 5-*exo*-trig cyclisation did take place, but the low yield and mixture of products precluded any conclusion on the formation of a radical **1-106**, or alkylcopper-species **1-107** as intermediate.



Scheme 1.32 Mechanistic investigation into the formation of a CF_3-radical intermediate

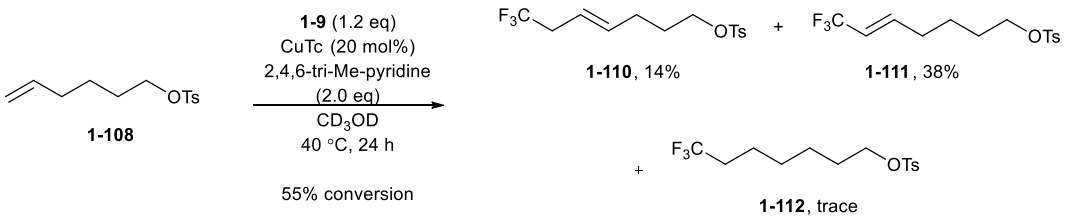
Experiments with several different radical inhibitors (not shown) did not give clear results, upon which the authors concluded that the mechanism was complex, and that further experiments would be necessary to elucidate the mechanistic pathway. This same conclusion was reached by the group of Wang on the basis of experiments with TEMPO as a radical inhibitor.

The group of Liu and Fu investigated the possible formation of a Cu-allyl intermediate. When the reaction of **1-108** was performed in CD_3OD without addition of the trifluoromethylating reagent, the starting material was recovered in >98% yield (Scheme 1.33). The absence of any isomerised product **1-109** and deuterated products **[D]1-108** and **[D]1-109** provided evidence against formation of a Cu-allyl intermediate under these conditions.



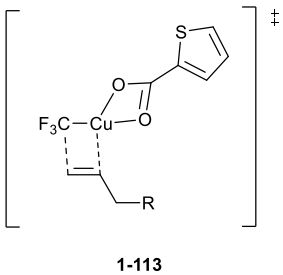
Scheme 1.33 Reaction of **1-108** in CD_3OD without added trifluoromethylating reagent

The reaction was also performed using the Umemoto reagent **1-9** (1.2 eq) and substrate **1-108** in CD_3OD (Scheme 1.34). This experiment resulted in formation of the vinylic trifluoromethylated product **1-111** as major product, in addition to formation of the expected product **1-110**, and a trace of the hydrotrifluoromethylated product **1-112**. Although the different ratio of products in comparison with the reaction in DMA as solvent could not be explained, further analysis did not show any formation of deuterated products, which was taken as additional evidence that a Cu-allyl intermediate was not formed under the reaction conditions.



Scheme 1.34 Allylic trifluoromethylation of **1-108** in CD_3OD

After performing DFT calculations a different mechanism was suggested by the authors, which was based on Cu-catalysed C-H activation with formation of a Heck-like four-membered ring transition state such as **1-113** (Scheme 1.35).

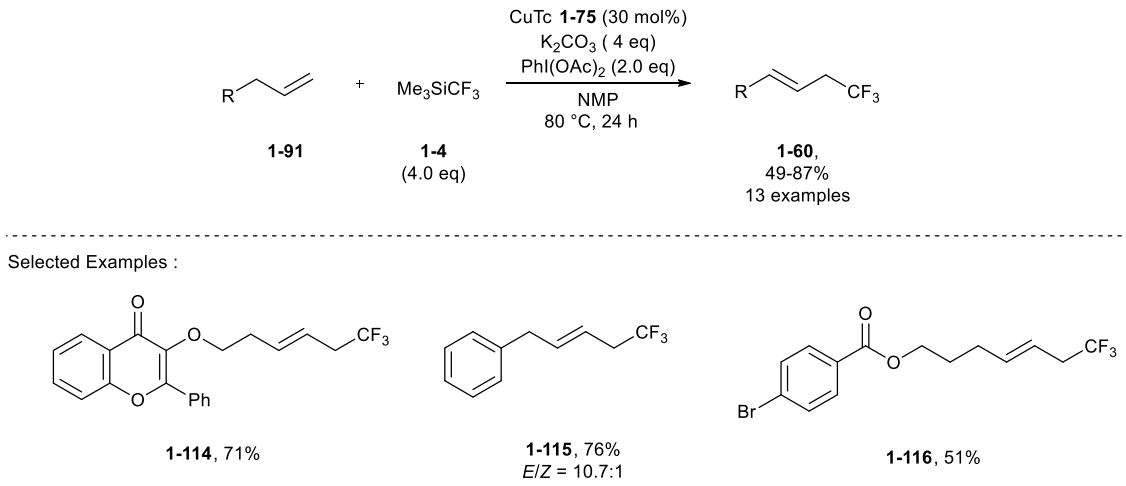


Scheme 1.35 Four membered Heck-like transition state

Despite the efforts of the groups of Buchwald, Wang and Lui and Fu, there is still much uncertainty about the mechanism of the Cu-catalysed allylic trifluoromethylation reaction.

1.4.4 Oxidative Allylic C-H Trifluoromethylation

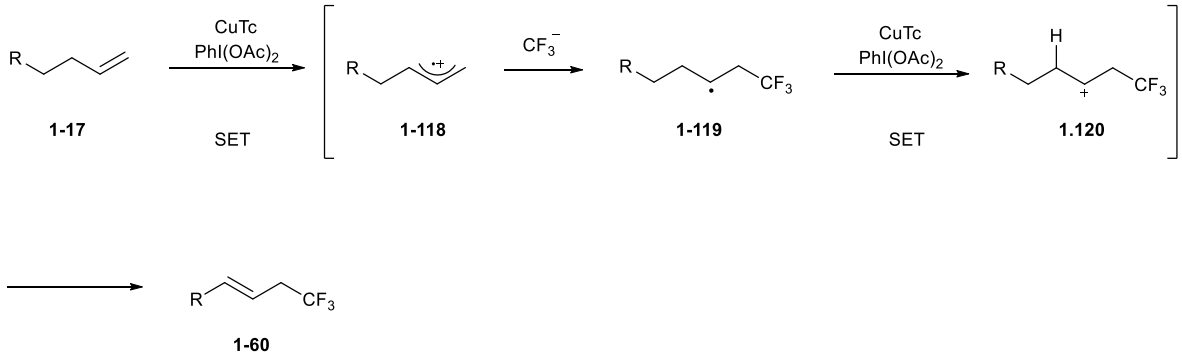
The use of the nucleophilic trifluoromethylating reagent Me_3SiCF_3 for allylic C-H trifluoromethylation was reported by the group of Qing (Scheme 1.36).[60] Allylic precursors **1-91** were treated with Me_3SiCF_3 **1-4** (4.0 eq) in the presence K_2CO_3 (4.0 eq), the oxidant $PhI(OAc)_2$ (2.0 eq), and a catalytic amount of CuTc **1-75** (30 mol%) in NMP at 80 °C, and provided the linear allylic trifluoromethylated products in moderate to good yields (49-87%). The scope of this method is similar to the allylic C-H trifluoromethylation methods mentioned in the previous section, with the exception that sensitive functional groups such as halides and epoxides were not tolerated under the reaction conditions.



Scheme 1.36 Oxidative C-H trifluoromethylation using Me_3SiCF_3

Analysis by ^{19}F NMR during the reaction did not show formation of peaks related to hypervalent iodine(III)-CF_3 species such as $PhI(OAc)CF_3$ (the product of the reaction of Me_3SiCF_3 and $PhI(OAc)_2$), which led to the conclusion this intermediate was not involved in the trifluoromethylation reaction. Experiments using either TEMPO or BHT as additive resulted in complete inhibition of the trifluoromethylation reaction, suggesting that radical intermediates were involved. In the reaction using TEMPO as an additive, no evidence was found for formation of either the TEMPO-CF_3 or TEMPO-allyl adduct, which possibly

ruled out a CF_3 radical or allyl radical as intermediate. Based on these results, the authors suggested a mechanism involving of formation of a radical cation intermediate **1-118**. This intermediate radical cation was proposed to form from SET to the alkene, involving the Cu-catalyst and $PhI(OAc)_2$ (Scheme 1.37). Reaction of this radical cation with the CF_3 anion, generated from Me_3SiCF_3, would then provide trifluoromethylated alkyl radical **1-119**. Oxidation of this radical by another SET would provide the cationic intermediate **1-120** which would afford the allylic trifluoromethylated product **1-60** upon elimination of a proton.

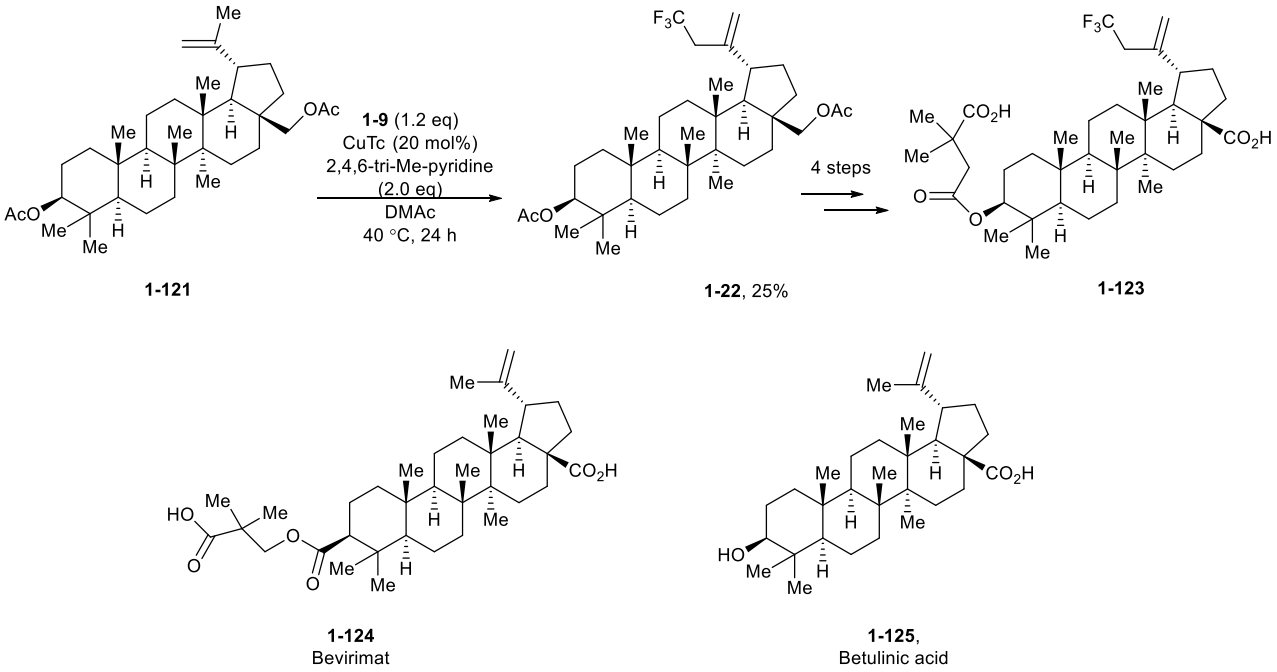


Scheme 1.37 Suggested mechanism for oxidative allylic C-H trifluoromethylation

1.4.5 Late-Stage Trifluoromethylation using C-H Allylic Trifluoromethylation

The discovery of new methods for allylic C-H trifluoromethylation opens up possibilities for synthesis of complex molecules through late-stage trifluoromethylation. The use of non-functionalised allylic precursors in this methodology is a distinct advantage, which often allows simplified synthesis in a reduced number of steps. The synthesis of a trifluoromethylated analogue of Bevirimat **1-124**, an anti-HIV drug based on betulinic acid **1-125**, is an example of this strategy (Scheme 1.38).[61] In this example, the protected betulinic acid precursor **1-121** could be trifluoromethylated on the allylic position in 25% yield, using allylic C-H trifluoromethylation methodology developed by Liu and Fu.[58] Deprotection, and installation of the side-chain then provided a trifluoromethylated

analogue of Bevirimat **1-120**, which showed similar anti-HIV activity as Bevirimat **1-123** itself.



Scheme 1.38 Synthesis of trifluoromethylated Beltanivir analogue

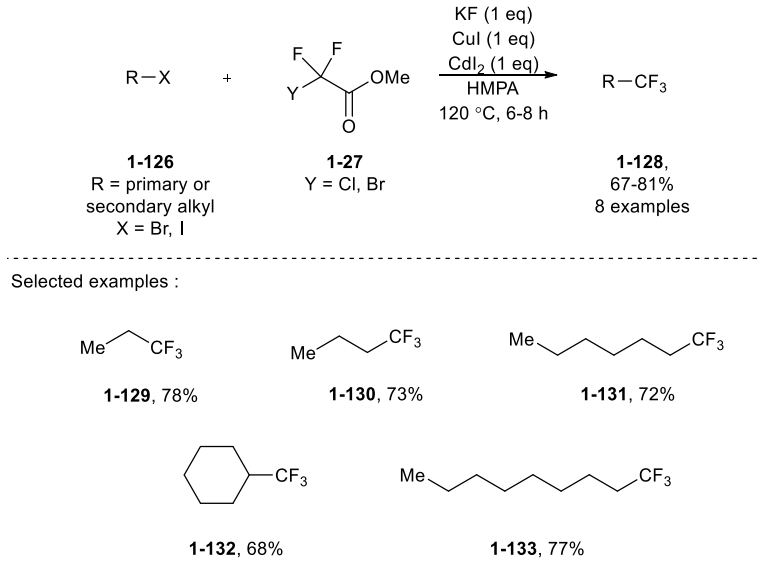
This example shows that late-stage trifluoromethylation of complex substrates can be a valuable strategy for the synthesis of new trifluoromethylated bioactive compounds and allows for fluorination of highly functionalised substrates.

1.5 Synthesis of Alkyl Trifluoromethyl Compounds

The formation of a Csp^3-CF_3 bond in alkyl trifluoromethyl compounds can be challenging due to the difficulty in generating a suitable, reactive nucleophilic or electrophilic trifluoromethylating species. Although many methods have been developed for the trifluoromethylation of activated substrates such as ketones and imines,[62] the synthesis of the Csp^3-CF_3 bond from unactivated precursors is far less common.

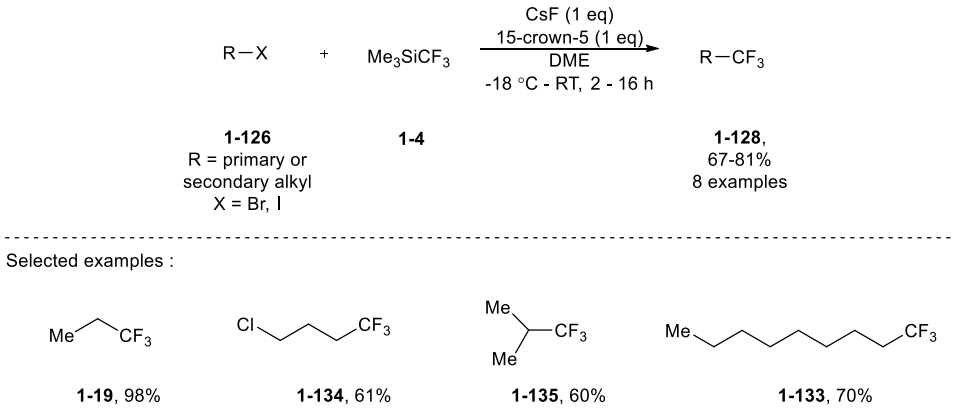
1.5.1 Nucleophilic Trifluoromethylation of Unactivated Alkyl Halides

Kobayashi reported an early, isolated example of trifluoromethylation of *n*-decyl iodide in moderate yield (48%), using a pre-generated $CuCF_3$ reagent in HMPA as solvent.[46] Further development of this methodology was focussed on the trifluoromethylation of more reactive allylic and benzylic halide substrates, and it was not until 1993 that a general method for trifluoromethylation of unactivated alkyl halides was developed by the group of Cheng (Scheme 1.39).[63] This method was based on the reaction of primary and secondary alkyl bromides and iodides with in-situ generated $[CF_3CuI]^-$ in HMPA, and provided the trifluoromethylated compounds in good yields. Alkyl bromides were found to be less reactive than the corresponding iodides, and under identical conditions alkyl chlorides did not provide any product. It was found that both CuI and CdI_2 were essential for the reaction to proceed, and the authors proposed a mechanism with formation of $[CF_3CuI]^-$ from CuI and the CF_3 anion. The CF_3 anion was proposed to be generated from the reaction of difluorocarbene (formed through decarboxylation of **1-127** with I^-) with F^-.



Scheme 1.39 Trifluoromethylation of alkyl halides using in-situ generated $CuCF_3$

The trifluoromethylation of alkyl halides without a transition metal additive was reported in 2007 by Tyrra and co-workers (Scheme 1.40).[64] A combination of Me_3SiCF_3 with a fluoride source (CsF/15-crown-5) was used as a nucleophilic trifluoromethylation reagent, in DME at low temperature (-18 °C). Trifluoromethylation of primary and secondary alkyl bromides and iodides proceeded in moderate to good yields (67%-81%). The reaction was very sensitive to the solvent and temperature used, and careful control of the conditions was necessary to avoid formation of alkenes and CF_3H as major products. Tertiary alkyl halides as well as secondary alkyl bromides could not be successfully trifluoromethylated, instead providing alkenes as main products.

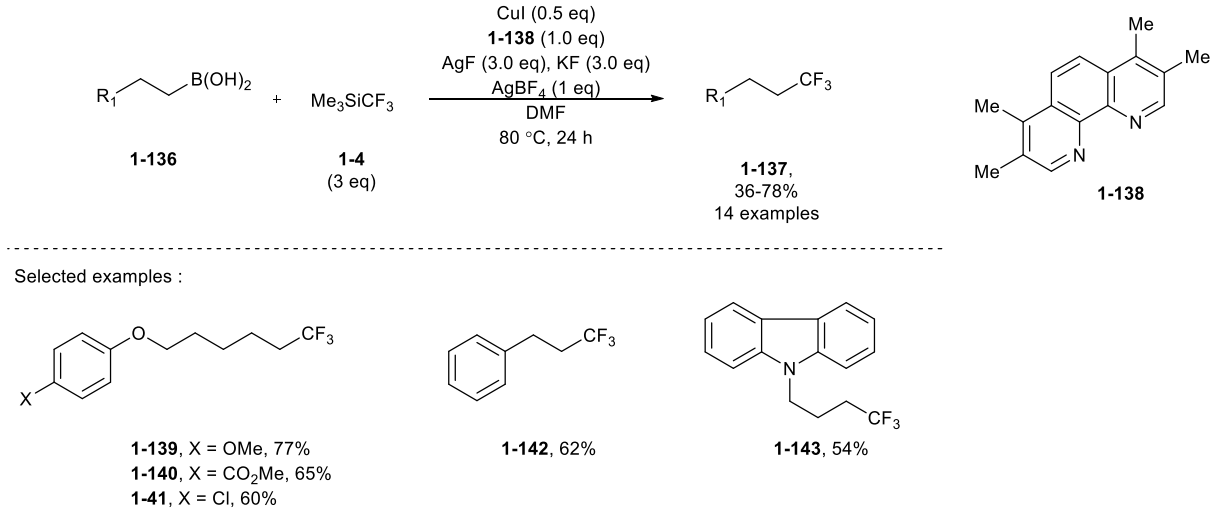


Scheme 1.40 Trifluoromethylation of alkylhalides using Me_3SiCF_3

1.5.2 Trifluoromethylation of Alkyl Boronic Acids

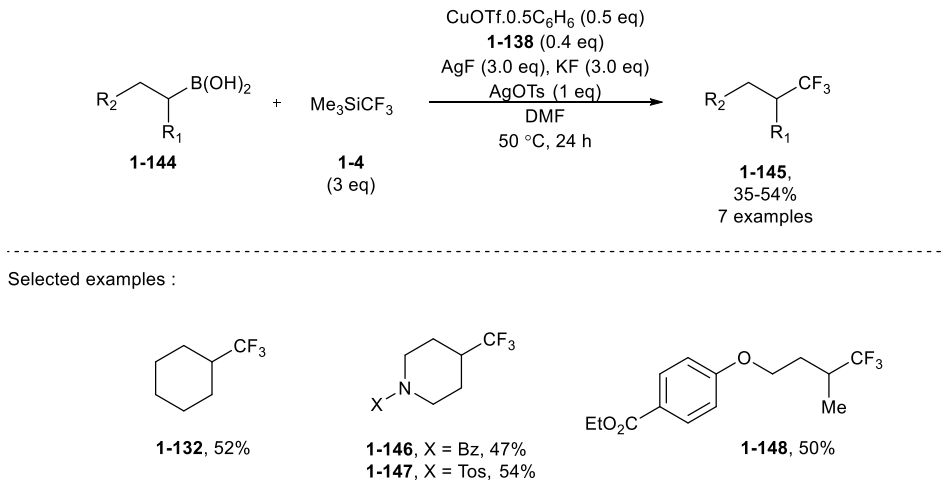
Primary and secondary alkyl boronic acids have also been used as substrates for the synthesis of aliphatic trifluoromethylated compounds. This challenging transformation was reported by the group of Yao Fu in 2012 (Scheme 1.41).[65] Primary alkylboronic acids were reacted with Me_3SiCF_3 as a nucleophilic trifluoromethylating reagent, in combination with substoichiometric amounts of CuI and the electron-rich phenanthroline ligand **1-138** in DMF, and provided the trifluoromethylated products in moderate to good yields (36-77%). Further screening showed $AgBF_4$ and KF as the most efficient oxidant and base. The role of AgF as an additive was not explained. Under these conditions, the amount of side-

products formed through beta-hydride elimination and proto-deborylation were lowest (<20%).



Scheme 1.41 Cu(I) mediated trifluoromethylation of primary alkylboronic acids

When secondary alkylboronic acids were used as substrates under the same conditions, the formation of elimination and proto-deboration products became the major reaction. Re-optimisation of the reaction conditions resulted in the use of CuOTf.0.5C_6H_6 (10 mol%) as the copper source, in combination with the ligand **1-138** (40 mol%) and AgOTs (1 eq) as the oxidant, at a slightly lower temperature (50 °C) in DMF as solvent. Under these conditions the secondary trifluoromethylated products were obtained in 35-54% yield (Scheme 1.42). There was no information given on the proposed mechanism of these transformations.

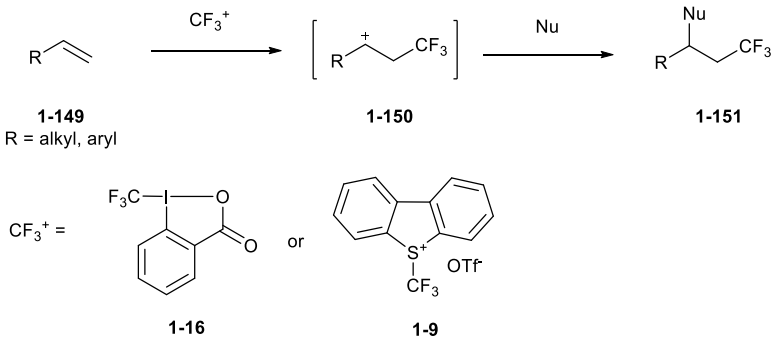


Scheme 1.42 Cu(I) mediated trifluoromethylation of secondary alkylboronic acids

The trifluoromethylation of alkylboronic acids shows a good functional group tolerance and is an interesting method for the synthesis of aliphatic trifluoromethylated compounds through late-stage trifluoromethylation. The trifluoromethylation of secondary alkyl boronic acids could in theory be used for introduction of stereogenicity, although more research needs to be done to understand the mechanism of this transformation.

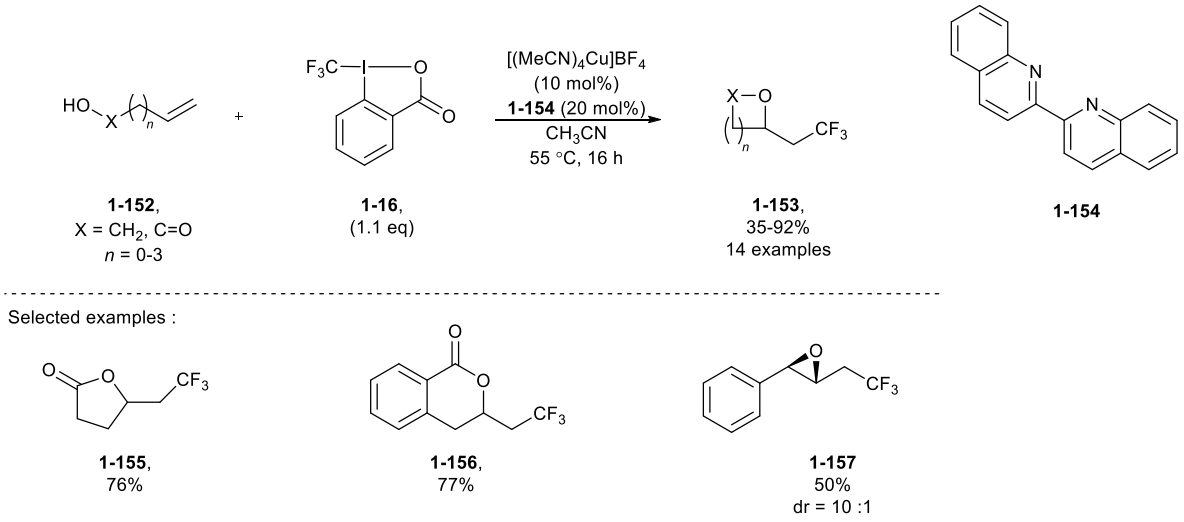
1.5.3 Oxytrifluoromethylation of Alkenes and Related Reactions

The development of methodology for trifluoromethylation of alkenes using electrophilic trifluoromethylating reagents, such as the Togni II reagent **1-16** and Umemoto reagent **1-9** (see previous sections) has resulted in new methods for the synthesis of β-functionalised primary alkyl trifluoromethyl compounds. A formal synthesis of this type is shown in Scheme 1.43. Synthesis of β–oxygen functionalised trifluoromethyl compounds from alkenes using water or other *O*-nucleophiles, also called oxytrifluoromethylation, is a powerful method to access a variety of new trifluoromethylated compounds.



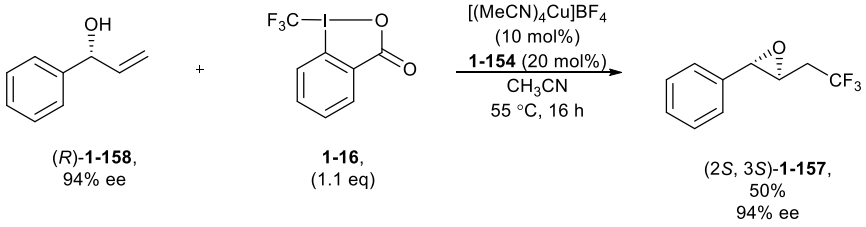
Scheme 1.43 Formal synthesis of β-functionalised primary alkyl trifluoromethyl compounds

Following the development of a method for allylic trifluoromethylation of alkenes,[56] the group of Buchwald reported a Cu(I)-catalysed oxytrifluoromethylation of unactivated alkenes based on a similar strategy (Scheme 1.44).[66] This transformation uses a catalytic system based on $[(MeCN)_4Cu]BF_4$ (10 mol%) and *bis*-quinolyl ligand **1-154** (20 mol%), which successfully favours the formation of the cyclised trifluoromethylated product **1-153** over the allylic trifluoromethylation product. The reaction uses a range of alcohol, phenol or carboxylic acid substituted terminal alkenes **1-152** as starting materials, in combination with the Togni II reagent **1-16** (1.1 eq) as trifluoromethyl source in CH_3CN. The three to six membered ring cyclised trifluoromethylated products **1-153** are provided in moderate to good yield (35-92%), with good functional group tolerance.



Scheme 1.44 Cu(I)-catalysed oxytrifluoromethylation of alkenes

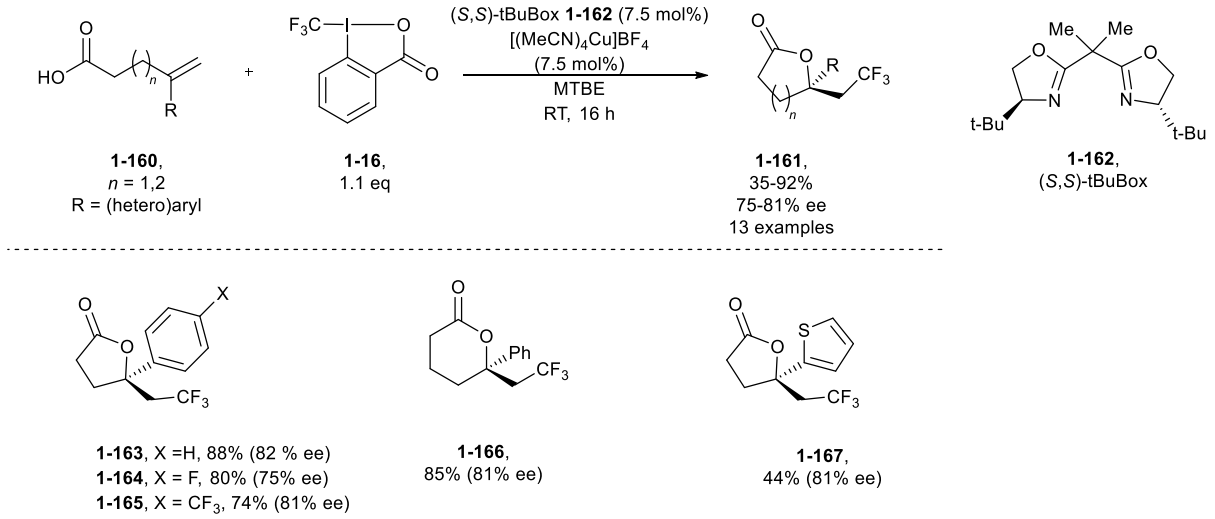
It was found that the reaction of enantioenriched alcohol **1-158** provided the corresponding cyclised trifluoromethyl ether **1-159** without erosion of the enantiomeric excess (Scheme 1.45).



Scheme 1.45 Transfer of chirality

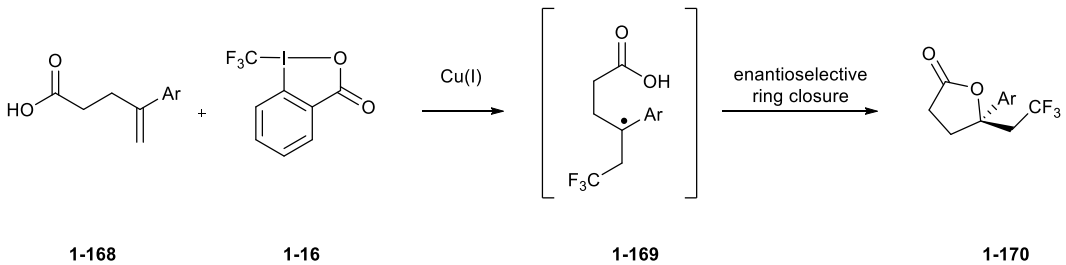
This discovery showed the potential of this methodology for introduction of stereogenicity, and led to the development of an enantioselective oxytrifluoromethylation process (Scheme 1.46). After optimisation with several different types of chiral *bis*-oxazolidine ligands, the use of chiral (*S*,*S*)-*t*-BuBox **1-162** (7.5 mol%), in combination with $[(MeCN)_4Cu]BF_4$ (7.5 mol%) was found to be most effective. The solvent had a significant influence on the enantioselectivity, and ethers were found to be superior to other types of solvents, with MTBE providing the best results. Under these conditions a range of (hetero)aryl substituted unsaturated acids **1-160** could be transformed into the

corresponding chiral trifluoromethylated lactones **1-161**, in moderate to good yields (35-92%) with good enantiomeric excess (75-81% ee).



Scheme 1.46 Enantioselective oxytrifluoromethylation of alkenes

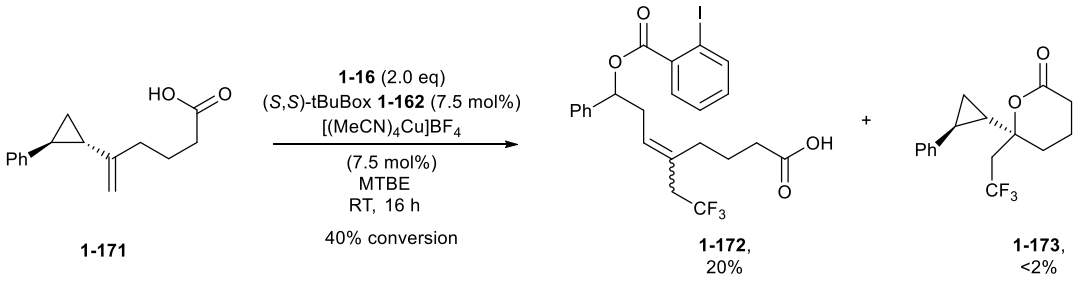
The authors proposed a mechanism involving addition of a CF_3-radical, generated from SET of the Cu(I) catalyst to the Togni II reagent **1-16**, to the alkene, providing radical intermediate **1-169**. This intermediate would then be trapped by the carboxylic acid nucleophile in an enantioselective cyclisation step.



Scheme 1.47 Proposed mechanism

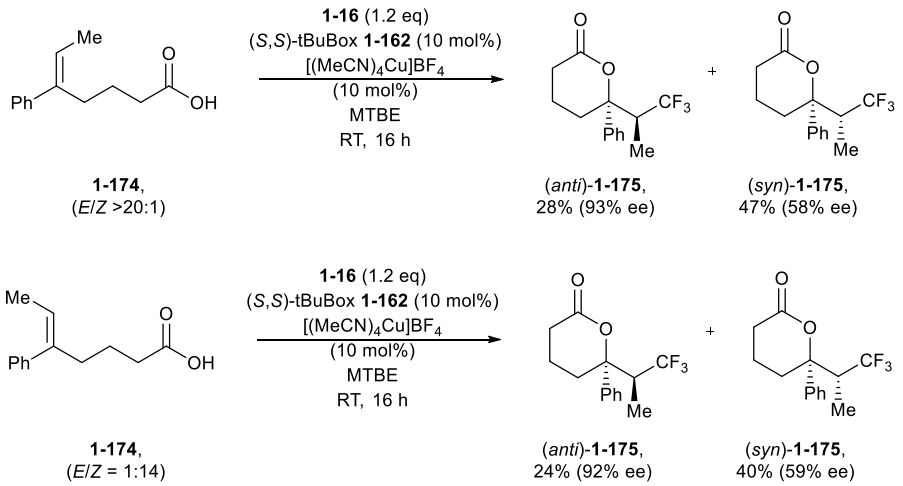
To investigate the presence of a radical intermediate such as **1-169**, the cyclopropyl substituted substrate **1-171** was subjected to the trifluoromethylation reaction conditions (Scheme 1.48). If a radical intermediate formed, this would be expected to provide ring-

opened trifluoromethylated products (see previous section and Section 2.1.1 for a more detailed explanation). The ring-opened trifluoromethylated product **1-172** was isolated as the major product in 20% yield (40% conversion), with formation of only traces of the cyclised product **1-173**. This result is in favour of formation of radical intermediate such as **1-169**.



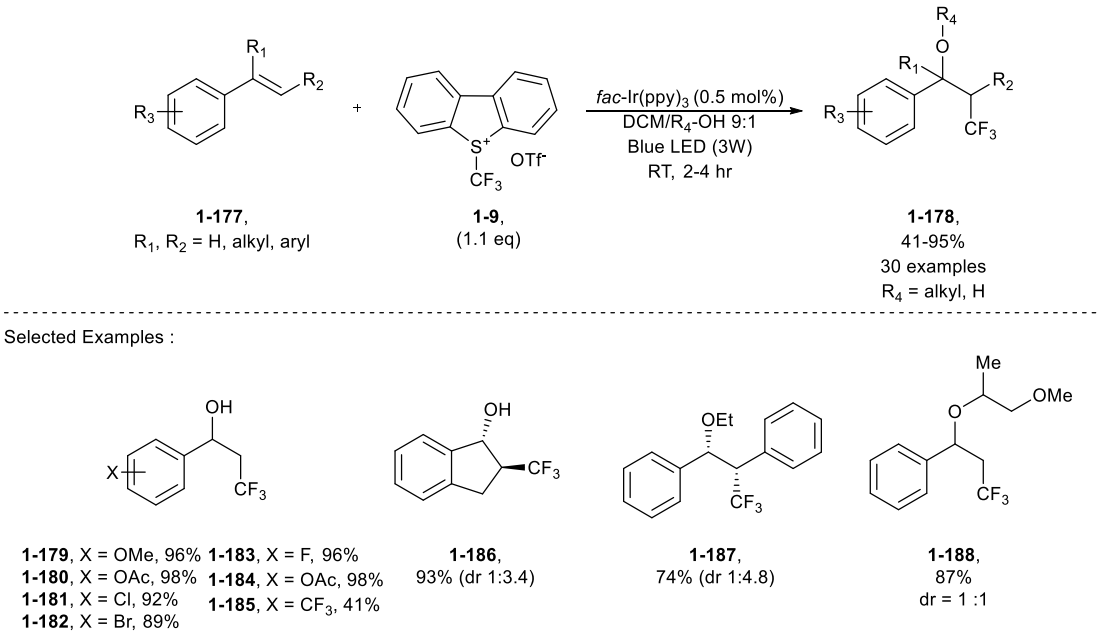
Scheme 1.48 Radical clock mechanistic investigations

Further mechanistic investigations focused on the trifluoromethylation-cyclisation of geometric isomers (*E*)-**1-174** and (*Z*)-**1-174** (Scheme 1.48). It was found that both isomers provided the trifluoromethylated product in a similar enantiomeric and diastereomeric ratio, regardless of double bond geometry. Based on this result, in addition to a further study on the exact ratio of the 4 stereoisomers formed, it was concluded that the trifluoromethylation step does not determine the stereoselectivity, but that the subsequent formation of the C-O bond proceeds in a stereoselective fashion. Further insight in the exact mechanism of the C-O bond formation was not obtained.



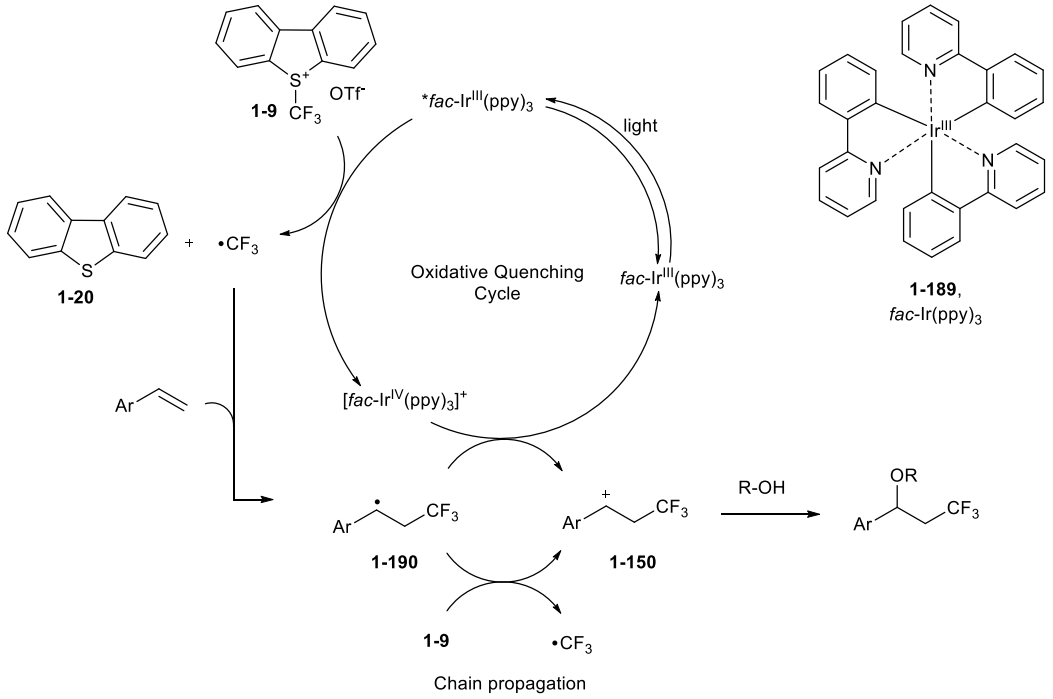
Scheme 1.49 Mechanistic investigations using tri-substituted alkenes

Oxytrifluoromethylation of activated alkenes such as styrenes was reported by the group of Akita and Koike.[67] In this process, the Umemoto reagent is used as the trifluoromethylating reagent in combination with fac-Ir(ppy)$_3$ **1-189** as a photoredox catalyst. The reaction is performed using an excess of the alcohol as the nucleophile, in DCM at room temperature under irradiation of the reaction mixture with blue LEDs. The reactions using H_2O as a nucleophile were performed in acetone as solvent. The mild reaction conditions allow for a good functional group tolerance, and a range of styrenes could be successfully used in this transformation. Unactivated alkenes were found to be unreactive.



Scheme 1.50 Photoredox-catalysed oxytrifluoromethylation of styrenes

The mechanism of this reaction was proposed to proceed by photoredox catalysis with an oxidative quenching cycle (Scheme 1.51). Irradiation of fac-$Ir^{III}(ppy)_3$ **1-189** with blue LEDs provides the exited state *fac-$Ir^{III}(ppy)_3$, which reacts with the Umemoto reagent **1-9** in a SET process to provide the CF_3-radical and the oxidant [fac-$Ir^{IV}(ppy)_3$]. The CF_3-radical then adds to the activated alkene, providing radical intermediate **1-190**. This radical intermediate is oxidized by [fac-$Ir^{IV}(ppy)_3$]$^+$, providing the cationic intermediate **1-150** and fac-$Ir^{III}(ppy)_3$, which completes the catalytic cycle. Trapping of the cationic intermediate **1-150** with the alcohol provides the oxytrifluoromethylated product. Cyclic voltammetry measurements and luminescence quenching experiments were found to be in favour of an oxidative quenching cycle. The possibility of a chain propagation mechanism in which the radical **1-190** is oxidized by the Umemoto reagent **1-9** with subsequent formation of a CF_3-radical could not be excluded.

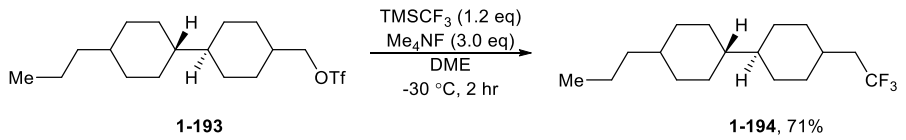


Scheme 1.51 Proposed mechanism of the oxytrifluoromethylation of styrenes

The use of photoredox catalysis in the di-functionalisation of activated alkenes has been extended to a range of other nucleophiles.[26e,31e] For example, the use of nitriles,[68] azides and amines[69] and carbon-nucleophiles[70] in the trifluoromethylation/di-functionalisation of activated alkenes under photoredox conditions have all been reported.

1.5.4 Applications of Aliphatic Trifluoromethylation

The introduction of a trifluoromethyl group on an Csp^3 carbon atom can be a challenging transformation. Traditionally, nucleophilic trifluoromethyl sources such as Me_3SiCF_3 **1-4** in combination with an activator were used, on alkyl halides or triflates as substrates. An example of the use of this methodology for late-stage trifluoromethylation was reported by the group of Kirsch, who developed the trifluoromethylation of alkyl triflates using Me_3SiCF_3 with TMAF as an activator for the synthesis of liquid crystal molecule **1-194** (Scheme 1.52).[71]

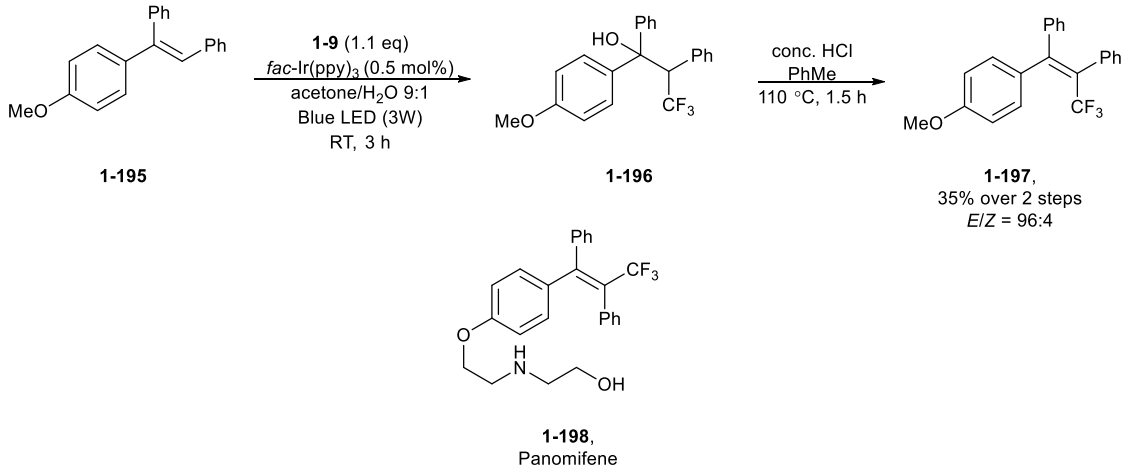


1-193 **1-194**, 71%

Scheme 1.52 Trifluoromethylation of alkyl triflates using Me_3SiCF_3 **1-4**

The development of new methodologies based on transition metal and photoredox catalysis, using ready-available alkylboronic acid and alkene precursors, has broadened the range of accessible aliphatic trifluoromethyl compounds. These methods have also provided new possibilities for the challenging process of stereospecific introduction of a trifluoromethyl group.

An example of the use of photoredox catalysed oxytrifluoromethylation for the synthesis of bioactive compounds was reported by Koike and Akita (Scheme 1.53).[67] Trifluoromethylated tetra-substituted alkene **1-197**, an intermediate in the synthesis of the anti-breast cancer drug Panomifene **1-198**, was obtained in two step from alkene **1-195**.



1-195 **1-196** **1-197**, 35% over 2 steps *E*/*Z* = 96:4

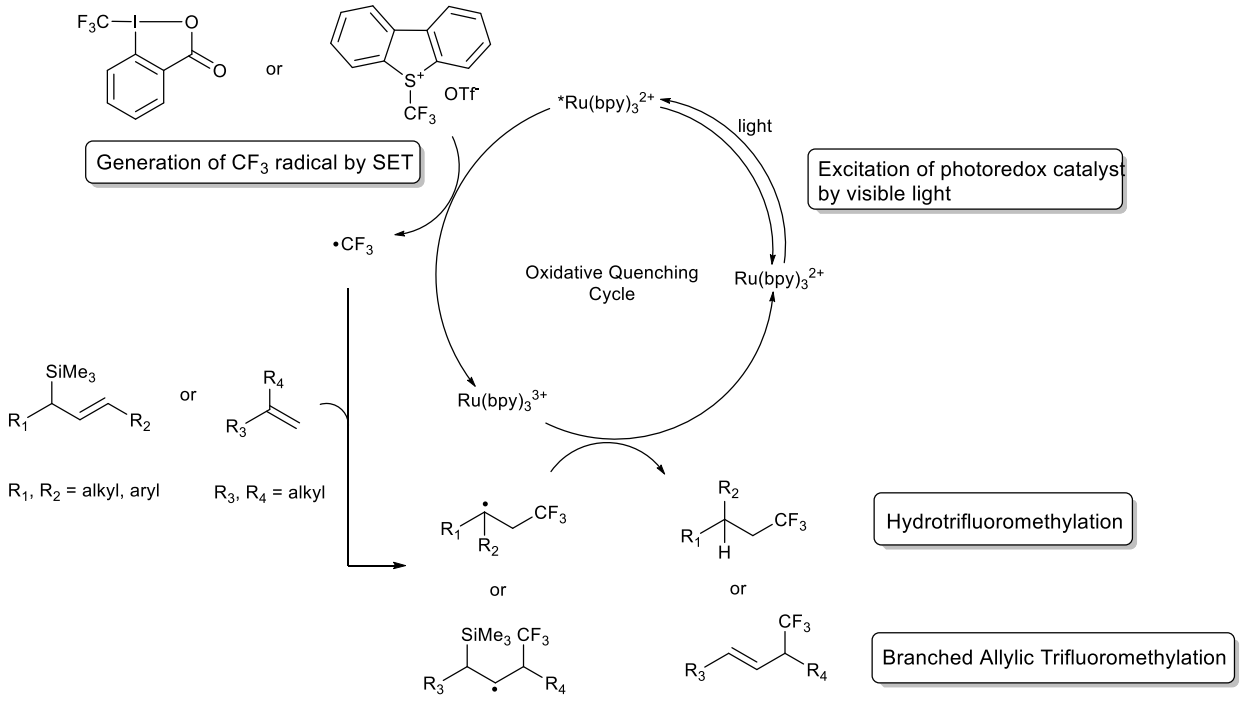
1-198, Panomifene

Scheme 1.53 Synthesis of Panomifene intermediate

1.6 Outline of this Thesis

The useful physical and chemical properties of the trifluoromethyl group have generated a growing amount of interest, which has led to the development of efficient and selective

methods for its incorporation in organic molecules. The majority of these methods concern the development of (hetero)aryl-CF_3 bond formation, with the synthesis of aliphatic and allylic trifluoromethyl compounds receiving much less attention. In this thesis, new methodology is presented for the synthesis of Csp^3-CF_3 bonds, using a combination of electrophilic trifluoromethylating reagents and photoredox catalysis (Scheme 1.54). Chapter 2 details our research into the synthesis of branched allylic trifluoromethyl compounds using allylsilanes as starting materials. In chapter 3 this research is extended to the hydrotrifluoromethylation of unactivated alkenes, which provides primary alkyl trifluoromethyl compounds. The mild conditions make these new trifluoromethylation methodologies broadly applicable and suitable for the late-stage trifluoromethylation of complex molecules.



Scheme 1.54 General mechanism for photoredox catalysed trifluoromethylation of alkenes

1.7 References

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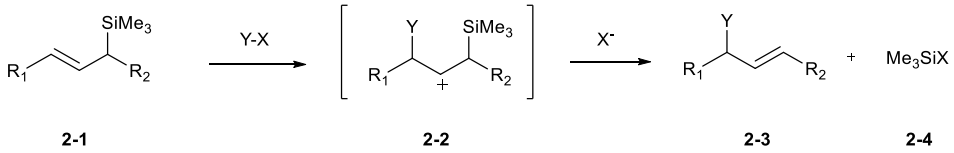
Chapter 2: Photoredox Catalysed Trifluoromethylation of Allylsilanes

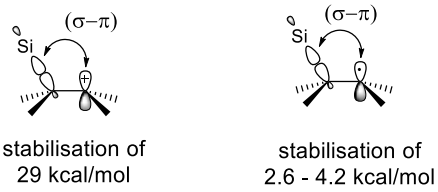
2.1 Introduction

Allylsilanes have been extensively used in organic synthesis as carbon nucleophiles and allyl-metal equivalents that are thermally stable and relatively inert towards water and oxygen.[1] In general, allylsilanes **2-1** react through the S_E2' mechanism in which the electrophile regioselectively attacks the terminal carbon atom of the allyl system (Scheme 2.1). The resulting β-silyl carbocation **2-2** then undergoes de-silylation providing the allylic product **2-3** together with Me_3SiX **2-3**.



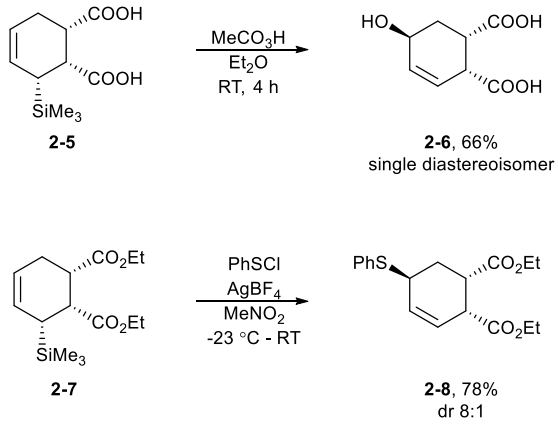
Scheme 2.1 S_E2' reaction of allylsilanes

The regioselectivity of this transformation can be explained by the ability of the silicon carbon bond to stabilise a β-carbocation (β-effect). The carbon-silicon bond can significantly stabilise β-carbocations through $\sigma_{Si\text{-}C} \rightarrow p$ hyperconjugation (29 kcal/mol) as shown in Scheme 2.2.[2] The stabilisation by hyperconjugation of the silicon-carbon bond was found to be most effective at dihedral angles of 180 °C (*anti*-periplanar) and 0 °C (*syn*-periplanar), when the empty p-orbital is parallel to the $\sigma_{Si\text{-}C}$ orbital.[2] The silicon-carbon bond has also been found to stabilise β-carboradicals, but to a lesser extent (2.6 - 4.2 kcal/mol).[3]



Scheme 2.2 Silicon $\sigma_{Si\text{-}C} \rightarrow p$ hyperconjugation

The attack of the electrophile was experimentally shown to take place *anti* with respect to the silicon atom in the reaction of cyclic allylsilanes **2.5** with peracetic acid, and **2.7** with $PhS^{+}[BF_4]^{-}$ generated from PhSCl and $AgBF_4$ (Scheme 2.3).[4]



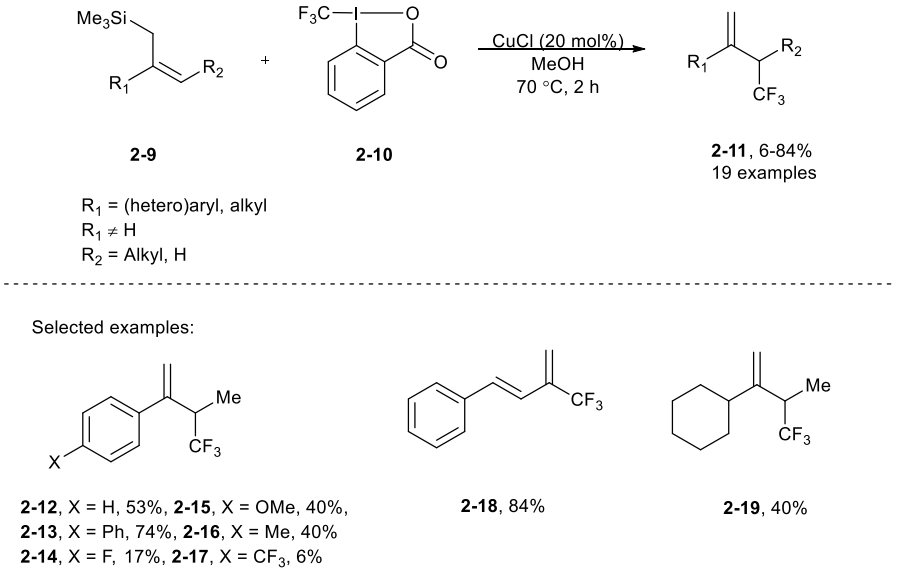
Scheme 2.3 Anti S_E2' mechanism with cyclic allylsilanes

This preference for *anti* attack of the electrophile has also been shown in the reaction of acyclic allylsilanes with various electrophiles (See section 2.3).

2.1.1 Copper Catalysed Trifluoromethylation of Allylsilanes

In 2012, the Gouverneur group reported the copper-catalysed trifluoromethylation of allylsilanes **2-9** using the Togni II reagent **2-10**.[5] Various substituted allylsilanes could be trifluoromethylated in short reaction times (2 h) using a catalytic amount of CuCl (20 mol%) in MeOH at 70 °C, providing the branched allylic trifluoromethylated products **2-11** in moderate to good yields (Scheme 2.4). The activation of the allylic position by the Me_3Si group was found to be crucial for trifluoromethylation to occur, and allowed for

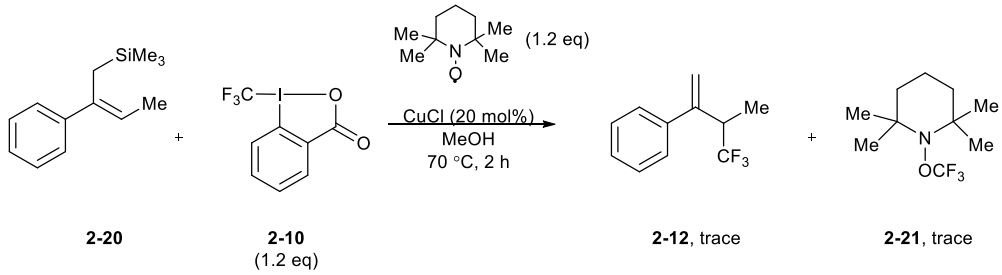
regioselective formation of the branched allylic trifluoromethylated products. In addition, the reaction did not proceed in absence of the Cu-catalyst.



Scheme 2.4 Cu(I) catalysed trifluoromethylation of allylsilanes

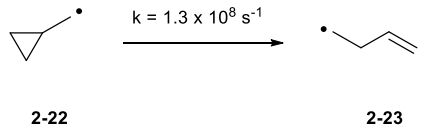
Further investigation into the scope revealed that a range of *gem*-disubstituted allylic trifluoromethylated products could be obtained, but that allylsilanes without a substituent in the β-position ($R_1 \neq H$ in Scheme 2.4) were found to be unreactive. The trifluoromethylation was also unsuccessful with γ-disubstituted allylsilanes, making it unsuitable for the synthesis of allylic quaternary trifluoromethyl compounds.

When the reaction was performed in the presence of the free radical quencher 2,2,6,6-tetramethyl-piperinyl-1-oxyl (TEMPO) only a trace of the desired product was formed, accompanied by a trace of the TEMPO-CF_3 adduct **2-21**, as shown by analysis with ^{19}F NMR. This result indicated that a CF_3-radical could potentially be involved as the trifluoromethylating species.



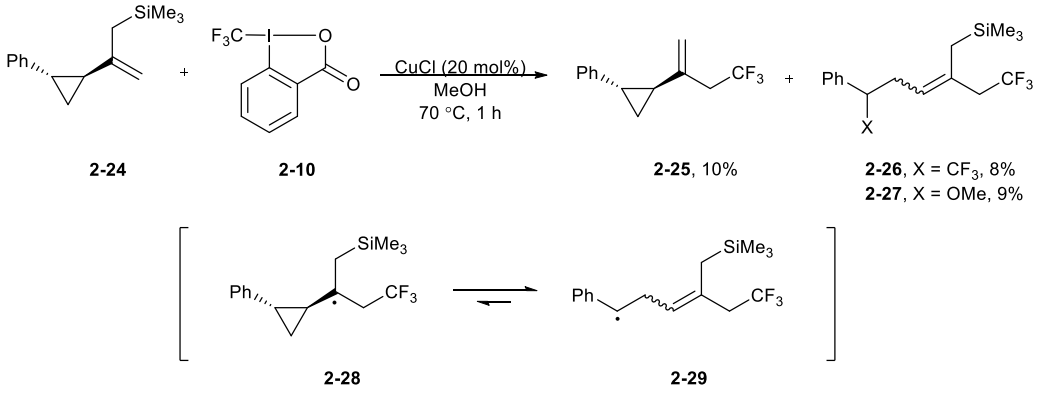
Scheme 2.5 Trifluoromethylation in the presence of TEMPO as additive

To investigate this possibility further, the trifluoromethylation of cyclopropyl-allylsilane **2-24** was performed (Scheme 2.7). The cyclopropylmethyl radical **2-22** is known to rearrange to the ring-opened but-3-enyl radical **2-23** with a reaction rate of $k = 1.3 \times 10^8\ s^{-1}$ (at 25 °C).[6] This very fast reaction rate makes this radical a good probe for investigating the presence of radical intermediates in chemical transformations.



Scheme 2.6 Radical ring-opening of cyclopropyl methyl radical **2-22**

If the cyclopropylcarbinyl radical **2-28** would form through addition of the CF_3-radical to **2-24**, ring-opening to radical **2-29** would be expected to take place, assuming the rate of ring-opening is faster than further reaction of radical **2-28**.

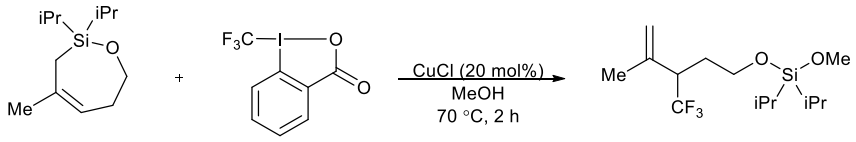


Scheme 2.7 Cyclopropyl radical clock experiment

The trifluoromethylation of **2-24** gave a complex mixture from which three main products could be isolated after careful purification (Scheme 2.7). Formation of product **2-25** and **2-27** could be tentatively explained by the formation of a putative β-silyl cationic intermediate, which undergoes either direct desilylation or ring opening followed by reaction with the solvent.

Involvement of a CF_3-radical was confirmed by the formation of the *bis*-trifluoromethylated product **2-26**, which could be rationalised by the combination of ring opened radical **2-29**, obtained after reaction of the allylsilane with the CF_3-radical followed by ring opening, with another CF_3 radical.

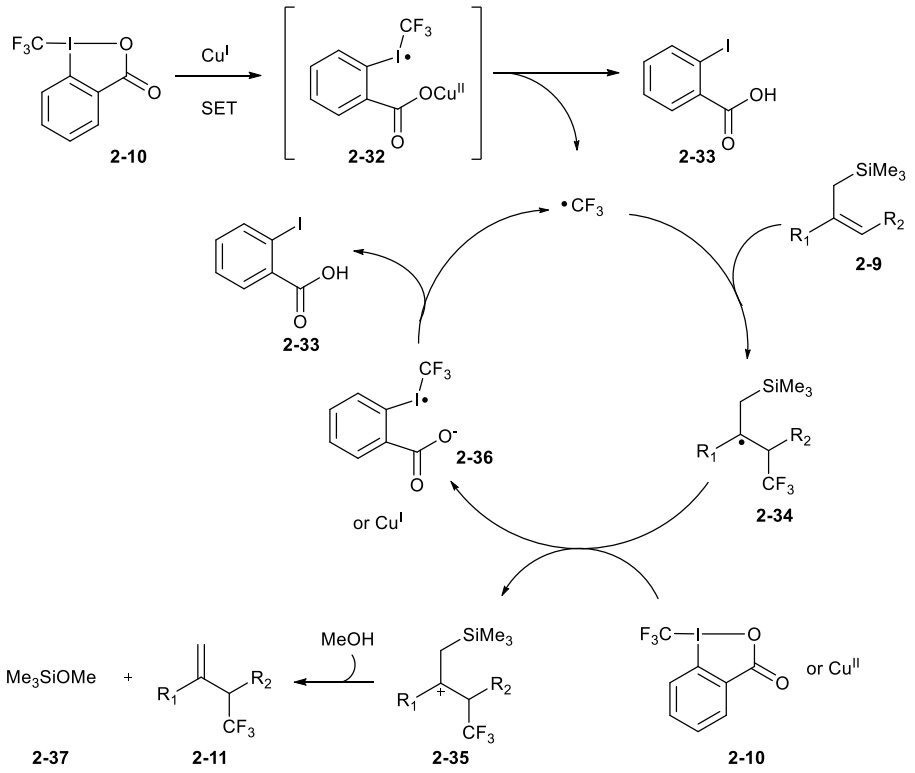
The cyclic allylsilane **2-30** was used to investigate the desilylation step (Scheme 2.8). Formation of the trifluoromethylated product **2-31** showed that the silyl group was captured by MeOH.



2-30 **2-10** **2-31**, 46%

Scheme 2.8 Trifluoromethylation of cyclic allylsilane **2-30**

Based on the combination of these results a putative mechanism involving a CF_3-radical as intermediate was proposed (Scheme 2.9).



Scheme 2.9 Proposed reaction mechanism

In the proposed mechanism, single electron transfer from CuCl to the Togni II reagent **2-10** generates an intermediate that collapses into the CF_3-radical and 2-iodobenzoic acid **2-33**. The CF_3-radical then adds to the allylsilane, providing β-silyl benzylic radical intermediate **2-34**. Oxidation of this radical intermediate by another molecule of the Togni II reagent (or Cu^{II}) provides the β-silyl cationic intermediate **2-35**, which is significantly stabilised by $\sigma_{Si\text{-}C} \rightarrow p$ hyperconjugation)[2a] and generates another CF_3-radical. Rapid desilylation of cationic intermediate **2-35** by MeOH provides the branched allylic trifluoromethylated product.

SET reactions with copper are well known,[7] and the putative mechanism involving generation of a CF_3 radical takes into account the observations made in the mechanistic experiments. However, it is not possible to exclude alternative mechanisms that do not involve radical intermediates. A polar mechanism involving electrophilic

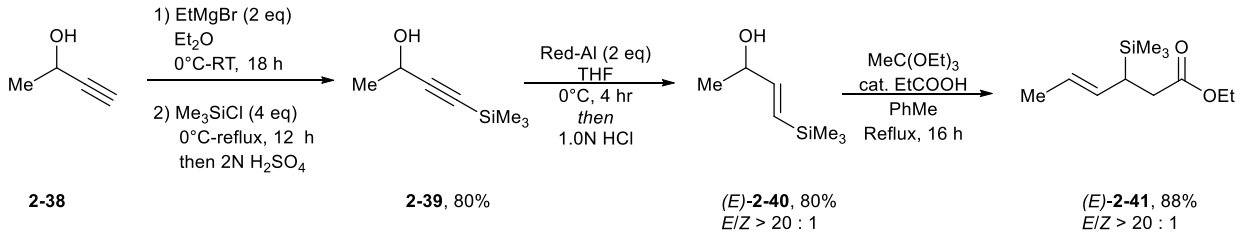
trifluoromethylation of the allylsilane, in which CuCl acts as a Lewis acid[5] cannot be excluded and may operate in parallel.

2.2 Optimisation of the Reaction Conditions

The work described in this chapter was carried out in collaboration with Dr. S. Mizuta and Dr. K. M. Engle.[8] The syntheses in Scheme 2.11, 2.15, 2.16 and 2.23 were performed by Dr. Satoshi Mizuta. Experimental data for these compounds can be found in the appendix.

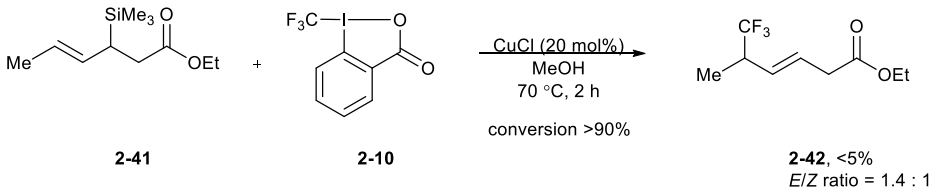
Following the successful synthesis of branched allylic CF_3 products, the next aim was to address the current limitations in the scope of this method. A survey of the literature for other mechanistic manifolds for the generation of CF_3 radical species led us to investigate photoredox catalysis (see section 1.2.4) as a mode of activation.

As initial substrate, ethyl (*E*)-3-(trimethylsilyl)hex-4-enoate **2-41** was chosen as a versatile carbon π-nucleophile and scaffold for introduction of chirality.[9] This allylsilane was synthesized starting from commercially available 3-butyn-2-ol **2-38** in three steps according to the known procedure developed by Procter *et al* (Scheme 2.10).[9b] Double deprotonation of **2-38** with EtMgBr (2 eq) in Et_2O at room temperature followed by reaction with Me_3SiCl (4 eq) provided a *bis*-silylated alkynol intermediate, which on quenching with 2N H_2SO_4 gave mono-silylated alkynylsilane **2-39** in 80% yield. Alkynylsilane **2-39** was then reacted with RedAl^{tm} (2 eq) in THF at 0 °C to provide (*E*)-vinylsilane **2-40** in *E*/*Z* ratio of >20:1, through chelation controlled reduction. Condensation of the vinylsilane with triethylorthoacetate in PhMe at reflux containing a catalytic amount of propionic acid, followed by Johnson-Claisen [3,3]-sigmatropic rearrangement provided ethyl (*E*)-3-(trimethylsilyl)hex-4-enoate **2-41** in 88% yield.



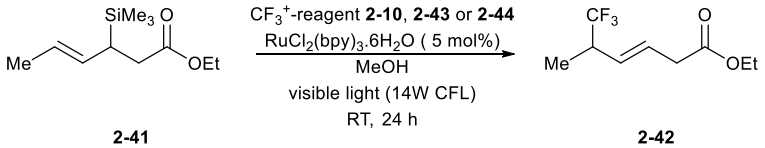
Scheme 2.10 Synthesis of ethyl (*E*)-3-(trimethylsilyl)hex-4-enoate **2-41**

Copper catalysed trifluoromethylation of ethyl (*E*)-3-(trimethylsilyl)hex-4-enoate **2-41** provided a low yield of trifluoromethylated product **2-42**. The reaction showed almost full conversion of starting material (>90%), with formation of a complex mixture of unindentified products. (Scheme 2.11).

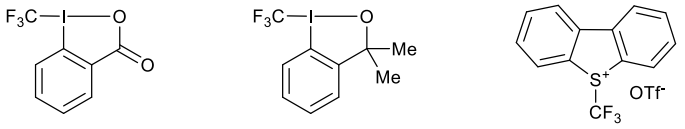


Scheme 2.11 Copper catalysed trifluoromethylation of ethyl (*E*)-3-(trimethylsilyl)hex-4-enoate **2-41**

To investigate the reactivity of allylsilane **2-41** towards trifluoromethylation under photoredox catalysis conditions, an optimisation study was performed using $RuCl_2(bpy)_3.6H_2O$ as the photoredox catalyst in combination with different trifluoromethylation reagents and solvents (Table 2.1).



2-41 **2-42**



2-10 **2-43** **2-44**

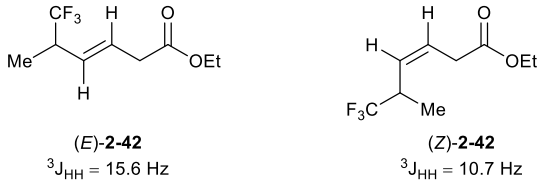
Entry[a,b]	CF_3^+-reagent	Conditions[c]	Yield[d]	E/Z ratio[e]
1	Togni II **2-10**	--	27%	2.5:1
2	Togni II **2-10**	48 h	55%	1.7:1
3	Togni II **2-10**	CH_3CN	17%	2.2:1
4	Togni II **2-10**	DMF	37%	1.8:1
5	Togni II **2-10**	DCM	22%	1.7:1
6	Togni II **2-10**	2% $Ru(bpy)_2.6H_2O$ 48 h	47%	1.7:1
7	Togni II **2-10**	no light	0%	--
8	Togni II **2-10**	no Ru	0%	--
9	Togni I **2-43**	--	0%	--
10	Togni I **2-43**	CH_3CN	0%	--
11	Togni I **2-43**	DMF	0%	--
12	Umemoto **2-44**	--	30%[f]	5.3:1
13	Umemoto **2-44**	EtOH	34%	4.3:1
14	Umemoto **2-44**[g]	--	35%	4.0:1
15	Umemoto **2-44**	CH_3CN	7%	8.0:1
16	Umemoto **2-44**	DMF	37%	5.4:1

[a] **2-41** (0.15 mmol), CF_3^+-reagent (0.27 mmol), $RuCl_2(bpy)_3.6H_2O$ (0.0075 mmol), MeOH (0.3 mL). [b] Reactions in entry 1-11,12 and 14 were performed by Dr. S. Mizuta. [c] Variation from the standard conditions. [d] Determined by ^{19}F NMR using PhF as internal standard. [e] Determined by ^{1}H and ^{19}F NMR. [f] Transesterifcation of **2-41** and **2-42**. [g] Reagent **2-44** with BF_4^- as counterion

Table 2.1 Reaction optimisation using ethyl (*E*)-3-(trimethylsilyl)hex-4-enoate **2-41**

A solution of (*E*)-3-(trimethylsilyl)hex-4-enoate, trifluoromethylating reagent **2-10**, **2-43** or **2-44** (1.2 - 1.8 eq) and a catalytic amount of the photoredox catalyst $RuCl_2(bpy)_3.6H_2O$ (5 mol%) in various solvents (0.5M) was stirred at room temperature under irradiation from a 14W fluorescent light source (common household light) at approx. 5 cm distance. After work-up a known amount of reference compound (PhF or $PhCF_3$) was added to the crude reaction mixture, and the yield and *E*/*Z* ratio of trifluoromethylated product **2-42** were determined using ^{19}F NMR. The double bond geometry of the major isomer was

assigned to be *E* by determination of $^{3}J_{HH}$ couplings constants of the double bond protons from the ^{1}H NMR spectrum (Scheme 2.12).[10]



Scheme 2.12 Assignment of (*E*) and (*Z*)-3-(trimethylsilyl)hex-4-enoate

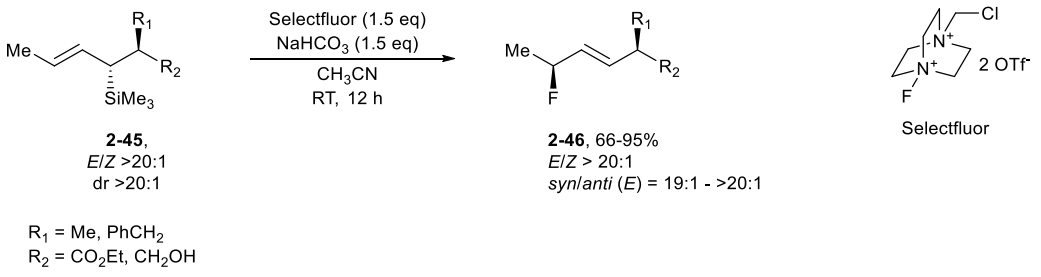
The results show that trifluoromethylation could be achieved using the Togni II reagent **2-10** and the Umemoto reagent **2-44** as the trifluoromethylating reagent, whereas the Togni I reagent **2-43** did not provide trifluoromethylated product (Table 2.1 entry 9-11). The Togni II reagent **2-10** provided ethyl (*E*)-6,6,6-trifluoro-5-methylhex-3-enoate **2-42** in 27% yield after 24 h irradiation with visible light (Table 2.1 entry 1), which increased to 55% after 48 h reaction time (Table 2.1 entry 2). The product was formed in an *E*/*Z* ratio of 1.7:1. MeOH was found to be the best solvent, with CH_3CN, DMF and DCM being less effective (Table 2.1 entry 3-5). A slightly lower yield of 47% was obtained when a lower loading of $Ru(bpy)_3Cl_2.6H_2O$ (2 mol%) was used (Table 2.1 entry 6). Both light and ruthenium photocatalyst were needed for the trifluoromethylation to proceed (Table 2.1 entry 7-8). The reaction using Umemoto reagent **2-44** as trifluoromethyl donor in MeOH required only 24 h to reach maximum conversion (as judged by TLC), but was complicated by transesterification of both the starting material **2-41** and the product **2-42** (Table 2.1 entry 12). Switching to EtOH as solvent resolved this issue and provided **2-42** in 30% yield in an *E*/*Z* ratio of 4.3:1 (Table 2.1 entry 13), an increase in selectivity towards formation of the *E*-isomer in comparison with the result of the Togni II reagent (E/Z ratio = 1.7:1, Table 2.1 entry 2). Independent experiments verified that both (*E*)-**2-41** and **2-42** (*E*/*Z* ratio = 1.7:1) did not show *E*/*Z* isomerisation under the reaction conditions. The counterion of the

Umemoto reagent did not influence the reaction, and the Umemoto reagent with a BF_4^- instead of OTf^- counterion gave the trifluoromethylated product in similar yield and *E*/*Z* ratio (Table 2.1 entry 14). Changing the solvent to CH_3CN resulted in only a low yield of trifluoromethylation (Table 2.1 entry 15), whereas the use of DMF gave the product in a similar yield to EtOH but with a slightly higher E/Z ratio of 5.4 (Table 2.1 entry 16).

From this study, the optimal conditions for trifluoromethylation were found to use the Togni II reagent **2-10** (1.8 eq) as the trifluoromethylating reagent, and $Ru(bpy)_3Cl_2.6H_2O$ (5 mol%) as the photoredox catalyst in MeOH as solvent, at room temperature under irradiation of a 14W CFL light source. EtOH was found to be the optimal solvent when the Umemoto reagent **2-44** (1.8 eq) was used as the trifluoromethylating reagent.

2.3 Stereoselective Trifluoromethylation of Allylsilanes

There are many examples of stereochemical control by the large and electropositive R_3Si-group in organic transformations.[11] Allylsilanes have proven to be very useful in this respect as carbon nucleophiles,- and found application in a variety of stereoselective C-C, C-N, C-O and C-S bond forming reactions with different electrophiles.[12] Reaction of acyclic allylsilanes with electrophiles have been shown to occur through a S_E2' mechanism, with addition taking place stereospecifically *anti* to the silicon group.[13] This strategy was used by our group in the diastereoselective electrophilic fluorination of *anti*-α-substituted allylsilanes **2-45** with Selectfluor, which gave the corresponding *syn*-(*E*)-allylic fluorides **2-46** in good yield and excellent selectivity (Scheme 2.13).[14]



2-45,
E/*Z* >20:1
dr >20:1

R_1 = Me, $PhCH_2$
R_2 = CO_2Et, CH_2OH

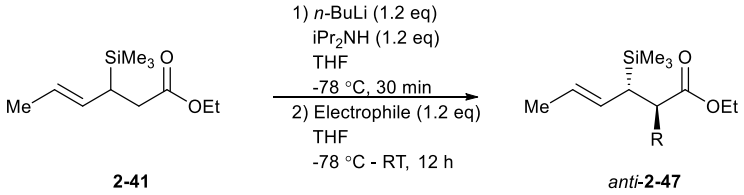
2-46, 66-95%
E/*Z* > 20:1
syn/*anti* (*E*) = 19:1 - >20:1

Scheme 2.13 Electrophilic fluorination of *anti*-α-substituted allylsilanes **2-45**

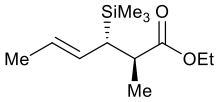
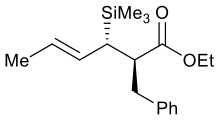
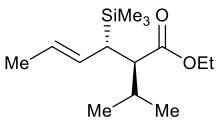
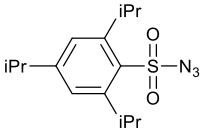
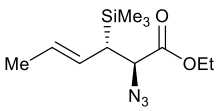
The high efficiency and selectivity achieved in this electrophilic fluorination reaction through the anti S_E2' mode of addition to the allysilane prompted us to use a similar strategy for the synthesis of diastereomerically enriched branched trifluoromethyl compounds.

2.3.1 Trifluoromethylation of diastereomerically Pure Allylsilanes

Using the optimized conditions, the photoredox catalysed trifluoromethylation was performed on a series of 2,3-*anti*-α-substituted-β-silyl-(*E*)-hex-4-enoates **2-47**, to investigate the efficiency of chirality transfer using diastereomerically pure allylsilanes. The substrates were synthesized by alkylation of ethyl (*E*)-3-(trimethylsilyl)hex-4-enoate **2-41**, using the procedure developed by Panek and co-workers (Table 2.2).[15]



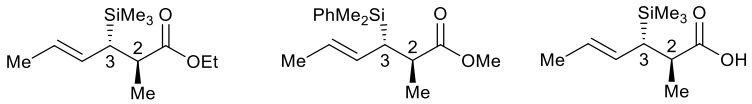
2-41 *anti*-**2-47**

Entry[a,b]	Electrophile	Product	Yield[c]
1	MeI		**2-48**, 66% dr >20:1
2	$PhCH_2Br$		**2-49**, 81% dr >20:1
3	*i*PrI[d]		**2-50**, 78% dr >20:1
4			**2-51**, 56% dr >20:1

[a] **2-41** (10 mmol), *n*-BuLi (12 mmol), iPr_2NH (12 mmol), electrophile (12 mmol), THF (16 mL). [b] Compound **2-50** and **2-51** were synthesized by Dr. K. Engle [c] Isolated yield after column chromatography. [c] THF/HMPA 4/1 was used as solvent.

Table 2.2 Synthesis of 2,3-*anti*-α-substituted-β-silyl-(*E*)-hex-4-enoates

Allylsilane **2-41** was deprotonated using LDA (1.2 eq), prepared in situ from the deprotonation of diisopropylamine by an equimolar amount of *n*-butyllithium, in THF at -78 °C followed by dropwise addition of the electrophile dissolved in THF and stirring at room temperature (12 hr). After work-up and purification by chromatography the 2,3-*anti*-α-substituted-β-silyl-(*E*)-hex-4-enoates **2-48** – **2-51** could be isolated in good yield and excellent diastereomeric ratio (dr > 20:1). Comparison of the vicinal coupling constants between C2/C3 stereogenic centres of *anti*-(*E*)-**2-48** ($^3J_{2H\text{-}3H}$) with the literature values for *anti*-(*E*)-**2-52**[15] and *anti*-(*E*)-**2-53**[16] confirmed the formation of the *anti*-isomer (Scheme 2.14).



anti-(*E*)-**2-48**
$^3J_{2H\text{-}3H}$ = 7.1 Hz

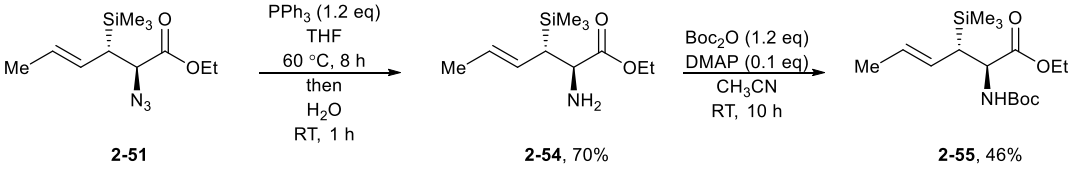
anti-(*E*)-**2-52**
$^3J_{2H\text{-}3H}$ = 7.2 Hz

anti-(*E*)-**2-53**
$^3J_{2H\text{-}3H}$ = 7.2 Hz

Scheme 2.14 Comparison of $^3J_{2H\text{-}3H}$ coupling constants

The structures of **2-49**, **2-50** and **2-51** were assigned in analogy with these results. For the formation of isopropyl substituted **2-50**, it was necessary to add HMPA (20 %v/v) as co-solvent to enhance the reactivity of the formed enolate,[17] and ensure efficient alkylation.

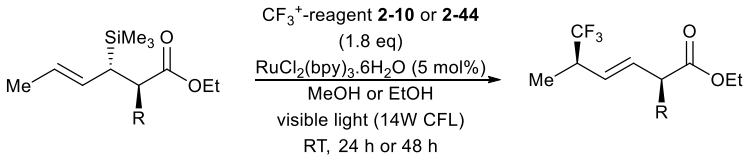
The azide-substituted allylsilane **2-51** was further converted into the BOC protected amine by reduction using triphenylphosphine, followed by the DMAP catalysed acylation with di-*tert*-butyl dicarbonate (Scheme 2.15).

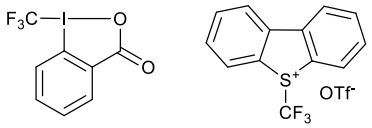


2-51 **2-54**, 70% **2-55**, 46%

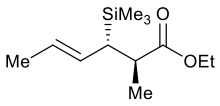
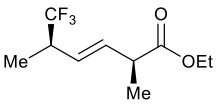
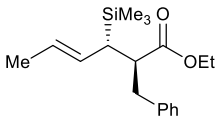
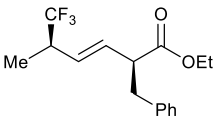
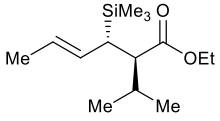
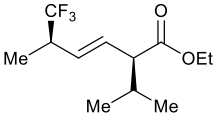
Scheme 2.15 Synthesis of *anti*-(*E*)-ethyl 2-[(*tert*-butoxycarbonyl)amino]-3-(trimethylsilyl)hex-4-enoate **2-55**

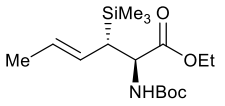
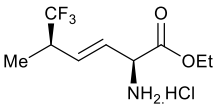
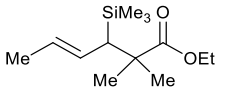
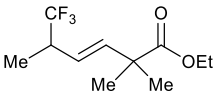
Anti α-Substituted allylsilanes **2-48** – **2-51** were subjected to the trifluoromethylation conditions using $RuCl_2(bpy)_3.6H_2O$ (5 mol%) and either the Togni II reagent **2-10** (1.8 eq) in MeOH (Method A), or the Umemoto reagent **2-44** (1.8 eq) in EtOH (Method B). The results are presented in Table 2.3.





2-10 **2-44**

Entry[a,b]	Allylsilane	Product	Method	Yield[c]	*E*/*Z* ratio[d]	*syn*/*anti* ratio[e]
1			A	**2-57**, 65%	15:1	6.1:1
			B	**2-57**, 33%	>20:1	7.0:1
2			A	**2-58**, 83%	15:1	10:1
			B	**2-58**, 24%	>20:1	8.6:1
3			A	**2-59**, 55%	>20:1	3.5:1
4			A	**2-60**, 52%[f]	>20:1[g]	4.5:1[g]

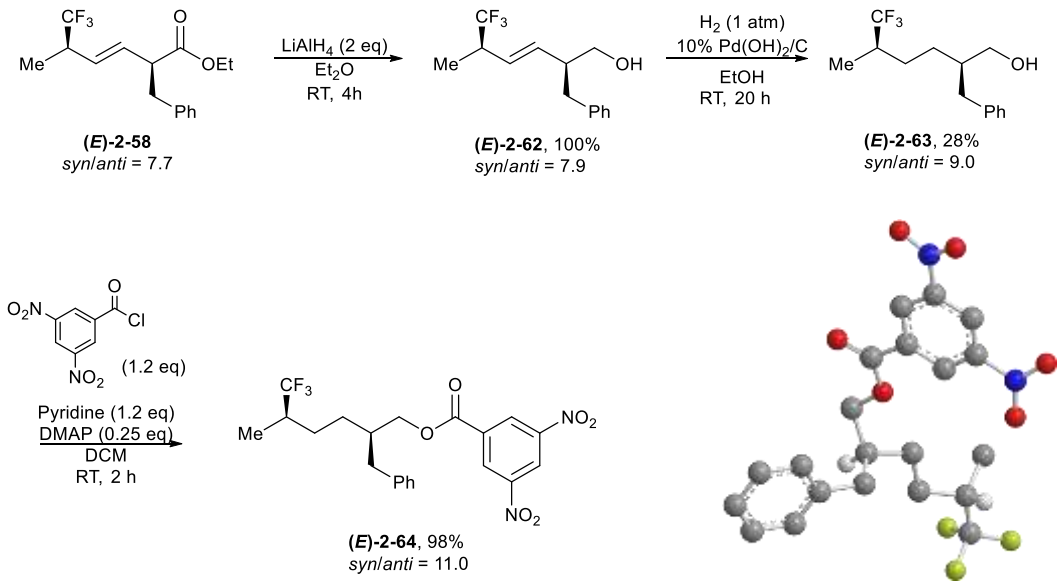
	 				
5	 	A	**2-61**, 50%	14:1	--
		B	**2-61**, 37%[h]	>20:1	--

[a] **Method A** : *anti*-**2-47** (0.25 mmol), Togni reagent **2-10** (0.45 mmol), $RuCl_2(bpy)_3.6H_2O$ (0.013 mmol), MeOH (0.5 mL), 48 hr. **Method B** : *anti*-**2-47** (0.25 mmol), Umemoto reagent **2-44** (0.45 mmol), $RuCl_2(bpy)_3.6H_2O$ (0.013 mmol), EtOH (0.5 mL), 24 hr. [b] Products **2-57**, **2-59** and **2-60** were synthesized by Dr. S. Mizuta [c] Isolated yield after column chromatography. [d] Determined from the crude reaction mixture by ^{19}F NMR using PhF or $PhCF_3$ as internal standard. [e] Determined from the crude reaction mixture by ^{19}F NMR using PhF. [f] Isolated product after deprotecting with HCl/EtOH. [g] Determined from the purified product **2-60** by ^{19}F NMR. [h] Yield determined by ^{19}F NMR using $PhCF_3$ as internal standard.

Table 2.3 Trifluoromethylation of α-substituted allylsilanes

The reactions were worked-up after 48 h (Method A using Togni II reagent **2-10**) or 24 h (Method B using Umemoto reagent **2-44**) and the *E*/*Z* and *syn*/*anti* ratio of the branched allylic trifluoromethylated products **2-57** – **2-61** were determined from the crude reaction mixture after work-up using ^{19}F NMR. The products were formed in high *E*/*Z* ratio and from the four possible isomers, the *syn*-(*E*) isomer was found to be the major product in all cases. Purification using column chromatography allowed for isolation of the allylic trifluoromethyl products *syn*-(*E*)-**2-57** - *syn*-(*E*)-**2-61**, but separation from the minor isomers proved not possible and the isolated products contained small amounts of the other isomers. Yields were generally lower (24 - 37%) using the Umemoto reagent **2-44** (Method B) but the products were formed with higher *E*-selectivity (*E*/*Z* ratio >20:1) in comparison with the procedure using the Togni II reagent **2-10** (Method A, yield 52 - 83%, *E*/*Z* ratio 14-15:1). The ^1H NMR spectrum of NHBoc substituted allylic trifluoromethyl product was complicated by the presence of rotamers, and analysis was performed on the amine *syn*-(*E*)-**2-60**, which could be obtained as the HCl salt after quantitative deprotection using HCl in EtOH.

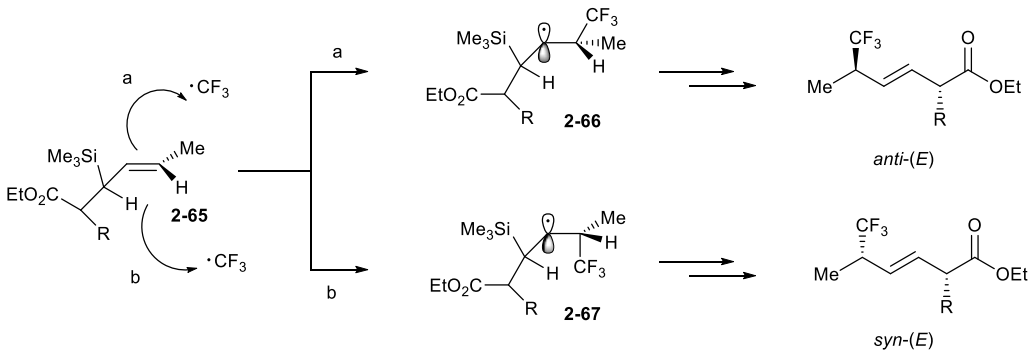
The relative stereochemistry of the major isomer of (*E*)-**2-58** could be unambiguously assigned as the *syn*-isomer through characterisation by single crystal X-ray diffraction of 3,5-dinitrophenylester *syn*-(*E*)-**2-64**, a solid which could be obtained in three steps from (*E*)-**2-58**. Reduction of the ester-group in **2-58** using $LiAlH_4$ in Et_2O provided alcohol (*E*)-**2-62** in quantitative yield. Reduction of the double bond in (*E*)-**2-63** using H_2 in combination with $Pd(OH)_2$ in EtOH provided saturated alcohol **2-63** in 28% yield, which could be acylated with 3,5-dinitrobenzoyl chloride to provide the 3,5-dinitrophenylester **2-64** in good yield (Scheme 2.16).



Scheme 2.16 Synthesis and determination of *syn*-geometry of 3,5-dinitrobenzoate ester **2-64**

The formation of the *syn*-(*E*) isomer as the major product in the trifluoromethylation of allylsilanes under photoredox conditions is consistent with approach of the electrophile (in this case the CF_3 radical) *anti* to the silyl-group in conformation **2-65**. Conformation **2-65** is favoured because of minimalisation of $A^{1,3}$ strain (Scheme 2.17).[18] The trifluoromethylated product is then provided by oxidation of the radical intermediate **2-67** to the corresponding β-silyl cationic intermediate followed by rapid de-silylation. This process shows that the silyl group is both regio- and stereo-directing, and is in line with the

anti-S_E2' mode of addition to allylsilanes which has been observed for many different electrophiles.[13]



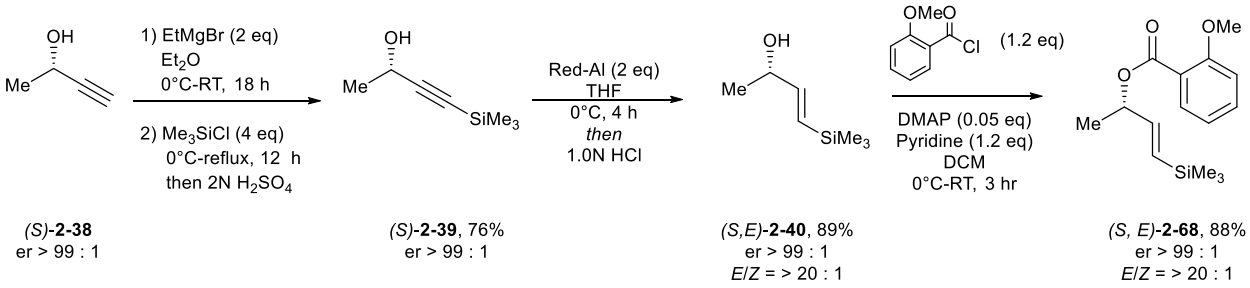
Scheme 2.17 Formation of *syn* and *anti* trifluoromethylated alkenes

Whereas both the trifluoromethylation using the Togni II reagent **2-10** and the Umemoto reagent **2-44** (Table 2.3) provided the products in high *E*/*Z* ratio, it was shown that appreciable amounts of the *anti*-isomer were formed. This can be explained by increased steric hindrance of the C_α-*Si* face (bottom face) by the R-substituent in conformation **2-65**, which disfavours the approach of the electrophile from this face, and results in formation of larger amounts of the *anti*-isomer originating from approach of the electrophile to the top face. This is in line with the observed significantly lower *syn*/*anti* ratio for the bulkier iPr and NHBoc and substituents (*syn*/*anti* = 3.5 for **2-59** and *syn*/*anti* = 4.5 for **2-60** respectively) in comparison with the ratio for **2-57** with a smaller Me substituent (*syn*/*anti* = 10).

2.3.2 Trifluoromethylation of Enantioenriched Allylsilanes

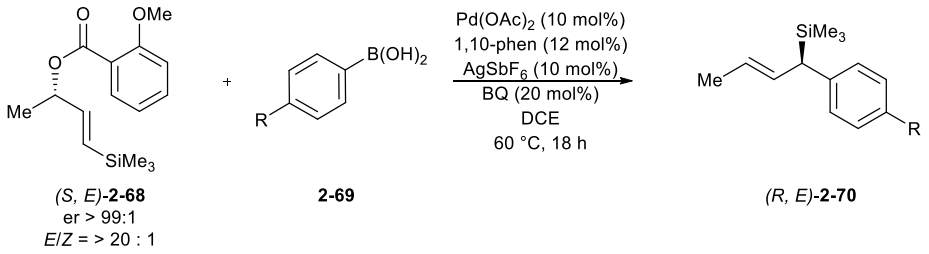
The successful photoredox catalysed trifluoromethylation of allylsilanes **2-47** led us to investigate the efficiency of chirality transfer in the trifluoromethylation of enantioenriched allylsilanes. As starting materials a series of enantioenriched α-aryl allylsilanes (*R*, *E*)-**2-70** were chosen, which could be synthesized from trimethylsilyl substituted allylic acetate (*S*, *E*)-**2-68**.[19] This enantioenriched, trimethylsilyl substituted building block **2-68** could be

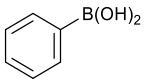
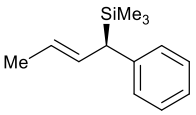
obtained in 4 steps from the commercially available chiral building block (*S*)-(-)-3-butyn-2-ol (*S*)-**2-38** (Scheme 2.18). Double silylation of (*S*)-**2-38**, followed by in-situ treatment with dilute acid (2N H_2SO_4) gave the alkynylsilane (*S*)-**2-39** in 76% yield, which was reduced by RedAl[tm] ($NaAlH_2(OCH_2CH_2OCH_3)_2$) under chelation control to afford vinylsilane (*S*, *E*)-**2-40** in a yield of 89% and excellent *E*/*Z* ratio (>20:1).[9b] Finally, DMAP catalysed acylation of vinylsilane (*S*, *E*)-**2-40** with *o*-methoxybenzoyl chloride in DCM gave the enantioenriched trimethylsilyl substituted allylic acetate (*S*, *E*)-**2-68** in 88% yield.

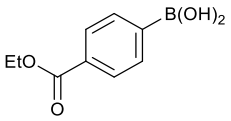
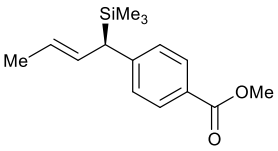
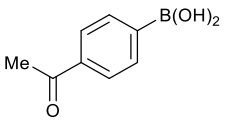
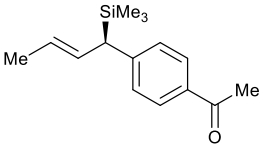


Scheme 2.18 Synthesis of enantioenriched vinylsilane (*S*, *E*)-**2-68**

The enantioenriched α-aryl allylsilanes (R, *E*)-**2-70** could then be synthesized by a palladium catalysed γ-selective arylation using (*S*, *E*)-**2-68** described by Li *et al* (Table 2.4).[19]



Entry[a,b]	Aryl Boronic Acid	Product	Yield[c,d,e]
1			**2-71**, 37% er = 97:3 *E*/*Z* > 20:1

2			**2-72**, 41% er = 99:1 *E*/*Z* > 20:1
3			**2-73**, 38% er = 99:1 *E*/*Z* > 20:1

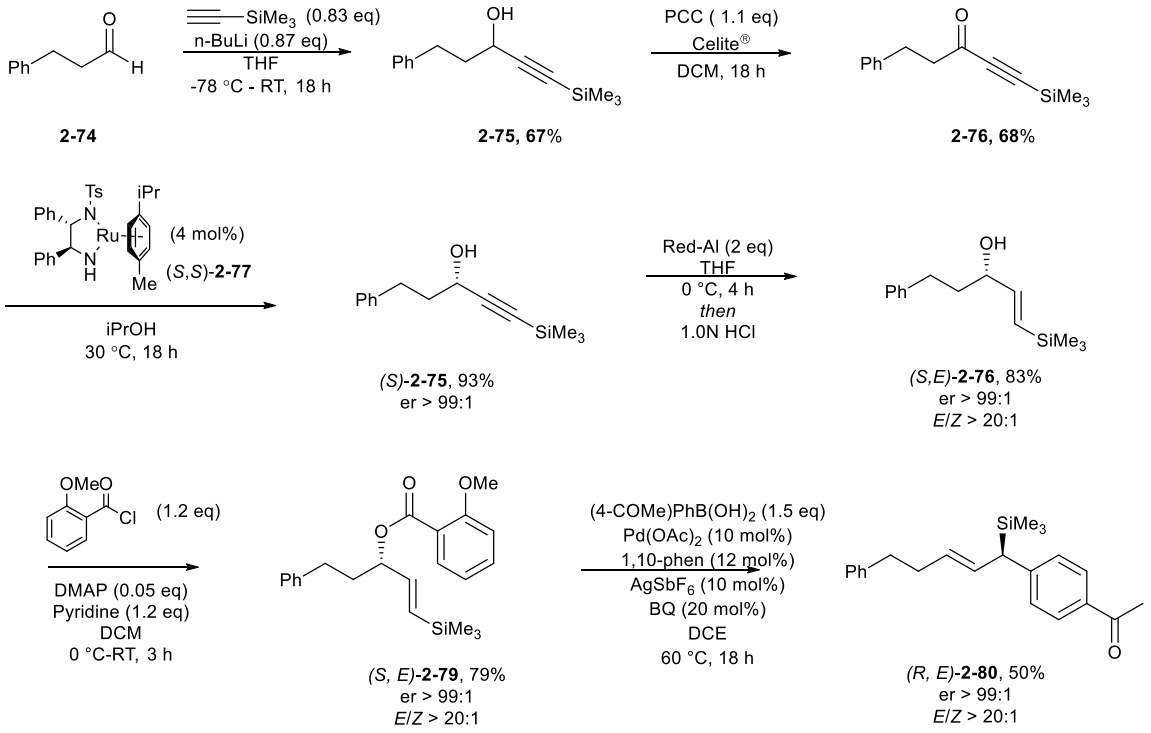
[a] Reaction conditions : (*S*, *E*)-**2-68** (3.0 mmol), $ArB(OH)_2$ (4.5 mmol), $Pd(OAc)_2$ (0.30 mmol), 1,10-phenantroline (0.36 mmol), $AgSbF_6$ (0.30 mmol), 1,4-benzoquinone (0.60 mmol) in DCE (20 mL). [b] Product **2-71** was made by Dr. K. M. Engle [c] *E*/*Z* ratio determined by ^1H NMR on crude reaction mixture. [d] Isolated yields after purification by column chromatography. [e] Enantiomeric ratio determined by chiral HPLC

Table 2.4 Synthesis of enantioenriched allylsilanes

A mixture of $Pd(OAc)_2$ (10 mol%), 1,10-phenanthroline (12 mol%), $AgSbF_6$ (10 mol%) and 1,4-benzoquinone (20 mol%) in DCE (0.15M) was briefly sonicated, after which allylic acetate (*S*, *E*)-**2-68** and aryl boronic acid (1.5 eq) were added. After stirring at 60 °C until complete conversion (18 h), the mixture was filtered over a short plug of silica with Et_2O and further purified by silica gel chromatography. When substituted arylboronic acids were used, it was found that the protodeborated sideproduct (methylbenzoate and acetophenone respectively) could not be separated from the allylsilane by column chromatography, and an additional distillation was necessary to obtain pure product. The er was determined by normal phase chiral HPLC. In this manner the α-aryl allylsilanes (*R*, *E*)-**2-70** were obtained in moderate yield (37-41%), with excellent er (97:3 for (*R*, *E*)-**2-71** and 99:1 for (*R*, *E*)-**2-72** and (*R*, *E*)-**2-73**) and *E*/*Z* ratio (>20:1).

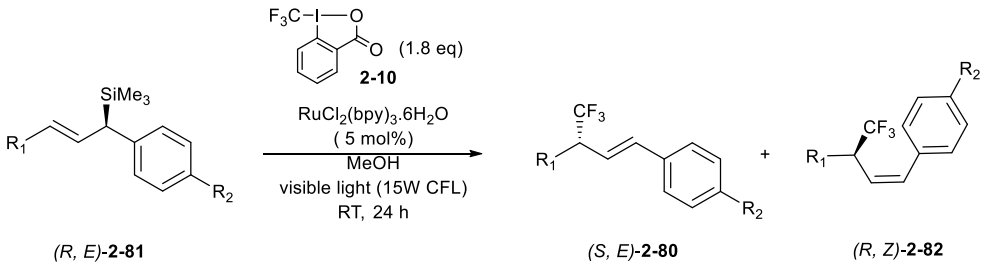
Chiral allylsilane (*R*, *E*)-**2-80** containing a phenylethyl side chain was synthesized according to a similar strategy (Scheme 2.19). Lithiation of trimethylsilylacetylene with *n*-BuLi (1.05 eq) at low temperature in THF, followed by treatment with 3-phenylpropanal **2-74** (1.2 eq), gave propargyl silane **2-75** in 67% yield. Oxidation with PCC in DCM at room temperature provided the corresponding ketone **2-76** in 68% yield. Chiral reduction of this

ketone using the (*S*,*S*)-Noyori catalyst (Ru[(S,S)-TsDPEN])p-cymene **2-77** (4 mol%) in *i*PrOH, then gave the corresponding chiral alcohol (*S*)-**2-75** in 93% yield and excellent er (>99:1).[20] Chelation controlled reduction of (*S*)-**2-75** using RedAl^{tm} (2 eq) in THF at 0 °C provided the vinylsilane (*S*, *E*)-**2-78** in good yield. Chiral allylsilane (*S*, *E*)-**2-80** could then be obtained in 50% yield and excellent enantiomeric ratio (er >99:1) and *E*/*Z* ratio (>20:1) by DMAP catalysed acylation of vinylsilane (*S*, *E*)-**2-79** with *o*-methoxybenzoyl chloride in DCM (79% yield), followed by palladium catalysed γ-selective arylation as described previously.

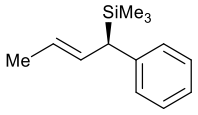
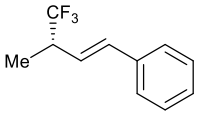
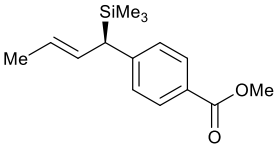
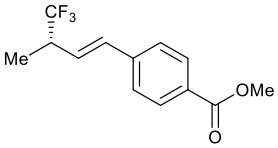
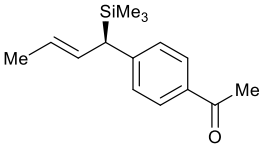
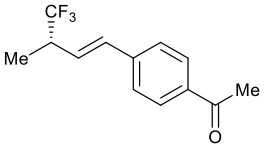
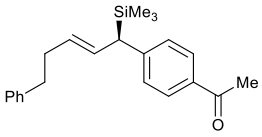
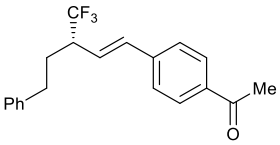


Scheme 2.19 Synthesis of enantioenriched allylsilane (*R*, *E*)-**2-80**

The enantioenriched α-aryl allylsilanes (*R*, *E*)-**2-71** - (*R*, *E*)-**2-73**, and (*R*, *E*)-**2-80** were subjected to the optimised trifluoromethylation conditions, using the Tongi II reagent **2-10** (Table 2.5).



(R, E)-**2-81** *(S, E)*-**2-80** *(R, Z)*-**2-82**

Entry [a.b]	**Allylsilane**	**Product**	***E*/*Z* ratio** [c]	**Yield**[d,e]	
				E-isomer	*Z*-isomer
1			5.0	(*E*)-**2-83**, 56% er = 85:15	nd[f]
2			7.0	(*E*)-**2-84**, 41% er = 87:13	nd[f]
3			7.0	(*E*)-**2-85**, 59% er = 88:12	(*Z*)-**2-85**, 9% er = 98:2
4			3.2	(*E*)-**2-85**, 42% er = 86:14	(*Z*)-**2-85**, 17% er = 98:2

[a] Reaction conditions : (*R, E*)-**2-71** (0.25 mmol), **2-10** (0.45 mmol), $RuCl_2(bpy).6H_2O$ (0.013 mmol) in MeOH (0.5 mL). [b] Compounds **2-83** and **2-85** were synthesized by Dr. S. Mizuta. [c] *E*/*Z* ratio determined by ^{19}F NMR on crude reaction mixture. [d] Isolated yields after purification by column chromatography. [e] Enantiomeric ratio determined by chiral HPLC. [f] nd = not determined.

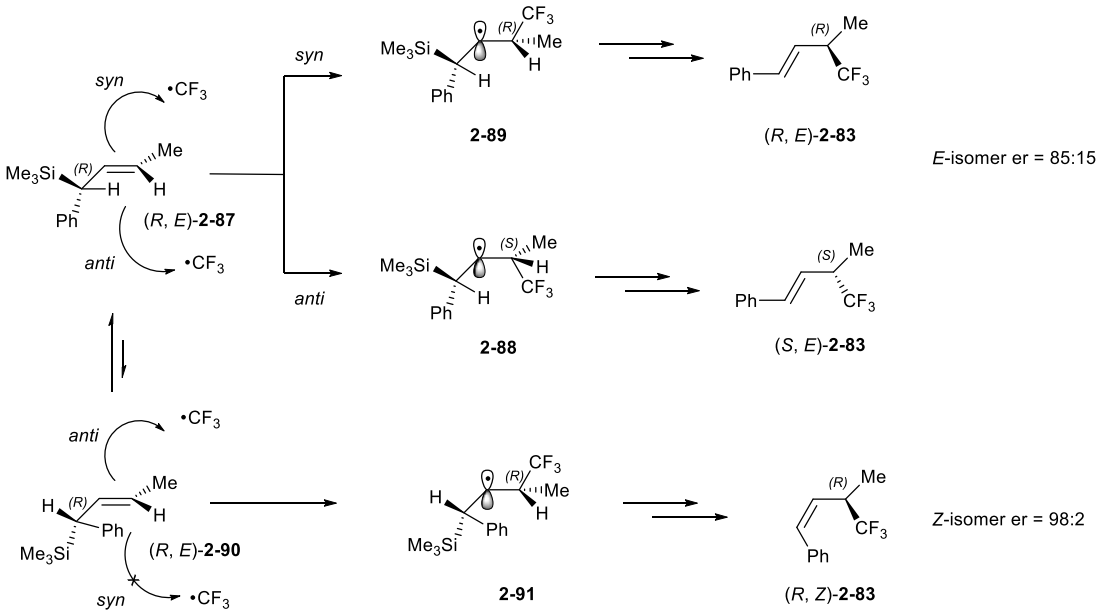
Table 2.5 Trifluoromethylation of enantioenriched allylsilanes

A solution of the enantioenriched α-aryl allylsilane, Togni II reagent **2-10** (1.8 eq) and a catalytic amount of the complex $RuCl_2(bpy)_3.6H_2O$ (0.05 eq) in MeOH (0.5M) was stirred at room temperature under irradiation with a 14W fluorescent light (common household light) source at approx. 5 cm distance. Analysis of an aliquot by TLC showed full conversion of starting material after 24 hr. The mixture was subjected to an aqueous work-

up and the *E*/*Z* ratio of trifluoromethylated product was determined by ^{19}F NMR, followed by purification using silica gel chromatography. The enantiomeric ratios of the product were determined by analysis using normal phase chiral HPLC. The trifluoromethylated products were obtained in moderate yield (41-59%) and predominantly formed as the *E*-isomer. The double bond geometry could be assigned by analysis of the ^{1}H and ^{19}F NMR spectra. Unsubstituted **2-83** was isolated in 56% yield as a mixture of isomers (*E*/*Z* ratio = 5.0), and the enantiomeric ratio of the main *E*-isomer was determined to be 85:15 (Table 2.5, entry 1). A similar result was obtained for the 4-carbomethoxy substituted **2-84**, which was isolated in 41% yield as a mixture with *E*/*Z* ratio = 7.0:1 and an enantiomeric ratio of 87:13 (Table 2.5, entry 2). Both substrates show an erosion of the enantiomeric ratio in comparison with the starting material ((*R*, *E*)-**2-71** and (*R*, *E*)-**2-72**, er > 99:1). For the *para*-acetyl substituted **2-85** and **2-86**, it was possible to separate the *E* and *Z* isomers by careful silica gel column chromatography. The major isomers **2-85** and **2-86** had *E* geometry, and could be isolated in 59% and 42% yield respectively with an er of 88:12 for (*E*)-**2-85** and 86:14 for (*E*)-**2-86** (Table 2.5, entry 3 and 4). The minor *Z*-isomers (*Z*)-**2-85** and (*Z*)-**2-85** did not show any erosion of enantiomeric ratio and could be isolated in 9% and 17% yield respectively, both with er = 98:2.

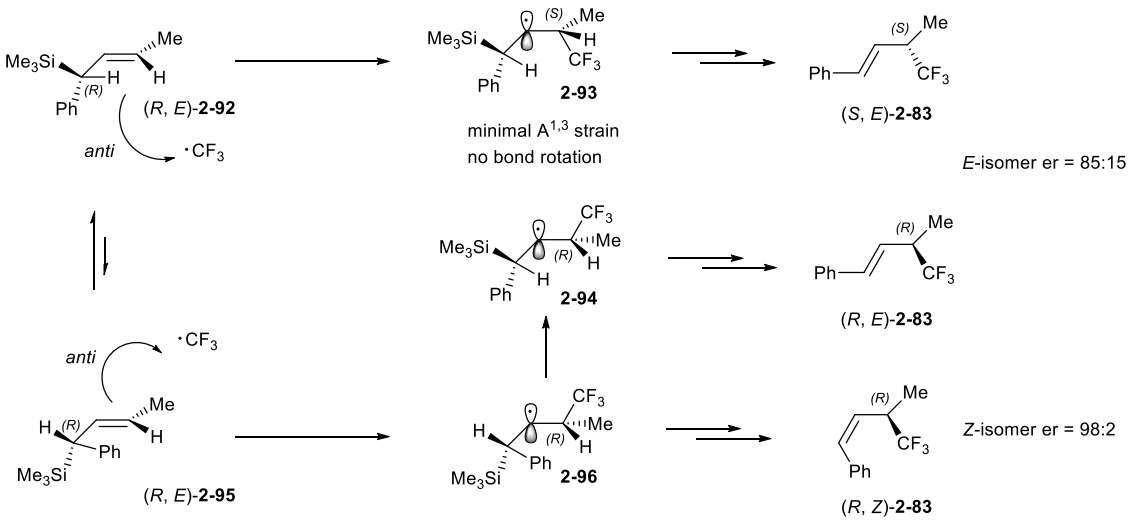
Based on previous work by Fleming and co-workers[21] we propose two possible explanations for the observed decrease in enantiomeric ratio in the *E*-isomer (er between 85:15 and 88:12) in comparison to the *Z*-isomer (er = 98:2). The first explanation takes into account the facial selectivity of the approach of the electrophile, in this case the CF_3 radical (see Scheme 2.20). In conformation **2-87**, which is favoured compared to **2-90** due to minimalisation of $A^{1,3}$-strain,[18] the approach predominantly occurs from the C_α-*Si* face, *anti* to the silyl-group, affording (*S*, *E*)-**2-88**. Due to the increased steric hindrance of the C_α-*Si* face by the aryl substituent in conformation **2-87**, formation of a small amount of the

(*R*, *E*)-**2-88** from C_α-*Re* approach (*syn* approach) of the electrophile also occurs, resulting in an erosion of the enantiomeric ratio. In comparison, approach from the C_α-*Re* face of the electrophile in the conformation **2-90** (*anti* to the silyl group) is hindered only by a small hydrogen substituent, resulting in exclusive formation of (*R*, *Z*)-2-88 without erosion of the enantiomeric ratio.



Scheme 2.20 Proposed pathway for erosion of entiomeric ratio

One could also assume that the approach of the electrophile occurs exclusively *anti* to the silyl group (approach from the C_α-*Re* face in conformation (*R*, *E*)-**2-92**, and the C_α-*Si* face in conformation (*R*, *E*)-**2-95**), but involves bond rotation prior to desilylation, to generate a cationic intermediate of lower energy (Scheme 2.21). Trifluoromethylation of the higher energy conformation (*R*, *E*)-**2-95** would result in formation of intermediate **2-96**, which can release $A^{1,3}$-strain by bond-rotation, resulting in the formation of lower energy radical intermediate **2-94**. Oxidation and de-silylation of **2-94** would result in formation of *E*-isomer (*R*, *E*)-**2-83**, which is the opposite enantiomer of (S, *E*)-**2-83** and thus results in erosion of the enatiomeric ratio.



Scheme 2.21 Proposed pathway for erosion of enantiomeric ratio by bond rotation

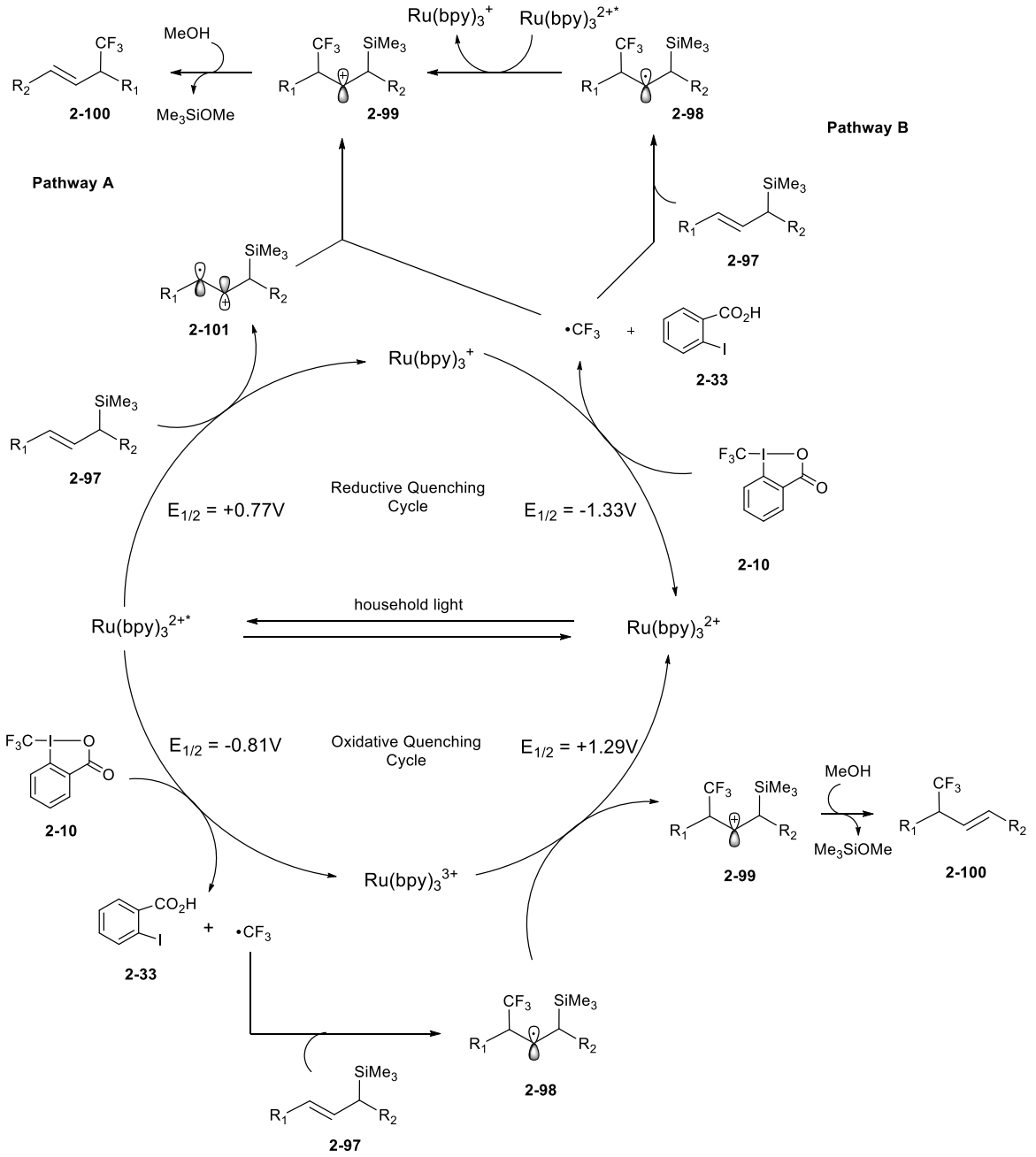
Although it is difficult to distinguish between these two possible mechanism, an argument can be made against the possibility of bond rotation since this would require the silicon to adopt an orthogonal position towards the β-carboradical (or β-carbocation if the bond rotation occurs after oxidation), in which there is no stabilisation from hyperconjugation.[2b] The absolute configuration of the *E*-isomers of (*E*)-**2-83** - (*E*)-**2-86** was assigned as *S* in analogy with the trifluoromethylation of **S-47** (see section 2.3.1), assuming an *anti*-S_E' mode of addition to the silyl group. The *Z*-isomers (*Z*)-**2-85** and (*Z*)-**2-86** was tentatively assigned to have the *R*-configuration in analogy with the previous reasoning supported by the work of Fleming. Attempts of crystallisation to determine the absolute configuration of (*Z*)-**2-85** and (*Z*)-**2-86** by single crystal X-ray diffraction were not successful.

2.4 Mechanistic Considerations

For the mechanistic studies on the photoredox catalysed trifluoromethylation of allylsilanes, we focused on the reaction conditions using the Togni II reagent **2-10**. A plausible mechanism involves generation of excited state $*Ru(bpy)_3^{2+}$ from visible light irradiation of the ground state $Ru(bpy)_3^{2+}$ complex (for more detail see section 1.2.4), as

detailed in Scheme 2.22. The excited state *$Ru(bpy)_3^{2+}$ ($E_{1/2}^{II/III}$ = -0.81V vs SCE in CH_3CN)[22] can enter an oxidative quenching cycle and donate an electron to the Togni II reagent **2-10**, with formation of the Togni II reagent radical anion and $Ru(bpy)_3^{3+}$, a strong oxidant ($E_{1/2}^{III/II}$ = +1.29V vs SCE in CH_3CN).[23] The radical anion collapses under formation of the CF_3 radical, which can add to the allylsilane **2-97** to generate the intermediate β-silyl carboradical species **2-98**. This intermediate radical then undergoes electron transfer from the strong oxidant $Ru(bpy)_3^{3+}$, to give the β–silyl cationic intermediate **2-99** and the ground state $Ru(bpy)_3^{2+}$, which completes the cycle. The cationic intermediate **2-99** undergoes rapid desilylation by MeOH to provide the branched allylic trifluoromethylated product **2-100**. Both the radical and cationic intermediate **2-98** and **2-99** are stabilised by $\sigma_{Si\text{-}C} \rightarrow p$ hyperconjugation, with the contribution to the stability of the radical being small (2.5 - 4.6 kcal/mol) in comparison with the significant stability imparted to the cation (29-30 kcal/mol).[2,3]

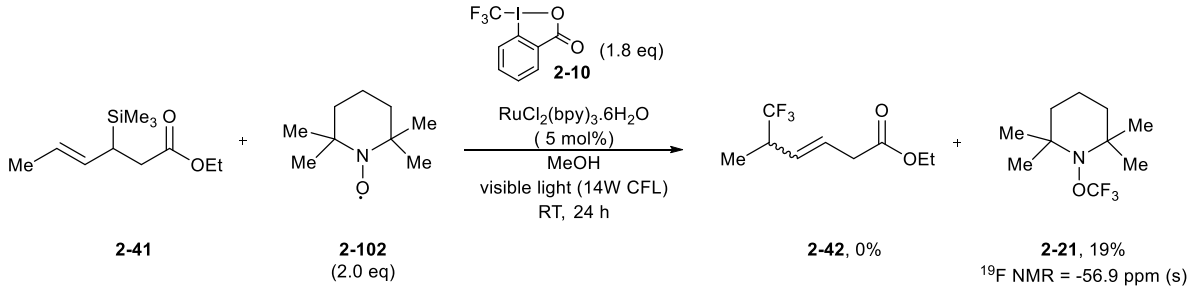
Alternatively the excited state *$Ru(bpy)_3^{2+}$ can enter a reductive quenching cycle ($E_{1/2}^{II/I}$ = +0.77 V in CH_3CN), in which it accepts an electron from the allylsilane, forming radical cation **2-101** and $Ru(bpy)_3^{+}$, a strong reductant ($E_{1/2}^{I/II}$ = -1.33 V in CH_3CN).[23] Electron transfer from $Ru(bpy)_3^{+}$ to the Togni II reagent **2-10** then generates the CF_3 radical and regenerates the ground state $Ru(bpy)_3^{2+}$. The CF_3 radical can combine with the radical cation **2-101** to give the trifluoromethylated β-silyl cationic intermediate **2-99** (Scheme 2.22, pathway A) which provides the trifluoromethylated product **2-100** after desilylation. In an alternative pathway (Scheme 2.22, pathway B) the CF_3-radical can react with another molecule of allylsilane and provide the trifluoromethylated product **2-100** after oxidation of the radical by the excited state *$Ru(bpy)_3^{2+}$ followed by desilylation.



Scheme 2.22 Mechanistic proposal for the photoredox catalysed trifluoromethylation of allylsilanes

To investigate the involvement of radical intermediates, the trifluoromethylation of allylsilane **2-41** was conducted with the free radical quencher 2,2,6,6-tetramethyl-1-piperinyloxy (TEMPO) **2-102** as additive (Scheme 2.23). Analysis of the reaction mixture with ^{19}F NMR after work-up, showed that the addition of TEMPO (2 eq) completely

supressed the formation of the trifluoromethylated product. The only fluorinated signal found was a singlet at -56.9 ppm, which could be identified as the TEMPO-CF_3 adduct **2-21** by comparing the ^{19}F NMR shift with the literature value.[23] This result indicates that involvement of radical species is possible, with formation of the TEMPO-CF_3 adduct as tentative evidence for formation of the CF_3-radical.

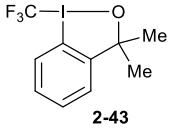
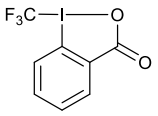
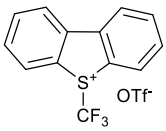


Scheme 2.23 Photoredox catalysed trifluoromethylation with radical quencher TEMPO as additive

In order to gain more insight in the electron transfer from the excited state $*Ru(bpy)_3^{2+}$ and the mechanistic pathway involving either an oxidative or reductive quenching cycle, we investigated the electrochemical behaviour of the reactants using cyclic voltammetry (CV). The CV measurements were performed by Dr. M. Médebielle at the University of Lyon.[24]

The cyclic voltammetry of the trifluoromethylating reagents **2-43**, **2-10** and **2-44** was investigated in different solvents, using a glassy carbon electrode and Bu_4NPF_6 as the supported electrolyte. For all reagents, the electrochemical data showed a first reduction peak (wave) that is irreversible, indicating that the reduction forms an unstable intermediate, which immediately reacts further to give a new product (see Experimental Procedures for details). This reduction was proposed to generate the CF_3-radical, through collapse of the unstable intermediate that forms when the trifluoromethylating reagent accepts an electron (see section 1.2.4 in introduction). In the case of the Umemoto reagent

2-44 a second, reversible reduction peak was visible at a more negative potential, which was assigned to the formation of the radical anion from dibenzothiophene after comparing the CV data with that of a commercial sample. Dibenzothiophene is formed as a side-product during the process of formation of the CF_3 radical, and was also observed by ^1H NMR in the crude reaction mixtures of the photoredox catalysed trifluoromethylation reactions. The cathodic peak potentials of the first electrochemical wave ($E_{pc}1$) of the tested trifluoromethylating reagents are listed in Table 2.6.

Entry[a]	CF_3 reagent	$E_{pc}1$[b] CH_3CN	$E_{pc}1$[b] MeOH	$E_{pc}1$[b] DMF
1	 **2-43**	-1.51 V	-	-2.35 V
2	 **2-10**	-0.79 V	-1.24 V	-1.67 V
3	 **2-44**	-0.32 V	-0.59 V	-0.54 V

[a] Measurements performed by Dr. M. Médebielle [b] 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. SCE (standard calomel electrode), scan rate: 0.2 V/s.

Table 2.6 Cyclic voltammetry measurements for trifluoromethylating reagents **2-43**, **2-10** and **2-44**

In the oxidative quenching cycle (Scheme 2.22), the excited state $*Ru(bpy)_3^{2+}$ is proposed to act as a reductant, and transfers an electron to the Togni II reagent **2-10**. The half wave potential for the oxidation of the excited state $*Ru(bpy)_3^{2+}$ has been calculated as $E_{1/2}^{II/III}$ = -0.81V vs SCE in CH_3CN,[23] which would be compatible with the electron acceptor capability of the Togni II reagent ($E_{pc}1$ = -0.79V vs SCE in CH_3CN). Based on this observation, it can be concluded that the oxidative quenching cycle is operative in the

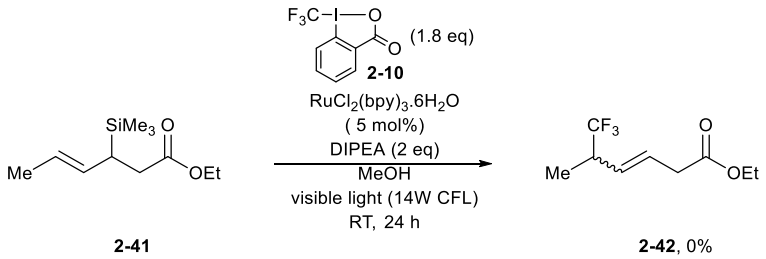
trifluoromethylation reaction of allylsilanes. The reduction of the Togni I reagent **2-43** ($E_{pc}1$ = -1.51V vs SCE in CH_3CN) by the excited state *$Ru(bpy)_3^{2+}$ would be expected to be much more difficult, and this is experimentally shown by the failure of this reagent to trifluoromethylate the allylsilane **2-41**in either CH_3CN, MeOH or DMF as solvent (Section 2.2 Table 2.1).

In the reductive quenching cycle the excited state *$Ru(bpy)_3^{2+}$ acts as an oxidizer and accepts an electron from the allylsilane to form the radical cation **2-101**. To investigate the feasibility of this step, the oxidation potential of ethyl (*E*)-3-(trimethylsilyl)hex-4-enoate **2-41** as a representative allyl silane was measured, using cyclic voltammetry in CH_3CN with a glassy carbon electrode and NBu_4PF_6 as the supporting electrolyte. The oxidation potential was determined to be in excess of 1.8 V vs SCE, which would make the oxidation of the allylsilane by the excited state *$Ru(bpy)_3^{2+}$ ($E_{1/2}^{II/I}$ = +0.77 V vs SCE in CH_3CN) thermodynamically very challenging. On the basis of this result it seems unlikely that a reductive quenching cycle is operative.

Although the experimental data seems to be supported by the CV data, it must be taking into account that the CV data is based upon the peak potential of irreversible reduction, and is only indicative of the electron acceptor capabilities of the compounds that were measured. It is therefore possible that the reduction of these compounds can take place at more positive potential. Electron transfer from a redox mediator in solution has been shown to be achievable at less negative potential compared to direct electrochemistry, for example in the reduction of CF_3I with aromatic radical anions,[25] and in the reduction of aromatic CF_2Br compounds with tetrakis dimethylaminoethene (TDAE).[26]

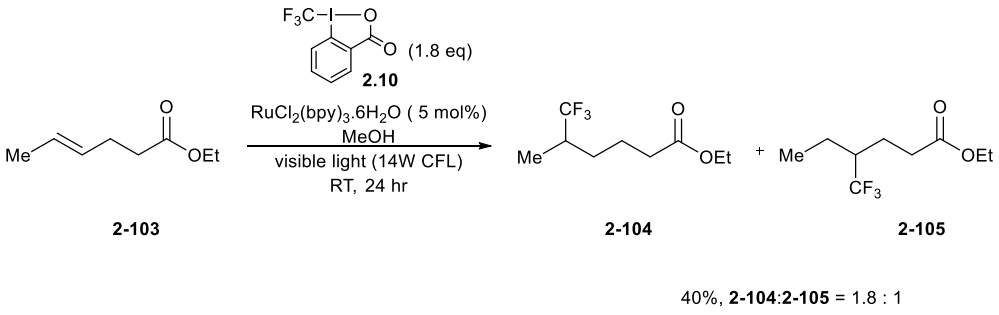
To further investigate the mechanistic possibility of a reductive quenching cycle, the trifluoromethylation of allylsilane **2-41** was run under the optimised conditions with addition of DIPEA (2 eq), a known reductive quencher for $Ru(bpy)_3^{2+}$ (Scheme 2.24).[27]

The absence of any trifluoromethylated product from this reaction, supports the conclusion that the reductive quenching cycle does not contribute to the formation of the CF_3 radical.



Scheme 2.24 Trifluoromethylation of allylsilane **2-41** in the presence of reductive quencher DIPEA

The importance of the directing and activating ability of the silyl substituent was demonstrated by the reaction of non-silyl containing (*E*)-ethyl hex-4-enoate **2-103** under the optimised trifluoromethylation conditions (Scheme 2.25). This reaction was unselective, and provided a mixture of two regioisomeric trifluoromethylated esters **2-104** and **2-105** (ratio **2-104**:**2-105** = 1.8 : 1), as determined by analysis with ^{19}F NMR and GC-MS, and comparison with an independently synthesized sample. This outcome is in contrast with the reactivity profile of the silyl activated **2-41**, which provides only the branched allylic trifluoromethylated product (see section 2.2).



Scheme 2.25 Trifluoromethylation of (*E*)-ethyl-hexyl-4-enoate

2.5 Conclusions

In conclusion, this chapter reports the photoredox catalysed trifluoromethylation of allylsilanes **2-40** and **2-70**, resulting in allylic trifluoromethylated products. The reaction was performed under irradiation of visible light using $RuCl_2(bpy)_3.6H_2O$ as the photoredox catalyst using either the Togni II reagent **2-10** or the Umemoto reagent **2-44** as suitable trifluoromethyl sources. The efficiency of chirality transfer was investigated in the trifluoromethylation of diastereomerically pure *anti* α-substituted allylsilanes **2-40**. The silicon substituent was instrumental in controlling the stereochemical outcome and the allylic trifluoromethylated products were produced in excellent *E*/*Z* ratio (>15:1), with a preference for the *syn*-isomer in accordance with the *anti* S_E2 mechanism. Chirality transfer was not complete, as varying amounts of the (*E*)-*anti*-isomers were formed during the reaction (*syn*/*anti* ratio between 3.5 and 10.0). Trifluoromethylation of enantioenriched α-aryl allylsilanes **2-81** (e.r. >99:1) provided access to chiral allylic trifluoromethylated products **2-82**. The allylic trifluoromethylated products were isolated in moderate yields, as a mixture in which the major product was the *E*-isomer. This isomer showed less than complete chiral transfer, and an erosion of the enatiomeric ratio (er between 85:15 and 88:12). In the cases where the minor *Z*-isomer could be obtained as a pure compound ((*Z*)-**2-85** and (*Z*)-**2-86**), it was found that chirality transfer for this isomer was essentially complete (er = 98:2).

An experiment in the presence of radical quencher TEMPO, revealed that the CF_3 radical could be an intermediate in this reaction. Further investigation into the possibility of generation of the CF_3 radical under photoredox conditions, and the pathway of the photoredox catalytic cycle, was conducted by measuring the redox potentials of the trifluoromethylating reagents and allylsilane starting material using cyclic voltammetry. These values were compared to the known half-wave potentials of the ground state and

excited photocatalyst, which showed that generation of a CF_3-radical from either the Togni II or Umemoto reagent was thermodynamically possible, and further allowed for more insight into the catalytic cycle. These experiments favoured the oxidative quenching cycle of the photoredox catalyst over the reductive quenching cycle. This conclusion was supported by the failure of trifluoromethylation in the presence of DIPEA, a known reductive quencher of $RuCl_2(bpy)_3.6H_2O$. Finally, the regio-directing ability of the silyl-group was established by reaction of a non-silyl containing alkene, which provided an inseparable mixture of trifluoromethylated alkyl products.

2.6 References

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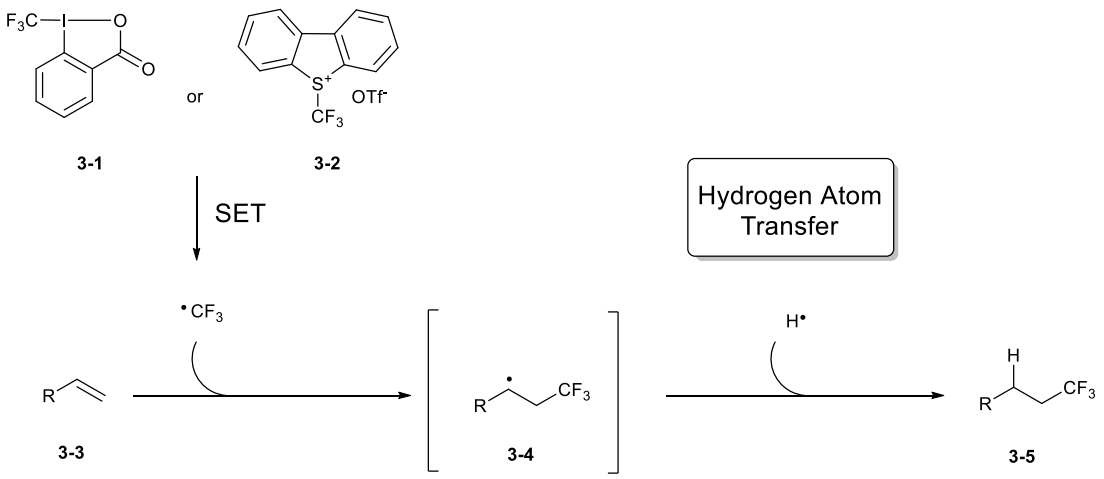
Chapter 3: Photoredox Catalysed Hydrotrifluoromethylation of Unactivated Alkenes

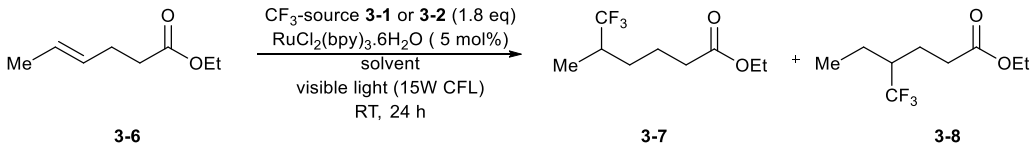
3.1 Introduction

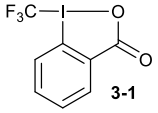
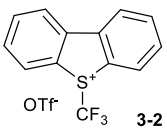
Alkenes are important, widely available, building blocks that have been used in a vast number of chemical transformations involving carbon-carbon and carbon-heteroatom bond formation.[1] As a carbon-carbon bond forming tool, direct hydroalkylation of alkenes is an important transformation, which has found widespread application in industrial processes and the synthesis of bioactive molecules.[2] Hydroalkylation can be achieved through the reductive addition of free radicals to alkenes, and this type of functionalisation has been successfully used for the catalytic hydroperfluoroalkylation of alkenes,[3] providing aliphatic perfluoroalkylated products that are difficult to synthesize using other methods. Despite the success in developing methods for hydroperfluoroalkylation, no examples of hydrotrifluoromethylation of alkenes have been reported in the literature.[4] This transformation would lead to the formation of otherwise difficult to access compounds containing an aliphatic CF_3 group, and therefore be a valuable tool for their synthesis (see Introduction Chapter). The successful photoredox catalysed trifluoromethylation of allylsilanes using a CF_3 radical as reactive species (see Chapter 2), prompted us to investigate the possibility of using this strategy for hydrotrifluoromethylation of alkenes (Scheme 3.1). If hydrogen atom transfer to the carbon radical **3-4** could be favoured, a net addition of HCF_3 across a double bond would result in formation of alkyl-CF_3 product **3-5**.



Scheme 3.1 Formal net addition of HCF_3 across a double bond

Preliminary results into the feasibility of this envisioned hydrotrifluoromethylation reaction were obtained from the mechanistic investigation on the influence of the silyl group on the regioselectivity of the photoredox catalysed trifluoromethylation of allylsilanes (see Section 2.3). When ester **3-6** was subjected to the optimized conditions (see Section 2.2) using either the Togni II reagent **3-1** in MeOH, (Table 3.1, entry 1) or the Umemoto reagent in EtOH (Table 3.1 entry 2), a mixture of trifluoromethylated products was obtained. These products were identified as the result of unselective formal HCF_3 addition across the double bond (see section 2.3).



Entry[a]	CF_3-reagent	Solvent	Yield (3-7:3-8)[b]
1	 3-1	MeOH	40% (1.8 : 1)
2	 3-2	EtOH	28% (2.2 : 1)

[a] **3-6** (0.15 mmol), $RuCl_2(bpy)_3.6H_2O$ (0.008 mmol), CF_3-source **3-1** or **3-2** (0.27 mmol), solvent [0.5M]. [b] Determined by ^{19}F NMR using $PhCF_3$ as internal standard.

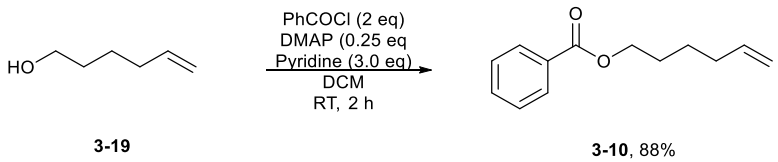
Table 3.1 Photoredox catalysed trifluoromethylation of ester **3-6**

3.2 Reaction Optimisation

The work in the next sections was carried out in collaboration with Dr S. Mizuta and Dr K. M. Engle.[5] The reactions in Scheme 3.2 and 3.3 were performed by Dr. K. M. Engle, and the reactions in Scheme 3.4 and 3.6 were performed by Dr. S. Mizuta. Experimental data for these compounds can be found in the appendix.

Investigation of the rate of addition of free radicals to alkenes, in addition to theoretical studies, have shown that attack on the less substituted carbon of an alkene is favoured, in large part because of steric reasons.[6] In the photoredox catalysed trifluoromethylation of ester **3.6** (see previous section) a mixture of products was obtained, which would be consistent with attack of a presumed CF_3 radical intermediate on both carbon atoms of the alkene. The preference for formation of ethyl 6,6,6-trifluoro-5-methylhexanoate **3-7** over ethyl 4-(trifluoromethyl)hexanoate **3-8** can be explained by the lower steric repulsion from attack on the carbon of the double bond substituted with a Me group in **3-6**.

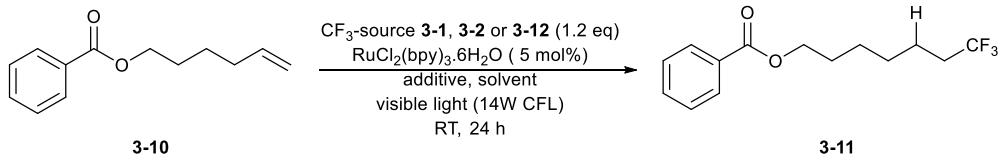
Addition of free radicals to terminal double bonds have been found to proceed with very good selectivity for attack on the terminal carbon of the alkene,[7] and in an effort to improve the selectivity of the photoredox catalysed hydrotrifluoromethylation, we decided to investigate the use of hex-5-en-1-yl benzoate **3-10** as a model substrate. Benzoate **3-11** was synthesized in 88% yield by DMAP catalysed benzoylation of hex-5-en-1-ol **3-19** (Scheme 3.2).



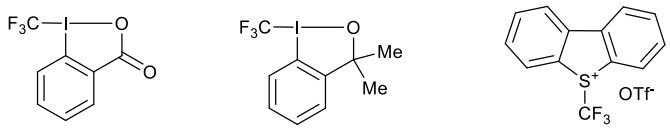
3-19 **3-10**, 88%

Scheme 3.2 Synthesis of model substrate **3-10**

The substrate **3-10** was subjected to trifluoromethylation under photoredox conditions. As a starting point, similar conditions as those used for trifluoromethylation of allylsilanes (See Chapter 2) were chosen, using the reagents **3-1**, **3-2** and **3-12** as trifluoromethyl source and a catalytic amount of $RuCl_2(bpy)_3.6H_2O$ as photoredox catalyst (Table 3.2). The Hantschz ester **3-13**, which has been successfully applied for this purpose in photoredox catalysed reduction of aromatic and aliphatic halides, was used as additive to investigate the effect of an added hydrogen atom source.[8]



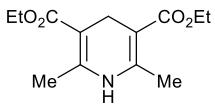
3-10 **3-11**



3-1 **3-12** **3-2**

Entry[a,b]	CF_3-source	Additive	Solvent	Yield[c]
1	Togni I, **3-12**	**3-13** (2 eq)	DMSO	17%
2	Togni II, **3-1**	**3-13** (2 eq)	DMSO	22%
3	Umemoto, **3-2**	**3-13** (2 eq)	DMSO	24%
4	Umemoto, **3-2**	**3-13** (2 eq)	DMF	30%
5	Umemoto, **3-2**	**3-13** (2 eq)	MeOH	35%
6	Umemoto, **3-2**	--	MeOH	67% (78%)
7	Togni I, **3-12**	--	MeOH	NR[d]
8	Togni II, **3-1**	--	MeOH	13%
9	Umemoto, **3-2**	--	EtOH	22%
10	Umemoto, **3-2**	--	iPrOH	10%
11	Umemoto, **3-2**	--	TFE	7%
12[e]	Umemoto, **3-2**	--	MeOH	43%

[a] **3-10** (0.15 mmol), $RuCl_2(bpy)_3.6H_2O$ (0.008 mmol), CF_3-source **3-1**, **3-2**, **3-12** (0.18 mmol), solvent [0.5M]. [b] Reactions in entry 1-5, 7 and 12 were performed by Dr. S. Mizuta [c] Determined by ^{19}F NMR using $PhCF_3$ as internal standard. Yield in parenthesis are from isolated compound. [d] NR = no reaction. [e] 2 mol% $RuCl_2(bpy)_3.6H_2O$ was used.



3-13,
diethyl 1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate

Table 3.2 Reaction optimisation using hex-5-en-1-yl benzoate **3-10**

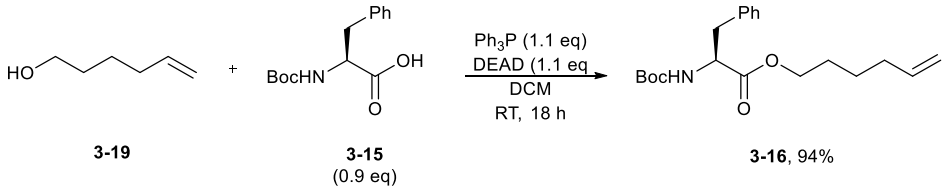
A solution of hex-5-en-1-yl benzoate **3-10**, trifluoromethylating reagent **3-1**, **3-2**, or **3-12** (1.2 eq) and a catalytic amount of the photoredox catalyst $RuCl_2(bpy)_3.6H_2O$ (5 mol%) in various solvents (0.5M) was stirred at room temperature, under irradiation from a 14W fluorescent light source (common household light) at approx. 5 cm distance. After work-up, a known amount of reference compound ($PhCF_3$) was added to the crude reaction mixture, and the yield of trifluoromethylated product **3-11** was determined using ^{19}F NMR. Initial experiments were performed using Hantzsch ester **3-13** as hydrogen atom donor in combination with the Togni I reagent **3-12**, the Togni II reagent **3-1** (Table 3.2, entry 1-2) or the Umemoto reagent **3-2** (Table 3.2, entry 3), in DMSO as solvent. Modest yields of 7,7,7-trifluoroheptyl benzoate **3-11** (17-24%) were obtained with all three trifluoromethylating reagents. Further experiments with the Umemoto reagent showed an increase in formation of the hydrotrifluoromethylated product when using MeOH as solvent (35%, Table 3.2 entry 5). The Umemoto reagent was completely consumed under these conditions. To investigate the use of MeOH as possible hydrogen donor[9] the reaction was conducted in the absence of the Hantzsch Ester **3-13**, which resulted in a significantly improved product yield of 67% (Table 3.2 entry 6). Use of the Togni I reagent **3-12** and the Togni II reagent **3-1** did not show any improvement under these conditions (Table 3.2, entry 7 and 8). Various other alcoholic solvents capable of hydrogen donation, such as EtOH, iPrOH and TFE provided the trifluoromethylated product in low yields ((Table 3.2, entry 9 - 11, yield 7 - 22%). The Ru photocatalyst had a lower solubility in these solvents, and did not completely dissolve at the concentration used (0.025M). Lower loading of $RuCl_2(bpy)_3.6H_2O$ (2 mol%) led to formation of the trifluoromethylated product in 43% yield (Table 3.2, entry 12), accompanied by significant amounts of 7,7,7-trifluoroheptan-1-ol, produced from the hydrolysis of ester **3-11** (21% yield, as determined by ^{19}F NMR from comparison with an authentic sample).

From this study, it was concluded that the conditions using the Umemoto reagent **3-2** (1.2 eq) in combination with $RuCl_2(bpy)_3.6H_2O$ (5 mol%) in MeOH (0.5M) provided the highest yield of hydrotrifluoromethylated product.

3.3 Hydrotrifluoromethylation of Unactivated Terminal Alkenes

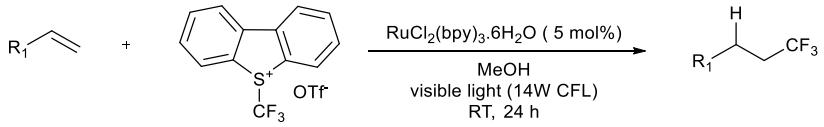
With the optimized conditions, the photoredox catalysed reductive trifluoromethylation was performed on a series of unactivated terminal alkenes.

Ester substituted terminal alkenes **3-17** and **3-18** were synthesized in good yield by reaction of hex-5-en-1-ol **3-19** with DCC (1 eq) and the heteroaromatic acid (1.1 eq ; nictonic acid for **3-17**, furan-3-carboxylic acid for **3-18**), using a catalytic amount of DMAP (10%) in DCM at room temperature. Amide **3-21** was synthesized in 94% yield in a similar fashion from benzylamine and 4-pentenoic acid.[10] Amino acid derived ester **3-16** could be synthesized in 99% yield by esterification of *N*-Boc-protected phenylalanine **3-15** (0.9 eq) under Mitsunobu conditions, using PPh_3 (1.1 eq) and DEAD (1.1 eq) in DCM at room temperature (Scheme 3.3).[11] Other starting materials **3-14**, **3-20** and **3-22 - 3-24** were commercially available.

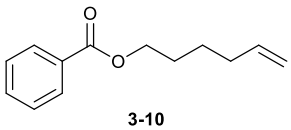
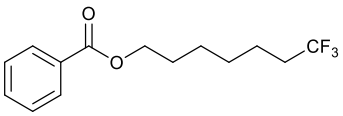
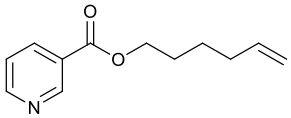
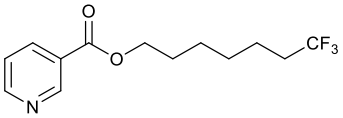
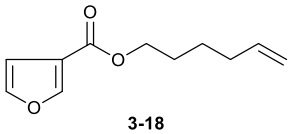
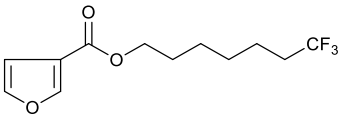
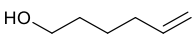
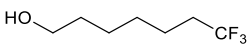
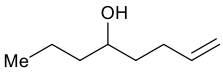
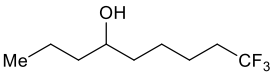
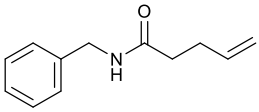
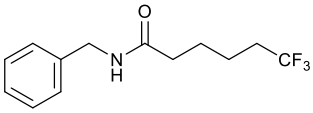
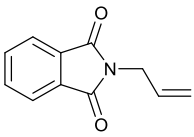
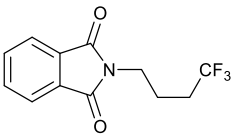
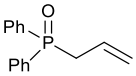
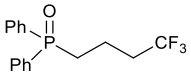
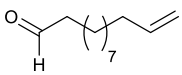
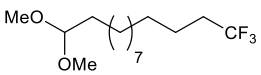


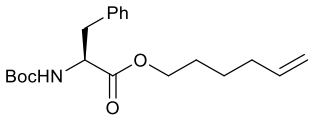
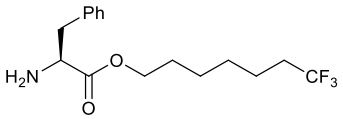
Scheme 3.3 Esterification of **3.15** under Mitsunobu conditons

Alkenes **3-16** – **3-24** were subjected to the optimized hydrotrifluoromethylation conditions, using the Umemoto reagent **3-2** and the photoredox catalyst $RuCl_2(bpy)_3.6H_2O$ in MeOH. The results are shown in table 3.3.



3.3 **3.2** **3.5**

Entry[a,b]	Alkene	Product	Yield[c]
1	 **3-10**		**3-11**, 78%
2	 **3-17**		**3-25**, 42%
3	 **3-18**		**3-26**, 33%
4	 **3-19**		**3-27**, 47%
5	 **3-20**		**3-28**, 60%
6	 **3-21**		**3-29**, 44%
7	 **3-22**		**3-30**, 57%
8	 **3-23**		**3-31**, 19%[d]
9	 **3-24**		**3-32**, 55%

10	 **3-16**		(*S*)-**3-33**, 52%

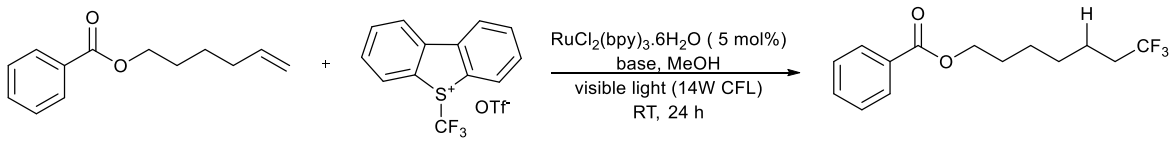
[a] Alkene (0.25 mmol), $RuCl_2(bpy)_3.6H_2O$ (0.013 mmol), Umemoto reagent **3-2** (0.30 mmol), MeOH [0.50M]. [b] Products **3.27**, **3.28**, **3.29**, **3.30**, **3.31**, and **3.33** were synthesized by Dr. S.Mizuta [c] Isolated yield after column chromatography.[d] Several unknown side products were detected by ^{19}F NMR analysis of the crude reaction mixture

Table 3.3 Hydrotrifluoromethylation of unactivated terminal alkenes

A solution of the alkene, the Umemoto reagent **3-2** (1.2 eq.) and the photoredox catalyst $RuCl_2(bpy)_3.6H_2O$ (5 mol%) in MeOH (0.5 M) was stirred at room temperature under irradiation from a 14W fluorescent light source (common household light) at approx. 5 cm distance. After quenching with sat. $NaHCO_3$ solution and work-up, the hydrotrifluoromethylated products were isolated as pure compounds using silica gel column chromatography. Small amounts of trifluoromethylated impurities from oxytrifluoromethylation and other side reactions could be detected in the crude reaction mixture (see Section 3.X Mechanistic Info further on), but these by-products could be removed upon purification. Under these conditions the hydrotrifluoromethylation reaction afforded the product in moderate to good yields, and the mild reaction conditions allowed for functional groups as esters, alcohols, amides, imides and carbamates to be tolerated. The benzoate **3-11** gave the trifluoromethylated product in 78% isolated yield (Table 3.3 entry 1), and heteroarene substituted unsaturated ester **3-17** and **3-18** containing a pyridine and furan moiety also provided the hydrotrifluoromethylated products, albeit in the slightly lower yields of 42% and 33% respectively (Table 3.3, entry 2 and 3). Careful analysis of the crude reaction mixture with ^{19}F NMR showed only traces of formation of the regioisomeric branched trifluoromethylated product. Both primary and secondary free hydroxyl groups were tolerated, and hex-5-en-1-ol **3-19** and oct-7-en-4-ol **3-20** could be hydrotrifluoromethylated in 44% and 60% yield (Table 3.3 entry 4 and 5) respectively. Alkene **3-21**, which containins a secondary amide, gave the trifluoromethylated product **3-29** in 44% yield (Table 3.3, entry 6), and a phthalimide group was also found to be stable

under the reaction conditions, as shown by formation of **3-30** in 57% yield (Table 3.3, entry 7). Hydrotrifluoromethylation of allyldiphenylphosphine oxide **3-23** proceeded in good conversion, but only a low yield **3-31** was obtained (19%, Table 3.3, entry 8). Analysis with ^{19}F NMR showed formation of several unidentified trifluoromethylated side-products in this reaction. When undec-10-enal **3-24** was subjected to the hydrotrifluoromethylation conditions it was found that the trifluoromethylated product had undergone acetalisation under the reaction conditions, with formation of dimethyl acetal **3-32** in 55% yield (Table 3.3, entry 9). The formation of the acetal **3-32** indicated that an acid, presumably TfOH, was produced during the reaction. This was also evident from the isolation of the deprotected trifluoromethylated amine (*S*)-**3-33** (Table 3.3 entry 11), after the hydrotrifluoromethylation under standard conditions of *N*-Boc-protected amino acid derived alkene (*S*)-**3-16**. The formation of acid on irradiation of sulfonium salts with UV or visible light has been reported, and has found application in photoinitiated cationic polymerisation.[12]

To facilitate the hydrotrifluoromethylation of acid-sensitive substrates, various inorganic and organic bases as additives were tested using the model substrate 7,7,7-trifluoroheptyl benzoate **3-10** under the standard reaction conditions (Table 3.4).



3-10 **3-2** **3-11**

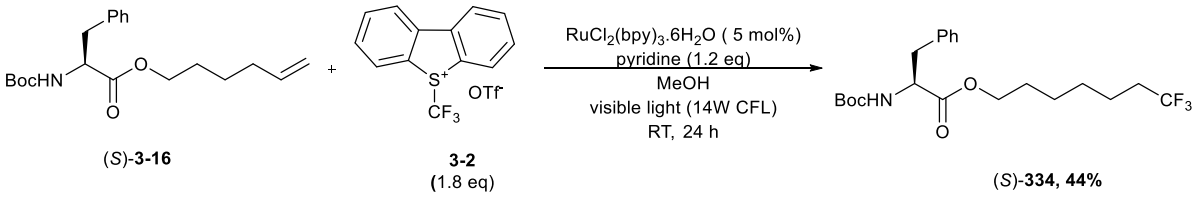
Entry[a,b]	Base	equiv.	Yield[c]
1	K_2CO_3	3	0%
2	KH_2PO_4	3	52%
3	NaH_2PO_4	3	41%
4	Na_2HPO_4	3	60%
5	DIPEA	2	13%
6	pyridine	1.2	75%
7	2,4,6-collidine	1.2	72%

[a] **3-10** (0.15 mmol), $RuCl_2(bpy)_3.6H_2O$ (0.008 mmol), Umemoto reagent **3-02** (0.18 mmol)mmol), solvent [0.5M]. [b] Reactions in entry 1-4 were performed by Dr. S.Mizuta. [c] Determined by ^{19}F NMR using $PhCF_3$ as internal standard.

Table 3.4 Screening of base additives for the hydrotrifluoromethylation reactions

A solution of the alkene, the Umemoto reagent **3-2** (1.2 eq.), the photoredox catalyst $RuCl_2(bpy)_3.6H_2O$ (5 mol%) and the base (1.2 - 3.0 eq) in MeOH (0.5 M) was stirred at room temperature under irradiation from a 14W fluorescent light source (common household light) at approx. 5 cm distance. After work-up, a known amount of reference compound ($PhCF_3$) was added to the crude reaction mixture and the yield of trifluoromethylated product **3-11** was determined using ^{19}F NMR. The inorganic base K_2CO_3 was successfully used in the photoredox catalysed trifluoromethylation of arylboronic acids by Sanford *et al*,[13] but resulted in a complete shutdown of the hydrotrifluoromethylation process (Table 3.4, entry 1). Transesterification was found to be the only reaction taking place. The additive KH_2PO_4, successfully used in photoredox catalysed trifluoromethylation of heteroarenes by MacMillan *et al*,[14] provided the hydrotrifluoromethylated product in 52 yield (Table 3.4 entry 2), slightly lower compared to the yield obtained under the standard conditions (68%, Table 3.4 entry 6). A similar

results was found when NaH_2PO_4 was used as additive (Table 3.4, entry 3). From the inorganic bases investigated, Na_2HPO_4 was shown to have the least influence on product formation, showing a 60% yield of **3-11** when it was used as an additive (Table 3.4, entry 4). Organic bases were found to be more effective as additives, and both pyridine (75% yield, Table 3.4 entry 6) and 2,4,6-collidine (72% yield, Table 3.4 entry 7) provided the hydrotrifluoromethylated product in good yield. The addition of DIPEA resulted in a decreased efficiency of the hydrotrifluoromethylation, which can presumably be attributed to the fact that this compound is a reductive quencher of the photoredox catalyst (see Chapter 2 Section 2.3). Pyridine was chosen as the preferred additive, and when the *N*-Boc-protected amino acid derived alkene (*S*)-**3-16** was subjected to the hydrotrifluoromethylation using this additive, a 44% yield of *N*-Boc-protected product (*S*)-**3-34** could be obtained (Scheme 3.4). No deprotection was found to take place under these conditions.



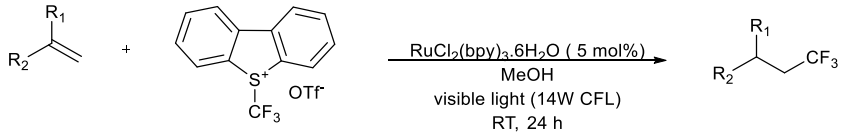
Scheme 3-4 Hydrotrifluoromethylation of (*S*)-**3-16** in the presence of pyridine

The addition of pyridine did not change the outcome of the hydrotrifluoromethylation reaction of undec-10-enal **3-24** (not shown), and acetalisation still took place under the reaction conditions, giving only dimethyl acetal **3-32** after isolation.

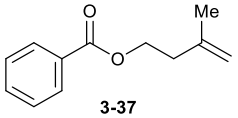
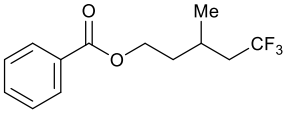
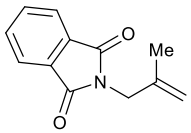
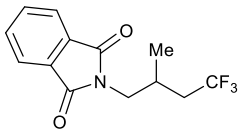
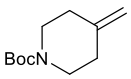
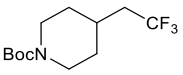
3.4 Hydrotrifluoromethylation of 1,1-Disubstituted Alkenes

1,1-Disubstituted alkenes were then subjected to the optimised hydrotrifluoromethylation conditions (Table 3.5). Starting alkene **3-37** could be prepared by benzoylation of 3-methylbut-3-en-1-ol, under similar conditions used for **3-10** (Section 3.3). Phthalimide

substituted **3-38** was obtained in 84% yield from the alkylation of potassium phthalimide with 3-chloro-2-methylpropene and K_2CO_3 in DMF at 80 °C. *N*-Boc-4-methylene piperidine **3-39** is commercially available.



3-35 3-2 3-36

Entry[a,b]	Alkene	Product	Yield[c]
1	 3-37		**3-40**, 53%
2	 3-38		**3-41**, 46%
3	 3-39		**3-42**, 64%[d]

[a] Alkene **3-35** (0.25 mmol), $RuCl_2(bpy)_3.6H_2O$ (0.013 mmol), Umemoto reagent **3-2** (0.30 mmol), MeOH [0.50M]. [b] Compound **3-40** was synthesized by Dr. S. Mizuta. [c] Isolated yield after column chromatography.[d] In the presence of pyridine (1.2eq)

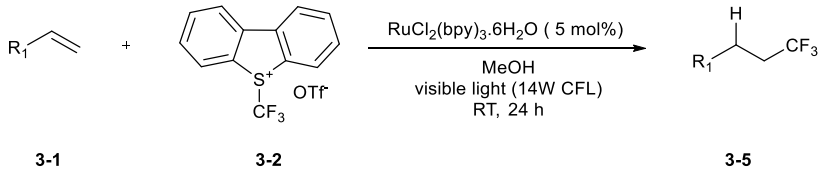
Table 3.5 Hydrotrifluoromethylation of 1,1-disubstituted alkenes

1,1-Substituted alkenes **3-35** were suitable substrates for the hydrotrifluoromethylation reaction, and benzoate **3-37** hydrotrifluoromethylated in 53% yield (Table 3.5, entry 1). Phthalimide substituted **3-38** provided the product in 47% yield (Table 3.5, entry 2). Cyclic alkenes could also be efficiently hydrotrifluoromethylated, and *N*-Boc-protected piperidine **3-42** was obtained in good yield, in the presence of pyridine (64% yield, Table 3.5, entry 3).

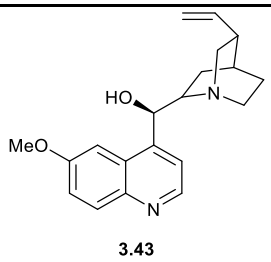
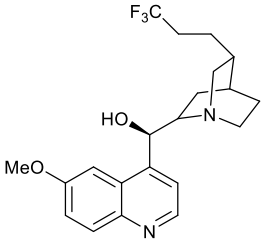
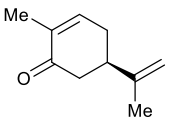
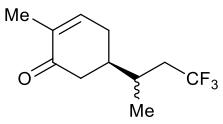
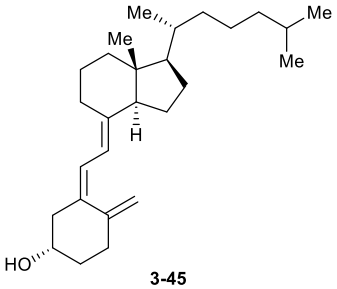
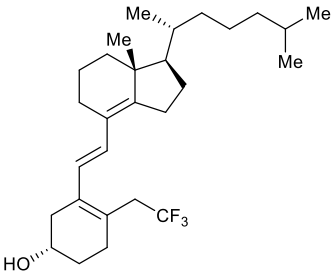
3.5 Late Stage Hydrotrifluoromethylation of Complex Molecules

The mild conditions and excellent functional group tolerance of the photoredox catalysed hydrotrifluoromethylation reaction makes this method very suitable for late stage synthesis

of trifluoromethylated compounds. To investigate the possibility of late stage trifluoromethylation, three complex (commercially available) starting materials, Quinine **3-46**, (*R*)-carvone **3-44** and Cholecalciferol (Vitamine D_3) **3-45**, were subjected to the optimised hydrotrifluoromethylation conditions (Table 3.6).



3-1 **3-2** **3-5**

Entry[a,b]	Alkene	Product	Yield[c]
1	 **3.43**		**3-46**, 57%
2	 **3-44**		**3-47**, 54% dr 1:1
3	 **3-45**		**3-48**, 39%

[a] alkene **3-1** (0.25 mmol), $RuCl_2(bpy)_3.6H_2O$ (0.013 mmol), Umemoto reagent **3-2** (0.30 mmol), MeOH (0.50M). [b] The compounds **3-46**, **3-47** and **3-48** were synthesized by Dr. S. Mizuta. [c] Isolated yield after column chromatography.

Table 3.6 Late stage hydrotrifluoromethylation of complex starting materials

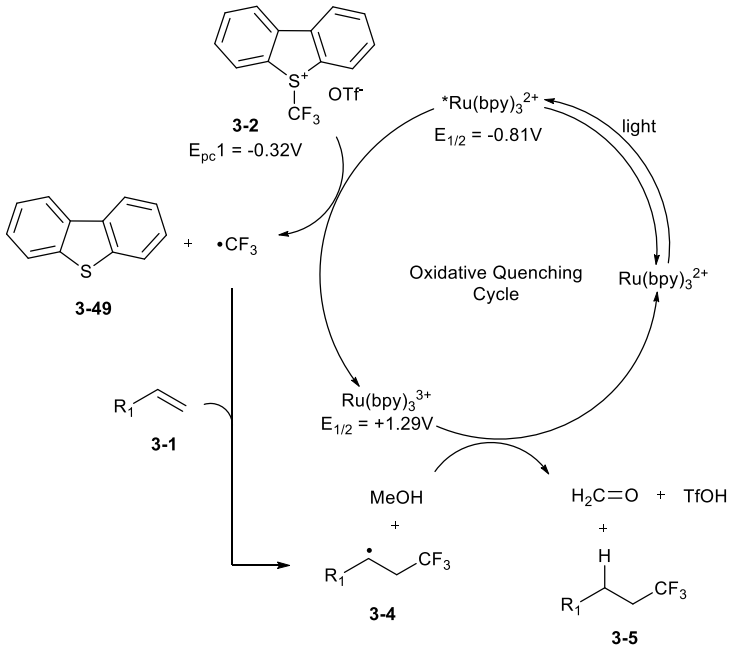
The hydrotrifluoromethylation of quinine **3-34** successfully afforded the hydrotrifluoromethylated product **3-46** in 57% yield (Table 3.6, entry 1), without any need

for protection of the free OH group. Chromatography on reversed-phase C18 silica gel was used to purify the product **3-46**. The terpenoid (*R*)-carvone **3-44** contains two different double bonds, and it was found that the terminal, more electron-rich double bond was hydrotrifluoromethylated with total chemoselectivity. The corresponding trifluoromethylated product **3-47** could be isolated in 54% with a dr of 1:1 (Table 3.6, entry 2). The selectivity for trifluoromethylation of the double bond can be explained by the formation of a CF_3 radical as the reactive species (see section 3.6 for further discussion). The CF_3 radical is an electrophilic radical with a low-lying singly occupied molecular orbital (SOMO),[15] and therefore reacts faster with double bonds which have a higher lying HOMO, such as electron-rich double bonds. Cholecalciferol (Vitame D_3) could also be successfully trifluoromethylated, but did not provide the hydrotrifluoromethylated product (see also next section). Instead, product **3-48** resulting from allylic trifluoromethylation could be isolated from the reaction mixture in 39% yield (Table 3.6, entry 3).

3.6 Mechanistic Considerations

For the mechanistic investigations of the photoredox catalysed hydrotrifluoromethylation of unactivated alkenes, we focused on the nature of the trifluoromethylation step and the hydrogen atom transfer. A plausible mechanism is shown in Scheme 3.5, and involves generation of excited state $*Ru(bpy)_3^{2+}$ from visible light irradiation of the ground state $Ru(bpy)_3^{2+}$ complex (for more detail see Introduction section 1.2.3 and 1.2.4). The excited state $*Ru(bpy)_3^{2+}$ then enters an oxidative quenching cycle, and donates an electron to the Umemoto reagent **3-2**, which generates a CF_3 radical and the strong oxidant $Ru(bpy)_3^{3+}$. The CF_3 radical then adds regioselectively to the alkene and generates radical **3-54**, which provides the trifluoromethylated product through hydrogen atom transfer. This hydrogen

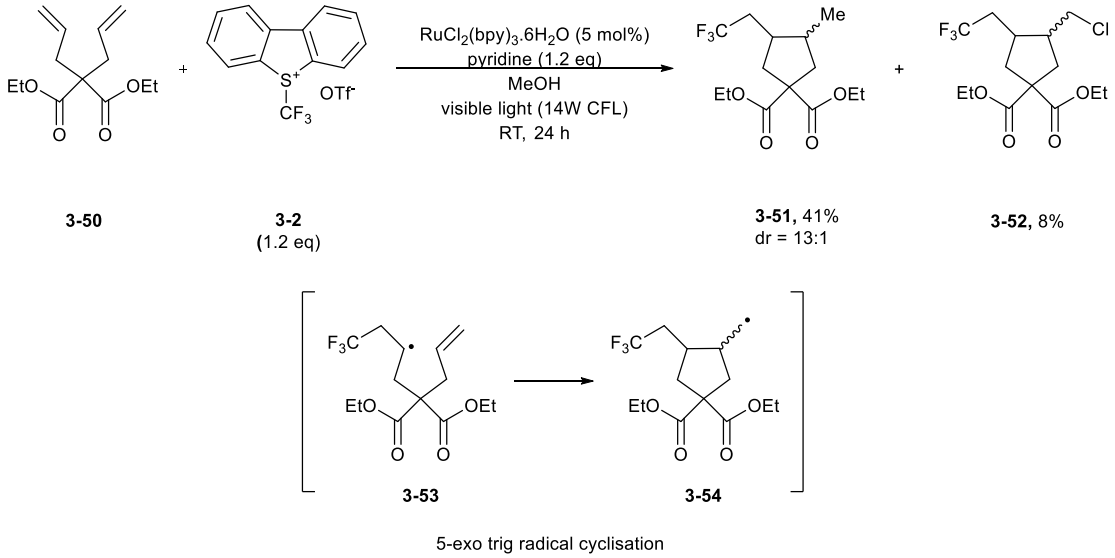
atom transfer step involves the oxidation of MeOH by the strong oxidant $Ru(bpy)_3^{3+}$, presumably to formaldehyde, with concomitant formation of the strong acid TfOH.



Scheme 3.5 Proposed mechanism for the hydrotrifluoromethylation of unactivated alkenes

3.6.1 Investigation in the Trifluoromethylating Step and Formation of Sideproducts

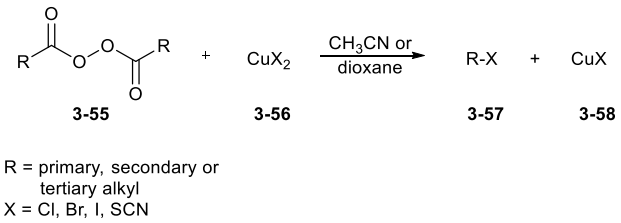
As shown in Chapter 2, the reduction potential of the Umemoto reagent[16] (-0.32V vs SCE in CH_3CN; section 2.3) is compatible with single electron transfer from the excited state *$Ru(bpy)_3^{2+}$ (-0.77V vs SCE in CH_3CN). This electron transfer step provides $Ru(bpy)_3^{3+}$ and the radical anion of the Umemoto reagent, which collapses into the CF_3 radical and dibenzothiophene **3-49**. To further investigate the presence of a CF_3 radical intermediate, diene **3-50** was subjected to the hydrotrifluoromethylation conditions (Scheme 3.6). Addition of the CF_3 radical to diene **3-50** would generate radical **3-53**, which would be expected to undergo facile 5-exo trig cyclisation to provide radical **3-54**.[17]



Scheme 3.6 Hydrotrifluoromethylation of diene **3-50**

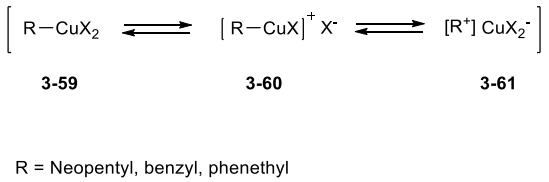
The hydrotrifluoromethylation of diene **3-50** resulted in the isolation of the cyclised trifluoromethylated product **3-51** as major product, in 41% yield and dr = 13:1 (Scheme 3.6). Chloro substituted **3-52** was isolated as minor product, in 8% yield. The ^{19}F NMR spectrum of the crude reaction mixture did not show formation of non-cyclised trifluoromethylated products. This result indicates that radical cyclisation takes place during the hydrotrifluoromethylation of diene **3-50** and is in favour of formation of a CF_3 radical as intermediate.

The chloro-substituted side-product **3-52** is proposed to originate from the oxidation of the cyclised radical **3-54** by $Ru(bpy)_3^{3+}$, with concomitant transfer of a chlorine atom. This transformation is similar to the oxidative ligand transfer process proposed by Kochi in the oxidation of alkyl radicals by metals such as Cu(II) and Pb(IV).[18] Kochi described the oxidation of alkyl radicals, generated from the decomposition of acylperoxides, with various Cu(II) salts to give the corresponding alkyl halides and thiocyanates (Scheme 3.7).



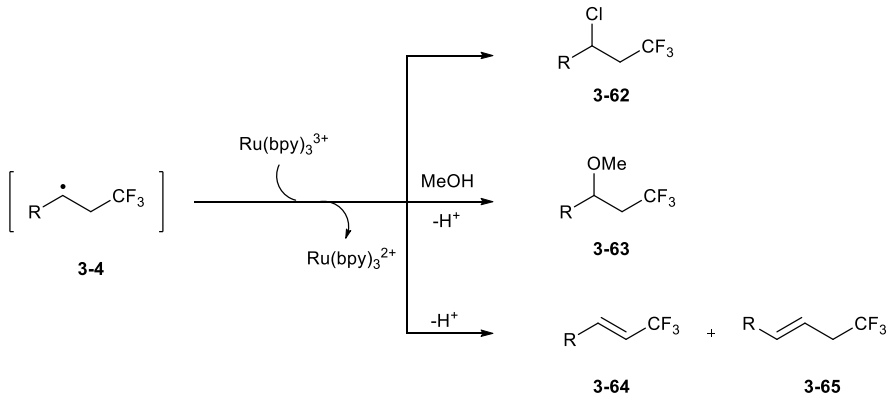
Scheme 3.7 Oxidative ligand transfer mechanism

Further mechanistic studies showed that an inner sphere atom-transfer mechanism was operating for most type of alkyl substituents, involving direct transfer of the ligand and a transition state containing free radical character. For substrates able to form stabilized carbocation intermediates, various amounts of rearrangement products were also obtained. For these substrates an outer sphere indirect transfer mechanism was also active, in which the transition state was predicted to have more carbocationic character, as shown in Scheme 3.8.[19]



Scheme 3.8 Outer sphere indirect transfer mechanism in oxidative ligand transfer

The proposed oxidation of the formed radical by the oxidant $Ru(bpy)_3^{3+}$ is a side-reaction that occurs to a certain extent with all substrates in the hydrotrifluoromethylation reaction (scheme 3.9). In addition to transfer of a chlorine atom as shown for **3-62**, reaction with MeOH, resulting in the formation of the corresponding oxytrifluoromethylated product **3-63**, was also found to occur. Vinylic or allylic trifluoromethylated compounds **3-64** and **3-65** could also be detected as side-products in certain cases.

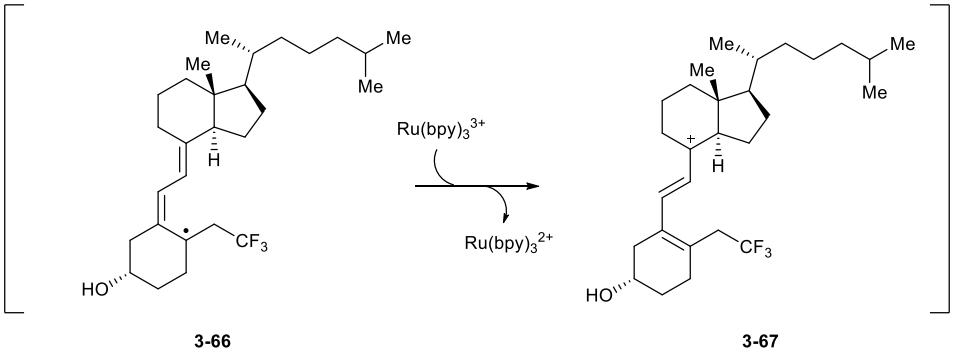


Scheme 3.9 Formation of side-products during the hydrotrifluoromethylation reaction

The process in which alkenes are formed after oxidation of alkyl radicals, designated as oxidative elimination, has been described by Kochi to occur simultaneously with oxidative ligand transfer. His research showed that the ratio of elimination versus substitution product could be qualitatively correlated to the stability of the formed carbocation on oxidation of the radical.[18a] For example, oxidation of primary radicals gave almost exclusively elimination products, whereas tertiary radicals provided a large amount of ligand substitution product. Further studies could not distinguish between a concerted process or a two-step mechanism in which a discrete carbocation is formed. The two-step mechanism adequately explains the results obtained from oxidation of radicals that give a more stabilised carbocation, such as tertiary, benzylic and allylic radicals, but the exclusive formation of alkenes from the oxidation of primary radicals cannot be explained by a formation of a high energy primary carbocation intermediate, and is more in favour of a concerted process.

For certain substrates in the hydrotrifluoromethylation reaction oxidative elimination became the major reaction pathway, for example in the trifluoromethylation of cholecalciferol (Vitamine D_3 **3-45**) shown in section 3.5 (Table 3.6, entry 3). In this case, it is proposed that the initially formed allylic carboradical **3-66** provides the rearranged carbocation **3-67** after oxidation, which generates the allylic trifluoromethylated product **3-**

48 after elimination of a proton (Scheme 3.10). The oxidation of radical **3-66** is proposed to be more facile because of the predicted relative stability of the tertiary allylic cation, which results in a lower ionisation potential for radical **3-66**.[18a]

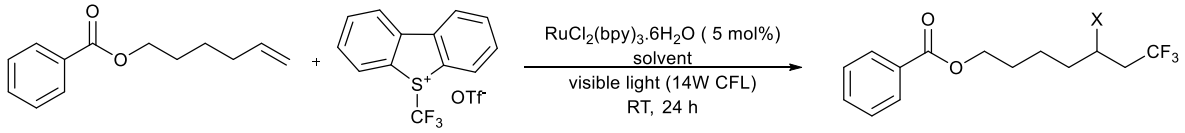


3-66 **3-67**

Scheme 3.10 Rearrangement of the trifluoromethylated allylic radical **3-66**

3.6.2 Insights in the Hydrogen Atom Transfer Mechanism

To investigate the hydrogen atom transfer step involving MeOH, the hydrotrifluoromethylation of **3-10** was performed under the optimised conditions using deuterated solvent (Scheme 3.7).



3-10 **3-2** **[D]3-11**, X = D
3-11, X = H

Entry[a,b]	Solvent	Yield[c]
1	CD_3OD	**[D]3-11**, 22%
2	CD_3OH	**[D]3-11**, 26%
3	CH_3OH/CD_3OD 1/1	**3-11**:**[D]3-11**, 1.5:1, 43%

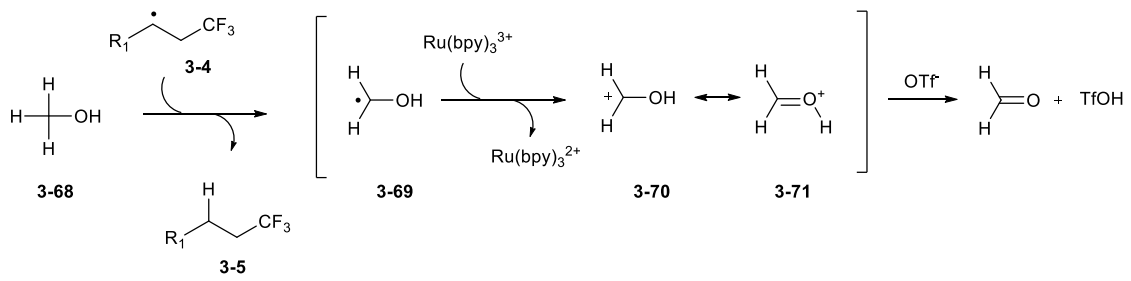
[a] alkene **3-10** (0.25 mmol), $RuCl_2(bpy)_3.6H_2O$ (0.013 mmol), Umemoto reagent **3-2** (0.30 mmol), solvent (0.50M). [b] Reactions in entry 1-3 were performed by Dr. S. Mizuta. [c] Isolated yield after column chromatography.

Table 3.7 Hydrotrifluoromethylation of **3-10** in deuterated sovent

When the reaction was performed in CD_3OD as solvent, the deuterated product [D]**3-11** could be isolated in 22% yield (Table 3.7, entry 1). The formation of [D]**3-11** could be

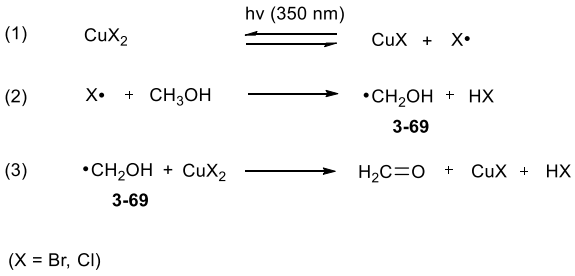
unambiguously established from the ^{13}C-NMR spectrum of the isolated compound, which showed a triplet of quartets at 21.5 ppm for the carbon bearing the deuterium atom (coupling with the deuterium atom and the three β-fluorine atoms from the CF_3). The signal for the CF_3 group in [D]**3-11** in the ^{19}F NMR spectrum showed a small, but significant, difference with the CF_3 of the non-deuterated compound **3-11** and careful analysis of the crude reaction mixture by ^{19}F NMR did not show formation of non-deuterated **3-11**. The lower yield obtained for deuterated **[D]3-11**, in comparison with the reaction in MeOH (78%, Table 3.2, entry 6), indicates that deuterium atom transfer is less efficient than hydrogen atom transfer in this reaction.[20] CD_3OH was then used as solvent, to determine if the hydrogen atom was transferred from either the CH_3 or the OH group of MeOH (Table 3.7, entry 2). From this experiment 28% of deuterated product **[D]3-11** could be obtained, and careful examination of the crude reaction mixture did not show formation of non-deuterated **3-11**, unambiguously establishing that the hydrogen atom is transferred from the CH_3 group of MeOH. When the reaction was run in a 1:1 mixture of MeOH and CD_3OD as solvent, a 43% yield of a mixture of **3-11** and **[D]-3-11** was obtained in a 1.5:1 ratio (Table 3.7 entry 3).

Based on these results, two possible mechanisms for the hydrogen transfer step can be postulated. In the first possible mechanism (Scheme 3.11) a hydrogen atom abstraction by the carboradical **3-4** from MeOH would generate the trifluoromethylated product **3-5** and radical **3-69**. Oxidation of this radical by the strong oxidant $Ru(bpy)_3^{3+}$ would result in formation of the resonance-stabilised carbocation **3-70**. Transfer of a proton to the triflate anion (from the Umemoto reagent **3-2**) would then generate formaldehyde and TfOH.



Scheme 3.11 Mechanism for hydrogen transfer from MeOH to radical **3-4**

This putative mechanism would account for the fact that the hydrogen atom is transferred from the CH_3 group in MeOH, as the H-CH_2OH bond has a lower estimated gas-phase bond dissociation energy (BDE = 96.1 kcal/mol) than the CH_3O-H bond (BDE = 104.6 kcal/mol).[21] A similar hydrogen transfer mechanism was found to operate in the photolysis of Cu(II) salts in MeOH, which has been used in the light induced polymerisation of acrylates. (Scheme 3.12).[22]

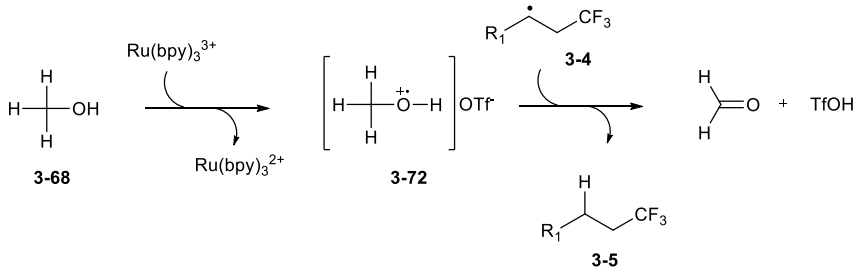


Scheme 3.12 Mechanism of photolysis of Cu(II) salts in MeOH

David *et al* reported that irradiation of CuX_2 (X = Br and Cl) with UV light (350 nm) in MeOH resulted in formation of formaldehyde and CuX. They showed that photolysis of CuX_2 resulted in formation of a halogen radical (Scheme 3.12, step 1), which abstracts a hydrogen of MeOH (Scheme 3-12, step 2). The resulting radical **3-69** is then oxidized by another molecule of CuX_2, with formation of formaldehyde, CuX and halogen acid (Scheme 3.12, step 3). The presence of CH_2OH radical **3-69** could be proven by the polymerisation under these conditions of methylmethacrylate (MMA), which incorporated

CH_2OH end groups. Formaldehyde could be determined from the reaction mixture by UV/Vis spectroscopy after derivatisation.

In the second possible mechanism, direct single electron oxidation of MeOH by the strong oxidant $Ru(bpy)_3^{3+}$ is proposed, and results in formation of the radical cation **3-72**. Hydrogen atom transfer from this radical cation would then provide the hydrotrifluoromethylated product **3-5**, with concomitant formation of the resonance stabilised cation **3-70**, which generates formaldehyde and TfOH as shown in the previous postulated mechanism (Scheme 3.13). An analogous mechanism has been proposed for hydrogen atom transfer from tertiary amines in which an iminium ion is formed after single electron oxidation and hydrogen atom transfer.[23] (Investigation into the cyclic voltammetry of MeOH on a glassy carbon electrode (for method see Chapter 2 Section 2.3) did not show any oxidation below +1.5V, which would make oxidation of MeOH by $Ru(bpy)_3^{3+}$ challenging.



Scheme 3.13 Mechanism for hydrogen transfer from MeOH to radical **3-4** after oxidation by $Ru(bpy)_3^{3+}$

Both of these tentative mechanisms account for the observed formation of a strong acid (see section 3.3). Based on the current observations, the hydrogen abstraction from MeOH by carboradical **3-4** is more likely to operate because of the similarity of the mechanism of hydrogen atom transfer in the photolysis of Cu(II) salts in MeOH, and the predicted challenging oxidation of MeOH by $Ru(bpy)_3^{3+}$.

3.7 Conclusions

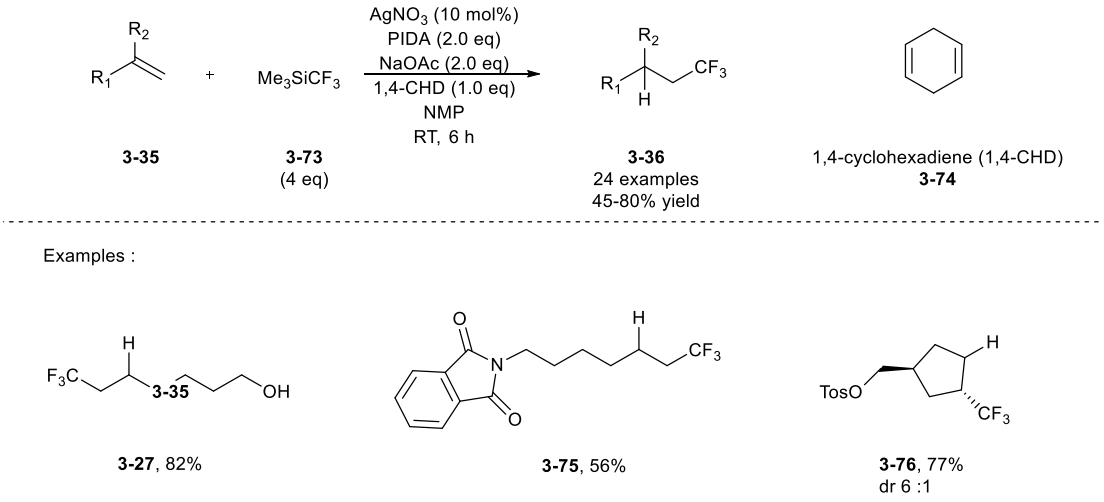
In summary, this chapter reports the synthesis of primary aliphatic CF_3 compounds using a photoredox catalysed hydrotrifluoromethylation of unactivated terminal alkenes. The reaction involves net addition of HCF_3 across the double bond, and provides the trifluoromethylated products with complete regioselectivity for the terminal position.

$RuCl_2(bpy)_3.6H_2O$ was used as the photoredox catalyst, in combination with the Umemoto reagent **3-2** as the trifluoromethyl source, in MeOH as solvent. 1,1-disubstituted terminal double bonds were also effectively hydrotrifluoromethylated and provided the products of regioselective HCF_3 addition in good yield. The mild conditions allowed for a broad functional group tolerance, and substrates with functional groups such as esters, amides, imides and unprotected alcohols could be successfully hydrotrifluoromethylated. Formation of an acid during the reaction, presumably TfOH, caused the deprotection of *N*-Boc protected amines and formation of dimethyl acetals from aldehyde substituents. Use of pyridine as an additive could successfully supress the deprotection of the *N*-Boc group, but did not prevent formation of acetals. The mild reaction conditions made this methodology suitable for late stage trifluoromethylation of complex molecules, and (*R*)-carvone **3-47**, cholecalciferol (Vitamine-D_3) **3-48** and quinine **3-46** were successfully hydrotrifluoromethylated under the optimised reaction conditions.

A mechanism was suggested on the basis of an oxidative quenching cycle for the photoredox catalyst, with formation of the CF_3 radical as the trifluoromethylating species. Observation of the product resulting from a radical 5 exo trig cyclisation from the hydrotrifluoromethylation of diene **3-50** was consistent with the formation of a CF_3 radical. Further experiments confirmed the role of MeOH as hydrogen atom donor. Through use of deuterated solvent it was established that the hydrogen atom is transferred from the CH_3

group of MeOH. The mechanism of the hydrogen transfer presumably involves oxidation of MeOH by $Ru(bpy)_3^{3+}$.

Two different methods for the hydrotrifluoromethylation of alkenes were reported shortly after the publication of the work described in this chapter. The first method was developed by the group of Qing, and uses a combination of $TMSCF_3$ (4 eq), $AgNO_3$ (0.1 eq) and the oxidant PIDA (2.0 eq) as the trifluoromethyl source (Scheme 3.14).[24] The reactions were run in NMP as solvent with NaOAc (2.0 eq) as a further additive. As hydrogen atom source 1,4-cyclohexadiene **3-74** was found to give the best yields. The hydrotrifluoromethylated products were formed in moderate to good yields, but in order to achieve these yields addition of a second portion of Me_3SiCF_3 (4.0 eq), PIDA (2 eq), NaOAc (2 eq) and **3-74** (1.0 eq) was necessary.

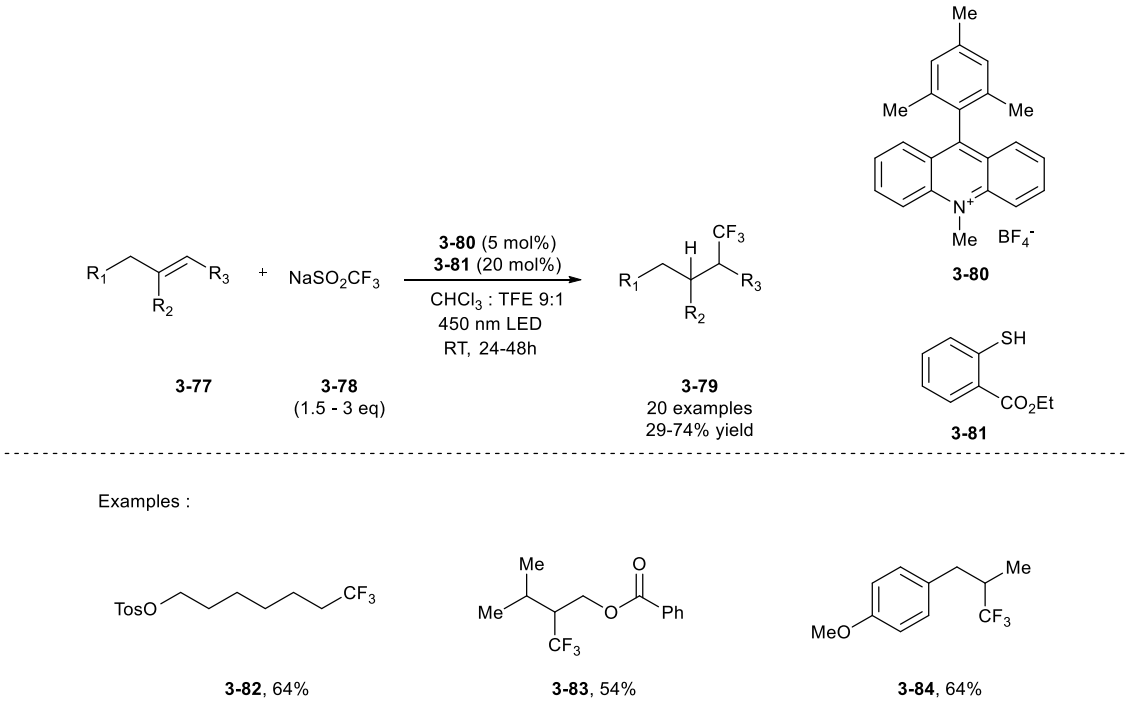


Scheme 3.14 Ag(I) catalysed hydrotrifluoromethylation of alkenes using Me_3SiCF_3

The authors postulated that the reaction proceeds with generation of a CF_3 radical as intermediate. The scope of the reaction is similar to the photoredox catalysed hydrpotrifluoromethylation described in this chapter.

Nicewicz *et al* reported the hydrotrifluoromethylation of styrenes and unactivated alkenes, using a *N*-Me-9-mesitylacridinium photoredox catalyst **3-80** (5 mol%) under irradiation of

450 nm LEDs.[25] $NaSO_2CF_3$ (1.5 - 3.0 eq) was used as a trifluoromethyl source, together with a combination of methyl thiosalicylate **3-81** (0.2 eq) and TFE (co-solvent with $CHCl_3$) as the hydrogen atom source.



Scheme 3.15 Hydrotrifluoromethylation of styrenes and alphatic alkenes using photoredox catalyst **3-80**

Trifluoromethylation was proposed to proceed through generation of the CF_3 radical from reduction of $NaSO_2CF_3$ by the strongly reducing exited state of **3-80**, which was formed on irradiation of the reaction mixture with 450 nm (blue) LED light. The yields and functional group tolerance of this method are similar to the method described in this chapter, but in addition to hydrotrifluoromethylation of unactivated aliphatic terminal alkenes it is the first to report the use of tri-substituted alkenes and styrenes as substrates.

3.8 References

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Chapter 4: Synthesis of ^{18}F-labelled Aryl-SCF_3, -OCF_3 and -OCF_2H using [^{18}F]Fluoride

4.1 Introduction to Fluorine-18 and Positron Emission Tomography (PET)

Positron emission tomography (PET) is a non-invasive imaging technique that enables quantitation of biological and physiological function *in vivo*, through the use of small organic molecular imaging probes, which are labelled with a short-lived positron emitting radioisotope such as ^{11}C, ^{13}N, ^{15}O and ^{18}F (Table 3.1).[1]

PET Radioisotope	Half-Life ($t_{½}$, min)	Decay Product	Maximum β^+ energy (keV)
^{11}C	20.4	^{11}B	960
^{13}N	9.97	^{13}C	1190
^{15}O	2.04	^{15}N	1720
^{18}F	109.7	^{18}O	635

Table 4.1 Properties of commonly used PET radioisotopes

After administration of the radiolabelled compound to the subject, the decaying isotope emits a positron which travels a short distance in the tissue (depending on the energy it contains), before colliding with an electron in an annihilation event that produces two coincident gamma ray photons at an approximate angle of 180 °C. When the gamma photons hit a ring of highly sensitive photon detectors that are placed around the subject they are converted into an electric signal. It is possible to determine the approximate place

of the annihilation event by detecting the simultaneously and perpendicular emitted photons. When enough of these events are detected the data can be processed, using mathematical modelling, into a 2D or 3D image, which shows the distribution of the radiotracer through the tissue.

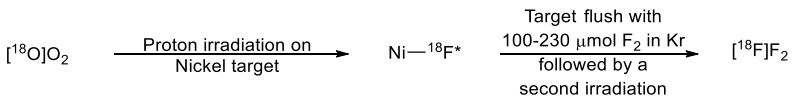
PET imaging has been used for *in vivo* diagnosis in a wide range of disease areas in oncology,[2] neurology (especially Alzheimer's and Parkinson's disease),[3] and cardiology[4] and can also be combined with techniques like CT and MRI that provide structural (anatomical) data. Dynamic acquisition of data has made it possible to measure the absolute concentrations of radiolabelled compounds in tissue over time, which is particularly useful for drug discovery and development.[5] Non-invasive pharmacokinetic studies can be conducted in living subjects and provide valuable information on biodistribution, metabolism and competition studies of drug candidates in both early and advanced stages of the drug discovery process. The very high sensitivity of PET (detection at picomolar concentration is possible) allows for these studies to be conducted with very low dosing of radiotracer (microdosing).[6] In the majority of cases there is no relevant pharmacological effect at this low dosing due to the low receptor occupancy of the target, and extensive toxicology and safety data of the compound administered are therefore not required.

4.1.1 Production of Fluorine-18 and Specific Activity

The short half-live of commonly used PET isotopes (see Table 4.1) present a significant challenge for the synthesis, purification and formulation of PET radiotracers and administration to the subject.[7] The generally accepted time for these operations with radiotracers containing a PET-isotope is 3 half-lives,[8] and to minimize decay it is necessary to incorporate the isotope in the later stages of the synthesis process, preferably in the last step. The properties of fluorine-18 as a PET isotope are favourable in this respect, because

of a relatively long half-life of 109.7 min. This allows for the transport of synthesized ^{18}F-radiotracers to the site of administration, and alleviates the need for on-site production of the PET isotope.

Fluorine-18 can be generated using a cyclotron, and is most frequently prepared by the bombardment of an 18-oxygen target with a beam of accelerated protons according to the $^{18}O(p,n)^{18}F$ nuclear reaction. Depending on the oxygen-18 source, it can be produced either as a nucleophilic reagent in the form of $[^{18}F]F^-$, or as an electrophilic reagent in the form of $[^{18}F]F_2$. Bombardment of $H_2{}^{18}O$ in a metal target produces nucleophilic $[^{18}F]F^-$, which is flushed from the cyclotron as a solution in $H_2{}^{18}O$. When $^{18}O_2$ is bombarded in a nickel or aluminium target the produced fluorine-18 adheres to the walls of the target (Scheme 4.1). The adhered fluorine-18 is flushed from the target walls with F_2 gas as a carrier gas followed by a second irradiation which stimulates isotope exchange and produces $[^{18}F]F_2$.[9]



Scheme 4.1 Production of $[^{18}F]F_2$ from $[^{18}O]O_2$

There are several drawbacks to the use of $[^{18}F]F_2$ in comparison with $[^{18}F]F^-$. Fluorine itself is a highly reactive and toxic gas, and requires specialist equipment for its use. This high reactivity often results in unselective reactions producing mixtures of ^{18}F-labelled products which, combined with the fact that a maximum theoretical radiochemical yield of only 50% can be obtained, often lead to a low radiochemical yield (RCY) of the desired ^{18}F labelled radiotracer. The issue of high reactivity has been addressed with the transformation of $[^{18}F]F_2$ into easier to handle and more selective electrophilic ^{18}F sources

such as [^{18}F]NFSI **[^{18}F]4-1**[10] and [^{18}F]Selectfluor **[^{18}F]4-2** (Scheme 4.2).[11] However, the maximum obtainable yield of 50% is still a major problem.

[^{18}F]NFSI, **[^{18}F]4.1** [^{18}F]Selectfluor, **[^{18}F]4.2**

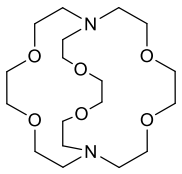
Scheme 4.2 Alternative electrophilic ^{18}F-sources

Because "cold" fluorine-19 containing F_2 is used as a carrier gas, the specific activity (SA) of the produced [^{18}F]F_2 is very low (<0.4 GBq/μmol)[12] in comparison with [^{18}F]F^-, which is produced without carrier (typically SA ≈ 1 - 5 TBq/μmol).[13] Specific activity is a measure of the contamination of the ^{18}F-labelled compound with the non-radioactive isotopic compound (referred to as cold compound), and an important variable in PET imaging. Radiotracers with low SA require administration of higher amounts to obtain a sufficient signal-to-noise ratio. This also increases the amount of cold product injected, which can lead to unwanted effects such as receptor saturation, leading to low uptake of ^{18}F-labelled radiotracer, or potentially harmful pharmacological effects which require additional, extensive toxicology studies.

4.1.2 Practical Use of [^{18}F]F^-

To generate a reactive [^{18}F]F^--source it is usually necessary to remove the $H_2{}^{18}O$, since hydration drastically diminishes the nucleophilicity of fluoride ions.[14] This is most often accomplished by trapping the [^{18}F]F^- on an anion exchange cartridge, followed by eluting with a mixture of CH_3CN/H_2O containing a weak base and multiple cycles of azeotropic drying using additional anhydrous CH_3CN.[15] The most frequently used counterions are K^+, in the form of K_2CO_3, and R_4N^+ (R = Bu or Et), but counter-ions such as Cs^+ , Rb^+ or Ag^+ have also been reported. In addition to weak base, an aminopolyether kryptand (such as

Kryptofix, also known as $K_{2.2.2}$, **4-3**) is often added to solubilize the $[^{18}F]F^-$ in CH_3CN, and generate a more reactive fluoride source by complexing the K^+ counterion. When larger counter-ions like Cs^+ and Rb^+ are used, addition of a kryptand is often omitted since these counter-ions already provide a more reactive fluoride because of their size.



4-3

Scheme 4.3 Structure of aminopolyether kryptand Kryptofix or $K_{2.2.2}$ **4-3**

The $[^{18}F]F^-$ solution produced in a cyclotron contains various heavy metal cations, which originate from the metal wall of the target chamber, in addition to variable other impurities that arise from formation of free radicals and radiolysis during bombardment.[16] Trapping on an anion cartridge can remove most of these contaminants, but elution from the cartridge can also introduce new impurities. If these contaminants are non-volatile they will remain after the azeotropic drying cycle, and can have a detrimental effect on the efficiency and reproducibility of ^{18}F-incorporation during the subsequent labelling procedure. This is due to the fact that the actual amount of fluoride ion produced by a cyclotron is very small (the amount is typically in the range of nano- to picograms), several orders of magnitude smaller than an impurity at ppm level. For this reason high purity of reagents and substrates is required to minimise interference of impurities on the labelling efficiency.

4.1.3 ^{18}F-Radiochemistry at Siemens Oxford Molecular Imaging Laboratory (SOMIL - University of Oxford) – Research Mode and Full Batch Isolation

For purpose of reaction optimisation and determination of substrate scope, the dried [^{18}F]KF complex obtained after elution through an anion exchange cartridge and azeotropic drying can be re-dissolved in CH_3CN. Aliquots with low activity (25-30 MBq) can be taken from this solution, which allows for multiple ^{18}F-labelling reactions to be conducted. To determine the radiochemical conversion (RCC) the reaction mixture is quenched with a solvent mixture containing H_2O (to dissolve the remaining [^{18}F]F^-), after which an aliquot is analysed by radio-TLC and radio-HPLC. The conversion of [^{18}F]F^- can be determined by radio-TLC, choosing a suitable eluent and comparing the activity on the base-line, from unreacted [^{18}F]F^-, with the activity from ^{18}F-containing organic material at higher R_f. The RCC is then determined by taking into account the purity of the ^{18}F-containing product, which is obtained by using radio-HPLC and comparing the retention time of the labelled product with that of the cold reference product. The RCC is usually determined as the average of at least two experiments, with the error defined as the standard deviation of the mean, and is corrected for decay of fluorine-18.

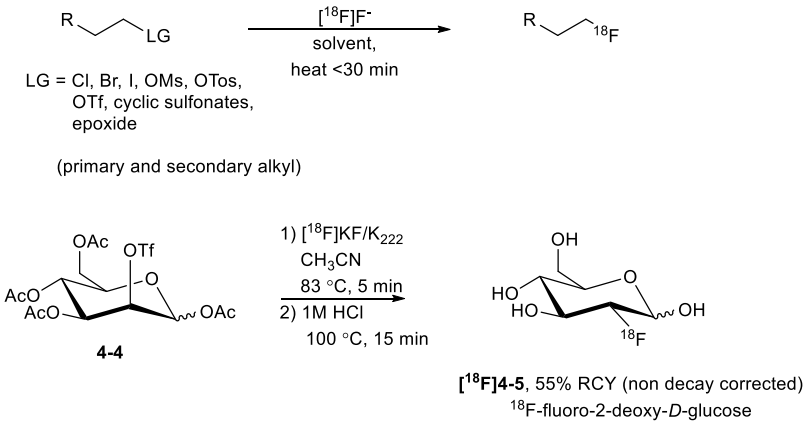
To produce and isolate ^{18}F-containing radiotracers the labelling procedure is carried out using the full batch [^{18}F]KF-complex (3 - 4 GBq) in one reaction. After quenching the ^{18}F-labelled radiotracer is obtained by injecting the crude reaction mixture on a semi-preparative HPLC-column with monitoring of UV- and radio-traces, and collecting the fraction containing the product. The radiochemical yield (RCY) is determined by comparing the collected activity with the starting activity of [^{18}F]KF-complex, and is not corrected for decay (non-decay corrected). For the calculation of the SA the mass of cold product is determined from the UV-signal, with a calibration curve of known concentration of the reference cold product. Alternatively, this can be done by injecting an aliquot of the

collected fraction with a known amount of radiation on an analytical HPLC-column, and determining the mass of cold product with a calibration curve as before.

In contrast to the experiments conducted under screening conditions, the full batch of dried [^{18}F]KF-complex contains additional K_2CO_3 (up to 3 mg) and kryptand (up to 15 mg), which have been used to elute the [^{18}F]F$^-$ from the anion exchange cartridge. The presence of these "impurities" can significantly alter the reaction conditions and have a detrimental effect on the efficiency of ^{18}F-incorporation, or cause degradation of the labelled radiotracer.[17] An estimation of the influence on the efficiency of labelling can be made from spiking the reactions run under screening conditions with additional K_2CO_3 and kryptand, and recording the RCC as described before. Often the relatively high basicity of K_2CO_3 can cause problems, and less basic alternative such as $K_2C_2O_4$, $KHCO_3$ and K_2HPO_4 or KH_2PO_4 have been successfully used.[17a] Crown ethers such as 18-crown-6, which do not containing a tertiary nitrogen atom, can be used as alternatives for kryptands.[18]

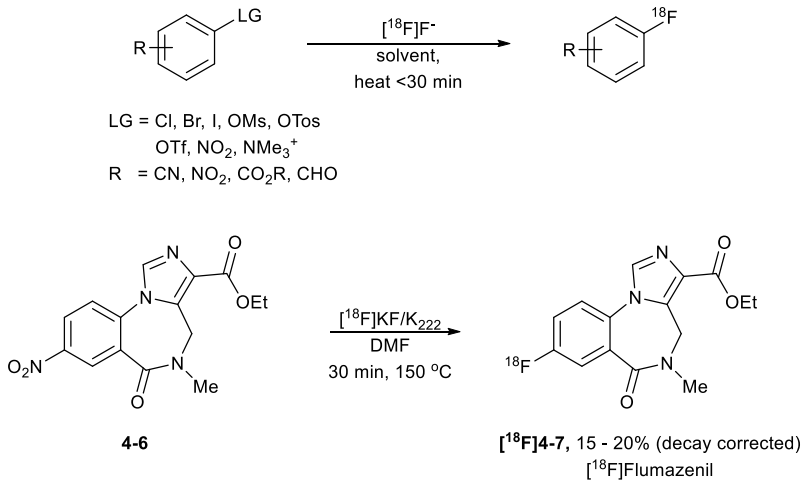
4.1.4 Nucleophilic ^{18}F-labelling Methods Using [^{18}F]F$^-$

The wide availability and potential for the synthesis of high SA radiotracers (>100 GBq/μmol) from no carrier added (n.c.a)[19] [^{18}F]F$^-$, make this the reagent of choice in ^{18}F-labelling. It is mainly used in classical nucleophilic substitution reactions to synthesize aliphatic C(sp^3)-^{18}F containing compounds, using halide and sulfonyl leaving groups (Scheme 4.4). The most widely used radiopharmaceutical, [^{18}F]2-deoxy-D-glucose, [^{18}F]FDG **4-5**, is synthesized by this route, through nucleophilic substitution of the triflate group in fully protected D-glucose derivate **4-4**, followed by deprotection.[20]



Scheme 4.4 Classic nucleophilic fluorination in the synthesis of C(sp^3)-^{18}F bonds and synthesis of [^{18}F]FDG from [^{18}F]KF/K_{222}

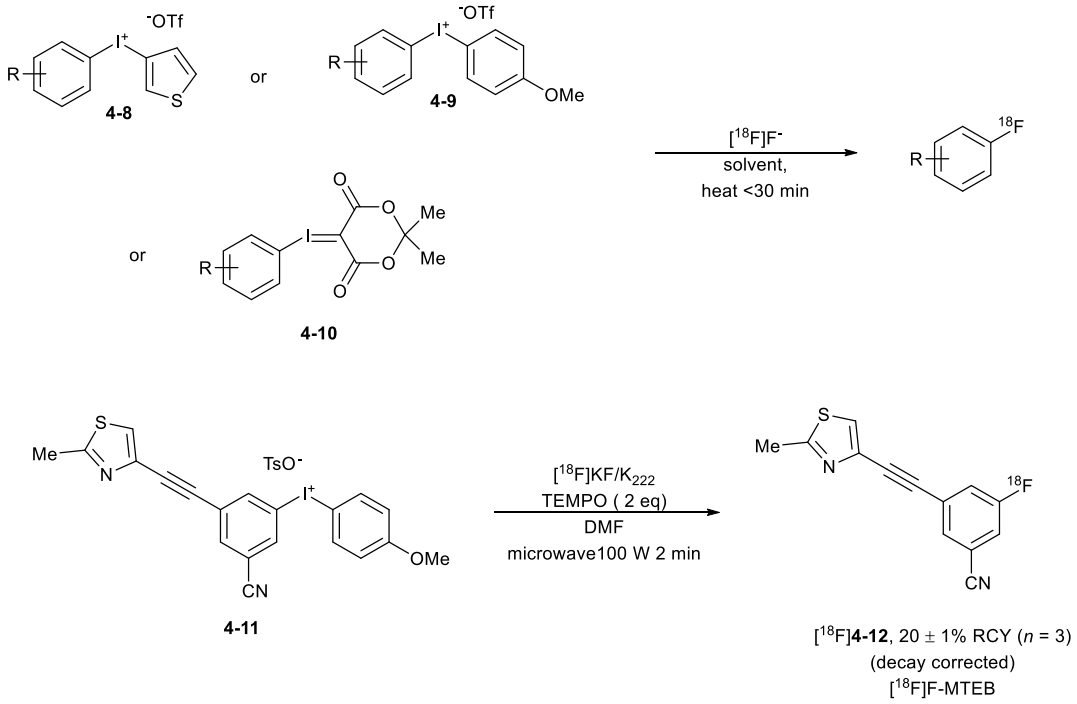
The other major use of [^{18}F]F^- is in aromatic substitution reaction (S_NAr) for the synthesis of ^{18}F labelled arenes (Scheme 4.5).[21] The reaction works best for electron poor arenes substituted with strong electron withdrawing leaving groups such as NO_2 and NMe_3^+. A recent example of this methodology is the synthesis of [^{18}F]Flumazenil **[^{18}F]4-7**, a PET radiotracer used for imaging of the central benzodiazepine receptor (cBZR), in 15 - 20% RCY (decay corrected) from the NO_2-precursor **4-6**.[22]



Scheme 4.5 Aromatic nucleophilic substitution (S_NAr) and synthesis of [^{18}F]Flumazenil

Despite the frequent use of this strategy it has the drawback of requiring high temperature to ensure sufficient ^{18}F-incorporation in short reaction times. These conditions are often not compatible with more sensitive functional groups and substrates. Also, the need for substrates containing electron withdrawing substituents limits the scope.

The research in aromatic ^{18}F-fluorination through S_NAr has mainly been focused on the development of better leaving groups, that allow more efficient ^{18}F-incorporation on a broader range of substrates containing electron-neutral and -rich substituents. This resulted in the development of iodonium leaving groups, such as diaryliodonium salts and iodonium ylides, which can provide good yields of ^{18}F-labelled arenes with a broader substrate scope (Scheme 4.6).[23] The PET radiotracer [^{18}F]F-MTEB [^{18}F]**4-12**, a high affinity radioligand for the metabotropic glutamate subtype 5 receptor (mGluR5), was synthesized from the corresponding iodonium precursor **4-11** in 20% RCY (decay corrected) in DMF with the [^{18}F]KF/K_{222} complex, under heating with microwave irradiation.[24] To obtain reproducible yields it was necessary to add TEMPO, which prevents decomposition of the iodonium precursor **4-11** under the reaction conditions.[25] This is often necessary in transformations of iodonium salts and ylides, since these starting materials are prone to decomposition, especially at elevated temperatures.



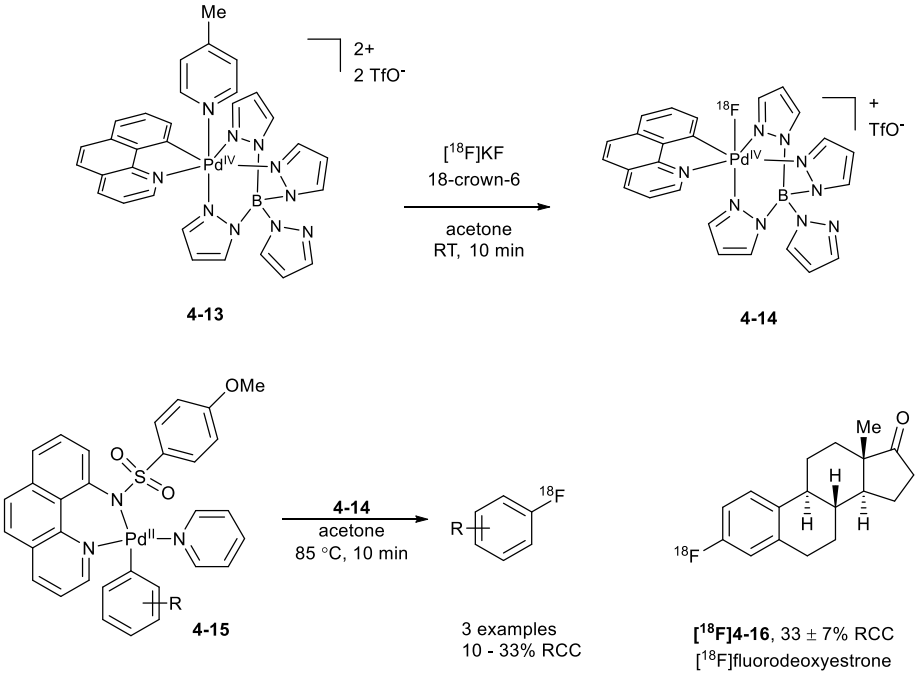
Scheme 4.6 Aryliodonium and iodonium ylide leaving groups for nucleophilic aromatic substitution with [^{18}F]F$^-$, and synthesis of [^{18}F]F-MTEB from an aryl iodonium precursor.

4.1.5 New Modes of Activation in ^{18}F-fluorination : Transition Metal Mediated ^{18}F-fluorination

Much progress has been made in the research of ^{18}F fluorination using thermal activation, and classical nucleophilic substitution (S_N2) and nucleophilic aromatic substitution (S_NAr) reactions have provided a range of radiotracers for PET imaging. However, the development of new radiotracers can still pose a significant challenge, due to harsh conditions and limitations in the substrate scope. Recent research into new activation modes in ^{18}F fluorination, other than thermal activation, has led to development of novel ^{18}F-labelling methodologies, which provide access to a broader range of ^{18}F-labelled compounds and radiotracers.[26]

The use of transition metal mediated ^{18}F-fluorination has provided a range of new methods for the synthesis of ^{18}F-(hetero)arenes. The power of these methods lie in the broad

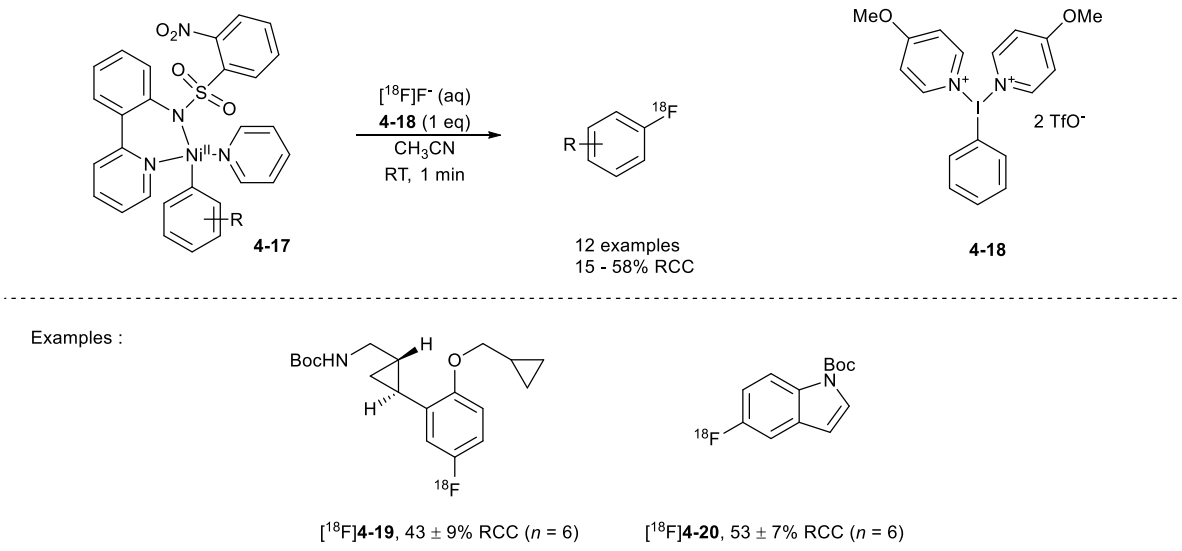
substrate scope, which usually tolerates highly functionalised starting materials with both electron-withdrawing and -donating functional groups, and mild reaction conditions.



Scheme 4.7 High valent Pd(IV)-mediated ^{18}F-fluorination of arenes

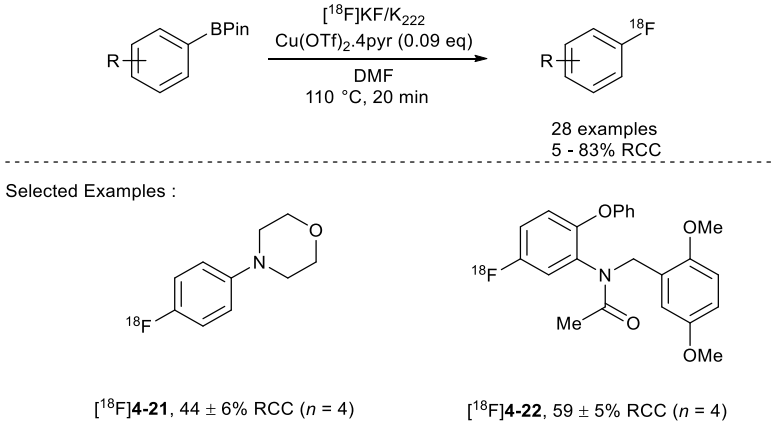
In 2011, Ritter *et al* developed the ^{18}F-fluorination of stable Pd-complexes **4-15** using an electrophilic, high valent ^{18}F-Pd(IV) species **4-14**, which could be synthesized from Pd(IV)-complex **4-13** and [^{18}F]KF (Scheme 4.7). Although only a small number of substrates were labelled, they were all ^{18}F-arenes that were highly functionalised and difficult to access by classical S_NAr methods.

This methodology was later simplified and extended to the use of stable Ni(II)-precursor complexes **4-17**, which could provide ^{18}F-labelled arenes in good RCC using oxidant **4-18**.[27] With this method, an aqueous solution of [^{18}F]F$^-$ can be used without the need for previous drying, as long as the volume is small (<50 μl).



Scheme 4.8 High-valent Nickel mediated ^{18}F-fluorination using aqueous [^{18}F]F$^-$

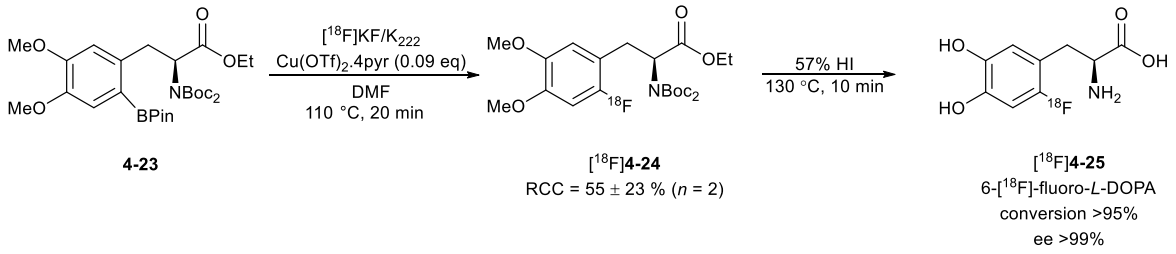
The use of easily accessible arylboronic acid pinacol esters (BPin) as starting materials for the synthesis of ^{18}F-labelled arenes, was reported by the group of Gouverneur in 2014.[28] The commercially available Cu(OTf)$_2$.4pyr complex was used as transition metal catalyst, and a broad range of aryl BPin-esters with both electron-withdrawing and -donating substituents could be efficiently radiolabelled (Scheme 4.9). The reaction gave low yields of ^{18}F-incorporation with unprotected phenol or aniline substrates.



Scheme 4.9 Copper mediated nucleophilic ^{18}F-fluorination of arenes

The versatility of this methodology was demonstrated with the synthesis of [^{18}F]3,4-dihydroxy-6-fluoro-*L*-phenylalanine **4-25**, [^{18}F]F-DOPA, an important radiotracer for PET

imaging of the dopaminergic system in the brain (Scheme 4.10).[29] This radiotracer was previously only available for clinical use through electrophilic fluorination with $[^{18}F]F_2$,[30] or by a multi-step building block approach based on nucleophilic aromatic substitution.[31]



4-23

[^{18}F]**4-24**
RCC = 55 ± 23 % (*n* = 2)

[^{18}F]**4-25**
6-[^{18}F]-fluoro-*L*-DOPA
conversion >95%
ee >99%

4.10 Synthesis of [^{18}F]F-DOPA by copper-mediated nucleophilic ^{18}F-fluorination

4.1.6 Synthesis of New ^{18}F-chemotypes

The previous examples have shown that the introduction of new activation modes in ^{18}F-fluorination can provide radiochemists with new methods for the synthesis of previously difficult to access ^{18}F-fluorinated arenes and radiotracers. Most of this research has been focused on the synthesis of ^{18}F-labelled (hetero)arenes, since this is a very important motif in medicinal chemistry, and many known bioactive compounds and registered pharmaceuticals contain an aromatic fluorine substituent.[32] However, new chemical motifs based on functional groups containing multiple fluorine atoms, such as fluorinated ethers and thioethers (SCF_3, OCF_3 and OCF_2H) have found increasing application in medicinal chemistry (see next section). In light of the increasing use of PET imaging as a tool in drug discovery and development, it is highly desirable to develop new methodology for the synthesis of ^{18}F-labelled variants of these functional groups.

4.2 Synthesis and Properties of Fluorinated Aryl(thio)ethers

The introduction of an α-fluorinated methyl(thio)ether (OCF_2H, OCF_3 or SCF_3) substituents into organic molecules can have a marked influence on their chemical and physical properties. Substitution of fluorine for hydrogen on the carbon atom in

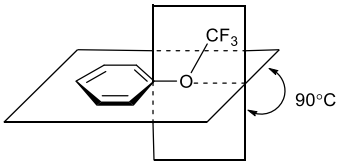
methyl(thio)ethers result in an increase of lipophilicity, which is caused by an overall reduction in polarisability. Lipophilicity can be measured as a partition coefficient in an *n*-octanol-water system (Log P or π), and is an important parameter for the design of biologically active compounds.[33] An increase in lipophilicity of a compound can be beneficial for the bioavailability by improving the transport through lipid membranes, and can also lead to increased binding to the target protein through better lipophilic interactions.[34] Where the presence of an OMe group on an arene does not alter the lipophilicity significantly (π = -0.02), the change to an OCF_3 group has a profound effect, as shown by the large partition coefficient (π = 1.04). The SCF_3 group shows an even higher lipophilicity (π = 1.44), which is comparable to the value for a *i*-Pr-group (π = 1.55).

Substituent	**π**
H	0
OMe	–0.02
OCF_3	1.04
SMe	0.61
SCF_3	1.44
i-Pr	1.55

Table 4.2 Lipophilicity of fluorinated methyl(thio)ethers

The presence of fluorine atoms also decreases the electron density of the non-bonding *p*-orbitals on the adjacent heteroatom, by delocalisation of the *p*-electrons into the non-bonding orbitals of the *anti*-periplanar fluorine atoms in the fluorinated alkyl group.[35] In trifluoromethoxybenzene this results in a disruption of the overlap of the non-bonding

orbitals on oxygen with the *p*-electrons of the aromatic ring. This results in a significant decreased rotational barrier, and allows the OCF_3 group to rotate out of the plane of the aromatic ring, and adopt an orthogonal conformation to minimize electronic repulsions (Scheme 4.11).



Scheme 4.11 Orthogonal conformation in $PhOCF_3$

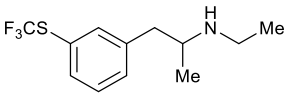
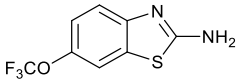
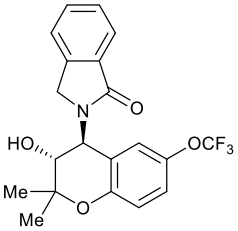
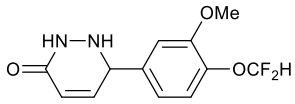
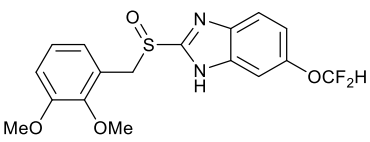
This conformational effect was predicted in 1977 by ^{19}F-NMR studies,[36] and later confirmed by X-Ray crystallography.[37] In one example of an aromatic SCF_3 group, the crystal structure shows the same orthogonal conformation.[38] This higher rotational freedom and conformational flexibility could be employed to facilitate binding in the active site of a target, and improve binding efficiency.

Analysis of several crystal structures of aromatic compounds containing an OCF_2H moiety showed no preference for an orthogonal conformation,[39] but it was found that the fluorine atoms can adopt two different conformations. In the endo-endo conformation both fluorine substituents are *anti*-periplanar to the oxygen lone pair (Scheme 4.12). In this conformation, similar to the OCF_3 group, the electron density of the oxygen non-bonding orbital is very low, and an orthogonal position to the aromatic ring is preferred. The endo-exo conformation has one fluorine atom in the *anti*-periplanar position, and does not show this preference.

Scheme 4.12 Two conformations of the OCF_2H group

It is predicted that, because of the difference in electron withdrawing effect on the oxygen non-bonding lone-pairs, these two conformations have very different polarities. The endo-endo conformation would be expected to be more lipophilic, resembling the OCF_3-group, and the endo-exo conformation more polar, in-between a OMe and a OCF_3-group.[39b] The ability of the OCF_2H group to adopt two different conformations that differ markedly in polarity, makes this moiety potentially adaptable to different molecular environments, which could be beneficial for target binding and binding efficiency.

There are several pharmaceuticals containing fluorinated methyl(thio)ether moiety known (Table 4.3).

Bioactive compound	**Structure**	**Indication**
Tiflorex		Anorexia Nervosa
Riluzole (Rilutek®)		Treatment of ALS (Amyotrophic Lateral Sclerosis) and Schizophrenia
Celikalim		Potassium channel activator (anti-hypertensive)
Zardaverine		Phosphodiesterase-4 inhibitor
(-)-Pantaprazole (Protonix®)		Proton Pump Inhibitor

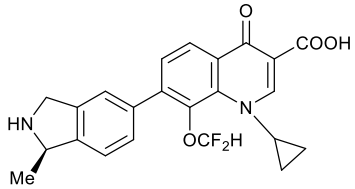
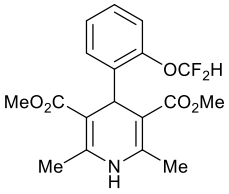
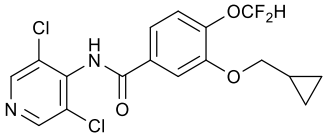
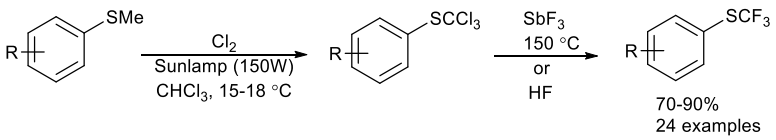
Garenoxacin (Geninax®)		Antibiotic
Riodipine (Foridon®, Ryosidine®)		Calcium channel blocker (anti-hypertensive)
Roflumilast (Daxas®, Dalisrep®)		Treatment of Chronic Obstructive Pulmonary Disease (COPD)

Table 4.3 Examples of bioactive compounds containing SCF_3, OCF_3 or OCF_2H groups

4.2.1 Methods for Aryl-SCF_3 Synthesis

The first reported synthesis of aryl trifluoromethylsulfides utilized the corresponding aryl trichloromethylsulfides, in a halogen exchange reaction with either SbF_3 or anhydrous HF without solvent at high temperature (Scheme 4.13).[40] This process is currently still very important for the production of commercially available aryl trifluoromethylsulfides. The required aryl trichloromethylsulfides can be synthesized by chlorination of aryl thiomethylethers with Cl_2 under irradiation with a sunlamp.



Scheme 4.13 Fluorination of aryl trichloromethylsulfides

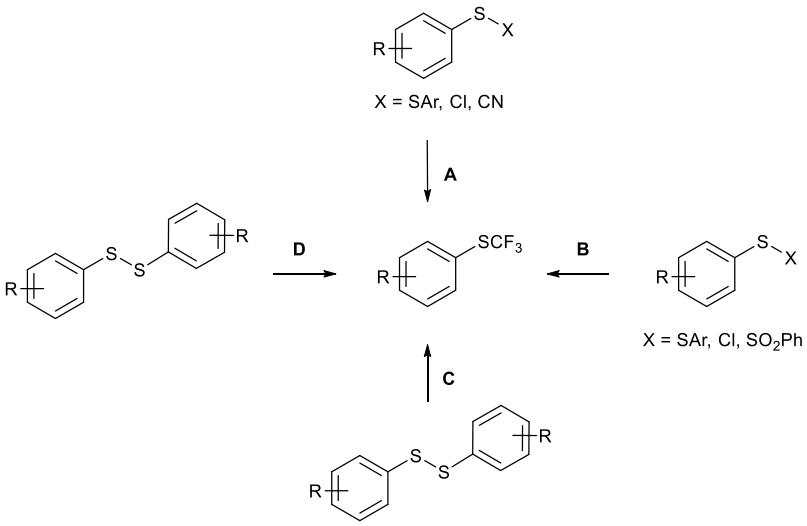
In 1981, a halogen exchange reaction of aryl bromodifluoromethylsulfides under milder conditions was reported by Suda *et al* (see scheme **4.14**).[41] This transformation was mediated by $AgBF_4$, which also acts as a fluoride source, and provided modest yields of

aryl trifluoromethylsulfides at room temperature, in either DCM or Et_2O as solvent. Experimental details were not provided.

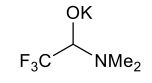
Scheme 4.14 $AgBF_4$ mediated halogen exchange reaction

4.2.1.1 Nucleophilic Thiotrifluoromethylation

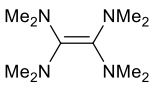
Synthesis of aryl trifluoromethylsulfides has also been achieved using nucleophilic trifluoromethylation (Table 4.4). Langlois reported trifluoromethylation of aryl disulfides, aryl sulfenyl chlorides and aryl sulfenyl cyanides, with a combination of TBAF and $TMSCF_3$ as a source of nucleophilic CF_3 anion in THF (Table 4.4, method A).[42] Roques showed that low temperature deprotonation of CF_3H with tBuOK in DMF gives rise to a CF_3K-DMF adduct, which provides aryl trifluoromethylsulfides in good yield when reacted with either aryl-disulfides, aryl sulfenyl chlorides or aryl thiosulfonates (Table 4.4 method B).[43] Aryl disulfides have also been shown to give moderate to good yields of aryl trifluoromethylsulfides when reacted with a formal CF_3 anion species, generated from high temperature decomposition of CF_3COOK in polar solvent (Table 4.4 method C),[44] or from 2 electron reduction of CF_3I with TDAE (Table 4.4 method D).[45] This last reaction has the advantage of utilizing both arylthio-moieties of the aryl disulfide, because the ArS^- formed in the substitution reaction can react with another equivalent of CF_3I to give a second molecule of $arylSCF_3$.



Method	Conditions	Yield
A	$TMSCF_3$, TBAF THF, 0 °C – RT	30 -70 % (5 examples)
B	CF_3H, KOtBu DMF, -40 °C	60-90% (3 examples)
C	CF_3COOK sulfolane or DMF, 180 °C	32-82% (7 examples)
D	CF_3I, TDAE DMF, 0 °C – RT	85-90% (3 examples)



CF_3K-DMF adduct



TDAE
tetrakis(dimethylamino)ethene

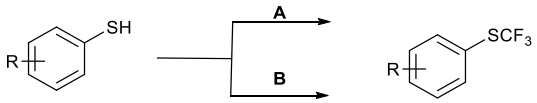
Table 4.4 Synthesis of aryl trifluoromethylsulfides by nucleophilic trifluoromethylation

Although use of nucleophilic trifluoromethylation reagents can provide aryl trifluoromethylsulfides in good yields, it is necessary to use prefunctionalised thiophenol derivatives.

4.2.1.2 Trifluoromethylation of Thiophenols

Simple thiophenols and thiophenolates have also been used as substrates for the synthesis of aryl trifluoromethylsulfides. Rábai *et al* reported the reaction of sodium thiophenolates, in-situ formed from thiophenols with a slight excess of NaH, with CF_3I in DMF at room temperature (Table 4.5, conditions A).[46] Both aryl and heteroaryl trifluoromethylsulfides could be obtained in low to excellent yields with this procedure. Substrates containing functional groups with acidic protons failed to give any product.

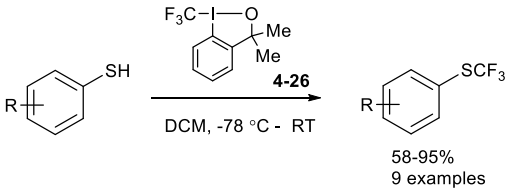
Thiophenols can also react with CF_3I without the need for in-situ deprotonation with strong base (Table 4.5, conditions B). Noel *et al* reported a method in which a combination of a wide range of thiophenols and CF_3I in CH_3CN, in the presence of a photoredox catalyst and under irradiation with visible light, provided (hetero)aryl-trifluoromethylsulfides in good to excellent yields.[47] This transformation could also be performed in a flow-reactor setup, which gave the aryl trifluoromethylsulfides in improved yields and very short reaction times (1 to 5 min).



Method	Conditions	Yield
A	NaH, CF_3I DMF, 0 °C – RT	22 - 88 % (14 examples)
B	CF_3I, Et_3N $Ru(bpy)_3Cl_2$ 24W CFL CH_3CN, RT	52 - 96% (26 examples)

Table 4.5 Trifluoromethylation of thiophenols using CF_3I

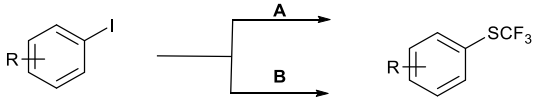
Thiophenols can be efficiently trifluoromethylated using the iodine(III) based electrophilic trifluoromethylating reagent **4-26** developed by Togni *et al* (Scheme **4.15**).[48] The reaction proceeds under very mild conditions and gives (hetero)aryl trifluoromethylsulfides in high yields. The mild, base-free conditions make the use of unprotected functional groups possible, and substrates containing free OH, NH_2 and COOH groups all react smoothly. Addition of the trifluoromethylating reagent at low temperature avoids the formation of aryl disulfides.



Scheme 4.15 Electrophilic trifluoromethylation of thiophenols

4.2.1.3 Transition Metal Mediated Synthesis of Aryl-SCF_3

The first transition metal mediated synthesis of (hetero)aryl trifluoromethylsulfides was reported as early as 1975 by Yagupolskii *et al*, who reacted an excess of $CuSCF_3$ with aryl iodides in polar solvents at high temperature (Table 4.6, method A).[49] This transformation gave better yields when aryl iodides with electron withdrawing substituents were used. In 2013, Hang and Weng *et al* reported the synthesis of the *bis*-pyridine complex of $CuSCF_3$, which enables thiotrifluoromethylation of aryl iodides with both electron donating and withdrawing substituents in CH_3CN (Table 4.6, method B), at slightly lower temperature (110 °C).[50]



Method	Conditions	Yield
A	$CuSCF_3$ DMF or NMP, 150 °C	30 - 80 % (12 examples)

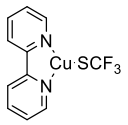
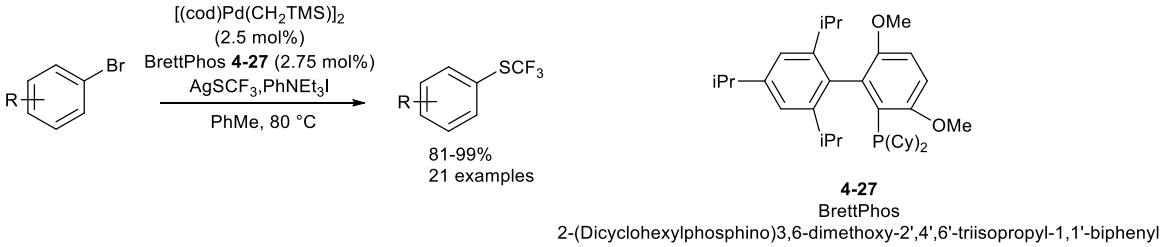
B	 CH_3CN, RT	57 - 85% (14 examples)

Table 4.6 Thiotrifluoromethylation of aryl iodides with $CuSCF_3$

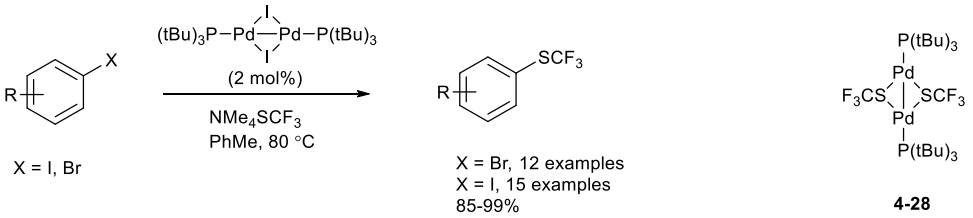
The scope of substrates for transition metal mediated thiotrifluoromethylation was expanded to aryl bromides by Buchwald *et al*, who developed a general method based on $[(cod)Pd(CH_2TMS)_2]$ as a catalyst and $AgSCF_3$ as the SCF_3-source (Scheme 4.16).[51] The reaction was most efficient in PhMe as solvent, using BrettPhos **4-27** as the ligand, and $Ph(Et)_3NI$ as an additive. The iodide was postulated to form the anionic 'ate'-complex $[IAgSCF_3]^-$ which demonstrates enhanced solubility and reactivity with respect to $AgSCF_3$ itself.[52]



Scheme 4.16 Pd-catalysed thiotrifluoromethylation of aryl bromides

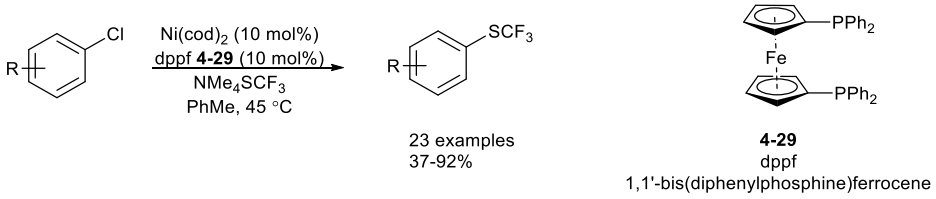
Recently, this reaction was extended to the use of air- and bench-stable dinuclear Pd(I)-catalysts by Schoenebeck *et al* (Scheme 4.17).[53] Thiotrifluoromethylation was carried out with pre-catalyst $(tBu)_3PPd_2I_2$ and NMe_4SCF_3 in PhMe at 80 °C, and a variety of electron-donating, -neutral and -withdrawing substituted aryl iodides and bromides provided thiotrifluoromethylated products in high yield. The air-stable bridged dinuclear Pd(I)-SCF_3 complex **4-28** could be isolated after the reaction by filtration over silica gel, and was

shown to be a competent catalyst in this transformation. Although the use of bench stable catalysts is an advantage, the reaction utilises NMe_4SCF_3 which, although thermally stable, is very moisture-sensitive.[54]



Scheme **4.17** Thiotrifluoromethylation using a dinuclear Pd(I)-catalyst

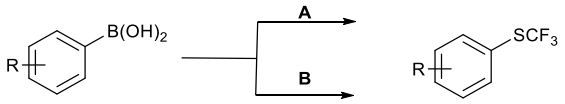
The use of nickel as transition metal has enabled the synthesis of aryl trifluoromethylsulfides from aryl chlorides (Scheme **4.18**). Reaction of $Ni(cod)_2$ as pre-catalyst, in combination with NMe_4SCF_3 and dppf as a ligand in PhMe at 45 °C, provided efficient thiotrifluoromethylation of a range of aryl chloride.[55] The mildness of these conditions allowed for a good functional group tolerance, but strongly electron donating substituted substrates were found to be unreactive and gave low conversion. Further studies revealed that when MeCN (1% v/v) was added to the reaction, a more reactive nitrile bound Ni(0) precatalyst was formed, that allowed efficient formation of thiotrifluoromethylated products from strongly electron-rich aryl chlorides.



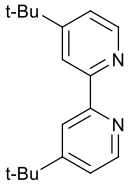
Scheme 4.18 Nickel catalysed thiotrifluoromethylation

Arylboronic acids have also been shown to be efficient coupling partners for transition metal mediated thiotrifluoromethylation (Table 4.7). Qing *et al* reported the use of a catalytic amount of CuSCN in combination with S_8, $TMSCF_3$ and Ag_2CO_3 as oxidant for

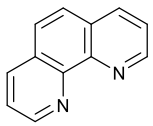
the thiotrifluoromethylation of a range of aryl boronic acids in good yield.[56] Mechanistic studies were in favour of trifluoromethylation of a Cu(I)-thiophenolate intermediate, instead of formation of $CuSCF_3$. Another method for thiotrifluoromethylation of arylboronic acids employing stoichiometric amounts of a $Cu(OTf)_2$ and the ligand dtbpy, in combination with NMe_4SCF_3 using air as oxidant was reported by Vicic *et al*.[57]



Method	Conditions	Yield
A	$TMSCF_3$, S_8 CuSCN (10 mol%) phen (20 mol%) K_3PO_4, Ag_2CO_3 4A MS DMF, RT	58 - 90 % (15 examples)
B	$Cu(OTf)_2$ (100%) dtbpy (100%) NMe_4SCF_3 THF, RT	70 - 91% (10 examples)



4-30
dtbpy
4,4'-di-*tert*-butyl-2,2'-bipyridine



4-31
phen
1,10-phenanthroline

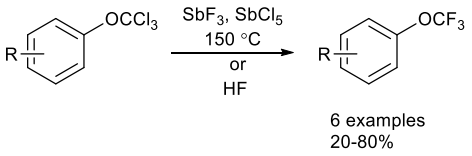
Table 4.7 Thiotrifluoromethylation of aryl boronic acids

The development of new, transition metal mediated syntheses of aryl trifluoromethylthioethers, using easily available halogenated aromatic or arylboronic acid

precursors, has had a significant impact on their availability, and allows for the synthesis of complex molecules containing an aromatic SCF_3 functional group.

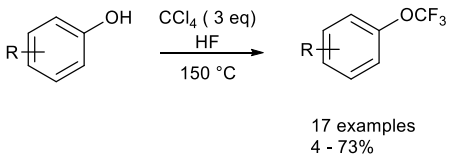
4.2.2 Methods for Aryl-OCF_3 Synthesis

The first synthesis of aryl trifluoromethylethers was reported in 1955 by Yagupolskii *et al*, who performed a halogen exchange reaction on aryl trichloromethylethers, using either a combination of SbF_3 and $SbCl_5$, or anhydrous HF at high temperature (Scheme 4.19).[58] The aryl trichloromethylethers were synthesized by chlorination of the corresponding anisole derivatives, but this method was only successful on substrates with electron-withdrawing groups.



Scheme 4.19 Fluorination of aryl trichloromethylethers

Feiring *et al* reported the use of phenols as starting material, in combination with HF and CCl_4, for synthesis of aryl trifluoromethylethers (Scheme 4.20).[59] The reaction tolerated both electron-withdrawing and -donating substituents, but *ortho*-substituted phenols were not effective substrates, and either failed or gave very low yields of the corresponding fluorinated products.

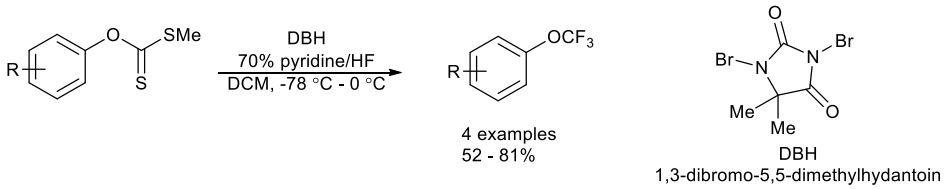


Scheme 4.20 Synthesis of aryl trifluoromethylethers from phenols

More recently, a combination of $SbF_3/SbCl_5$ at high temperature (140 - 180 °C) has been successfully applied to the synthesis of trifluoromethoxy substituted pyridines.[37c] The

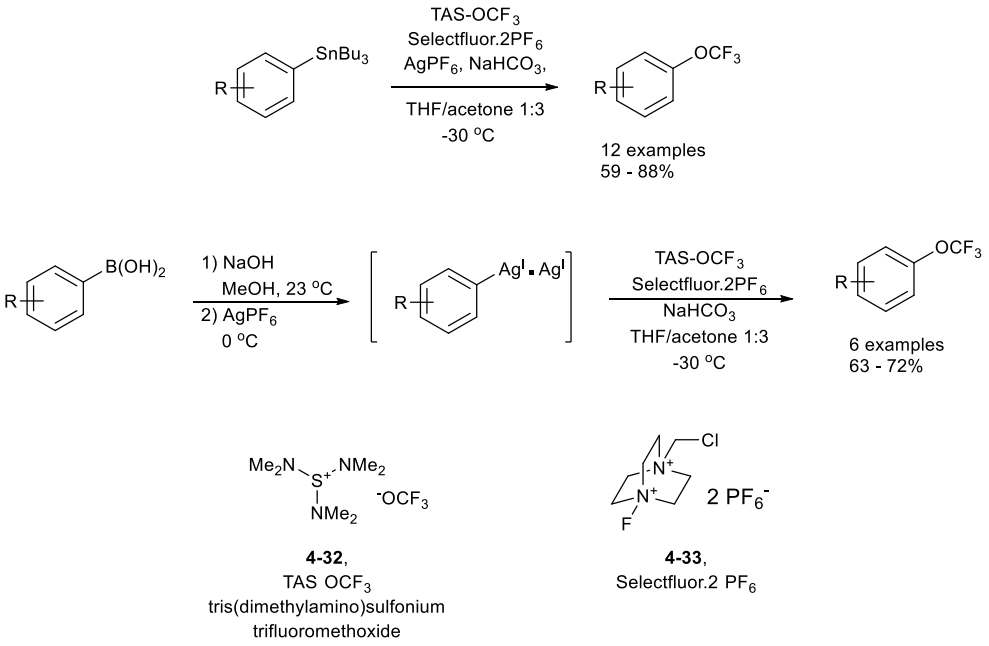
halogen exchange reaction is currently still valuable for industrial synthesis of aryl trifluoromethylethers because of the lack of other suitable methods.[60]

Aryl trifluoromethoxyethers have also been synthesized *via* oxidative desulfuration-fluorination of aryl methylxanthates (Scheme 4.21).[61] Treatment of aryl methylxanthates with DBH and a large excess of pyridine/HF (Olah's reagent), in DCM at low temperature, provided aryl trifluoromethylethers in good yield. The scope of this transformation is limited because the use of electron-rich arenes often gives rise to side products resulting from electrophilic aromatic bromination.



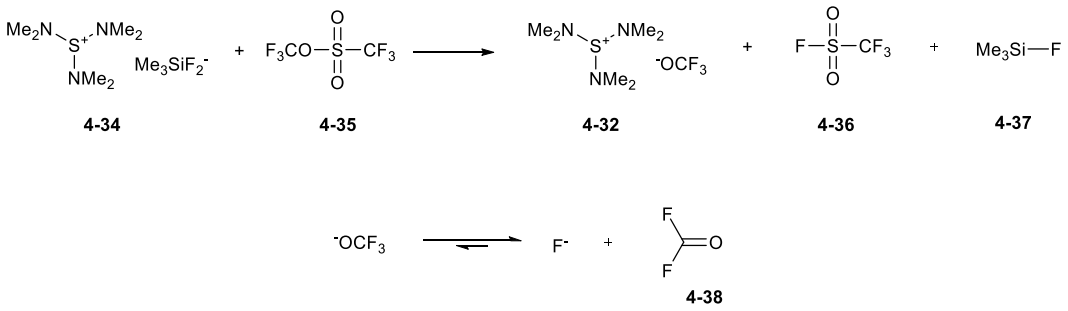
Scheme 4.21 Oxidative desulfuration-fluorination of aryl methylxanthates

In 2011, the Ritter group reported the trifluoromethoxylation of aryl stannanes and arylboronic acids mediated by Ag(I).[62] The reaction uses *in situ* generated trifluoromethoxide salt **4-32** as trifluoromethoxylating reagent, in combination with Selectfluor **4-33** as an oxidant, and gives good yields of aryl trifluoromethylethers with a high functional group tolerance. Aryl stannanes could be converted in one step, but with arylboronic acids formation of an aryl-silver complex and solvent change prior to trifluoromethoxylation were necessary. Low temperatures are necessary to avoid decomposition of the postulated bimetallic aryl-silver complex, and the OCF_3^--anion.



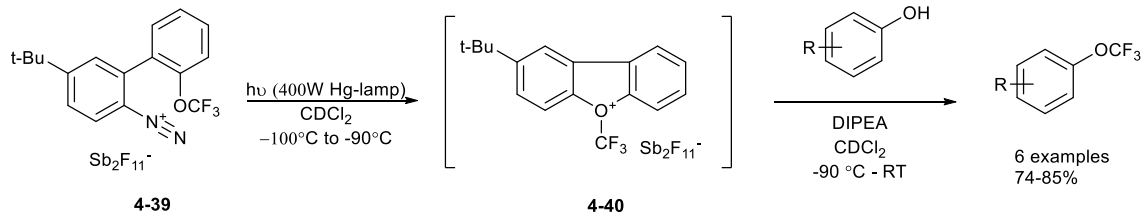
Scheme 4.22 Silver-mediated trifluoromethoxylation of aryl stannanes and arylboronic acids

The TAS-OCF_3 reagent **4-32** can be synthesized from reaction of the fluoride source TASF **4-34** with CF_3OTf **4-35**, and generates the gaseous CF_3SO_2F **4-35** as by-product (see Scheme 4.23).[63] The OCF_3-anion itself is thermally unstable, and can release fluoride to generate the toxic gas difluorophosgene **4.38**. This decomposition reaction can occur even at lower temperatures, but large cations like the TAS cation have been known to stabilise the OCF_3-anion in relation to formation of fluoride and difluorophosgene.[64]



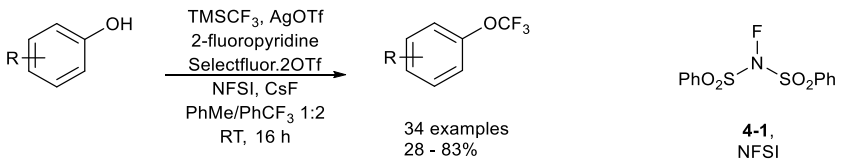
Scheme 4.23 Synthesis and decomposition of OCF_3^--anion

Direct *O*-trifluoromethylation of phenols has only recently been developed as an effective transformation for the synthesis of aryl trifluoromethylethers. In 2007, Umemoto *et al* reported the in-situ synthesis of CF_3-onium salt **4-40** from diazonium precursor **4-39**, using irradiation with a high pressure Hg lamp at low temperature (see Scheme 4.24).[65] The CF_3-onium salt is a very reactive electrophilic trifluoromethylating reagent, and reacts smoothly at low temperature with both electron-rich and -poor phenols to give the corresponding aryl trifluoromethylethers in good yield. Due to the high reactivity of **4-40** it is thermally unstable, and decomposes even at -70 °C with a measured half-life at 415 min.



Scheme 4.24 Electrophilic trifluoromethylation of phenols with CF_3-onium salt **4-40**

Very recently Qing *et al* reported an Ag(I) mediated oxidative trifluoromethylation of phenols using $TMSCF_3$ with CsF as fluoride source, and a combination of Select2OTf **4-2** and NFSI **4-1** as oxidants.[66] The best yields were obtained using a mixture of PhMe and $PhCF_3$ as solvent and 2-fluoropyridine as an additive, and a broad range of aryl trifluoromethylethers could be obtained under these conditions. When electron-rich phenols were used as starting material another additive, 2,4-di-*tert*-butyl-phenol, was needed to suppress side-reactions and provide useful yields of product.

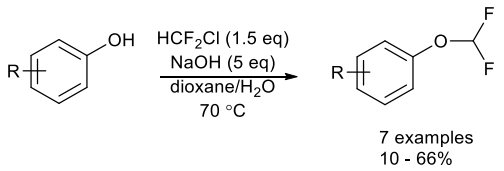


Scheme 4.25 Oxidative trifluoromethylation of phenols

These examples show that the synthesis of aryl trifluoromethylethers is possible from a diverse set of substrates. Recent contributions have made it possible to use easily accessible starting materials, under mild conditions. Despite this progress there is still a need for development of more general procedures that can provide aryl trifluoromethylethers with a broad scope, under mild conditions.

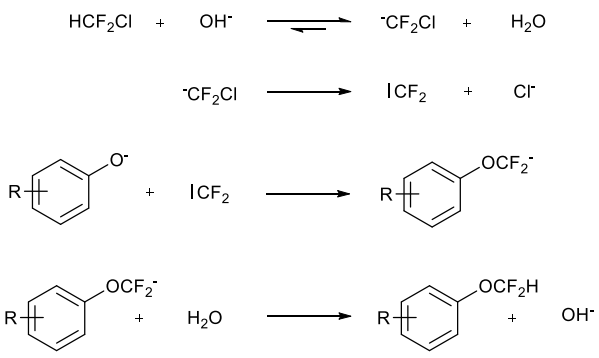
4.2.3 Methods for Aryl-OCF_2H Synthesis

Aryl difluoromethylethers are in general synthesized from the corresponding phenols under basic conditions by difluoromethylation with difluorocarbene, which can be generated in-situ from stable precursors. In 1960, Miller *et al* reported the use of gaseous HCF_2Cl for difluoroalkylation of phenols (Scheme 4.26).[67] The reaction worked well for electron-rich and -neutral phenols, but *para*-NO_2 phenol gave only a 10% yield.



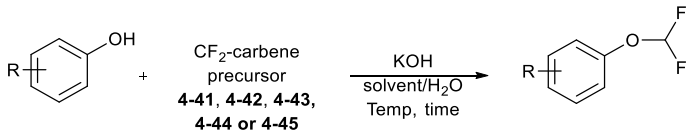
Scheme 4.26 Difluoromethylation of phenols using gaseous HCF_2Cl

Under the basic conditions HCF_2Cl is deprotonated to give CF_2Cl^-, which collapses into difluorocarbene and Cl^- (scheme 4.27). The generated difluorocarbene is attacked by the phenolate, which generates an aryl difluoroalkoxide that is protonated by H_2O to provide the aryl difluoromethyl ether.



Scheme 4.27 Mechanism of difluoroalkylation of phenols with HCF_2Cl under basic conditions

More recently new difluorocarbene sources have been developed to avoid the use of HCF_2Cl, which is an ozone depleting substance and greenhouse gas (Table 4.8). In 2006 Hu *et al* reported the commercially available 2-chloro-2,2'-difluoroacetophenone **4-41** as a difluorocarbene precursor (Table 4.8, method A).[68] Use of 5 eq of **4-41** and a large excess of KOH was necessary for good yields of aryl difluoromethylethers. Both electron-rich and neutral substrates gave good yields, while electron-poor substrates were not investigated. The same group reported chlorodifluoromethyl phenyl sulfone **4-42** as an improved difluorocarbene source in 2007 (Table 4.8, method B).[69] Although not commercially available, **4-42** proved to be a superior reagent to **4-41** in terms of stoichiometry, substrate scope and yield. Both electron-rich and -poor substrates provided good to excellent yields of aryl difluoromethylethers. Further improvement was reported by Zafrani and Segall in 2009, who used commercially available ethyl bromodifluoromethylphosphonate **4-43** as a very efficient difluorocarbene source (Table 4.8 method C).[70] Good to excellent yields were obtained under mild conditions in fast reaction times (30 min). Although a large excess of base was still used, the mild conditions allowed for the first time the use of arenes substituted with enolizable aldehydes and ketones.



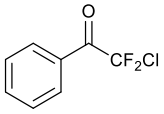
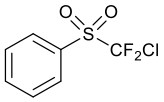
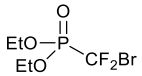
Method	Presursor	Eq.	Conditions	Yield
A	 **4-41**	5	KOH (21 eq) CH_3CN/H_2O 80 °C, 4 h	51 -79 % (13 examples)
B	 **4-42**	2.3	KOH (11 eq) CH_3CN/H_2O 50 °C, 5 h	65-96% (16 examples)
C	 **4-43**	2	KOH (20 eq) CH_3CN/H_2O -78 °C to RT, 0.5 h	60-98% (9 examples)
D	HCF_2OTf**, 4-44**	3	KOH (12 eq) CH_3CN/H_2O RT, 5 min	51-92% (17 examples)
E	Me_3SiCF_2Br**, 4-45**	2	KOH (6 eq) DCM/H_2O 0 °C, 0.5 h	58-95% (12 examples)

Table 4.8 Difluoromethylation of phenols with different difluorocarbene sources

Even faster reaction times of less than 5 min were reported by Hartwig *et al* who used difluoromethyltriflate **4-44** as the difluorocarbene source (Table 4.8 method D).[71] The short reaction times allowed for a broad substrate scope. Also, a two-step one-pot procedure of oxidation or palladium catalysed hydroxylation, followed by difluoromethylation with **4-45**, allowed for the synthesis of aryl difluoromethylethers from respectively aryl boronic esters and halides. Hu *et al* reported another example of difluoromethylation under mild conditions with fast reaction times, by using Me_3SiCF_2Br as difluorocarbene source (Table 4.8 method E).[72] The underlying mechanism of all these reactions are very similar, and involves generation of CF_2Cl^- (or CF_2Br^- in case of **4-44** and **4-45**), which collapses into

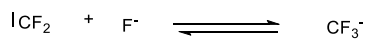
difluorocarbene (see Scheme 4.27). The difference in yield and scope in these methods originates from the efficiency with which the difluorocarbene is generated.

4.2.4 Adaptation of Existing Methods for Aryl-SCF_3 –OCF_3 and –OCF_2H Synthesis for ^{18}F-radiolabelling

With the existing methodologies it is possible to efficiently synthesize (hetero)aromatic α-fluorinated methyl(thio)ethers (OCF_2H, OCF_3 or SCF_3) from a variety of precursors. Aryl trifluoromethylsulfides have been synthesized from thiophenol derivatives in combination with different trifluoromethylation reagent such as Me_3SiCF_3, CF_3H, CF_3I and the Togni I reagent**.** Recent advances in transition metal mediated thiotrifluoromethylation enabled the use of aryl chlorides, bromides, iodides and boronic acids as starting materials, usually in combination with nucleophilic thiotrifluoromethyl anion equivalents such as $CuSCF_3$, $AgSCF_3$ and NMe_4SCF_3. Fewer options are available for the synthesis of aryl trifluoromethylethers, but with the existing methods it is possible to use both phenols and aryl boronic acids as easily available starting materials.

However, the adaptation of these methodologies to ^{18}F-labelling and the synthesis of ^{18}F-aryl-trifluoromethylsulfides and -trifluoromethylethers is made difficult by the restrictions in available ^{18}F-sources (see section 4.1). In addition, most of the current methodologies introduce all the fluorine atoms in a single step, which would be very challenging for adaptation in ^{18}F-labelling, considering the nanomolar concentration in which [^{18}F]F^- is available.

The synthesis of ^{18}F-labelled aryl difluoromethylethers from ^{18}F-labelled difluorocarbene is made difficult by the formation of the CF_3-anion when difluorocarbene is generated in the presence of fluoride (Scheme 4.28).



Scheme 4.28 Equilibrium between difluorocarbene and the CF_3-anion

Recent strategies have made use of this equilibrium for the generation of $[^{18}F]CuCF_3$ from CuI and $[^{18}F]F^-$ in combination with $ClCF_2CO_2Et$ as difluorocarbene source,[73] and generation of $[^{18}F]SCF_3^-$ from $[^{18}F]F^-$ and $Ph_3P^+CF_2CO_2^-$ as difluorocarbene source.[74] No products related to ^{18}F-difluorocarbene were reported to form in these reactions, a fact that shows that formation of ^{18}F-labelled difluorocarbene in the presence of $[^{18}F]F^-$ is more likely to form $[^{18}F]CF_3^-$, which would make the synthesis of ^{18}F-aryl difluoromethylethers by this route challenging. The synthesis of an ^{18}F-labelled OCF_3-anion reagent, such as $[^{18}F]$TAS-OCF_3, for the ^{18}F-trifluoromethoxylation of arenes is also expected to be very challenging, considering the reported instability of this anion with respect to formation of difluorophosgene and fluoride (see previous section).

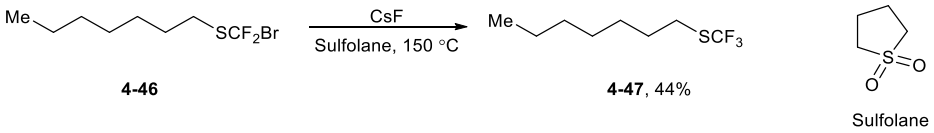
Currently, the only methodology that has potential for adaptation to radiolabelling of the SCF_3, OCF_3 and OCF_2H motifs is a halogen exchange reaction, in which $[^{18}F]F^-$ can be used as a nucleophilic ^{18}F source. The use of mono- or di-fluorinated halogen precursors would allow for the introduction of a single ^{18}F atom, using easily available $[^{18}F]F^-$ sources, which can be produced in high SA. In the following sections our research into a new method for the ^{18}F-labelling of aromatic di- and tri-fluoromethyl(thio)ethers from $[^{18}F]F^-$, using Ag(I)-mediated halogen exchange as a new activation mode for ^{18}F-fluorination is described.

4.3 Synthesis of $[^{18}F]$ArylSCF$_3$ from $[^{18}F]F^-$

The radiochemistry experiments described in this section were carried out in collaboration with Dr M. Tredwell.[75]

Formation of aryl trifluoromethylsulfides from halogenated aryl methylsulfides precursors using halogen exchange usually employs an excess of corrosive and toxic reagents at elevated temperature, and these conditions are difficult to adapt to ^{18}F-labelling (see

section 4.2.4). An isolated example of halogen exchange using a nucleophilic fluoride source (CsF), in polar solvent (sulfolane) at elevated temperature (150 °C), is the formation of alkyl trifluoromethylsulfide **4-47** in moderate yield from alkyl bromodifluoromethylsulfide precursor **4-46**.[41]

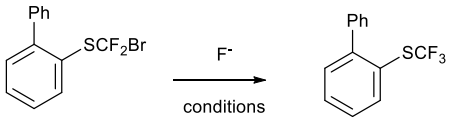


4-46 **4-47**, 44% Sulfolane

Scheme 4.29 Fluorination of alkyl bromodifluoromethylsulfide **4-46** with CsF in sulfolane

4.3.1 Preliminary Investigations

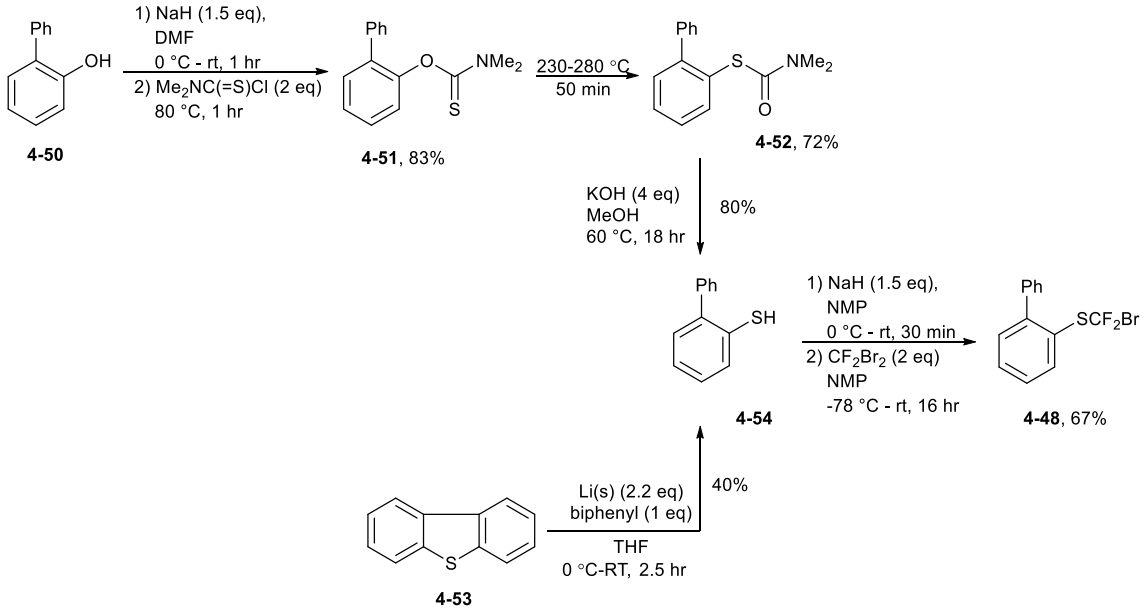
These conditions were taken as a starting point for preliminary investigation into the fluorination of aryl bromodifluoromethylsulfides using a nucleophilic fluoride source, and conditions that are compatible with ^{18}F-radiolabelling. As a model substrate [1,1'-biphenyl]-2-yl(bromodifluoromethyl)sulfide **4-49** was chosen, which has been successfully fluorinated by Umemoto using SbF_3 at high temperature.[76] The fluorinated product, [1,1'-biphenyl]-2-yl(trifluoromethyl)sulfide **4-49**, is a non-volatile and stable solid which can be easily analysed.



4-48 **4-49**

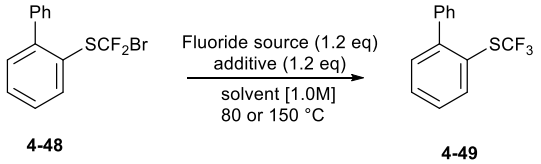
Scheme 4.30 Model substrate for arylSCF_3 synthesis by nucleophilic fluorination

The brominated precursor **4-48** was synthesized by alkylation of [1,1'-biphenyl]-2-thiol **4-54** with CF_2Br_2 in NMP.[78] The required thiophenol **4-54** could be obtained in three steps from 2-phenyl-phenol **4-50** as reported by Umemoto,[78] or by reduction of dibenzothiophene **4-53** using Li metal.[77]



Scheme 4.31 Synthesis of model substrate **4-48**

In preliminary screening experiments, **4-48** was reacted with different fluoride sources (KF in combination with 18-crown-6 or TBAF.3H_2O) which were chosen for their compatibility with ^{18}F-labelling conditions. After stirring at elevated temperatures in different polar solvents for 24 hrs, the reaction was allowed to cool to room temperature and an aliquot of the reaction was analysed by ^{19}F NMR spectroscopy.



4-48 **4-49**

Entry[a]	Fluoride source	Solvent, Temp., Time	Conversion[b]	Yield[b]
1	KF, 18-crown-6	Sulfolane, 150°C, 24 h	97%	16%
2	KF, 18-crown-6	DMF, 150°C, 2 h	61%	6%
3	TBAF.3H_2O	*t*BuOH, 80°C, 24 h	10%	7%

[a] Reaction conditions : **4-48** (0.1 mmol), KF (0.12 mmol) or TBAF.3H_2O (1.2 mmol), 18-crown-6 (0.12 mmol) in solvent [1.0M]. [b] Estimated by ^{19}F NMR using $PhCF_3$ as an internal reference.

Table 4.9 Nucleophilic fluorination of bromide **4-48**

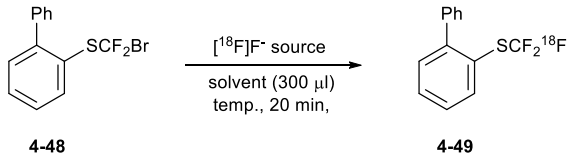
High conversion of starting material into non-identified, mainly non-fluorinated products was observed from analysis of the reaction using KF/18-crown-6 as a reagent by ^{19}F NMR. Fluorinated product **4-49** was formed in low yields (16% and 6% respectively, Table 4.9 entry 1 and 2). The reaction with TBAF.3H_2O was conducted in *t*-BuOH, which has been shown to enhance the reactivity and moderate the basicity of fluoride due to limited solvation by the bulky alcohol, thus providing higher yields and avoiding side reactions.[78] However, the reaction with TBAF.3H_2O in *t*BuOH at reflux also showed a low yield of product **4-49** (7%, Table 4.9 entry 3), although a much lower conversion of starting material was observed (10%). The identity of **4-49** could be unambiguously established by comparison with an authentic sample.

From these preliminary results it can be concluded that successful nucleophilic fluorination of aryl bromodifluoromethylsulfides with an F^- source is possible, but high temperature are necessary and yields are generally low. These conditions show similarity with the

conditions used in nucleophilic ^{18}F-radiofluorination (see section 4.1.3), and were therefore taken as a starting point for the development of a method for the synthesis of ^{18}F-arylSCF_3 compounds.

4.3.2 Nucleophilic ^{18}F-Radiofluorination of Aryl Bromodifluoromethylsulfides by Thermal Activation

Having validated that the synthesis of aryl trifluoromethylthioethers by nucleophilic fluorination under thermal activation is possible, we turned our attention to the development of reaction conditions that would allow for the synthesis of radiolabelled ^{18}F-arylSCF_3 compounds using an ^{18}F-fluoride source. To this end, **4-48** was reacted with either [^{18}F]KF/$K_{2.2.2}$ complex or [^{18}F]Et_4NF (prepared from $Et_4NHCO_3^-$ as precursor) in different polar solvents at elevated temperatures. Both ^{18}F-sources were obtained from [^{18}F]F^-(aq) produced by a cyclotron, using an ion exchange cartridge followed by azeotropic drying with CH_3CN as described in section 4.1.3.



4-48 **4-49**

Entry[a]	[^{18}F]F$^-$ source	Solvent	Temp.	RCC[b]
1	[^{18}F]KF/$K_{2.2.2}$	^{t}BuOH	80°C	0% (*n* = 2)
2	[^{18}F]KF/$K_{2.2.2}$	DMF	150°C	0% (*n* = 2)
3	[^{18}F]KF/$K_{2.2.2}$	Sulfolane	180°C	0% (*n* = 2)
4	[^{18}F]KF/$K_{2.2.2}$	DMSO	180°C	0% (*n* = 2)
5	[^{18}F]Et_4NF	^{t}BuOH	80°C	0% (*n* = 2)
6	[^{18}F]Et_4NF	DMF	150°C	0% (*n* = 2)
7	[^{18}F]Et_4NF	Sulfolane	200°C	1 ± 1% (*n* = 2)

[a] Reaction conditions : **4-48** (0.04 mmol), [^{18}F]KF/$K_{2.2.2}$ or [^{18}F]Et_4NF (typical activity 25-30 MBq), solvent (300 µl). [b] as determined by radio-TLC and radio-HPLC, details see SI.

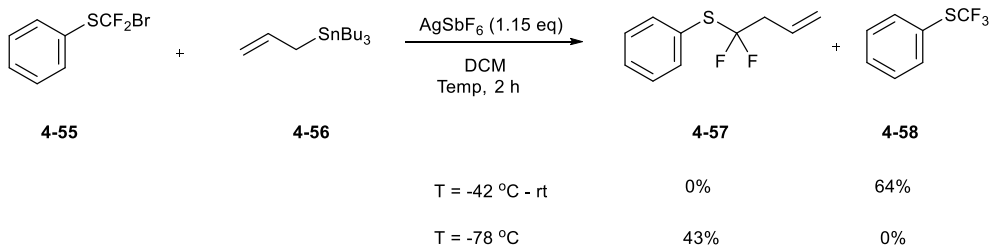
Table 4.10 Radiofluorination of **4-48** with [^{18}F]KF/$K_{2.2.2}$ complex by thermal activation.

Using different polar solvents and temperatures up to 180 °C, no ^{18}F-incorporation was found to take place when [^{18}F]KF/$K_{2.2.2}$ was used, and formation of the desired [^{18}F]SCF_3 containing product **[**^{18}F]**449** was not observed (Table 4.10 entry 1-4). With [^{18}F]Et_4NF as the radioactive fluoride source only a trace of **[**^{18}F]**449** was obtained, under very forcing conditions (Table 4.10 entry 7).

4.3.3 Ag(I)-mediated Halogen Exchange of Aryl Bromodifluoromethylsulfides

The unsuccessful attempt to synthesize ^{18}F-arylSCF_3 compounds using a classical substitution strategy with [^{18}F]F$^-$ by thermal activation, led us to consider a different mode of activation. In 1981, Suda *et al* demonstrated that both alkyl- and aryl bromodifluoromethylsulfides can be fluorinated in moderate yields, using $AgBF_4$ in either DCM or Et_2O at room temperature (see previous section).[41] Reutrakul *et al*. observed

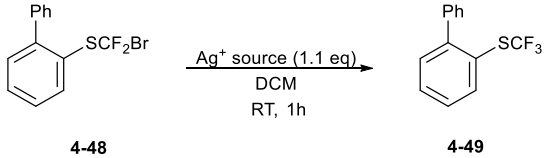
formation of aryl thiotrifluoromethylethers as side-products in the difluoro(phenylthio)methylation reaction of allyl stannanes with $ArSCF_2Br$, mediated by Ag(I) salts (scheme 4.32).[79] When the reaction was performed with either $AgBF_4$ or $AgSbF_6$ at temperatures higher than -42 °C, exclusive formation of aryl thiotrifluoromethylethers was observed. The authors proposed an aryldifluoromethylthio-cation as intermediate, for which tentative evidence was given by low temperature (-70 °C) ^{13}C NMR studies, in addition to DFT calculations.



Scheme 4.32 Ag(I) mediated allylation of **4-55** and formation of **4-57** as side-product

These results show that a halogen exchange reaction mediated by Ag(I)-salts can provide efficient fluorination of aryl bromodifluoromethylthioethers under very mild conditions.

To further investigate the Ag(I)-mediated halogen exchange reaction as a new activation mode for ^{18}F-fluorination, the reactivity of model substrate **4-48** with $AgBF_4$ was probed. In an adaptation of the conditions developed by Suda *et al*,[77] **4-48** was treated with $AgBF_4$ (1.1 eq) in DCM at room temperature, giving a 31% yield of aryl trifluoromethylthioether **4-49** (Tabel 4.11, entry 1). $AgSbF_6$ was also effective in providing **4-49**, albeit in a lower yield with several unidentified side-products (Table 4.11 entry 2). In both reactions the starting material was completely consumed.



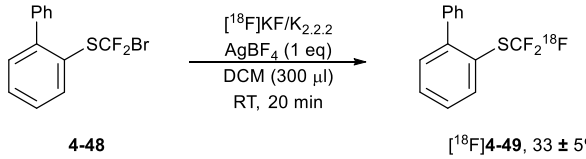
Entry[a]	Ag^+-source	Yield[b]
1	$AgBF_4$	31% (54%)
2	$AgSbF_6$	(24%)

[a] Reaction conditions : **4-48** (0.10 mmol), Ag^+-source (0.11 mmol), DCM (1.0 mL). [b] Isolated yields in parenthesis. Yields estimated by ^{19}F NMR using $PhCF_3$ as an internal reference in parenthesis

Table 4.11 Fluorination of $ArSCF_2Br$ with Ag(I) salts

4.3.4 Ag(I)-mediated Halogen Exchange ^{18}F-fluorination of Aryl Bromodifluoromethylsulfides

The conditions for the successful fluorination of **4-49** using a halex exchange reaction mediated by $AgBF_4$ were adapted to the ^{18}F-fluorination of aryl bromodifluoromethylthioethers. $[^{18}F]KF/K_{2.2.2}$ complex (~4 GBq) was obtained from $[^{18}F]F^-$(aq), using an ion exchange cartridge followed by azeotropic drying with CH_3CN. The complex was re-dissolved in CH_3CN (800 μl), and a small aliquot (10 – 50 μL) of this solution (~30 MBq) was added to a V-vial containing $AgBF_4$ (0.04 mmol). The CH_3CN was completely removed by heating at 100 °C under a stream of nitrogen for 2 min, after which a solution of **4-48** (1 eq) in DCM (300 μl) was added. The mixture was stirred for 20 min. at room temperature after which it was quenched with a mixture of $EtOH/H_2O$ (9/1, 500 μl). The radiochemical yield was determined by radio-TLC and radio-HPLC as described in section 4.1.3. Following this procedure $[^{18}F]$**4-49** was obtained in 33 ± 5% RCC (Scheme 4.33).



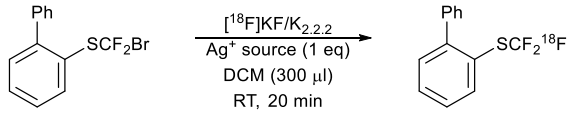
4-48 [^{18}F]**4-49**, 33 ± 5%

Scheme 4.33 $AgBF_4$ mediated radiofluorination of **4-48**

This result shows that if an Ag(I)-salt is added as an activator, the ^{18}F incorporation to give [^{18}F]**4-49** can proceed under very mild conditions at room temperature. However, it needs to be taken into account that the BF_4-anion can act as a source of fluorine and is known to facilitate isotope exchange,[80] which can result in low SA of the ^{18}F-fluorinated product, making $AgBF_4$ an undesirable means of activation.

4.3.4.1 Reaction Optimisation

Encouraged by the successful ^{18}F-fluorination of **4-48** using $AgBF_4$ as activator other Ag(I)-sources were investigated (Table 4.12), using the procedure described in the previous section. To avoid formation of non-labelled **4-49**, which would lower the SA, Ag(I) sources containing anions which are not a nucleophilic source of fluoride where selected for further screening.



4-48 [^{18}F]**4-49**

Entry[a]	Ag^+ source	RCC[b]
1	$AgBF_4$	33 ± 5% (*n* = 2)
2	AgF	0% (*n* = 2)
3	Ag_2O	0% (*n* = 2)
4	Ag_2CO_3	0% (*n* = 2)
5	AgTFA	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)

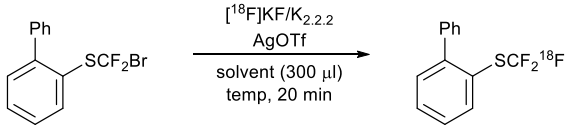
10	$AgNTf_2$	73 ± 4% (*n* = 2)
11	LiOTf	0% (*n* = 2)
12	$Cu(OTf)_2$	0% (*n* = 2)

[a] Reaction conditions : 4-48 (0.04 mmol), [^{18}F]KF/$K_{2.2.2}$ (typical activity 25-30 MBq), Ag^+ source (0.04 mmol), DCM (300 μl).
[b] as determined by radio-TLC and radio-HPLC, details see SI.

Table 4.12 Screening of Ag(I) sources

While the use of a variety of other Ag(I) salts did not result in ^{18}F-incorporation (Table 4.12 entry 2-8), it was found that Ag(I) salts with weakly coordinating anions, AgOTf (Table 4.12 entry 9) and $AgNTf_2$ (Table 4.12 entry 10), provided the radio-fluorinated product [^{18}F]**4-49** in good RCC (60 ± 4% for AgOTf, 73 ± 4% for $AgNTf_2$). Control experiments using LiOTf (Table 4.12 entry 11) and $Cu(OTf)_2$ (Table 4.12 entry 12) confirmed that Ag(I) is essential for the reaction to proceed.

AgOTf was selected for further optimisation experiments, and a range of solvents were investigated (Table 4.13) using the procedure described in the previous section.



4-48 [^{18}F]**4-49**

Entry[a]	Solvent	Temp	RCC[b]
1	DCM	rt	60 ± 4% (*n* = 10)
2	DCE	rt	79 ± 3% (*n* = 2)
3[c]	DCE	60°C	81 ± 3% (*n* = 2)
4	Et_2O	rt	0% (*n* = 2)
5	CH_3CN	rt	0% (*n* = 2)

6	DMF	rt	0% (n = 2)

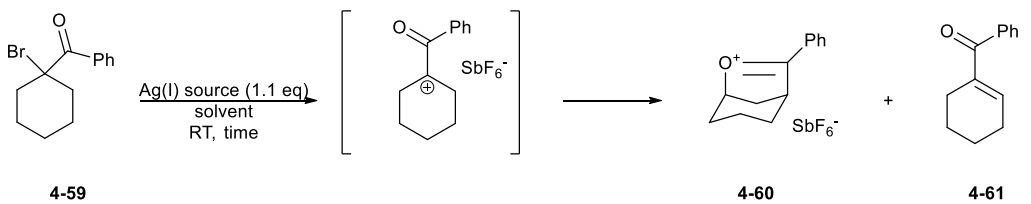
[a] Reaction conditions : **4-48** (0.04 mmol), [^{18}F]KF/$K_{2.2.2}$ (typical activity 25-30 MBq), AgOTf (0.04 mmol), DCM (300 µl). [b] as determined by radio-TLC and radio-HPLC, details see SI. [c] 0.08 mmol AgOTf was used.

Table 4.13 Solvent optimisation

Chlorinated non-polar solvents DCM and DCE provided [^{18}F]**4-49** in 60 ± 4% and 73 ± 4% RCC respectively (Table 4.13 entry 1 and 2). Running the reaction in DCE at 60°C using AgOTf (2 eq) gave a slightly higher RCC of ^{18}F-fluorinated product (81 ± 3%), in comparison with the reaction performed at room temperature.

When more polar solvents like Et_2O (Table 4.13 entry 4), CH_3CN (Table 4.13 entry 5) and DMF (Table 4.13 entry 6) were used, the ^{18}F-fluorination did not proceed at all and no product was formed. It was found that when the reaction was run in DCM as a solvent, even small amounts of CH_3CN were inhibiting the formation of [^{18}F]**4-49**, and CH_3CN from the dispensed aliquots of [^{18}F]KF/$K_{2.2.2}$ complex had to be completely removed by heating under a stream of nitrogen to ensure ^{18}F-fluorination to occur.

A possible explanation for this remarkable solvent effect lies in the fact that Ag(I)-salts can form complexes with molecules containing free lone-pairs or π-electrons. Binding enthalpies for solvents such as CH_3CN, DMF and Et_2O and the Ag(I)-cation have been determined experimentally and by DFT calculations, and are in the range of 30-50 kcal/mol.[81] The bound solvent could potentially influence the electrophilicity of the Ag(I)-cation and thus alter the reactivity towards halogen abstraction. This was experimentally shown by Bégué *et al*,[82] who studied the halogen abstraction of α-bromo ketone **4-59** with $AgSbF_6$ in different solvents (Table 4.14).



4-59 **4-60** **4-61**

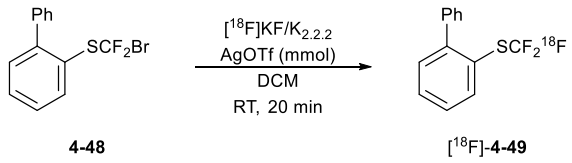
Entry	Ag(I) source	Solvent	Time	Conversion	Yield 4-60	Yield 4-61
1	$AgSbF_6$	DCM	2 min	100%	80%	20%
2	$AgSbF_6.nCH_3CN$[a]	DCM	72 hrs	10%	0%	10%
3	$AgSbF_6$	CH_3CN	72 hrs	15%	0%	15%

[a] the number of n was not specified.

Table 4.14 Influence of solvation on reactivity Ag(I) source

The reaction was very fast when DCM was used as a solvent, reaching full conversion in 2 min and producing cation **4-60** as major product,[83] together with elimination product **4-61** (Table 4.14 entry 1). When the preformed $AgSbF_6.nCH_3CN$ complex (no number for n was reported) was used, the reaction slowed down drastically with only 10% conversion observed after 72 hrs (Table 4.14 entry 2). In this reaction the elimination product **4-61** was formed as the sole product. This result was similar to when $AgSbF_6$ was used in CH_3CN as a solvent (Table 4.14 entry 3).

Next, the stoichiometry of the reaction was investigated. A reduction in the amount of either precursor or Ag(I) salt could be beneficial for specific activity, and ease of purification at a later stage.



4-48 [18F]-**4-49**

Entry	4-48 (mmol)	AgOTf (mmol)	DCM (μl)	RCC[b]
1	0.04	0.04	300	60 ± 4% (*n* = 10)
2	0.02	0.04	300	39 ± 2% (*n* = 2)
3	0.01	0.04	300	18 ± 1% (*n* = 2)
4	0.04	0.02	300	21 ± 3% (*n* = 2)
5	0.04	0.004	300	34 ± 9% (*n* = 2)
6	0.004	0.004	300	8 ± 8% (*n* = 2)
7	0.02	0.02	300	31 ± 2% (*n* = 2)
8	0.02	0.02	150	44 ± 2% (*n* = 2)

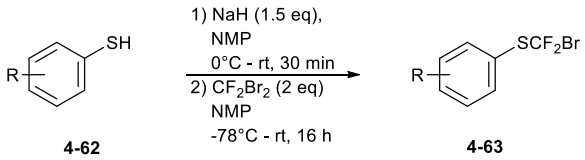
[a] Reaction conditions : **4-48** (see table), [18F]KF/$K_{2.2.2}$ (typical activity 25-30 MBq), AgOTf (see table), DCM (see table). [b] as determined by radio-TLC and radio-HPLC, details see SI.

Table 4.15 Stoichiometry investigation

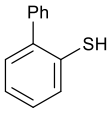
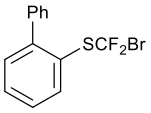
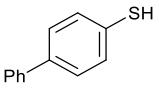
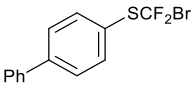
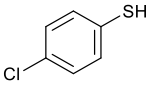
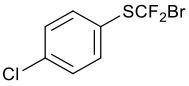
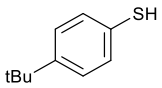
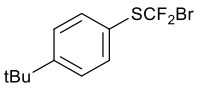
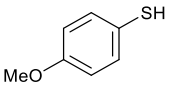
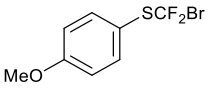
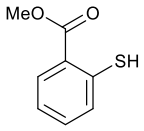
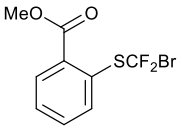
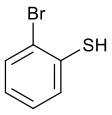
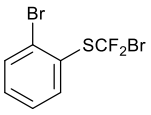
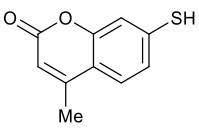
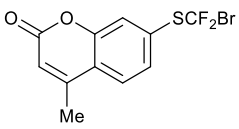
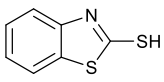
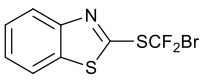
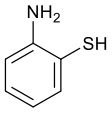
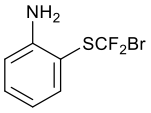
Reducing the amount of aryl bromodifluoromethylsulfide precursor **4-48** resulted in less efficient radiolabelling, with [^{18}F]**4-49** formed in 39 ± 2% and 18 ± 1% RCC respectively when the reaction was performed with 0.02 mmol (0.5 eq) or 0.01 (0.25 eq) **4-48** (Table 4.15 entry 2 and 3). Using fewer equivalents of Ag(I) salt with respect to **4-48** was also found to be detrimental, and a 2-fold or 10-fold reduction in the amount of AgOTf resulted in lower RCC (21 ± 3% and 34 ± 9%, Table 4.15 entry 4 and 5). When the amounts of precursor and AgOTf were lowered simultaneously the radiolabelling was again less efficient (Table 4.15, entry 6 and 7). Finally, the reaction was performed at higher concentration with both less precursor and AgOTf, under which conditions a RCC of 44 ± 2% was obtained (Table 4.15, entry 8). From these result it can be concluded that the original conditions showed the highest RCC into [^{18}F]**4-49** (60 ± 4%, Table 4.15 entry 1). A reduction of the amount of precursor could however be desired, since this will reduce the amount of non ^{18}F-containing side products formed during the reaction, and aid in the final purification of the desired ^{18}F-containing product. This could be beneficial if the method was to be used for the synthesis of [^{18}F]SCF_3 containing radiotracers for clinical imaging. In this case the reaction can be run at a higher concentration, using half the amount of precursor and AgOTf, with a slight reduction in RCC (44 ± 2%, Table 4.15 entry 8).

4.3.4.2 Preparation of Aryl Bromodifluoromethylsulfides

Using the optimised reaction conditions for the Ag(I) mediated ^{18}F-radiofluorination of aryl bromodifluoromethylsulfides, the scope and limitations were investigated. To this end, the synthesis of a variety of different aryl bromodifluoromethylsulfides was performed by alkylation of sodium thiophenolates with CF_2Br_2.[80,84]



4-62 **4-63**

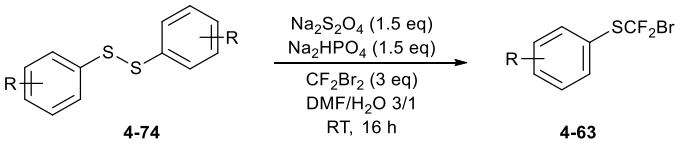
Entry[a]	Thiophenol	Product	Yield[b]
1			**4-64**, 67%
2			**4-65**, 52%
3			**4-66**, 36%
4			**4-67**, 68%
5			**4-68**, 42%
6			**4-69**, 14%
7			**4-70**, 57%
8			**4-71**, 51%
9			**4-72**, 62%
10			**4-73**, 0%

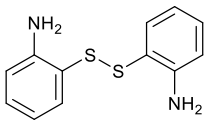
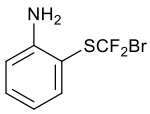
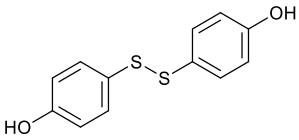
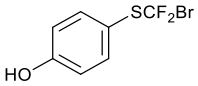
[a] **4-62** (5.0 mmol), NaH (7.5 mmol), CF_2Br_2(10 mmol), 5 ml NMP. [b] isolated yields after column chromatography or distillation.

Table 4.16 Synthesis of aryl bromodifluoromethylsulfides

Various thiophenols were reacted with NaH (60% dispersion on oil, 1.5 eq) in degassed NMP to give a solution of sodium thiophenolates. This solution was cooled to -78 °C and CF_2Br_2 (2 eq) was added in one portion, after which the reaction was allowed to warm to room temperature overnight (16 h). The aryl bromodifluoromehylsulfide **4-64 – 4-72** could be isolated as stable compounds, upon aqueous work-up and purification by silica gel column chromatography. The reaction tolerates both electron donating and electron withdrawing substituents, and provides aryl bromodifluoromethylsulfides in low to moderate yields (Table 4.16 entry 1-7). Heterocyclic thiophenols with a coumarine or benzothiazole framework were also tolerated, and gave satisfactory yields of products (Table 4.16 entry 8-9). When 2-aminothiophenol was reacted the desired product was not formed (Table 4.16 entry 10), and decomposition occurred accompanied by formation of unknown side-products.

Aryl bromodifluoromethylsulfides containing functional groups with acidic hydrogens could not be synthesized from the corresponding thiophenolates, because the formation of dianions hindered the reaction. To enable the synthesis of these compounds, a method was used which utilizes aryl disulfides as starting materials.[85] To a solution of aryldisulfides **4-74** in DMF/H_2O 3/1 was added a solution of $Na_2S_2O_4$ (1.5 eq) and Na_2HPO_4 (1.5 eq) in H_2O. To the resulting mixture, cooled in a waterbath, was added CF_2Br_2 (3 eq) after which the reaction was stirred at room temperature for 16h.



Entry[a]	Thiophenol	Product	Yield[b]
1			**4-75**, 93%
2			**4-76**, 49%[c]

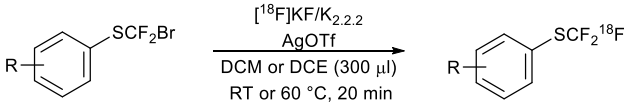
[a] **4-74** (5 mmol), NaS_2O_4 (7.5 mmol), Na_2HPO_4 (7.5 mmol), CF_2Br_2(15 mmol), 75 ml DMF, 25 mL H_2O. [b] isolated yields after column chromatography. [c] Slowly decomposes at rt.

Table 4.17 Synthesis of aryl bromodifluoromethylsulfides with acidic hydrogens

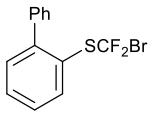
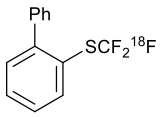
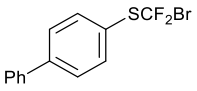
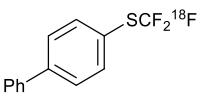
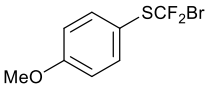
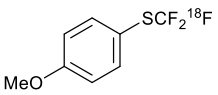
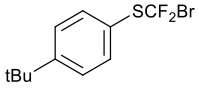
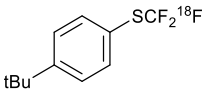
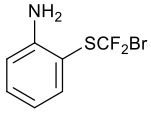
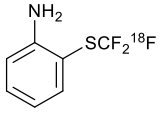
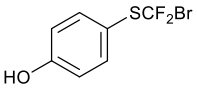
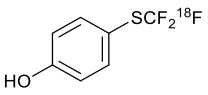
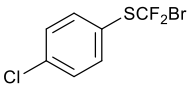
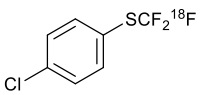
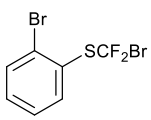
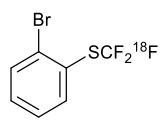
Under these conditions the *ortho*-NH_2, and *para*-OH substituted aryl bromodifluoromethylsulfide **4-75** and **4-76** were isolated in 93% and 49% yield (Table 4.17 entry 1 and 2). The yield of **4-76** was slightly lower because of its slow decomposition at room temperature.

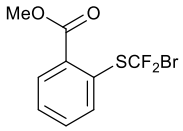
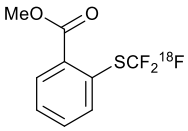
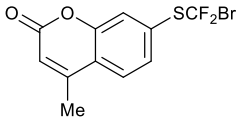
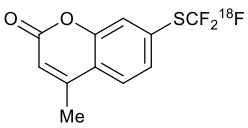
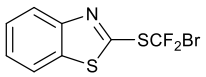
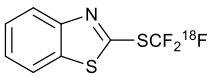
4.3.4.3 Scope and Limitations

Aryl bromodifluoromethylsulfides **4-63** were subjected to Ag(I) mediated ^{18}F-radiofluorination using the [^{18}F]KF/$K_{2.2.2}$ complex. The optimised conditions were applied using AgOTf (1 eq) in DCM (0.12M) at room temperature (Table 4.18, method A), in addition to conditions at higher temperature, AgOTf (2 eq) in DCE (0.12M) at 60°C (Table 4.18, method B).



4-63 [18F]**4-77**

Entry[a]	Precursor	Product	RCC[b]	
			Method A	Method B
1	 **4-64**	 [18F]**4-49**	60 ± 4% (*n* = 10)	81 ± 3% (*n* = 4)
2	 **4-65**	 [18F]**4-90**	12 ± 2% (*n* = 4)	6 ± 2% (*n* = 4)
3	 **4-68**	 [18F]**4-91**	36 ± 2% (*n* = 4)	74 ± 3% (*n* = 4)
4	 **4-67**	 [18F]**4-92**	34 ± 3% (*n* = 4)	92 ± 0% (*n* = 4)
5	 **4-75**	 [18F]**4-93**	35 ± 2% (*n* = 4)	40 ± 2% (*n* = 4)
6	 **4-76**	 [18F]**4-94**	16 ± 2% (*n* = 4)	21 ± 1% (*n* = 4)
7	 **4-66**	 [18F]**4-95**	2 ± 0% (*n* = 4)	46 ± 11% (*n* = 4)
8	 **4-70**	 [18F]**4-96**	2 ± 1% (*n* = 4)	55 ± 6% (*n* = 2)

9	 **4-69**	 [^{18}F]**4-97**	1 ± 1% (*n* = 4)	2 ± 1% (*n* = 4)
10	 **4-71**	 [^{18}F]**4-98**	1 ± 0% (*n* = 4)	37 ± 5% (*n* = 4)
11	 **4-72**	 [^{18}F]**4-99**	0% (*n* = 4)	0% (*n* = 4)

[a] Reaction conditions : **4-63** (0.04mmol), [^{18}F]KF/$K_{2.2.2}$ (typical activity 25-30 MBq), **Method A** : AgOTf (0.04 mmol), DCM (300 µl), rt, 20 min; **Method B** : AgOTf (0.08 mmol)), DCE (300 µl), 60°C, 20 min. [b] as determined by radio-TLC and radio-HPLC, details see Experimental Section.

Table 4.18 Ag(I) mediated ^{18}F-radiofluorination of aryl bromodifluoromethylsulfides

A solution of azeotropically dried [^{18}F]KF/$K_{2.2.2}$ complex (~30 MBq) in CH_3CN, prepared from [^{18}F]F^- (aq) as described in section 4.1.3, was added to AgOTf, and the solvent was removed at 100 °C under a stream of nitrogen. A solution of aryl bromodifluoromethylsulfides **4-63** in DCM (300 µL) was added, and the resulting mixture was stirred for 20 min at room temperature, after which it was quenched with EtOH/H_2O (9/1, 500 µl). The yield was determined by analysis of an aliquot of the quenched reaction mixture by radio TLC, taking into account the purity measured by radio-HPLC as described in section 4.1.3. The results show that at room temperature, with AgOTf (1 eq) in DCM (Method **A**), aryl bromodifluoromethylsulfides with electron donating substituents provide ^{18}F-arylSCF_3 products with RCC from 34 ± 3% up to 60 ± 4% (Table 4.18 entry 1, 2 and 4). Under these conditions unprotected NH_2 and OH substituents on the aromatic ring are tolerated, and [^{18}F]**4-93** and [^{18}F]**4-94** are formed in 35 ± 2% and 16 ± 2% RCC respectively (Table 4.18 entry 5 and 6). The reaction at room temperature does not proceed effectively when more electron poor substrates are used. Halogen substituents in either the

ortho- or *para*-position give only traces of product (Table 4.18 entry 7 and 8), whereas the stronger electron withdrawing methyl ester substituted [^{18}F]**4-97** shows no product formation at all (Table 4.18 entry 9). Heterocyclic bromodifluoromethylsulfides [^{18}F]**4-98** and [^{18}F]**4-99** also do not react under these conditions. When the reaction is performed at 60 °C using AgOTf (2 eq) in DCE (Method **B**), an increase in yield in ^{18}F-radiofluorination is shown for almost all substrates. Halogen substituted aryl bromodifluoromethylsulfides **4-66** and **4-70** both reacted successfully under these conditions, leading to formation of [^{18}F]**4-95** and [^{18}F]**4-96** in 46 ± 11% and 55 ± 6% RCC (Table 4.18 entry 7 and 8). For strongly electron withdrawing substituents the reaction still did not proceed, and methyl ester substituted **4-69** gave only traces of ^{18}F-incorporation (Table 4.18 entry 9). Heterocyclic **4-71** containing the SCF_2Br-group on the aromatic ring showed a marked increase in yield, and could be efficiently radiolabelled in 37 ± 5% RCC (Table 4.18 entry 10). Benzothiazole **4-72** which has the SCF_2Br-group substituted on the thiazole ring was not reactive. The result of 4-phenyl substituted **4-65** under both sets of conditions (Table 4.18 entry 2) were anomalous compared to the other substrates, and only low yields of ^{18}F-radiofluorination were obtained with formation of several unknown side-products.

These results will be discussed further in section 4.6.

4.4 Synthesis of [^{18}F]ArylOCF$_3$ from [^{18}F]F$^-$

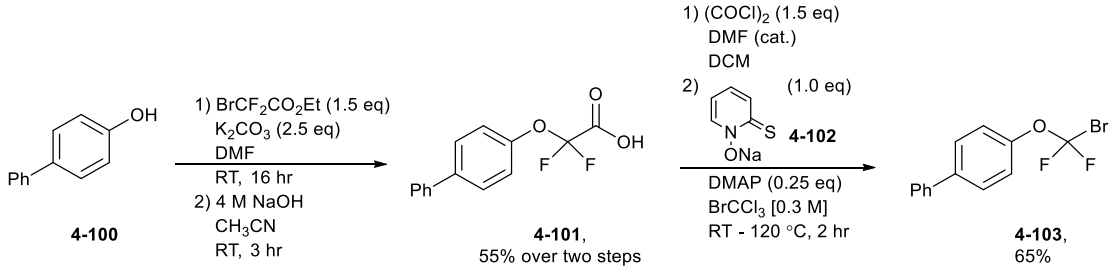
The radiochemistry work described in this section was carried out in collaboration with Dr. M. Tredwell and T. Khotavivattana.[76] Synthesis of non-radioactive starting materials (Scheme 4.34 and 4.36, Table 4.20) was performed by T.Khotavivattana. Experimental data for these compounds can be found in the appendix.

With the exception of the halogen exchange reaction, none of the existing methods for the synthesis of aryl trifluoromethylethers can be easily adapted for use in radiolabelling and synthesis of the [^{18}F]OCF_3 motif (see section 4.2.2). Synthesis of aryl trifluoromethylethers

by halogen exchange often uses harsh conditions with excess of fluorinating reagent, but isolated examples using $AgBF_4$ in combination with aryl bromodifluoromethylether precursors have been reported in the patent literature.[86] These conditions are very similar in comparison with the synthesis of ^{18}F-labelled aryl trifluoromethylthioethers (see section 4.3), and provide a good starting point for the development of a Ag(I) mediated synthesis of arenes with an [^{18}F]OCF_3 motif.

4.4.1 Optimisation of the Reaction Conditions

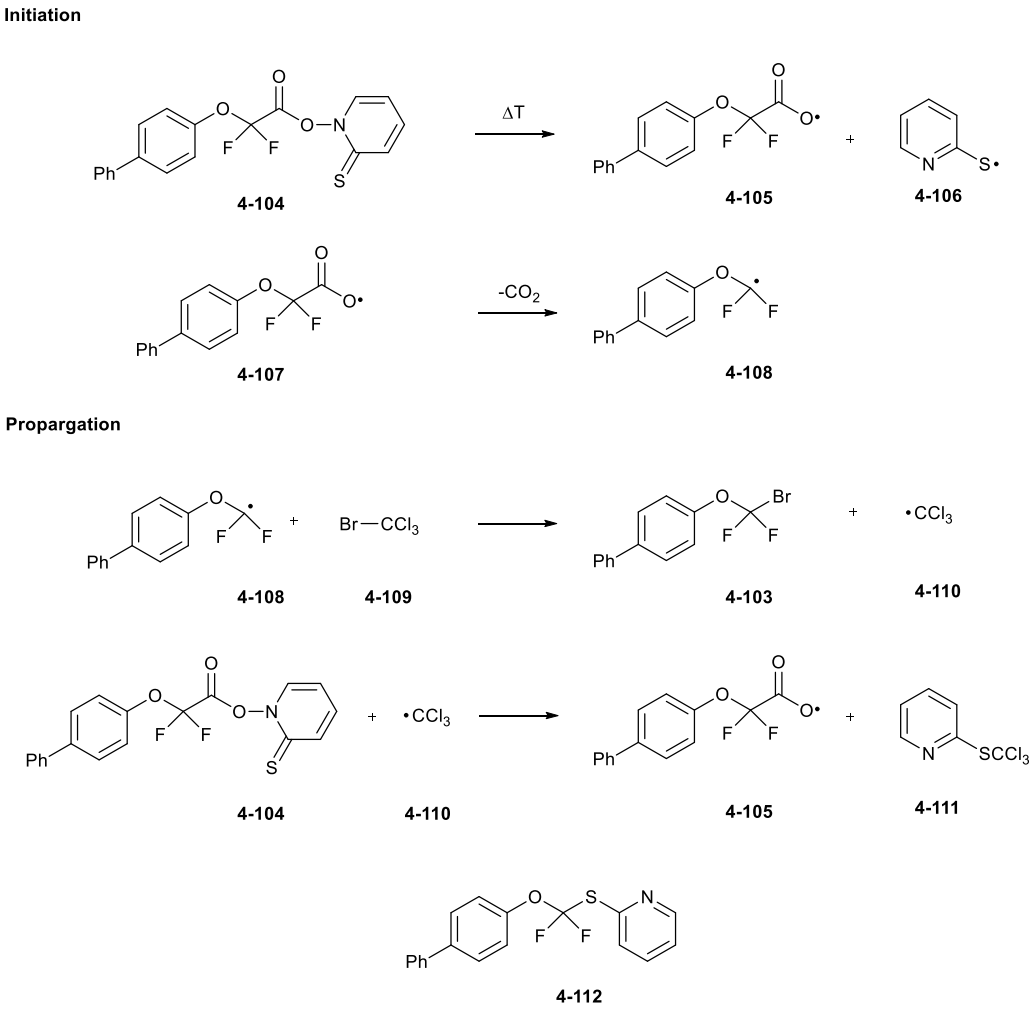
The stable, non-volatile crystalline compound 4-(bromodifluoromethoxy)-1,1'-biphenyl **4-103** was chosen as a model substrate (Scheme 4.34).



Scheme 4.34 Synthesis of model substrate 4-(bromodifluoromethoxy)-1,1'-biphenyl

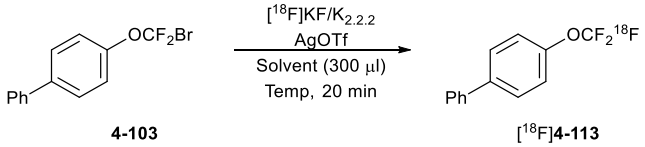
The substrate **4-103** was synthesized starting from 4-phenylphenol **4-100**, which was alkylated with $BrCF_2CO_2Et$ (1.5 eq) and K_2CO_3 (2.5 eq) in DMF, and subsequently hydrolysed with NaOH (4.0M, 5 eq), to provide the phenoxydifluoroacetic acid derivate **4-101** in 55% yield. Treatment of the acid **4-101** with oxalyl chloride (1.5 eq) provided the acid chloride, which was transformed into Barton ester (*N*-hydroxypyridine-2-thione ester) **4-104**, using the sodium salt of 1-hydroxy-pyridine-2-thione (1.0 eq) and a sub-stoichiometric amount of DMAP (0.25 eq) in $BrCCl_3$ (0.3M) as solvent at room temperature. Heating the reaction mixture to reflux (120 °C) resulted in formation of 4-(bromodifluoromethoxy)-1,1'-biphenyl **4-103** in 65% yield according to the mechanism shown in Scheme 4-35.

Formation of radicals from *N*-hydroxypyridine-2-thione esters is facilitated by the weak N-O bond, which can be homolytically cleaved by either light or heating.[87] The radical bromination is initiated by heating of *N*-hydroxypyridine-2-thione ester **4-104**, which results in formation of a difluorocarboxyl radical **4-105** that rapidly loses CO_2 to afford the corresponding difluoroalkyl radical **4-108** (Scheme 4.35). This radical can then abstract a bromine atom from the solvent $BrCCl_3$, to give the product 4-(bromodifluoromethoxy)-1,1'-biphenyl **4-103** and a CCl_3-radical. The chain is propagated by reaction of the Cl_3C-radical with another molecule of the *N*-hydroxypyridine-2-thione ester **4-104**, which forms a new difluorocarboxyl radical **4-105** and the side-product 2-((trichloromethyl)thio)pyridine **4-11**. It is also possible for the difluoroalkyl radical **4-105** to act as a chain propagator (not shown in scheme 4.35), which results in the formation of the unwanted 2-thiopyridine substituted product **4-112**.



Scheme 4.35 Mechanism for radical bromination of Barton ester **4-104**

The optimised conditions for the ^{18}F-radiofluorination of aryl bromodifluoromethylsulfides (see Section 3.3) were used as a starting point, with the model substrate 4-(bromodifluoromethoxy)-1,1'-biphenyl **4-103** and AgOTf as the Ag(I) source.



Entry[a]	Solvent	Temp	AgOTf	RCC[b]
1	DCM	rt	1 eq	1 ± 1% (*n* = 2)
2	DCE	rt	1 eq	2 ± 1% (*n* = 2)

3	DCE	60 °C	1 eq	8 ± 2% (*n* = 2)
4	CH_3CN	60 °C	1 eq	0% (*n* = 2)
5	PhMe	110 °C	1 eq	18 ± 3% (*n* = 2)
6	DCE	60 °C	2 eq	24 ± 3% (*n* = 2)

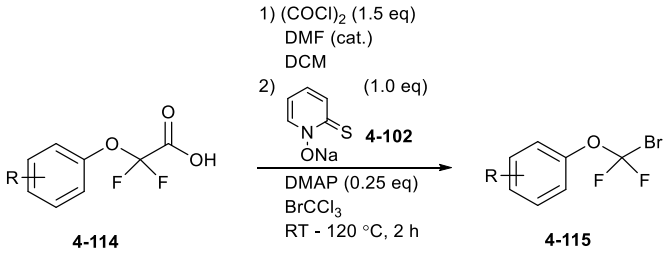
[a] Reaction conditions : **4-103** (0.04 mmol), [^{18}F]KF/$K_{2.2.2}$ (typical activity 25-30 MBq), AgOTf (see table), solvent (300 µl). [b] as determined by radio-TLC and radio-HPLC, details see Experimental Section.

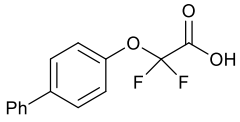
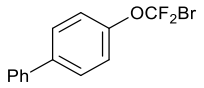
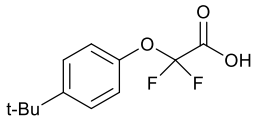
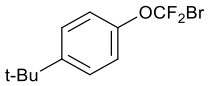
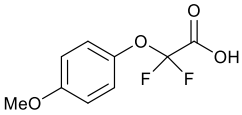
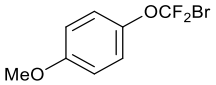
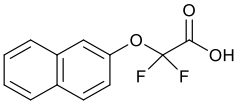
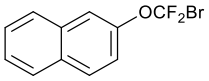
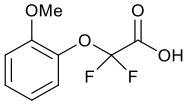
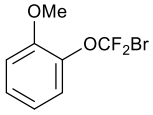
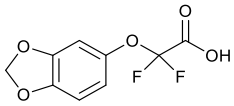
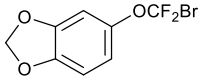
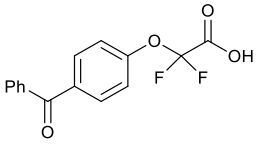
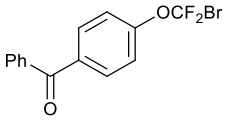
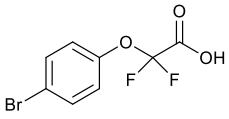
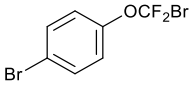
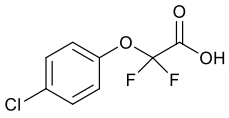
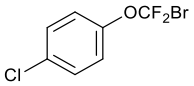
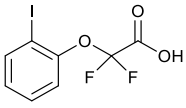
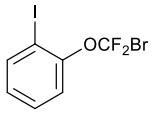
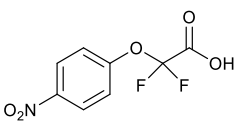
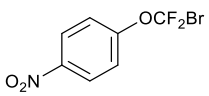
Table 4.19 Solvent optimisation

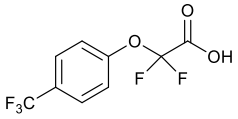
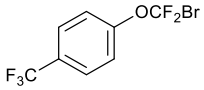
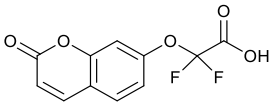
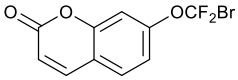
Initial reaction of **4-103** with [^{18}F]KF/$K_{2.2.2}$ complex in DCM or DCE at room temperature mediated by AgOTf (1 eq) gave only traces of ^{18}F-incorporation (Table 4.19 entry 1 and 2). Performing the reaction at higher temperature (60 °C) increased the RCC to 8 ± 2% (Table 4.19 entry 3). Changing the solvent to CH_3CN did not give any product (Table 4.19 entry 4), but a further increase to 18 ± 3% RCC was observed at 110 °C in PhMe (Table 4.19 entry 5). Finally, the best conditions were found by increasing the amount of AgOTf to 2 eq, and using DCE as solvent at 60 °C, which gave [^{18}F]**4-113** in 24 ± 3% RCC (Table 4.19 entry 6).

4.4.2 Preparation of Aryl Bromodifluoromethylethers

A series of aryl bromodifluoromethylethers **4-116 - 4-127** were prepared from aryloxydifluoroacetic acids **4-114**, according to the radical bromination procedure previously described (see section 3.4.3). The aryloxydifluoroacetic acids **4-114** were prepared by alkylation of the corresponding phenol with $BrCF_2CO_2Et$, followed by hydrolysis with NaOH (see previous section and Appendix for details), or in 1 step by alkylation with $ClCF_2COOH$ in the presence of an excess of NaH in dioxane.[88]



Entry[a]	Starting Material	Product	Yield[b]
1			**4-103**, 65%
2			**4-116**, 60%
3			**4-117**, 65%
4			**4-118**, 59%
5			**4-119**, 58%
6			**4-120**, 58%
7			**4-121**, 62%
8			**4-122**, 61%
9			**4-123**, 49%
10			**4-124**, 47%
11			**4-125**, 38%

12			**4-126**, 31%
13			**4-127**, 35%

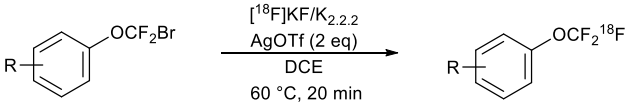
[a] Reaction conditions : **4-114** (4.0 mmol), $(COCl)_2$ (6.0 mmol), DMF (0.40 mmol) DCM (8.0 mL) then sodium *N*-hydroxy-2-thiopyridone (4.0 mmol), DMAP (1.0 mmol), $BrCCl_3$ (12 mL). [b] Isolated yields after purification by column chromatography.

Table 4.20 Synthesis of aryl bromodifluoromethylethers

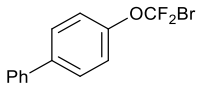
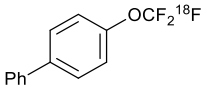
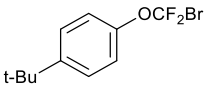
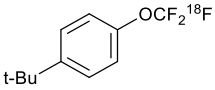
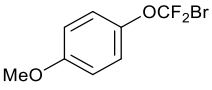
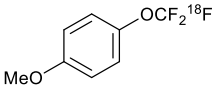
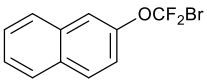
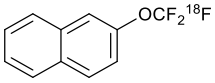
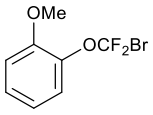
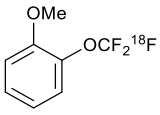
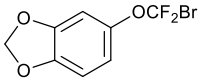
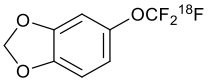
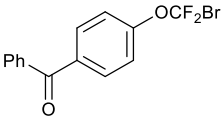
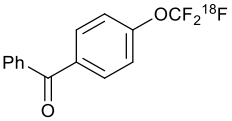
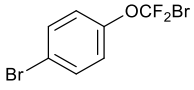
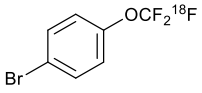
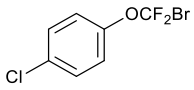
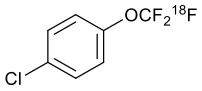
The decarboxylative radical bromination facilitates good yields for substrates with electron-donating substituents (58 - 65 %, Table 4.20 entry 1-6). Similar yields (47 - 62%) were obtained with weakly electron-withdrawing substituted starting materials (Table 4.20 entry 7-10). Strongly electron withdrawing substituents, such as $-CF_3$ and $-NO_2$, gave brominated products in slightly lower yields (31 - 38%, Table 4.20 entries 11-12). A lower yield was also obtained for the coumarine derived bromodifluoromethylether **4-127** (35%, Table 4.20 entry 13). The mechanism for this decarboxylative radical bromination has been detailed in section 4.4.1.

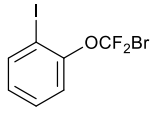
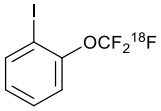
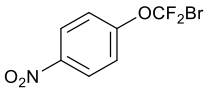
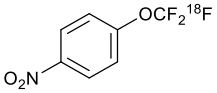
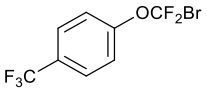
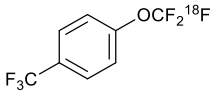
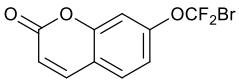
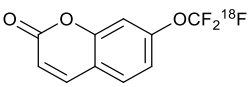
4.4.3 Scope and Limitations

Aryl bromodifluoromethylethers **4-115** were subjected to Ag(I) mediated ^{18}F-radiofluorination, under the optimised conditions (see section 4.4.1) using the $[^{18}F]KF/K_{2.2.2}$ complex and AgOTf (2 eq) in DCE (0.12M) at 60 °C.



4-115 [18F]**4-128**

Entry[a]	Substrate	Product	RCC[b]
1	 **4-103**		[18F]**4-129**, 24 ± 2% (*n* = 4)
2	 **4-116**		[18F]**4-130**, 33 ± 2% (*n* = 4)
3	 **4-117**		[18F]**4-131**, 48 ± 4% (*n* = 4)
4	 **4-118**		[18F]**4-132**, 29 ± 5% (*n* = 4)
5	 **4-119**		[18F]**4-133**, 10 ± 2% (*n* = 4)
6	 **4-120**		[18F]**4-134**, 72 ± 3% (*n* = 4)
7	 **4-121**		[18F]**4-135**, 15 ± 2% (*n* = 4)
8	 **4-122**		[18F]**4-136**, 8 ± 1% (*n* = 4)
9	 **4-123**		[18F]**4-137**, 7 ± 2% (*n* = 4)

10	 **4-124**		[^{18}F]**4-138**, 1 ± 0% (*n* = 4)
11	 **4-125**		[^{18}F]**4-139**, 2 ± 1% (*n* = 4)
12	 **4-126**		[^{18}F]**4-140**, 1 ± 0% (*n* = 4)
13	 **4-127**		[^{18}F]**4-141**, 7 ± 0% (*n* = 4)

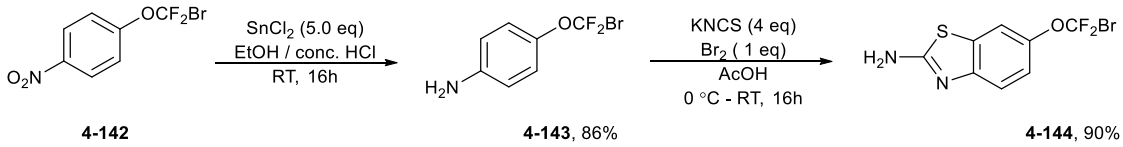
[a] Reaction conditions : **4-115** (0.04 mmol), [^{18}F]KF/$K_{2.2.2}$ (typical activity 25-30 MBq), AgOTf (0.04 mmol), DCE (300 µl). [b] as determined by radio-TLC and radio-HPLC, details see Experimental Section.

Table 4.21 ^{18}F-fluorination of arylbromodifluoromethylethers

To a solution of azeotropically dried [^{18}F]KF/$K_{2.2.2}$ complex (~30 MBq) in CH_3CN, prepared from [^{18}F]F^- (aq) as described in section 4.1.3, was added AgOTf (2 eq) and the solvent was removed at 100 °C under a stream of nitrogen. A solution of aryl bromodifluoromethylether **4-115** in DCE [0.12M] was added, and the resulting mixture was stirred for 20 min at 60 °C, after which it was quenched with EtOH/H_2O (9/1, 500 µl). The yield was determined by analysis of an aliquot of the quenched reaction mixture by radio TLC taking into account the purity measured by radio-HPLC, as described in section 4.1.3. The results show moderate to good reactivity for electron rich aryl bromodifluoromethylethers. Electron donating substituents in the *para*-position favour ^{18}F-incorporation with formation of *para*-phenyl, *para*-*t*Bu and *para*-methoxy substituted ^{18}F-aryltrifluoromethylethers [^{18}F]**4-129**, [^{18}F]**4-130** and [^{18}F]**4-131** in 24 ± 2% (Table 4.21 entry 1), 33 ± 2% (Table 4.21 entry 2) and 48 ± 4% RCC (Table 4.21 entry 3), respectively. A similar RCC is obtained for the 2-naphthalene derived [^{18}F]**4-132**, 29 ± 5%

(Table 4.21 entry 4). Substitution in the *ortho*-position is less favoured, with *ortho*-methoxy substituted [^{18}F]**4-133** affording a lower RCC of 10 ± 2% (Table 4.21 entry 5). Strongly electron rich substrates show good reactivity, and 1,3-benzodioxole-derived [^{18}F]**4-134** is formed in 72 ± 3% RCC (Table 4.21 entry 6). However, with more electron-poor substrates the ^{18}F-incorporation is less effective. The *para*-benzoyl substituted [^{18}F]**4-135** is formed in 15 ± 3% yield (Table 4.21 entry 7), and halogen substituted *para*-bromo [^{18}F]**4-136** and *para*-chloro substituted [^{18}F]**4-137** in 8 ± 1% (Table 4.21 entry 8) and 7 ± 2% (Table 4.21 entry 9) respectively. Substitution in the *ortho*-position is again shown to be less favourable, with *ortho*-iodo [^{18}F]**4-138** showing only traces of ^{18}F-incorporation (Table 4.21 entry 10). Strongly electron withdrawing substituents are not tolerated, and both the *para*-CF_3 (Table 4.21 entry 11) and *para*-NO_2 (Table 4.21 entry 12) show only traces of the desired ^{18}F-containing products. An example of successful ^{18}F-incorporation for a heterocyclic substrate is demonstrated by the formation of coumarine derived [^{18}F]**4-141** in 7 ± 0% RCC (Table 4.21 entry 13). These results will be discussed further in section 4.6.

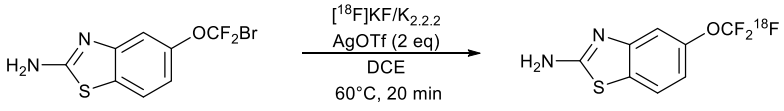
To demonstrate the application of the Ag(I)-mediated halogen exchange reaction to the synthesis of complex and pharmacologically interesting compounds, the synthesis of [^{18}F]Riluzole was performed. The starting 6-(bromodifluoromethoxy)benzo[d]thiazol-2-amine **4-144** could be obtained from *para*-NO_2 substituted bromodifluoromethylether **4-142** in two steps (Scheme 4.36). Reduction with $SnCl_2$ gave the corresponding aniline derivate (86% yield), which could be transformed into the required 2-aminobenzothiazol in excellent yield (90%), using a combination of KNCS and Br_2 in AcOH.[89]



4-142 **4-143**, 86% **4-144**, 90%

Scheme 4.36 Synthesis of Riluzole precursor **4-144**

Using the optimized conditions found for aryl bromodifluoromethylethers, [^{18}F]Riluzole [^{18}F]**4-144** could be synthesized in 29 ± 5% RCC (Scheme 4.37).



4-144 [^{18}F]-Riluzole [^{18}F]**4-144**, 29 ± 5% (*n* = 4)

Scheme 4.37 Synthesis of [^{18}F]Riluzole

4.5 Synthesis of [^{18}F]ArylOCF$_2$H from [^{18}F]F$^-$

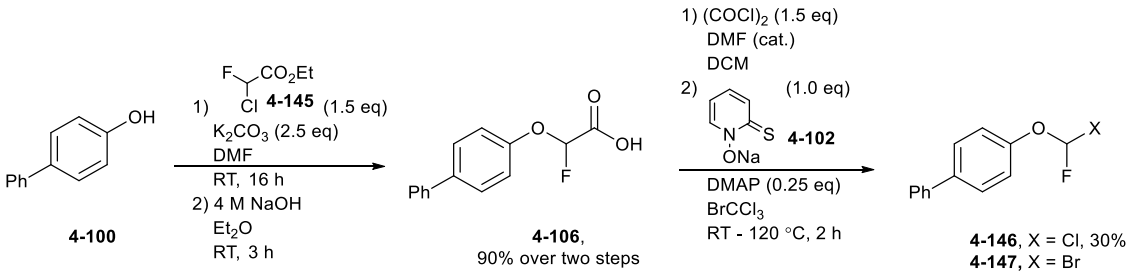
The radiochemistry work described in this section was carried out in collaboration with Dr M. Tredwell and T. Khotavivattana.[76] Synthesis of non-radioactive starting materials (Scheme 4.38 and Table 4.23) was performed by T.Khotavivattana.

The successful use of the halogen exchange activation mode for ^{18}F-fluorination in the synthesis of ^{18}F-labelled aryl trifluoromethyl(thio)ethers (see section 4.3 and 4.4), make this strategy promising for the synthesis of ^{18}F-labelled aryl difluoromethyl ethers, and led us to investigate the use of this methodology for the synthesis of ^{18}F-fluorinated aryl difluoromethylethers.

4.5.1 Optimisation of the Reaction Conditions

Initially 4-(bromofluoromethoxy)-1,1'-biphenyl **4-147** was chosen as model substrate, as it was expected to be a solid and not volatile. It was anticipated that **4-147** could be synthesized analogous to the biphenyl bromodifluoromethylether **4-103** (see section 4.4). To this end, 4-phenylphenol **4-100** was alkylated with ethyl 2-chloro-2-fluoroacetate **4-145**

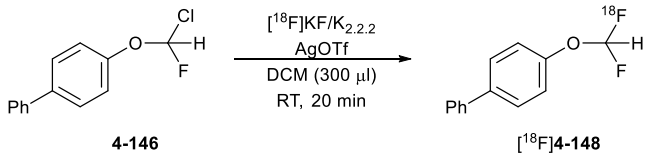
(1.5 eq) and K_2CO_3 (2.5 eq) in DMF followed by hydrolysis with 4M NaOH, affording 2-([1,1'-biphenyl]-4-yloxy)-2-fluoroacetic acid **4-146** in 90% yield. The mono-fluoro acid **4-106** was converted to the acid chloride using oxalyl chloride (1.5 eq), which was subjected without further purification to a similar decarboxylative radical bromination procedure as used for the di-fluoroacid **4-101** (see section 4.4.2). From this reaction a solid was isolated after rapid flash column chromatography over silica, which after careful analysis was identified as the chloro-derivative 4-(chlorofluoromethoxy)-1,1'-biphenyl **4-146**. The definitive proof of the structure was given by analysis of the high-res mass spectrum, which showed the isotopic mass and isotope pattern which would be expected for chloro substituted **4-146** (see Appendix for a detailed spectrum). It is postulated that the bromide **4-147** is the initial product of the reaction (mechanism see section 4.4.2), but that a substitution reaction with chloride ions present in the reaction mixture takes place which leads to exclusive formation of the chloro-derivative **4-146**.



Scheme 4.38 Synthesis of 4-(chlorofluoromethoxy)-1,1'-biphenyl

Although **4-146** could be isolated in pure form after rapid flash column chromatography, it was found to be a very reactive electrophile and sensitive to hydrolysis. Therefore, it was best stored at 2-8 °C and protected against moisture to minimize decomposition.

In a preliminary experiment the reactivity of 4-(chlorofluoromethoxy)-1,1'-biphenyl **4-146** towards the $[^{18}F]F^-/K_{2.2.2}$ complex was investigated.



4-146 [18F]**4-148**

Entry[a]	AgOTf	RCC[b]
1	--	19 ± 4% (*n* = 2)
2	1 eq	70 ± 3% (*n* = 4)

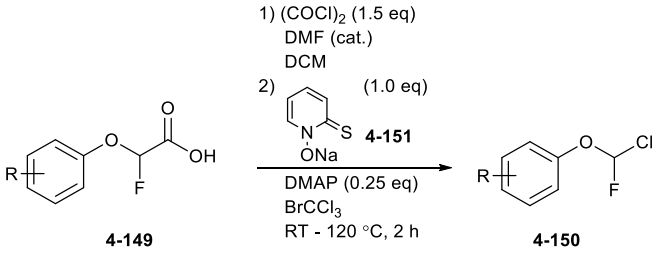
[a] Reaction conditions : **4-146** (0.04 mmol), [18F]KF/$K_{2.2.2}$ (typical activity 25-30 MBq), AgOTf (0.04 mmol), DCM (300 µl). [b] as determined by radio-TLC and radio-HPLC, details see Experimental Section.

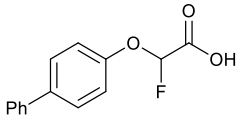
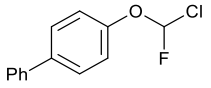
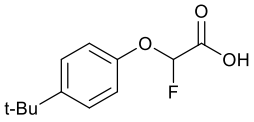
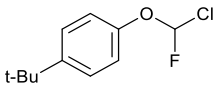
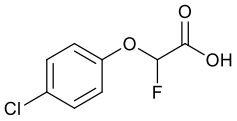
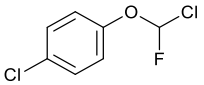
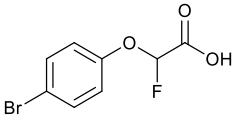
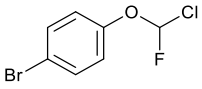
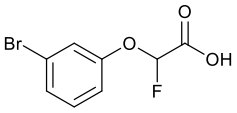
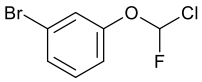
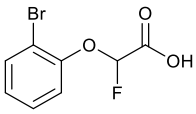
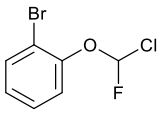
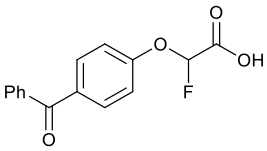
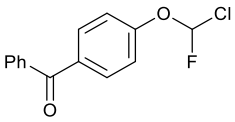
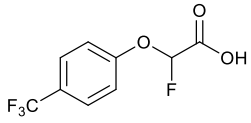
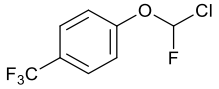
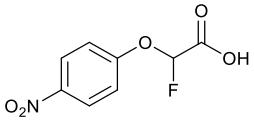
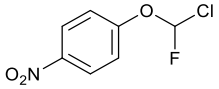
Table 4.22 ^{18}F-fluorination of 4-(chlorofluoromethoxy)-1,1'-biphenyl **4-146**

Following the procedure described in Section 4.4.3, formation of [^{18}F]4-(difluoromethoxy)-1-1'-biphenyl [^{18}F]**4-148** in low RCC was observed (19 ± 4% ; Table 4.22 entry 1) when **4-146** was reacted with [^{18}F]$F^-/K_{2.2.2}$ complex (~30 MBq) in DCM (0.12M), in the absence of AgOTf. Addition of AgOTf (1 eq) showed a dramatic increase in ^{18}F-incorporation and provided [^{18}F]**4-148** in 70% yield (Table 4.22 entry 2).

4.5.2 Preparation of Aryl Chlorofluoromethylethers

A range of aryl chlorofluoromethylethers **4-150** were synthesized from the corresponding monofluoroacids **4-149** using the decarboxylative radical bromination procedure (see section 4.4.1). In all cases chloro substituted ethers were obtained, as shown after analysis of high-res mass spectra. The monofluoroacids **4-149** were synthesized in two steps from the corresponding phenols, according to the same procedure as 4-(chlorofluoromethoxy)-1,1'-biphenyl **4-146** (see previous section and 4.4.2).



Entry[a]	Starting Material	Product	Yield[b]
1			**4-146**, 30%
2			**4-151**, 12%
3			**4-152**, 32%
4			**4-153**, 30%
5			**4-154**, 32%
6			**4-155**, 40%
7			**4-156**, 20%
8			**4-157**, 18%
9			**4-158**, 39%

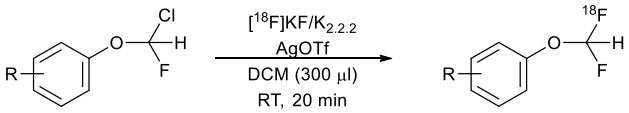
[a] Reaction conditions : **4-149** (4.0 mmol), $(COCl)_2$ (6.0 mmol), DMF (0.40 mmol) DCM (8.0 mL) then sodium *N*-hydroxy-2-thiopyridone (4.0 mmol), DMAP (1.0 mmol), $BrCCl_3$ (12 mL). [b] Isolated yields after purification by column chromatography.

Table 4.23 Synthesis of aryl chlorofluoromethylethers

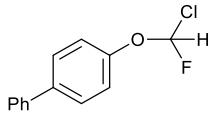
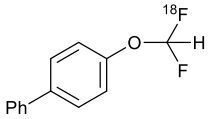
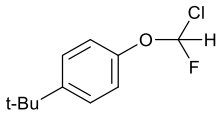
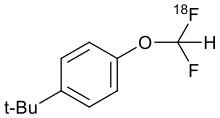
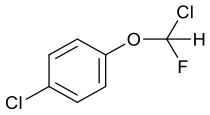
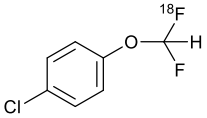
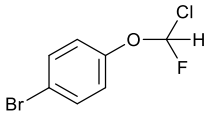
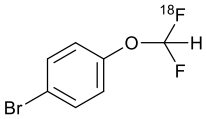
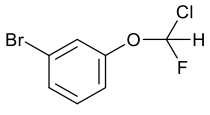
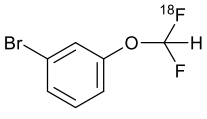
Isolated yields of aryl chlorofluoromethylethers **4-150** were generally low (12-40%) regardless of the nature of the substituents on the aromatic ring (Table 4.23 entry 1-9). The lower yields could in part be caused by the lower stability of these compounds, compared to the aryl difluorobromomethylethers (see section 4.4.2).

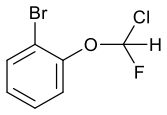
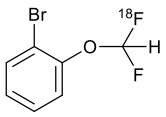
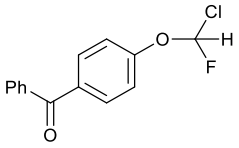
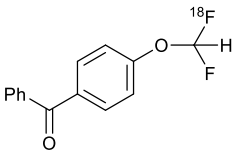
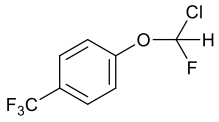
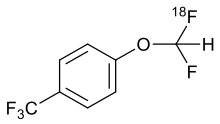
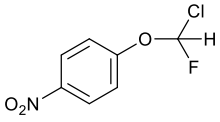
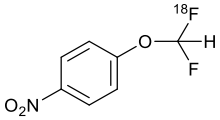
4.5.3 Scope and Limitations

The aryl chlorofluoromethylethers **4-150** were subjected to the AgOTf mediated ^{18}F-fluorination procedure (Table 4.24).



4-150 [^{18}F]**4-159**

Entry[a]	Substrate	Product	Yield[b]
1	 **4-146**		[^{18}F]**4-148**, 70 ± 3% (*n* = 4)
2	 **4-151**		[^{18}F]**4-160**, 75 ± 3% (*n* = 4)
3	 **4-152**		[^{18}F]**4-161**, 79 ± 5% (*n* = 4)
4	 **4-153**		[^{18}F]**4-162**, 67 ± 3% (*n* = 4)
5	 **4-154**		[^{18}F]**4-163**, 68 ± 2% (*n* = 4)

6	 **4-155**		[^{18}F]**4-164**, 79 ± 3% (*n* = 4)
7	 **4-156**		[^{18}F]**4-165**, 73 ± 5% (*n* = 4)
8	 **4-157**		[^{18}F]**4-166**, 66 ± 2% (*n* = 4)
9	 **4-158**		[^{18}F]**4-167**, 73 ± 4% (*n* = 4)

[a] Reaction conditions : **4-150** (0.04 mmol), [^{18}F]KF/$K_{2.2.2}$ (typical activity 25-30 MBq), AgOTf (0.04 mmol), DCM (300 µl). [b] as determined by radio-TLC and radio-HPLC, details see Experimental Section.

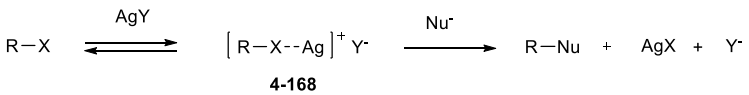
Table 4.24 Ag(I) mediated ^{18}F-fluorination of aryl chlorofluoromethylethers

To a solution of azeotropically dried [^{18}F]KF/$K_{2.2.2}$ complex (~30 MBq) in CH_3CN, prepared from cyclotron produced [^{18}F]F^- (aq) as described in section 4.1.3, was added AgOTf (1 eq) and the solvent was removed at 100 °C under a stream of nitrogen. A solution of aryl chlorofluoromethylethers **4-150** in DCM (0.12M) was added, and the resulting mixture was stirred for 20 min at room temperature, after which it was quenched with EtOH/H_2O (9/1, 500 µl). The yield was determined by analysis of an aliquot of the quenched reaction mixture by radio TLC, taking into account the purity measured by radio-HPLC as described in section 1.4.3. Under these conditions a range of aryl chlorofluoromethylethers with both electron donating and electron withdrawing substituents showed good ^{18}F-incorporation. Electron rich substrates as the *para*-phenyl

substituted **4-146** (Table 4.24, entry 1) and *para*-tBu substituted **4-151** (Table 4.24 entry 2) gave the corresponding [^{18}F]-aryldifluoromethylethers in good RCC, 70 ± 3% for [^{18}F]**4-146** and 75 ± 3% for [^{18}F]**4-160**. Less electron rich substrates **4-152** (Table 4.24 entry 3) and **4-153** (Table 4.24 entry 4), with *para*-chloro and *para*-bromo substituents respectively, gave similarly good RCC (79 ± 3% for [^{18}F]**4-161** and 67 ± 3% for [^{18}F]**4-162**). Both *meta*- and *ortho*- substitution was tolerated for the bromo substituent with [^{18}F]**4-163** being formed in 68 ± 2% RCC (Table 4.24 entry 5) and [^{18}F]**4-164** in 79 ± 3% RCC (Table 4.24 entry 6). The presence of the more electron withdrawing *para*-benzoyl substituent in **4-156** did not have a detrimental effect on the ^{18}F-incorporation, and [^{18}F]**4-163** was formed in 73 ± 5% RCC (Table 4.24 entry 7). Even strongly electron withdrawing groups like *para*-CF_3 in **4-157** and *para*-NO_2 in **4-158** were tolerated with a RCC of 66 ± 2% for [^{18}F]**4-166** (Table 4.24 entry 8) and 73 ± 4% for [^{18}F]**4-167** (Table 4.24 entry 9) respectively. These results will be discussed further in section 4.6.

4.6 Comments on the Reaction Mechanism

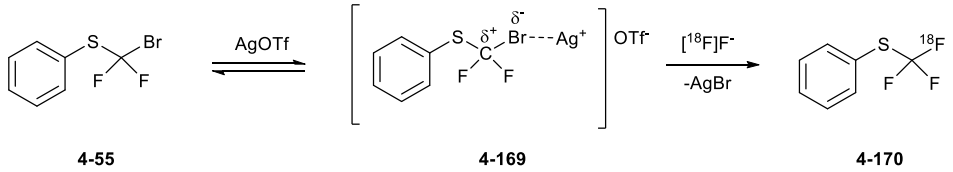
It has been shown that Ag^+-ions can assist in the heterolysis of alkyl halides and facilitate nucleophilic substitution reactions (Scheme 4.39).[90] Formation of a Ag(I)-halide complex **4-177** is postulated, but further mechanistic studies were not in favour of the formation of a free carbocation as an intermediate. For alkyl halides which can form stabilised carbocations similarities with an S_N1-type of process were observed, for example in product distribution.[91]



Scheme 4.39 Ag^+-ion facilitated nucleophilic substitution

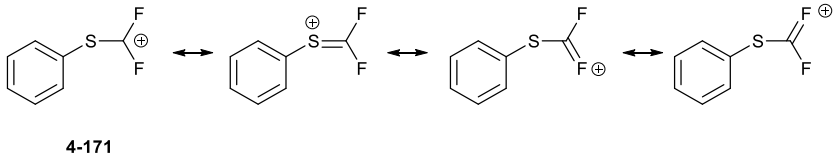
4.6.1 Reactivity of Aryl-SCF_2Br in the Ag(I)-mediated ^{18}F-fluorination

A possible mechanism for the Ag(I)-mediated ^{18}F-fluorination of aryl bromodifluoromethylsulfides involves generation of a Ag(I)-halogen complex **4-169**, with a partial positive charge on the di-fluorinated carbon atom (scheme 4.40). Attack of nucleophilic $[^{18}F]F^-$ on this intermediate complex provides the ^{18}F-fluorinated product with concomitant precipitation of AgBr.



Scheme 4.40 Possible mechanism for the Ag(I)-mediated fluorination

Halogen abstraction from an aryl bromodifluoromethylsulfide would theoretically generate an difluoro(arylthio)methylium cation **4-180**, in which the charge can be delocalized over both the fluorine and the sulfur atoms (Scheme 4.41).



Scheme 4.41 Charge delocalisation in the difluoro(arylthio)methylium cation

Charge delocalisation due to the presence of an α-heteroatom (in this case sulfur) can effectively stabilize cations and greatly enhance the rate of their formation.[92] Although the fluorine atoms in the putative difluoro(arylthio)methylium cation **4-171** destabilize a cationic center due to their high electronegativity and negative inductive effect, this effect is counteracted by resonance stabilization through π-donation of the 2p-orbital of the fluorine atoms into the vacant carbon 2p-orbital. From the negative Hammett σ_R value of fluorine[93], and the stability order of α-fluorinated cations calculated from the gas phase

hydride affinities ($CHF_2^+ > CH_2F^+ > CF_3^+ > CH_3^+$)[94] it can be postulated that the resonance stabilization outweighs the destabilizing negative inductive effect. This implies that both the α-fluorine and sulfur substituents can contribute to the stabilization of a positive charge in the proposed intermediate complex **4-169**.

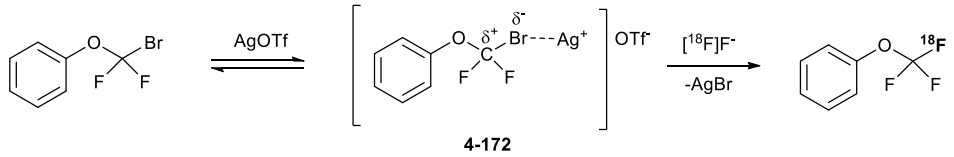
The results of the Ag(I)-mediated ^{18}F-fluorination of aryl bromodifluoromethylsulfides (section 4.3.4.3 Table 4.18) are in agreement with formation of a carbocation such as **4-171**. Substrates with electron donating substituents (section 4.3.4.3, Table 4.18, entry 1, 3-6), which would contribute to the stability of the postulated Ag(I) complexed intermediate **4-169** and its formation, provide ^{18}F-fluorinated products in good yields at room temperature. These yields improve at higher temperature (60 °C) and higher Ag(I)-content (2 eq), which is expected since both these conditions favor product formation. The *para*-phenyl substituted **4-65** shows results that are anomalous, and low yields were obtained at both room temperature and 60°C (Section 4.3.4.3, Table 4.18 entry 2). There is no adequate explanation for this result at this moment.

Substrates with strong electron withdrawing groups were not reactive at either room temperature or 60 °C, and did not show any ^{18}F-incorporation (Section 4.3.4.3, Table 4.18 entry 9, 11). These results are also in agreement with formation of an intermediate such as **4-169**, since electron withdrawing substituents would significantly destabilize the formation of a partial positive charge, and result in failure of the reaction. When weakly electron withdrawing substituents such as -Cl and -Br are used at room temperature no ^{18}F-incorporation is observed, but at 60 °C with twice the quantity of AgOTf the yields of ^{18}F-fluorinated product are acceptable (Section 4.3.4.3, Table 4.18 entry 7-8). These two examples show the limits of what is possible with this methodology, and suggest that significant stabilization of the partial positive charge in intermediate **4-169** is necessary for efficient reaction at room temperature. By increasing the reaction temperature and amount

of Ag(I) the reaction can be made to proceed on slightly electron poor substrates, but under these conditions there is no reaction with substrates that contain strongly electron withdrawing substituents. This trend is also apparent in the heterocyclic substrate **4-72**, containing an electron-poor benzothiazole moiety (σ_R = 0.02)[96] with the SCF_2Br-group attached on the carbon atom between the hetero-atoms, which does not react at either room temperature or higher temperature.

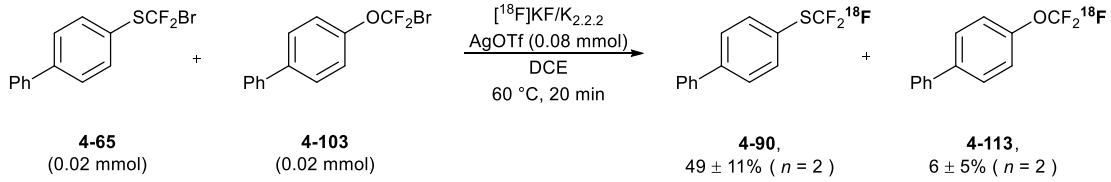
4.6.2 Reactivity of Aryl-OCF_2Br versus Aryl-SCF_2Br in the Ag(I)-mediated ^{18}F-fluorination

The scope of the Ag(I)-mediated ^{18}F-fluorination of aryl difluorobromomethylethers is restricted to substrates with electron donating substituents, and either weak or strong electron withdrawing substituents provide only traces of product. These results again predict formation of an intermediate bearing a partial positive charge (scheme 4.42), as suggested for the Ag(I) mediated ^{18}F-fluorination of aryl bromodifluoromethylsulfides.



Scheme 4.42 Possible mechanistic pathway for the Ag(I)-mediated fluorination

To investigate the reactivity of aryl-SCF_2Br versus aryl-OCF_2Br, a competition experiment was performed (Scheme **4.43**), in which equal amounts (0.02 mmol) of *para*-Ph substituted **4-65** and **4-103** were reacted with [^{18}F]KF/$K_{2.2.2}$ complex (25-30 MBq) and AgOTf (0.08 mmol) in DCE (0.12M) at 60 °C. The preferential formation of the ^{18}F-arylSCF_3 product over ^{18}F-arylOCF_3 confirms the higher reactivity of the former.

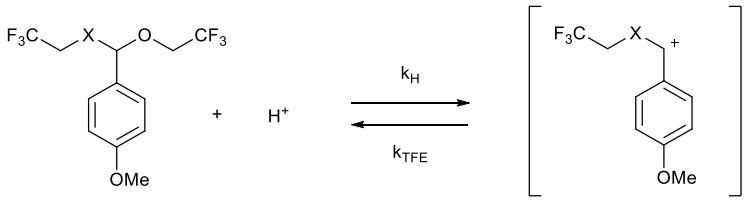


4-65 (0.02 mmol) + **4-103** (0.02 mmol) → **4-90**, 49 ± 11% (*n* = 2) + **4-113**, 6 ± 5% (*n* = 2)

Scheme 4.43 Competition experiment

If both substrates follow the mechanistic pathway in which a partially charged intermediate is formed, the higher electronegativity of oxygen (3.44 on the Pauling scale)[95] in comparison with sulfur (2.58 on the Pauling scale)[98] could be a factor influencing the reactivity of $ArSCF_2Br$ versus $ArOCF_2Br$. This would imply that intermediate **4-178** is inductively more destabilized in comparison to the oxygen analogue **4-178a**.

To investigate the stability of thiocarbenium ions in comparison with oxocarbenium ions, Jagannadham *et al* determined the rate constants for acid mediated formation of α-sulfur cation **4-183** and α-oxygen cation **4-184** from the corresponding trifluoroethanol adducts **4-181** and **4-182** (Table 4.25).[96]



4-173, X = S
4-174, X = O

4-175, X = S
4-176, X = O

Entry	X	k_H ($M^{-1}s^{-1}$)	k_{TFE} ($M^{-1}s^{-1}$)	K_{TFE}
1	**4-173**, X = S	5.4 x 10^{-3}	2.4 x 10^{2}	2.3x10^{-5}
2	**4-174**, X = O	0.23	2.2 x 10^{5}	1.0x10^{-6}

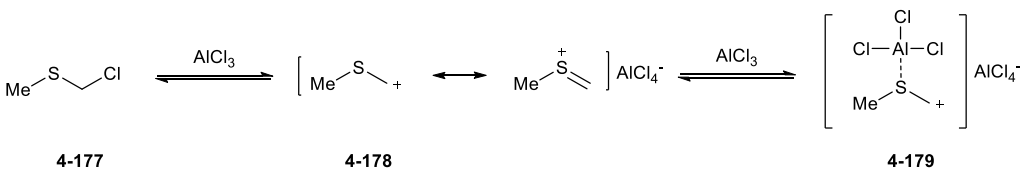
Table 4.25 Determination of rate and equilibrium constants for formation of **4-175** and **4-176**

The equilibrium constant K_{TFE}, calculated from the experimentally determined rate constants ($K_{TFE} = k_H / k_{TFE}$), showed that α-sulfur cation **4-175** (K_{TFE} = 2.3 x 10^{-5}) was

slightly more stabilized towards the ground state than the α-oxygen cation **4-176** (K_{TFE} = $1.0x10^{-6}$). Theoretical calculations of the gas-phase stability of the methyl cation stabilised by either an α -SMe or α -OMe group, showed a similar small preference for stabilisation by sulfur in comparison with oxygen of 2 - 3 kcal/mol.[97] However, the rate constants show that α-oxygen trifluoroethoxy adduct **4-174** is more reactive (k_H = 0.23 M/s for **4-174** vs k_H = 5.4 x 10^{-3} for **4-173**), meaning that the less thermodynamically stable cation **4-184** is formed more rapidly than **4-175**. The authors contributed this to either differences in ground state stabilisation between **4-173** and **4-174**, or a higher energy transition state for **4-175** in comparison with **4-176**.

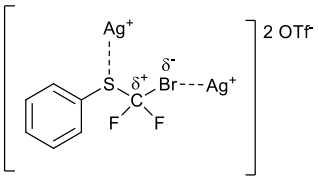
This data suggests that the partial positive charge in sulfur containing Ag(I)-complexed intermediate **4-169** would indeed be expected to be slightly more stabilised in comparison with the charge in oxygen containing intermediate **4-172**, but that this cannot adequately explain the observed difference in reactivity between $ArSCF_2Br$ and $ArOCF_2Br$ in the Ag(I)-mediated ^{18}F-fluorination.

It has been shown that Lewis acid complexation of thiocarbenium ions can increases their electrophilicity. Olah *et al* found that the $AlCl_3$-mediated alkylation of aromatics with $MeSCH_2Cl$ **4-177** proceeded with a much higher rate and conversion when 2 equivalents of $AlCl_3$ were used with respect to the electrophile.[98] The authors attributed this to the formation of intermediate **4-179**, which is made more electrophilic by complexation with a second molecule of $AlCl_3$.



Scheme 4.42 Lewis acid complexation of cationic intermediates

In analogy, it could be possible that the electrophilicity of sulfur containing Ag(I)-complexed intermediate **4-169** could be enhanced by the complexation with another molecule of Ag^+, to give a postulated intermediate such as **4-180**. This tentative formation of a more electrophilic complex could in part explain the observed difference in reactivity between $ArSCF_2Br$ and $ArOCF_2Br$.



4-180

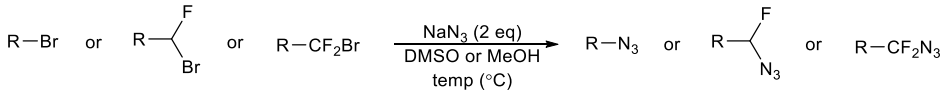
Scheme 4.43 Proposed intermediate from double Ag^+-complexation

4.6.3 Reactivity of ArOCFCl in the Ag(I)-mediated ^{18}F-fluorination

Aryl chlorofluoromethylethers are effective substrates for the Ag(I)-mediated ^{18}F-fluorination, and good yields of ^{18}F-arylOCF_2H products are obtained regardless of the presence of electron-donating or electron-withdrawing substituents. This reactivity is in contrast with that of the previously discussed di-fluorinated substrates, in which electron withdrawing substituents prevent effective ^{18}F-fluorination. The significant increase of ^{18}F-incorporation which is observed when 4-(bromofluoromethoxy)-1,1'-biphenyl **4-147** is reacted in the presence of AgOTf in comparison to the reaction without AgOTf, suggests that formation of an Ag(I)-halogen complex is also possible in this reaction. However, the lower sensitivity of ^{18}F-incorporation to the inductive effect of the substituents on the aromatic ring could suggest that there is a lower amount of partial positive charge in the formed intermediate, and that the reaction shows less S_N1 and more S_N2 character.

The effect of fluorine substituents on the rate of bimolecular nucleophilic substitution of primary alkyl and benzylic bromides has recently been investigated.[99] The results show a very large inhibiting effect on S_N2 reaction for α,α-difluorinated benzylic- and primary

alkyl-bromides, with benzylic substrates reacting up to 172000 times slower, and primary alkyl substrates up to 13250 times slower than their non-fluorinated analogues (see Table 4.26). The influence of mono-fluorinated substituted halides was investigated for primary alkyl bromides, showing only a small inhibiting effect and mono-fluorinated substrates were found to react 7 times slower than non-fluorinated substrates. The large difference between mono- and di-fluorinated substrates was largely attributed to the electrostatic repulsion interaction between the incoming nucleophile and the electron-cloud of the fluorine atoms.



Substrate	Solvent	Temp (°C)	k_2	k_{rel}
$PhCH_2Br$	DMSO	15	7.48×10^8	172000
$PhCF_2Br$	DMSO	15	4.35×10^3	
n-$C_7H_{15}Br$	MeOH	50	6.89×10^5	13250
n-$C_5H_{11}CF_2Br$	MeOH	50	$<5.2 \times 10^1$ [a]	
n-$C_7H_{15}Br$	DMSO	50	1.59×10^8	7
n-$C_8H_{17}CFBr$	DMSO	50	2.26×10^7	

[a] No reaction was observed after 20 days; the maximum rate was approximated by assuming 0.5% product could be detected

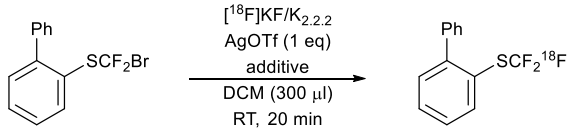
Table 4.26 Inhibiting effect of fluorine on S_N2 reactions

With the assumption that the reaction of aryl chlorofluoromethylethers proceeds with considerably more S_N2 character, this observation would offer a plausible explanation for the much higher reactivity of aryl monochlorofluoromethyl ethers (ArOCFCl) in comparison to the aryl bromodifluoromethyl(thio)ethers (ArSCF2Br and ArOCF2Br) in the Ag(I) mediated ^{18}F-fluorination.

4.7 Full Batch Isolation Experiments

The radiochemistry work described in this section was carried out in collaboration with Dr M. Tredwell and T. Khotavivattana.[76]

With the successful validation of the Ag(I) mediated ^{18}F-fluorination for the synthesis of ^{18}F aryl-SCF_3, -OCF_3 and -OCF_2H derivatives, we turned our attention to developing a protocol for the isolation of these radiotracers using a full batch of cyclotron produced ^{18}F-fluoride (~ 4 GBq). To investigate the influence of the larger amounts of base and kryptand present during a full batch reaction (see section 4.1.3), screening experiments of the ^{18}F-fluorination of **4-48** with several additives (Table 4.27) were conducted. The amount of additive was chosen to be the same as the amount used for eluting the [^{18}F]F^- from the anion exchange cartridge.



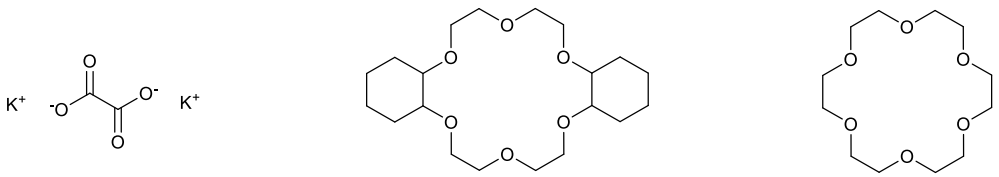
4-48 [^{18}F]**4-49**

Entry[a]	Additive	RCC[b]
1	--	60 ± 4% (*n* = 10)
2	K_2CO_3 (0.014 mmol) $K_{2.2.2}$ (0.027 mmol)	6 ± 0% (*n* = 2)
3	$K_{2.2.2}$ (0.027 mmol)	9 ± 0% (*n* = 2)
4	K_2CO_3 (0.014 mmol)	29 ± 1% (*n* = 2)
5	Et_4NHCO_3 (0.052 mmol)	0% (*n* = 2)
6	$K_2C_2O_4.H_2O$ (0.011 mmol)	51 ± 4% (*n* = 2)

[a] Reaction conditions : **4-48** (0.04 mmol), [^{18}F]KF/$K_{2.2.2}$ (typical activity 25-30 MBq), AgOTf (0.04 mmol), additive (see tabe), DCM (300 µl). [b] as determined by radio-TLC and radio-HPLC, details see Experimental Section.

Table 4.27 Effect of additives on ^{18}F-incorporation of **4-48**

From the spiking experiments it was immediately apparent that a combination of added K_2CO_3 and $K_{2.2.2}$ was detrimental to ^{18}F-incorporation, and 6 ± 0% RCC was obtained (entry 2) in comparison with 60 ± 4% RCC for the un-spiked reaction (Table 4.27 entry 1). Further experiments showed that the kryptand $K_{2.2.2}$ was largely responsible for the lower RCC (9 ± 0% RCC, Table 4.27 entry 3), whereas the effect of K_2CO_3 was more moderate (29 ± 1% RCC, Table 4.27 entry 4). The effect of added Et_4NHCO_3, which can be used as a precursor for the alternative ^{18}F-fluoride source [^{18}F]Et_4NF, was even more pronounced and no ^{18}F-incorporation was observed (Table 4.27 entry 5). Using the less basic $K_2C_2O_4.H_2O$ as additive did not influence the efficieny of ^{18}F-incorporation, and [^{18}F]**4-49** was obtained in 51 ± 4% (Table 4.27 entry 6).



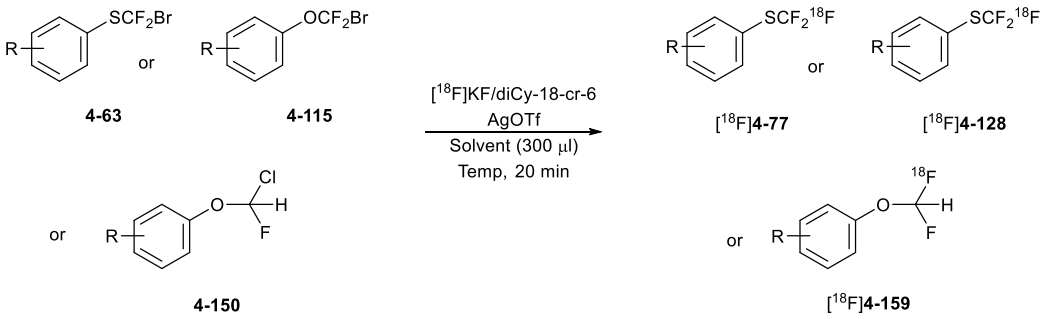
4-181 **4-182** **4-183**

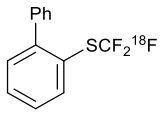
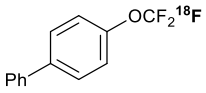
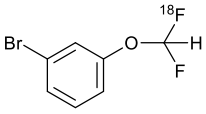
Scheme 4.44 Alternative base and crown ether additives

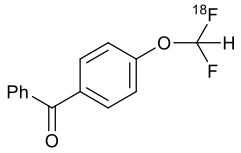
The results of the spiking experiments show that the use of $K_2CO_3/K_{2.2.2}$ in the elution of [^{18}F]F^- from the anion exchange cartridge could result in lower ^{18}F-incorporation. The elution conditions for the isolation experiments were therefore adjusted, with $K_2C_2O_4.H_2O$ (0.012 mmol, 4 mg) and diCy-18-crown-6 (0.038 mmol, 14 mg) used as substitutes for K_2CO_3 and $K_{2.2.2}$. A small amount of K_2CO_3 (0.0014 mmol, 0.2 mg) was added to increase the basicity of the eluting mixture, to avoid loss of activity by formation of [^{18}F]HF during the subsequent azeotropic drying step.[100] The dicyclohexyl substituted crown-ether **4-182** was used to improve the solubility of the formed [^{18}F]KF/crown-ether complex, and was most efficiently transferred to the reaction vial using MeOH as a solvent. Elution with

unsubstituted 18-crown-6 **4-183** resulted in a [^{18}F]KF/18-crown-6 complex that was difficult to dissolve in either MeOH or CH_3CN,[101] and could therefore not be transferred to the reaction vial.

From these observations a new protocol for the isolation of ^{18}F aryl-SCF_3, -OCF_3 and -OCF_2H derivatives from a full batch of [^{18}F]F^- was developed, and applied to a selected range of substrates (Table 4.28).



Entry[a]	Product	Conditions	Starting Activity[b] (MBq)	Isolated Activity[c] (MBq)	RCY	SA (GBq/ µmol)
1		AgOTf (1 eq) DCM, rt	2080	169	[^{18}F]**4-49** 8 ± 2% (n = 3)	0.32
			1890	197		
			1942	79		
2		AgOTf (2 eq) DCE, 60°C	1725	237	[^{18}F]**4-113** 10 ± 3% (n = 2)	0.08
			588	40		
4		AgOTf (1 eq) DCM, rt	1510	509	[^{18}F]**4-163** 32 ± 2% (n = 2)	0.04
			658	195		

5		AgOTf (1 eq) DCM, rt	1982 327	242 106	[^{18}F]**4-165** 22 ± 10% (*n* = 2)	0.17

[a] Reaction conditions : substrate (0.04 mmol), [^{18}F]KF/diCy-18-cr-6 (activity see table) , AgOTf (0.04 mmol), solvent (300 µl), Temp (see table), 20 min. [b] activity measured after drying procedure and solvent removal. See Experimental Section for details. [c] as determined by isolation after prep-HPLC. See Experimental Section for details.

Table 4.28 Isolation of ^{18}F aryl-SCF_3, -OCF_3 and -OCF_2H derivatives

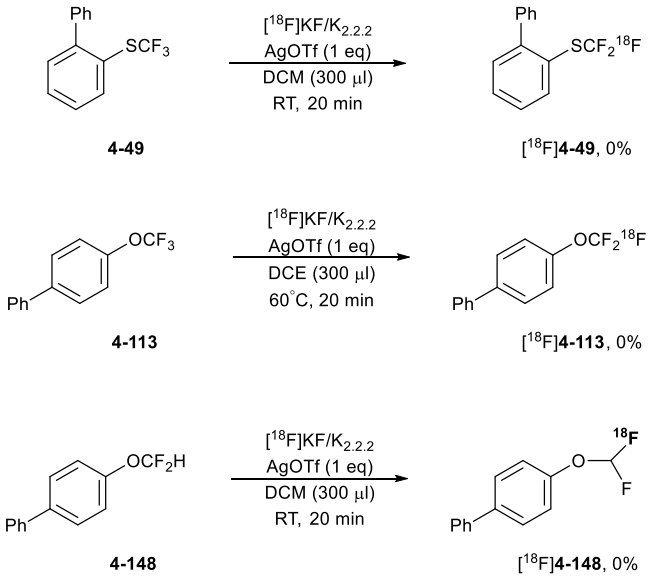
A solution of azeotropically dried [^{18}F]KF/diCy-18-cr-6 complex (~ 2 GBq) in MeOH, prepared from [^{18}F]F^- (aq) as described in section 4.1.3, was added to AgOTf and the solvent was removed at 100 °C under a stream of nitrogen. A solution of the substrate in either DCM (0.12M) or DCE (0.12M) was added, and the reaction was stirred for 20 min at the indicated temperature, after which it was filtered and purified by prep-HPLC with monitoring of UV- and radio-traces. The product was collected, and an aliquot was analysed by analytical HPLC to confirm the identity of the radiotracer by comparison of the retention time with that of the cold reference. The SA was calculated by determining the mass of cold product from the UV-trace and a calibration curve. This optimized protocol could be successfully used for the isolation of ^{18}F aryl-SCF_3, -OCF_3 and -OCF_2H derivatives [^{18}F]**4-63**¸ [^{18}F]**115**, and [^{18}F]**150** in activities ranging from 79 Mbq to 509 MBq (starting from ~2 Gbq of [^{18}F]F^-). The labelled *ortho*-Ph substituted aryl thiotrifluoromethyl ether [^{18}F]**4-49** could be isolated in 8 ± 2% RCY with an activity of up to 197 MBq, and a SA of 0.32 GBq/µmol. The ^{18}F-aryl trifluoromethylether [^{18}F]**4-113** was isolated in up to 237 MBq of activity in 10 ± 3% RCY, and slightly lower SA values (0.08 GBq/µmol). In line with previously obtained results (see section 4.5), ^{18}F-aryl difluoromethylethers [^{18}F]-**163** and [^{18}F]**165** showed efficient ^{18}F-incorporation, which resulted in isolation of higher amounts of activity and good RCY. The *meta*-bromo substituted [^{18}F]**4-163** could be isolated in up to 509 MBq (32 ± 2% RCY) and the para-

benzoyl [^{18}F]**4-165** in up to 242 MBq (22 ± 10% RCY). The SA was in the same range as the other substrate classes, 0.04 GBq/mmol and 0.17 GBq/mmol for [^{18}F]**4-163** and [^{18}F]4-**165** respectively.

The ^{18}F aryl-SCF_3, -OCF_3 and -OCF_2H derivatives [^{18}F]**4-63**, [^{18}F]**115**, and [^{18}F]**150** could all be isolated in amounts of activity which are more than sufficient for application in PET-imaging. The RCY is generally lower compared to the RCC (determined from batch reactions, see sections 4.3, 4.4 and 4.5). This observation can in part be explained by losses during transfer and HPLC purification of the ^{18}F-labelled compounds. The SA was determined to be in the range of 0.04 - 0.32 GBq/μmol. These low values indicate a relatively large amount of "cold" product is formed during the reaction, and suggest a source of unlabelled fluoride is present during the reaction.[102]

4.7.1 Investigation Into the Cause of Low SA

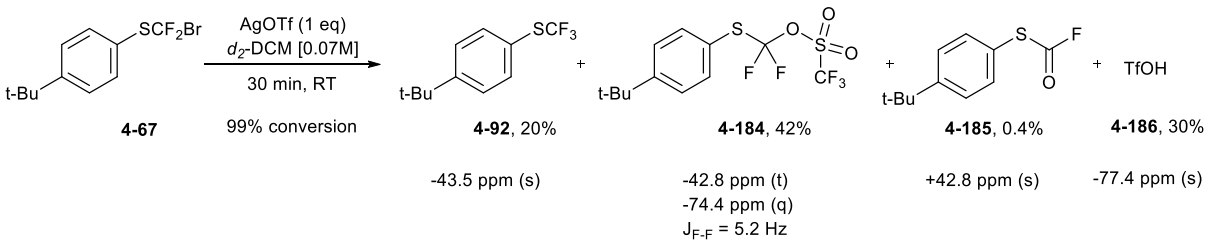
A possible cause of the observed low SA could be isotope exchange of the fluorinated product under the reaction conditions. To investigate this possibility, unlabelled aryl-SCF_3, -OCF_3 and -OCF_2H derivatives **4-49**, **4-113** and **4-148** were submitted to the Ag(I) mediated ^{18}F-fluorination reaction conditions using [^{18}F]KF/$K_{2.2.2}$ complex (25-30 MBq) (Scheme **4.45**).



Scheme 4.45 Investigation into isotope exchange of aryl-SCF_3, -OCF_3 and -OCF_2H derivatives

No ^{18}F-incorporation was detected when **4-49**, **4-113** and **4-148** were reacted with $[^{18}F]KF/K_{2.2.2}$ complex in the presence of AgOTf (1 eq for **4-49** and **4-148**, 2 eq for **4-113**) in either DCM at room temperature (for **4-49** and **4-148),** or DCE at 60 °C (for **4-113**). These results indicate that isotope exchange did not take place, and therefore is not the cause of the low SA.

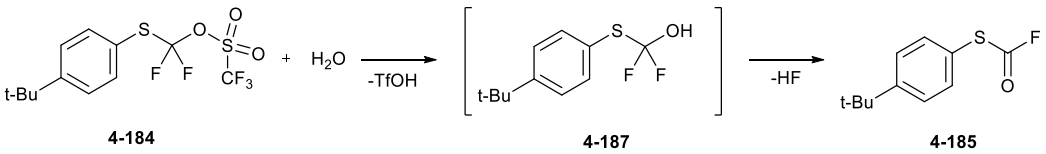
To investigate if the substrate could be the source of unlabelled fluoride, the cold reaction of 1-{[bromo(difluoro)methyl]sulfanyl}-4-*tert*-butylbenzene **4-67** with AgOTf was performed without an added fluoride source, and analysed by ^{19}F NMR (Scheme 4.46).



Scheme 4.46 Reaction of **4-67** and AgOTf without an added fluoride-source

To a solution of *para-t*Bu substituted **4-67** in d_2-DCM (0.07M) was added AgOTf (1 eq), and after 30 min stirring at room temperature the mixture was analysed by ^{19}F NMR, using $PhCF_3$ (1 eq) as a reference. The analysis showed almost full conversion of **4-67**, and formation of a new product with a singlet at -43.5 ppm, which was assigned to the fluorinated product **4-92**. Two other signals, a triplet at -42.8 ppm (J_{F-F} = 5.2 Hz) and a quartet at -74.4 ppm (J_{F-F} = 5.2 Hz), were tentatively assigned to **4-184**, in analogy with other known compounds containing the CF_2OTf moiety.[103] A very small singlet at +42.8 ppm was tentatively assigned to **4-185**, in analogy with the known phenyl thiofluoroformate.[104] The singlet at -77.4 ppm was tentatively assigned as TfOH.

The formation of fluorinated product **4-92** (20% yield compared to reference) shows that the starting bromide **4-67** in combination with AgOTf can generate a source of fluoride. A possible mechanism for this process could be hydrolysis of the difluoromethyltriflate intermediate **4-184** by adventitious H_2O (Scheme 4.47). This hydrolysis would results in formation of TfOH and an unstable difluoro-alcohol intermediate **4-187**, which eliminates HF to give the thiofluoroformate **4-185**. The formation of a very small amount of **4-185** could be tentatively confirmed by ^{19}F NMR. The predicted sensitivity of thiofluoroformate **4-185** to hydrolysis (which would produce another equivalent of HF) could account for the detection of only a small quantity of **4-185** in the reaction mixture.



Scheme 4.47 Hydrolysis of difluoromethyltriflate intermediate **4-184**

This ^{19}F-NMR experiment shows that a possible explanation for the observed low SA could be the formation of [^{19}F]HF, caused by hydrolysis of a reaction intermediate by

adventitious H_2O, which competes in the fluorination reaction with $[^{18}F]F^-$ and causes formation of cold ^{19}F-product.

Formation of $[^{19}F]F^-$, and competing formation of the cold ^{19}F-product was also found to occur in the ^{18}F-trifluoromethylation of aryliodides using in-situ generated $[^{18}F]CuCF_3$,[74] and thiotrifluoromethylation of alkylhalides with in-situ generated $[^{18}F]SCF_3^-$.[75] Isolated compounds from both these methods, are reported to have SA ≈ 0.1 GBq/μmol, which is in the same range as obtained with the Ag(I)-mediated ^{18}F-fluorination of mono- and difluorobromomethyl(thio)ethers.

4.8 Conclusions

In conclusion, this chapter reports the synthesis of previously unknown ^{18}F-chemotypes $[^{18}F]SCF_3$, $[^{18}F]OCF_3$ and $[^{18}F]OCF_2H$ using a new activation mode of $[^{18}F]F^-$.

A method for the synthesis of ^{18}F-arylSCF_3 compounds from $[^{18}F]F^-$ was developed using an Ag(I)-mediated halogen exchange reaction on an aryl difluorobromomethylsulfide precursor. The reaction proceeds under mild conditions with AgOTf (1 eq) in chlorinated solvent (DCM) at room temperature and provides good RCC up to 60 ± 4% for substrates with electron donating groups. RCCs up to 92 ± 0% were obtained at higher temperature (60 °C) and increased AgOTf loading (2 eq), in DCE as solvent. Electron neutral and electron poor substrates gave only low ^{18}F-incorporation at room temperature but could be obtained in moderate RCC, up to 46 ± 11% at 60°C. Strong electron withdrawing substituents were not tolerated, and no ^{18}F-incorporation was obtained, even at higher temperature. The use of an Ag(I)-salt was essential, and no ^{18}F-incorporation was found to take place under classical substitution conditions in polar solvent with thermal activation up to 200°C.

The halogen exchange method could be extended to the synthesis of a range of ^{18}F-arylOCF_3 and ^{18}F-arylOCF_2H compounds. Up to 79 ± 3% RCC was obtained for ^{18}F-

arylOCF$_2$H compounds at room temperature, and both electron withdrawing and donating substituents displayed efficient ^{18}F-incorporation. The halogenated precursors for the synthesis of ^{18}F-arylOCF$_3$ compounds were considerably less reactive, and ^{18}F-incoporation was only achieved at higher temperature (60°C) with lower RCC. The method could also be used in late stage synthesis of complex and biologically active molecules, as shown by the synthesis of [^{18}F]Riluzole, a PET-isotope labelled version of the registered drug that has been used in the treatment of ALS and schizophrenia.

Finally, a protocol was developed for the isolation of ^{18}F-labelled arylSCF$_3$, -OCF$_3$ and -OCF$_2$H compounds starting from a full batch (~ 2 GBq) of [^{18}F]F$^-$. The ^{18}F-labelled products could be isolated in activities up to 509 MBq, with up to 32% RCY and SA up to 0.32 Gbq/μmol. A possible explanation for the low SA could be attributed to release of a source of cold fluoride from the hydrolysis of the intermediate complex of substrate and AgOTf, caused by the presence of adventitious H_2O.

4.9 References

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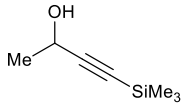
Chapter 5: Experimental Procedures and Characterisation Data

All NMR spectra were recorded on Bruker DPX200, AV400, AVB400, AVC500, AVB500 and DRX500 spectrometers. Proton and carbon-13 NMR spectra are reported as chemical shifts (δ) in parts per million (ppm) relative to the solvent peak using the Bruker internal referencing procedure (edlock). Fluorine-19 NMR spectra are referenced relative to $CFCl_3$ in $CDCl_3$. Coupling constants (*J*) are reported in units of hertz (Hz). The following abbreviations are used to describe multiplicities – s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br. s (broad singlet). High resolution mass spectra (HRMS, *m/z*) were recorded on a Bruker MicroTOF spectrometer using positive electrospray ionization (ESI^+) or on a Micromass GCT spectrometer using filed ionization (FI^+) or chemical ionization (CI^+). Infrared spectra were recorded either as the neat compound or in a solution using a Bruker Tensor 27 FT-IR spectrometer. Absorptions are reported in wavenumbers (cm^{-1}) and only peaks of interest are reported. Optical rotations were measured on a PerkinElmer Polarimeter model 341 Specific rotations are reported in 10^{-1} deg cm^2 g^{-1} and concentrations in g/100 mL. Melting points of solids were measured on a Griffin apparatus and are uncorrected. IUPAC names were obtained using the ACD/I-Lab service. Solvents were purchased from Fisher, Rathburn or Sigma-Aldrich. When dry solvents were required they were purified by expression through an activated alumina column built according to the procedures described by Pangborn and Grubbs.[1] Chemicals were purchased from Acros, Alfa Aesar, Fisher, Fluorochem, Sigma-Aldrich and used as received. Reactions were monitored by thin-layer chromatography (TLC) carried out on Merck Kiesegel 60 F254 plates, silica gel column chromatography was performed over Merck silica gel C60 (40-60 μm).

Experimental Data for Chapter 2

4-(Trimethylsilyl)but-3-yn-2-ol 2-39

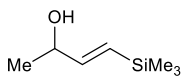


A solution of EtMgBr (made from ethyl bromide (13.4 mL, 180 mmol) and Mg turnings (4.0 g, 165 mmol)) in Et_2O (100 mL) was cooled in an ice-bath after which a solution of 3-butyn-2-ol (5.88 mL, 75.0 mmol) in Et_2O (50 mL) was added dropwise over 90 min. During the addition a gelatinous precipitate forms which is difficult to stir. The mixture was allowed to stand overnight at room temperature (18 hr), after which TMSCl (20.9 mL, 165 mmol) was added dropwise over 15 min. The resulting mixture was heated to reflux in an oilbath, and stirred for 5 hr after which it was allowed to cool to room temperature. The mixture was then cooled in an ice-bath and 1.4 M H_2SO_4 (100 mL) was cautiously added. The mixture was allowed to warm to room temperature and extracted with Et_2O (3 x 100 mL). The pooled organic layers were washed with H_2O (150 mL), brine (150 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography (eluent: Et_2O/30-40 petroleum ether 5/95 to 10/90) provided the title compound (8.57 g, 80% yield) as a yellow oil.

(^{1}H NMR, 400 MHz, $CDCl_3$) δ = 0.18 (s, 9H), 1.46 (d, J = 6.6 Hz, 3 H), 1.81 (br. s, 1 H), 4.52 (q, J = 6.6 Hz, 1 H).

Data consistent with literature values.[1]

(*E*)-4-(Trimethylsilyl)but-3-en-2-ol 2-40

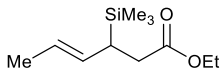


A mixture of $NaAlH_2(OCH_2CH_2OMe)_2$ (RedAl^{tm}, 3.4 M in toluene, 70.0 mL, 239 mmol) in Et_2O (100 mL) was cooled in an ice-bath and a solution of 4-(trimethylsilyl)but-3-yn-2-ol (8.50 g, 59.7 mmol) in Et_2O (20 mL) was added dropwise over 30 min. The reaction mixture was stirred for 5 hr at room temperature after which it was cooled in an ice-bath and quenched very carefully with 3.6 N H_2SO_4 (300 mL). The mixture was allowed to warm to room temperature and extracted with Et_2O (3 x 100 mL). The pooled organic layers were washed with H_2O (150 mL), brine (150 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography (eluent: Et_2O/30-40 petroleum ether 1/4) provided the title compound (6.92 g, 80% yield) as a yellow oil.

(^{1}H NMR, 200 MHz, $CDCl_3$) δ = 0.08 (s, 9 H), 1.27 (d, J = 6.5 Hz, 3H), 4.29 (qdd, J_1 = 6.4, J_2 = 5.0, J_3 = 1.2 Hz, 1 H), 5.83 (dd, J_1 = 18.7, J_2 = 1.2 Hz, 1 H), 6.10 (dd, J_1 = 18.7, J_2 = 5.0 Hz, 1 H).

Data consistent with literature values.[2]

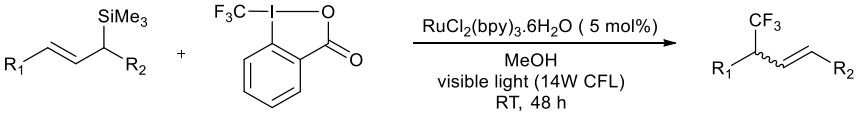
Ethyl (*E*)-3-(trimethylsilyl)hex-4-enoate 2-41



To a solution of (*E*)-4-(trimethylsilyl)but-3-en-2-ol (4.92 g, 34.6 mmol) in toluene (35 mL) under nitrogen was added $MeC(OEt)_3$ (6.12 mL, 33.4 mmol) and propionic acid (0.1 mL, 1.33 μmol). The reaction mixture was lowered into a pre-heated 120 °C oilbath and stirred under reflux for 16 hr. An aliquot of the mixture was analysed by TLC (eluent Et_2O/n-hexane 1/4) which showed some starting material still remaining so another portion of $MeC(OEt)_3$ (6.12 mL, 33.4 mmol) was added and reflux was continued for another 16 hr. The mixture was allowed to cool to room temperature and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography (gravity ; eluent EtOAc/Petrol 40-60 9/1) provided the title compound (6.43g, 87% yield) as a colourless oil.

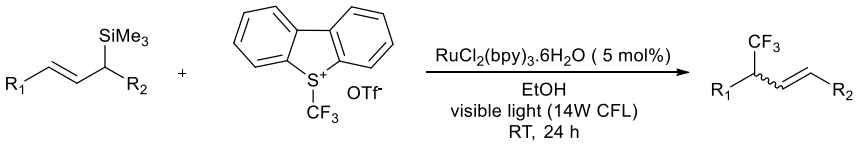
(^{1}H NMR, 400 MHz, $CDCl_3$) δ = -0.01 (s, 9 H), 1.24 (t, *J* = 7.2 Hz, 2 H), 1.65 (d, *J* = 4.9 Hz, 3 H), 1.93 - 2.02 (m, 1 H), 2.25 - 2.41 (m, 2 H), 4.12 (q, *J* = 7.2 Hz, 2 H), 5.27 - 5.32 (m, 2 H). Data consistent with literature values.[3]

General procedure A



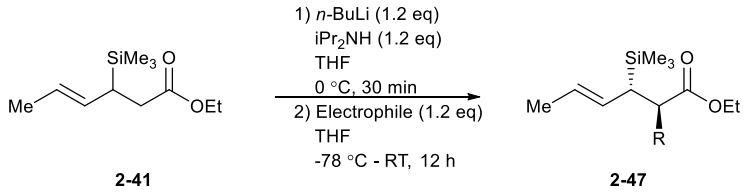
A vial was charged with allylsilane (0.25 mmol), $Ru(bpy)_3Cl_2$•$6H_2O$ (9.0 mg, 0.013 mmol, 5.0 mol%), Togni reagent II (0.45 mmol, 1.8 eq) and MeOH (0.50 mL). The vial was exposed to a 14 W fluorescent light bulb at room temperature while stirring for 48 h. The mixture was quenched with sat. $NaHCO_3$ solution (10 mL) and extracted with Et_2O (2 x 10 mL). The pooled organic phases were washed with H_2O (10 mL) and brine (10 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude mixture was analysed by ^{19}F NMR to determine the isomeric ratio and then purified by silica gel column chromatography.

General procedure B



Allylsilane (0.25 mmol), $Ru(bpy)_3Cl_2$•$6H_2O$ (9.0 mg, 0.013 mmol, 5.0 mol%), Umemoto reagent (0.45 mmol, 1.8 eq) and EtOH (0.50 mL) were placed in a vial which was equipped with a magnetic stir bar. The vial was exposed to a 14 W fluorescent light bulb at room temperature while stirring for 24 h. The mixture was quenched with sat. $NaHCO_3$ solution (10 mL) and extracted with Et_2O (2 x 10 mL). The pooled organic phases were washed with H_2O (10 mL) and brine (10 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude mixture was analysed by ^{19}F NMR to determine the isomeric ratio and then purified by silica gel column chromatography.

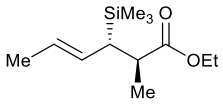
General procedure C



2-41 **2-47**

To a solution of iPr_2NH (2.10 mL. 12.0 mmol) in THF (9 mL) at 0 °C was added *n*-BuLi (7.50 mL, 12.0 mmol, 1.6 M, in hexane) and the reaction was allowed to stir for 30 min. The solution was cooled to −78 °C and a solution of (*E*)-3-(trimethylsilyl)hex-4-enoate (2.10 g, 10 mmol) in THF (4.50 mL) was added via a syringe. The light yellow solution was stirred for 30 min. A solution of electrophile (12.0 mmol) in THF (2 mL) was added dropwise, and the reaction mixture was allowed to warm to room temperature and stir for 12 h. The reaction was quenched by the addition of a saturated NH_4Cl solution at 0 ˚C and the aqueous phase was extracted with Et_2O (50 mL). The combined organic phases were washed with water (50 mL) and brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by silica gel column chromatography afforded diastereomerically pure 2,3-*anti*-α-substituted-β-silyl-(*E*)-hex-4-enoate.

***anti*-(*E*) Ethyl 2-methyl-3-(trimethylsilyl)hex-4-enoate 2-48**

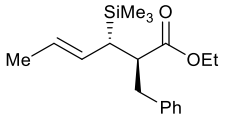


The title compound was prepared following General procedure C using iPr_2NH (0.91 mL, 6.5 mmol), *n*-BuLi (4.1 mL, 6.5 mmol, 1.6 M in hexanes), (*E*)-3-(trimethylsilyl)hex-4-enoate (1.07 g, 5.0 mmol), MeI (0.37 mL, 6.0 mmol) and THF (20 mL). The crude product was purified by silica gel column chromatography (eluent: Et_2O/*n*-hexane 5/95) provided the title compound (0.80 g, 70% yield) as a colourless oil.

(^{1}H NMR, 400 MHz, $CDCl_3$)δ = 0.00 (s, 9H), 1.14 (d, *J* = 7.0 Hz, 3H), 1.25 (t, *J* = 7.2 Hz, 3H), 1.67 (d, *J* = 4.9 Hz, 3H), 1.91 (dd, J_1 = 10.0 Hz, J_1 = 7.0 Hz, 2H), 2.58 (app. q, *J* = 7.0 Hz), 4.03-4.07 (m, 2H), 5.20-5.36 (m, 2H); (^{13}C NMR 100 MHz, $CDCl_3$) δ -2.3, 14.2, 15.6, 18.1, 36.4, 39.8, 60.0, 125.3, 127.9, 176.5.

Data consistent with literature values.[4]

***anti*-(*E*) Ethyl 2-benzyl-3-(trimethylsilyl)hex-4-enoate 2-49**

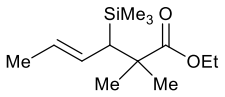


The title compound was prepared following General Procedure C using iPr_2NH (390 μL, 2.80 mmol), *n*-BuLi (1.75 mL, 2.80 mmol, 1.6 M in hexanes), (*E*)-3-(trimethylsilyl)hex-4-enoate (430 mg, 2.00 mmol), benzyl bromide (380 μL, 3.20 mmol) and THF (10 mL). The crude product was purified by silica gel column chromatography (eluent: Et_2O/*n*-hexane 2.5/97.5 to 5/95) provided the title compound (550 mg, 70% yield) as a colourless oil.

(^{1}H NMR, 400 MHz, $CDCl_3$)δ = 0.00 (s, 9H), 0.98 (t, *J* = 7.2 Hz, 3H), 1.70 (d, *J* = 4.7 Hz), 1.85-1.93 (m, 1H), 2.63-2.77 (m, 2H), 2.96 (dd, J_1 = 12.4, J_2 = 2.6 Hz, 1H), 3.87 (qd, J_1 = 7.1, J_2 = 1.7 Hz, 2H), 5.33-5.45 (m, 2H), 7.10-7.18 (m, 2H), 7.21 (dd, J_1 = 7.8 Hz, J_2 = 0.7 Hz, 2 H); (^{13}C NMR 100 MHz, $CDCl_3$) δ -2.9, 13.5, 17.4, 36.5, 38.5, 48.4, 59.4, 125.0, 126.0, 128.1, 128.8, 128.9, 129.6, 140.1, 174.2.

Data consistent with literature values.[4]

Ethyl (*E*)-2,2-dimethyl-3-(trimethylsilyl)hex-4-enoate



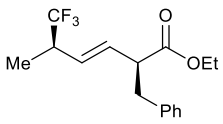
To a solution of iPr_2NH (500 μL. 3.60 mmol) in THF (20 mL) at 0 ˚C was added *n*-BuLi (1.44 mL, 3.60 mmol, 2.5 M in hexanes) and the reaction was allowed to stir for 30 min. The

solution was cooled to -78 °C and a solution of *anti*-(*E*) ethyl 2-methyl-3-(trimethylsilyl)hex-4-enoate (460 mg, 2.00 mmol) in THF (2 mL) was added via a syringe. The light yellow solution was stirred for 30 min after which the temperature was allowed to rise to -40 °C. MeI (220 μL, 3.60 mmol) was added dropwise, and the reaction mixture was allowed to warm to room temperature and stir for 16 h. The reaction was quenched by the addition of a saturated NH_4Cl solution at 0 °C and the aqueous phase was extracted with Et_2O (50 mL). The combined organic phases were washed with water (50 mL) and brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Analysis of the crude product by ^1H NMR still showed starting material remaining so the procedure was repeated using iPr_2NH (360 μL, 2.60 mmol), *n*-BuLi (640 μL, 2.60 mmol, 2.5 M in hexanes), MeI (150 μL, 2.40 mmol) in THF (15 mL). After work-up the crude product was purified by silica gel column chromatography (eluent: n-hexane to Et_2O/*n*-hexane 5/95) to provide the title compound (202 mg, 42%) as a yellow oil.

(^1H NMR, 200 MHz, $CDCl_3$)δ = -0.01 (s, 9H), 1.14 (s, 3H), 1.20 (s, 3 H), 1.25 (t, *J* = 7.1 Hz, 3H), 1.68 (d, *J* = 4.8 Hz, 3 H), 1.89-2.02 (m, 1H), 3.95-4.21 (m, 2 H), 5.26-5.36 (m, 2H)

Data consistent with literature values.[4]

syn-(_E_)-Ethyl 2-benzyl-6,6,6-trifluoro-5-methylhex-3-enoate 2-58



Conditions A:

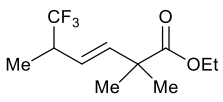
The title compound was prepared using General Procedure A using *anti*-(*E*) Ethyl 2-benzyl-3-(trimethylsilyl)hex-4-enoate (76 mg, 0.25 mmol), Togni II reagent (0.14 g, 0.45 mmol), $Ru(bpy)_3Cl_2•6H_2O$ (9.0 mg, 0.013 mmol) and MeOH (0.50 mL). The isomeric ratio was determined by ^{19}F NMR analysis of the crude mixture (*E/Z* = 15 : 1, *syn/anti*(*E*) = 10).

Purification by silica gel column chromatography (eluent: EtOAc/*n*-hexane 5/95) provided the title compound (63 mg, 83% yield, *E/Z* = 19 : 1, *syn/anti*(*E*) = 9.0 : 1) as a colourless oil.

Conditions B:

The title compound was prepared using General Procedure B using *anti*-(*E*) Ethyl 2-benzyl-3-(trimethylsilyl)hex-4-enoate (76 mg, 0.25 mmol), Umemoto reagent (0.18 mg, 0.45 mmol), $Ru(bpy)_3Cl_2•6H_2O$ (9.0 mg, 0.013 mmol) and EtOH (0.50 mL). The isomeric ratio was determined by ^{19}F NMR analysis of the crude mixture (*E/Z* = >20 : 1, *syn/anti*(*E*) = 8.6 : 1). Purification by silica gel column chromatography (eluent: EtOAc/*n*-hexane 5/95) provided the title compound (18 mg, 24% yield, *E/Z* = >20 : 1, *syn/anti*(*E*) = 9.3 : 1) as a colourless oil. (^1H NMR 500 MHz, $CDCl_3$) δ 1.18 (m, 6H), 2.78-2.85 (m, 1H), 2.84 (dd, J_1 = 7.6 Hz, J_2 = 13.6 Hz, 1H), 3.08 (dd, J_1 = 7.6 Hz, J_2 = 13.6 Hz, 1H), 3.29 (q, *J* = 7.6 Hz, 1H), 4.10 (q, *J* = 7.0 Hz, 1H), 4.11 (q, *J* = 7.3 Hz, 1H), 5.38 (dd, J_1 = 7.9 Hz, J_2 = 15.8 Hz, 1H), 5.79 (dd, J_1 = 8.8 Hz, J_2 =15.8 Hz, 1H), 7.15 (d, *J* = 7.0 Hz, 2H), 7.21 (t, *J* = 7.6 Hz, 1H), 7.27 (t, *J* = 7.6 Hz, 2H); (^{13}C NMR 125 MHz, $CDCl_3$) δ 13.4 (q, *J* = 1.9 Hz), 14.0, 38.8, 41.4 (q, *J* = 27.5 Hz), 51.0, 60.7, 126.5, 126.9 (q, *J* = 277.7 Hz), 127.9 (q, *J* = 2.8 Hz), 128.3, 129.1, 132.1, 173.1; ^{19}F NMR (377 MHz, $CDCl_3$) δ -72.72 (d, *J* = 9.2 Hz, 3F); IR (neat) ν 2986, 1731, 1258, 1171, 1125, 1017, 971, 911, 857 cm^{-1}; HRMS (TOF-ESI) *m/z* Calcd for $C_{16}H_{19}F_3NaO_2$ $[M+Na]^+$ 323.1221, found 323.1229.

(*E*)-Ethyl 6,6,6-trifluoro-2,2,5-trimethylhex-3-enoate 2-61



Conditions A:

The title compound was prepared using General Procedure A using ethyl (*E*)-2,2-dimethyl-3-(trimethylsilyl)hex-4-enoate (0.12 g, 0.50 mmol), Togni II reagent (0.28g, 0.90 mmol),

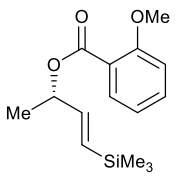
$Ru(bpy)_3Cl_2 \cdot 6H_2O$ (19 mg, 0.025 mmol) and MeOH (1.0 mL). The isomeric ratio was determined by ^{19}F NMR analysis of the crude mixture (*E/Z* = 14 : 1). Purification by silcia gel column chromatography (eluent: EtOAc/*n*-hexane 2/98) provided the title compound (59 mg, 50% yield, *E/Z* = >20 : 1) as a colourless oil.

(^1H NMR 500 MHz, $CDCl_3$) δ 1.21 (d, *J* = 6.9 Hz, 3H), 1.24 (t, *J* = 7.0 Hz, 3H), 1.30 (s, 6H), 2.79-2.91 (m, 1H), 4.13 (q, *J* = 7.0 Hz, 2H), 5.43 (dd, J_1 = 7.9 Hz, J_2 =15.8 Hz, 1H), 5.89 (d, *J* = 15.8 Hz, 1H); (^{13}C NMR 125 MHz, $CDCl_3$) δ 13.5 (q, *J* = 1.9 Hz), 14.1, 24.7, 24.9, 41.5 (q, *J* = 27.2 Hz), 44.1, 60.8, 123.1 (q, *J* = 2.9 Hz), 127.2 (q, *J* = 277.7 Hz), 139.5, 176.0; (^{19}F NMR 377 MHz, $CDCl_3$) δ -72.87 (d, *J* = 8.0 Hz, 3F); IR (neat) ν 2985, 1731, 1464, 1386, 1258, 1127, 1019, 972, 864 cm^{-1}; HRMS (TOF-ESI) *m/z* Calcd for $C_{11}H_{17}F_3NaO_2$ $[M+Na]^+$ 261.1083, found 261.1073.

Conditions B:

The title compound was prepared using General Procedure B using *anti*-(*E*) Ethyl 2-methyl-3-(trimethylsilyl)hex-4-enoate (57 mg, 0.25 mmol), Umemoto reagent (0.18g, 0.45 mmol), $Ru(bpy)_3Cl_2 \cdot 6H_2O$ (9.0 mg, 0.013 mmol) and EtOH (0.50 mL). $PhCF_3$ (12 μl, 0.10 mmol) was added as reference and the yield and isomeric ratio was determined by ^{19}F NMR analysis of the crude mixture (yield 37% yield, *E/Z* = >20 : 1).

(*S, E*)-[4-(Trimethylsilyl)but-3-en-2-yl]-2'-methoxybenzoate 2-68

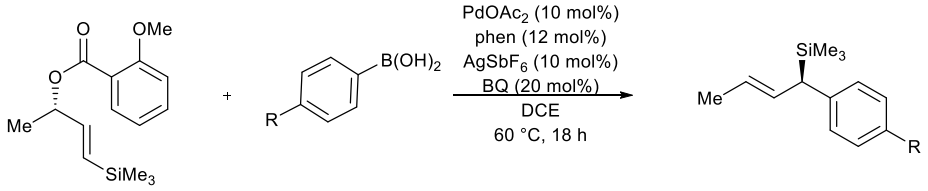


(*S, E*)-4-trimethylsilyl-but-3-en-2-ol (1.40 g, 9.70 mmol)[3] was dissolved in CH_2Cl_2 (20 mL) and pyridine (940 μL, 11.6 mmol), *o*-methoxybenzoyl chloride (1.73 mL, 11.6 mmol) and

DMAP (590 μg, 0.49 μmol) were sequentially added at 0˚C. The mixture was allowed to warm to room temperature and stir for 3 h before being quenched with H_2O (20 mL). The organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic phases were washed with H_2O (20 mL) and brine (20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo.* The crude residue was purified by silica gel column chromatography (eluent: EtOAc/*n*-hexane 1/4) to afford the title compound (2.38g, 88% yield) as a colourless oil.

(^{1}H NMR 400 MHz, $CDCl_3$) δ 0.08 (s, 9H), 1.42 (d, J = 6.6 Hz, 3H), 3.90 (s, 3H), 5.57-5.63 (m, 1H), 5.97 (d, J = 18.7 Hz, 1H), 6.11 (dd, J_1 = 4.8 Hz, J_2 =18.7 Hz, 1H), 6.97-7.01 (m, 2H), 7.47 (dd, J_1 = 1.8 Hz, J_2 = 8.3 Hz, 1H), 7.82 (dd, J_1 = 1.8 Hz, J_2 = 8.1 Hz, 1H); (^{13}C NMR 100 MHz, $CDCl_3$) δ -1.4, 19.9, 55.9, 72.5, 112.0, 120.1, 120.6, 130.3, 131.4, 133.3, 144.8, 159.1, 165.3; IR (neat) ν 2955, 1725, 1601, 1491, 1464, 1437, 1294, 1246, 1129, 1074, 1025, 988, 835, 753 cm^{-1}; HRMS (ESI) *m/z* Calcd for $C_{15}H_{22}O_3NaSi$ $[M+Na]^+$ 301.1236, found 301.1230.

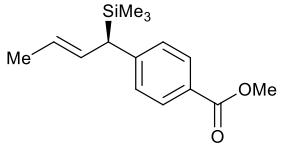
General procedure D



According to the literature procedure,[5] a 100 mL round bottom flask containing a magnetic stir bar was charged with $Pd(OAc)_2$ (0.54 mmol), 1,10-phenanthroline (0.65 mmol), $AgSbF_6$ (0.54 mmol) and 1,4-benzoquinone (1.08 mmol). 1,2-Dichloroethane (35 mL) was introduced and the mixture was sonicated at 25 ˚C for 1 min, then stirred at 25˚C for 3 min to give a yellow suspension. Arylboronic acid (8.1 mmol) and (*S*, *E*)-4-(trimethylsilyl)but-3-en-2-yl 2-

methoxybenzoate (5.4 mmol) were sequentially added and the resulting mixture was heated at 60 ˚C for 18 h. After cooling to room temperature, the mixture was filtered through a short pad of silica gel then washed with Et_2O (50 mL), and the filtrate was concentrated *in vacuo*. The crude residue was purified by silica gel column chromatography (eluent: *n*-hexane) to afford the allylsilane as a colourless oil. The enantiomeric purity was determined by chiral HPLC analysis.

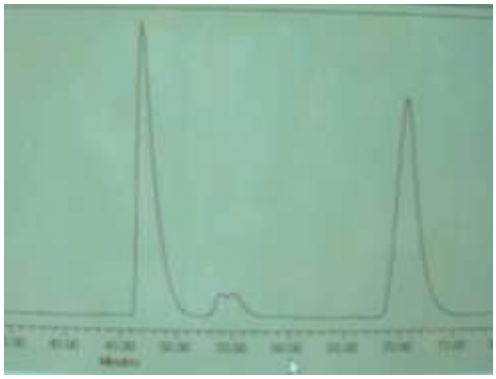
(*R*,*E*)-Methyl 4-[1-(trimethylsilyl)but-2-en-1-yl]benzoate 2-72



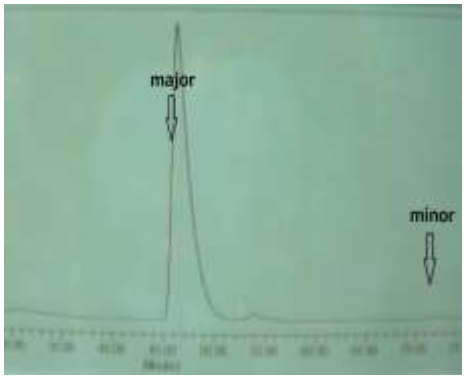
The title compound was prepared according to the General Procedure D using $Pd(OAc)_2$ (45 mg, 0.20 mmol), 1,10-phenanthroline (43 mg, 0.24 mmol), $AgSbF_6$ (69 mg, 0.20 mmol), 1,4-benzoquinone (43 mg, 0.40 mmol), 4-methoxycarbonylphenylboronic acid (0.54 mg, 3.0 mmol), (*S, E*)-4-(trimethylsilyl)but-3-en-2-yl 2-methoxybenzoate (0.56 mg, 3.0 mmol) and 1,2-dichloroethane (12 mL). After 18 h, the reaction mixture was subjected to the workup described in the General Procedure D and purified by silica gel column chromatography (eluent: EtOAc/*n*-hexane 1/15) followed by kügelrohr distillation (oven temp. 120 ˚C, < 1.0 mmHg) to afford the title compound (200 mg, 38% yield, >99:1 er) as a colourless oil.

(^{1}H NMR 500 MHz, $CDCl_3$) δ -0.08 (s, 9H), 1.72 (dd, J_1 = 1.1 Hz, J_2 = 6.5 Hz, 3H), 2.98 (d, J = 10.1 Hz, 1H), 3.90 (s, 3H), 5.44 (dqd, J_1 = 0.7 Hz, J_2 = 6.5 Hz, J_3 = 15.0 Hz, 1H), 5.81 (qdd, J_1 = 1.4 Hz, J_2 = 10.1 Hz, J_3 = 15.0 Hz, 1H), 7.12 (m, 2H), 7.93 (m, 2H); (^{13}C NMR 100 MHz, $CDCl_3$) δ -3.1, 18.9, 45.5, 51.9, 124.4, 126.3, 126.9, 129.0, 129.6, 149.2, 167.3; IR (neat) ν 2953, 1721, 1278, 838 cm^{-1}; HRMS (CI+) *m/z* Calcd for $C_{15}H_{23}O_2Si$ $[M+H]^+$ 263.1467, found 263.1475. $[\alpha]_D^{20}$ = -36.5 (c = 1.0, $CHCl_3$). The enantiomeric purity of (*R*,*E*)-**2-72** was determined by HPLC analysis (CHIRACEL® OD-H column, 4.6 mm x 250 mm, *n*-

hexane, 0.5 min/mL, 25 ˚C, UV detector (254 nm)), t_R (major) = 45.9 min and t_R (minor) = 70.7 min.



***rac*-2-72**

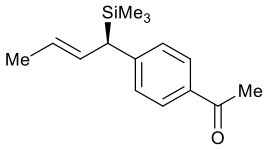


(*R*)-2-72

Time (min)	Area	%area
46.816	53475496	50.04
69.521	53396720	49.96

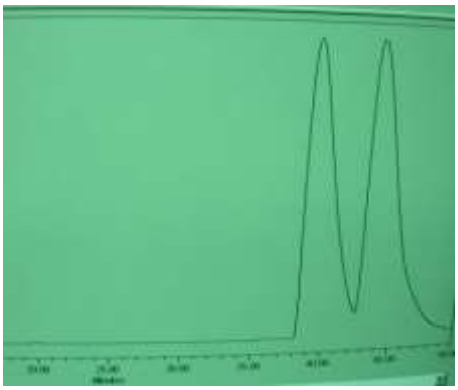
Time (min)	Area	%area
45.942	27257018	99.25
70.681	205629	0.75

(*R*,*E*)-4'-(1-(Trimethylsilyl)but-2-en-1-yl]acetophenone 2-73



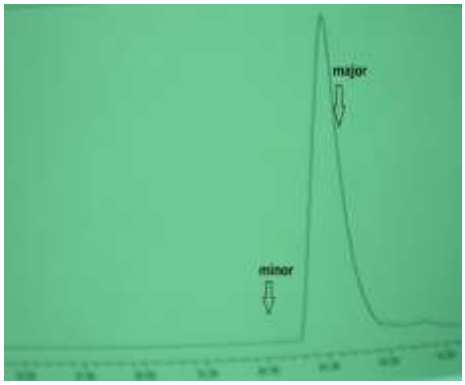
The title compound was prepared according to General Procedure D using $Pd(OAc)_2$ (810 μg, 360 μmol), 1,10-phenanthroline (780 μγ, 430 μmol), $AgSbF_6$ (123 mg, 350 μmol), 1,4-benzoquinone (117 mg, 1.08 mmol), 4-acethylphenylboronic acid (882 mg, 5.39 mmol), (*S*, *E*)-4-(trimethylsilyl)but-3-en-2-yl 2-methoxybenzoate (1.00 g, 3.59 mmol) and 1,2-dichloroethane (24.0 mL). After 24 h, the reaction mixture was subjected to the workup described in the General Procedure D and purified by silica gel column chromatography (eluent: EtOAc/*n*-hexane 10/90) followed by kügelrohr distillation (oven temp. 120 ˚C, < 1.0 mmHg) to afford the title compound (369 mg, 41% yield, >99:1 er) as a colourless oil.

(^{1}H NMR 400 MHz, $CDCl_3$) δ 0.04 (s, 9H), 1.72 (d, *J* = 6.6 Hz, 3H), 2.57 (s, 3H), 3.00 (d, *J* = 9.8 Hz, 1H), 5.40-5.48 (m, 1H), 5.81 (dd, J_1 = 10.1, J_2 = 14.6 Hz, 1H), 7.14 (d, *J* = 8.3 Hz, 2H), 7.86 (d, *J* = 8.3 Hz, 2H); (^{13}C NMR 100 MHz, $CDCl_3$) δ -3.1, 18.1, 26.4, 43.6, 124.4, 127.0, 128.5, 128.9, 133.7, 149.6, 197.8; IR (neat) ν 2958, 1679, 1601, 1414, 1358, 1269, 1247, 1179, 965, 836, 748, 692 cm^{-1}; HRMS (ESI+) *m/z* Calcd for $C_{15}H_{22}OSi$ $[M]^+$ 269.1335, found 269.1332; $[\alpha]_D^{20}$ = -56.0 (c = 1.0, MeOH). The enantiomeric purity of (1*R*,2*E*)-**2-73** was determined by HPLC analysis (CHIRACEL® OD-H column, 4.6 mm x 250 mm, *n*-hexane, 0.5 min/mL, 25 ˚C, UV detector (254 nm)), t_R (minor) = 39.3 min and t_R (major) = 43.9 min.



***rac*-2-73**

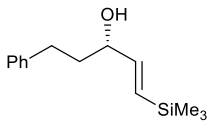
Time (min)	Area	%area
39.317	44715854	48.52
43.633	47450135	51.48



(1*R*, 2*E*)-2-73

Time (min)	Area	%area
–	–	–
43.865	69504196	>99

(*S*,*E*)-5-Phenyl-1-(trimethylsilyl)pent-1-en-3-ol 2-78



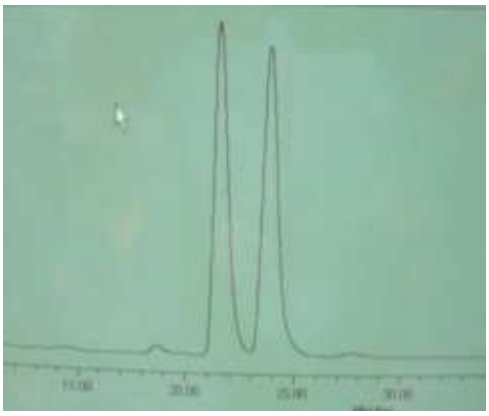
To a solution of RedAl^{tm} (5.15 mL, 65% solution in toluene, 17.5 mmol) in Et_2O (10 ml) was slowly added a solution of (*S*)-5-phenyl-1-(trimethylsilyl)pent-1-yn-3-ol[6] (2.32 g, 10.0 mmol)

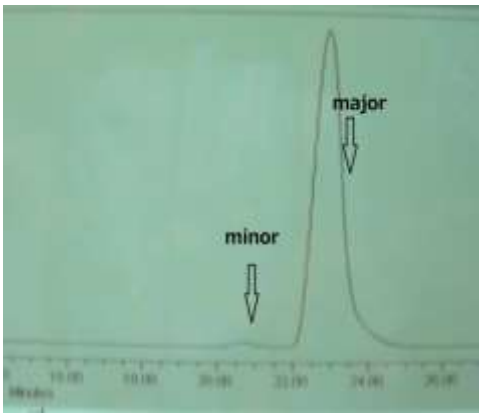
in Et_2O (5 mL) at 0 ˚C. The mixture was stirred at 0 ˚C for 10 min and then at room temperature for 2 h, after which the mixture was quenched at 0 ˚C with 3.6 N H_2SO_4 (40 ml). The aqueous layer was extracted with Et_2O (3 × 30 mL), and the combined organic layers were washed with H_2O (30 mL) and brine (30 mL) then dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was purified by silica gel column chromatography (eluent: EtOAc/*n*-hexane 95/5 to 90/10) provided the title compound (1.95 g, 81% yield, >99:1 er) as a pale yellow oil.

Data consistent with literature values.(^{1}H NMR 200 MHz, $CDCl_3$) δ 0.08 (s, 9 H), 1.78-1.94 (m, 2 H), 2.59-2.87 (m, 2 H), 4.13 (qd, J_1 = 6.0, J_2 = 1.0 Hz, 1 H), 5.87 (dd, J_1 = 18.8, J_2 = 1.0 Hz, 1 H), 6.08 (dd, J_1 = 18.8, J_2 = 5.0 Hz, 1 H), 7.14-7.35 (m, 5 H); (^{13}C NMR 62.5 MHz, $CDCl_3$) δ -0.9, 32.2, 38.9, 74.3 , 126.3, 128.9, 129.0, 130.0, 142.4, 148.74.

Data consistent with literature values.[7]

The enantiomeric purity of (1*S*,2*E*)-5-phenyl-1-(trimethylsilyl)pent-1-en-3-ol was determined by HPLC analysis: CHIRACEL® OJ-H column, 4.6 mm x 250 mm, *n*-hexane/*i*-PrOH = 97:3, 0.3 min/mL, 25 ˚C, UV detector (220 nm), t_R (minor) = 20.6 min and t_R (major) = 22.7 min. $[\alpha]_D^{20}$ = +9.3 (c = 1.0, $CHCl_3$).





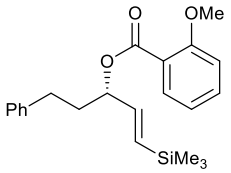
rac-**2-78**

Time (min)	Area	%area
21.528	26221517	49.08
23.701	27209317	50.92

(*S*,*E*)-**2-78**

Time (min)	Area	%area
20.577	40282	0.44
22.678	9033395	99.56

(*S*,*E*)-[5-Phenyl-1-(trimethylsilyl)pent-1-en-3-yl]-2'-methoxybenzoate 2-79

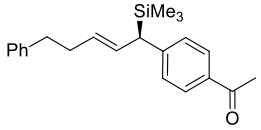


(*S*,*E*)-5-phenyl-1-(trimethylsilyl)pent-1-en-3-ol (1.29 g, 5.50 mmol) was dissolved in CH_2Cl_2 (12 mL) and pyridine (1.31 mL, 16.5 mmol), *o*-methoxybenzoyl chloride (1.63 mL, 11.0 mmol) and DMAP (670 μg, 550 μmol) were sequentially added at 0 ˚C. The mixture was allowed to warm to room temperature and stirred for 4 h before being quenched with H_2O (20 mL). The organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2 (2x20 mL). The combined organic phases were washed with H_2O (20 mL) and brine (20 mL), then dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude residue was purified by silica gel column chromatography (eluent: EtOAc/*n*-hexane = 10/90) to provide the title compound (1.78 g, 88% yield, >99:1 er) as a colourless oil. Data consistent with literature values.[5]

(^{1}H NMR 200 MHz, $CDCl_3$) δ 0.08 (s, 9 H), 1.98 - 2.18 (m, 2H), 2.62 - 2.89 (m, 2 H), 3.93 (s, 3 H), 5.56 (td, J_1 = 6.3, J_1 = 4.3 Hz, 1 H), 5.97 (d, J_1 = 18.8 Hz, 1 H), 6.09 (dd, J_1 =18.8, J_2 = 4.3 Hz, 1 H), 6.95 - 7.08 (m, 2 H), 7.12 - 7.37 (m, 5 H), 7.43 - 7.57 (m, 1 H), 7.82 (dd, J_1 = 7.9, J_2 = 1.8 Hz, 1 H).

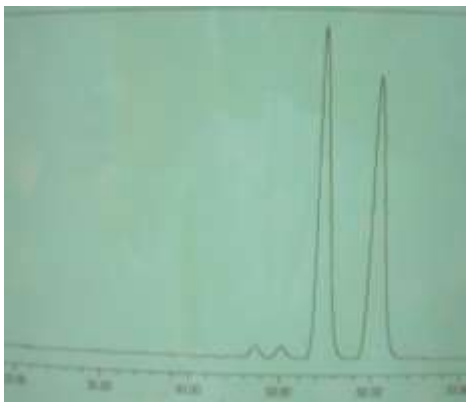
The enantiomeric purity of (*S*,*E*)-**2-79** was determined by HPLC analysis: CHIRACEL® OD-H column, 4.6 mm x 250 mm, *n*-hexane/*i*-PrOH = 99:1, 0.4 min/mL, 25 ˚C, UV detector (210 nm), t_R (minor) = 18.7 min and t_R (major) = 20.2 min). $[\alpha]_D^{20}$ = +15.2 (c = 1.0, $CHCl_3$).

(*R*,*E*)-4'-[5-phenyl-1-(trimethylsilyl)pent-2-en-1yl]acetophenone 2-80

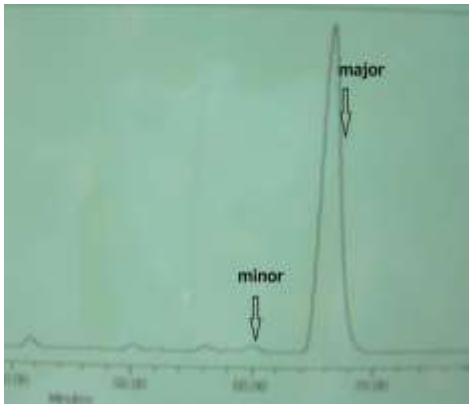


The title compound was prepared according to the General Procedure D using $Pd(OAc)_2$ (67 mg, 0.30 mmol), 1,10-phenanthroline (65 mg, 0.36 mmol), $AgSbF_6$ (0.10 g, 0.30 mmol), 1,4-benzoquinone (65 mg, 0.60 mmol), 4-acethylphenylboronic acid (0.74 g, 4.5 mmol), (*S*,*E*)-5-phenyl-1-(trimethylsilyl)pent-1-en-3-yl 2-methoxybenzoate (1.1 g, 3.0 mmol) and 1,2-dichloroethane (20 mL). After 24 h, the reaction mixture was subjected to the workup described in the General Procedure D and purified by silica gel column chromatography (eluent: EtOAc/*n*-hexane 1/10) to afford the title compound (0.50 g, 50% yield) as a colourless oil. Characterization data was in accordance with literature values.[5]

$[\alpha]_D^{20}$ = -24.2 (c = 0.5, MeOH). The enantiomeric purity of (1*R*,2*E*)-**2-80** was determined by HPLC analysis (CHIRACEL® OD-H column, 4.6 mm x 250 mm, *n*-hexane/ *i*-PrOH = 99:1, 0.5 min/mL, 25 ˚C, UV detector (254 nm)), t_R (minor) = 54.2 min and t_R (major) = 65.6 min.



rac-2-80

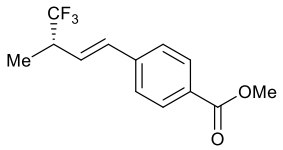


(*R*)-2-80

Time (min)	Area	%area
54.242	10844960	49.86
60.129	10908247	50.14

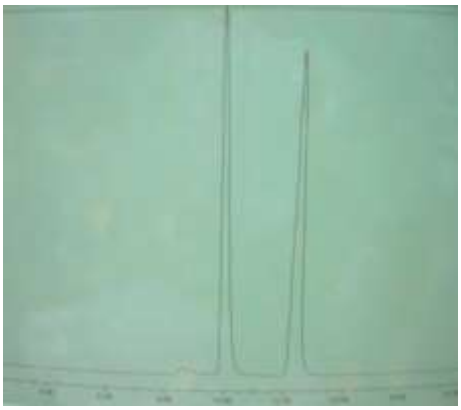
Time (min)	Area	%area
-	-	-
65.614	13472478	>99

(+)-(*E*)-Methyl 4-(4,4,4-trifluoro-3-methyl-but-1-en-1yl)benzozate 2-84

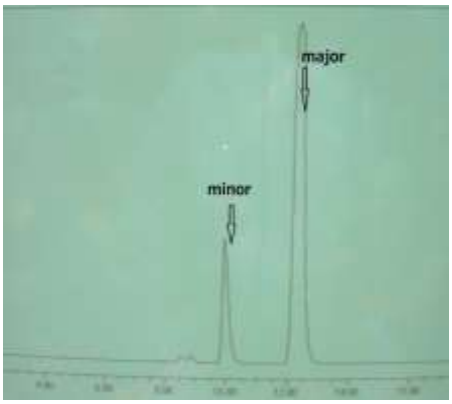


The title compound was prepared following General Procedure A using (*R*,*E*)-Methyl 4-[1-(trimethylsilyl)but-2-en-1-yl]benzoate **2-72** (66 mg, 0.25 mmol, >99:1 er), Togni reagent II (0.14 mg, 0.45 mmol), $Ru(bpy)_3Cl_2 \bullet 6H_2O$ (9.0 mg, 0.013 mmol) and MeOH (0.50 mL). The isomeric ratio was determined by ^{19}F NMR analysis of the crude mixture (*E/Z* = 7.2 : 1). Purification by silica gel column chromatography (eluent: EtOAc/*n*-hexane 99.5/0.5 to 98/2) provided the title compound (27 mg, 41% yield, 87:13 er) as a colourless oil.

(^1H NMR 400 MHz, $CDCl_3$) δ, 1.35 (d, *J* = 7.1 Hz, 3H), 2.92-3.06 (m, 1H), 3.92 (s, 3H), 6.24 (dd, J_1 = 8.0 Hz, J_2 =15.7 Hz, 1H), 6.62 (d, *J* = 15.7 Hz, 1H), 7.45 (d, *J* = 8.3 Hz, 2H), 8.00 (d, *J* = 8.3 Hz, 2H); (^{13}C NMR 125 MHz, $CDCl_3$) δ 13.5 (q, *J* = 1.9 Hz), 41.9 (q, *J* = 27.5 Hz), 52.1, 126.3, 126.8 (q, *J* = 2.9 Hz), 126.9 (q, *J* = 277.7 Hz), 129.4, 130.0, 133.2, 140.7, 166.8; (^{19}F NMR 236 MHz, $CDCl_3$) δ -72.8 (d, *J* = 8.7 Hz, 3F); IR (neat) ν 2992, 2954, 1722, 1281, 1258, 1177, 1127 cm^{-1}; HRMS (CI+) *m/z* Calcd for $C_{13}H_{14}O_2F_3$ $[M+H]^+$ 259.0946, found 259.0951; $[\alpha]_D^{20}$ = +13.0 (c = 1.0, $CHCl_3$). The enantiomeric purity of the title compound was determined by HPLC analysis (CHIRACEL® OD-H column, 4.6 mm x 250 mm, *n*-hexane/*i*-PrOH = 97:3, 0.5 min/mL, 25 ˚C, UV detector (270 nm)), t_R (minor) = 10.0 min and t_R (major) = 12.3 min.



rac-(*E*)-2-84

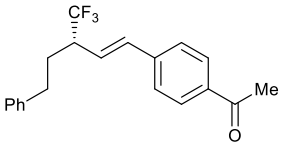


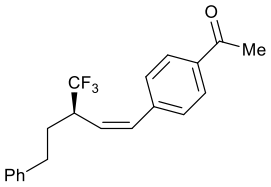
(+)-(*E*)-2-84

Time (min)	Area	%area
10.016	39889062	49.06
12.287	41411488	50.94

Time (min)	Area	%area
10.001	7588683	14.04
12.264	46470119	85.96

4'-[5-phenyl-3-(trifluoromethyl)pent-1-en-1-yl)]-acetophenone 2-86



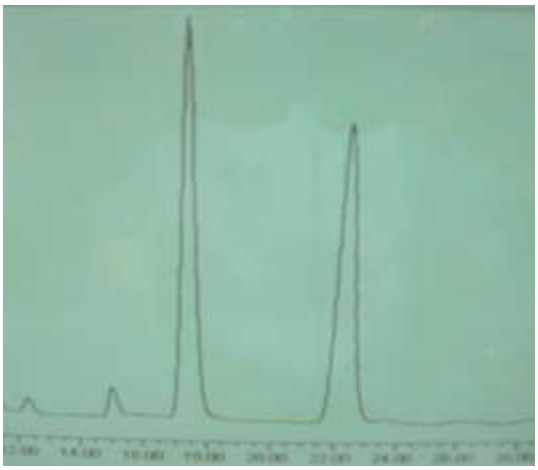


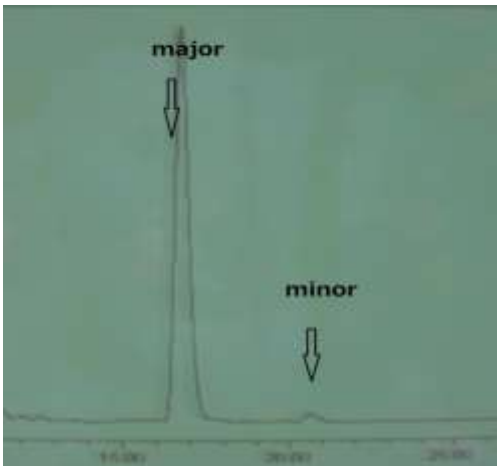
The title compound was prepared following General Procedure A using (*R*,*E*)-4'-[5-phenyl-1-(trimethylsilyl)pent-2-en-1yl]acetophenone (84 mg, 0.25 mmol, >99:1 er), Togni reagent II (0.14 g, 0.45 mmol), $Ru(bpy)_3Cl_2•6H_2O$ (9.0 mg, 0.013 mmol) and MeOH (0.50 mL). The isomeric ratio was determined by ^{19}F NMR analysis of the crude mixture (*E*/*Z* = 3.2 : 1). Purification by silica gel column chromatography (eluent: EtOAc/*n*-hexane 97/3) enabled the isolation of the *Z*-isomer (14 mg, 17% yield, 98:2 er) as a colourless oil and the *E*-isomer (35 mg, 42% yield, 88:12 er) as a colourless oil, respectively.

(+)-(*Z*)-4'-[5-phenyl-3-(trifluoromethyl)pent-1-en-1-yl)]-acetophenone 2-86

(^1H NMR 500 MHz, $CDCl_3$) δ 1.81-1.89 (m, 1H), 2.11-2.18 (m, 1H), 2.43 (dt, J_1 = 7.9 Hz, J_2 = 16.7 Hz, 1H), 2.68 (s, 3H), 2.74 (dd, J_1= 5.4 Hz, J_2 = 9.2 Hz, 1H), 3.28-3.37 (m, 1H), 6.71

(t, *J* = 11.7 Hz, 1H), 6.94 (d, *J* = 11.7 Hz, 1H), 7.01-7.03 (m, 2H), 7.19-7.21 (m, 3H), 7.33 (d, *J* = 8.5 Hz, 2H), 7.97 (d, *J* = 8.5 Hz, 2H); (^{13}C NMR 125 MHz, $CDCl_3$) δ 26.6, 30.2 (q, *J* = 1.9 Hz), 32.2, 44.6 (q, *J* = 26.5 Hz), 126.1, 126.9 (q, *J* = 277.7 Hz), 127.0 (q, *J* = 2.8 Hz), 128.3, 128.4, 128.6, 128.6, 134.4, 136.0, 140.3, 141.0, 197.6; (^{19}F NMR 236 MHz, $CDCl_3$) δ -72.87 (d, *J* = 8.7 Hz, 3F); IR (neat) ν 1683, 1604, 1455, 1358, 1252, 1155, 1113, 956, 855, 747, 700 cm^{-1}; HRMS (EI/FI) *m/z* Calcd for $C_{20}H_{19}F_3O$ $[M]^+$ 333.1388, found 333.1382; $[\alpha]_D^{20}$ = +10.0 (c = 0.25, MeOH). The enantiomeric purity was determined by HPLC analysis (CHIRACEL® OD-H column, 4.6 mm x 250 mm, *n*-hexane/*i*-PrOH = 97:3, 0.5 min/mL, 25 ˚C, UV detector (270 nm)), t_R (major) = 16.7 min and t_R (minor) = 20.6 min.





rac-(*Z*)-2-86

Time (min)	Area	%area
17.410	9450711	50.62
22.155	9218568	49.38

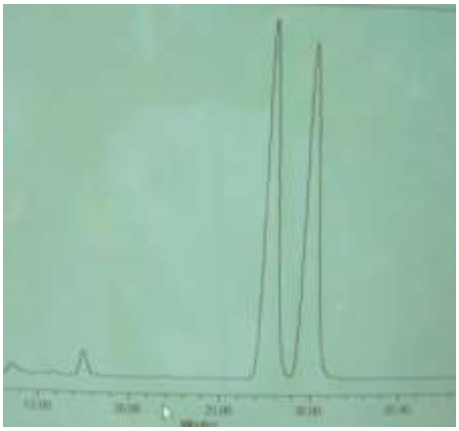
(+)-(*Z*)-2-86

Time (min)	Area	%area
16.669	65400952	98.10
20.606	1267420	1.90

(+)-(*E*)-4'-[5-phenyl-3-(trifluoromethyl)pent-1-en-1-yl)]-acetophenone 2-86

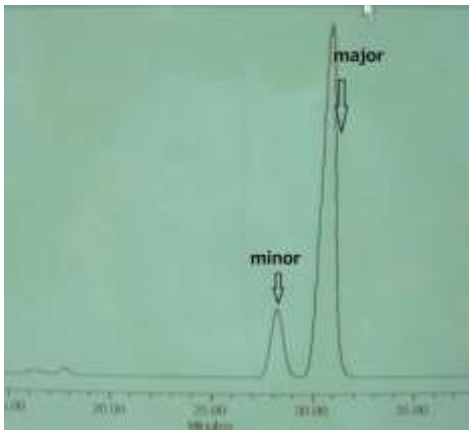
(^{1}H NMR 500 MHz, $CDCl_3$) δ 1.90-1.97 (m, 1H), 2.17-2.24 (m, 1H), 2.57-2.64 (m, 1H), 2.62 (s, 3H), 2.80 (dt, J_1 = 5.1 Hz, J_2 = 9.5 Hz, 1H), 2.68 (dqd, J_1 = 3.5 Hz, J_2 = 7.3 Hz, J_3 = 18.6

Hz, 1H), 6.15 (dd, J_1 = 9.5 Hz, J_2 = 16.0 Hz, 1H), 6.61 (d, J = 16.0 Hz, 1H), 7.18 (d, J = 7.6 Hz, 2H), 7.23 (t, J = 7.3 Hz, 1H), 7.31 (t, J = 7.3 Hz, 2H), 7.49 (d, J = 8.2 Hz, 2H), 7.95 (d, J = 8.2 Hz, 2H); (^{13}C NMR 125 MHz, $CDCl_3$) δ 26.6, 29.2 (q, J = 1.9 Hz), 32.4, 47.2 (q, J = 26.5 Hz), 125.6 (q, J = 1.9 Hz), 126.3, 126.6, 126.7 (q, J = 277.7 Hz), 128.4, 128.6, 128.8, 135.3, 136.5, 140.4, 140.6, 197.5; (^{19}F NMR 236 MHz, $CDCl_3$) δ -70.17 (d, J = 8.5 Hz, 3F); IR (neat) ν 1677, 1601, 1360, 1261, 1160, 1113, 1072, 972, 957, 902, 859, 770, 689, 676 cm^{-1}; HRMS (EI/FI) *m/z* Calcd for $C_{20}H_{19}F_3O$ $[M]^+$ 332.1388, found 332.1376; $[\alpha]_D^{20}$ = +105.2 (c = 0.25, MeOH). The enantiomeric purity was determined by HPLC analysis (CHIRACEL® OD-H column, 4.6 mm x 250 mm, *n*-hexane/*i*-PrOH = 97/3, 0.5 min/mL, 25 ˚C, UV detector (270 nm)), t_R (minor) = 28.1 min and t_R (major) = 30.4 min.



rac-(*E*)-2-86

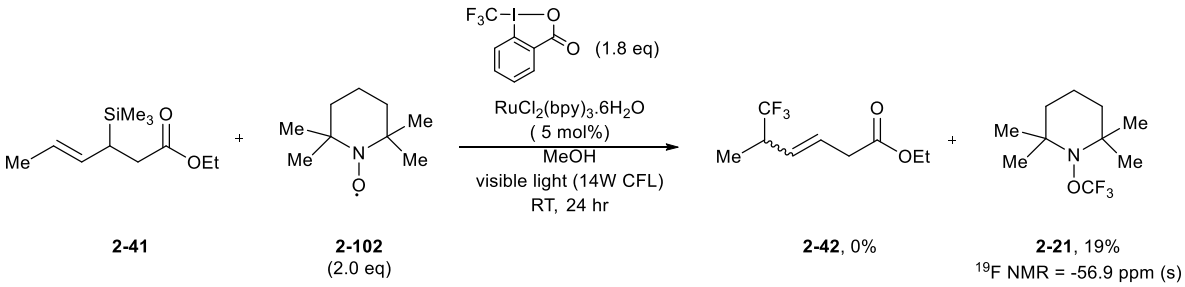
Time (min)	Area	%area
27.604	9450711	50.62
29.693	9218568	49.38



(+)-(*E*)-2-86

Time (min)	Area	%area
28.146	1698300	14.96
30.430	9654929	85.04

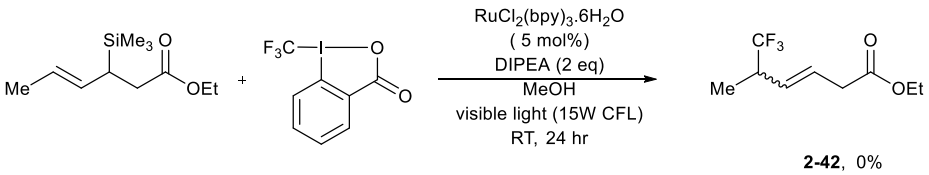
Control reaction in the presence of TEMPO



2-41 | **2-102** (2.0 eq) | **2-42**, 0% | **2-21**, 19% ^{19}F NMR = -56.9 ppm (s)

Ethyl (*E*)-3-(trimethylsilyl)hex-4-enoate (32 mg, 0.15 mmol), 2,2,6,6-tetramethyl-1-piperidinyloxy (47 mg, 0.30 mmol), $Ru(bpy)_3Cl_2$•$6H_2O$ (6.5 mg, 8.0 μmol, 5.0 mol%), Togni reagent II (57 mg, 0.18 mmol, 1.8 eq) and MeOH (0.30 mL) were placed in a vial which was exposed to a 14 W fluorescent light bulb at room temperature while stirring for 24 h. The mixture was quenched with sat. $NaHCO_3$ solution (10 mL) and extracted with Et_2O (2 x 10 mL). The pooled organic phases were washed with H_2O (10 mL) and brine (10 mL), dried over $MgSO_4$ and concentrated *in vacuo* after which $PhCF_3$ (12 μL, 0.10 mmol) was added as a reference. Analysis of the crude reaction mixture was analysed by ^{19}F NMR showed formation of a singlet at -56.9 ppm as the only fluorinated product, which was identified as the TEMPO-CF_3 adduct.[8]

Reaction with DIPEA as additive

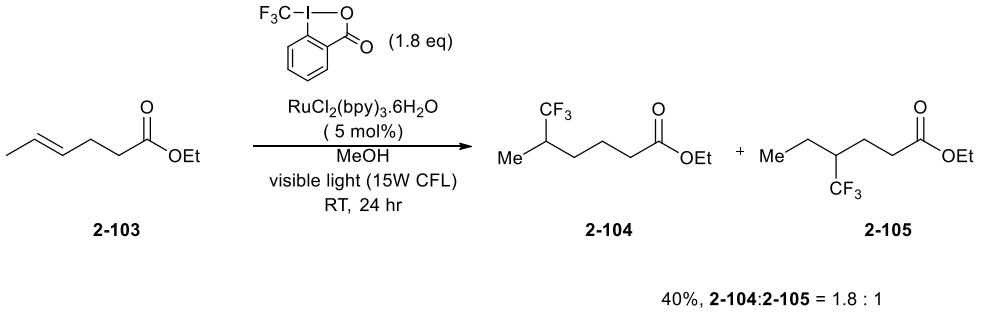


2-42, 0%

Ethyl (*E*)-3-(trimethylsilyl)hex-4-enoate (32 mg, 0.15 mmol), DIPEA (52 μL, 0.30 mmol), $Ru(bpy)_3Cl_2$•$6H_2O$ (6 mg, 0.008 mmol, 5.0 mol%), Togni reagent II (57 mg, 0.18 mmol, 1.8 eq) and MeOH (0.30 mL) were placed in a vial which was exposed to a 14 W fluorescent light bulb at room temperature while stirring for 48 h. The mixture was quenched with sat.

$NaHCO_3$ solution (10 mL) and extracted with Et_2O (2 x 10 mL). The pooled organic phases were washed with H_2O (10 mL) and brine (10 mL), dried over $MgSO_4$ and concentrated *in vacuo* after which $PhCF_3$ (12 μL, 0.15 mmol) was added as a reference. Analysis of the crude reaction mixture was analysed by ^{19}F NMR showed no formation of ethyl 6,6,6-trifluoro-5-methylhex-3-enoate **2-42**.

Trifluoromethylation of (*E*)-ethyl hex-4-enoate



(*E*)-ethyl hex-4-enoate (32 mg, 0.25 mmol), $Ru(bpy)_3Cl_2•6H_2O$ (9.0 mg, 0.013 mmol, 5.0 mol%), Togni reagent II (0.14 mg, 0.43 mmol, 1.8 eq) and MeOH (0.50 mL) were placed in a vial which was exposed to a 14 W fluorescent light bulb at room temperature while stirring for 24 h. The mixture was quenched with sat. $NaHCO_3$ solution (10 mL) and extracted with Et_2O (2 x 10 mL). The pooled organic phases were washed with H_2O (10 mL) and brine (10 mL), dried over $MgSO_4$ and concentrated *in vacuo* after which $PhCF_3$ (12 μL, 0.15 mmol) was added as a reference. Analysis of the crude reaction mixture by ^{19}F NMR, ^{1}H NMR and GC/MS showed formation of a mixture of ethyl 6,6,6-trifluoro-5-methylhexanoate **2-104** and ethyl 4-(trifluoromethyl)hexanoate **2-105** in 40% yield (ratio **2-104**:**2-105** 1.8:1).

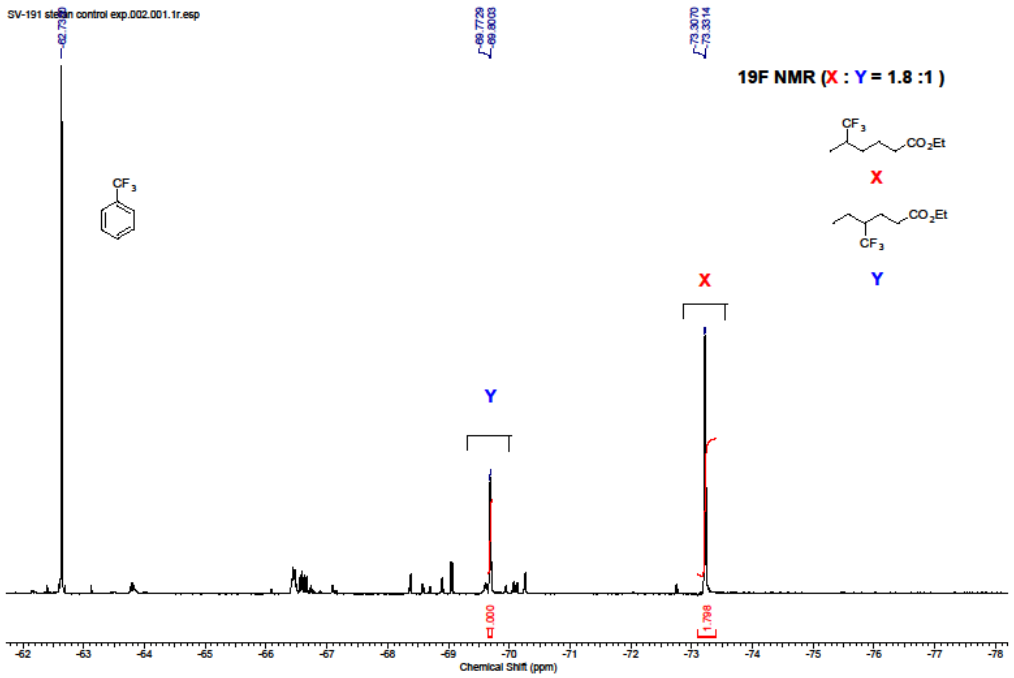
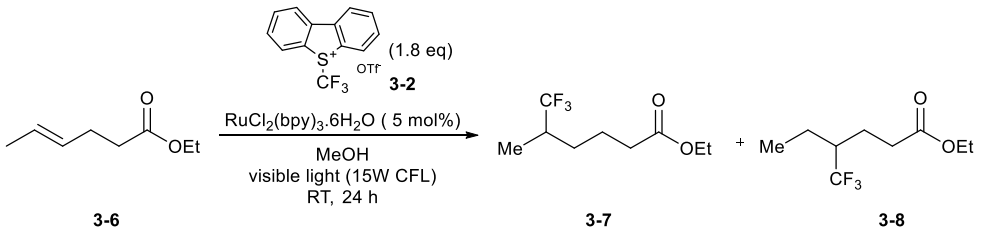


Figure 1. ^{19}F NMR spectra of the crude mixture (377 MHz, $CDCl_3$, ratio **X**:**Y** = 1.8:1)

Experimental Data for Chapter 3

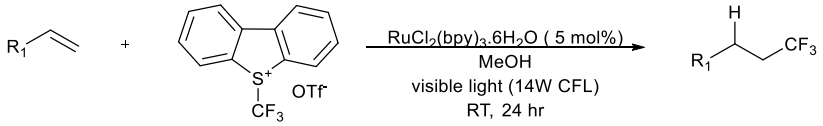
Trifluoromethylation of (*E*)-ethyl hex-4-enoate



(*E*)-ethyl hex-4-enoate (35 mg, 0.25 mmol), $Ru(bpy)_3Cl_2 \bullet 6H_2O$ (9.0 mg, 0.013 mmol, 5.0 mol%), Umemoto reagent (0.11 mg, 0.27 mmol, 1.8 eq) and MeOH (0.50 mL) were placed in a vial which was exposed to a 14 W fluorescent light bulb at room temperature while stirring for 24 h. The mixture was quenched with sat. $NaHCO_3$ solution (10 mL) and extracted with Et_2O (2 x 10 mL). The pooled organic phases were washed with H_2O (10 mL) and brine (10 mL), dried over $MgSO_4$ and concentrated *in vacuo* after which $PhCF_3$ (12 μL, 0.15 mmol)

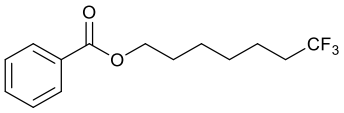
was added as a reference. Analysis of the crude reaction mixture by ^{19}F NMR, ^{1}H NMR and GC/MS showed formation of a mixture of ethyl 6,6,6-trifluoro-5-methylhexanoate **3-7** and ethyl 4-(trifluoromethyl)hexanoate **3-8** in 28% yield (**3-7**:**3-8** = 2.2:1).

General Procedure A



The alkene (0.15 mmol), $Ru(bpy)_3Cl_2 \bullet 6H_2O$ (7.5 μmol), Umemoto reagent (0.18 mmol) and MeOH (0.30 mL) were placed in a vial which was equipped with a magnetic stir bar. The vial was exposed to a 14 W fluorescent light bulb at room temperature while stirring for 24 hrs. . The mixture was quenched with sat. $NaHCO_3$ solution (10 mL) and extracted with Et_2O (2 x 10 mL). The pooled organic phases were washed with H_2O (10 mL) and brine (10 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude mixture was purified by silica gel column chromatography.

7,7,7-trifluoroheptyl benzoate 3-11

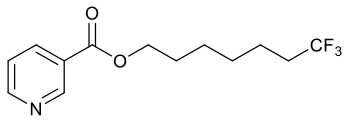


The title compound was prepared following General procedure A using hex-5-en-1-yl benzoate (31 mg, 0.15 mmol), $Ru(bpy)_3Cl_2 \bullet 6H_2O$ (6 mg, 8.0 μmol), Umemoto reagent (72 mg, 0.18 mmol) and MeOH (0.30 mL). The crude product was purified by silica gel column chromatography (eluent: Et_2O/*n*-hexane = 1/20) to provide the title compound (19 mg, yield 78% yield) as a colourless oil.

(^{1}H NMR 500 MHz, $CDCl_3$) δ 1.44-1.50 (m, 4H), 1.57-1.62 (m, 2H), 1.80 (quint, J = 6.6 Hz, 2H), 2.04-2.14 (m, 2H), 4.34 (t, J = 6.3 Hz, 2H), 7.45 (t, J = 7.9 Hz, 2H), 7.51 (tt, J_1 = 1.5 Hz,

J_2 = 7.6 Hz, 1H), 8.05 (dd, J_1 = 1.5 Hz, J_2 = 8.6 Hz, 2H); (^{13}C NMR 125 MHz, $CDCl_3$) δ 21.8 (q, J = 2.9 Hz), 25.7, 28.4, 28.5, 33.6 (q, J = 28.4 Hz), 64.8, 127.2 (q, J = 274.8 Hz), 128.3, 129.5, 130.4, 132.9, 166.6; (^{19}F NMR 377 MHz, $CDCl_3$) δ -66.34 (t, J = 11.5 Hz, 3F); IR (neat) ν 2945, 1718, 1272, 1254, 1138, 1134, 711 cm^{-1}; HRMS (ESI) *m/z* Calcd for $C_{14}H_{17}F_3NaO_2$ $[M+Na]^+$ 297.1072, found 297.1073.

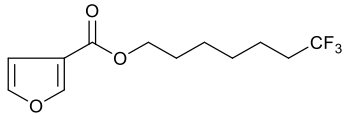
7,7,7-Trifluoroheptyl nicotinate 3-25



The title compound was prepared following General procedure A using hex-5-en-1-yl nicotinate (51 mg, 0.25 mmol), $Ru(bpy)_3Cl_2$•$6H_2O$ (9.0 mg, 0.013 mmol), Umemoto reagent (0.12 g, 0.30 mmol) and MeOH (0.50 mL). The crude product was purified by silica gel column chromatography (eluent: EtOAc/*n*-hexane = 15/85 to 20/80 to 30/70) to provide the title compound (19 mg, 78%) as a colourless oil.

(^{1}H NMR 500 MHz, $CDCl_3$) δ 1.46-1.59 (m, 4 H), 1.61-1.71 (m, 2 H), 1.86 (quin, J = 7.0 Hz, 2 H) 2.07-2.22 (m, 2 H), 4.42 (t, J = 6.6 Hz, 2 H), 7.50 (br. dd, J_1 = 7.9, J_2 = 4.7 Hz, 1 H), 8.40 (dt, J_1 = 7.9, J_2 = 1.9 Hz, 1 H), 8.85 (d, J_1 =3.4 Hz, 1 H), 9.29 (br. s, 1H); (^{13}C NMR 125 MHz, $CDCl_3$) δ 22.2 (q, J = 2.8 Hz), 26.1, 28.8, 28.9, 34.1 (q, J = 28.7 Hz), 65.8, 123.9, 126.9, 127.6 (q, J = 276.5 Hz), 137.8, 151.0, 153.5, 165.6; (^{19}F NMR 377 MHz, $CDCl_3$) δ -66.34 (t, J = 12 Hz, 3F); IR (neat) ν 2944, 1723, 1591, 1282, 1254, 1133, 742 ; HRMS(TOF-CI) *m/z* Calcd. for $C_{13}H_{17}F_3NO_2$ $[M+H]^+$ 276.1211 found 276.1205.

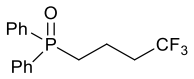
7,7,7-Trifluoroheptyl furan-3-carboxylate 3-26



The title compound was prepared following General procedure A using hex-5-en-1-yl furan-3-carboxylate (49 mg, 0.25 mmol), $Ru(bpy)_3Cl_2 \cdot 6H_2O$ (9.0 mg, 0.013 mmol), Umemoto reagent (0.12 mg, 0.30 mmol) and MeOH (0.50 mL). The crude product was purified by silica gel column chromatography (eluent: EtOAc/30-40 petroleum ether = 10/90) to provide the title compound (23 mg, 33%) as a colourless oil.

(^{1}H NMR 500 MHz, $CDCl_3$) δ 1.40-1.50 (m, 4 H), 1.55-1.63 (m, 2 H), 1.77 (quin, J = 6.9 Hz, 2 H), 2.03-2.14 (m, 2 H), 4.31 (t, J = 6.6 Hz, 2 H), 6.52 (dd, J_1 = 3.5, J_2 = 1.9 Hz, 1 H), 7.18 (dd, J_1 = 3.5, J_2 = 0.9 Hz, 1 H), 7.58 (dd, J_1 =1.7, J_2 = 0.8 Hz, 1 H); (^{13}C NMR 125 MHz, $CDCl_3$) δ 20.8 (q, J = 2.7 Hz), 24.6, 27.3, 27.4, 32.6 (q, J = 27 Hz), 63.7, 100.8, 116.8, 126.2 (q, J = 277 Hz), 143.8, 145.2, 157.8; (^{19}F NMR 377 MHz, $CDCl_3$) δ -66.37 (t, J = 12 Hz, 3F); IR (neat) ν 2942, 1727, 1474, 1296, 1255, 1180, 1120, 764; HRMS(TOF-CI) *m/z* Calcd. for $C_{12}H_{16}F_3O_3$ $[M+H]^+$ 265.1052 found 265.1056.

Diphenyl(4,4,4-trifluorobutyl)phosphine oxide 3-31

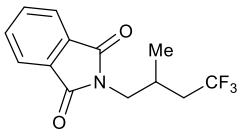


The title compound was prepared following General Procedure A using allyldiphenylphosphine oxide (61 mg, 0.25 mmol), $Ru(bpy)_3Cl_2.6H_2O$ (9.0 mg, 0.013 mmol), Umemoto reagent (0.12 mg, 0.30 mmol) and MeOH (0.50 mL). The crude product was purified by silica gel column chromatography (eluent: EtOAc/*n*-hexane 40/60 to 70/30) to provide the title compound (15 mg, 19% yield) as a beige colored solid containing <5% of impurities.

(^{1}H NMR 400 MHz, $CDCl_3$) δ 1.85-1.99 (m, 2H), 2.17-2.40 (m, 4H), 7.45-7.59 (m, 6H), 7.70-7.78 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.8, 28.7 (d, J = 71.5 Hz), 34.3 (qd, J_1 = 28.6 Hz, J_2 = 13.3 Hz), 126.7 (q, J = 276.6 Hz), 128.8 (d, J = 11.4 Hz), 130.9 (d, J = 9.5 Hz), 132.0 (d, J = 1.9 Hz), 132.3 (d, J = 99.2 Hz); ^{19}F NMR (377 MHz, $CDCl_3$) δ -66.40 (t, J = 10.8 Hz,

3F); IR (neat) ν 3429, 3058, 2950, 1438, 1285, 1177, 1121, 746, 719, 695; HRMS(ESI-TOF) *m/z* Calcd. for $C_{16}H_{17}F_3OP$ $[M-H]^-$ 313.0964 found 313.0952. M.p. 79-82 °C.

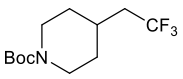
2-(4,4,4-Trifluoro-2-methylbutyl)isoindoline-1,3-dione 3-41



The title compound was prepared following General Procedure A using 2-(2-methylallyl)isoindoline-1,3-dione (50 mg, 0.25 mmol), $Ru(bpy)_3Cl_2.6H_2O$ (9.0 mg, 0.013 mmol), Umemoto reagent (0.12 mg, 0.30 mmol) and MeOH (0.50 mL). The crude product was purified by silica gel column chromatography (eluent: EtOAc/*n*-hexane 3:97 to 5:95) to provide the title compound (31 mg, 46% yield) as a colourless oil.

(^{1}H NMR 400 MHz, $CDCl_3$) δ 1.08 (d, J = 6.9 Hz, 3H), 1.92-2.08 (m, 1H), 2.14-2.30 (m, 1H), 2.33-2.47 (m, 1H), 3.58 (dd, J_1 = 13.7, J_2 = 7.1 Hz, 1 H), 3.65 (dd, J_1 = 13.7, J_2 = 7.4 Hz, 1 H), 7.71-7.78 (m, 2H), 7.83-7.90 (m, 2H); (^{13}C NMR (125 MHz, $CDCl_3$) δ 17.6, 27.8 (q, J = 2.7 Hz), 38.0 (q, J = 27.7 Hz), 43.4, 123.4, 126.7 (q, J = 276.6 Hz), 131.8, 134.1, 168.5; (^{19}F NMR 377 MHz, $CDCl_3$) δ -63.37 (t, J = 11.4 Hz, 3F); IR (neat) ν 2972, 2941, 1712, 1402, 1389, 1254, 724, 714; HRMS(EI/FI) *m/z* Calcd. for $C_{13}H_{12}F_3NO_2$ $[M]^+$ 271.0820 found 271.0828; mp : 54-57^{o}C.

***tert*-Butyl 4-(2,2,2-trifluoroethyl)piperidine-1-carboxylate 3-42**



The title compound was prepared following General Procedure A using *tert*-butyl 4-methylenepiperidine-1-carboxylate (42 mg, 0.25 mmol), $Ru(bpy)_3Cl_2.6H_2O$ (9.0 mg, 0.013 mmol), Umemoto reagent (0.12 mg, 0.30 mmol), pyridine (15 μL, 0.30 mmol) and MeOH

(0.50 mL). The crude product was purified by silica gel column chromatography (eluent: EtOAc/*n*-hexane 20/80) to provide the title compound (46 mg, 64% yield) as a pale yellow solid.

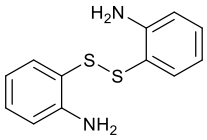
(^{1}H NMR 400 MHz, $CDCl_3$) δ 1.15-1.28 (m, 2H), 1.46 (s, 9H), 1.72-1.90 (m, 3H), 2.04 (qd, J_1 = 11.3 Hz, J_2 = 6.6 Hz, 2H), 2.72 (td, J_1 = 13.4 Hz, J_2 = 2.4 Hz, 2H), 4.02-4.17 (m, 2H); (^{13}C NMR 125 MHz, $CDCl_3$) δ 28.4, 30.5 (q, J = 2.3 Hz), 31.9, 40.0 (q, J = 26.7 Hz), 43.5 (br. s.), 79.5, 126.8 (q, J = 277.5 Hz), 154.7; (^{19}F NMR 377 MHz, $CDCl_3$) δ -63.27 (t, J = 10.9 Hz, 3F); IR (neat) ν 2977, 2931, 2856, 1690, 1422, 1234, 1147, 1051; HRMS (ESI-TOF) *m/z* Calcd. for $C_{12}H_{20}F_3NNaO_2$ [M+Na] 290.1338 found 290.1340; m.p. 30-32 ^{o}C.

Experimental Data for Chapter 4

General Procedure A[9]

A mixture of thiophenol (20 mmol) and DMSO (10 mmol) was stirred at room temperature for 24 hours and reaction mixture was evaporated *in vacuo* to remove DMS. EtOH (5 mL) was added and the resulting mixture was stirred at 0 to 5 °C for 30 min. The suspension was filtered to give the crude product as a solid precipitate that was used in the next step without further purification.

2,2'-Disulfanediyldianiline

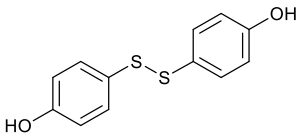


The title compound was prepared following General Procedure A using 2-aminothiophenol (2.10 mL, 20.0 mmol) and DMSO (700 μL, 10.0 mmol). The title compound (1.82 g, 73% yield) was isolated as a bright yellow solid.

(^{1}H NMR, 400 MHz, DMSO-d_6) δ = 5.47 (br. s, 4H), 6.44 (td, J = 7.6, 1.4 Hz, 2H), 6.75 (dd, J = 8.3, 2.2 Hz, 2H), 7.02 (dd, J = 7.7, 1.6 Hz, 2H), 7.13-7.06 (m, 2H); (^{13}C NMR, 101 MHz,

DMSO-d_6) δ = 115.3, 116.5, 117.0, 131.6, 135.9, 150.2; Mp. 87-89 °C. Data consistent with literature values.[10]

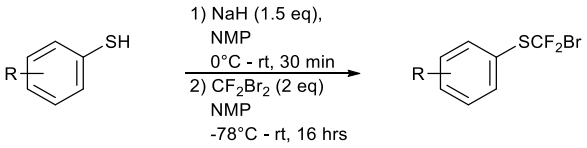
4,4'-Disulfanediyldiphenol



The title compound was prepared following General Procedure A using 4-mercaptophenol (2.59 g, 20.0 mmol) and DMSO (700 μL, 10.0 mmol). The title compound (1.04 g, 42% yield) was isolated as a white solid.

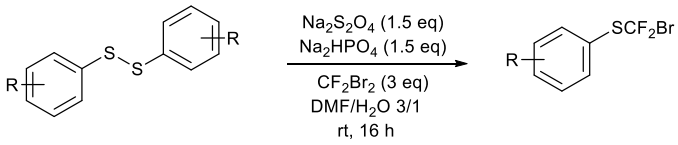
(^{1}H NMR, 200 MHz, DMSO-d_6) δ = 6.72-6.84 (m, 4H), 7.23-7.36 (m, 4H), 9.86 (br. s, 2H); Mp. 121-124 °C. Data consistent with literature values.[11]

General Procedure B



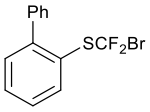
A suspension of NaH (60% in mineral oil, 0.30 mg, 7.5 mmol) in degassed NMP (5 mL) was cooled to 0 °C and the appropriate thiophenol (5.0 mmol) was added in one portion. The mixture was stirred at 0 °C for 10 min then warmed up to room temperature and stirred for another 30 min. The reaction mixture was then cooled to -78 °C and CF_2Br_2 (0.55 mL, 6.0 mmol) was added in one portion after which the cooling bath was removed and stirring was continued at room temperature for 18 hours. H_2O (30 mL) was added and the mixture was extracted with MTBE (3 x 25 mL). The organic layers were washed with H_2O (30 mL), brine (30 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography.

General Procedure C



A solution of $Na_2S_2O_4$ (85% pure, 1.54 g, 7.50 mmol) and Na_2HPO_4 (1.06 g, 7.50 mmol) in H_2O (20 mL) was added in one portion to a mixture of the appropriate arenedisulfide (5.00 mmol) in a mixture of DMF (75 mL) and H_2O (5 mL) at 0 °C. CF_2Br_2 (1.37 mL, 15.0 mmol) was added in one portion and the reaction mixture was stirred at room temperature for 18 hours. The mixture was poured into H_2O (200 mL) and extracted with MTBE (3 x 100 mL). The organic layers were washed with H_2O (100 mL), brine (100 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography.

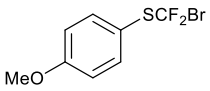
2-{[Bromo(difluoro)methyl]sulfanyl}biphenyl 4-64



The title compound was prepared following General Procedure B using 2-phenylthiophenol (1.10 g, 6.00 mmol), NaH (60% in mineral oil, 360 mg, 9.00 mmol), CF_2Br_2 (1.10 mL, 12.0 mmol) and NMP (6 mL). The crude product was purified by silica gel column chromatography (eluent: *n*-pentane) to provide the title compound (1.27 g, 67% yield) as a white solid.

(^{1}H NMR, 400 MHz, $CDCl_3$) δ = 7.30-7.35 (m, 2H), 7.40-7.48 (m, 5H), 7.52-7.57 (m, 1H), 7.80-7.86 (m, 1H); (^{19}F NMR, 377 MHz, $CDCl_3$) δ = -21.2 (s, 2F). Data consistent with literature values.[12]

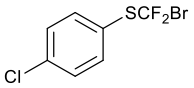
1-{[Bromo(difluoro)methyl]sulfanyl}-4-methoxybenzene 4-68



The title compound was prepared following General Procedure B using 4-methoxythiophenol (0.62 mL, 5.0 mmol), NaH (60% in mineral oil, 0.30 g, 7.5 mmol), CF_2Br_2 (0.90 mL, 10 mmol) and NMP (5 mL). The crude product was purified by silica gel column chromatography (eluent: *n*-pentane) to provide the title compound (0.57 g, 42% yield) as a colourless oil.

(^{1}H NMR, 400 MHz, $CDCl_3$) δ = 3.85 (s, 3H), 6.90-7.00 (m, 2H), 7.55-7.62 (m, 2H); (^{13}C NMR, 101 MHz, $CDCl_3$) δ = 55.5, 114.9, 117.9, 119.8 (t, *J* = 339.3 Hz), 138.4, 162.0; (^{19}F NMR, 377 MHz, $CDCl_3$) δ = -23.0 (s, 2F). Data consistent with literature values.[13]

1-{[Bromo(difluoro)methyl]sulfanyl}-4-chlorobenzene 4-66

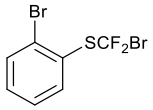


The title compound was prepared following General Procedure B using 4-chlorothiophenol (1.44 g, 10 mmol), NaH (60% in mineral oil, 0.6 g, 15 mmol) and NMP (10 mL). The crude product was purified by vacuum distillation to provide the title compound (0.98 g, 72% yield, 98% pure) as a colourless liquid, with 2% impurity of 4-ClPhSCF$_2$H.

(^{1}H NMR, 400 MHz, $CDCl_3$) δ = 7.40-7.46 (m, 2H), 7.57-7.63 (m, 2H); (^{13}C NMR, 101 MHz, $CDCl_3$) δ = 118.8 (t, *J* = 338.6 Hz), 125.5, 129.8, 137.6, 137.9; (^{19}F NMR, 377 MHz, $CDCl_3$) δ = -22.5 (s, 2F); IR (neat) ν 1573, 1476, 1391, 1089, 1062, 1014, 840, 821, 747; HRMS (EI/FI) *m/z* Calcd for $C_7H_4BrClF_2S$ $[M]^+$ 271.8874 found 271.8882; Bp. 58-59 °C (1 mbar).

Characteristic data for 4-ClPhSCF$_2$H: (^{1}H NMR, 400 MHz, $CDCl_3$) δ = 6.82 (t, *J* = 57.0 Hz, 1H), 7.36-7.40 (m, 2H), 7.51-7.55 (m, 2H); (^{19}F NMR, 377 MHz, $CDCl_3$) δ = -91.7 (d, *J* = 57.0 Hz, 2F).

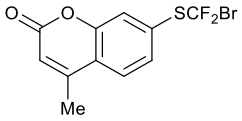
1-Bromo-2-{[bromo(difluoro)methyl]sulfanyl}benzene 4-70



The title compound was prepared following General Procedure B using 2-bromothiophenol (1.20 mL, 10.0 mmol), NaH (60% in mineral oil, 600 mg, 15.0 mmol), CF_2Br_2 (1.83 mL, 20.0 mmol) and NMP (10 mL). The crude product was purified by silica gel column chromatography (eluent: *n*-pentane) to provide the title compound (1.80 g, 57% yield) as a colourless oil.

(^{1}H NMR, 400 MHz, $CDCl_3$) δ = 7.33-7.42 (m, 2H), 7.72-7.76 (m, 1H), 7.77-7.82 (m, 1H); (^{19}F NMR, 377 MHz, $CDCl_3$) δ = -22.0 (s, 2F). Data consistent with literature values.[14]

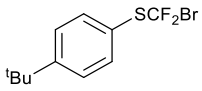
7-{[Bromo(difluoro)methyl]sulfanyl}-4-methyl-2*H*-chromen-2-one 4-71



The title compound was prepared following General Procedure B using 7-mercapto-4-methylcoumarine (0.96 g, 5.0 mmol), NaH (60% in mineral oil, 0.30 g, 7.5 mmol), CF_2Br_2 (0.90 mL, 10 mmol) and NMP (5 mL). The crude product was purified by silica gel column chromatography (eluent: EtOAc/*n*-hexane 1/9) to provide the title compound (0.81 g, 51% yield) as a yellow solid.

(^{1}H NMR, 400 MHz, $CDCl_3$) δ = 2.47 (d, *J* = 1.3 Hz, 3H), 6.38-6.41 (m, 1H), 7.56 (dd, *J* = 1.6, 8.2 Hz, 1H), 7.62-7.68 (m, 2H); (^{13}C NMR, 101 MHz, $CDCl_3$) δ = 18.7, 116.8, 118.3 (t, *J* = 338.6 Hz), 121.9, 124.0, 125.4, 130.8, 131.1, 151.4, 153.3, 159.7; (^{19}F NMR, 377 MHz, $CDCl_3$) δ = -21.9 (s, 2F); IR (neat) ν 3056, 1723, 1598, 1396, 1382, 1172, 1064, 902, 865, 820; HRMS (ESI) *m/z* Calcd for $C_{11}H_7BrF_2NaO_2S$ $[M+Na]^+$ 342.9205, found 342.9210; Mp. 110-112 °C.

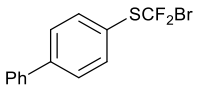
1-{[Bromo(difluoro)methyl]sulfanyl}-4-*tert*-butylbenzene 4-67



The title compound was prepared following General Procedure B using 4-*tert*-butyl-thiophenol (0.86 mL, 5.0 mmol), NaH (60% in mineral oil, 0.30 g, 7.5 mmol), CF_2Br_2 (0.90 mL, 10 mmol) and NMP (5 mL). The crude product was purified by silica gel column chromatography (eluent: *n*-pentane) to provide the title compound (1.0 g, 68% yield) as a colourless oil.

(^{1}H NMR, 400 MHz, $CDCl_3$) δ = 1.35 (s, 9H), 7.43-7.49 (m, 2H), 7.57-7.62 (m, 2H); (^{13}C NMR, 101 MHz, $CDCl_3$) δ = 31.2, 34.9, 119.5 (t, *J* = 339.3 Hz), 123.8, 126.5, 136.2, 154.6; (^{19}F NMR, 377 MHz, $CDCl_3$) δ = -22.2 (s, 2F); IR (neat) ν 2965, 2906, 2871, 1062, 906, 841, 828, 730; HRMS (EI/FI) *m/z* Calcd for $C_{11}H_{13}BrF_2S$ $[M]^+$ 293.9889, found 293.9893.

[1,1'-Biphenyl]-4-yl(bromodifluoromethyl)sulfane 4-65

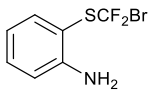


The title compound was prepared following General Procedure B using 4-phenyl-thiophenol[15] (0.93 mL, 5.0 mmol), NaH (60% in mineral oil, 0.30 g, 7.5 mmol), CF_2Br_2 (0.90 mL, 10 mmol) and NMP (5 mL). The crude product was purified by silica gel column chromatography (eluent: *n*-pentane) to provide the title compound (0.82 g, 52% yield) as a white solid.

(^{1}H NMR, 400 MHz, $CDCl_3$) δ = 7.39-7.45 (m, 1H), 7.46-7.52 (m, 2H), 7.60-7.69 (m, 4H), 7.72-7.77 (m, 2H); (^{13}C NMR, 101 MHz, $CDCl_3$) δ = 119.3 (t, *J* = 338.6 Hz), 125.9, 127.2, 128.1, 128.2, 129.0, 136.8, 139.7, 144.0; (^{19}F NMR, 377 MHz, $CDCl_3$) δ = -22.1 (s, 2F); IR

(neat) ν 3030, 1478, 1058, 830, 759, 721; HRMS (EI/FI) *m/z* Calcd for $C_{13}H_9BrF_2S$ $[M]^+$ 313.9576, found 313.9580; Mp. 28-30 °C.

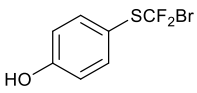
2-{[Bromo(difluoro)methyl]sulfanyl}aniline 4-75



The title compound was prepared following General Procedure C using 2,2'-disulfanediyldianiline (1.24 g, 5.00 mmol), $Na_2S_2O_4$ (85% pure; 1.54 g, 7.50 mmol), Na_2HPO_4 (1.06 g, 7.50 mmol), CF_2Br_2 (1.37 mL, 15.0 mmol) in DMF (75 mL) and H_2O (20 mL). The crude product was purified by silica gel column chromatography (eluent: CH_2Cl_2/*n*-pentane 90/10 to 80/20) to provide the title compound (1.18 g, 92% yield, >95% pure) as a pale yellow solid (contains <5% inseparable impurities by ^{19}F NMR).

(^1H NMR, 400 MHz, $CDCl_3$) δ = 4.45 (br. s, 2H), 6.69-6.78 (m, 2H), 7.23-7.31 (m, 1H), 7.46 (dd, *J* = 1.2, 7.8 Hz, 1H); (^{13}C NMR, 101 MHz, $CDCl_3$) δ = 109.5, 115.8, 118.6, 119.7 (t, *J* = 340.9 Hz), 133.3, 139.2, 150.2; (^{19}F NMR, 377 MHz, $CDCl_3$) δ = -22.0 (s, 2F); IR (neat) ν 3464, 3350, 3049, 1614, 1478, 1065, 1048, 830, 754; HRMS (ESI) *m/z* Calcd for $C_7H_7BrF_2NS$ $[M+H]^+$ 253.9442, found 253.9445; Mp. 47-50 °C.

4-{[Bromo(difluoro)methyl]sulfanyl}phenol 4-76

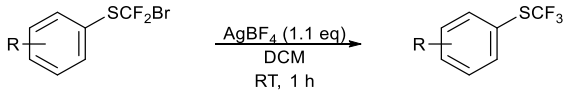


The title compound was prepared following General Procedure C using 4,4'-disulfanediyldiphenol (1.00 g, 4.00 mmol), $Na_2S_2O_4$ (85% pure; 1.23 g, 6.00 mmol), Na_2HPO_4 (850 mg, 6.00 mmol), CF_2Br_2 (1.10 mL, 12.0 mmol) in H_2O (16 mL) and DMF (60 mL). The crude product was purified by silica gel column chromatography (eluent: EtOAc/*n*-

hexane 5/95 to 1/9 to 2/8) to provide the title compound (0.63 g, 62% yield) as a pale yellow solid.

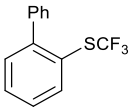
(^{1}H NMR, 400 MHz, $CDCl_3$) δ = 5.15 (br. s, 1H), 6.77-6.83 (m, 2H), 7.44-7.50 (m, 2H); (^{13}C NMR, 101 MHz, $CDCl_3$) δ = 116.5, 119.8 (t, *J* = 337.5 Hz), 138.7, 158.3; (^{19}F NMR, 377 MHz, $CDCl_3$) δ = -23.1 (s, 2F); IR (neat) ν 3309, 1441, 1069, 1053, 834, 757; HRMS (ESI) *m/z* Calcd for $C_7H_4BrF_2OS$ $[M-H]^-$ 252.9140, found 252.9139; M.p. 32-35 °C.

General Procedure D



To a solution of the halogenated precursor (0.25 mmol) in CH_2Cl_2 (2.5 mL) was added $AgBF_4$ (54 mg, 0.28 mmol) at room temperature. The reaction mixture was stirred at room temperature for 1 hour then filtered over a plug of silica and concentrated *in vacuo*. If necessary, products were further purified by silica gel column chromatography (eluent: *n*-pentane).

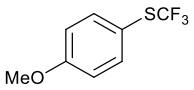
2-[(Trifluoromethyl)sulfanyl]biphenyl 4-49



The title compound was prepared following General Procedure D using 2-{[Bromo(difluoro)methyl]sulfanyl}biphenyl (31 mg, 0.10 mmol) and $AgBF_4$ (21 mg, 0.11 mmol) in CH_2Cl_2 (1.0 mL).The title compound (10 mg, 39% yield) was isolated as a white solid.

(^{1}H NMR, 400 MHz, $CDCl_3$) δ = 7.30-7.35 (m, 2H), 7.38-7.48 (m, 5H), 7.50-7.56 (m, 1H), 7.82 (app d, *J* = 8.1 Hz, 1H); (^{19}F NMR, 377 MHz, $CDCl_3$) δ = -42.0 (s, 3F). Data consistent with literature values.[16]

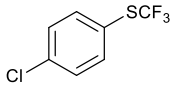
1-Methoxy-4-[(trifluoromethyl)sulfanyl]benzene 4-91



The title compound was prepared following General Procedure D using 1-{[bromo(difluoro)methyl]sulfanyl}-4-methoxybenzene (54 mg, 0.20 mmol) and $AgBF_4$ (78 mg, 0.40 mmol) in CH_2Cl_2 (1.0 mL). The title compound (42 mg, 98% yield) was isolated as colourless oil.

(^{1}H NMR, 400 MHz, $CDCl_3$) δ = 3.85 (s, 3H), 6.91-6.96 (m, 2H), 7.56-7.61 (m, 2H); (^{19}F NMR, 377 MHz, $CDCl_3$) δ = -43.9 (s, 3F). Data consistent with literature values.[17]

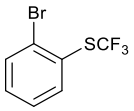
1-Chloro-4-[(trifluoromethyl)sulfanyl]benzene 4-95



The title compound was prepared following General Procedure D using 1-{[bromo(difluoro)methyl]sulfanyl}-4-chlorobenzene (54 mg, 0.20 mmol) and $AgBF_4$ (78 mg, 0.40 mmol) in CH_2Cl_2 (1.0 mL). The title compound (29 mg, 68% yield) was isolated as colourless oil.

(^{1}H NMR, 400 MHz, $CDCl_3$) δ = 7.39-7.45 (m, 2H) 7.57-7.63 (m, 2H); (^{19}F NMR, 377 MHz, $CDCl_3$) δ = -42.8 (s, 3F). Data consistent with literature values.[18]

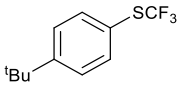
1-Bromo-2-[(trifluoromethyl)sulfanyl]benzene 4-96



The title compound was prepared following General Procedure D using 1-bromo-2-{[bromo(difluoro)methyl]sulfanyl}benzene (80 mg, 0.25 mmol) and $AgBF_4$ (54 mg, 0.28 mmol) in CH_2Cl_2 (2.5 mL). The crude product was purified by silica gel column chromatography (eluent: *n*-pentane) to provide the title compound (33 mg, 65% yield) as a colourless oil.

(^{1}H NMR, 400 MHz, $CDCl_3$) δ = 7.30-7.42 (m, 2H), 7.74 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.76-7.82 (m, 1H); (^{19}F NMR, 377 MHz, $CDCl_3$) δ = -42.0 (s, 3F). Data consistent with literature values.[19]

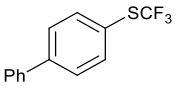
1-*tert*-Butyl-4-[(trifluoromethyl)sulfanyl]benzene 4-92



The title compound was prepared following General Procedure D using 1-{[bromo(difluoro)methyl]sulfanyl}-4-*tert*-butylbenzene (80 mg, 0.25 mmol) and $AgBF_4$ (54 mg, 0.28 mmol) in CH_2Cl_2 (2.5 mL). The crude product was purified by silica gel column chromatography (eluent: *n*-pentane) to provide the title compound (39 mg, 66% yield) as a colourless oil.

(^{1}H NMR, 400 MHz, $CDCl_3$) δ = 1.25 (s, 9H), 7.33-7.38 (m, 2H), 7.50 (d, *J* = 8.3 Hz, 2H); (^{19}F NMR, 377 MHz, $CDCl_3$) δ = -43.0 (s, 3F). Data consistent with literature values.[11]

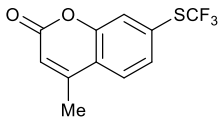
4-[(Trifluoromethyl)sulfanyl]biphenyl 4-90



The title compound was prepared following General Procedure D using [1,1'-biphenyl]-4-yl(bromodifluoromethyl)sulfane (80 mg, 0.25 mmol) and $AgBF_4$ (54 mg, 0.28 mmol) in CH_2Cl_2 (2.5 mL). The crude product was purified by silica gel column chromatography (eluent: *n*-pentane) to give the product (57 mg, 90% yield) as a white solid.

(^{1}H NMR, 400 MHz, $CDCl_3$) δ = 7.40-7.46 (m, 1H), 7.46-7.53 (m, 2H), 7.60-7.68 (m, 4H), 7.75 (d, *J* = 8.3 Hz, 2H); (^{19}F NMR, 377 MHz, $CDCl_3$) δ = -42.7 (s, 3F). Data consistent with literature values.[11]

4-Methyl-7-[(trifluoromethyl)sulfanyl]-2*H*-chromen-2-one 4-98



The title compound was prepared following General Procedure D using 7-{[bromo(difluoro)methyl]sulfanyl}-4-methyl-2*H*-chromen-2-one (96 mg, 0.30 mmol) and $AgBF_4$ (117 mg, 0.60 mmol) in CH_2Cl_2 (1.5 mL). The title compound was isolated as white solid (19 mg, 24% yield).

(^{1}H NMR, 400 MHz, $CDCl_3$) δ = 2.47 (d, *J* = 1.4 Hz, 3H), 6.32 (q, *J* = 1.4 Hz, 1H), 7.56 (dd, J_1 = 1.7 Hz, J_1 = 8.3 Hz, 1H), 7.63-7.68 (m, 2H); (^{13}C NMR, 101 MHz, $CDCl_3$) δ = 17.6, 115.8, 120.7, 123.0, 127.3 (q, *J* = 1.9 Hz), 128.2, 129.9 (q, *J* = 309.0 Hz), 152.3, 150.3, 158.7 (^{19}F NMR, 377 MHz, $CDCl_3$) δ = -41.8 (s, 3F); IR (neat) ν 3060, 2919, 2860, 2360, 1770, 1741, 1164, 865; HRMS (ESI) *m/z* Calcd for $C_{11}H_7F_3NaO_2S$ $[M+Na]^+$ 283.0011 found 283.0010; Mp. 125-127 °C.

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 222 (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.

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

General Procedure for the ^{18}F-fluorination of Aryl-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.

General Procedure for the [^{18}F]fluorination of Aryl-OCF_2Br

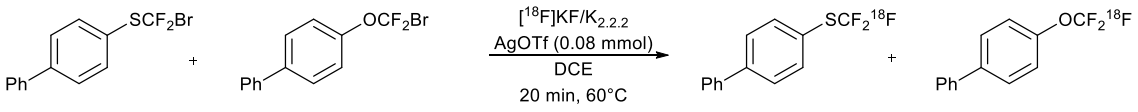
To a V-vial containing AgOTf (20 mg, 0.08 mmol) and a magnetic stirrer bar was added [^{18}F]KF/K_{222} (~30 MBq) in MeCN (~30 μL). The MeCN was removed by heating (100 °C) the vial under a stream of N_2. Upon cooling of the V-vial, a solution of precursor (0.04 mmol)

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.

General Procedure for the [^{18}F]fluorination of Aryl-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.

Competition Experiment



4-65 0.02 mmol + **4-103** 0.02 mmol → **[^{18}F]4-90** + **[^{18}F]4-113**

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).

Flow rate 1 ml/min

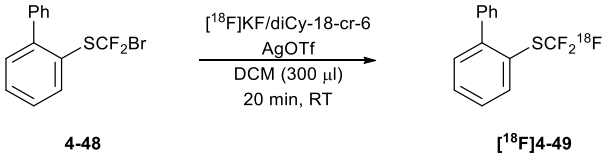
0-30 min (65% MeCN) (isocratic)

[^{18}F]4-(trifluoromethoxy)biphenyl, R_t = 18.2 min

[^{18}F][1,1'-Biphenyl]-4-yl(bromodifluoromethyl)sulfane, R_t = 24.5 min

Product	**RCC**		**RCC (*n* = 2)**
	Reaction 1	**Reaction 2**	
[^{18}F][1,1'-biphenyl]-4-yl(trifluoromethyl)sulfane, **[^{18}F]4-90**	37%	60%	49 ± 11%
[^{18}F]4-(trifluoromethoxy)biphenyl, **[^{18}F]4-113**	2%	11%	6 ± 5%

Isolation procedure for [^{18}F]2-[(Trifluoromethyl)sulfanyl]biphenyl and determination of RCY and SA



4-48 **[^{18}F]4-49**

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 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)

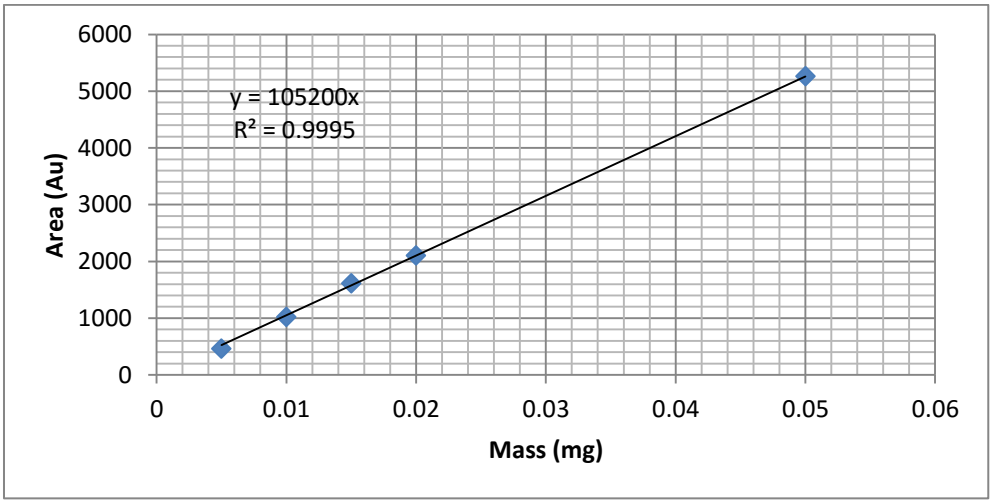
17-27 min (80% MeCN) (isocratic)

27-32 min (95% MeCN) (isocratic)

[^{18}F]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 2-[(Trifluoromethyl)sulfanyl]biphenyl 4-49



Peak area = 6504.8

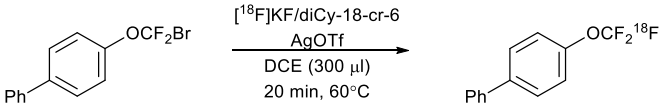
Amount of cold ^{19}F- product **4-49** = 6504.8/105200 = 0.062 mg

Amount of **4-49** (MW = 254.3) in μmol = 0.24 μmol

Activity = 79 MBq

SA = (79/0.24)/1000 = 0.32 GBq/μmol

Isolation procedure for [^{18}F]4-(Trifluoromethoxy)biphenyl and determination of RCY and SA



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 approximately 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)

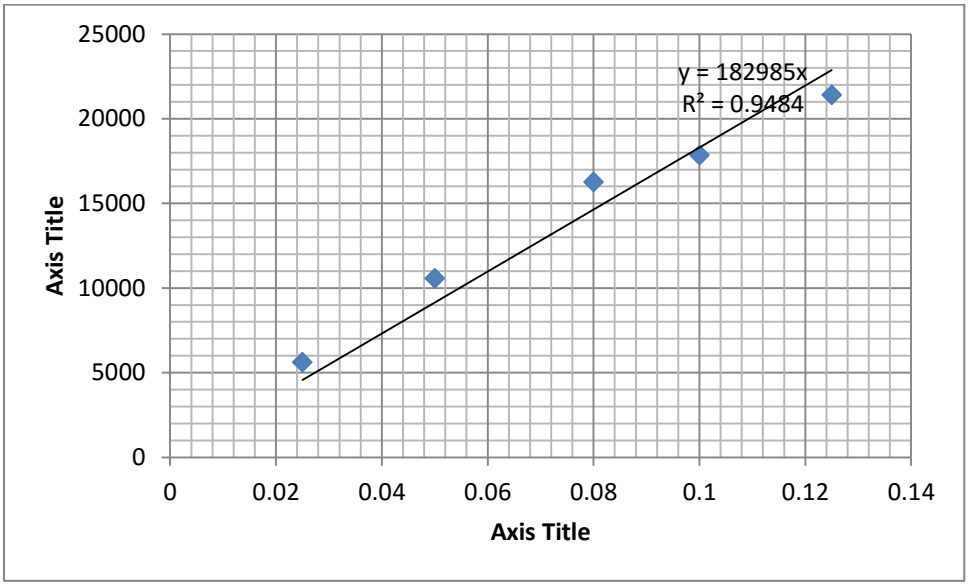
17-27 min (80% MeCN) (isocratic)

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 4-(Trifluoromethoxy)biphenyl 4-113



Peak area = 122054

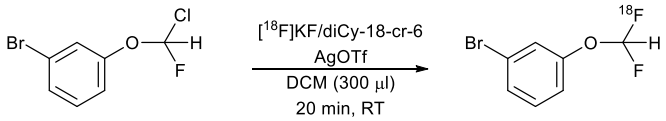
Amount of cold ^{19}F- product **4-113** = 122054/182985 = 0.67 mg

Amount of **4-113** (MW = 238.2) in μmol = 2.80 μmol

Activity = 237 MBq

SA = (237/2.80)/1000 = 0.08 GBq/μmol

Isolation procedure for [^{18}F]1-Bromo-3-(difluoromethoxy)benzene and determination of RCY and SA



4-155 **[^{18}F]4-163**

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

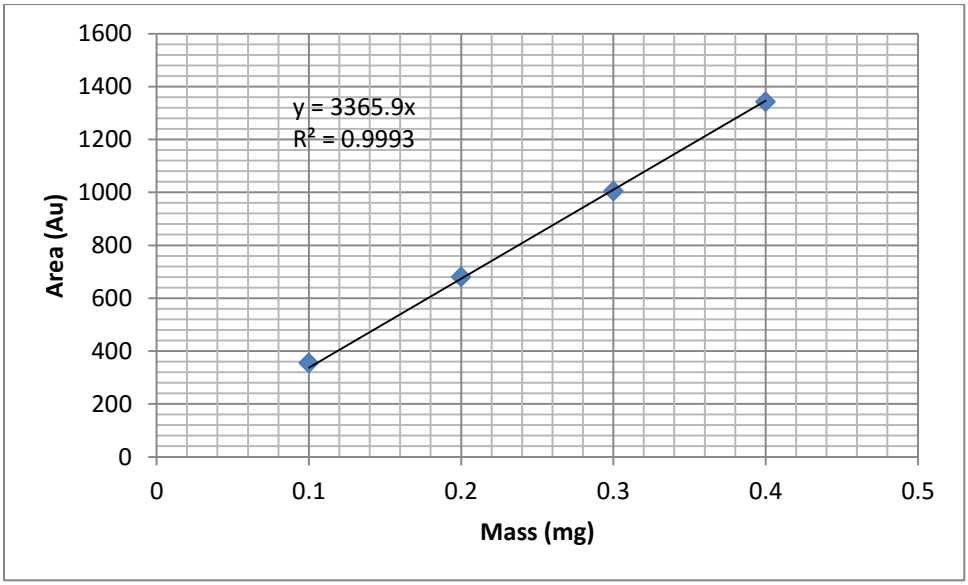
0-16 min (50% MeCN) (isocratic)

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 1-Bromo-3-(difluoromethoxy)benzene 4-163



Peak area = 10032.2

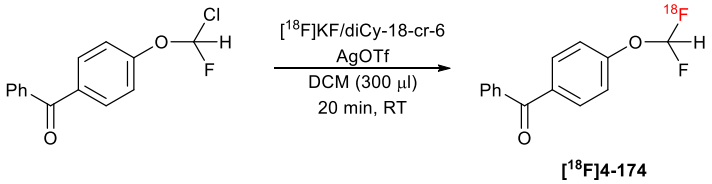
Amount of cold ^{19}F- product **4-163** = 10032/3365.9 = 2.98 mg

Amount of **4-163** (MW = 223.0) in μmol = 13.4 μmol

Activity = 509 MBq

SA = (509/13.4)/1000 = 0.04 GBq/μmol

Isolation procedure for [^{18}F]4-(Difluoromethoxy)phenyl](phenyl)methanone and determination of RCY and SA



[^{18}F]4-174

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

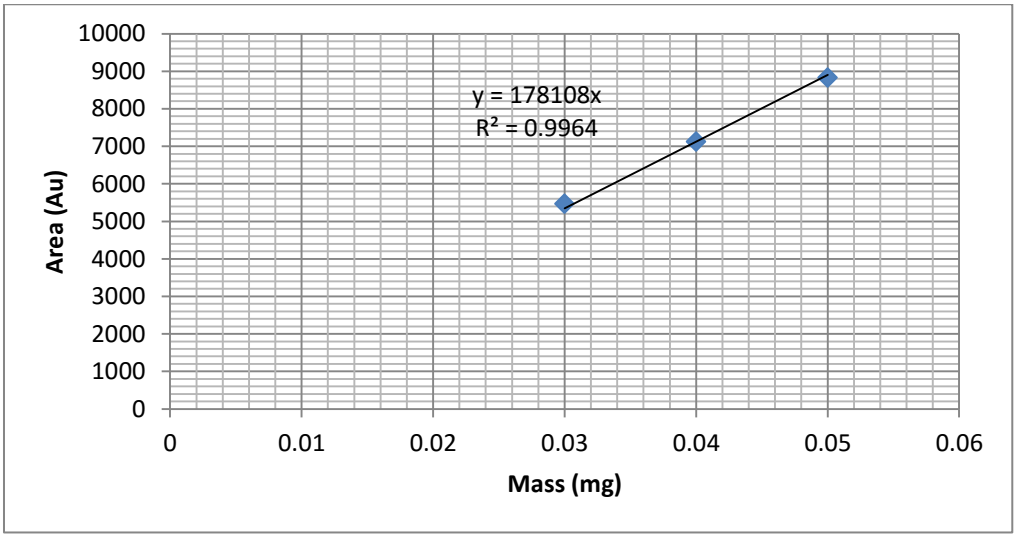
0-17 min (50% MeCN) (isocratic)

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 = 22 ± 10% (*n* = 2).

Calibration curve 4-(Difluoromethoxy)phenyl](phenyl)methanone 4-165



Peak area = 60260.8

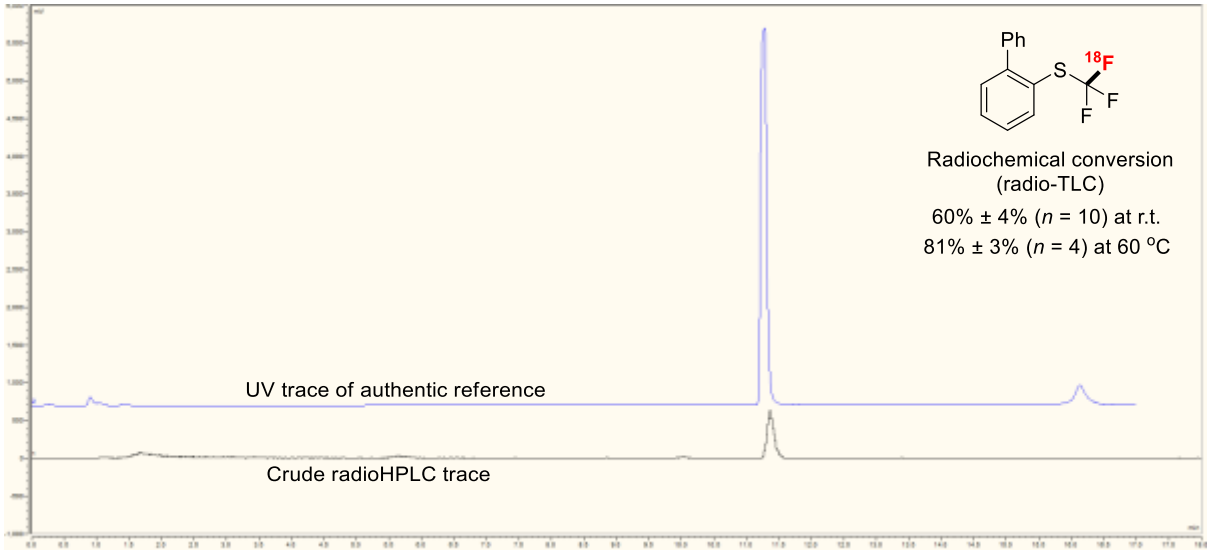
Amount of cold ^{19}F- product **4-165** = 60260.8/178108 = 0.34 mg

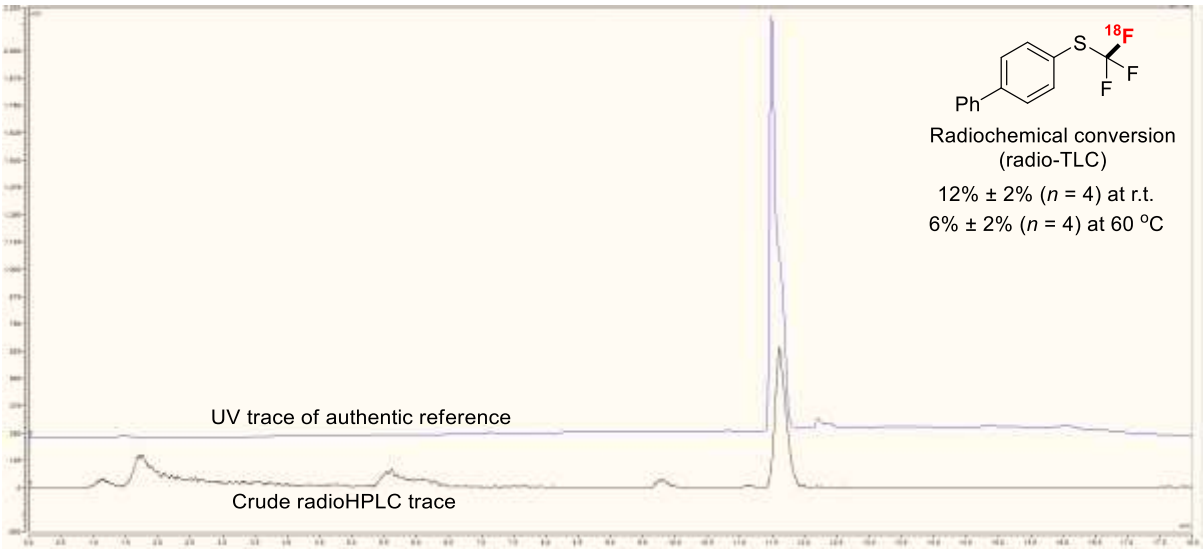
Amount of **4-165** (MW = 247.2) in μmol = 1.37 μmol

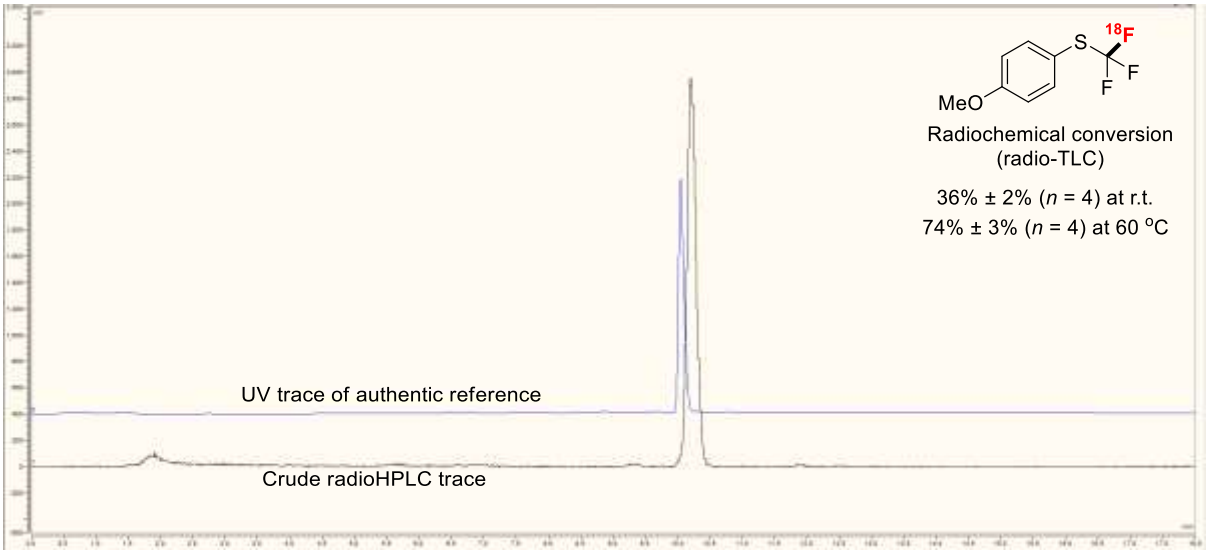
Activity = 242 MBq

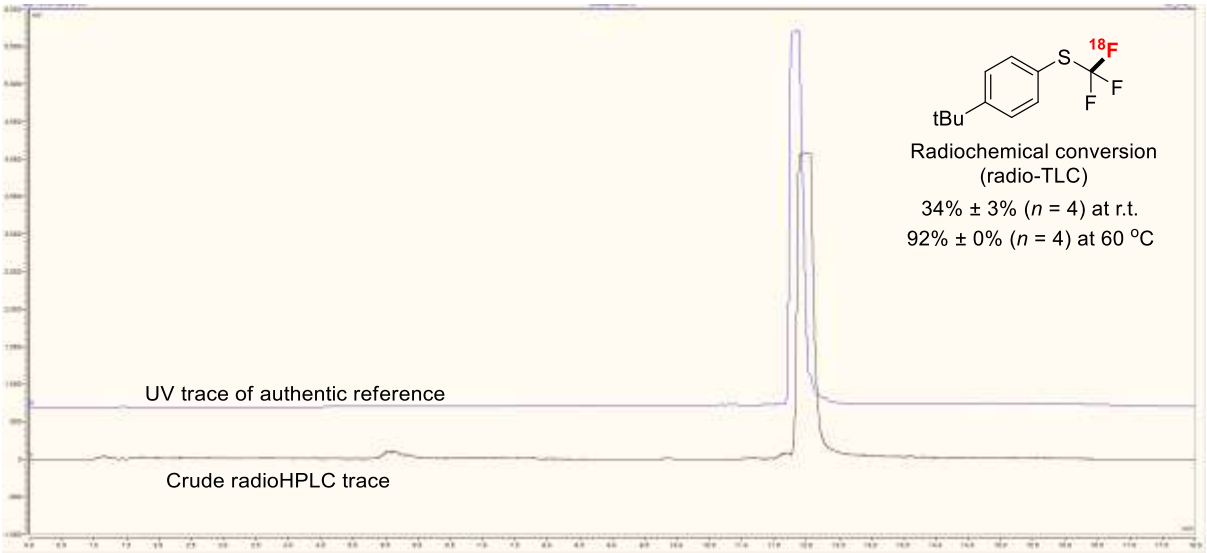
SA = (242/1.37)/1000 = 0.18 GBq/μmol

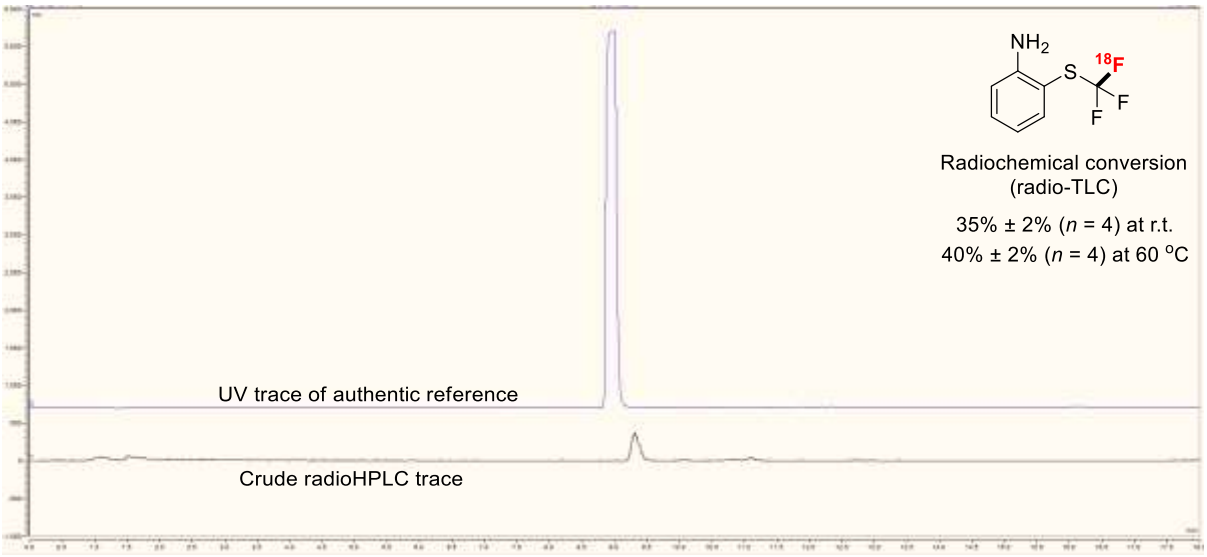
Radio-HPLC traces with Authenthic UV-traces overlaid

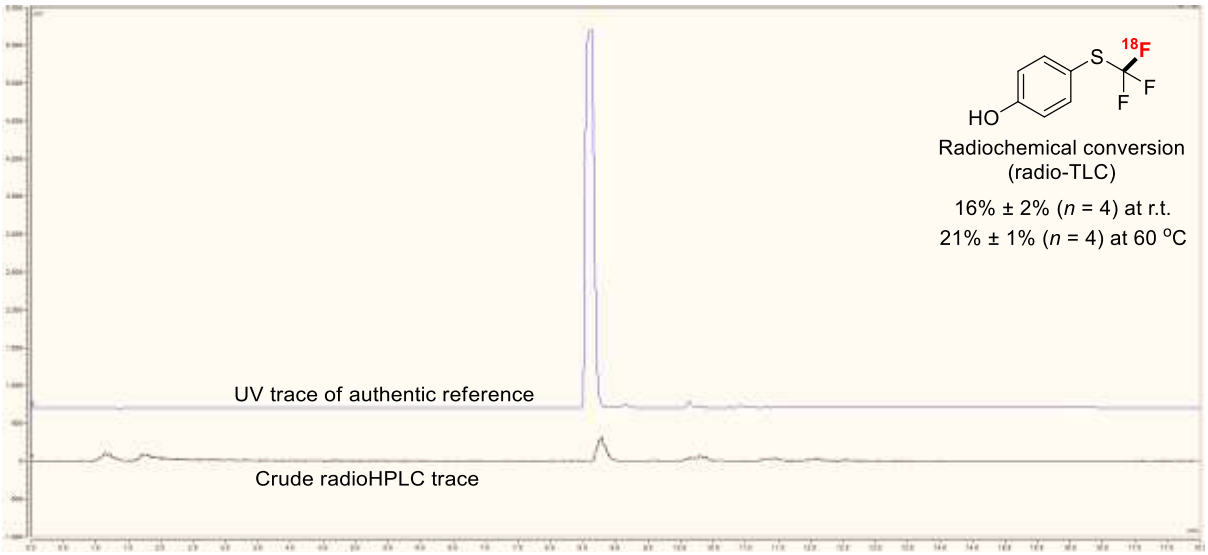


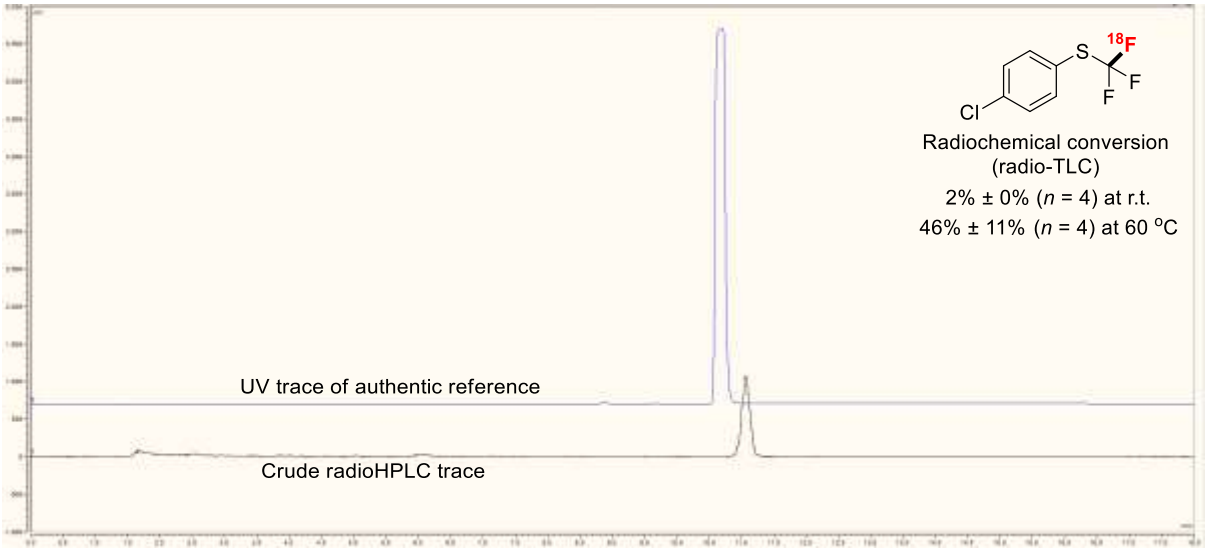

Ph
S
18F
F
F
Radiochemical conversion
(radio-TLC)
12% ± 2% (n = 4) at r.t.
6% ± 2% (n = 4) at 60 °C
UV trace of authentic reference
Crude radioHPLC trace

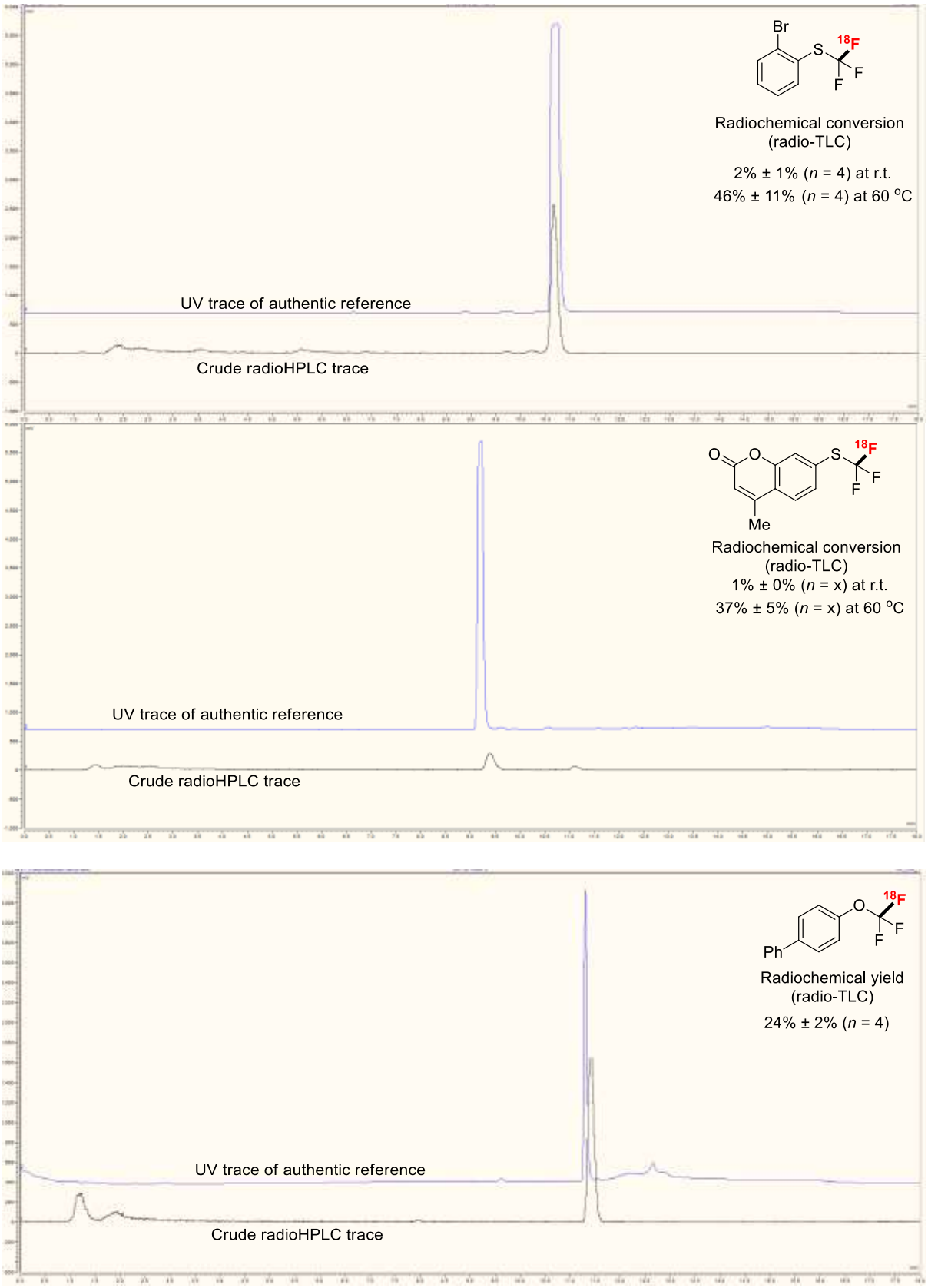

MeO
S
18F
F
F
Radiochemical conversion
(radio-TLC)
36% ± 2% (n = 4) at r.t.
74% ± 3% (n = 4) at 60 °C
UV trace of authentic reference
Crude radioHPLC trace

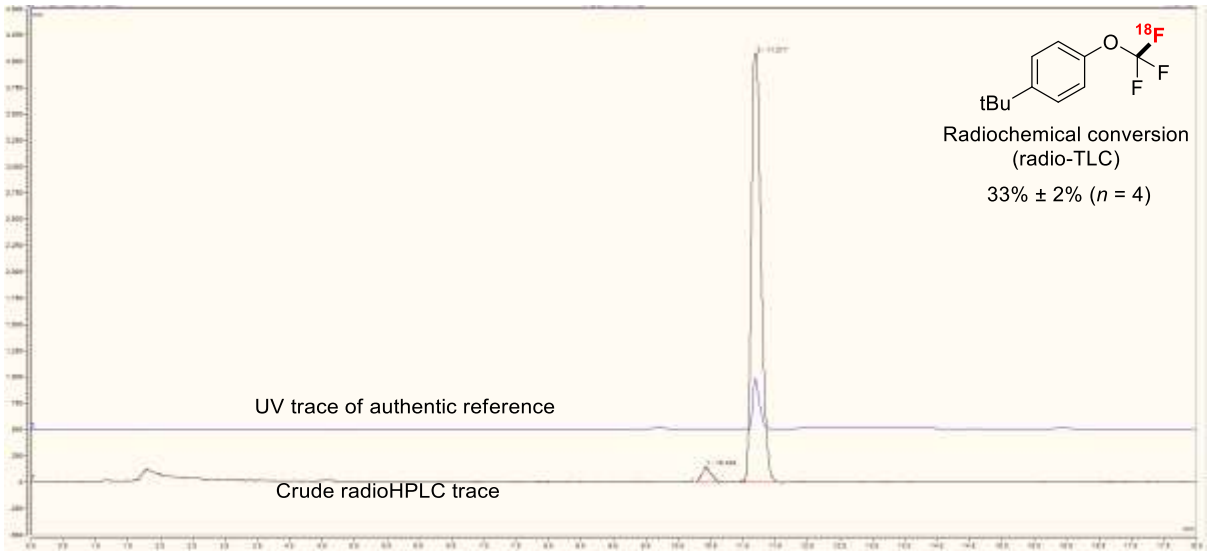

tBu
S
18F
F
F
Radiochemical conversion
(radio-TLC)
34% ± 3% (n = 4) at r.t.
92% ± 0% (n = 4) at 60 °C
UV trace of authentic reference
Crude radioHPLC trace

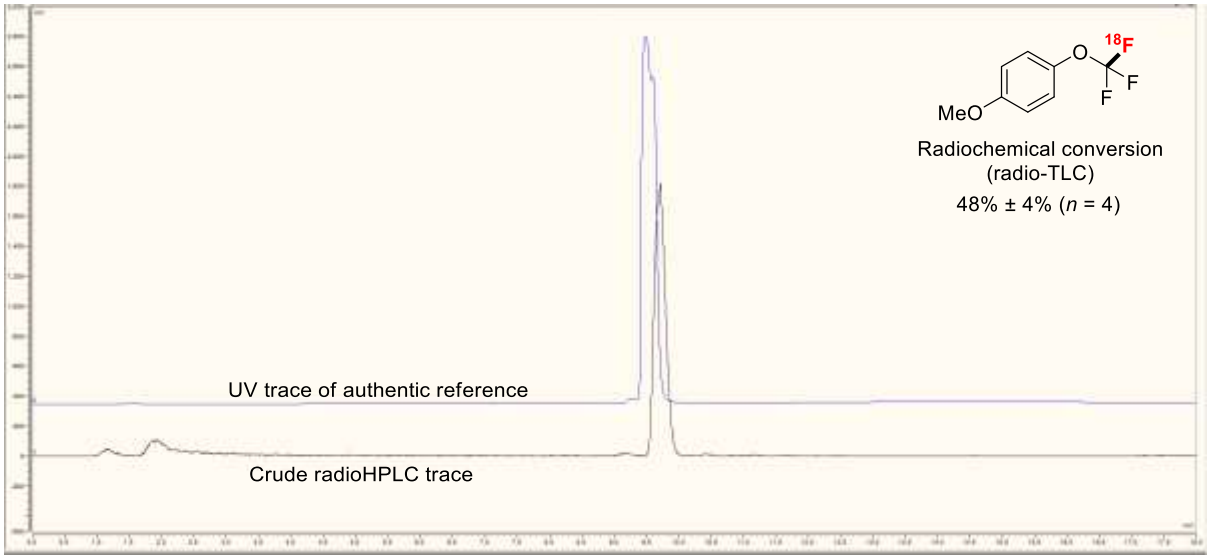

NH2
S
18F
F
F
Radiochemical conversion
(radio-TLC)
35% ± 2% (n = 4) at r.t.
40% ± 2% (n = 4) at 60 °C
UV trace of authentic reference
Crude radioHPLC trace

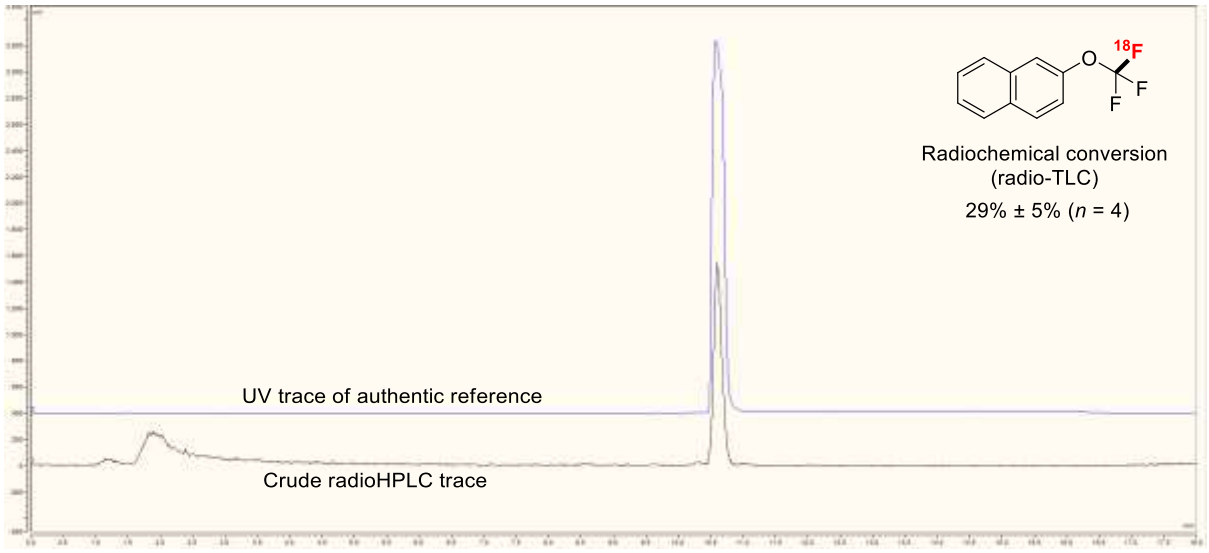

HO
S
18F
F
F
Radiochemical conversion
(radio-TLC)
16% ± 2% (n = 4) at r.t.
21% ± 1% (n = 4) at 60 °C
UV trace of authentic reference
Crude radioHPLC trace

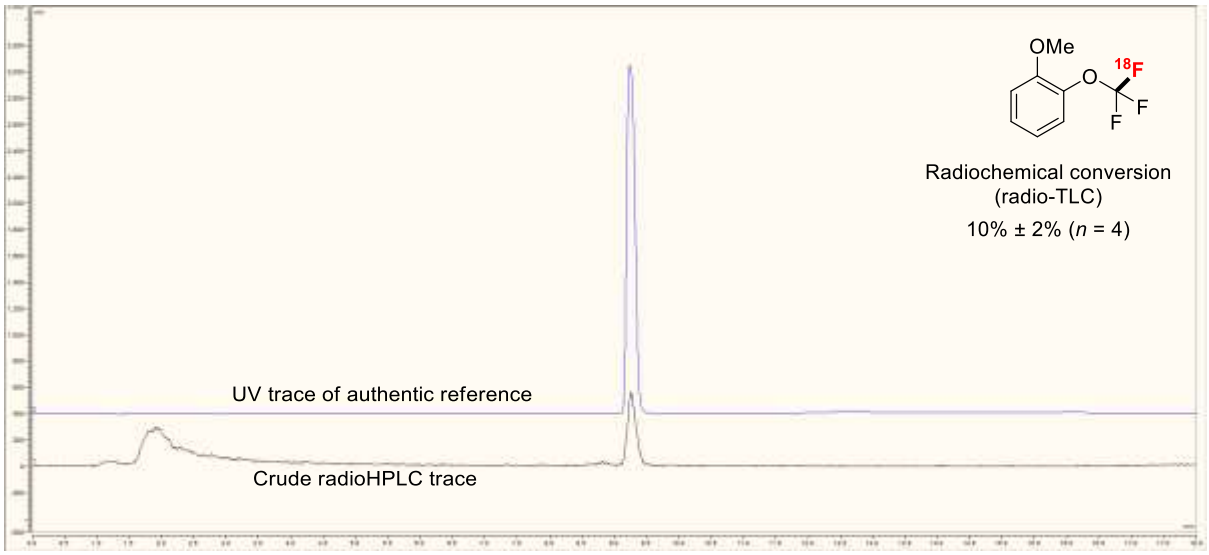

Cl
S
18F
F
F
Radiochemical conversion
(radio-TLC)
2% ± 0% (n = 4) at r.t.
46% ± 11% (n = 4) at 60 °C
UV trace of authentic reference
Crude radioHPLC trace

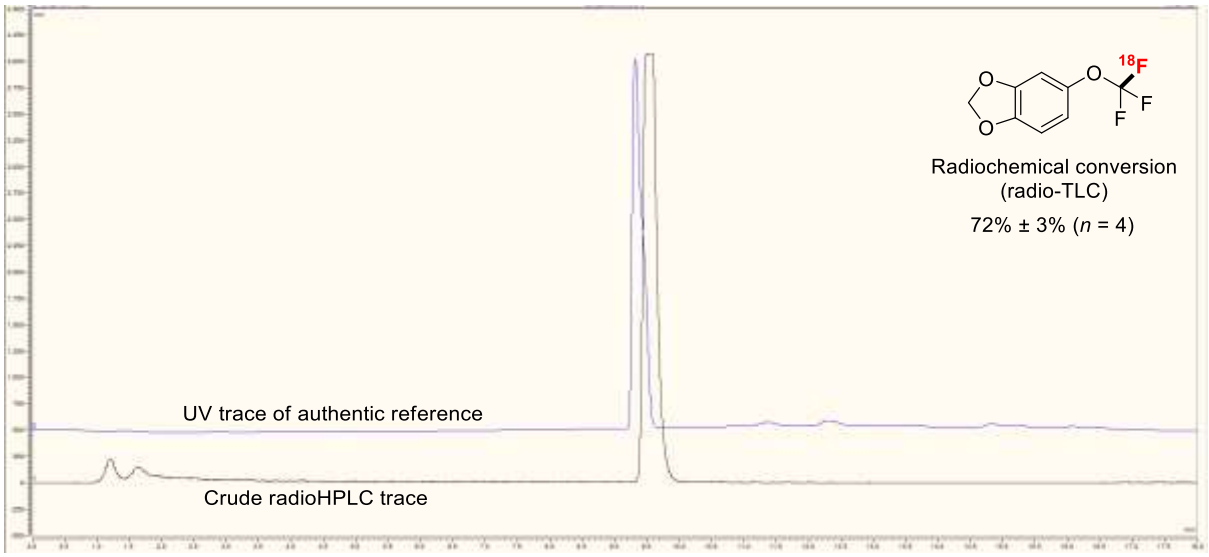

Br
S
18F
F
F
Radiochemical conversion
(radio-TLC)
2% ± 1% (n = 4) at r.t.
46% ± 11% (n = 4) at 60 °C
UV trace of authentic reference
Crude radioHPLC trace
O
O
S
18F
F
F
Me
Radiochemical conversion
(radio-TLC)
1% ± 0% (n = x) at r.t.
37% ± 5% (n = x) at 60 °C
UV trace of authentic reference
Crude radioHPLC trace
O
18F
F
F
Ph
Radiochemical yield
(radio-TLC)
24% ± 2% (n = 4)
UV trace of authentic reference
Crude radioHPLC trace

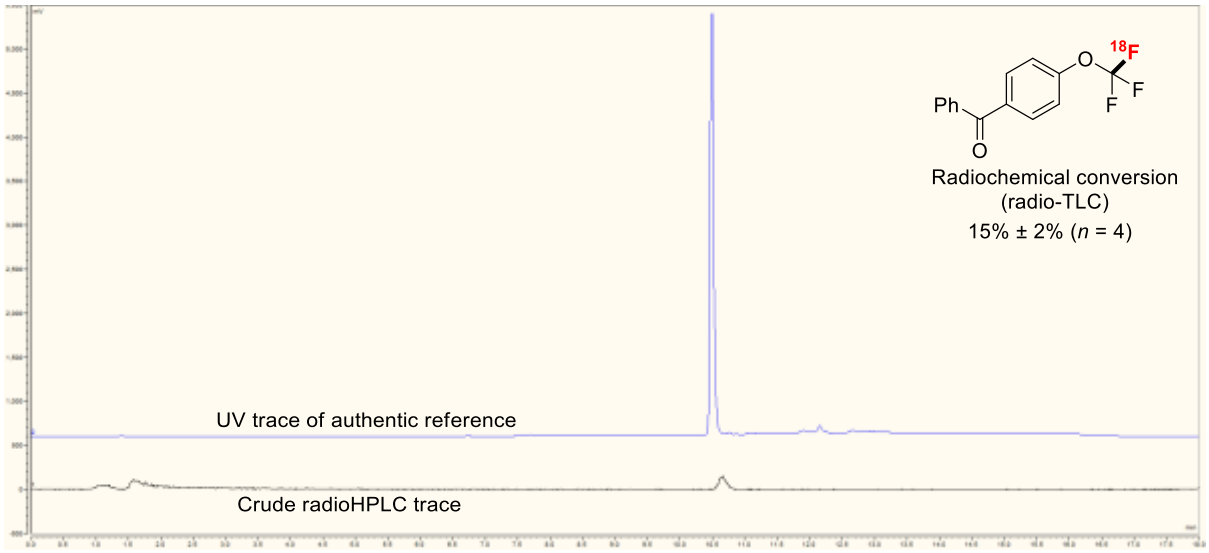

tBu
Radiochemical conversion
(radio-TLC)
33% ± 2% (*n* = 4)
UV trace of authentic reference
Crude radioHPLC trace

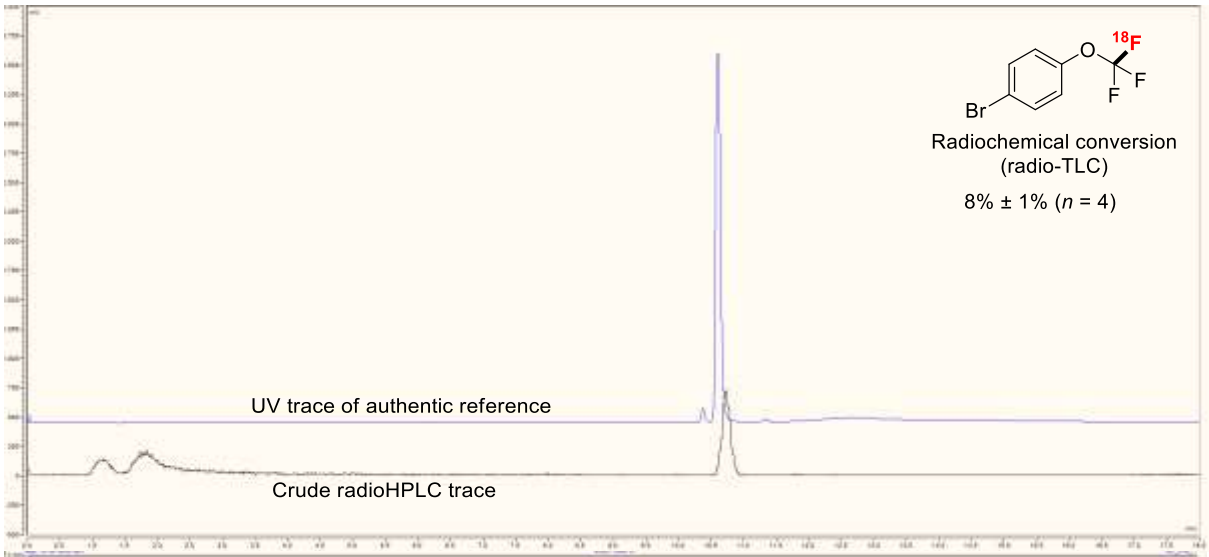

MeO
Radiochemical conversion
(radio-TLC)
48% ± 4% (*n* = 4)
UV trace of authentic reference
Crude radioHPLC trace

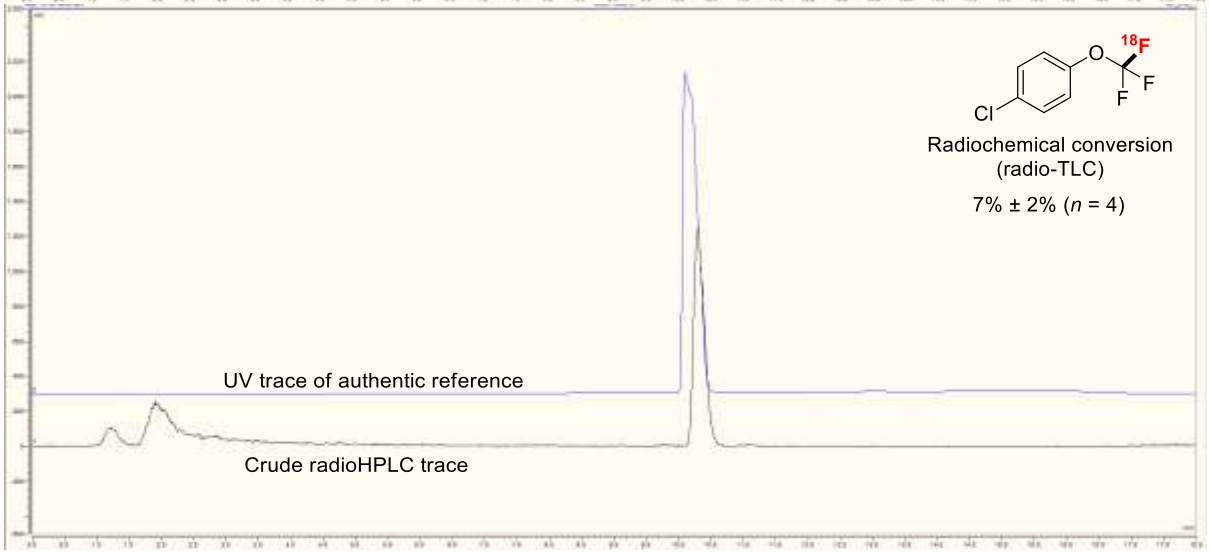

Radiochemical conversion
(radio-TLC)
29% ± 5% (*n* = 4)
UV trace of authentic reference
Crude radioHPLC trace

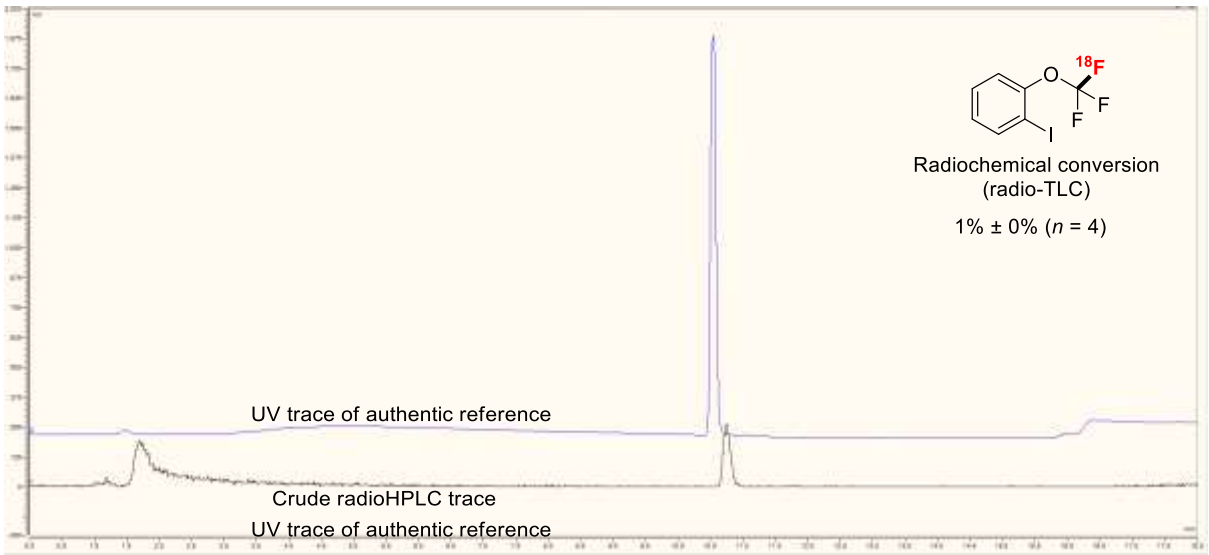

OMe
O
18F
F
F
Radiochemical conversion
(radio-TLC)
10% ± 2% (n = 4)
UV trace of authentic reference
Crude radioHPLC trace


O
O
O
18F
F
F
Radiochemical conversion
(radio-TLC)
72% ± 3% (n = 4)
UV trace of authentic reference
Crude radioHPLC trace

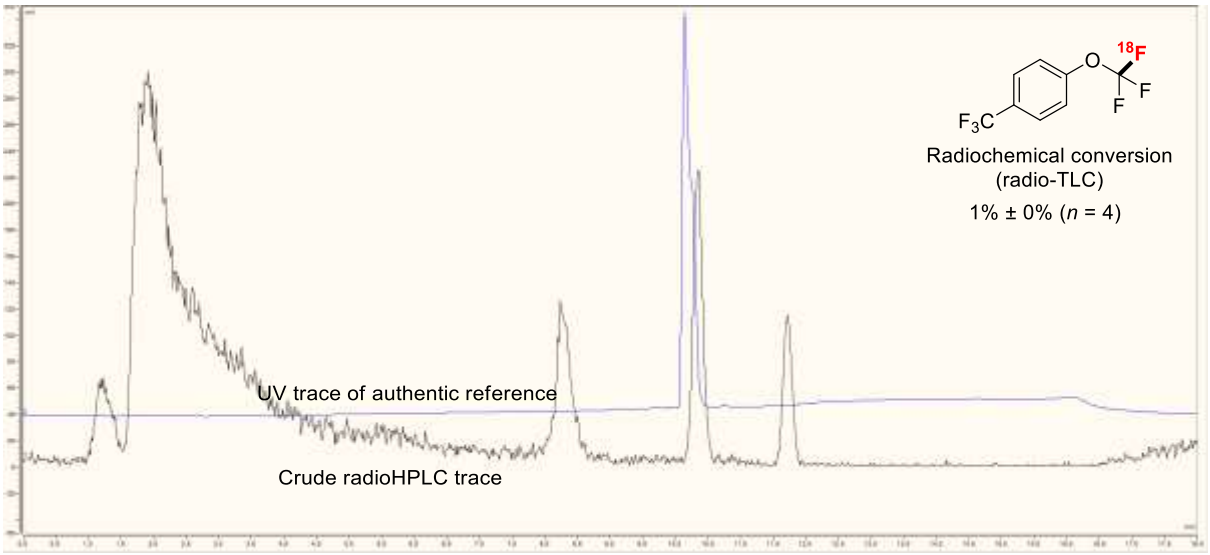

Ph
O
O
18F
F
F
Radiochemical conversion
(radio-TLC)
15% ± 2% (n = 4)
UV trace of authentic reference
Crude radioHPLC trace

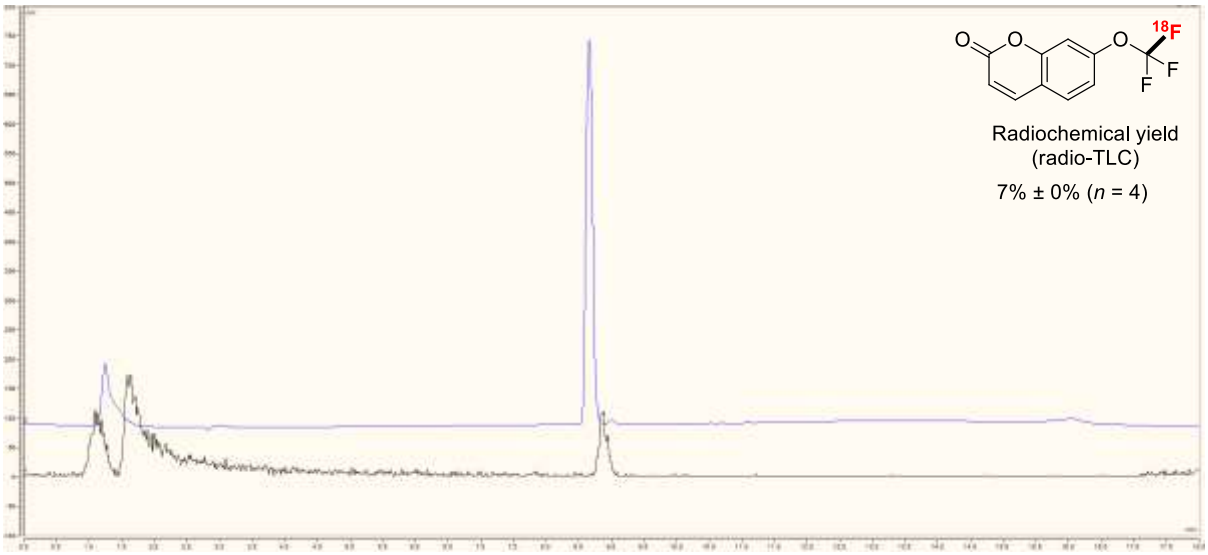


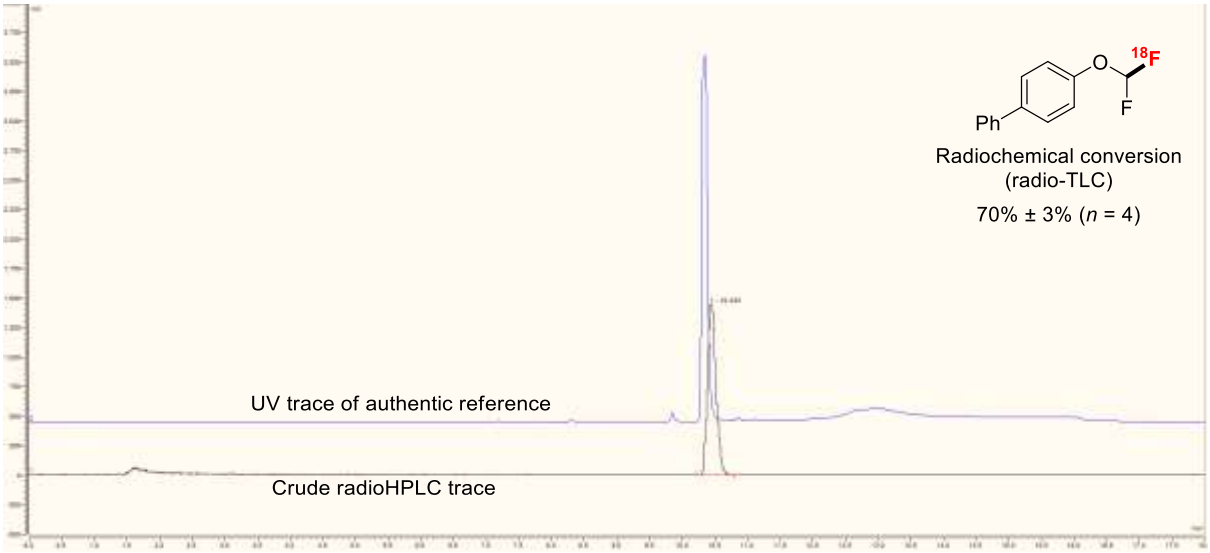


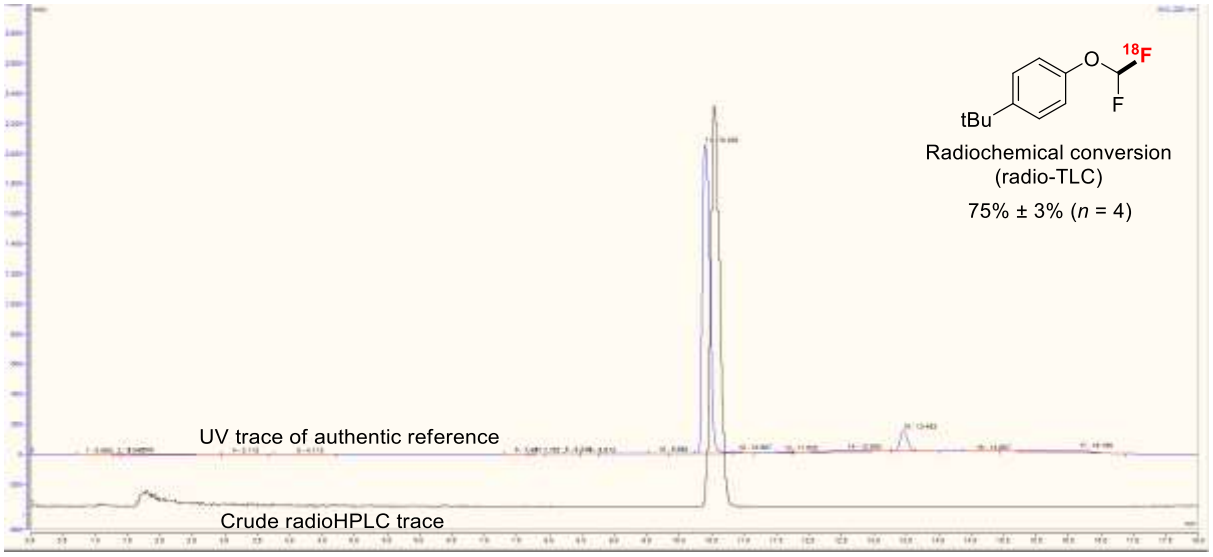


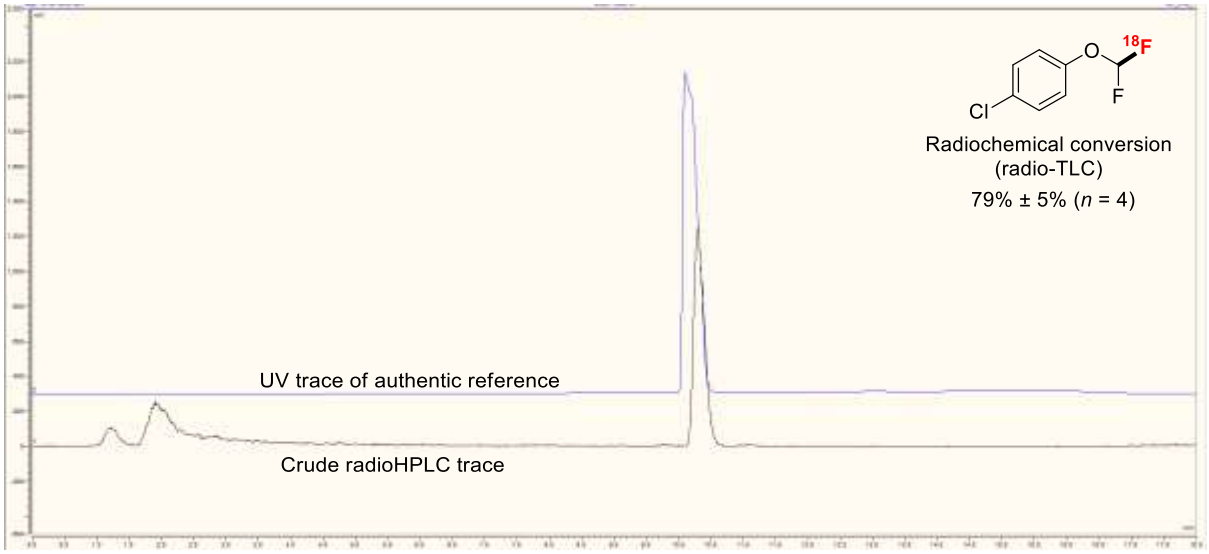
Crude radioHPLC trace

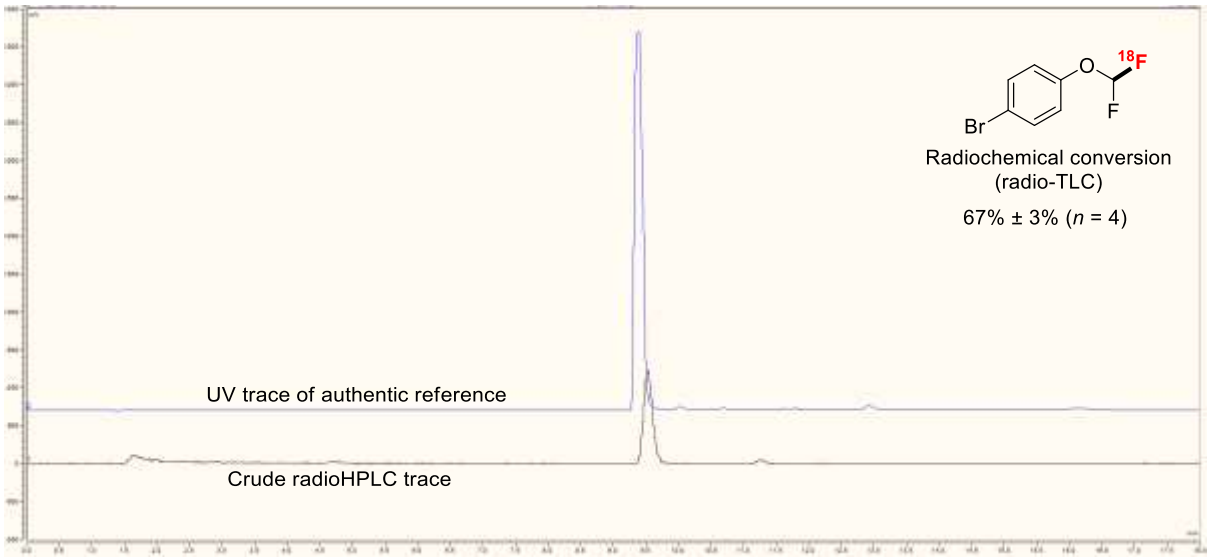

Radiochemical conversion
(radio-TLC)
1% ± 0% (*n* = 4)
UV trace of authentic reference
Crude radioHPLC trace

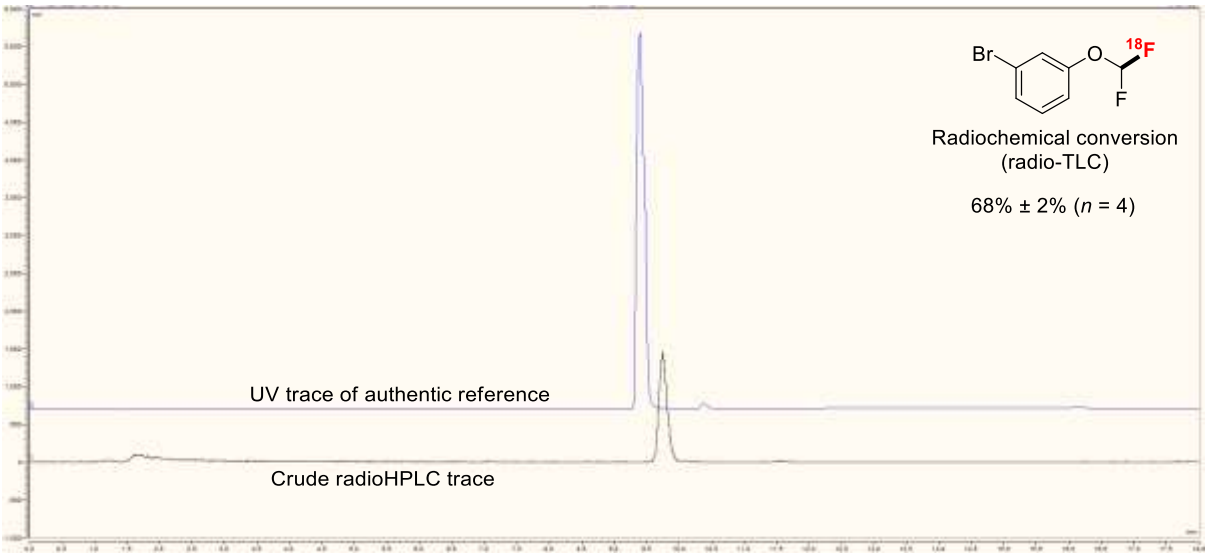

Radiochemical yield
(radio-TLC)
7% ± 0% (*n* = 4)

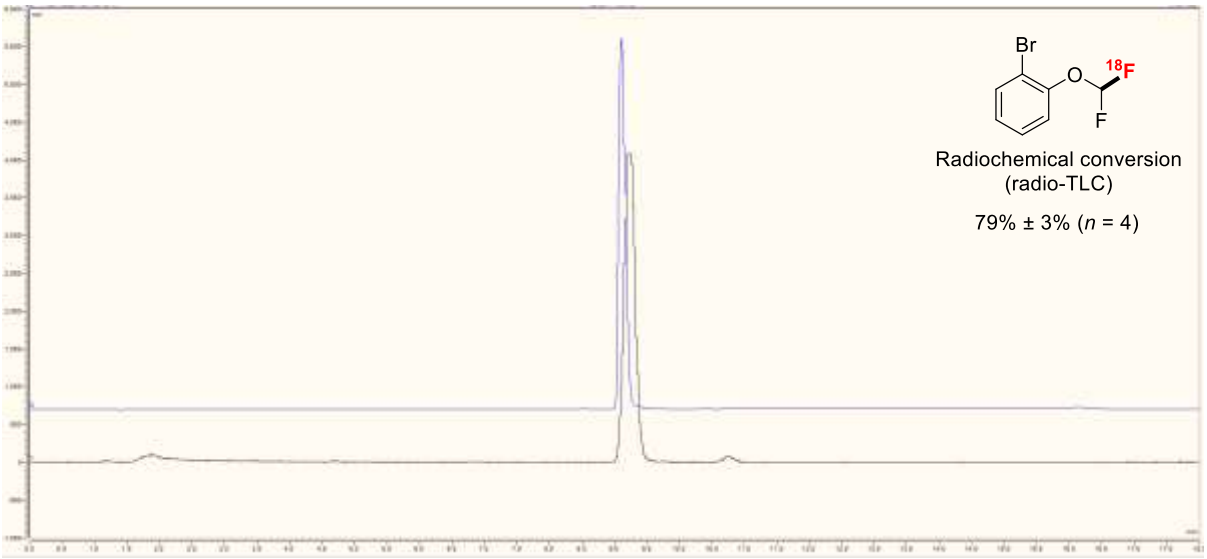

Radiochemical conversion
(radio-TLC)
70% ± 3% (*n* = 4)
UV trace of authentic reference
Crude radioHPLC trace

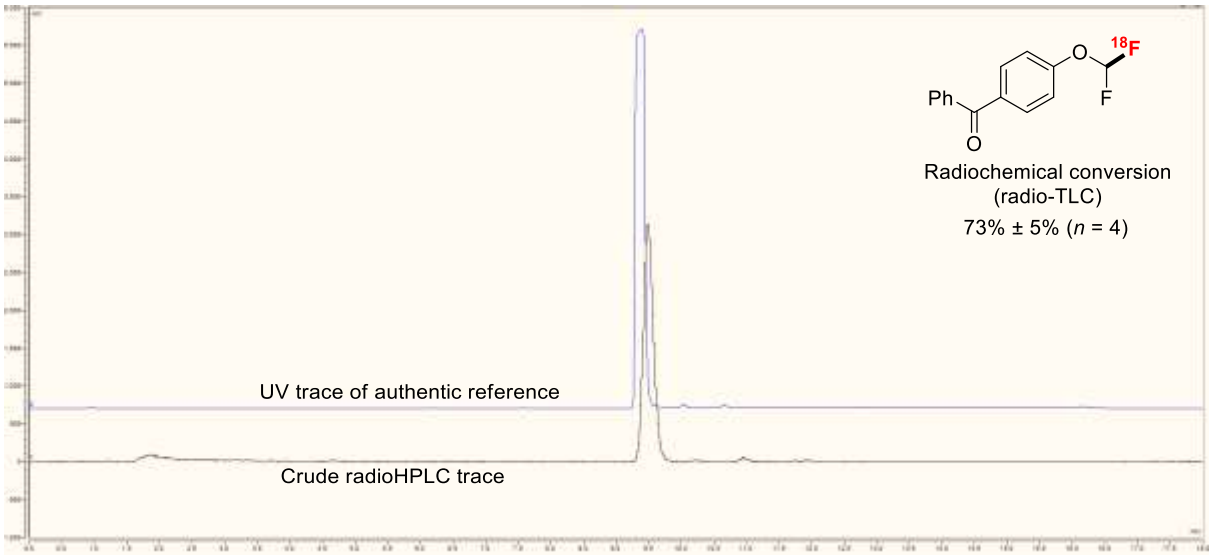

tBu
O
18F
F
Radiochemical conversion
(radio-TLC)
75% ± 3% (n = 4)
UV trace of authentic reference
Crude radioHPLC trace

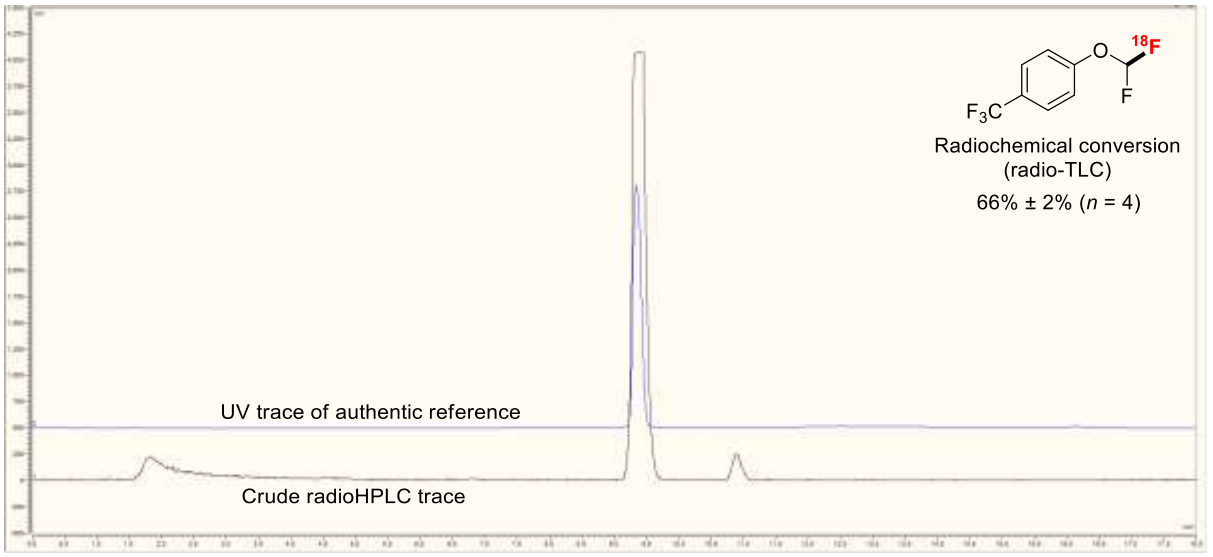

Cl
O
18F
F
Radiochemical conversion
(radio-TLC)
79% ± 5% (n = 4)
UV trace of authentic reference
Crude radioHPLC trace

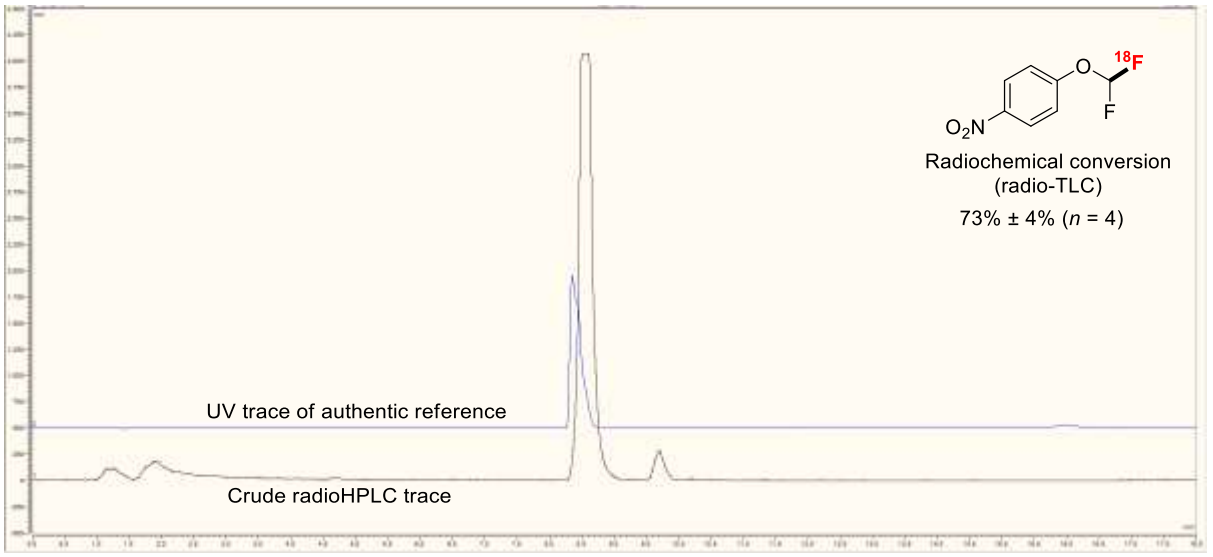

Br
O
18F
F
Radiochemical conversion
(radio-TLC)
67% ± 3% (n = 4)
UV trace of authentic reference
Crude radioHPLC trace


Br
O
18F
F
Radiochemical conversion
(radio-TLC)
68% ± 2% (n = 4)
UV trace of authentic reference
Crude radioHPLC trace


Br
O
18F
F
Radiochemical conversion
(radio-TLC)
79% ± 3% (n = 4)


Ph
O
O
18F
F
Radiochemical conversion
(radio-TLC)
73% ± 5% (n = 4)
UV trace of authentic reference
Crude radioHPLC trace


F3C
O
18F
F
Radiochemical conversion
(radio-TLC)
66% ± 2% (n = 4)
UV trace of authentic reference
Crude radioHPLC trace


O2N
O
18F
F
Radiochemical conversion
(radio-TLC)
73% ± 4% (n = 4)
UV trace of authentic reference
Crude radioHPLC trace

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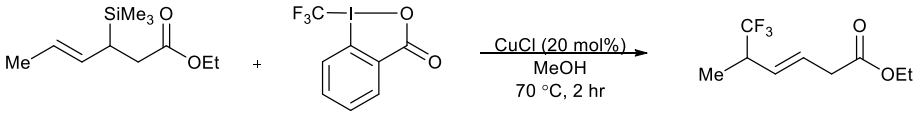
Appendix A: Experimental Data for Compounds synthesized by co-workers

This appendix contains the experimental data of the compounds which were synthesised by co-workers Dr S. Mizuta, Dr K. M. Engle and T. Khotavivattana, as referenced in Chapter 2, 3 and 4.

Chapter 2

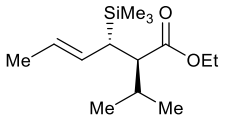
Trifluoromethylation of ethyl (*E*)-3-(trimethylsilyl)hex-4-enoate 2-42 using copper-catalysis.



2-41 **2-10** **2-42**, <5%
E/*Z* ratio = 1.4

A 5 mL vial was charged with ethyl (*E*)-3-(trimethylsilyl)hex-4-enoate (54 mg, 0.25 mmol) and CuCl (5.0 mg, 20 mol%). MeOH (0.50 mL) and the Togni II reagent (95 mg, 0.30 mmol) were added under Ar atmosphere. The reaction mixture was stirred for 2 h at 70 ˚C after which it was allowed to cool to room temperature. The mixture was quenched with sat. $NaHCO_3$ solution (10 mL) and extracted with Et_2O (2 x 10 mL). The pooled organic phases were washed with H_2O (10 mL) and brine (10 mL), dried over $MgSO_4$ and concentrated *in vacuo*. PhF (24 μl, 0.25 mmol) was added as an internal standard and the crude product was analysed by ^{1}H NMR and ^{19}F NMR.

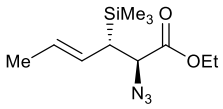
***anti*-(*E*)-Ethyl 2-isopropyl-3-(trimethylsilyl)hex-4-enoate 2-50**



The title compound was prepared following General procedure C using iPr_2NH (390 μL, 2.80 mmol), *n*-BuLi (1.75 mL, 2.80 mmol, 1.6 M in hexanes), (*E*)-3-(trimethylsilyl)hex-4-enoate (430 mg, 2.00 mmol), 2-bromopropane (280 μL, 3.00 mmol), THF (20 mL) and HMPA (5 mL). The crude product was purified by silica gel column chromatography (eluent: Et_2O/n-hexane 2.5/97.5 to 5/95) provided the title compound (400 mg, 78% yield) as a colourless oil.

(^{1}H NMR 400 MHz, $CDCl_3$) δ = -0.07 (s, 9H), 0.82 (d, *J* = 7.0 Hz, 3H), 0.92 (d, *J* = 7.0 Hz, 3H), 1.26 (t, *J* = 7.2 Hz, 3H), 1.66 (dd, J_1 = 6.4 Hz, J_2 = 1.6 Hz, 3H), 1.90-2.02 (m, 2H), 2.39 (dd, J_1 = 12.0 Hz, J_2 = 4.4 Hz, 1H), 4.05-4.20 (m, 2H), 5.08 (ddd, J_1 = 15.2, J_2 = 11.2 Hz, J_3 = 1.6 Hz, 1H), 5.27-5.35 (m, 1H); (^{13}C NMR 100 MHz, $CDCl_3$) δ -2.4, 14.3, 15.8, 18.1, 21.5, 29.0, 32.9, 50.5, 59.7, 124.4, 129.5, 174.3; IR (neat) ν 2960, 1730, 1248, 1144, 837 cm^{-1}; HRMS (EI/FI) *m/z* Calcd for $C_{14}H_{28}O_2Si$ $[M]^+$ 256.1859, found 256.1861.

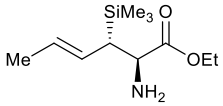
anti-(_E_)-Ethyl 2-azido-3-(trimethylsilyl)hex-4-enoate 2-51



The title compound was prepared following General procedure C using iPr_2NH (390 μL, 2.80 mmol), *n*-BuLi (1.75 mL, 2.80 mmol, 1.6 M in hexanes), (*E*)-3-(trimethylsilyl)hex-4-enoate (430 mg, 2.00 mmol), 2,4,6-triisopropylbenzenesulfonyl azide (650 mg, 2.10 mmol) and THF (20 mL). The crude product was purified by silica gel column chromatography (eluent: Et_2O/n-hexane 5/95) provided the title compound (290 mg, 56% yield) as a colourless oil.

(^{1}H NMR 400 MHz, $CDCl_3$) δ -0.05 (s, 9H), 1.28 (t, *J* = 7.2 Hz, 3H), 1.66 (d, *J* = 5.2 Hz, 3H), 2.08 (dd, J_1 = 9.2 Hz, J_2 = 6.0 Hz, 1H), 3.96 (d, *J* = 6.0 Hz, 1H), 4.13-4.28 (m, 2H), 5.25-5.43 (m, 2H); (^{13}C NMR 100 MHz, $CDCl_3$) δ -2.6, 14.2, 18.1, 36.6, 61.5, 63.5, 125.6, 127.2, 170.5; IR (neat) ν 2959, 2102, 1741, 1248, 1192, 1096, 1030, 838 cm^{-1}; HRMS (TOF-ESI) *m/z* Calcd for $C_{11}H_{21}N_3NaO_2Si$ $[M+Na]^+$ 278.1295, found 278.1292.

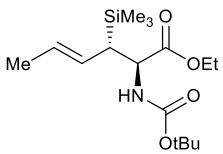
anti-(_E_)-Ethyl 2-amino-3-(trimethylsilyl)hex-4-enoate 2-54



To a solution of *anti*-(*E*)-ethyl 2-azido-3-(trimethylsilyl)hex-4-enoate (250 mg, 0.980 mmol) in THF (2 mL) was added PPh_3 (308 mg, 1.17 mmol) at room temperature. The reaction mixture was heated to 60 ˚C and stirred for 8 h. The reaction mixture was cooled to room temperature and distilled H_2O (1 mL) was added after which the solution was allowed to stir for 1 hr. The organic layer was separated, and the aqueous phase was extracted with Et_2O (2 × 10 mL). The combined organic phases were washed with water (50 mL), brine (50 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by silica gel column chromatography (eluent: EtOAc/*n*-hexane = 1/2) provided the title compound (159 mg, 71% yield) as a colourless oil.

(^{1}H NMR 400 MHz, $CDCl_3$) δ 0.04 (s, 9H), 1.25 (t, J = 7.3 Hz, 3H), 1.58 (br. s, 2H) 1.66 (d, J = 4.5 Hz, 3H), 1.94 (dd, J_1 = 4.5 Hz, J_2 = 9.8 Hz, 1H), 3.56 (d, J = 4.5 Hz, 1H), 4.09-4.18 (m, 2H), 5.32-5.35 (m, 2H); (^{13}C NMR 100 MHz, $CDCl_3$) δ -2.2, 14.4, 18.2, 38.4, 55.5, 60.6, 125.9, 126.7, 176.0; IR (neat) ν 2956, 1731, 1245, 1197, 1027, 959, 862, 836, 750, 691 cm^{-1}; HRMS (EI/FI) *m/z* Calcd for $C_{11}H_{23}NO_2Si$ $[M]^+$ 229.1494, found 229.1498.

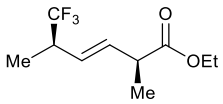
Ethyl _anti_-(_E_)-2-[(_tert_-butoxycarbonyl)amino]-3-(trimethylsilyl)hex-4-enoate 2-55



To a solution of (*E*)-*anti*-ethyl 2-amino-3-(trimethylsilyl)hex-4-enoate (0.11 g, 0.48 mmol) in MeCN (3 mL) was added DMAP (6.0 mg, 0.050 mmol) and Boc_2O (126 mg, 0.58 mmol) at room temperature, and the reaction mixture was stirred for 10 h. The solvent was removed *in*

vacuo, and the crude mixture was purified by silica gel column chromatography (eluent: EtOAc/*n*-hexane 1/10) provided the title compound (73 mg, 46% yield) as a white solid. (^{1}H NMR 400 MHz, $CDCl_3$) δ 0.05 (s, 9H), 1.25 (t, J = 7.3 Hz, 3H), 1.45 (s, 9H), 1.66 (dd, J_1 = 6.3 Hz, J_2 = 1.3 Hz, 3H), 2.00 (dd, J_1 = 4.1 Hz, J_2 = 10.4 Hz, 1H), 4.11 - 4.21 (m, 2H), 4.46 (dd, J_1 = 9.5 Hz, J_2 = 4.1 Hz, 1H), 4.99 (br. d, J = 9.5 Hz, 1H), 5.25 (dd, J_1 = 14.9 Hz, J_2 = 10.4 Hz, 1H), 5.36 (qd, J_1 = 14.9 Hz, J_2 = 6.3 Hz, 1H); (^{13}C NMR 125 MHz, $CDCl_3$) δ -2.6, 14.3, 18.2, 28.3, 37.1, 54.1, 61.0, 79.7, 125.5, 127.5, 155.3, 172.8; IR (neat) ν 3400, 2900, 1740, 1687, 1535, 1365, 1348, 1250, 1200, 1167, 1097, 1030, 872, 839 cm^{-1}; HRMS (TOF-ESI) *m/z* Calcd for $C_{16}H_{31}NNaO_4Si$ $[M+Na]^+$ 352.1911, found 352.1915.

syn-(_E_) Ethyl 6,6,6-trifluoro-2,5-dimethylhex-3-enoate 2-57



Conditions A:

The title compound was prepared using General Procedure A using *anti*-(*E*) ethyl 2-methyl-3-(trimethylsilyl)hex-4-enoate (57 mg, 0.25 mmol), Togni II reagent (0.14 g, 0.45 mmol), $Ru(bpy)_3Cl_2$•$6H_2O$ (9.0 mg, 0.013 mmol) and MeOH (0.50 mL). The isomeric ratio was determined by ^{19}F NMR analysis of the crude mixture (*E/Z* = 7.0 : 1, *syn*/*anti* (*E*) = 15 : 1). Purification by silica gel column chromatography (eluent: EtOAc/*n*-hexane = 5/95 to 10/90) provided the title compound (36 mg, 65% yield, *E/Z* = 15 : 1, *syn*/*anti*(*E*) = 7.4 : 1) as a colourless oil.

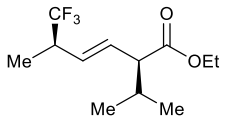
Conditions B:

The title compound was prepared using General Procedure B using *anti*-(*E*) Ethyl 2-methyl-3-(trimethylsilyl)hex-4-enoate (57 mg, 0.25 mmol), Umemoto reagent (0.18 g, 0.45 mmol), $Ru(bpy)_3Cl_2$•$6H_2O$ (9.0 mg, 0.013 mmol) and EtOH (0.50 mL). The isomeric ratio was

determined by ^{19}F NMR analysis of the crude mixture (*E/Z* = >20 : 1, *syn*:*anti* (*E*) = 6.1 : 1). Purification by silica gel column chromatography provided the title compound (19 mg, 33% yield, *E/Z* = >20 : 1, *syn*:*anti* (*E*) = 6.4 : 1) as a colourless oil.

(^1H NMR 500 MHz, $CDCl_3$) δ 1.22 (d, *J* = 7.3 Hz, 3H), 1.26 (t, *J* = 7.3 Hz, 3H), 1.28 (d, *J* = 7.0 Hz, 3H), 2.80-2.91 (m, 1H), 3.11-3.17 (m, 1H), 4.14 (q, *J* = 7.3 Hz, 1H), 4.15 (q, *J* = 7.3 Hz, 1H), 5.49 (dd, J_1 = 7.9 Hz, J_2 =15.5 Hz, 1H), 5.78 (dd, J_1 = 7.9 Hz, J_2 =15.5 Hz, 1H); (^{13}C NMR 125 MHz, $CDCl_3$) δ 13.4 (q, *J* = 2.8 Hz), 14.1, 17.2, 41.4 (q, *J* = 27.5 Hz), 42.8, 60.7, 126.2 (q, *J* = 2.8 Hz), 127.0 (q, *J* = 277.7 Hz), 134.0, 173.2; (^{19}F NMR 377 MHz, $CDCl_3$) *δ* -72.90 (d, *J* = 9.2 Hz, 3F); IR (neat) ν 2985, 1734 1462, 1260, 1174, 1129, 1073, 1015, 970 cm^{-1}; HRMS (EI/FI) *m/z* Calcd for $C_{10}H_{15}F_3O_2$ $[M]^+$ 224.1027, found 224.1024.

syn-(_E_)-Ethyl 6,6,6-trifluoro-2-isopropyl-5-methylhex-3-enoate 2-59



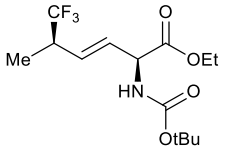
Conditions A:

The title compound was prepared using General Procedure A using *anti*-(*E*) ethyl 2-isopropyl-3-(trimethylsilyl)hex-4-enoate (64 mg, 0.25 mmol), Togni II reagent (0.14 g, 0.45 mmol), $Ru(bpy)_3Cl_2•6H_2O$ (9.0 mg, 0.013 mmol) and MeOH (0.5 mL). The isomeric ratio was determined by ^{19}F NMR analysis of the crude mixture (*E/Z* = >20 : 1, *syn/anti* (*E*) = 3.5 : 1). Purification by silica gel column chromatography (eluent: EtOAc/*n*-hexane 5/95) provided the title compound (35 mg, 55% yield, *E/Z* = >20 : 1, *syn/anti* (*E*) = 6.6 : 1) as a colourless oil.

(^1H NMR 500 MHz, $CDCl_3$) δ 0.88 (d, *J* = 6.6 Hz, 3H), 0.93 (d, *J* = 6.6 Hz, 3H), 1.21 (d, *J* = 7.0 Hz, 3H), 1.27 (t, *J* = 7.3 Hz, 3H), 1.96-2.05 (m, 1H), 2.70 (dd, J_1 = 8.5 Hz, J_2 = 9.5 Hz, 1H), 2.82-2.93 (m, 1H), 4.15 (q, *J* = 7.0 Hz, 1H), 4.16 (q, *J* = 7.3 Hz, 1H), 5.43 (dd, J_1 = 8.2 Hz, J_2 = 15.8 Hz, 1H), 5.71 (dd, J_1 = 9.5 Hz, J_2 = 15.8Hz, 1H); (^{13}C NMR 125 MHz, $CDCl_3$)

δ 13.5 (q, *J* = 2.9 Hz), 14.2, 19.5, 20.6, 30.9, 41.7 (q, *J* = 27.5 Hz), 56.8, 60.4, 127.1 (q, *J* = 277.7 Hz), 128.2 (q, *J* = 1.9 Hz), 132.1, 173.6; ^{19}F NMR (377 MHz, $CDCl_3$) δ -72.84 (d, *J* = 8.1 Hz, 3F); IR (neat) ν 2964, 1732, 1258, 1175, 1123, 1017, 975, 840 cm^{-1}; HRMS (FI/EI) *m/z* Calcd for $C_{12}H_{19}F_3O_2$ $[M]^+$ 252.1337, found 252.1337.

syn-(_E_)-Ethyl 2-[(_tert_-butoxycarbonyl)amino]-6,6,6-trifluoro-5-methylhex-3-enoate

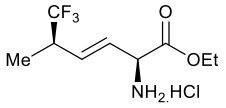


Conditions A:

The title compound was prepared using General Procedure A using *anti*-(*E*)-Ethyl 2-[(*tert*-butoxycarbonyl)amino]-3-(trimethylsilyl)hex-4-enoate (50 mg, 0.25 mmol), Togni II reagent (0.14 g, 0.45 mmol), $Ru(bpy)_3Cl_2•6H_2O$ (9.0 mg, 0.013 mmol) and MeOH (0.50 mL). Purification by silica gel column chromatography (eluent: EtOAc/*n*-hexane 10/90) provided the title compound (26 mg, 52% yield) as a colourless oil.

(^{1}H NMR 400 MHz, $CDCl_3$) δ 1.22 (d, *J* =7.1 Hz, 3H), 1.28 (t, *J* = 7.3 Hz, 3H), 1.46 (s, 9H), 2.86-2.95 (m 1H), 4.17-4.29 (m, 2H), 4.84 (br. s, 1H), 5.19 (br. s, 1H), 5.68-5.80 (m, 2H). The presence of rotamers was confirmed by NMR analysis. IR (neat) ν 2982, 1715, 1499, 1368, 1258, 1164, 1126, 1019, 970, 863 cm^{-1}; HRMS (TOF-ESI) *m/z* Calcd for $C_{14}H_{22}F_3NNaO_2$ $[M+Na]^+$ 348.1386, found 348.1393.

syn-(_E_)-Ethyl 2-amino-6,6,6-trifluoro-5-methylhex-3-enoate hydrogenchloride 2-60

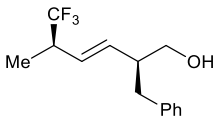


syn-(*E*)-Ethyl 2-[(*tert*-butoxycarbonyl)amino]-6,6,6-trifluoro-5-methylhex-3-enoate (210 μg, 650 μmol) was treated with HCl (1.00 mL, 1.25 M in EtOH) and stirred for 24 h. The mixture

was evaporated to yield the title compound (17 mg, quant.) as a yellow oil. The isomeric ratio was determined by ^{19}F NMR analysis (*E/Z* = >20 : 1, *syn*/*anti* (*E*) = 4.5 : 1).

(^{1}H NMR 500 MHz, $CDCl_3$) δ 1.25 (d, *J* = 6.9 Hz, 3H), 1.28 (t, *J* = 7.0 Hz, 3H), 2.94-3.05 (m, 1H), 4.20-4.33 (m, 2H), 4.73 (br. s, 1H), 5.98 (dd, J_1 = 5.4 Hz, J_2 = 15.8 Hz, 1H), 6.08 (dd, J_1 = 6.9 Hz, J_2 = 15.8 Hz, 1H), 8.96 (br. s, 3H); (^{13}C NMR 125 MHz, $CDCl_3$) δ 13.5 (q, *J* = 2.8 Hz), 13.8, 41.0 (q, *J* = 28.4 Hz), 54.6, 62.9, 124.5, 126.6 (q, *J* = 277.7 Hz), 134.0 (q, *J* = 2.8 Hz), 167.7; (^{19}F NMR 377 MHz, $CDCl_3$) δ -72.33 (d, *J* = 9.2 Hz, 3F); IR (neat) ν 2917, 1745, 1508, 1258, 1222, 1176, 1129, 1017, 972, 859 cm^{-1}; HRMS (TOF-ESI) *m/z* Calcd for $C_9H_{15}F_3NO_2$ $[M]^+$ 226.1055, found 226.1049.

2-benzyl-6,6,6-trifluoro-5-methylhex-3-en-1-ol 2-62

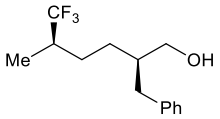


A solution of a *syn*/*anti-(E,Z)* mixture of ethyl 2-benzyl-6,6,6-trifluoro-5-methylhex-3-enoate (83 mg, 0.27 mmol, *E/Z* = >20 : 1, *syn*/*anti* (*E*) = 7.7 : 1) in Et_2O (3.0 mL) was added dropwise to a slurry of $LiAlH_4$ (20 mg, 0.53 mmol) in Et_2O (3.0 mL) and allowed to stir at room temperature for 4 h. The reaction was quenched with sat. aqueous NH_4Cl at 0 ˚C, and the aqueous phase was extracted with Et_2O (3 x 5 mL). The organic phase was washed with distilled water (5 mL) and brine (5 mL), dried over $MgSO_4$ and concentrated *in vacuo* to give 2-benzyl-6,6,6-trifluoro-5-methylhex-3-en-1-ol (76 mg, quant.) as a colourless oil which was used without further purification. The isomeric ratio was determined by ^{19}F NMR analysis of the crude mixture (*E/Z* = >15 : 1, *syn*/*anti* (*E*) = 7.9 : 1).

Characterization data for the *syn*-(*E*)-isomer: (^{1}H NMR 400 MHz, $CDCl_3$) δ 1.19 (d, *J* = 6.8 Hz, 3H), 2.50-2.58 (m, 1H), 2.65 (dd, J_1 = 7.6 Hz, J_2 = 13.4 Hz, 1H), 2.71-2.87 (m, 2H), 3.51 (dd, J_1 = 7.1 Hz, J_2 = 10.6 Hz, 1H), 3.62 (dd, J_1 = 5.0 Hz, J_2 = 10.6 Hz, 1H), 5.41 (dd, J_1 = 7.6

Hz, J_2 = 15.4 Hz, 1H), 5.78 (dd, J_1 = 8.1 Hz, J_2 = 15.4 Hz, 1H), 7.14 (d, J = 7.3 Hz, 2H), 7.20 (t, J = 7.3 Hz, 1H), 7.26-7.30 (m, 2H); (^{19}F NMR 377 MHz, $CDCl_3$) δ -72.2 (d, J = 9.2 Hz, 3F); HRMS (EI/FI) m/z Anal. Calcd for $C_{14}H_{17}F_3O$ $[M]^+$ 258.1224, found 258.1232.

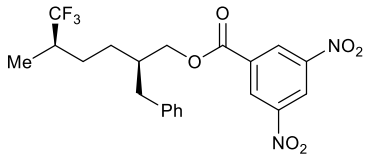
syn-2-Phenyl-6,6,6-trifluoro-5-methylhexan-1-ol 2-63



2-Benzyl-6,6,6-trifluoro-5-methylhex-3-en-1ol (36 mg, 0.14 mmol), 10% w/w $Pd(OH)_2/C$ (10 mg), and EtOH (1.0 mL) were subjected to a reaction flask. The flask was sealed, the air was substituted with H_2 using two vacuum/H_2 balloon cycles and the mixture was stirred for 20 h at room temperature. The reaction mixture was filtered through a Celite pad and washed with EtOH (5.0 mL). The filtrate was concentrated *in vacuo* to afford *syn*-2-benzyl-6,6,6-trifluoro-5-methylhexan-1-ol (10 mg, 28% yield) as a colourless oil. The isomeric ratio was determined by ^{19}F NMR analysis (*syn*/*anti* = 9.0 : 1).

Characterization data for the *syn*-isomer : (^{1}H NMR 500 MHz, $CDCl_3$) δ 1.06 (d, J = 7.0 Hz, 3H), 1.26-1.40 (m, 2H), 1.51-1.57 (m, 1H), 1.71-1.84 (m, 2H), 2.04-2.13 (m, 1H), 2.62 (dd, J_1 = 7.0 Hz, J_2 = 13.6 Hz, 1H), 2.71 (dd, J_1 = 7.6 Hz, J_2 = 13.6 Hz, 1H), 3.53-3.59 (m, 2H), 7.18 (d, J = 6.7 Hz, 2H), 7.21 (d, J = 7.3 Hz, 1H), 7.30 (t, J = 7.6 Hz, 2H); (^{13}C NMR 125MHz, $CDCl_3$) δ 12.5 (q, J = 2.8 Hz), 26.7 (q, J = 1.9 Hz), 27.6, 37.6, 38.1 (q, J = 26.5 Hz), 42.4, 64.3, 126.0, 128.4, 128.4 (q, J = 277.7 Hz), 129.1, 140.3; (^{19}F NMR 377 MHz, $CDCl_3$) δ -73.29 (d, J = 9.2 H, 3F).

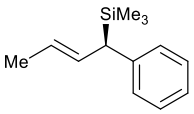
syn-2-Benzyl-6,6,6-trifluoro-5-methylhexyl 3,5-dinitrobenzoate 2-64



2-benzyl-6,6,6-trifluoro-5-methylhexanol (10 mg, 28 μmol, *syn*/*anti* = 9.0 : 1) was dissolved in CH_2Cl_2 (1.0 mL) and pyridine (2.5 μL, 31 μmol), 3,5-dinitrobenzoyl chloride (7.0 mg, 31 μmol) and DMAP (1.0 mg, 8 μmol) were added at room temperature. The mixture was stirred for 2 h at room temperature, after which H_2O (5 mL) was added to the reaction mixture. The aqueous phase was extracted with CH_2Cl_2 (3 x 5 mL) and the pooled organic layers were washed with H_2O (5 mL) and brine (5 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue was purified by silica gel column chromatography (eluent: EtOAc/*n*-hexane 1/4) to afford the title compound (13 mg, 98% yield) as a yellow solid. The isomeric ratio was determined by ^{19}F NMR analysis (*syn*/*anti* = 11.0 : 1).

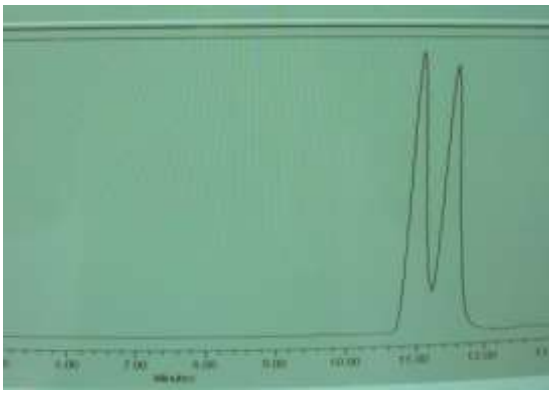
Characterization data for *syn*-2-benzyl-6,6,6-trifluoro-5-methylhexyl 3,5-dinitrobenzoate : (^1H NMR 400 MHz, $CDCl_3$) δ 1.10 (d, J = 7.1 Hz, 3H), 1.47-1.64 (m, 3H), 1.76-1.89 (m, 1H), 2.11-2.28 (m, 2H), 2.72 (dd, J_1 = 8.1 Hz, J_2 = 13.9 Hz, 1H), 2.82 (dd, J_1 = 6.3 Hz, J_2 = 13.9 Hz, 1H), 4.38 (d, J = 5.6 Hz, 2H), 7.13-7.29 (m, 5H), 9.03 (s, 2H), 9.23 (s, 1H); (^{13}C NMR 125 MHz, $CDCl_3$) δ 13.6 (q, J = 2.9 Hz), 26.8, 28.3, 38.0 (q, J = 26.5 Hz), 38.4, 39.4, 68.8, 122.4, 126.3, 128.2 (q, J = 277.7 Hz), 128.6, 128.9, 129.3, 133.7, 139.2, 148.6, 162.4; (^{19}F NMR 377 MHz, $CDCl_3$) δ -72.10 (d, J = 9.2 Hz, 3F); HRMS (TOF-ESI) *m/z* Calcd for $C_{21}H_{21}F_3N_2NaO_6$ $[M+Na]^+$ 477.1246, found 477.1244.

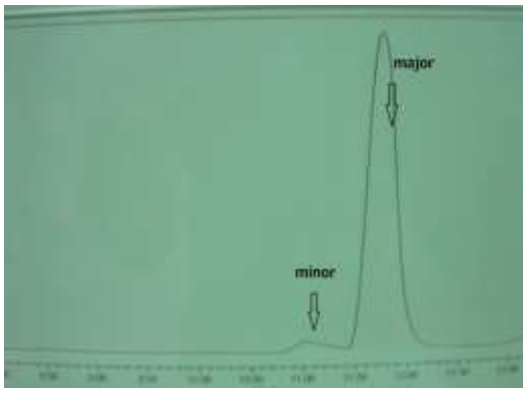
[(*R*,*E*)-1-(Trimethylsilyl)-2-buten-1-yl]-benzene 2-71



The title compound was prepared according to General Procedure D using $Pd(OAc)_2$ (121 mg, 540 μmol), 1,10-phenanthroline (117 mg, 650 μmol), $AgSbF_6$ (186 mg, 540 μmol) 1,4-benzoquinone (117 mg, 1.08 mmol), phenylboronic acid (988 mg, 8.10 mmol), (*S*, *E*)-4-(trimethylsilyl)but-3-en-2-yl 2-methoxybenzoate (1.50 g, 5.40 mmol) and 1,2-dichloroethane (35 mL). After 24 h, the reaction mixture was subjected to the workup described in the General Procedure D and purified by silica gel column chromatography (eluent: EtOAc/*n*-hexane = 10/90) to provide the title compound (411 mg, 37% yield, 97:3 er) as a colourless oil.[1]

(^{1}H NMR, 400 MHz, $CDCl_3$) δ 0.00 (s, 9H), 1.75 (d, J = 6.3 Hz, 3H), 2.92 (d, J = 9.8 Hz, 1H), 5.45 (qd, J_1 = 6.3, J_2 = 14.9 Hz, 1H), 5.84 (dd, J_1 = 9.6 Hz, J_1 = 14.9 Hz, 1H), 7.10-7.15 (m, 3H), 7.27-7.31 (m, 2H); (^{13}C NMR, 100 MHz, $CDCl_3$) δ -3.0, 18.1, 42.8, 123.5, 124.4, 127.1, 128.2, 130.2, 143.2; IR (neat) ν 2958, 1493, 1247, 1084, 964, 861, 833, 762, 741, 698 cm^{-1}; HRMS (EI) *m/z* Calcd for $C_{13}H_{20}Si$ $[M]^+$ 204.1329, found 204.1334; $[\alpha]_D^{20}$ = -40.1 (c = 2.0, $CHCl_3$). The enantiomeric purity of (*R*, *E*)-**2-71** was determined by HPLC analysis (CHIRACEL® OD-H column, 4.6 mm × 250 mm, *n*-hexane, 0.4 min/mL, 25 ˚C, UV detector (235 nm)), t_R (minor) = 11.0 min and t_R (major) = 11.7 min. The absolute configuration at C-2 was assigned as *R* on the basis of the sign of the optical rotation, consistent with the corresponding data for the *R* compound previously reported in the literature.





rac-2-71

Time (min)	Area	%area
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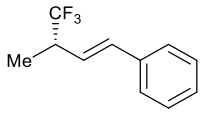
11.386	13136761	50.18

(*R*,*E*)-2-71

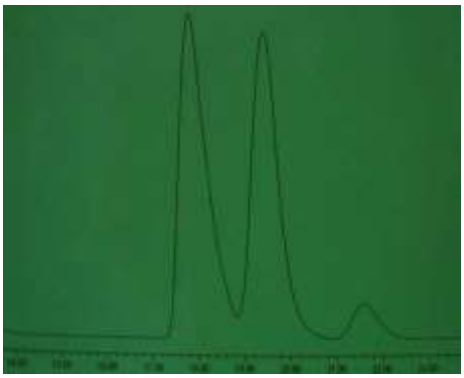
Time (min)	Area	%area
11.029	1744541	3.35
11.672	50289489	96.65

(+)-(*E*)-(4,4,4-Trifluoro-3-methylbut-1-en-1-yl)benzene 2-83



The title compound was prepared according to General Procedure A using [(*R*,*E*)-1-(trimethylsilyl)-2-buten-1-yl]-benzene (51 mg, 0.25 mmol, 97:3 er), Togni reagent II (0.14 g, 0.45 mmol), $Ru(bpy)_3Cl_2•6H_2O$ (9.0 mg, 0.013 mmol) and MeOH (0.50 mL). The isomeric ratio was determined by ^{19}F NMR analysis of the crude mixture (*E/Z* = 5.0:1). Purification by silica gel column chromatography (eluent: *n*-hexane) provided the title compound (28 mg, 56% yield, *E/Z* = 5.0 : 1, 85:15 er) as a colourless oil. The enantiomeric purity of the title compound was determined by HPLC analysis (CHIRACEL® OJ-H column, 4.6 mm × 250 nm, *n*-hexane, 0.5 min/mL, 25 ˚C, UV detector (220 nm)), t_R (minor) = 17.6 min and t_R (major) = 19.0 min.

(^1H NMR 400 MHz, $CDCl_3$) δ 1.33 (d, *J* = 7.0 Hz, 3H), 2.99-3.09 (m, 1H), 6.12 (dd, J_1 = 8.1 Hz, J_2 = 15.9 Hz, 1H), 6.58 (d, *J* = 16.9 Hz, 1H), 7.26-7.29 (m, 1H), 7.34 (t, *J* = 7.8 Hz, 2H), 7.39 (d, *J* = 7.6 Hz, 2H); (^{13}C NMR 125 MHz, $CDCl_3$) δ 13.6 (q, *J* = 1.9 Hz), 41.9 (q, *J* = 27.5 Hz), 124.2 (q, *J* = 2.8 Hz), 126.4, 127.2 (q, *J* = 277.7 Hz), 128.0, 128.6, 134.1. 136.3; (^{19}F NMR 377 MHz, $CDCl_3$) δ -72.53 (d, *J* = 9.2 Hz, 3F); IR (neat) ν 1258, 1172, 1123, 1070, 1016, 965, 839, 747, 693 cm^{-1}; HRMS (EI/SI) *m/z* Calcd for $C_{11}H_{11}F_3$ $[M]^+$ 200.0808, found 200.0813. $[\alpha]_D^{20}$ = +6.4 (c = 0.5, MeOH).



***rac*-(*E*)-2-83**

Time (min)	Area	%area
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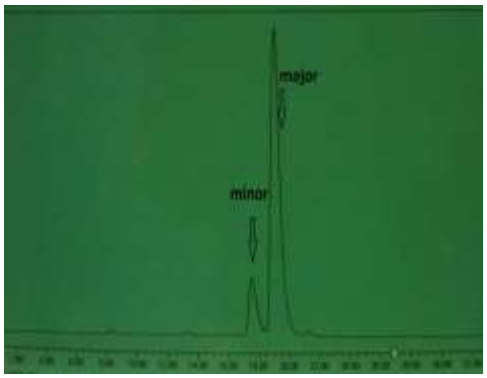
19.355	3531036	47.46



(*S*, *E*)-2-83

Time (min)	Area	%area
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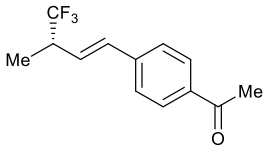
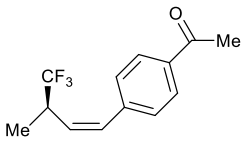
19.043	12424533	85.66

4'-(4,4,4-Trifluoro-3-methylbut-1-3-en-1-yl)-acetophenone 2-85



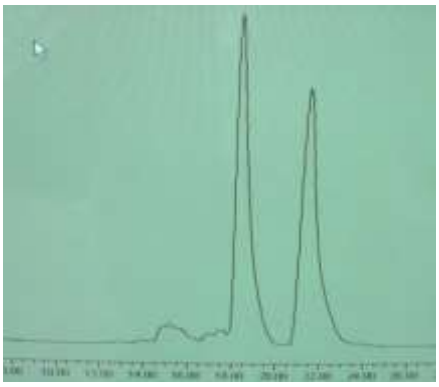


The title compound was prepared following General Procedure A using (*R*,*E*)-4'-[(1-(trimethylsilyl)but-2-en-1-yl]acetophenone (0.12 g, 0.50 mmol, >99:1 er), Togni reagent II (0.28 g, 0.90 mmol), $Ru(bpy)_3Cl_2 \bullet 6H_2O$ (19 mg, 0.025 mmol) and MeOH (1.0 mL). The isomeric ratio was determined by ^{19}F NMR analysis of the crude mixture (*E*/*Z* = 7.0 : 1). Purification by silica gel column chromatography (eluent: *n*-hexane) enabled to isolate *Z*-isomer (11 mg, 9% yield, 98:2 er) as a colourless oil and the *E*-isomer (71 mg, 59% yield, 88:12 er) as a colourless oil, respectively.

(-)-(*Z*)-4'-(4,4,4-Trifluoro-3-methylbut-1-3-en-1-yl)-acetophenone 2-85

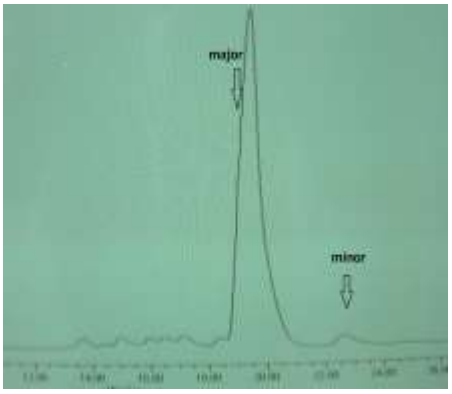
(^1H NMR 500 MHz, $CDCl_3$) δ 1.23 (d, *J* = 6.9 Hz, 3H), 2.62 (s, 3H), 3.31-3.41 (m, 1H), 5.69 (t, *J* = 11.0 Hz, 1H), 6.72 (d, *J* = 11.0 Hz, 1H), 7.33 (d, *J* = 8.2 H, 2H), 7.96 (d, *J* = 8.2 Hz, 2H); (^{13}C NMR 125 MHz, $CDCl_3$) δ 14.3 (q, *J* = 2.8 Hz), 26.6, 37.5 (q, *J* = 27.4 Hz), 127.2

(q, *J* = 277.7 Hz), 128.4 (q, *J* = 2.8 Hz), 128.5, 128.6, 132.3, 136.0, 141.0, 197.5; (^{19}F NMR 236 MHz, $CDCl_3$) δ -72.51(d, *J* = 8.4 Hz, 3F); IR (neat) ν 1683, 1605, 1357, 1259, 1168, 1129, 1104, 1069, 1013, 857, 739, 696 cm^{-1}; HRMS (ESI) *m/z* Calcd for $C_{13}H_{13}F_3ONa$ $[M+Na]^+$ 265.0813, found 265.0811; $[\alpha]_D^{20}$ = -24.0 (c = 0.3, MeOH). The enantiomeric purity was determined by HPLC analysis (CHIRACEL® OJ-H column, 4.6 mm x 250 mm, *n*-hexane/*i*-PrOH = 99:1, 0.5 min/mL, 25 ˚C, UV detector (270 nm)), t_R (minor) = 19.1 min and t_R (major) = 22.2 min.



rac-(*Z*)-2-85

Time (min)	Area	%area
18.390	4080200	49.13
21.258	4172594	50.87



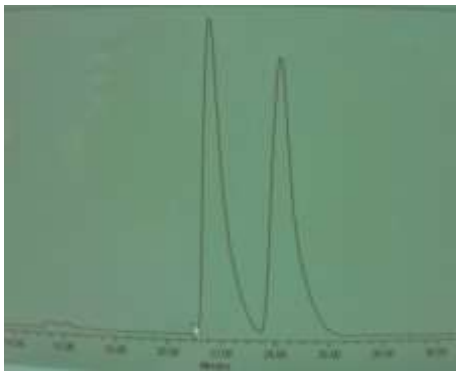
(-)-(*Z*)-2-85

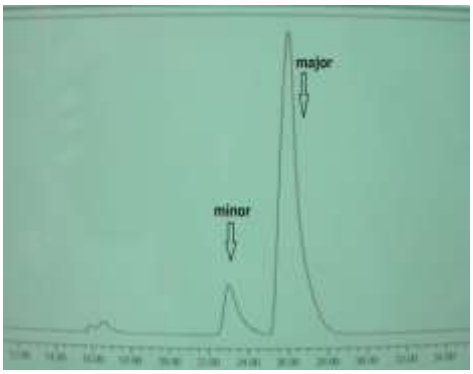
Time (min)	Area	%area
19.114	25950110	98.02
22.230	525539	1.98

(+)-(*E*)-4'-(4,4,4-Trifluoro-3-methylbut-1-3-en-1-yl)-acetophenone 2-85

(^{1}H NMR 500 MHz, $CDCl_3$) δ 1.35 (d, *J* = 7.3 Hz, 3H), 2.61 (s, 3H), 3.02-3.13 (m, 1H), 6.25 (dd, J_1 = 7.9 Hz, J_2 = 16.1 Hz, 1H), 6.63 (d, *J* = 16.1 Hz, 1H), 7.47 (d, *J* = 8.5 Hz, 2H), 7.93 (d, *J* = 8.5 Hz, 2H); (^{13}C NMR 125 MHz, $CDCl_3$) δ 13.5 (q, *J* = 2.8 Hz), 26.6, 41.4 (q, *J* = 27.5 Hz), 126.5, 126.9 (q, *J* = 277.7 Hz), 127.1 (q, *J* = 2.8 Hz), 128.8, 133.1, 136.4, 140.8, 197.5; (^{19}F NMR 236 MHz, $CDCl_3$) δ -72.81 (d, *J* = 8.7 Hz, 3F); IR (neat) ν 1681, 1604, 1359, 1226, 1171, 1123, 1070, 969, 817 cm^{-1}; HRMS (EI/FI) *m/z* Calcd for $C_{13}H_{13}F_3O$ $[M]^+$

242.0914, found 242.0918. $[\alpha]_D^{20}$ = +11.0 (c = 0.5, MeOH). The enantiomeric purity was determined by HPLC analysis (CHIRACEL® OJ-H column, 4.6 mm x 250 mm, *n*-hexane, 0.5 min/mL, 25 ˚C, UV detector (270 nm)), t_R (minor) = 23.0 min and t_R (major) = 25.7 min.





rac-(*E*)-2-85

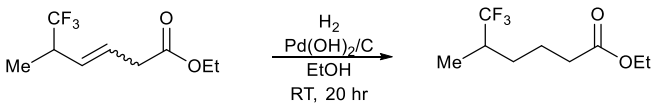
Time (min)	Area	%area
21.665	30651524	50.33
24.057	30246626	49.67

(+)-(*E*)-2-85

Time (min)	Area	%area
23.005	8329315	12.2
25.685	59871798	87.8

Ethyl 6,6,6-trifluoro-5-methylhexanoate **2-104** was prepared by an alternative method shown in below.

Ethyl 6,6,6-trifluoro-5-methylhexanoate 2-104



2-42 **2-104**, 89%

Ethyl 6,6,6-trifluoro-5-methylhex-3-enoate (30 mg, 0.14 mmol), 10% w/w $Pd(OH)_2/C$ (10 mg) and EtOH (1.0 mL) were added to a reaction flask. The flask was sealed, the air was substituted with H_2 using two vacuum/H_2 cycles and the mixture was stirred for 20 h. The reaction mixture was filtered through a Celite pad and washed with EtOH (5.0 mL). The filtrate was concentrated *in vacuo* to afford the title compoud (27 mg, 89% yield) as a colourless oil.

(^{1}H NMR 500 MHz, $CDCl_3$) δ 1.12 (d, *J* = 7.0 Hz, 3H), 1.26 (t, *J* = 7.3 Hz, 3H), 1.32-1.39 (m, 1H), 1.59-1.82 (m, 3H), 2.10-2.20 (m, 1H), 2.31-2.34 (m, 2H), 4.14 (q, *J* = 7.3 Hz, 2H); (^{13}C NMR 125 MHz, $CDCl_3$) δ 12.6 (q, *J* = 2.9 Hz), 14.2, 22.0, 28.8 (q, *J* = 2.9 Hz), 34.0, 37.7 (q, *J* = 26.5 Hz), 60.4, 128.3 (q, *J* = 277.7 Hz), 173.1; (^{19}F NMR 377 MHz, $CDCl_3$) δ -72.28 (d, *J* = 9.2 Hz, 3F); IR (neat) ν 2986, 1734, 1469, 1374, 1264, 1164, 1127, 1025, 847 cm^{-1}; HRMS (FI/EI) *m/z* Calcd for $C_9H_{15}F_3O_2$ $[M]^+$ 212.1026, found 212.1024.

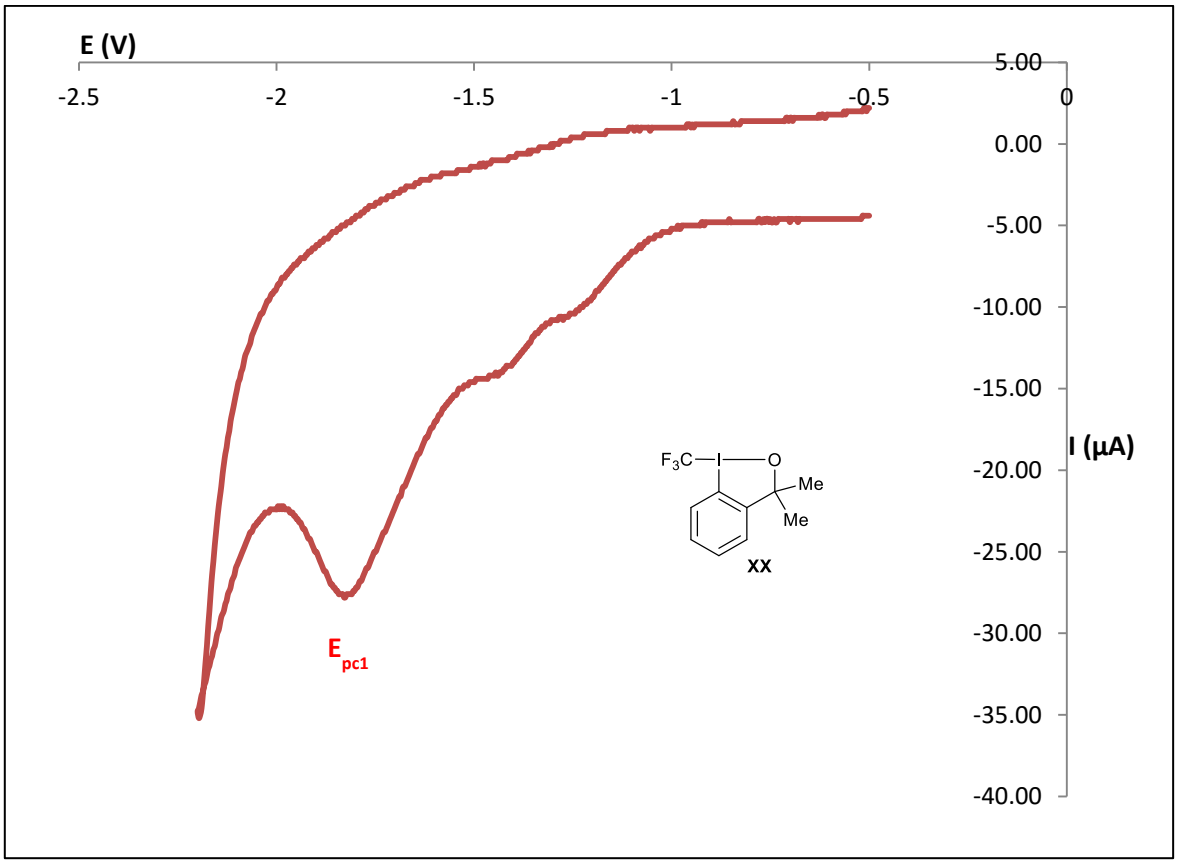
Characterization data for ethyl 4-(trifluoromethyl)hexanoate **2-105** : (^{19}F NMR 377 MHz, $CDCl_3$) δ -69.78 (d, *J* = 9.2 Hz, 3F) ; HRMS (FI/EI) *m/z* Calcd for $C_9H_{19}F_3NO_2$ $[M\text{-}NH_4]^+$ 230.1368, found 230.1359.

Cyclic Voltammetry Measurements

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 (working electrode, diameter = 3 mm), platinum wire auxiliary electrode and a non-aqueous Ag/Ag^+ (0.01 M $AgNO_3$ + 0.1 M *n*-Bu_4NClO_4) system in acetonitrile as the reference electrode. All solutions of the compounds under the study were 0.1 M in the supporting electrolyte *n*-Bu_4NPF_6 (Fluka *puriss* electrochemical grade) with the voltage scan rate of 0.2 V s^{-1}. Anhydrous solvents were obtained from Fisher Scientific. Solutions (2.5 mL) were thoroughly bubbled with dry nitrogen for 15 min to remove oxygen before any experiment and kept under positive pressure of nitrogen. Under these experimental conditions the $[FeCp_2]/[FeCp_2]^+$ couple, used as internal reference for potential measurements, was located at $E_{1/2}$ = +0.050 V in DMF, $E_{1/2}$ = +0.046 V in CH_3CN and $E_{1/2}$ = +0.065 V in MeOH. Conversion factors (SCE *vs.* Ag/Ag^+).[2]

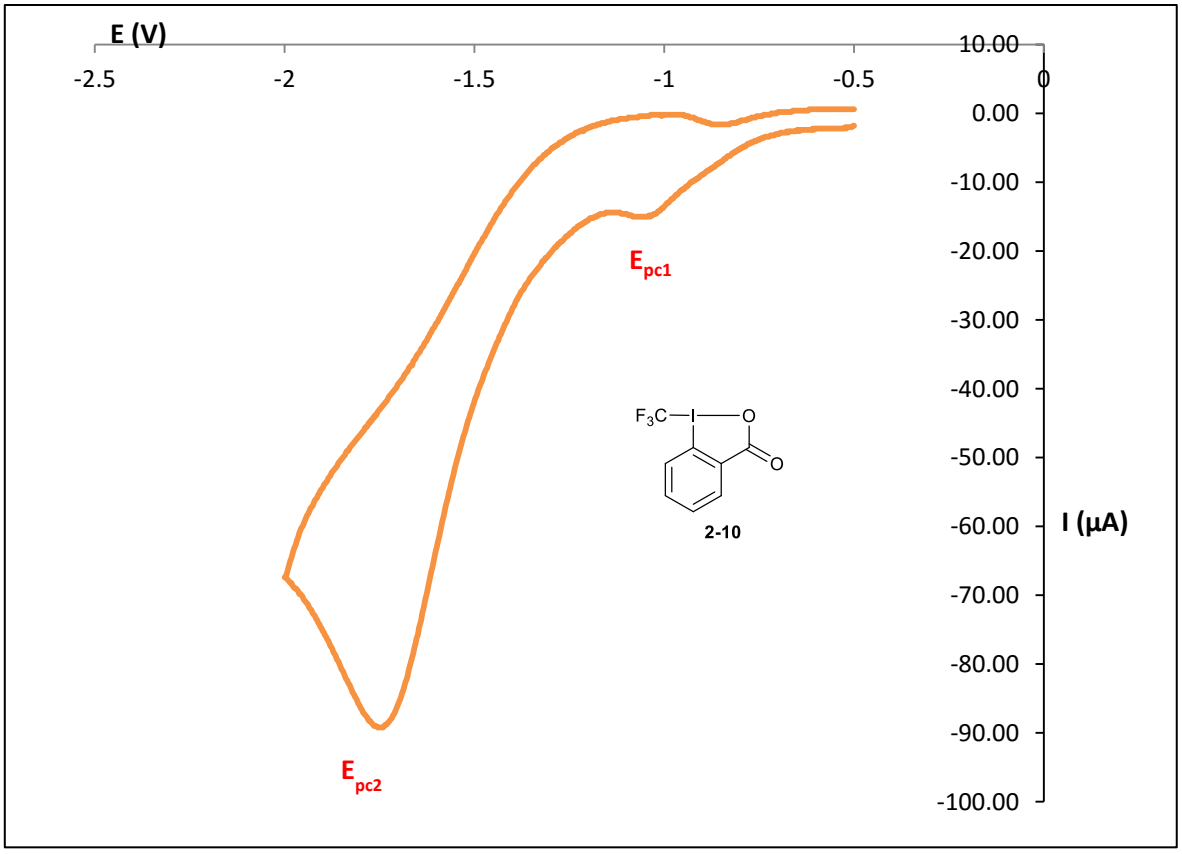
In our conditions $E_{1/2}$ (V *vs.* $[FeCp_2]/[FeCp_2]^+$) = +0.35 V *vs.* SCE in MeCN, $E_{1/2}$ (V *vs.* $[FeCp_2]/[FeCp_2]^+$) = +0.36 V *vs.* SCE in DMF and $E_{1/2}$ (V *vs.* $[FeCp_2]/[FeCp_2]^+$) = +0.38 V *vs.* SCE in MeOH.

Selected Cyclic Voltammetry Spectra



Cyclic voltammetry of Togni I reagent **2-43** in anhydrous acetonitrile (C = 1.72 mM) + 0.1 M *n*-Bu_4NPF_6, glassy carbon electrode, scan rate = 0.2 V s^{-1}, T = 293K. Scanning potential from -0.5 V to -2.2 V, then -2.2 V to - 0.5 V.

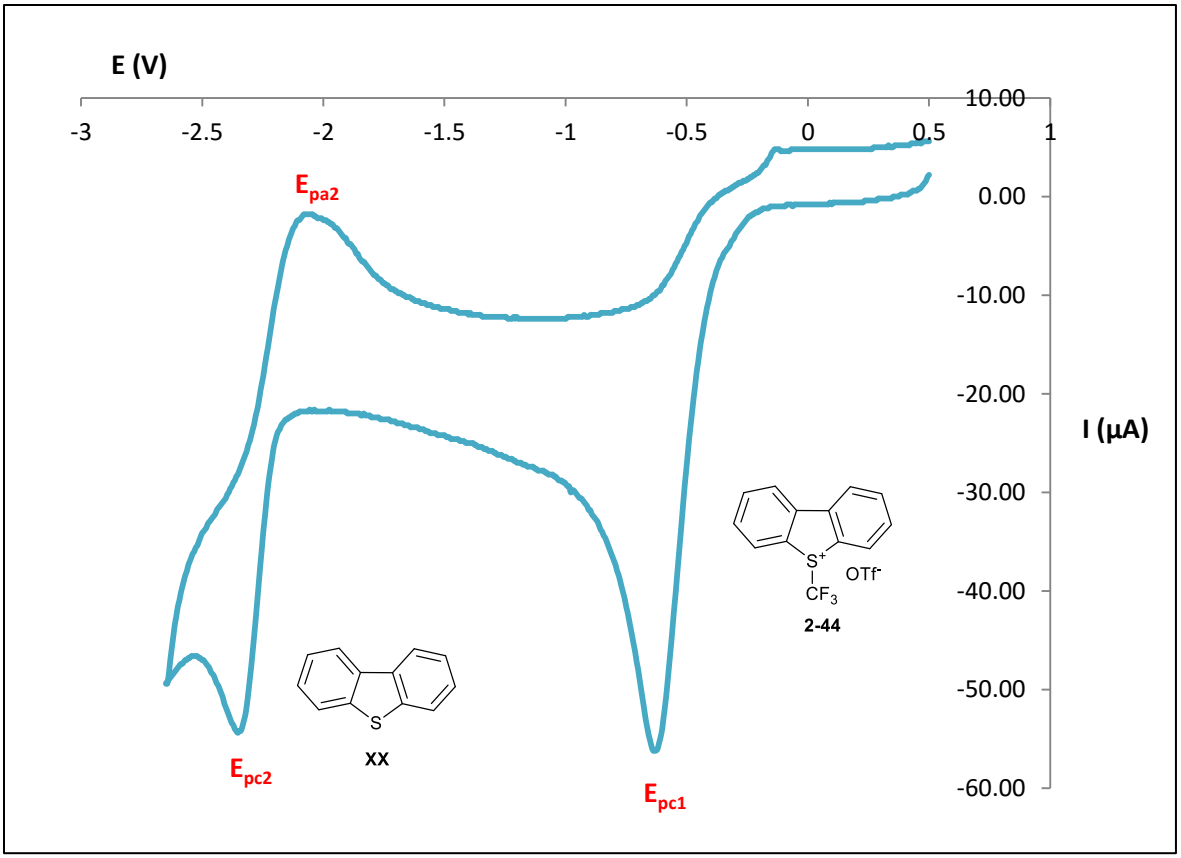
Epc1 = -1.80V vs $[FeCp_2]/[FeCp_2]^+$. Irreversible reduction of **2-43**



Cyclic voltammetry of Togni II reagent **2-10** (Epc1 = in anhydrous acetonitrile (C = 1.74 mM) + 0.1 M *n*-Bu_4NPF_6, glassy carbon electrode, scan rate = 0.2 V s^{-1}, T = 293K. Scanning potential from -0.5 V to -2.0 V, then -2.0 V to -0.5 V.

Epc1 = -1.14V vs $[FeCp_2]/[FeCp_2]^+$. Irreversible reduction of **2-10**

Epc2 = -1.73 vs $[FeCp_2]/[FeCp_2]^+$. Tentatively assigned as the ireversible reduction of o-iodobenzoic acid



Cyclic voltammetry of Umemoto reagent (C = 1.69 mM) in anhydrous acetonitrile + 0.1 M *n*-Bu_4NPF_6, glassy carbon electrode, scan rate = 0.2 V s^{-1}, T = 293K. Scanning potential from +0.5 V to -2.65 V, then -2.65 V to +0.5 V.

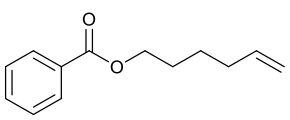
Epc1 = -0.60V vs $[FeCp_2]/[FeCp_2]^+$. Irreversible reduction of **2-44**

Epc2 = -2.19V vs $[FeCp_2]/[FeCp_2]^+$. Reversible reduction of dibenzothiophene

[1] T. Hayashi, M. Konishi, Y. Okamoto, K. Kabeta, M. Kumada, *J. Org. Chem.* **1986**, *51*, 3772-3781
[2] a) J. O. Howell, J. M. Goncalves, C. Amatore, L. Klasnic, R. M. Wightman, J. K. Kochi, *J. Am. Chem. Soc.* 1984, *106*, 3968-3976; b) C. Amatore, C. J. Lefrou, *J. Electroanal. Chem.* 1992, *325*, 239-246.

Chapter 3

Hex-5-en-1-yl benzoate 3-10

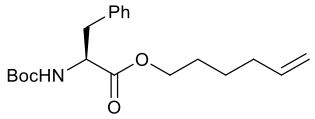


A solution of hex-5-en-1-ol (2.51 g, 25.0 mmol) in CH_2Cl_2 (50 mL) was cooled to 0 °C in an ice bath and DMAP (306 mg, 2.50 mmol) and pyridine (6.10 mL, 75.0 mmol) were added successively, followed by dropwise addition of benzoyl chloride (5.80 mL, 50.0 mmol). The solution was allowed to warm to room temperature and stir for 2 hrs. The reaction was quenched with H_2O (20 mL), and the aqueous phase was extracted with CH2CL2 (2 × 20 mL). The organic layers were combined, washed with H_2O (100 mL) and brine (100 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography (eluent: 30-40 petroleum ether to EtOAc/30-40 petroleum ether 1/16) to provide the title compound as a colourless oil (4.50 g, 88% yield).

(^{1}H NMR 400 MHz, $CDCl_3$) δ 1.54-1.60 (m, 2H), 1.79 (quint, J = 6.8 Hz, 2H), 2.13 (q, J = 7.2 Hz, 2H), 4.33 (t, J = 6.4 Hz, 2H), 4.96-5.07 (m, 2H), 5.83 (ddt, J_1 = 10.2 Hz, J_2 = 16.8 Hz, J_3 = 6.8 Hz, 1H), 7.42-7.46 (m, 2H), 7.53-7.58 (m, 1H), 8.03-8.06 (m, 2H); (^{13}C NMR 100 MHz, $CDCl_3$) δ 25.3, 28.1, 33.3, 64.9, 114.9, 128.3, 129.5, 130.4, 132.8, 138.4, 166.7; IR (neat) ν 2938, 1719, 1452, 1272, 1113, 711 cm^{-1}; HRMS (ESI) *m/z* Calcd for $C_{13}H_{16}NaO_2$ $[M+Na]^+$ 227.1037, found 226.9513.

Data consistent with literature values.[1]

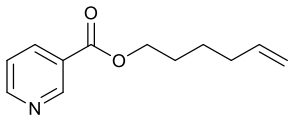
(*S*)-Hex-5-en-1-yl 2-((*tert*-butoxycarbonyl)amino)-3-phenylpropanoate 3-16



Boc-Phe-OH (2.65 g, 10 mmol), hex-5-en-1-ol (1.10 g, 11 mmol), triphenylphosphine (2.89 g, 11 mmol) were added to CH_2Cl_2 (80 mL). DEAD (1.7 mL, 11 mmol) was added dropwise, and the reaction was allowed to stir at room temperature for 18 hrs. The solvent was removed *in vacuo*, and the residue was dissolved in a minimal amount of Et_2O

(approximately 70 mL). The flask was transferred to a -20 °C freezer for several hours, at which point a large quantity of colourless crystals of triphenylphospine oxide were observed. The mixture was filtered through a plug of cotton, and the filtrate was concentrated *in vacuo*. The crude product was purified by silica gel column chromatography (eluent: EtOAc/30-40 petroleum ether 10/90) to provide the title compound (3.44 g, 99% yield) as a colourless oil. (^{1}H NMR 400 MHz, $CDCl_3$) δ 1.42 (s, 9H), 1.60 (quint, J = 6.4 Hz, 2H), 2.05 (q, J = 6.0 Hz, 2H), 3.03-3.13 (m, 2H), 4.04-4.14 (m, 2H), 4.54-4.59 (m, 1H), 4.96-5.03 (m, 2H), 5.77 (ddt, J_1 = 10.2 Hz, J_2 = 16.8 Hz, J_3 = 6.8 Hz, 1H), 7.13 (d, J = 6.8 Hz, 2H), 7.21-7.30 (m, 3H); (^{13}C NMR 100 MHz, $CDCl_3$) δ 25.0, 27.9, 28.3, 33.2, 38.4, 54.5, 65.3, 79.8, 114.9, 127.0, 128.5, 129.3, 136.1, 138.2, 155.1, 172.0; IR (neat) ν 3367, 2977, 1714, 1497, 1366, 1249, 1166 cm^{-1}; HRMS (EI/FI) *m/z* Calcd for $C_{20}H_{29}NO_4$ $[M]^+$ 347.2097, found 347.2094.

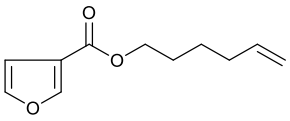
Hex-5-en-1-yl nicotinate 3-17



To a flame-dried 100 mL two-neck flask containing a magnetic stir bar, were added 5-hexen-1-ol (1.20 mL, 10.0 mmol), nicotinic acid (1.35 g, 11.0 mmol), DMAP (122 mg, 1.00 mmol), and CH_2Cl_2 (20 mL). The solution was cooled to 0 °C in an ice bath. DCC (2.27 g, 11.0 mmol) in CH_2Cl_2 (20 mL) was added dropwise. The solution was allowed to warm to room temperature and stir for 12 hrs, during which time a cloudy white precipitate was observed. The crude reaction mixture was then loaded directly onto a bed of silica gel for purification *via* column chromatography (eluent: EtOAc/*n*-hexane 70/30), which provided the title compound (1.78 g, 94% yield) as a white solid.

(^{1}H NMR 400 MHz, $CDCl_3$) δ 1.54 (tt, *J* = 7.5Hz, 2H), 1.79 (tt, *J* = 7.0 Hz, 2H), 2.11 (dt, *J* = 7.0 Hz, 2H), 4.35 (t, *J* = 6.5 Hz, 2H), 4.97 (ddt, *J* = 10.0 Hz, 2.0 Hz, 1.5 Hz, 1H), 5.02 (ddt, J_1 = 17.0 Hz, J_2 = 2.0 Hz, J_3 = 1.5 Hz, 1H), 5.80 (ddt, J_1 = 17.0 Hz, J_2 = 10.0 Hz, J_3 = 7.0 Hz, 1H), 7.38 (dd, J_1 = 8.0 Hz, J_2 = 5.0 Hz, 1H), 8.28 (dt, J_1 = 8.0 Hz, J_2 = 2.0 Hz, 1H), 8.76 (dd, J_2 = 5.0 Hz, J_2 = 1.5 Hz, 1H), 9.21 (d, *J* = 1.5 Hz, 1H). (^{13}C NMR 100 MHz, $CDCl_3$) δ 25.2, 28.0, 33.2, 65.3, 115.0, 123.2, 126.3, 137.0, 138.2, 150.9, 153.3, 165.3. IR (neat) ν 2939, 1724, 1115, 1591, 742. HRMS (TOF MS CI+) calc for $C_{12}H_{16}NO_2$ $[M+H]^+$ 206.1181, found 206.1181.

Hex-5-en-1-yl furan-3-carboxylate 3-18



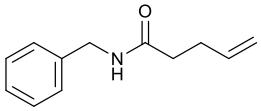
A solution of hex-5-en-1-ol (1.20 mL, 10 mmol) in CH_2Cl_2 (20 mL) was cooled to 0 °C in an ice bath and DMAP (122 mg, 1 mmol) and pyridine (2.4 mL, 30 mmol) were added successively, followed by dropwise addition of 2-furoyl chloride (2.0 mL, 20 mmol). The solution was allowed to warm to room temperature and stir for 2 hrs. The reaction was quenched with H_2O (20 mL), and the aqueous phase was extracted with CH_2Cl_2 (2 × 20 mL). The organic layers were combined, washed with H_2O (100 mL) and brine (100 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography (eluent: 30-40 petroleum ether to EtOAc/*n*-hexane 10:90 to 20:80) to provide the title compound (1.71 g, 84% yield) as a colourless oil.

(^{1}H NMR 400 MHz, $CDCl_3$) δ 1.39-1.49 (m, 2H), 1.63-1.74 (m, 2H), 1.99-2.09 (m, 2H), 4.23 (t, *J* = 6.7 Hz, 2H) 4.89 (ddt, J_1 = 10.2 Hz, J_2 = 2.1 Hz, J_3 = 1.2 Hz, 1 H), 4.95 (dq, J_1 = 17.1 Hz, J_2 = 1.7 Hz, 1 H), 5.73 (ddt, J_1 = 17.1 Hz, J_2 = 10.3 Hz, J_3 = 6.6 Hz, 1H), 6.43 (dd, J_1 = 3.4 Hz, J_2 = 1.7 Hz, 1H), 7.09 (dd, J_1 = 3.6, J_1 = 0.9 Hz, 1H), 7.50 (dd, J_1 = 1.7

Hz, J_2 = 1.0 Hz, 1H); (^{13}C NMR 100 MHz, $CDCl_3$) δ 25.1, 28.1, 33.3, 64.8, 111.8, 114.9, 117.7, 138.3, 144.8, 146.1, 158.8.

Data consistent with literature values.[2]

_N_-Benzylpent-4-enamide 3-21

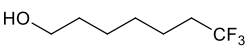


A solution of 4-pentenoic acid (1.00 g, 10.0 mmol), benzylamine (1.07 g, 10.0 mmol), DMAP (122 mg, 1.00 mmol) in CH_2Cl_2 (20 mL) was cooled to 0 °C in an ice bath and DCC (2.27 g, 11.0 mmol) in anhydrous CH_2Cl_2 (20 mL) was added dropwise. The solution was allowed to warm to room temperature and stir for 12 h, during which time a cloudy white precipitate was observed. The crude reaction mixture was then loaded directly onto a bed of silica gel for purification *via* column chromatography (eluent: EtOAc/30-40 petroleum ether 4/1 to 1/1) to provide the title compound (1.78 g, 94% yield) as a white solid.

(^{1}H NMR 400 MHz, $CDCl_3$) δ 2.27-2.31 (m, 2H), 2.37-2.42 (m, 2H), 4.40 (d, J = 5.6 Hz, 1H), 5.08-4.98 (m, 2H), 5.81 (ddt, J_1 = 6.4 Hz, J_2 = 10.4 Hz, J_2 = 17.2 Hz, 1H), 6.20 (br. s, 1H), 7.24-7.28 (m, 3H), 7.30-7.34 (m, 2H); (^{13}C NMR 100 MHz, $CDCl_3$) δ 29.5, 35.7, 43.4, 115.5, 127.3, 127.7, 128.5, 136.9, 138.3, 172.2; HRMS (ESI) *m/z* Calcd for $C_{12}H_{15}NNaO$ $[M+Na]^+$ 212.1046, found 212.1037. M.p. 42-46 °C

Data consistent with literature values.[3]

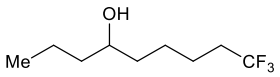
7,7,7-Trifluoroheptan-1-ol 3-27



The title compound was prepared following General Procedure A using 5-hexen-1-ol (40 mg, 0.40 mmol), $Ru(bpy)_3Cl_2.6H_2O$ (15 mg, 0.020 mmol), Umemoto reagent (0.19 mg, 0.48 mmol) and MeOH (0.80 mL). The crude product was purified by silica gel column chromatography (eluent: EtOAc/*n*-hexane = 1/4) to provide the title compound (31 mg, 47% yield) as a colourless oil.

(^{1}H NMR 500 MHz, $CDCl_3$) δ 1.39-1.42 (m, 4H), 1.51 (br. s, 1H), 1.54-1.61 (m, 4H), 2.07 (tq, J_1 = 7.9 Hz, J_2 = 11.1 Hz, 2H), 3.65 (t, J = 6.6 Hz, 2H); (^{13}C NMR 125 MHz, $CDCl_3$) δ 21.8 (q, J = 2.8 Hz), 25.3, 28.4, 32.4, 33.6 (q, J = 27.5 Hz), 62.7, 127.2 (q, J = 274.8 Hz); (^{19}F NMR 377 MHz, $CDCl_3$) δ -66.42 (t, J = 12.2 Hz, 3F), IR (neat) ν 3338, 2940, 1252, 1134, 1046 cm^{-1}; HRMS (EI/FI) *m/z* Calcd for $C_7H_{14}F_3O$ $[M+H]^+$ 170.0918 found 170.0915.

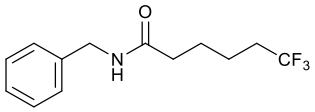
1,1,1-Trifluorononan-5-ol 3-28



The title compound was prepared following General Procedure A using oct-1-en-4-ol (50 mg, 0.39 mmol), $Ru(bpy)_3Cl_2.6H_2O$ (15 mg, 0.020 mmol), Umemoto reagent (0.19 g, 0.47 mmol) and MeOH (0.80 mL). The crude product was purified by silica gel column chromatography (eluent: EtOAc/*n*-hexane = 1/30 to 1/20) to provide the title compound (46 mg, 60% yield) as a colourless oil.

(^{1}H NMR 400 MHz, $CDCl_3$) δ 0.85 (t, J = 7.1 Hz, 3H), 1.18-1.74 (m, 10H), 1.97-2.01 (m, 2H), 3.54 (sept, J = 4.0 Hz, 2H); (^{13}C NMR 125 MHz, $CDCl_3$) δ 14.0, 18.3 (q, J = 2.8 Hz), 22.7, 28.0, 33.7 (q, J = 28.4 Hz), 36.2, 37.3, 71.5, 127.2 (q, J = 274.8 Hz); (^{19}F NMR 236 MHz, $CDCl_3$) δ -66.80 (t, J = 11.0 Hz, 3F), IR (neat) ν 3356, 1252, 1140 cm^{-1}; HRMS (EI/FI) *m/z* Calcd for $C_9H_{15}F_3$ $[M-H_2O]^+$ 180.1126, found 180.1327.

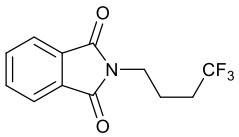
N-Benzyl-6,6,6-trifluorohexanamide 3-29



The title compound was prepared following General Procedure A using *N*-benzylpent-4-enamide (47 mg, 0.25 mmol), Umemoto reagent (0.12 mg, 0.30 mmol), $Ru(bpy)_3Cl_2.6H_2O$ (9.0 mg, 0.013 mmol) and MeOH (0.50 mL). The crude product was purified by silica gel column chromatography (eluent: EtOAc/*n*-hexane /1) to provide the title compound (28 mg, 44% yield) as a white crystalline solid.

(^{1}H NMR 500 MHz, $CDCl_3$) δ 1.57-1.63 (m, 2H), 1.72-1.78 (m, 2H), 2.05-2.15 (m, 2H), 2.24 (t, *J* = 7.4 Hz, 2H), 4.44 (d, *J* = 5.7 Hz, 2H), 5.84 (s, 1H), 7.26-7.30 (m, 3H), 7.34 (t, *J* = 7.1 Hz, 2H); (^{13}C NMR 125 MHz, $CDCl_3$) δ 21.6 (q, *J* = 2.9 Hz), 24.6, 33.5 (q, *J* = 28.6 Hz), 36.0, 43.6, 127.6, 127.0 (q, *J* = 276.2 Hz), 127.8, 128.7, 138.2, 172.0; (^{19}F NMR 377 MHz, $CDCl_3$) δ -66.35 (t, *J* = 10.9 Hz); IR (neat) ν 2941, 1644, 1551, 1455, 1390, 1255, 1135, 1028 cm^{-1}; HRMS (ESI) *m/z* Calcd for $C_{13}H_{16}F_3NNaO$ $[M+Na]^+$ 282.1073, found 282.1068; M.p. 54-59 ˚C.

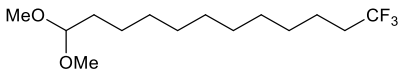
***N*-(4,4,4-trifluorobutyl)phthalimide 3-30**



The title compound was prepared following General Procedure A using *N*-allylphthalimide (47 mg, 0.25 mmol), $Ru(bpy)_3Cl_2•6H_2O$ (9.0 mg, 0.013 mmol), Umemoto reagent (0.12 g, 0.30 mmol) and MeOH (0.50 mL). The crude product was purified by silica gel column chromatography (eluent: EtOAc/*n*-hexane 1/20) to provide the title compound (37 mg, 57% yield) as a white solid.

(^{1}H NMR 500 MHz, $CDCl_3$) δ 1.86-1.92 (m, 2H), 2.04-2.15 (m, 2H), 3.69 (t, J = 7.0 Hz, 2H), 7.66 (dd, J_1 = 3.2 Hz, J_2 = 5.4 Hz, 2H), 7.79 (dd, J_1 = 3.2 Hz, J_2 = 5.4 Hz, 2H); (^{13}C NMR 125 MHz, $CDCl_3$) δ 21.5 (q, J = 2.9 Hz), 31.5 (q, J = 28.4 Hz), 36.7, 123.4, 126.7 (q, J = 274.8 Hz), 131.9, 134.1, 168.2; (^{19}F NMR 236 MHz, $CDCl_3$) δ -66.80 (t, J = 10.5 Hz, 3F); IR (neat) ν 1694, 1340, 1350, 1241,1173, 1087, 998, 912, 856, 716 cm^{-1}; HRMS (EI/FI) *m/z* Calcd for $C_{12}H_{10}F_3NO_2$ $[M]^+$ 257.0664, found 257.0666; m.p. 54-55 °C.

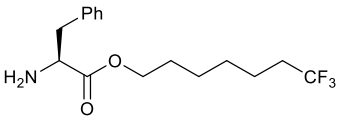
12,12,12-Trifluorododecanal dimethylacetal 3-32



The title compound was prepared following General Procedure A using undecylenic aldehyde (42 mg, 0.25 mmol), $Ru(bpy)_3Cl_2.6H_2O$ (15 mg, 0.020 mmol), Umemoto reagent (193 mg, 0.48 mmol) and MeOH (0.80 mL). The crude product was purified by silica gel column chromatography (eluent: EtOAc/*n*-hexane 20/80) to provide the title compound (39 mg, 55% yield) as a colourless oil.

(^{1}H NMR 500 MHz, $CDCl_3$) δ 1.28-1.36 (m, 14H), 1.52-1.62 (m, 4H), 2.06 (tq, J_1 = 7.9 Hz, J_2 = 11.1 Hz, 2H), 3.32 (s, 6H), 4.36 (t, J = 5.7 Hz, 1H); (^{13}C NMR 125 MHz, $CDCl_3$) δ 21.8 (q, J = 2.8 Hz), 24.6, 28.7, 29.1, 29.3, 29.41, 29.43, 29.5, 32.5, 33.7 (q, J = 28.4 Hz), 52.6, 104.6, 127.3 (q, J = 274.8 Hz); (^{19}F NMR 377 MHz, $CDCl_3$) δ -66.42 (t, J = 12.2 Hz, 3F), IR (neat) ν 2927, 2856, 1465, 1387, 1254, 1126, 1053 cm^{-1}; HRMS (EI/FI) *m/z* Calcd for $C_{13}H_{24}F_3O$ $[M\text{-}OMe]^+$ 253.1779 found 253.1815.

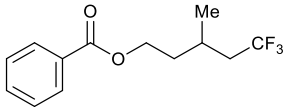
(*S*)-7,7,7-trifluoroheptyl 2-amino-3-phenylpropanoate 3-33



The title compound was prepared following General Procedure A using (*S*)-hex-5-en-1-yl 2-amino-3-phenylpropanoate (87 mg, 0.25 mmol), $Ru(bpy)_3Cl_2.6H_2O$ (9.0 mg, 0.013 mmol), Umemoto reagent (0.12 g, 0.30 mmol) and MeOH (0.50 mL). The crude product was purified by silica gel column chromatography (eluent: EtOAc/*n*-hexane 1/2) to provide the title compound (41 mg, 52 % yield) as a colourless oil.

(^{1}H NMR 400 MHz, $CDCl_3$) δ 1.25-1.32 (m, 4H), 1.48-1.59 (m, 5H), 2.01 (tq, J_1 = 7.8 Hz, J_2 = 11.0 Hz, 2H), 2.83 (dd, J_1 = 7.8 Hz, J_2 = 13.4 Hz, 1H), 3.01 (dd, J_1 = 5.6 Hz, J_2 = 13.4 Hz, 1H), 3.68 (t, J = 5.9 Hz, 1H), 4.04 (t, J = 6.6 Hz, 2H), 7.14 (d, J = 6.8 Hz, 2H), 7.19 (dt, J_1 = 2.4 Hz, J_2 = 7.3 Hz, 1H), 7.24 (d, J = 7.3 Hz, 2H); (^{13}C NMR 125 MHz, $CDCl_3$) δ 21.7 (q, J = 2.8 Hz), 25.5, 28.3, 28.3, 33.6 (q, J = 27.5 Hz), 41.2, 55.8, 64.8, 126.8, 127.2 (q, J = 274.8 Hz), 128.5, 129.3, 137.2, 175.0; (^{19}F NMR 377 MHz, $CDCl_3$) δ -66.36 (t, J = 12.1 Hz, 3F); IR (neat) ν 2944, 1733, 1253, 1178, 1137, 837, 745, 700 cm^{-1}; HRMS (EI/FI) *m/z* Calcd for $C_{16}H_{23}F_3NO_2$ $[M+H]^+$ 318.1673 found 318.1675; $[\alpha]_D^{20}$ = +17.4 (c = 0.50, MeOH).

5,5,5-Trifluoro-3-methylpentyl benzoate 3-40

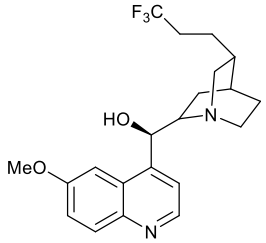


The title compound was prepared following General Procedure A using 3-methylbut-3-en-1-yl benzoate (48 mg, 0.25 mmol), $Ru(bpy)_3Cl_2.6H_2O$ (9.0 mg, 0.013 mmol), Umemoto reagent (0.12 g, 0.30 mmol) and MeOH (0.5 mL). The crude product was purified by silica gel column chromatography (eluent: EtOAc/*n*-hexane 5/95) to provide the title compound (35 mg, 53% yield) as a colourless oil.

(^{1}H NMR 500 MHz, $CDCl_3$) δ 1.13 (d, J = 7.0 Hz, 3H), 1.68-1.75 (m, 1H), 1.91-1.98 (m, 1H), 2.00-2.26 (m, 3H), 4.38-4.41 (m, 2H), 7.46 (t, J = 7.6 Hz, 2H), 7.58 (dt, J_1 = 1.3 Hz,

J_2 = 7.6 Hz, 1H), 8.04 (dd, J_1 = 1.3 Hz, J_2 = 8.5 Hz, 2H); (^{13}C NMR 125 MHz, $CDCl_3$) δ 19.6, 25.1 (d, J = 1.9 Hz), 35.3, 40.2 (q, J = 26.5 Hz), 62.4, 127.0 (q, J = 275.8 Hz), 128.4, 129.5, 130.1, 133.0, 166.5; (^{19}F NMR 236 MHz, $CDCl_3$) δ -63.72 (t, J = 10.8 Hz, 3F), IR (neat) ν 1718, 1271, 1140, 1111, 1070, 1050, 1027, 709 cm^{-1}; HRMS (EI/FI) *m/z* Calcd for $C_{13}H_{15}F_3O_2$ $[M]^+$ 260.1024 found 260.1023.

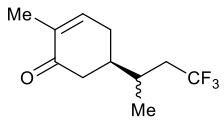
(1*R*)-(6-methoxyquinolin-4-yl)((1S,4S,5R)-5-(3,3,3-trifluoropropyl)quinuclidin-2-yl)methanol 3-46



The title compound was prepared following General Procedure A using Quinine (81 mg, 0.25 mmol), $Ru(bpy)_3Cl_2.6H_2O$ (9.0 mg, 0.013 mmol), Umemoto reagent (0.12 g, 0.30 mmol) and MeOH (0.50 mL). Purification by preparative TLC on C18 reversed phase silica (eluent: EtOAc/MeOH 90/1) gave the title compound (56 mg, 57% yield) as a yellow solid.

(^{1}H NMR 500 MHz, $CDCl_3$) δ 1.40-1.54 (m, 4H), 1.65 (br. s, 1H), 1.80-1.82 (m, 1H), 1.87-2.04 (m, 4H), 2.40 (br. d, J = 13.6 Hz, 1H), 2.69-2.75 (m, 1H), 3.11-3.19 (m, 2H), 3.69 (br. s, 1H), 3.81 (s, 3H), 5.73 (br.s, 1H), 7.14 (d, J = 2.6 Hz, 1H), 7.24 (dd, J_1 = 2.6 Hz, J_2 = 9.2 Hz, 1H), 7.52 (d, J = 4.8 Hz, 1H), 7.90 (d, J = 9.2 Hz, 1H), 8.62 (d, J = 4.8 Hz, 1H); (^{13}C NMR 125 MHz, $CDCl_3$) δ 20.4, 25.4, 26.5 (q, J = 1.9 Hz), 27.2, 31.7 (q, J = 29.4 Hz), 34.2, 43.2, 55.8, 57.6, 59.8, 70.4, 100.9, 118.5, 121.6, 126.3 (q, J = 274.8 Hz), 130.1, 144.1, 146.7, 147.4, 157.9; (^{19}F NMR 236 MHz, $CDCl_3$) δ -66.73 (t, J = 10.8 Hz, 3F), IR (neat) ν 2970, 1739, 1434, 1365 cm^{-1}; HRMS (ESI) *m/z* Calcd for $C_{21}H_{26}F_3N_2O_2$ $[M+H]^+$ 395.1946, found 395.1941. $[\alpha]_D^{20}$ = -96.9 (c = 0.80, MeOH).

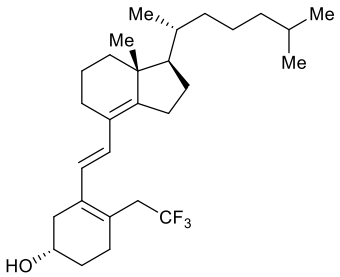
(*R*)-2-methyl-5-(4,4,4-trifluorobutan-2yl)cyclohex-2-enone 3-47



The title compound was prepared following General Procedure A using (*R*)-carvone (50 mg, 0.33 mmol), $Ru(bpy)_3Cl_2.6H_2O$ (12 mg, 0.017 mmol), Umemoto reagent (0.16 mg, 0.40 mmol) and MeOH (0.70 mL). The crude product was purified by silica gel column chromatography (eluent: EtOAc /*n*-hexane 1/30) to provide title compound (40 mg, 54% yield, dr = 1 : 1) as a colourless oil. The isomeric ratio was determined by ^{19}F NMR analysis.

Characterization data for the mixture of isomers of **3-47** (dr = 1:1): (^1H NMR 400 MHz, $CDCl_3$) δ 1.04-1.06 (m, 3H), 1.79 (s, 3H), 1.90-1.96 (m, 2H), 2.11-2.23 (m, 4H), 2.29-2.33 (m, 1H), 2.44-2.51 (m, 1H), 6.75-6.76 (m, 1H); (^{13}C NMR 125 MHz, $CDCl_3$) δ 15.6, 15.6, 16.1, 16.3, 26.2, 29.8, 31.3 (q, *J* = 2.9 Hz), 31.4 (q, *J* = 1.9 Hz), 37.5 (q, *J* = 22.7 Hz), 37.7 (q, *J* = 22.7 Hz), 40.07, 40.12, 40.3, 41.9, 127.1 (q, *J* = 127.05 Hz), 135.57, 135.60, 144.3, 144.4, 199.36, 199.40; (^{19}F NMR 236 MHz, $CDCl_3$) δ -63.51 (t, *J* = 11.0 Hz, 1.5F), -63.52 (t, *J* = 11.0 Hz, 1.5F) IR (neat) ν 224,1672, 1367, 1281, 1254, 1154, 1150, 1113, 1052 cm^{-1}; HRMS (ESI) *m/z* Calcd for $C_{11}H_{15}F_3NaO$ $[M+Na]^+$ 243.0960, found 243.0967.

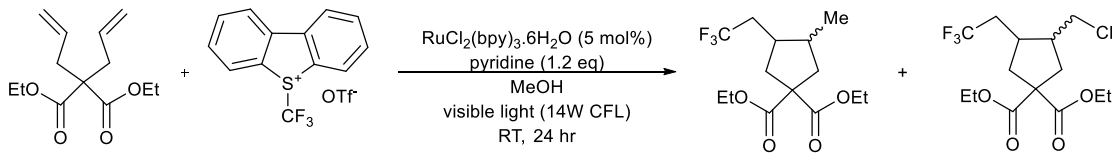
(*S*)-3-((*E*)-2-((1*R*,7a*R*)-7a-methyl-1-((*R*)-6-methylheptan-2-yl)-2,3,5,6,7,7a-hexahydro-1H-inden-4-yl)vinyl)-4-(2,2,2-trifluoroethyl)cyclohex-3-en-1-ol 3-48



The title compound was prepared following General Procedure A using Cholecalciferol (96 mg, 0.25 mmol), $Ru(bpy)_3Cl_2.6H_2O$ (9.0 mg, 0.013 mmol), Umemoto reagent (0.12 g, 0.30 mmol) and MeOH (0.50 mL). The crude product was purified by silica gel column chromatography (eluent: EtOAc/*n*-hexane 1/30) to provide the title compound (44 mg, 39% yield) as a pale yellow oil.

(^{1}H NMR 400 MHz, $CDCl_3$) δ 0.87 (d, *J* = 6.6 Hz, 6H), 0.88 (s, 3H), 0.95 (d, *J* = 6.6 Hz, 3H), 1.04-1.20 (m, 8H), 1.37-1.40 (m, 3H), 1.51-1.56 (m, 2H), 1.65-1.69 (m, 4H), 1.87-1.91 (m, 2H), 1.93-2.07 (m, 4H), 2.13-2.17 (m, 2H), 2.25-2.29 (m, 1H), 2.50 (dd, J_1 = 4.0 Hz, J_2 = 16.7 Hz, 1H), 2.77 (dq, J_1 = 11.4 Hz, J_2 = 14.5 Hz, 1H), 2.87 (dq, J_1 = 11.4 Hz, J_2 = 14.5 Hz, 1H), 3.91-3.98 (m, 1H), 5.80 (d, *J* = 12.4 Hz, 1H), 5.97 (d, *J* = 12.4 Hz, 1H); (^{13}C NMR 125 MHz, $CDCl_3$) δ 18.1, 19.0, 19.4, 22.6, 22.8, 23.7, 26.4, 26.97, 27.01, 27.8, 28.0, 30.9, 34.7, 35.9, 36.9, 37.5 (q, *J* = 28.4 Hz), 38.3, 39.5, 43.5, 56.1, 66.7, 122.2 (q, *J* = 1.9 Hz), 125.1, 126.5 (q, *J* = 277.7 Hz), 127.1, 131.5, 134.8, 148.8; (^{19}F NMR 236 MHz, $CDCl_3$) δ -63.31 (t, *J* = 11.3 Hz, 3F); IR (neat) ν 3500, 2953, 1717, 1465, 1367, 1256, 1130, 909, 733 cm^{-1}; HRMS (ESI) *m/z* Calcd for $C_{28}H_{43}F_3NaO$ $[M+Na]^+$ 475.3150 found 475.3158; $[\alpha]_D^{20}$ = +28.1 (c = 0.42, MeOH).

Diethyl 3-methyl-4-(2,2,2-trifluoroethyl)cyclopentane-1,1-dicarboxylate 3-51 and diethyl 3-(chloromethyl)-4-(2,2,2-trifluoroethyl)cyclopentane-1,1-dicarboxylate 3-52



3-51 **3-52**

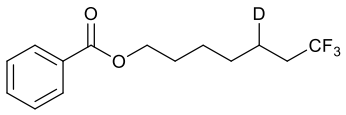
The title compound was prepared following General Procedure A using diethyl 2,2-diallylmalonate (60 mg, 0.25 mmol), $Ru(bpy)_3Cl_2.6H_2O$ (9.0 mg, 0.013 mmol), Umemoto reagent (0.12 g, 0.30 mmol), pyridine (15 μL, 0.30 mmol) and MeOH (0.50 mL). The

crude product was purified by silica gel column chromatography (eluent: EtOAc/*n*-hexane 5/95) to provide **3-51** (32 mg, 41% yield, dr = 13:1) as a colourless oil and **3-52** (8 mg, 8% yield) as a colourless oil.

Characterization data for the *major* isomer of **3-51** (*major/minor* = 13:1): (^{1}H NMR 500 MHz, $CDCl_3$) δ 0.91 (d, *J* = 7.0 Hz, 3H), 1.29 (t, *J* = 7.3 Hz, 3H), 2.06-2.26 (m, 4H), 2.39-2.40 (m, 2H), 2.48-2.54 (m, 2H), 4.23 (q, *J* = 7.3 Hz, 2H), 4.24 (q, *J* = 7.3 Hz, 2H); (^{13}C NMR 125 MHz, $CDCl_3$) δ 14.0, 14.9, 35.0 (q, *J* = 28.4 Hz), 35.9, 36.5 (q, *J* = 1.9 Hz), 37.9, 41.1, 58.6, 61.5, 61.6, 127.1 (q, *J* = 274.8 Hz) 172.52, 172.54; ^{19}F NMR (377 MHz, $CDCl_3$) δ -64.63 (t, *J* = 10.4 Hz, 3F), IR (neat) ν 2980, 1728, 1249, 1183, 1152, 1117, 856 cm^{-1}; HRMS (EI/FI) *m/z* Calcd for $C_{14}H_{21}F_3NaO_4$ $[M+Na]^+$ 333.1286 found 333.1284.

Characterization data for **3-52**: (^{1}H NMR 400 MHz, $CDCl_3$) δ 1.18 (t, *J* =7.1 Hz, 3H), 1.19 (t, *J* = 7.1 Hz, 3H), 1.96-2.26 (m, 4H), 2.42-2.51 (m, 4H), 3.37 (dd, J_1 = 7.1 Hz, J_2 = 11.0 Hz, 1H), 3.44 (dd, J_1 = 6.4 Hz, J_2 = 11.0 Hz, 1H), 4.13 (q, *J* = 7.1 Hz, 4H); (^{19}F NMR 377 MHz, $CDCl_3$) δ -64.42 (t, *J* = 10.4 Hz, 3F); HRMS (ESI) *m/z* Calcd for $C_{14}H_{20}ClF_3NaO_4$ $[M+Na]^+$ 344.1002 found 344.1008.

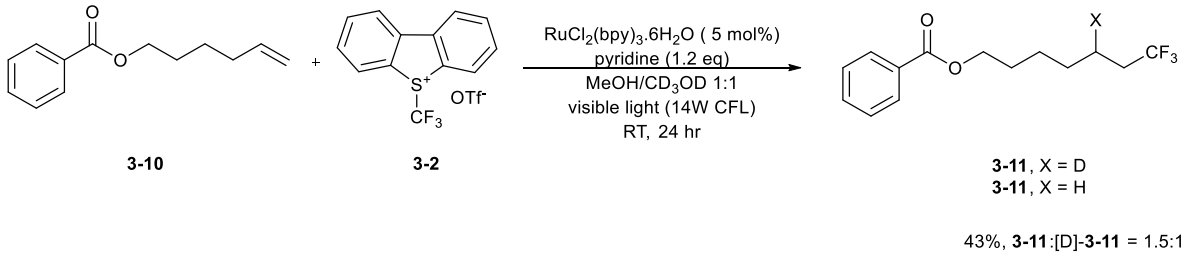
5-Deuterio-7,7,7-trifluoroheptyl benzoate [D]-**3-11**



A) The title compound was prepared following General Procedure A using hex-5-en-1-yl benzoate (51 mg, 0.25 mmol), $Ru(bpy)_3Cl_2.6H_2O$ (9.0 mg, 0.013 mmol), Umemoto reagent (0.12 g, 0.30 mmol) and CD_3OD (0.50 mL). The crude product was purified by silica gel column chromatography (eluent: Et_2O/*n*-hexane 5/95) to provide the title compound (18 mg, 26% yield) as a colourless oil. (^{1}H NMR 400 MHz, $CDCl_3$) δ 1.42-1.52 (m, 4H), 1.56-1.61 (m, 1H), 1.80 (quint., *J* = 6.6 Hz, 2H), 2.08 (dq, J_1 = 7.8 Hz,

J_2= 11.0 Hz, 2H), 4.33 (t, J = 6.6 Hz, 2H), 7.46 (t, J = 7.8 Hz, 2H), 7.57 (tt, J_1 = 1.4 Hz, J_2 = 7.4 Hz, 1H), 8.05 (dd, J_1 = 1.4 Hz, J_2 = 8.6 Hz, 2H); (^{13}C NMR 125 MHz, $CDCl_3$) δ 21.5 (tq, J_1 = 2.8 Hz, J_2 = 19.0 Hz), 25.7, 28.3, 28.5, 33.6 (q, J = 27.9 Hz), 64.8, 127.2 (q, J = 273.9 Hz), 128.4, 129.5, 130.6, 132.9, 166.6; (^{19}F NMR 377 MHz, $CDCl_3$) δ -66.37 (t, J = 10.4 Hz, 3F); IR (neat) ν 2937, 1717, 1270, 1256, 1141, 1111, 710 cm^{-1}; HRMS (EI/FI) *m/z* Calcd for $C_{14}H_{16}DF_3O_2$ $[M]^+$ 275.1243, found 275.1240.

B) The title compound was prepared following General Procedure A using hex-5-en-1-yl benzoate (51 mg, 0.25 mmol), $Ru(bpy)_3Cl_2.6H_2O$ (9.0 mg, 0.013 mmol), Umemoto reagent (0.12 g, 0.30 mmol) and CD_3OH (0.5 mL). The crude product was purified by silica gel column chromatography (eluent: Et_2O/*n*-hexane 5/95) to provide the title compound (15 mg, 22% yield) as a colourless oil.



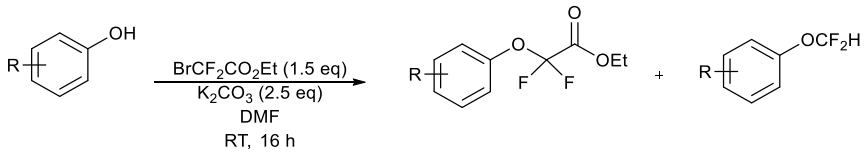
3-10 **3-2** **3-11**, X = D **3-11**, X = H

43%, **3-11**:[D]-**3-11** = 1.5:1

The title compound was prepared following General Procedure A using hex-5-en-1-yl benzoate (51 mg, 0.25 mmol), $Ru(bpy)_3Cl_2$•$6H_2O$ (9.0 mg, 0.013 mmol), Umemoto reagent (0.12 g, 0.30 mmol), MeOH (0.25 mL) and CD_3OD (0.25 mL). The crude product was purified by silica gel column chromatography (eluent: Et_2O/*n*-hexane = 5:95) to provide the title compound (29 mg, 43% yield) as a colourless oil. The isomeric ratio was determined by ^{19}F NMR analysis (**3-11**:[D]-**3-11** = 1.5 : 1).

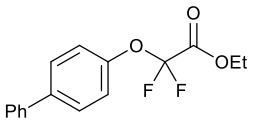
Chapter 4

General Procedure E



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 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)(difluoro)acetate 4-101

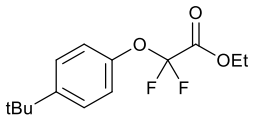


The title compound was prepared following General Procedure E using K_2CO_3 (3.46 g, 25.0 mmol), 4-phenylphenol (1.70 g, 10.0 mmol), ethyl bromodifluoroacetate (3.21 mL, 25.0 mmol) and DMF (20 mL). The crude product was purified by silica gel column chromatography (eluent: EtOAc/*n*-hexane 3/97) to provide the title compound (1.60 g, 55% yield) as a white solid.

(^{1}H NMR, 400 MHz, $CDCl_3$) δ = 1.40 (t, *J* = 7.2 Hz, 3H), 4.42 (q, *J* = 7.1 Hz, 2H), 7.31 (d, *J* = 8.8 Hz, 2H), 7.37-7.40 (m, 1H), 7.44-7.48 (m, 2H), 7.56-7.61 (m, 4H); (^{13}C NMR, 101 MHz, $CDCl_3$) δ = 13.8, 63.7, 114.0 (t, *J* = 272.6 Hz) , 121.9, 127.1, 127.5, 128.2, 128.8, 139.4, 140.0, 148.8, 159.8 (t, *J* = 41.3 Hz); (^{19}F NMR, 377 MHz, $CDCl_3$) δ = -76.3 (s, 2F);

IR (neat) ν 1775, 1515, 1486, 1378, 1341, 1171, 1134, 1008, 854; HRMS (ESI) *m/z* Calcd for $C_{16}H_{14}F_2NaO_3$ $[M+Na]^+$ 315.0803, found 315.0803; Mp. 59-60 °C.

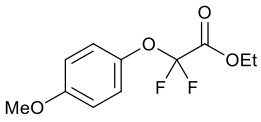
Ethyl (4-*tert*-butylphenoxy)(difluoro)acetate



The title compound was prepared following General Procedure E using K_2CO_3 (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: Et_2O/30-40 petroleum ether 4/96) to provide the title compound (1.97 g, 72% yield) as a colourless oil.

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

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

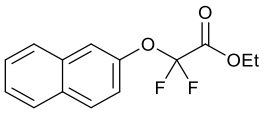


The title compound was prepared following General Procedure E using K_2CO_3 (13.8 g, 100.0 mmol), 4-methoxyphenol (4.97 g, 40.0 mmol), ethyl bromodifluoroacetate (7.70 mL, 60.0 mmol) and DMF (80 mL). The crude product was purified by silica gel column

chromatography (eluent: Et_2O/*n*-pentane 10/90) to provide the title compound (5.46 g, 55% yield) as a colourless oil.

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

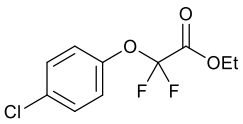
Ethyl 2,2-difluoro-2-(naphthalen-2-yloxy)acetate



The title compound was prepared following General Procedure E using K_2CO_3 (6.91 g, 50.0 mmol), 2-napthol (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: Et_2O/*n*-pentane 3/97) to provide the title compound (2.00 g, 38% yield) as a colourless oil.

(^{1}H NMR, 400 MHz, $CDCl_3$) δ = 1.39 (t, *J* = 7.1 Hz, 3H), 4.41 (q, *J* = 7.1 Hz, 2H), 7.38 (dd, J_1 = 2.5 Hz, J_2 = 9.1 Hz, 1H), 7.48-7.56 (m, 2H), 7.70 (s, 1H), 7.82-7.88 (m, 3H); (^{13}C NMR, 101 MHz, $CDCl_3$) δ = 13.8, 63.7, 114.2 (t, *J* = 272.2 Hz), 118.6, 121.0, 126.0, 126.8, 127.7, 129.7, 131.5, 133.6, 147.1, 159.8 (t, *J* = 41.3 Hz); (^{19}F NMR, 377 MHz, $CDCl_3$) δ = -76.1 (s, 2F); IR (neat) ν 1774, 1601, 1511, 1466, 1377, 1339, 1158, 1011, 961, 855; HRMS (ESI) *m/z* Calcd for $C_{14}H_{12}O_3F_2Na$ $[M+Na]^+$ 289.0647, found 289.0643.

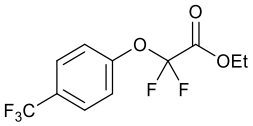
Ethyl 2-(4-chlorophenoxy)-2,2-difluoroacetate



The title compound was prepared following General Procedure E using K_2CO_3 (13.8 g, 100 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: Et_2O/*n*-pentane 1/99) to provide the title compound (3.75 g, 38% yield) as a colourless oil.

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

Ethyl difluoro[4-(trifluoromethyl)phenoxy]acetate

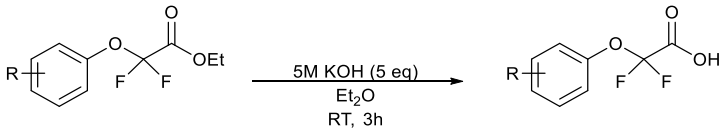


The title compound was prepared following General Procedure E using K_2CO_3 (6.91 g, 50.0 mmol), 4-(trifluoromethyl)phenol (3.24 g, 20.0 mmol), ethyl bromodifluoroacetate (3.85 mL, 30.0 mmol) and DMF (40 mL). The crude product was purified by silica gel column chromatography (eluent: Et_2O/*n*-pentane 1/99) to provide the title compound (1.36 g, 24% yield) as a colourless oil.

(^{1}H NMR, 400 MHz, $CDCl_3$) δ = 1.38 (t, *J* = 7.2 Hz, 3H), 4.41 (q, *J* = 7.2 Hz, 2H), 7.34 (d, *J* = 8.6 Hz, 2H), 7.66 (d, *J* = 8.6 Hz, 2H); (^{13}C NMR, 101 MHz, $CDCl_3$) δ = 13.8, 63.4, 113.8 (t, *J* = 274.2 Hz), 121.6, 123.7 (q, *J* = 271.8 Hz), 127.0 (q, *J* = 3.7 Hz), 128.5 (q, *J* =

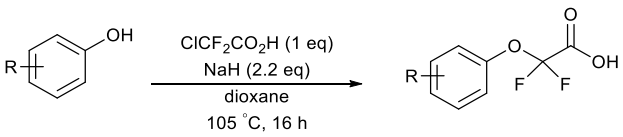
33.1 Hz), 152.02, 159.3 (t, J = 40.5 Hz); (^{19}F NMR, 377 MHz, $CDCl_3$) δ = -62.4 (s, 3F), -76.7 (s, 2F); IR (neat) ν 1779, 1617, 1515, 1379, 1325, 1212, 1126, 1065, 1017, 857; HRMS (EI/FI) *m/z* Calcd for $C_{11}H_9F_5O_3$ $[M]^+$ 284.0472, found 284.0479.

General Procedure F



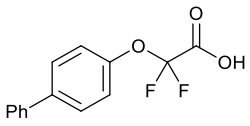
To a solution of the appropriate ester (5.0 mmol) in Et_2O (25 mL) was added 5 M aq. NaOH (25.0 mmol). The reaction mixture was stirred at room temperature for 3 hours before diluting with Et_2O (25 mL). The reaction mixture was extracted with sat. aq. $NaHCO_3$ (3 x 20 mL). The combined aqueous layers were acidified to pH 1 with 1M 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 G



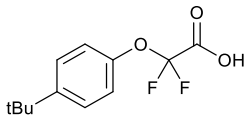
To a solution of an appropriate phenol (10.0 mmol) in dioxane (30 mL) was added chlorodifluoroacetic acid (10.0 mmol). The mixture was cooled to 0 ˚C and NaH (60% in mineral oil, 22.0 mmol) was slowly added. The reaction mixture was heated under reflux for 16 hours. The mixture was extracted with sat.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



The title compound was prepared following General Procedure F 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). The title compound (588 mg, quant. yield) was isolated as a grey solid. (^{1}H NMR, 400 MHz, $CDCl_3$) δ = 7.33 (d, *J* = 8.6 Hz, 2H), 7.36-7.41 (m, 1H), 7.45-7.49 (m, 2H), 7.57-7.62 (m, 4H), 9.77 (br. s, 1H); (^{13}C NMR, 101 MHz, $CDCl_3$) δ = 113.7 (t, *J* = 272.2 Hz), 121.9, 127.1, 127.6, 128.4, 128.9, 139.7, 139.9, 148.5, 163.1 (t, *J* = 42.9 Hz); (^{19}F NMR, 377 MHz, $CDCl_3$) δ = -76.6 (s, 2F); IR (neat) ν 3063, 1776, 1519, 1487, 1452, 1248, 1208, 1190, 1174, 1155, 1101, 1008, 850; HRMS (ESI) *m/z* Calcd for $C_{14}H_9F_2O_3$ $[M-H]^-$ 263.0525, found 263.0521; Mp. 103-105 °C.

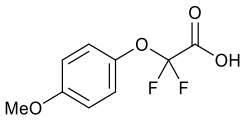
2,2-Difluoro-2-(4-*tert*-butylphenoxy)acetic acid



The title compound was prepared following General Procedure F using ethyl 2,2-difluoro-2-(4-tert-butylphenoxy)acetate (1.63 g, 6.0 mmol), 5 M aq. NaOH (6 mL, 30.0 mmol) and MeCN (30 mL); The title compound (1.40 g, 96% yield) was isolated as a white solid. (^{1}H NMR, 400 MHz, $CDCl_3$) δ = 1.33 (s, 9H), 7.17 (app d, *J* = 9.0 Hz, 2H), 7.40 (dt, J_1 = 2.6 Hz, J_2 = 9.0 Hz, 2H), 9.90 (br. s, 1H); (^{13}C NMR, 101 MHz, $CDCl_3$) δ = 31.3, 34.5, 113.6 (t, *J* = 274.6 Hz), 121.1, 126.6, 146.7, 149.6, 164.2 (t, *J* = 42.9 Hz); (^{19}F NMR, 377 MHz, $CDCl_3$) δ = -76.6 (s, 2F); IR (neat) ν 2965, 1765, 1509, 1366, 1176, 1105, 1016, 833,

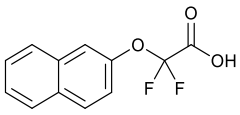
804; HRMS (ESI) *m/z* Calcd for $C_{12}H_{14}F_2NaO_3$ $[M+Na]^+$ 267.0803 found 267.0810; Mp. 66-68 °C.

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



The title compound was prepared following General Procedure F 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). The title compound (2.57 g, 98% yield) was isolated as white solid. (^{1}H NMR, 400 MHz, $CDCl_3$) δ = 3.83 (s, 3H), 6.90 (dt, J_1 = 2.9 Hz, J_2 = 9.1 Hz, 2H), 7.18 (d, J = 9.1 Hz, 2H), 10.20 (br. s, 1H); (^{13}C NMR, 101 MHz, $CDCl_3$) δ = 55.7, 113.6 (t, J = 271.9 Hz), 114.7, 123.0, 142.5, 157.8, 163.6 (t, J = 42.5 Hz); (^{19}F NMR, 377 MHz, $CDCl_3$) δ = -77.0 (s, 2F); IR (neat) ν 2987, 1775, 1506, 1466, 1379, 1342, 1299, 1252, 1192, 1033, 844; HRMS (ESI) *m/z* Calcd for $C_9H_7F_2O_4$ $[M-H]^-$ 217.0318, found 217.0323; Mp. 55-57 °C.

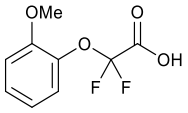
2,2-Difluoro-2-(naphthalen-2-yloxy)acetic acid



The title compound was prepared following General Procedure F 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); The title compound (773 mg, 81% yield) was isolated as a white solid. (^{1}H NMR, 400 MHz, $CDCl_3$) δ = 7.39 (dd, J_1 = 2.2 Hz, J_2 = 9.1 Hz, 1H), 7.50-7.57 (m, 2H), 7.72 (s, 1H), 7.83-7.89 (m, 3H), 9.10 (br. s, 1H); (^{13}C NMR, 101 MHz, $CDCl_3$) δ = 113.8 (t, J = 272.2 Hz), 118.7, 120.9, 126.2, 127.0, 127.8, 129.9, 131.7, 133.6, 146.8,

163.8 (t, *J* = 41.7 Hz); (^{19}F NMR, 377 MHz, $CDCl_3$) δ = -76.4 (s, 2F); IR (neat) ν 3544, 2362, 1711, 1636, 1598, 1466, 1338, 1245, 1133, 961, 893; HRMS (EI/FI) *m/z* Calcd *m/z* Calcd for for $C_{12}H_7O_3F_2$ $[M-H]^-$ 237.0369 found 237.0367; Mp. 75-77 °C.

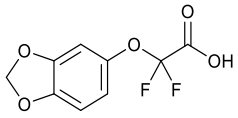
2,2-Difluoro-2-(2-methoxyphenoxy)acetic acid



The title compound was prepared following General Procedure G using guaiacol (1.10 mL, 10.0 mmol), dioxane (30 mL), chlorodifluoroacetic acid (850 μL, 10.0 mmol) and NaH (60% in mineral oil, 880 mg, 22.0 mmol). The title compound (1.64 g, 75% yield) was isolated as a beige solid.

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

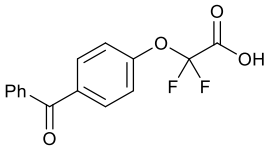
(1,3-Benzodioxol-5-yloxy)(difluoro)acetic acid



The title compound was prepared following General Procedure G using sesamol (1.38 g, 10.0 mmol), dioxane (30 mL), chlorodifluoroacetic acid (850 μL, 10.0 mmol) and NaH (60% in mineral oil, 880 mg, 22.0 mmol). The title compound (1.72 g, 74% yield) was isolated as an orange solid.

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

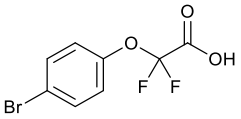
2-(4-benzoylphenoxy)-2,2-difluoroacetic acid



The title compound was prepared following General Procedure F using ethyl 2-(4-benzoylphenoxy)-2,2-difluoroacetate (1.28 g, 4.00 mmol), 5 M aq. NaOH (4.00 mL, 20.0 mmol) and Et_2O (20 mL). The title compound (1.05 g, 95% yield) was isolated as a white solid.

(^{1}H NMR, 400 MHz, $CDCl_3$) δ = 7.35 (d, *J* = 8.6 Hz, 2H), 7.51 (t, *J* = 7.7 Hz, 2H), 7.64 (t, *J* = 7.3 Hz, 1H), 7.80 (d, *J* = 7.3 Hz, 2H), 7.86 (d, *J* = 8.6 Hz, 2H), 8.59 (br. s, 1H); (^{13}C NMR, 101 MHz, $CDCl_3$) δ = 113.8 (t, *J* = 273.8 Hz), 120.9, 128.5, 130.2, 132.2, 133.1, 134.9, 136.8, 153.0, 161.1 (t, *J* = 41.3 Hz), 197.1; (^{19}F NMR, 377 MHz, $CDCl_3$) δ = -77.0 (s, 2F); IR (neat) ν 1774, 1645, 1598, 1503, 1448, 1279, 1168, 1016, 926, 851; HRMS (ESI) *m/z* Calcd for $C_{15}H_9F_2O_4$ $[M-H]^-$ 291.0474, found 291.0469.

2-(4-Bromophenoxy)-2,2-difluoroacetic acid

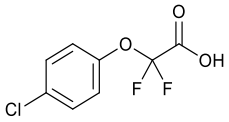


The title compound was prepared following General Procedure F using ethyl 2-(4-bromophenoxy)-2,2-difluoroacetate (1.48 g, 5.0 mmol), 5 M aq. NaOH (5 mL, 25.0 mmol)

and MeCN (25 mL). The title compound (880 mg, 66% yield) was isolated as a white solid.

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

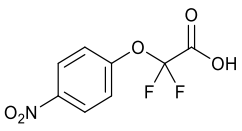
2-(4-Chlorophenoxy)-2,2-difluoroacetic acid



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

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

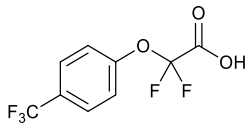
2,2-Difluoro-2-(4-nitrophenoxy)acetic acid



The title compound was prepared following General Procedure F using ethyl 2,2-difluoro-2-(4-nitrophenoxy)acetate (522 mg, 2.00 mmol), 5 M aq. NaOH (2.00 mL, 10.0 mmol) and Et_2O (10 mL). The title compound (314 mg, 67% yield) was isolated as a pale yellow solid.

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

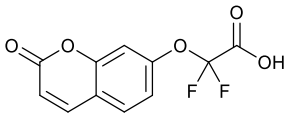
Difluoro[4-(trifluoromethyl)phenoxy]acetic acid



The title compound was prepared following General Procedure F using ethyl difluoro[4-(trifluoromethyl)phenoxy]acetate (1.14 g, 4.00 mmol), 5 M aq. NaOH (4.00 mL, 20.0 mmol) and MeCN (20 mL); (508 mg, 50% yield, white solid).

(^{1}H NMR, 400 MHz, $CDCl_3$) δ = 7.36 (d, J = 8.6 Hz, 2H), 7.67 (d, J = 8.6 Hz, 2H), 8.80 (br. s, 1H); (^{13}C NMR, 101 MHz, $CDCl_3$) δ = 113.5 (t, J =274.2 Hz), 121.7, 128.6 (q, J = 271.8 Hz), 127.2 (q, J = 3.7 Hz), 129.3 (q, J = 33.1 Hz), 151.7, 163.0 (t, J = 41.7 Hz); (^{19}F NMR, 377 MHz, $CDCl_3$) δ = -62.5 (s, 3F), -71.2 (s, 2F); IR (neat) ν 1769, 1615, 1515, 1326, 1125, 1065, 1018, 846, 807; HRMS (EI/FI) *m/z* Calcd for $C_9H_5F_5O_3$ $[M]^+$ 256.0159, found 256.0164; Mp. 36-38 °C.

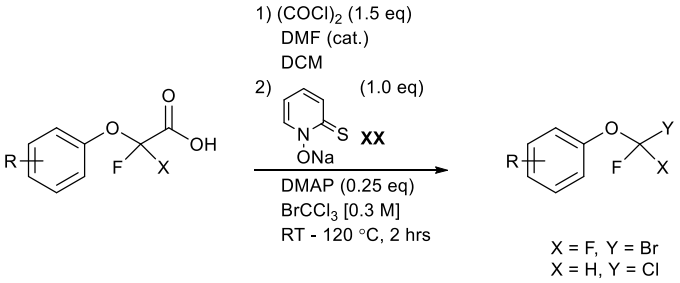
Difluoro[(2-oxo-2H-chromen-7-yl)oxy]acetic acid



The title compound was prepared following General Procedure E using K_2CO_3 (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 F using 5 M aq. NaOH (4.00 mL, 20.0 mmol) and Et_2O (20 mL) to provide the title compound (677 mg, 13% yield) as a white solid.

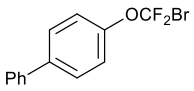
(^{1}H NMR, 400 MHz, DMSO-d_6) δ = 6.51 (d, *J* = 9.5 Hz, 1H), 7.24-7.30 (m, 2H), 7.82 (d, *J* = 8.6 Hz, 1H), 8.09 (d, *J* = 9.5 Hz, 1H); (^{13}C NMR, 101 MHz, DMSO-d6) δ = 109.2, 114.6 (t, *J* = 274.2 Hz), 116.4, 117.4, 117.6, 130.5, 144.0, 151.9, 154.7, 160.0, 160.6 (t, *J* = 39.5 Hz); (^{19}F NMR, 377 MHz, DMSO-d6) δ = -76.6 (s, 2F); IR (neat) ν 3667, 3071, 2980, 2867, 1776, 1654, 1621, 1604, 1563, 1502, 1156, 1127, 1079, 990; HRMS (ESI) *m/z* Calcd for $C_{11}H_6O_5F_2Na$ $[M+Na]^+$ 279.0076 found 279.0075; Mp. 132-135 °C.

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.

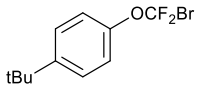
4-[Bromo(difluoro)methoxy]biphenyl 4-103



The title compound was prepared following General Procedure H using (biphenyl-4-yloxy)(difluoro)acetic acid (1.19 g, 4.50 mmol), CH_2Cl_2 (7.5 mL), DMF (35 µL, 450 µmol), oxalyl chloride (579 µL, 6.75 mmol), $BrCCl_3$ (12 mL), 4-dimethylaminopyridine (137 mg, 1.13 mmol) and sodium-*N*-hydroxy-2-thiopyridone (671 mg, 4.50 mmol). The crude product was purified by silica gel column chromatography (eluent: Et_2O/*n*-pentane 1/99) to provide the title compound (871 mg, 65% yield) as a white solid.

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

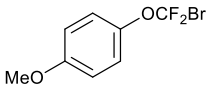
1-(Bromodifluoromethoxy)-4-(*tert*-butyl)benzene 4-116



The title compound was prepared following General Procedure H using 2,2-difluoro-2-(4-*tert*-butylphenoxy)acetic acid (0.73 g, 3.0 mmol), CH_2Cl_2 (5 mL), DMF (23 µL, 0.30 mmol), oxalyl chloride (0.39 mL, 4.5 mmol), $BrCCl_3$ (8 mL), 4-dimethylaminopyridine (91 mg, 0.75 mmol) and sodium-*N*-hydroxy-2-thiopyridone (0.45 g, 3.0 mmol). The crude product was purified by silica gel column chromatography (eluent: Et_2O/*n*-pentane 1/99) to provide the title compound (0.50 g, 60% yield) as a pale yellow oil.

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

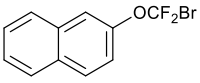
1-(Bromodifluoromethoxy)-4-methoxybenzene 4-117



The title compound was prepared following General Procedure H using 2,2-difluoro-2-(4-methoxyphenoxy)acetic acid (0.87 g, 4.0 mmol), CH_2Cl_2 (8.0 mL), DMF (31 µL, 0.40 mmol), oxalyl chloride (0.52 mL, 6.0 mmol), $BrCCl_3$ (12 mL), 4-dimethylaminopyridine (0.12 mg, 1.0 mmol) and sodium-*N*-hydroxy-2-thiopyridone (0.66 g, 4.0 mmol). The crude product was purified by silica gel column chromatography (eluent: Et_2O/*n*-pentane 2/98) to provide the title compound (0.66 mg, 65% yield) as a colourless oil.

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

2-(Bromodifluoromethoxy)naphthalene 4-118

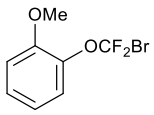


The title compound was prepared following General Procedure H using 2,2-difluoro-2-(naphthalen-2-yloxy)acetic acid (0.36 mg, 1.5 mmol), CH_2Cl_2 (2.5 mL), DMF (12 µL, 0.15

mmol), oxalyl chloride (0.19 mL, 2.3 mmol), $BrCCl_3$ (9 mL), 4-dimethylaminopyridine (46 mg, 0.38 mmol) and sodium-*N*-hydroxy-2-thiopyridone (0.22 g, 1.5 mmol). The crude product was purified by silica gel column chromatography (eluent: Et_2O/*n*-pentane 1/99) to provide the title compound (0.24 g, 59% yield) as a yellow solid.

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

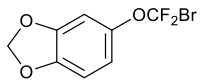
1-(Bromodifluoromethoxy)-2-methoxybenzene 4-119



The title compound was prepared following General Procedure H using 2,2-difluoro-2-(2-methoxyphenoxy)acetic acid (0.66 mg, 3.0 mmol), CH_2Cl_2 (5 mL), DMF (23 µL, 0.30 mmol), oxalyl chloride (0.39 mL, 4.5 mmol), $BrCCl_3$ (8 mL), 4-dimethylaminopyridine (91 mg, 0.75 mmol) and sodium-*N*-hydroxy-2-thiopyridone (0.45 mg, 3.0 mmol). The crude product was purified by silica gel column chromatography (eluent: Et_2O/*n*-pentane 1/99) to provide the title compound (443 mg, 58% yield) as a colourless oil.

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

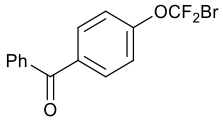
5-(Bromodifluoromethoxy)-1,3-benzodioxole 4-120



The title compound was prepared following General Procedure H using (1,3-benzodioxol-5-yloxy)(difluoro)acetic acid (0.93 mg, 4.0 mmol), CH_2Cl_2 (8 mL), DMF (31 µL, 0.40 mmol), oxalyl chloride (0.52 mL, 6.0 mmol), $BrCCl_3$ (12 mL), 4-dimethylaminopyridine (0.12 mg, 1.0 mmol) and sodium-*N*-hydroxy-2-thiopyridone (0.60 g, 4.0 mmol). The crude product was purified by silica gel column chromatography (eluent: Et_2O/*n*-pentane 10/90) to provide the title compound (622 mg, 58% yield) as a colourless oil.

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

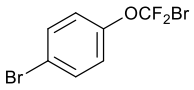
(4-(Bromodifluoromethoxy)phenyl)(phenyl)methanone 4-121



The title compound was prepared following General Procedure H using 2-(4-benzoylphenoxy)-2,2-difluoroacetic acid (0.42 g, 1.5 mmol), CH_2Cl_2 (2.5 mL), DMF (12 µL, 0.15 mmol), oxalyl chloride (0.19 mL, 2.3 mmol), $BrCCl_3$ (9 mL), 4-dimethylaminopyridine (46 mg, 0.38 mmol) and sodium-*N*-hydroxy-2-thiopyridone (0.22 g, 1.5 mmol). The crude product was purified by silica gel column chromatography (eluent: Et_2O/*n*-pentane 10/90) to provide the title compound (0.30g, 62% yield) as a white solid.

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

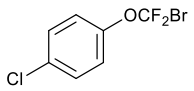
1-Bromo-4-(bromodifluoromethoxy)benzene 4-122



The title compound was prepared following General Procedure H using (4-bromophenoxy)(difluoro)acetic acid (0.40 g, 1.5 mmol), CH_2Cl_2 (2.5 mL), DMF (12 µL, 0.15 mmol), oxalyl chloride (0.19 mL, 2.25 mmol), $BrCCl_3$ (9 mL), 4-dimethylaminopyridine (46 mg, 0.38 mmol) and sodium-*N*-hydroxy-2-thiopyridone (0.22 g, 1.5 mmol). The crude product was purified by silica gel column chromatography (eluent: Et_2O/*n*-pentane 0.5/99.5) to provide the title compound (0.28 g, 61% yield) as a colourless oil.

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

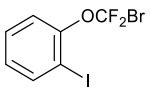
1-(Bromodifluoromethoxy)-4-chlorobenzene 4-123



The title compound was prepared following General Procedure H using 2-(4-chlorophenoxy)-2,2-difluoroacetic acid (0.89 g, 4.0 mmol), CH_2Cl_2 (8.0 mL), DMF (31 μL, 0.40 mmol), oxalyl chloride (0.52 mL, 6.0 mmol), $BrCCl_3$ (12 mL), 4-dimethylaminopyridine (0.12 mg, 1.0 mmol) and sodium-*N*-hydroxy-2-thiopyridone (0.60 g, 4.0 mmol). The crude product was purified by silica gel column chromatography (eluent: *n*-pentane) to provide the title compound (0.51 mg, 49% yield) as a colourless oil.

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

Bromo(difluoro)methyl 2-iodophenyl ether 4-124

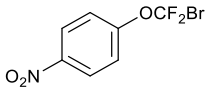


The title compound was prepared following General Procedure G using 2-iodophenol (2.20 g, 10.0 mmol), dioxane (30 mL), chlorodifluoroacetic acid (0.85 mL, 10.0 mmol) and NaH (60% in mineral oil, 1.00 g, 25.0 mmol). The crude mixture was then subjected to conditions described by General Procedure H using CH_2Cl_2 (4 mL), DMF (19.0 μL, 240 μmol), oxalyl chloride (309 μL, 3.6 mmol), $BrCCl_3$ (7 mL), 4-dimethylaminopyridine (730 μg, 600 μmol) and sodium-*N*-hydroxy-2-thiopyridone (358 mg, 2.40 mmol). The crude product was purified by silica gel column chromatography (eluent: Et_2O/*n*-pentane 0.5/99.5) to provide the title compound (393 mg, 47% yield) as a colourless oil.

(^{1}H NMR, 400 MHz, $CDCl_3$) δ = 7.04-7.08 (m, 1H), 7.33-7.43 (m, 2H), 7.90 (dd, J_1 = 1.5 Hz, J_2 = 7.8 Hz, 1H); (^{13}C NMR, 101 MHz, $CDCl_3$) δ = 89.9, 114.2 (t, J = 309.9 Hz), 121.5, 128.4, 129.7, 140.3, 151.1; (^{19}F NMR, 377 MHz, $CDCl_3$) δ = -14.9 (s, 2F); IR (neat)

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

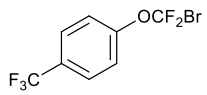
1-(Bromodifluoromethoxy)-4-nitrobenzene 4-125



The title compound was prepared following General Procedure H using 2,2-difluoro-2-(4-nitrophenoxy)acetic acid (0.23 g, 1.0 mmol), CH_2Cl_2 (2 mL), DMF (8.0 µL, 0.10 mmol), oxalyl chloride (0.13 mL, 1.5 mmol), $BrCCl_3$ (3 mL), 4-dimethylaminopyridine (31 mg, 0.25 mmol) and sodium-*N*-hydroxy-2-thiopyridone (0.15 mg, 1.0 mmol). The crude product was purified by silica gel column chromatography (eluent: Et_2O/*n*-pentane 1/99) to provide the title compound (0.10 g, 38% yield) as a colourless oil.

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

1-(Bromodifluoromethoxy)-4-(trifluoromethyl)benzene 4-126

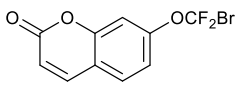


The title compound was prepared following General Procedure H using 2,2-difluoro-2-(4-(trifluoromethyl)phenoxy)acetic acid (1.0 g, 4.0 mmol), CH_2Cl_2 (8.0 mL), DMF (31 µL, 0.40 mmol), oxalyl chloride (0.52 mL, 6.0 mmol), $BrCCl_3$ (12 mL), 4-dimethylaminopyridine (0.12 mg, 1.0 mmol) and sodium-*N*-hydroxy-2-thiopyridone (0.60

g, 4.0 mmol). The crude product was purified by silica gel column chromatography (eluent: *n*-pentane) to provide the title compound (0.36 g, 31% yield) as a colourless oil.

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

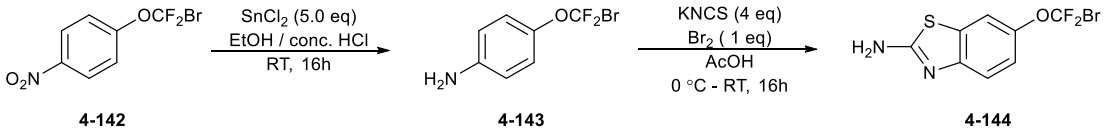
7-(Bromodifluoromethoxy)-2H-chromen-2-one 4-127



The title compound was prepared following General Procedure H using difluoro[(2-oxo-2H-chromen-7-yl)oxy]acetic acid (0.51 g, 2.0 mmol), CH_2Cl_2 (3.5 mL), DMF (15 µL, 0.20 mmol), oxalyl chloride (0.26 mL, 3.0 mmol), $BrCCl_3$ (5.5 mL), 4-dimethylaminopyridine (61 mg, 0.50 mmol) and sodium-*N*-hydroxy-2-thiopyridone (0.30 g, 2.0 mmol). The crude product was purified by silica gel column chromatography (eluent: Et_2O/*n*-pentane 30/70) to provide the title compound (0.20 g, 35% yield) as a pale yellow solid.

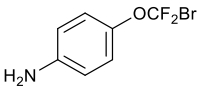
(^{1}H NMR, 400 MHz, $CDCl_3$) δ = 6.46 (d, *J* = 9.5 Hz, 1H), 7.17-7.24 (m, 2H), 7.55 (d, *J* = 8.6 Hz, 1H), 7.73 (d, *J* = 9.5 Hz, 1H); (^{13}C NMR, 101 MHz, $CDCl_3$) δ = 109.8, 113.8 (t, *J* = 310.3 Hz), 116.8, 117.4, 129.0, 142.5, 152.6, 154.6, 159.8; (^{19}F NMR, 377 MHz, $CDCl_3$) δ = -16.4 (s,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

Synthesis of 6-[Bromo(difluoro)methoxy]-1,3-benzothiazol-2-amine 4-144



4-142 **4-143** **4-144**

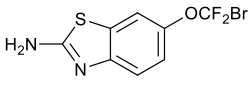
4-(Bromo(difluoro)methoxy)aniline 4-143



To a solution of 1-(bromodifluoromethoxy)-4-nitrobenzene (961 mg, 3.60 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 a nitrogen atmosphere, after which it was poured on to sat. $NaHCO_3$ (200 mL) and extracted with EtOAc (3 × 50 mL). The 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: EtOAc/*n*-pentane 25/75) to provide the title compound (739 mg, 86% yield) as pale yellow oil.

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

6-[Bromo(difluoro)methoxy]-1,3-benzothiazol-2-amine 4-144



To a solution of 4-(bromodifluoromethoxy)aniline (714 mg, 3.00 mmol) in AcOH (5 mL) was added KSCN (1.17 g, 12.0 mmol) and a solution of Br_2 (0.154 mL, 3.00 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) and extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with brine (100 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography (eluent: EtOAc/*n*-pentane 50/50) to provide the title compound (798 mg, 90% yield) as pale yellow solid.

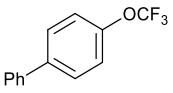
(^{1}H NMR, 400 MHz, $CDCl_3$) δ = 5.98 (br. s, 2H), 7.19 (d, *J* = 8.30 Hz, 1H), 7.50 (d, *J* = 8.80 Hz, 2H); (^{13}C NMR, 101 MHz, $CDCl_3$) δ = 114.4, 115.2 (t, *J* = 308.0 Hz), 119.3, 120.0, 132.0, 145.7, 150.8, 167.0; (^{19}F NMR, 377 MHz, $CDCl_3$) δ = -15.8 (s, 2F); IR (neat) ν 3432, 3411, 3287,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

General Procedure I

4-115 **4-128**

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.

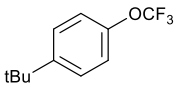
4-(Trifluoromethoxy)biphenyl 4-129



The title compound was prepared following General Procedure I using 4-[bromo(difluoro)methoxy]biphenyl (30 mg, 0.10 mmol), CH_2Cl_2 (1 mL) and $AgBF_4$ (21 mg, 0.11 mmol). The crude product was purified by silica gel column chromatography (eluent: Et_2O/*n*-pentane 1/99) to provide the title compound (22 mg, 93% yield) as a white solid.

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

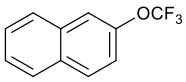
1-*tert*-Butyl-4-(trifluoromethyl)benzene 4-130



The title compound was prepared following General Procedure I using 4-[1-(bromodifluoromethoxy)-4-(*tert*-butyl)benzene (70 mg, 0.25 mmol), CH_2Cl_2 (2.5 mL), $AgBF_4$ (54 mg, 0.28 mmol). The crude product was purified by silica gel column chromatography (eluent: Et_2O/*n*-pentane 0.5/99.5) to provide the title compound (34 mg, 63% yield) as a pale yellow oil.

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

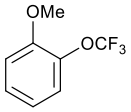
2-(Trifluoromethoxy)naphthalene 4-132



The title compound was prepared following General Procedure I using 2-(bromodifluoromethoxy)naphthalene (50 mg, 0.25 mmol), CH_2Cl_2 (2.5 mL), and $AgBF_4$ (54 mg, 0.28 mmol). The crude product was purified by silica gel column chromatography (eluent: Et_2O/ *n*-pentane 1/99) to provide the title compound (38 mg, 72% yield) as a pale yellow oil.

(^{1}H NMR, 400 MHz, $CDCl_3$) δ = 7.37 (d, *J* = 9.1 Hz, 1H), 7.51-7.58 (m, 2H), 7.70 (s, 1H), 7.84-7.90 (m, 3H); (^{13}C NMR, 101 MHz, $CDCl_3$) δ = 118.1, 120.1, 120.7 (q, *J* = 256.7 Hz), 126.3, 127.0, 127.8, 130.0, 131.7, 133.5, 146.8; (^{19}F NMR, 377 MHz, $CDCl_3$) δ = -57.7 (s, 3F). Data consistent with literature values.[5]

1-Methoxy-2-(trifluoromethoxy)benzene 4-133



The title compound was prepared following General Procedure I using 1-(bromodifluoromethoxy)-2-methoxybenzene (63 mg, 0.25 mmol), CH_2Cl_2 (2.5 mL) and $AgBF_4$ (54 mg, 0.28 mmol). The crude product was purified by silica gel column chromatography (eluent: Et_2O/*n*-pentane 2/98) to provide the title compound (25 mg, 52% yield) as a yellow oil.

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

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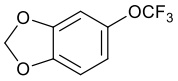
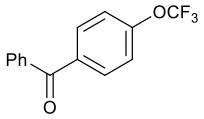
5-(Trifluoromethoxy)-1,3-benzodioxole 4-134



To a solution of 5-(bromodifluoromethoxy)-1,3-benzodioxole (0.16 g, 0.60 mmol) in CH_2Cl_2 (1.2 mL) was added $AgBF_4$ (0.13 g, 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 CH_2Cl_2 (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: Et_2O/*n*-pentane 2/98) to provide 101 mg of an inseparable mixture of the title compound (56% yield) and the bromodifluoromethoxy starting material (20% yield). An analytically pure sample was prepared by preparative reverse-phase HPLC.

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

Phenyl-(4-(trifluoromethoxy)phenyl)methanone 4-135



The title compound was prepared following General Procedure I using (4-(bromodifluoromethoxy)phenyl)(phenyl)methanone (78 mg, 0.25 mmol), CH_2Cl_2 (2.5 mL) and $AgBF_4$ (54 mg, 0.28 mmol). The crude product was purified by silica gel column chromatography (eluent: Et_2O/*n*-pentane 20/80) to provide the title compound (57 mg, 85% yield) as a white solid.

(^{1}H NMR, 400 MHz, $CDCl_3$) δ = 7.32-7.34 (m, 2H), 7.49-7.53 (m, 2H), 7.62 (tt, J_1 = 1.9 Hz, J_2 = 7.5 Hz, 1H), 7.79-7.82 (m, 2H), 7.88 (dt, J_1 = 2.4 Hz, J_2 = 8.8 Hz, 2H); (^{13}C NMR, 101 MHz, $CDCl_3$) δ = 120.2, 120.3 (t, J = 258.3 Hz), 128.4, 129.9, 131.9, 132.7, 135.8, 137.1, 152.1, 195.1; (^{19}F NMR, 377 MHz, $CDCl_3$) δ = -57.6 (s, 3F). Data consistent with literature values.[6]

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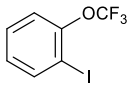
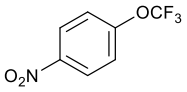
1-Iodo-2-(trifluoromethoxy)benzene 4-138



The title compound was prepared following General Procedure I using bromo(difluoro)methyl 2-iodophenyl ether (87 mg, 0.25 mmol), CH_2Cl_2 (2.5 mL) and $AgBF_4$ (54 mg, 0.28 mmol). The crude product was purified by silica gel column chromatography (eluent: Et_2O/*n*-pentane 2/98) to provide the title compound (43 mg, 60% yield) as a colourless oil.

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

1-Nitro-4-(trifluoromethoxy)benzene 4-139

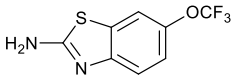


The title compound was prepared following General Procedure I using 1-(bromodifluoromethoxy)-4-nitrobenzene (27 mg, 0.10 mmol), CH_2Cl_2 (1 mL) and $AgBF_4$

(21 mg, 0.11 mmol). The crude product was purified by silica gel column chromatography (eluent: Et_2O/*n*-pentane 2/98) to provide the title compound (14 mg, 70% yield) as a yellow oil.

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

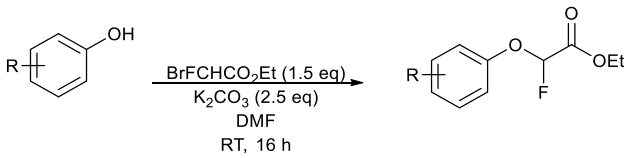
2-Amino-6-(trifluoromethoxy)-1,3-benzothiazole 4-144



To a solution of 4-(trifluoromethoxy)aniline (177 mg, 1.00 mmol) in AcOH (2 mL) was added KSCN (389 mg, 4.00 mmol) and a solution of Br_2 (51.0 μL, 1.00 mmol) in AcOH (1 mL) at 0 ˚C. The reaction mixture was stirred at room temperature for 16 hours under a nitrogen atmosphere. The reaction mixture was poured on to sat. $NaHCO_3$ (200 mL) and extracted with EtOAc (3 × 50 mL). Combined organic layers were washed with brine (100 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography (eluent: EtOAc/*n*-pentane 50/50) to provide the title compound (230 mg, 98% yield) as pale yellow solid.

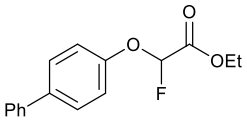
(^{1}H NMR, 400 MHz, $CDCl_3$) δ = 5.99 (br. s, 2H), 7.17 (dd, J_1 = 1.5 Hz, J_2 = 8.8 Hz, 1H), 7.48 (d, J = 8.80 Hz, 2H); (^{13}C NMR, 101 MHz, $CDCl_3$) δ = 114.1, 119.2, 119.7, 120.5 (q, J = 256.7 Hz), 132.0, 144.0, 150.7, 167.0; (^{19}F NMR, 377 MHz, $CDCl_3$) δ = -58.2 (s, 3F). Data consistent with literature values.[7]

General Procedure J



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.

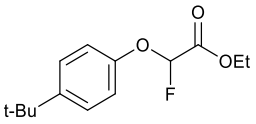
Ethyl (biphenyl-4-yloxy)(fluoro)acetate



The title compound was prepared following General Procedure J using K_2CO_3 (3.46 g, 25.0 mmol), 4-phenylphenol (1.70 g, 10.0 mmol), DMF (20 mL) andethyl bromofluoroacetate (1.77 mL, 15.0 mmol). The crude product was purified by silica gel column chromatography (eluent: Et_2O/30-40 petroleum ether 15/85) to provide the title compound (2.57 g, 94% yield) as a white solid.

(^{1}H NMR, 400 MHz, $CDCl_3$) δ = 1.41 (t, *J* = 7.1 Hz, 3H), 4.40 (q, *J* = 7.1 Hz, 2H), 6.04 (d, *J* = 60.0 Hz, 1H), 7.24 (d, *J* = 8.6 Hz, 2H), 7.36-7.40 (m, 1H), 7.45-7.49 (m, 2H), 7.58-7.62 (m, 4H); (^{13}C NMR, 101 MHz, $CDCl_3$) δ = 13.9, 62.5, 102.5 (d, *J* = 231.3 Hz), 117.7, 126.8, 127.2, 128.4, 128.9, 137.5, 140.1, 155.1, 163.9 (d, *J* = 31.0 Hz); (^{19}F NMR, 377 MHz, $CDCl_3$) δ = -129.3 (d, *J* = 60.0 Hz, 1F); IR (neat) ν 1768, 1608, 1518, 1486, 1217, 1103, 1007, 838; HRMS (ESI) *m/z* Calcd for $C_{16}H_{15}FNaO_3$ $[M+Na]^+$ 297.0897, found 297.0891; Mp. 28-29 °C.

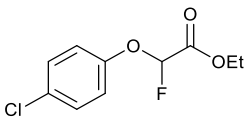
Ethyl (4-*tert*-butylphenoxy)(fluoro)acetate



The title compound was prepared following General Procedure J using K_2CO_3 (13.8 g, 100.0 mmol), 4-*tert*-butylphenol (6.00 g, 40.0 mmol), DMF (80 mL) and ethyl bromofluoroacetate (7.10 mL, 60.0 mmol). The crude product was purified by silica gel column chromatography (eluent: Et_2O/30-40 petroleum ether 10/90) to provide the title compound (7.92 g, 78% yield) as a colourless oil.

(^{1}H NMR, 400 MHz, $CDCl_3$) δ = 1.32 (s, 9H), 1.37 (t, *J* = 7.1 Hz, 3H), 4.37 (q, *J* = 7.1 Hz, 2H), 5.95 (d, *J* = 60.4 Hz, 1H), 7.08 (d, *J* = 8.8 Hz, 2H), 7.37 (dt, J_1 = 2.6 Hz, J_2 = 8.8 Hz, 2H); (^{13}C NMR, 101 MHz, $CDCl_3$) δ = 13.9, 31.4, 34.3, 62.5, 102.8 (d, *J* = 231.3 Hz), 117.0, 126.6, 147.3, 153.6 (d, *J* = 3.2 Hz), 164.1 (d, *J* = 31.8 Hz); (^{19}F NMR, 377 MHz, $CDCl_3$) δ = -128.9 (d, *J* = 60.4 Hz, 1F); IR (neat) ν 2964, 1769, 1608, 1511, 1364, 1216, 1185, 1097, 1014, 965, 833; HRMS (ESI) *m/z* Calcd for $C_{14}H_{19}FNaO_3$ $[M+Na]^+$ 277.1210, found 277.1208.

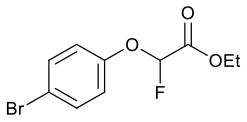
Ethyl (4-chlorophenoxy)(fluoro)acetate



The title compound was prepared following General Procedure J using K_2CO_3 (6.91 g, 50.0 mmol), 4-chlorophenol (2.57 g, 20.0 mmol), DMF (40 mL) and ethyl bromofluoroacetate (3.55 mL, 30.0 mmol). The crude product was purified by silica gel column chromatography (eluent: Et_2O/*n*-pentane 10/90) to provide the title compound (3.38 g, 72% yield) as a colourless oil.

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

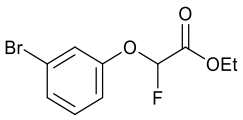
Ethyl (4-bromophenoxy)(fluoro)acetate



The title compound was prepared following General Procedure J using K_2CO_3 (10.4 g, 75.0 mmol), 4-bromophenol (5.19 g, 30.0 mmol), DMF (60 mL) and ethyl bromofluoroacetate (5.32 mL, 45.0 mmol). The crude product was purified by silica gel column chromatography (eluent: Et_2O/*n*-pentane 10/90) to provide the title compound (4.46 g, 54% yield) as a colourless oil.

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

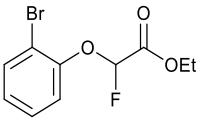
Ethyl (3-bromophenoxy)(fluoro)acetate



The title compound was prepared following General Procedure J using K_2CO_3 (10.4 g, 75.0 mmol), 3-bromophenol (5.19 g, 30.0 mmol), DMF (60 mL) and ethyl bromofluoroacetate (5.32 mL, 45.0 mmol). The crude product was purified by silica gel column chromatography (eluent: Et_2O/*n*-pentane 10/90) to provide the title compound (6.88 g, 83% yield) as a colourless oil.

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

Ethyl (2-bromophenoxy)(fluoro)acetate

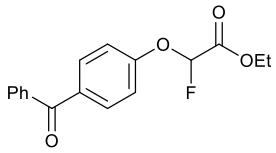


The title compound was prepared following General Procedure J using K_2CO_3 (6.91 g, 50.0 mmol), 2-bromophenol (3.46 g, 20.0 mmol), DMF (40 mL) and ethyl bromofluoroacetate (3.55 mL, 30.0 mmol). The crude product was purified by silica gel column chromatography (eluent: Et_2O/*n*-pentane 20/80) to provide the title compound (4.68 g, 85% yield) as a colourless oil.

(^{1}H NMR, 400 MHz, $CDCl_3$) δ = 1.38 (t, *J* = 7.1 Hz, 3H), 4.33-4.44 (m, 2H), 5.91 (d, *J* = 59.2 Hz, 1H), 7.04-7.08 (m, 1H), 7.23 (dt, J_1 = 1.4 Hz, J_2 = 8.1 Hz, 1H), 7.30-7.34 (m, 1H), 7.60 (dd, J_1 = 1.5 Hz, J_2 = 7.8 Hz, 1H); (^{13}C NMR, 101 MHz, $CDCl_3$) δ = 14.0, 62.6,

103.0 (d, *J* = 233.7 Hz), 114.0 (d, *J* = 1.6 Hz), 119.2, 126.0, 128.8, 133.8, 152.5 (d, *J* = 3.2 Hz), 163.5 (d, *J* = 31.0 Hz); (^{19}F NMR, 377 MHz, $CDCl_3$) δ = -130.0 (d, *J* = 59.0 Hz, 1F); IR (neat) ν 1766, 1579, 1477, 1445, 1384, 1218, 1134, 1095, 1028, 965, 857; HRMS (EI/FI) *m/z* Calcd for $C_{10}H_{10}BrFO_3$ $[M]^+$ 275.9797, 275.9795.

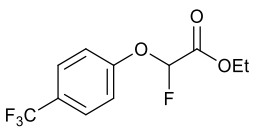
Ethyl (4-benzoylphenoxy)(fluoro)acetate



The title compound was prepared following General Procedure J using K_2CO_3 (6.91 g, 50.0 mmol), 4-hydroxybenzophenone (3.96 g, 20.0 mmol), DMF (40 mL) and ethyl bromofluoroacetate (3.55 mL, 30.0 mmol). The crude product was purified by silica gel column chromatography (eluent: Et_2O/*n*-pentane 30/70) to provide the title compound (5.50 g, 91% yield) as a pale yellow oil.

(^{1}H NMR, 400 MHz, $CDCl_3$) δ = 1.38 (t, *J* = 7.2 Hz, 3H), 4.38 (q, *J* = 7.2 Hz, 2H), 6.08 (d, *J* = 59.2 Hz, 1H), 7.21 (d, *J* = 8.6 Hz, 2H), 7.47-7.51 (m, 2H), 7.59 (tt, J_1 = 1.9 Hz, J_2 = 7.5 Hz, 1H), 7.76-7.78 (m, 2H), 7.85 (dt, J_1 = 2.3 Hz, J_2 = 8.8 Hz, 2H); (^{13}C NMR, 101 MHz, $CDCl_3$) δ = 13.9, 62.8, 101.6 (d, J = 233.7 Hz), 116.6, 128.3, 129.8, 132.3, 132.4, 133.5, 137.5, 158.6 (d, *J* = 2.4 Hz), 163.5 (d, *J* = 31.0 Hz), 195.3; (^{19}F NMR, 377 MHz, $CDCl_3$) δ = -130.8 (d, *J* = 59.0 Hz, 1F); IR (neat) ν 1766, 1656, 1600, 1505, 1447, 1278, 1218, 1174, 1151, 1096, 1025, 939, 924, 848; HRMS (ESI) *m/z* Calcd for $C_{17}H_{16}FO_3$ $[M+H]^+$ 303.1027 found 303.1022.

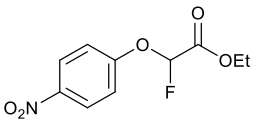
Ethyl fluoro[4-(trifluoromethyl)phenoxy]acetate



The title compound was prepared following General Procedure J using K_2CO_3 (6.91 g, 50.0 mmol), 4-(trifluoromethyl)phenol (3.24 g, 20.0 mmol), DMF (60 mL) and ethyl bromofluoroacetate (3.55 mL, 30.0 mmol). The crude product was purified by silica gel column chromatography (eluent: Et_2O/*n*-pentane 10/90) to provide the title compound (4.74 g, 89% yield) as a colourless oil.

(^{1}H NMR, 400 MHz, $CDCl_3$) δ = 1.37 (t, *J* = 7.2 Hz, 3H), 4.38 (q, *J* = 7.2 Hz, 2H), 6.02 (d, *J* = 59.2 Hz, 1H), 7.22 (d, *J* = 8.7 Hz, 2H), 7.63 (d, *J* = 8.7 Hz, 2H); (^{13}C NMR, 101 MHz, $CDCl_3$) δ = 13.9, 62.8, 101.8 (d, *J* = 233.7 Hz), 117.3 (d, *J* = 1.6 Hz), 123.9 (q, *J* = 271.5 Hz), 126.6 (q, *J* = 32.9 Hz), 127.3 (q, *J* = 4.0 Hz), 157.9, 163.3 (d, *J* = 31.0 Hz); (^{19}F NMR, 377 MHz, $CDCl_3$) δ = -62.1 (s, 3F), -130.9 (d, *J* = 59.0 Hz, 1F); IR (neat) ν 1766, 1616, 1517, 1325, 1222, 1166, 1113, 1065, 1113, 1065, 1014, 966, 840; HRMS (EI/FI) *m/z* Calcd for $C_{11}H_{10}F_4O_3$ $[M]^+$ 266.0566, found 266.0558.

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

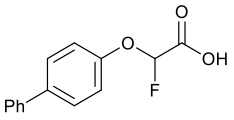


The title compound was prepared following General Procedure J using K_2CO_3 (6.91 g, 50.0 mmol), 4-nitrophenol (2.78 g, 20.0 mmol), DMF (40 mL) and ethyl bromofluoroacetate (3.55 mL, 30.0 mmol). The crude product was purified by silica gel column chromatography (eluent: 50% Et_2O in *n*-pentane) to provide the title compound (4.48 g, 92% yield) as a pale yellow oil.

(^{1}H NMR, 400 MHz, $CDCl_3$) δ = 1.37 (t, *J* = 7.2 Hz, 3H), 4.38 (q, *J* = 7.2 Hz, 2H), 6.07 (d, *J* = 58.4 Hz, 1H), 7.23 (dt, J_1 = 2.7 Hz, J_2 = 9.1 Hz, 2H), 8.25 (dt, J_1 = 2.7 Hz, J_2 = 9.1 Hz, 2H); (^{13}C NMR, 101 MHz, $CDCl_3$) δ = 13.9, 63.0, 101.2 (d, *J* = 235.2 Hz), 117.1 (d, *J* = 1.6 Hz), 144.0, 125.9, 159.8 (d, *J* = 2.4 Hz), 163.0 (d, *J* = 30.2 Hz); (^{19}F NMR, 377 MHz,

$CDCl_3$) δ = -132.0 (d, *J* = 59.0 Hz, 1F); IR (neat) ν 1762, 1615, 1594, 1520, 1494, 1345, 1297, 1218, 1174, 1092, 1011, 965, 851; HRMS (EI/FI) *m/z* Calcd for $C_{10}H_{10}FNO_5$ $[M]^+$ 243.0543, found 243.0.544.

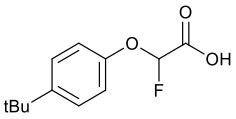
(Biphenyl-4-yloxy)fluoroacetic acid 4-106



The title compound was prepared following General Procedure F using ethyl (biphenyl-4-yloxy)fluoroacetate (2.19 g, 8.00 mmol), 5 M aq. NaOH (8.00 mL, 40.0 mmol) and Et_2O (40 mL). The title compound (1.89 g, 96% yield) was isolated as a white solid.

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

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

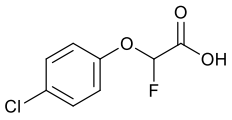


The title compound was prepared following General Procedure F using ethyl (4-*tert*-butylphenoxy)(fluoro)acetate (2.03 g, 8.00 mmol), 5 M aq. NaOH (8.00 mL, 40.0 mmol) and Et_2O (40 mL). The title compound (1.48 g, 81% yield) was isolated as a white solid.

(^{1}H NMR, 400 MHz, $CDCl_3$) δ = 1.33 (s, 9H), 6.02 (d, *J* = 59.7 Hz, 1H), 7.09 (dt, J_1 = 2.5 Hz, J_2 = 8.9 Hz, 2H), 7.39 (dt, J_1 = 2.5 Hz, J_2 = 8.9 Hz, 2H), 9.15 (br. s, 1H); (^{13}C NMR, 101 MHz, $CDCl_3$) δ = 31.4, 34.4, 102.3 (d, *J* = 231.3 Hz), 117.0, 126.7, 168.4 (d, *J* = 31.8 Hz), 147.7, 153.4 (d, *J* = 3.2 Hz); (^{19}F NMR, 377 MHz, $CDCl_3$) δ = -129.2 (d, *J* = 60.7 Hz, 1F); IR (neat) ν 3050, 2965, 1748, 1510, 1351, 1265, 1219, 1184, 1129, 1103, 1028, 961, 905, 830; HRMS (ESI) *m/z* Calcd for $C_{12}H_{14}FO_3$ $[M-H]^-$ 225.0933, found 225.0931; Mp. 63-65 °C.

Data consistent with literature values.[8]

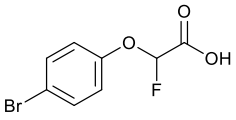
2-(4-Chlorophenoxy)-2-fluoroacetic acid



The title compound was prepared following General Procedure F using ethyl (4-chlorophenoxy)(fluoro)acetate (1.86 g, 8.00 mmol), 5 M aq. NaOH (8.00 mL, 40.0 mmol) and Et_2O (40 mL). The title compound (1.24 g, 76% yield) was isolated as a white solid.

(^{1}H NMR, 400 MHz, DMSO-d_6) δ = 6.40 (d, *J* = 58.7 Hz, 1H), 7.18 (dt, J_1 = 2.8 Hz, J_2 = 9.1 Hz, 2H), 7.44 (dt, J_1 = 2.8 Hz, J_2 = 9.1 Hz, 2H), 14.20 (br. s, 1H); (^{13}C NMR, 101 MHz, DMSO-d_6) δ = 101.7 (d, *J* = 229.7 Hz), 118.6, 127.9, 129.8, 154.0 (d, *J* = 2.4 Hz), 165.2 (d, *J* = 29.4 Hz); (^{19}F NMR, 377 MHz, DMSO-d_6) δ = -132.8 (d, *J* = 59.0 Hz, 1F); IR (neat) ν 3102, 2987, 1755, 1589, 1489, 1214, 1173, 1090, 1011, 962, 827; HRMS (ESI) *m/z* Calcd for $C_8H_5ClFO_3$ $[M-H]^-$ 202.9917 found 202.9924; Mp. 77-79 °C.

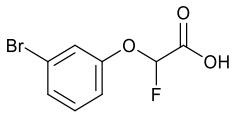
2-(4-Bromophenoxy)-2-fluoroacetic acid



The title compound was prepared following General Procedure F using ethyl (4-bromophenoxy)(fluoro)acetate (2.22 g, 8.00 mmol), 5 M aq. NaOH (8.00 mL, 40.0 mmol) and Et_2O (40 mL). The title compound (1.65 g, 83% yield) was isolated as a white solid. (^{1}H NMR, 400 MHz, DMSO-d_6) δ = 6.39 (d, J = 58.7 Hz, 1H), 7.13 (dt, J_1 = 2.7 Hz, J_2 = 9.1 Hz, 2H), 7.57 (dt, J_1 = 2.7 Hz, J_2 = 9.1 Hz, 2H), 14.25 (br. s, 1H); (^{13}C NMR, 101 MHz, DMSO-d_6) δ = 100.6 (d, J = 228.9 Hz), 115.7, 119.0, 132.7, 154.4, 165.1 (d, J = 29.4 Hz); (^{19}F NMR, 377 MHz, DMSO-d_6) δ = -132.8 (d, J = 59.0 Hz, 1F).

Data consistent with literature values.[16]

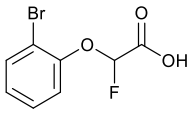
2-(3-Bromophenoxy)-2-fluoroacetic acid



The title compound was prepared following General Procedure F using ethyl (3-bromophenoxy)(fluoro)acetate (2.22 g, 8.00 mmol), 5 M aq. NaOH (8.00 mL, 40.0 mmol) and Et_2O (40 mL). The title compound (1.77 g, 89% yield) was isolated as a white solid. (^{1}H NMR, 400 MHz, $CDCl_3$) δ = 6.04 (d, J = 58.9 Hz, 1H), 7.12 (dd, J_1 = 2.2 Hz, J_2 = 8.3 Hz, 1H), 7.27 (t, J = 8.3 Hz, 1H), 7.35-7.36 (m, 2H), 9.63 (br. s, 1H); (^{13}C NMR, 101 MHz, $CDCl_3$) δ = 101.8 (d, J = 232.9 Hz), 116.1, 121.0, 123.0, 128.0, 131.0, 156.0 (d, J = 3.2 Hz), 168.0 (d, J = 31.8 Hz); (^{19}F NMR, 377 MHz, $CDCl_3$) δ = -130.3 (d, J = 59.0 Hz, 1F); IR (neat) ν 3550, 3083, 1772, 1709, 1589, 1473, 1357, 1272, 1223, 1106, 1049, 965, 908, 866; HRMS (EI/FI) *m/z* Calcd for $C_8H_6BrFO_3$ $[M]^+$ 247.9484, found 247.9488; Mp. 64-67 °C.

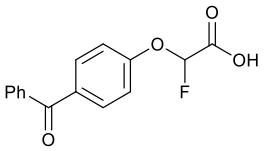
Data consistent with literature values.[16]

2-(2-Bromophenoxy)-2-fluoroacetic acid



The title compound was prepared following General Procedure F using ethyl (2-bromophenoxy)(fluoro)acetate (2.22 g, 8.00 mmol), 5 M aq. NaOH (8.00 mL, 40.0 mmol) and Et_2O (40 mL). The title compound (1.65 g, 83% yield) was isolated as a white solid. (^{1}H NMR, 400 MHz, DMSO-d_6) δ = 6.42 (d, J = 58.2 Hz, 1H), 7.11 (td, J_1 = 1.5 Hz, J_2 = 7.2 Hz, 1H), 7.33 (d, J = 8.3 Hz, 1H), 7.43 (td, J_1 = 1.5 Hz, J_2 = 7.8 Hz, 1H), 7.68 (dd, J_1 = 1.5 Hz, J_2 = 7.8 Hz, 1H), 14.28 (br. s, 1H); (^{13}C NMR, 101 MHz, DMSO-d_6) δ = 102.0 (d, J = 230.5 Hz), 112.2, 117.2, 125.6, 129.8, 133.6, 151.8, 165.0 (d, J = 29.4 Hz); (^{19}F NMR, 377 MHz, DMSO-d_6) δ = -132.5 (d, J = 59.0 Hz, 1F); IR (neat) ν 2978, 2362, 1755, 1580, 1479, 1442, 1359, 1281, 1228, 1170, 1140, 1114, 1022, 920; HRMS (EI/FI) *m/z* Calcd for $C_8H_5O_3BrF$ $[M-H]^-$ 246.9401, found 246.9393; Mp. 58-60 °C.

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

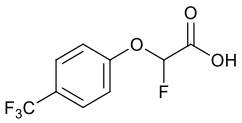


The title compound was prepared following General Procedure F using ethyl (4-benzoylphenoxy)(fluoro)acetate (2.42 g, 8.00 mmol), 5 M aq. NaOH (8.00 mL, 40.0 mmol) and Et_2O (40 mL). The title compound (2.07 g, 94% yield) was isolated as a white solid.

(^{1}H NMR, 400 MHz, DMSO-d_6) δ = 6.56 (d, J = 58.2 Hz, 1H), 7.32 (d, J = 8.6 Hz, 2H), 7.56 (t, J = 7.6 Hz, 2H), 7.67 (tt, J_1 = 1.9 Hz, J_2 = 7.3 Hz, 1H), 7.71-7.73 (m, 2H), 7.81 (dt, J_1 = 2.4 Hz, J_2 = 9.1 Hz, 2H); (^{13}C NMR, 101 MHz, DMSO-d_6) δ = 101.0 (d, J = 230.5 Hz), 116.3, 128.6, 129.5, 132.2, 132.5, 132.6, 137.2, 158.3 (d, J = 2.4 Hz), 165.2 (d, J = 29.4 Hz), 194.5; (^{19}F NMR, 377 MHz, DMSO-d_6) δ = -133.5 (d, J = 59.0 Hz, 2F); IR

(neat) ν 3550, 2362, 1708, 1647, 1599, 1281, 1227, 1108, 1043, 923, 845; HRMS (ESI) *m/z* Calcd for $C_{15}H_{12}FO_4$ $[M+H]^+$ 275.0714, found 275.0715; Mp. 106-108 °C.

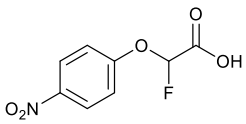
2-Fluoro-2-(4-(trifluoromethyl)phenoxy)acetic acid



The title compound was prepared following General Procedure F using ethyl fluoro[4-(trifluoromethyl)phenoxy]acetate (2.13 g, 8.00 mmol), 5 M aq. NaOH (8.00 mL, 40.0 mmol) and Et_2O (40 mL). The title compound (1.81 g, 95% yield) was isolated as a white solid.

(^{1}H NMR, 400 MHz, $CDCl_3$) δ = 6.10 (d, *J* = 58.9 Hz, 1H), 7.25 (d, *J* = 8.6 Hz, 2H), 7.66 (d, *J* = 8.6 Hz, 2H), 9.47 (br. s, 1H); (^{13}C NMR, 101 MHz, $CDCl_3$) δ = 101.4 (d, *J* = 234.4 Hz), 117.3, 123.8 (q, *J* = 271.8 Hz), 127.0 (q, *J* = 33.4 Hz), 127.7 (q, *J* = 3.7 Hz), 157.7, 168.0 (d, *J* = 31.8 Hz); (^{19}F NMR, 377 MHz, $CDCl_3$) δ = -62.1 (s, 3F), -131.2 (d, *J* = 59.0 Hz, 1F); IR (neat) ν 2929, 1745, 1614, 1517, 1357, 1324, 1275, 1230, 1171, 1122, 1063, 1044, 1015, 836; HRMS (EI/FI) *m/z* Calcd for $C_9H_6F_4O_3$ $[M]^+$ 238.0253, found 238.0254; Mp. 72-75 °C.

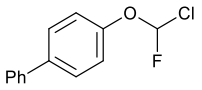
2-Fluoro-2-(4-nitrophenoxy)acetic acid



The title compound was prepared following General Procedure F using ethyl 2-fluoro-2-(4-nitrophenoxy)acetate (2.92 g, 12.0 mmol), 5 M aq. NaOH (12.0 mL, 60.0 mmol) and Et_2O (60 mL). The title compound (2.44 g, 95% yield) as a white solid.

(^{1}H NMR, 400 MHz, DMSO-d_6) δ = 6.61 (d, J = 57.7 Hz, 1H), 7.38 (dt, J_1 = 2.7 Hz, J_2 = 9.2 Hz, 2H), 8.29 (dt, J_1 = 2.7 Hz, J_2 = 9.2 Hz, 2H); (^{13}C NMR, 101 MHz, DMSO-d_6) δ = 100.9 (d, J = 230.5 Hz), 117.0, 126.0, 143.3, 159.7 (d, J = 2.4 Hz), 164.8 (d, J = 28.6 Hz); (^{19}F NMR, 377 MHz, DMSO-d_6) δ = -134.7 (d, J = 57.2 Hz, 1F); IR (neat) ν 3226, 1787, 1594, 1512, 1494, 1347, 1240, 1171, 1114, 1017, 856; HRMS (ESI) *m/z* Calcd for $C_8H_5FNO_5$ $[M-H]^-$ 214.0157 found 214.0162; Mp. 113-115 °C.

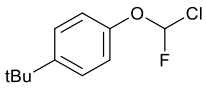
4-(Chlorofluoromethoxy)-1,1'-biphenyl 4-146



The title compound was prepared following General Procedure H using biphenyl-4-yloxy)fluoroacetic acid (0.25g, 1.0 mmol), CH_2Cl_2 (2 mL), DMF (8.0 µL, 0.10 mmol), oxalyl chloride (0.13 mL, 1.5 mmol), $BrCCl_3$ (3 mL), 4-dimethylaminopyridine (31 mg, 0.25 mmol) and sodium-*N*-hydroxy-2-thiopyridone (0.15 mg, 1.0 mmol). The crude product was purified by silica gel column chromatography (eluent: Et_2O/*n*-pentane 1/99) to provide the title compound (70 mg, 30% yield) as a white solid.

(^{1}H NMR, 400 MHz, $CDCl_3$) δ = 7.11-7.15 (m, 2H), 7.15 (d, J = 60.6 Hz, 1H), 7.26 (tt, J_1 = 2.2 Hz, J_2 = 7.3 Hz, 1H), 7.33-7.37 (m, 2H), 7.45-7.51 (m, 4H); (^{13}C NMR, 101 MHz, $CDCl_3$) δ = 112.2 (d, J = 273.4 Hz), 120.1, 127.0, 127.4, 128.4, 128.8, 138.7, 140.0, 151.6; (^{19}F NMR, 377 MHz, $CDCl_3$) δ = -73.3 (d, J = 60.7 Hz, 1F); IR (neat) ν 3034, 1608, 1516, 1485, 1451, 1353, 1294, 1213, 1186, 1105, 1008, 860; HRMS (EI/FI) *m/z* Calcd for $C_{13}H_{10}ClFO$ $[M]^+$ 236.0404, found 236.0365; Mp. 32-34 °C.

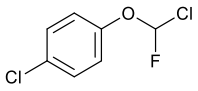
1-(*tert*-Butyl)-4-(chlorofluoromethoxy)benzene 4-151



The title compound was prepared following General Procedure H using 2-(4-(*tert*-butyl)phenoxy)-2-fluoroacetic acid (1.1 g, 4.0 mmol), CH_2Cl_2 (8 mL), DMF (31 µL, 0.40 mmol), oxalyl chloride (0.52 mL, 6.0 mmol), $BrCCl_3$ (12 mL), 4-dimethylaminopyridine (0.12 g, 1.0 mmol) and sodium-*N*-hydroxy-2-thiopyridone (0.60 g, 4.0 mmol). The crude product was purified by silica gel column chromatography (eluent: Et_2O/*n*-pentane 1/99) to provide the title compound (0.11 g, 12% yield) as pale yellow oil.

(^{1}H NMR, 400 MHz, $CDCl_3$) δ = 1.33 (s, 9H), 7.08-7.12 (m, 2.5H), 7.27 (s, 0.5H), 7.39 (dt, J_1 = 2.7 Hz, J_2 = 8.8 Hz, 2H); (^{13}C NMR, 101 MHz, $CDCl_3$) δ = 31.4, 34.4, 112.4 (d, J = 272.6 Hz), 119.3, 126.6, 148.5, 150.0; (^{19}F NMR, 377 MHz, $CDCl_3$) δ = -73.0 (d, J = 62.4 Hz, 1F); IR (neat) ν 2964, 1510, 1365, 1294, 1203, 1174, 1121, 1093, 1014, 829; HRMS (EI/FI) *m/z* Calcd for $C_{11}H_{14}ClFO$ $[M]^+$ 216.0717, found 216.0724.

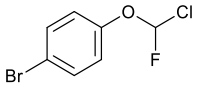
1-Chloro-4-(chlorofluoromethoxy)benzene 4-152



The title compound was prepared following General Procedure H using 2-(4-chlorophenoxy)-2-fluoroacetic acid (0.82 g, 4.0 mmol), CH_2Cl_2 (8 mL), DMF (31 µL, 0.40 mmol), oxalyl chloride (0.52 mL, 6.0 mmol), $BrCCl_3$ (12 mL), 4-dimethylaminopyridine (0.12 g, 1.0 mmol) and sodium-*N*-hydroxy-2-thiopyridone (0.60 g, 4.0 mmol). The crude product was purified by silica gel column chromatography (eluent: Et_2O/*n*-pentane 0.5/99.5) to provide the title compound (0.25 g, 32% yield) as colourless oil.

(^{1}H NMR, 400 MHz, $CDCl_3$) δ = 7.10-7.14 (s, 2.5H), 7.26 (s, 0.5H), 7.35 (dt, J_1 = 2.8 Hz, J_2 = 8.8 Hz, 2H); (^{13}C NMR, 101 MHz, $CDCl_3$) δ = 111.9 (d, J = 275.0), 121.6, 129.7, 131.1, 150.5; (^{19}F NMR, 377 MHz, $CDCl_3$) δ = -73.9 (d, J = 60.7 Hz, 1F); IR (neat) ν 1414, 1324, 1272, 1172, 1131, 1099, 1070, 1053, 1020, 961, 889, 830; HRMS (EI/FI) *m/z* Calcd for $C_7H_5Cl_2FO$ $[M]^+$ 193.9701, found 193.9694.

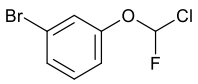
1-Bromo-4-(chloro(fluoro)methoxy)benzene 4-153



The title compound was prepared following General Procedure H using 2-(4-bromophenoxy)-2-fluoroacetic acid (1.0g, 4.0 mmol), CH_2Cl_2 (8 mL), DMF (31 µL, 0.40 mmol), oxalyl chloride (0.52 mL, 6.0 mmol), $BrCCl_3$ (12 mL), 4-dimethylaminopyridine (0.12 g, 1.0 mmol) and sodium-*N*-hydroxy-2-thiopyridone (0.60 g, 4.0 mmol). The crude product was purified by silica gel column chromatography (eluent: Et_2O/*n*-pentane 1/99) to provide the title compound (0.28 g, 30% yield) as a colourless oil.

(^{1}H NMR, 400 MHz, $CDCl_3$) δ = 6.97 (dtd, J_1 = 0.7 Hz, J_2 = 2.7 Hz, J_3 = 9.1 Hz, 2H), 7.10 (d, J = 60.2 Hz, 1H), 7.41 (dt, J_1 = 2.7 Hz, J_2 = 9.1 Hz, 2H); (^{13}C NMR, 101 MHz, $CDCl_3$) δ = 111.8 (d, J = 275.0 Hz), 118.7, 121.9, 132.7, 151.0; (^{19}F NMR, 377 MHz, $CDCl_3$) δ = -73.9 (d, J = 59.0 Hz, 1F); IR (neat) ν 1484, 1294, 1195, 1099, 1067, 1009, 851, 823; HRMS (EI/FI) *m/z* Calcd for $C_7H_5BrClFO$ $[M]^+$ 237.9196, found 237.9198.

1-Bromo-3-(chloro(fluoro)methoxy)benzene 4-154

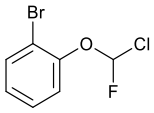


The title compound was prepared following General Procedure H using 2-(3-bromophenoxy)-2-fluoroacetic acid (1.0 g, 4.0 mmol), CH_2Cl_2 (8 mL), DMF (31 µL, 0.40 mmol), oxalyl chloride (0.52 mL, 6.0 mmol), $BrCCl_3$ (12 mL), 4-dimethylaminopyridine (0.12 g, 1.0 mmol) and sodium-*N*-hydroxy-2-thiopyridone (0.60 g, 4.0 mmol). The crude product was purified by silica gel column chromatography (eluent: Et_2O/*n*-pentane 1/99) to provide the title compound (0.31 g, 32% yield) as a pale yellow oil.

(^{1}H NMR, 400 MHz, $CDCl_3$) δ = 7.01-7.04 (m, 1.5H), 7.14-7.18 (m, 1.5H), 7.25-7.30 (m, 2H); (^{13}C NMR, 101 MHz, $CDCl_3$) δ = 111.8 (d, J = 275.0 Hz), 118.9, 122.7, 123.4, 128.8,

130.8, 152.6; (^{19}F NMR, 377 MHz, $CDCl_3$) δ = -74.1 (d, *J* = 60.7 Hz, 1F); IR (neat) ν 1582, 1472, 1427, 1293, 1189, 1092, 1065, 1017, 877, 832; HRMS (EI/FI) *m/z* Calcd for $C_7H_5BrClFO$ $[M]^+$ 237.9196, found 237.9247.

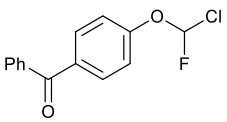
1-Bromo-2-(chloro(fluoro)methoxy)benzene 4-155



The title compound was prepared following General Procedure H using 2-(2-bromophenoxy)-2-fluoroacetic acid (1.0 g, 4.0 mmol), CH_2Cl_2 (8 mL), DMF (31 µL, 0.40 mmol), oxalyl chloride (0.52 mL, 6.0 mmol), $BrCCl_3$ (12 mL), 4-dimethylaminopyridine (0.12 g, 1.0 mmol) and sodium-*N*-hydroxy-2-thiopyridone (0.60 mg, 4.0 mmol). The crude product was purified by silica gel column chromatography (eluent: Et_2O/*n*-pentane 1/99) to provide the title compound (0.39 g, 40% yield) as a colourless oil.

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

4-(Chloro(fluoro)methoxy)phenyl)(phenyl)methanone 4-156

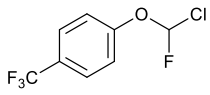


The title compound was prepared following General Procedure H using 2-(4-benzoylphenoxy)-2-fluoroacetic acid (1.1 g, 4.0 mmol), CH_2Cl_2 (8 mL), DMF (31 µL, 0.40 mmol), oxalyl chloride (0.52 mL, 6.0 mmol), $BrCCl_3$ (12 mL), 4-dimethylaminopyridine

(0.12 g, 1.0 mmol) and sodium-*N*-hydroxy-2-thiopyridone (0.60 g, 4.0 mmol). The crude product was purified by silica gel column chromatography (eluent: Et_2O/*n*-pentane 15/85) to provide the title compound (0.21 g, 20% yield) as pale yellow oil.

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

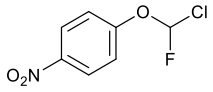
1-(Chloro(fluoro)methoxy)-4-(trifluoromethyl)benzene 4-157



The title compound was prepared following General Procedure H using 2-fluoro-2-(4-(trifluoromethyl)phenoxy)acetic acid (952 mg, 4.0 mmol), CH_2Cl_2 (8 mL), DMF (31 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 (0.16 g, 18% yield) as a colourless oil.

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

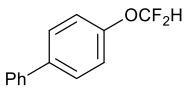
1-(Chloro(fluoro)methoxy)-4-nitrobenzene 4-158



The title compound was prepared following General Procedure H using 2-fluoro-2-(4-nitrophenoxy)acetic acid (0.86 g, 4.0 mmol), CH_2Cl_2 (8.0 mL), DMF (31 µL, 0.40 mmol), oxalyl chloride (0.52 mL, 6.0 mmol), $BrCCl_3$ (12 mL), 4-dimethylaminopyridine (122 mg, 1.0 mmol) and sodium-*N*-hydroxy-2-thiopyridone (0.60 mg, 4.0 mmol). The crude product was purified by silica gel column chromatography (eluent: Et_2O/*n*-pentane 20/80) to provide the title compound (0.32 g, 39% yield) as a pale yellow oil.

(^{1}H NMR, 400 MHz, $CDCl_3$) δ = 7.24 (s, 0.5H), 7.30 (dt, J_1 = 2.8 Hz, J_2 = 9.1 Hz, 2H), 7.39 (s, 0.5H), 8.28 (dt, J_1 = 2.8 Hz, J_2 = 9.1 Hz, 2H); (^{13}C NMR, 101 MHz, $CDCl_3$) δ = 111.1 (t, *J* = 276.6 Hz), 119.7, 125.6, 144.8, 156.4; (^{19}F NMR, 377 MHz, $CDCl_3$) δ = -76.6 (d, *J* = 59.0 Hz, 2F); IR (neat) ν 1615, 1594, 1520, 1493, 1344, 1299, 1219, 1173, 1077, 1013, 872, 848; HRMS (EI/FI) *m/z* Calcd for $C_7H_5ClFNO_3$ $[M]^+$ 204.9942, found 204.9939.

4-(Difluoromethoxy)biphenyl 4-168

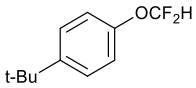


To a pressure tube containing a mixture of 4-phenylphenol (85 mg, 0.50 mmol) and aqueous KOH (1.5 mL, 25 wt%, ca. 8 mmol), was added a solution of chlorodifluoroacetophenone (0.48 g, 2.5 mmol) in MeCN (1.5 mL) at -78 ˚C. The reaction tube was sealed and heated to 80 ˚C for 4 hr. The reaction was quenched by addition of water, and the aqueous phase was extracted with Et_2O (2 x 10 mL). The pooled organic phases were washed with brine, then dried over $MgSO_4$, filtered and concentrated *in vacuo*.

Purification by silica gel column chromatography (eluent: EtOAc/*n*-hexane = 1:40) gave the title compound (51 mg, 47%) as a colourless solid.

(^{1}H NMR, 400 MHz, $CDCl_3$) δ = 6.44 (t, *J* = 74.0 Hz, 1H), 7.09 (d, *J* = 8.6 Hz, 2H), 7.26 (tt, J_1 = 2.0 Hz, J_2 = 7.3 Hz, 1H), 7.35 (t, *J* = 7.4 Hz, 2H), 7.49-7.45 (m, 4H); (^{13}C NMR, 101 MHz, $CDCl_3$) δ = 116.0 (t, *J* = 259.9 Hz), 119.9, 127.1, 127.5, 128.5, 128.9, 138.6, 140.1, 150.6; (^{19}F NMR, 377 MHz, $CDCl_3$) δ = -81.9 (d, *J* = 74.6 Hz, 2F). Data consistent with literature values.[9]

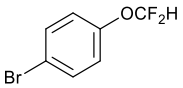
1-*tert*-Butyl-4-(difluoromethoxy)benzene 4-169



To a Schlenck tube was added (4-*tert*-butylphenoxy)(difluoro)acetic acid (0.12 g, 0.50 mmol), Selectfluor^{TM} (0.71 g, 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: Et_2O/*n*-pentane 1/99) to provide the title compound (78 mg, 78% yield) as a colourless oil.

(^{1}H NMR, 400 MHz, $CDCl_3$) δ = 1.33 (s, 9H), 6.49 (t, *J* = 74.3 Hz, 1H), 7.06 (d, *J* = 8.8 Hz, 2H), 7.38 (dt, J_1 = 2.6 Hz, J_2 = 8.8 Hz, 2H); (^{13}C NMR, 101 MHz, $CDCl_3$) δ = 31.4, 34.4, 116.1 (t, *J* = 259.1 Hz), 119.1, 126.7, 148.4, 148.9 (t, *J* = 2.8 Hz); (^{19}F NMR, 377 MHz, $CDCl_3$) δ = -80.4 (d, *J* = 74.6 Hz, 2F). Data consistent with literature values.[10]

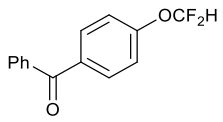
1-Bromo-4-(difluoromethoxy)benzene 4-171



The title compound was prepared following General Procedure E using K_2CO_3 (6.91 g, 50.0 mmol), 4-bromophenol (3.46 g, 20.0 mmol), DMF (40 mL) and ethyl bromodifluoroacetate (3.85 mL, 30.0 mmol). The crude product was purified by silica gel column chromatography (eluent: Et_2O/*n*-pentane 3/97) to provide the title compound (1.16 g, 26% yield) as a colourless oil.

(^{1}H NMR, 400 MHz, $CDCl_3$) δ = 6.49 (t, *J* = 73.4 Hz, 1H), 7.04-7.01 (m, 2H), 7.49 (dt, J_1 = 2.7 Hz, J_2 = 9.1 Hz, 2H); (^{13}C NMR, 101 MHz, $CDCl_3$) δ = 115.6 (t, *J* = 261.5 Hz), 118.5, 121.5, 132.8, 150.0; (^{19}F NMR, 377 MHz, $CDCl_3$) δ = -81.2 (d, *J* = 72.8 Hz, 2F). Data consistent with literature values.[4]

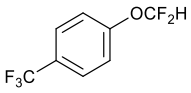
4-(Difluoromethoxy)phenyl](phenyl)methanone 4-174



The title compound was prepared following General Procedure E using K_2CO_3 (6.91 g, 50.0 mmol), 4-hydroxybenzophenone (3.96 g, 20.0 mmol), DMF (40 mL) and ethyl bromodifluoroacetate (3.85 mL, 30.0 mmol). The crude product was purified by silica gel column chromatography (eluent: Et_2O/*n*-pentane 5/95) to provide the title compound (1.33 g, 27% yield) as a colourless oil.

(^{1}H NMR, 400 MHz, $CDCl_3$) δ = 6.63 (t, *J* = 73.1 Hz, 1H), 7.22 (d, *J* = 8.8 Hz, 2H), 7.48-7.52 (m, 2H), 7.61 (tt, J_1 = 1.9 Hz, J_2 = 7.5 Hz, 1H), 7.77-7.80 (m, 2H), 7.86 (dt, J_1 = 2.3 Hz, J_2 = 8.8 Hz, 2H); (^{13}C NMR, 101 MHz, $CDCl_3$) δ = 115.4 (t, J = 256.5 Hz), 118.6, 128.4, 129.9, 132.2, 132.5, 134.4, 137.4, 154.2 (t, *J* = 2.8 Hz), 195.3; (^{19}F NMR, 377 MHz, $CDCl_3$) δ = -81.7 (d, *J* = 72.8 Hz, 2F). Data consistent with literature values.[11]

1-(Difluoromethoxy)-4-(trifluoromethyl)benzene 4-175



The title compound was prepared following General Procedure E using K_2CO_3 (6.91 g, 50.0 mmol), 4-(trifluoromethyl)phenol (3.24 g, 20.0 mmol), DMF (40 mL) and ethyl bromodifluoroacetate (3.85 mL, 30.0 mmol). The crude product was purified by silica gel column chromatography (eluent: Et_2O/*n*-pentane 1/99) to provide the title compound (957 mg, 23% yield) as a colourless oil.

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

References

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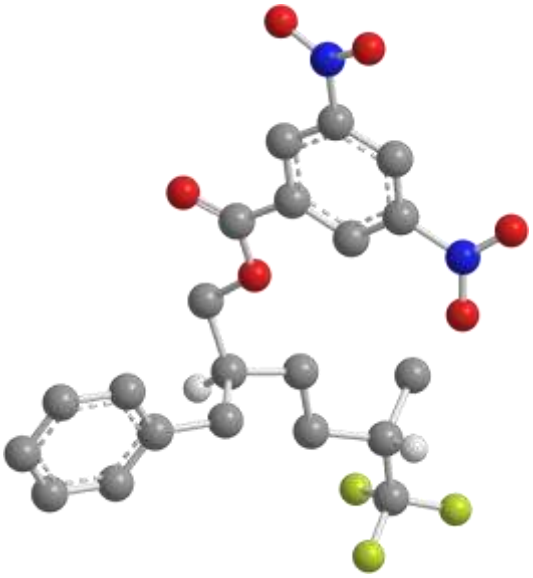
Appendix B: X-Ray crystal structure data for (*RS*,*RS*)-2-64



X-ray crystal structure determination for 2-64 (selected H atoms are omitted for clarity)

Crystals suitable for X-ray diffraction analysis were obtained by recrystallizing *syn*-2-benzyl-6,6,6-trifluoro-5-methylhexyl 3,5-dinitrobenzoate **2-64** from *n*-hexane and dichloromethane.

X-ray diffraction data were collected at 100 K[1] with synchrotron radiation using I19 (EH1) at Diamond Light Source (λ = 0.6889 Å).[2] Raw frame data were reduced using CrysAlisPro (Agilent Technologies, 2010). The structure was solved with SuperFlip[3] and refined using CRYSTALS;[4] all non-hydrogen atoms were refined with anisotropic thermal parameters and hydrogen atoms were added at idealised positions. On refinement, the structure was found to be disordered, containing ca. 8% of anti-2-benzyl-6,6,6-trifluoro-5-methylhexyl 3,5-dinitrobenzoate, consistent with NMR results.

X-ray crystal structure data for **2-64** [$C_{21}H_{21}F_3N_2O_6$]: M = 454.40, monoclinic, space group $P\ 2_1/n$, a = 11.5035(1) Å, b = 7.3244(1) Å, c = 25.6429(5) Å, β = 99.0882(14)°, V =

2133.45(5) Å^3, Z = 4, μ = 0.121 mm^{-1}, clear plate, crystal dimensions = 0.02 × 0.07 × 0.10 mm^3. A total of 7606 unique reflections were measured for $1 < \theta < 32$ and 7592 reflections were used in the refinement. The final parameters were wR_2 = 0.122 and R_1 = 0.057 [I>–3.0σ(I)]. X-ray crystal structure determination was performed by Dr Amber L. Thompson, Chemistry Research Laboratory, University of Oxford, U.K.

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